GlyCon: Glycaemic control of stress hyperglycaemia in intensive care units

by

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To Nicky,

for making of this a much more joyful and fun journey... every day.

Abstract

Background and aims

Untreated stress-induced hyperglycaemia in critically ill patients has been associated with harmful effects, which can even be fatal. Current evidence about the optimal glycaemic targets, and the most effective and safest methods of glycaemic control (GC) in intensive care units (ICU), is contradictory. GlyCon study aimed to investigate the effectiveness, efficiency and safety of the monitoring and insulin treatment methods for GC implemented in the seven ICUs of an NHS ICU network in the UK. In addition, GlyCon study also aimed to explore the contents of the local protocols for GC of these ICUs, as well as the views of ICU professionals about several aspects of GC.

Methodology

A multi-method study was undertaken, comprising three sub-studies: (1) a document review of the protocols for GC designed by and implemented at each of the participating ICUs, using techniques of inductive content analysis and descriptive statistics; (2) an online survey to ICU medical and nursing staff, on their opinion about effective GC, and deviations from protocol instructions, which was analysed using descriptive statistics and logistic regression; (3) A retrospective study about the methods and outcomes of GC, based on a review of electronic and manual medical records of a stratified random sample of 146 patients admitted to the seven participating ICUs during 2012 and 2013. The main analyses of association between the exposures and the primary outcome measure (percentage of time with glycaemic levels of 4-10mmol/L, or TIR, which was transformed into the odds of being within that range at any time, or odds of IR), were mainly based on generalised estimating equations using the logit link, and autoregressive correlation structure. Secondary outcome measures of time-efficiency and safety were also investigated, and analysed using univariate statistics and multiple log-linear regression.

Results

The protocols for GC implemented in the seven ICUs differed greatly in their target patients, target glycaemic levels, recommended methods for monitoring, and insulin titration algorithms, among others.

Most of the 40 respondents to the survey agreed that TIR≥75% constitutes good GC and TIR<50% constitutes poor GC. Opinions were divided on intermediate levels of TIR, with professionals having more experience in intensive care tending to rate such intermediate TIR as poor GC more often than their less experienced colleagues. Most of the proposed protocol deviations were considered as major by at least two thirds of the respondents. Professionals' role (nurse vs. physician) and their number of years of experience were significantly associated with different views.

The blood glucose (BG) monitoring frequencies and insulin hourly dosages, at each glycaemic status, differed by ICU, and between patients with and without diabetes. Non-adherence to protocol instructions regarding BG monitoring and insulin infusion rates occurred more often than not. The median (IQR) TIR was 91% (81-96%) and 56% (34-71%) among patients without and with diabetes, respectively. A number of time-dependent and time-constant factors were associated with higher odds of IR at any time. Time-constant protective factors included: having spent more than 20% of admission time receiving insulin during hyperglycaemia, certain ICU protocols, and lower levels of severity on admission. Time-dependent protective factors were: the number of hours from admission, and the dobutamine and insulin hourly dosages. Time-dependent detrimental factors were: non-adherence to protocol insulin instructions, the hourly nutritional energy administered, and the hourly dosage of certain drugs, including adrenaline and hydrocortisone.

Conclusions

Protocols for GC, practice of GC, and outcomes of GC, all differed significantly across hospitals. Some protocols seemed more effective, time-efficient or safe than others, but there was a high incidence of non-adherence to protocol instructions in all ICUs. This contrasts with professionals rating deviations from protocols as major, more often than not. Certain monitoring and insulin treatment methods for GC were more effective, and some were more time-efficient than others, particularly among patients without diabetes. There is a clear need for protocols to include different recommendations for patients with diabetes, as well as to formally emphasise the importance of GC also in patients without diabetes. ICU multidisciplinary teams should be involved in the development of these protocols, and their views should be accounted for in research studies about the effectiveness of GC in the ICU.

Memorandum

This thesis entitled "GlyCon: Glycaemic control of stress hyperglycaemia in intensive care units" is submitted for the degree of Doctor of Philosophy in the School of Health Sciences at The University of Nottingham.

This thesis is based entirely on the work carried out by the author except where stated otherwise in the text. This work was carried out between October 2012 and October 2016 at The University of Nottingham (UK) under the supervision of Dr Gary Adams and Dr Richard Windle.

All the work and ideas recorded in this thesis are original except where acknowledged in the text or by reference.

The work contained in this thesis has not been previously submitted for any qualification at this or any other University or Examining Body.

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Scholarly outputs

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Different views of medical and nursing professionals on the methods for glycaemic control implemented in intensive care. A cross-sectional study in seven hospitals within the UK. 28th Annual Congress of the European Society of Intensive Care Medicine (ESICM), 3–7 October 2015, Berlin (Germany).

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GlyCon study protocol: a retrospective study of glycaemic control methods of stress hyperglycaemia implemented in NHS ICUs. Research Saturday. School of Health Sciences, University of Nottingham. 29 June 2013.

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Abbreviations

ADA	American Diabetes Association
BG	Blood glucose
BMI	Body Mass index
CI	Confidence interval
CMP	Case mix program (of ICNARC)
CV	Coefficient of variation
EE	Energy expenditure
EES	Effectiveness, efficiency and safety
EN	Enteral nutrition
GC	Glycaemic control
GV	Glycaemic variability
HbA1c	Glycosylated haemoglobin A1c
HDU	High dependency unit
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive care unit
IIT	Intensive insulin therapy
IIR	Insulin infusion rate
IQR	Inter-quartile range
U	International units (of insulin)
IV	Intravenous
LOS	Length of stay
MICU	Medical intensive care unit
MTCCN	Mid Trent Critical Care Network
NHS	National Health System
IR (Odds of)	(Odds of) being in a pre-specified glucose range
OR	Odds ratio
POC	Point of care
RCT	Randomized controlled trial
SC	Subcutaneous
SD	Standard Deviation
SICU	Surgical intensive care unit

TGC	Tight glycaemic control (p4 intro)
TIR	Percentage of time spent in a pre-specified glucose range
TPN	Total parenteral nutrition
TTR	Time to range
UL	Upper limit (of the glycaemic target)
UL10	Upper limit of the glycaemic target is 10mmol/L
UL83	Upper limit of the glycaemic target is 8.3mmol/L or lower
VRIII	Variable Rate Intravenous Insulin Infusion (p20)

Chapter 1
Introduction

Critical patients are the most severely ill patients admitted to hospitals, in a state where death is likely or imminent. Intensive care medicine has evolved as a branch of medicine dedicated to identify and treat those patients whose fatal ending may be avoided (Mitchell, 2010). Increasing this survival usually depends on an early and timely diagnosis, and the continuous assessment and treatment implemented simultaneously (Mitchell, 2010). For this, patients are admitted to intensive care units (ICU), highly specialised services where they are continuously monitored and closely cared for.

During the past few decades, intensive care has undergone enormous changes, mainly as a consequence of important technological developments, and the advances in the available evidence (Kelly et al., 2014). However, as with many other medical fields, evidence about the impact and quality of the care provided in the ICU is often not so clear or free from uncertainties. This is also the case with the management of stress hyperglycaemia in critically ill patients.

Stress hyperglycaemia

During critical illness, the injury, infection or other severe acute event affecting the patient, are stressors that cause physiologic and behavioural adaptive responses to them, constituting what is known as stress response. As part of this response, there are important changes in the endogenous metabolism of the patient, which can result in stress-induced hyperglycaemia, or stress hyperglycaemia for short. Stress hyperglycaemia is the increase of glycaemic levels (or blood glucose, BG) above normal levels, which revert to normal when the critical condition is resolved (Dungan et al., 2009). The prevalence of events of stress hyperglycaemia varies depending on the glycaemic levels used to define it, as well as on various patient and therapy related factors. In a large database study, Swanson et al. (2011) found a prevalence of BG measurements above 10mmol/L in 32.2% patient-days.

While the exact mechanisms of glucose physiology during a critical condition are still not fully understood (Preiser et al., 2016), it is widely accepted that the main mechanisms causing stress hyperglycaemia are an intense and complex counter-regulatory hormone and immune response, which causes an increase in hepatic production of glucose and peripheral

insulin resistance (Preiser, 2013; McDonnell & Umpierrez, 2012; Dungan et al., 2009). It is believed that this increase in the available glucose levels in the blood is a beneficial mechanism by which the higher energy demands of vital non-insulin-dependent tissues, including the brain and immune cells, are satisfied (Marik & Bellomo, 2013). Indeed, some clinicians and researchers support the idea that stress hyperglycaemia should not be treated unless it is too high (such as >12.2mmol/L) or too prolonged (Marik, 2016; Marik & Bellomo, 2013). Also, more severely ill patients have greater likelihood of suffering hyperglycaemia, and thus it is not clear whether this condition is just a marker of severity (Marik & Bellomo, 2013).

However, the bulk of the current evidence suggests associations between acute states of hyperglycaemia in ICU and adverse effects, which are more pronounced among patients without a history of diabetes. These effects include higher rates of sepsis, prolonged length of stays (LOS) and other general complications, as well as higher mortality rates (Krinsley & Preiser, 2015; Buchleitner et al., 2012; Chase, Shaw, et al., 2008; Van den Berghe, Wilmer, Hermans, et al., 2006; Van den Berghe et al., 2001). Amongst such studies are randomised controlled trials (RCT) that have demonstrated that treating stress hyperglycaemia can reduce its potentially severe or even fatal effects. This is especially so in surgery patients, particularly cardiac surgery patients, when iatrogenic hypoglycaemia secondary to the treatment of hyperglycaemia is avoided (Lanspa et al., 2013; Van den Berghe et al., 2001).

Glycaemic control methods of stress hyperglycaemia

Despite the general agreement that some type of treatment is necessary to control stress hyperglycaemia, during the past two decades an intense debate has been taking place among the scientific and clinical communities about how, and to what extent, stress hyperglycaemic events should be treated in the different types of ICU patients.

In 2001 and 2006, two landmark randomised controlled trials (RCT) in the field of glycaemic control (GC) of stress hyperglycaemia demonstrated that tight glycaemic control (TGC) targeting normal glycaemic levels (4.4-6.1mmol/L) using intensive insulin therapy (IIT) improved the outcomes of critically ill surgical and medical patients, particularly among patients without a history of diabetes (Van den Berghe, Wilmer, Hermans, et al., 2006; Van den Berghe et al., 2001). These trials were very influential and marked a shift in the management of stress hyperglycaemia towards TGC, in many ICUs worldwide (Niven et al., 2015; Paddle et al., 2011).

However, numerous subsequent RCTs and observational studies obtained contradictory results that concluded against TGC (NICE-SUGAR Study Investigators et al., 2009; Preiser et al., 2009; Arabi et al., 2008; De La Rosa et al., 2008; Brunkhorst et al., 2008). The main

argument against TGC in these studies was a lack of clinical benefit, together with an increased risk of severe hypoglycaemia secondary to TGC approaches. Hypoglycaemia, especially when it is severe (BG<2.2mmol/L) has also been associated with harmful effects, including a higher risk of mortality (Krinsley et al., 2013; Krinsley & Grover, 2007; Van den Berghe, Wilmer, Hermans, et al., 2006; Finney et al., 2004; Van den Berghe et al., 2001). As a consequence of these findings, many ICUs turned their backs on TGC, and adopted less strict approaches targeting higher than normal glycaemic levels that could be safely achieved.

Among the possible reasons that have been suggested to explain why these studies found such conflicting results, are differences in the characteristics of patients and care provided in each of the studies (Kavanagh & McCowen, 2010), differences in the levels of quality of the investigations (Marik & Bellomo, 2013), and lack of the resources and skills needed to achieve TGC safely (Qaseem et al., 2011; Kavanagh & McCowen, 2010; Van den Berghe et al., 2009; Kelly et al., 2006).

This disagreement about the glycaemic levels that should be targeted in the ICU, as well as about the most effective and safest GC approaches to achieve them, are an important barrier to the development of common standards for GC of the critically ill. Consequently, at present, the recommendations of existing national and international guidelines about the optimal glycaemic targets and management methods of stress hyperglycaemia in the ICU have important differences among each other (American Diabetes Association, 2014; Dellinger et al., 2013; Australian Diabetes Society, 2012b, 2012a; Diringer et al., 2011; Moghissi et al., 2009; Lazar et al., 2009).

The aim of clinical protocols is to reduce variability of practice and improve clinical outcomes (Wilson et al., 2007). Due to the discrepant evidence and lack of standardisation regarding the management of stress hyperglycaemia, local protocols for GC, developed by the ICUs where they are implemented, differ significantly. Previous studies have shown that local protocols differ both in their glycaemic targets and in the recommended methods to achieve them (Niven et al., 2015; J. Orban et al., 2013; Tomlinson et al., 2012; Paddle et al., 2011; Cook et al., 2009; Wilson et al., 2007; Mackenzie et al., 2005). However, there is a lack of studies exploring in detail the individual instructions to deal with each specific glycaemic scenario stated in protocols for GC.

Evaluation of glycaemic control

Despite most ICUs developing their own protocol for GC, there is evidence that protocols are often not adhered to (Leape et al., 2003). Thus, it could be misleading to evaluate the impact and quality of GC protocols, unless the GC methods that are actually implemented in

the ICU are investigated (Kavanagh & Nurok, 2016). Currently, there is scarce evidence about the extent to which such methods for GC implemented in the real critical care setting are successful in achieving their aim of stabilising patients' BG levels within a safe glycaemic range (Studer et al., 2010; Van den Berghe & Van den Berghe, 2004).

Besides the ICU patients themselves, the main stakeholders in the development and implementation of protocols for GC in ICUs are the professionals who develop and implement them. Therefore their views about the aims and implementation of such protocols can be crucial in the evaluation of the implemented GC methods (EFQM, 2012). At present, there is a lack of evidence about the opinion of ICU professionals regarding effective and safe GC, and about the role of protocols for GC.

1.1 The GlyCon study

Based on these grounds, the GlyCon study was designed to investigate three areas where gaps were identified in the current evidence:

1) what different ICUs recommend for the GC of their patients, as stated in their protocols;
2) what professionals think about GC; and
3) how effective, as well as how efficient and safe, the methods for GC implemented in the real critical care setting are.

In order to answer these questions, a multi-centre study, with a multi-method design, was carried out in the seven UK NHS ICUs of the Mid Trent Critical Care Network. The multi-method design resulted in three sub-studies.

The first sub-study was a review and comparison of the protocols for GC implemented in all seven ICUs of the network. This provided a detailed picture about the written instructions that guide clinical practice in different ICUs.

The second sub-study was an online survey of ICU professionals, about different aspects of GC. Results of the survey shed light on how professionals view effective and safe GC, and what they opine about deviating from certain protocols instructions.

The third sub-study was a retrospective research about the methods and outcomes of GC implemented in ICU, based on different types of medical records of patients admitted to the ICUs of the seven study hospitals during 2012 and 2013. This was the largest part of GlyCon and was designed to address the main aim of the study: to investigate the relationship between different methods for GC implemented in the seven ICUs of an ICU network, and their levels of effectiveness, in terms of the percentage of time that patients spent within the

glycaemic range of 4-10mmol/L (time in range, TIR). The main study hypothesis was that more frequent monitoring during hyperglycaemias higher than 10mmol/L, and longer percentages of the time spent in those hyperglycaemias, were associated with higher TIR. A number of metrics of time-efficiency and safety were also explored as secondary outcome measures. The retrospective data were also used to assess the level of adherence to protocol instructions in the individual ICUs, and, in some instances, how this related to the outcome measures.

Impact of GlyCon study

The findings of GlyCon, together with the latest evidence about the management of stress hyperglycaemia in critically ill patients, guided the development of a series of recommendations for the quality improvement of GC in ICU. The implementation of these recommendations in the participating ICUs should help with the improvement of the effectiveness, efficiency and safety of the methods for GC that they implement. Thus GlyCon is a clear example of an applied clinical research study.

1.2 Overview of the thesis

Following this introduction, the state-of-the-art about stress hyperglycaemia in critically ill patients, and its management, is presented in Chapter 2. The review starts with a description of the complexity of the pathophysiology of stress hyperglycaemia in critically ill patients, followed by a summary of the existing different glycaemic targets and methods for GC recommended or implemented in the ICU. The different metrics proposed for the evaluation of GC are reviewed, and the role of ICU professionals in the successful implementation of effective and safe GC is discussed. From this literature review, a number of gaps are identified in the state-of-the-art, which led to the motivation and objectives of the GlyCon study.

Chapter 3 provides an overview of the overall methodology used in the study, including the justification for the study design, as well as methodological and philosophical considerations. The study setting and the ethical considerations of the overall study are described in detail in this chapter, followed by a brief summary of the methods used in each of the three sub-studies. Full details about these individual methods are given in the subsequent three chapters dedicated to each of the sub-studies.

Chapter 4, Chapter 5 and Chapter 6 deal with each of the sub-studies individually. Each of these chapters includes a brief summary of the relevant evidence motivating the study,

followed by details about the methods, results and discussion of the results of the sub-study. This structure, where the methods, results and discussion are presented in order, for each sub-study separately, was chosen in order to allow for more fluid reading where the method of the study is followed by its results and their interpretation and discussion.

The first of the sub-studies (Chapter 4) is the review of the GC protocols implemented in the seven GlyCon ICUs. For this, a generic tool was developed to be used as a framework for the systematic qualitative and quantitative description and comparison of the contents of protocols for GC. This tool was used to compare the format and contents of the protocols for GC of the participating ICUs.

The second sub-study is the online survey of ICU professionals, which is presented in Chapter 5. The survey was specifically designed for GlyCon study, and its aims were mainly descriptive, in order to both reduce the gap in current knowledge, and to help understand and interpret the results of the subsequent retrospective review of GlyCon. The professionals' responses were analysed in relation to the respondents' role in the ICU and their level of experience.

Chapter 6 is dedicated to the GlyCon retrospective study. This was the largest and most complex part of GlyCon, making this the longest chapter of the thesis. The large amount of data that were collected and analysed led to a multitude of results. These are divided in two sections within the chapter: the first relates to missing data, baseline clinical and demographic data, and implemented methods for GC; the second presents the outcomes of the implemented GC, including the main outcome measures of effectiveness, and the secondary outcome measures of efficiency and safety. These results are interpreted and discussed in the context of the knowledge gained from the previous two sub-studies.

The final Chapter (Chapter 7) presents an overall summary of the GlyCon study and the main conclusions derived from it. This is followed by a series of recommendations based on the findings of the three sub-studies, complemented with current evidence. This ending to the thesis emphasises the applicability of this research study for the quality improvement of the health care provided in intensive care.

Chapter 2
Literature review and study aims

This chapter starts with an introduction to critical care and the complexity of the pathophysiology of stress hyperglycaemia in critically ill patients. This is followed by a summary of the different methods for glycaemic control (GC) to deal with stress hyperglycaemia, as proposed by the scientific and clinical communities. Relevant national and international guidelines on the management of stress hyperglycaemia, as well as the role of locally designed and implemented protocols of intensive care units (ICUs), are also described. This review highlights the wide variability between the protocols for GC adopted in UK NHS ICUs, and, consequently, the need for studying in depth the performance of these protocols.

Current evidence, which indicates that there exists a low level of adherence to GC protocol instructions in ICUs, is presented. Low adherence to GC protocols necessitates that studies on the impact of GC methods take into account actual clinical practice, rather than just the protocols themselves. Within this context, the various methods and metrics proposed to date for the evaluation of the effectiveness, efficiency and safety of the methods for GC, are described. In these evaluations, the importance of considering the views of ICU professionals on GC, as key stakeholders in the quality improvement of GC in the ICU, is highlighted. This chapter concludes with the aims and objectives of the study presented in the rest of this thesis.

Literature review search strategy

This literature review was initiated at the beginning of the study, between October 2012 and June 2013, and updated continuously throughout the whole duration of the study, up until July 2016. The search strategy has included several search engines and databases: Medline through OVID interface; Cochrane Reviews; Trip Database and Google Scholar.

The types of studies considered in this review were systematic reviews and meta-analyses, clinical trials and randomised control trials (RCT), observational studies, as well as published protocols and guidelines. Only studies limited to adult humans were considered. Publication languages included English and Spanish. No restrictions in the dates of publication were made.

Free text search within the title or abstract of publications included:

- Search #1 to identify literature related to stress hyperglycaemia in intensive care: [glyce?mic OR glucose OR hyperglyc?emia] AND [(intensive care) OR (critical care) OR (critically ill) OR (critical illness)] NOT [(neonatal) OR (p?ediatric) OR (child$)].
- Search #2 to identify literature related to protocols for glycaemic control: [#1 search] AND [protocol OR algorithm OR treatment OR therapy].
- Search #3 to identify literature on adherence to protocols for glycaemic control: [#1 search] AND [#2 search] AND [adherence OR compliance];
- Search #4 to identify literature on evaluations of glycaemic control: [#1 search] AND [#2 search] AND [evaluation OR effectiveness OR efficacy OR safety OR performance OR quality];
- Search #5 to identify literature on professionals' opinions on glycaemic control: [#1 search] AND [#2 search] AND [(opinion OR view OR perception OR attitude OR survey OR interview) AND (professional OR nurs$ OR physician OR doctor OR intensivist)].

The library catalogue of the University of Nottingham was used to find books on human physiology, clinical nutrition, critical care and clinical research methods. Different websites related to UK NHS, healthcare provision and research within the UK, as well as websites of relevant organisations and specialty societies related to critical care, were also reviewed.

2.1 Critical care

Acute hospitals admit patients with a wide range of acute conditions, which can be grouped depending on the level of care needed during their admission. In the UK, patients are classified into four groups, depending on the level of care they need (UK Department of Health, 2000). Level-0 patients have the least severe conditions. Level-1 patients are those whose care requires the additional advice and support from the critical care team. Both level-0 and level-1 patients can be treated in normal wards within an acute hospital. Level-2 patients require more detailed observation or more complex interventions or post-operative care. These include patients requiring the support of a single organ system failure, except for advanced respiratory support. Level-3 patients are those with the highest level of severity, having a life-threatening condition, and requiring either advanced respiratory support alone, or the support of two or more organ systems.

The numeration of the UK classification is opposite to that of critical care centres in the USA. In a three-level scale (from I to III), level-I critical care centres in the USA are able to

provide comprehensive critical care for a wide range of critical disorders, while level-III critical care centres are the most limited in their capacity to provide such care (Haupt et al., 2003). The UK patient classification system is used throughout this thesis.

Critical care is the close and constant care and treatment provided to level-2 and level-3 patients in order to keep their body functioning. It is provided in special hospital wards, which include High Dependency Units (HDU) for level-2 patients and ICUs for level-3 patients. A "combined ICU/HDU" is a unit that combines beds for level-3 and for level-2 patients. The care of these patients is very specialised and complex, and needs to be provided by specially-trained health care professionals with a high level of expertise, including nursing and medical staff among others. Highly specialised devices for organ support and monitoring of the body functioning are used in all ICUs (Torpy et al., 2009).

The ten most common reasons for admission in ICUs or combined HDU/ICUs from England, Wales and Northern Ireland, based on approximately eight years of data up to 2003, are listed in Table 2.1 (Harrison et al., 2004). While ICUs often admit a mix of different patient populations, including patients after surgery, some ICUs are specialised in surgical patients (SICU), while others are specialised in medical patients (MICU). There are also some further specialised ICUs that focus on patients admitted for cardiac conditions, including those after cardiac surgery (cardiac ICU or CICU), or patients admitted for neurological disorders, including those after neurosurgery (neurocritical care units) (Torpy et al., 2009).

Table 2.1 – Ten most common reasons for admission to ICU or HDU/ICU in UK during 1994-2003

Reason for admission	n (%)
Surgical	
Aortic or iliac dissection or aneurysm	7406 (5.7)
Large bowel tumour	2846 (2.2)
Oesophageal or gastro-oesophageal tumour	1899 (1.5)
Non-traumatic large bowel perforation or rupture	1864 (1.4)
Non-surgical	
Pneumonia, no organism isolated	4792 (3.7)
Bacterial pneumonia	3344 (2.6)
Septic shock	2501 (1.9)
Acute myocardial infarction	2398 (1.9)
Asthma attack in new or known asthmatic	1889 (1.5)
Status epilepticus or uncontrolled seizures	1809 (1.4)
N=129,452 admissions to 128 adult, general critical care units. Source: Harrison et al. (2004)	

Mortality among critically ill patients is high, with more than 40% of patients dying either within the ICU (more than 29%), or within hospital after ICU discharge (more than 11%) (Soares et al., 2012, p. 135). The elevated mortality rates among critically ill patients are mainly due to the failure of multiple organ systems which does not resolve, and vulnerability to infectious complications, rather than to the reason for admission or the severity level on admission (Vanhorebeek et al., 2006).

2.2 Stress hyperglycaemia during critical illness

During critical illness, the metabolic response of a patient to the injury, infection or any other critical condition entails important changes in the endogenous metabolism. One of the consequences of these changes is stress hyperglycaemia.

2.2.1 Glucose metabolism in healthy individuals

Metabolism refers to all the processes that are responsible for the generation of energy from nutrients, and for the synthesis or degradation of nutrient molecules. These occur through different pathways. Catabolic pathways are those in which complex biological molecules, which can be obtained through exogenous sources such as feeding, or from the endogenous sources of humans' cellular reserves, are broken down into simpler metabolic substrates. Anabolic pathways are the converse process, where complex molecules are synthesised from simpler precursors. Catabolic pathways are usually energy producing reactions (exergonic), while anabolism requires an energy input to be completed (endergonic) (Greenway, 2005).

Glucose is the main source of energy in human metabolism, and many tissues, including the brain and red blood cells, require an uninterrupted source of glucose that provides the energy they need (Greenway, 2005). In healthy adults there is a continuous balance between the production and the use of most metabolic substrates, including glucose, in a process known as homeostasis. As a consequence of this homeostatic balance between production and use of glucose, the levels of glucose in the blood, also known as glycaemic or blood glucose (BG) levels, are kept relatively constant, even between meals (Wischmeyer, 2010). Healthy people without diabetes are able to keep their fasting BG levels within 3.5-6mmol/L, which is considered as a normal or euglycaemic level, while people with diabetes usually have fasting BG levels above 7mmol/L (American Diabetes Association, 2004).

When endogenous glucose is needed, it can be produced through the degradation of the more complex carbohydrate molecules of glycogen, known as glycogenolysis; and through the synthesis of new glucose molecules from non-carbohydrate metabolites, such us lactate,

glycerol (obtained from the degradation of lipids), and amino acids (obtained from the degradation of proteins), in a process known as gluconeogenesis. Glucose is then used gradually through processes of degradation of its molecules, known as glycolysis (Frayn & Akanji, 2011; Marieb & Hoehn, 2010).

Excess glucose molecules that are not immediately required, are stored within the cells. This storage is mainly in the form of glycogen, through a process called glycogenesis. Within the liver, besides glycogenesis, these excess glucose molecules can also be used for the synthesis of fats, known as lipogenesis; and for the synthesis of non-essential amino acids (Kavanagh & McCowen, 2010).

Metabolic reactions are largely regulated by hormones. The main effects of key hormones involved in the regulation of glycaemic levels are summarised in Table 2.2. Among these, insulin and glucagon are two essential and key hormones, produced in the pancreas, for the regulation of glucose metabolism. Insulin is produced to counter-regulate, and in response to, high glycaemic levels, while glucagon is produced to counter-regulate, and in response to, low glycaemic levels (Marieb & Hoehn, 2010).

Table 2.2 – Main actions of key hormones involved in glucose metabolism

Hormone	Endocrine tissue / gland	Main actions in glucose metabolism	Effects on glycaemic levels
Insulin	β-cells of the pancreas	(a) Glucose uptake of insulin-sensitive tissues; (b) glycogenesis; (c) lipogenesis; (d) stimulation of active transport of amino acids into muscle cells; (e) stimulation of protein synthesis; (f) suppression of hepatic gluconeogenesis	↓BG
Glucagon	α-cells of the pancreas	(a) Glycogenolysis; (b) gluconeogenesis; (c) lipolysis	↑BG
Somatostatin	δ-cells of the pancreas	Inhibition of secretion of both insulin and glucagon	↑↓BG
Glucocorticoids: cortisol corticosterone cortisone	Adrenal cortex of the suprarenal glands	Stimulation of hepatic gluconeogenesis; and inhibition of glucose uptake in peripheral tissues Important role in resisting stress	↑BG
Catecholamines: adrenalin noradrenalin	Adrenal medulla of the suprarenal glands	Stimulation of hepatic gluconeogenesis and glycogenolysis Important role in resisting stress	↑BG
Human growth hormone (hGH)	Adenohypo-physis of the hypophysis	(a) Stimulation of the active transport of amino acids into cells, especially muscle cells; (b) stimulation of protein synthesis; (c) gluconeogenesis; (d) lipolysis	↑BG
Thyroxin	Follicular cells of the thyroid gland	(a) Stimulation of protein synthesis; (b) gluconeogenesis; (c) lipolysis	↑BG

↑BG: increases glycaemic levels; ↓BG: decreases glycaemic levels; ↑↓BG: it can increase or decrease glycaemic levels
Sources: Marieb & Hoehn (2010), Dungan et al. (2009)

One of the main effects of insulin is the regulation of glucose uptake by body cells. Insulin-mediated glucose uptake is a multistage process in which insulin stimulates the translocation of the glucose transporter 4 (GLUT-4, which facilitates the glucose transport from the blood into the cell) from intracellular stores to the cell membrane. This glucose uptake occurs in insulin-sensitive cells such as hepatocytes (in the liver), myocytes (in the muscle) and adipocytes (in fatty tissues) (Chang et al., 2004). It has been estimated that insulin-mediated glucose uptake accounts for approximately 15% to 25% of the total systemic glucose utilisation of the human body (Marik & Bellomo, 2013).

Non-insulin-mediated glucose uptake occurs through a movement of glucose down a concentration gradient across the cell membrane, which is mediated by the glucose transporters GLUT-1 and GLUT-3. Hence, for this to take place there has to be a higher glucose concentration in the blood than within the cell. Non-insulin-mediated glucose uptake occurs in both insulin-sensitive and non-insulin-sensitive tissues (Chang et al., 2004). Main non-insulin dependent tissues are the central and peripheral nervous system, the bone marrow, white and red blood cells, and the reticule-endothelial system.

2.2.2 Glucose metabolism in critically ill patients

An acute severe insult, such as trauma, major surgery or an acute myocardial infarction, are events that constitute a threat to homeostasis, and are often referred to as stressors. Stress, which is the adaptive response to a stressor, includes physiologic and behavioural components, and provides a survival advantage. However, if this response is prolonged it can actually become detrimental (Mechanick, 2015).

As part of this response, there are important changes in the normal metabolism of glucose in critically ill patients, which can result in hyperglycaemia. Hyperglycaemia is the increase of glycaemic levels above normal levels. Events of dysregulation of glycaemic levels, such as hyperglycaemia, are also known as dysglycaemia. Although they have similarities, the aetiology of acute hyperglycaemia in critically ill patients is different from that of the chronic hyperglycaemia in patients with type 2 diabetes (Preiser et al., 2014). Type 2 diabetes is caused by insulin resistance and impaired insulin secretion by the pancreas. In critically ill patients, there is mainly an increase in hepatic gluconeogenesis, as well as peripheral insulin resistance, which are driven by the intense counter-regulatory hormone and immune responses to the critical condition (Dungan et al., 2009).

The hormone response is characterised by a high release of predominantly catabolic hormones. These include catecholamines, mainly adrenaline and noradrenaline (also known as epinephrine and norepinephrine), glucagon, cortisol and growth hormone (Dungan et al.,

2009). The output of adrenal cortisol has been found to be up to 10 times higher with severe stress; and the plasma adrenaline and noradrenaline can be up to 50 and 10 times higher, respectively, in patients with shock (Marik & Bellomo, 2013). Adrenaline, cortisol and growth hormone influence the peripheral insulin resistance. Glucagon, adrenaline and cortisol stimulate gluconeogenesis (predominantly in the liver). Catecholamines and glucagon trigger glycogenolysis, and adrenaline and cortisol help to perpetuate it (Preiser, 2013; McDonnell & Umpierrez, 2012).

At the same time, the immune system responds with an increase in pro-inflammatory cytokines, including interleukins (IL) IL-1 and IL-6, and tumour necrosis factor alpha (TNF-α). These also cause an insulin resistance in insulin-sensitive tissues (Preiser, 2013; McDonnell & Umpierrez, 2012).

As a result of these neuroendocrine and immune responses, there is a significant increase in available energy and other key substrates for critical non-insulin dependent tissues, including the brain and the immune system, in an attempt to fight against the critical condition. This happens together with a reduction in glucose uptake in muscles, including the heart and skeletal muscle, as well as in the liver and adipose tissues (Wischmeyer, 2010; Dungan et al., 2009). The overall effect is an increase in the total body glucose uptake, through the elevated glucose uptake via non-insulin-dependent pathways. Despite this, the levels of glucose in the blood may increase above normal levels, causing acute hyperglycaemia.

The incidence and duration of this hyperglycaemia varies depending on numerous patient-related and therapy-induced factors (see sections 2.2.3.3, 2.3, and 2.6.2.). In addition, it has been shown that glycaemic levels follow the 24-hour circadian rhythm among critically ill patients, with BG levels tending to be lower in the morning (Egi et al., 2007). From the same multi-centre retrospective study, Egi et al. (2007) concluded that the incidence and duration of hyperglycaemia in critically ill patients were also lower in the morning.

If patients do not recover within a few days after the onset of the critical condition, they may enter a chronic or established phase. During the chronic phase, the circulating levels of growth hormone, cortisol, catecholamines and cytokines are usually decreased (Vanhorebeek et al., 2006). However, the peripheral insulin resistance persists during this phase, together with the peripheral resistance to the effects of growth hormone, thyroid hormone and cortisol (Preiser et al., 2014). While there are important differences in the metabolic response during the chronic phase of the critical condition, including a relative immunosuppression, the status of hyperglycaemia can remain during this phase (Vanhorebeek et al., 2006).

2.2.3 Stress hyperglycaemia in critically ill patients

The hyperglycaemia, which can occur during the acute and/or chronic phases of the critical condition, as a metabolic response to such critical status, reverts to normal when the critical condition is resolved. This phenomenon is known as stress-induced hyperglycaemia or stress hyperglycaemia (Dungan et al., 2009).

2.2.3.1 Diagnosis of stress hyperglycaemia

Currently there is no clear agreement on what threshold of BG level would constitute stress hyperglycaemia in critically ill patients. At the time of writing, the latest definition proposed by the American Diabetes Association (ADA) suggests that any random glycaemia above 10mmol/L or fasting glycaemia above 7.8mmol/L, among hospitalised patients, can be considered as stress hyperglycaemia (American Diabetes Association, 2011, 2014). For patients with diabetes, Dungan et al. (2009) proposed that patients with a previously well controlled glycosylated haemoglobin (HbA1c) below 7%, whose glycaemic levels are consistently higher than the threshold defined for patients without diabetes, would qualify as suffering from stress hyperglycaemia. However, as will be discussed in section 2.3.1, there are crucial discrepancies in the available literature about which BG levels should be considered as optimal for ICU patients.

2.2.3.2 Prevalence of stress hyperglycaemia

Studies reporting the prevalence of stress hyperglycaemia in the ICU provide varying figures, depending on the cut-off levels used to define the hyperglycaemic event, as well as on patients' severity and condition. Farrokhi et al. (2011) found that 31% of ICU patients had at least one glycaemic measurement above 11.1mmol/L and Cook et al. (2009) found that at least one random glucose >10mmol/L occurred in 46% of patients. In their analysis of 12,176,299 BG measurements from 653,359 ICU patients in 575 hospitals in the USA, Swanson et al. (2011) found a prevalence of BG>10mmol/L of 32.2% of patient-days. These figures indicate that stress hyperglycaemia is a relatively common occurrence in ICU patients.

2.2.3.3 Factors contributing to the development of stress hyperglycaemia

In the hospital setting, there are other factors, besides the metabolic stress response, which can contribute to the development of stress hyperglycaemia in critically ill patients. Among these is the administration of commonly used medications in the treatment of critical patients, such as exogenous glucocorticoids and catecholamines, as these add up to the effect of endogenous hormones (Dungan et al., 2009). Another important influential component of patients' therapy is the administration of enteral and parenteral nutrition support. Especially

during the early phases of the critical insult, when the body is producing the energy required from endogenous pathways, there may be the risk of over-feeding the patient and increasing the risk or severity of hyperglycaemia (Preiser et al., 2015). Further details about the treatment related factors affecting the development or duration of stress hyperglycaemia will be discussed in sections 2.3.4 and 2.6.2.2

There are also a number of patient inherent factors that may affect the metabolic stress response, including gender (Drolz et al., 2014), age (Lazzeri et al., 2012), certain ethnicities (Mostafa et al., 2012; Dickinson et al., 2002) and the body mass index (BMI) (Pieracci et al., 2008). During the first 72 hours after admission, the energy expenditure at rest, adjusted for body weight, was found to be significantly lower amongst women who were overweight, defined by BMI≥25kg/m^2, as compared to overweight men (Drolz et al., 2014). Aging was found to be associated with an impaired sensitivity to glucose of the β-cells of the pancreas, as well as an impaired compensation to insulin resistance of these cells (Lazzeri et al., 2012). Also, literature suggests that, when compared with Western Europeans, South Asians have higher HbA1c, fasting plasma glucose and plasma glucose two hours after a standard dose of oral glucose (Mostafa et al., 2012). South East Asians were also found to have higher glycaemia after a meal (known as postprandial glycaemia) and lower insulin sensitivity, as compared to European and Arabic Caucasian subjects (Dickinson et al., 2002). High values of BMI in surgical ICU patients were associated with higher insulin resistance, although obese patients did not experience longer periods of hyperglycaemia than non-obese ones (Pieracci et al., 2008).

The reason for admission has also been found to affect the metabolic response during critical illness. Rady et al. (2005) found higher prevalence of severe hyperglycaemia among ICU patients admitted for surgery when compared with ICU patients admitted for medical reasons. These authors mention that the intensity of the surgical trauma and inflammatory response exacerbate the magnitude and duration of hyperglycaemia. Ljungqvist et al. (2010) documented that up to 90% of insulin sensitivity could be lost after a surgical operation, especially major surgery.

Further details about how patient inherent factors can affect the duration of hyperglycaemia are described in section 2.6.2.1.

2.2.3.4 Effects of stress hyperglycaemia

Stress hyperglycaemia in the critically ill is generally viewed as an adaptive survival response. Until the beginning of the 21st century, it was generally believed that, as a beneficial response, acute hyperglycaemia did not need to be treated. However, during the last 15 years, the evidence that links stress hyperglycaemia to detrimental effects in critically

ill patients has increased remarkably. At present, these two positions, which view stress hyperglycaemia either as a beneficial response that may not need to be treated (Marik, 2016; Kaukonen et al., 2014; Marik & Bellomo, 2013), or as a response that can be maladaptive and induce complications if it is not treated (Gunst & Van den Berghe, 2016; Finfer et al., 2013; Van den Berghe, 2012; NICE-SUGAR Study Investigators et al., 2009) coexist among the scientific and clinical communities. Further details about these two positions are described within the next two sections.

2.2.4 Stress hyperglycaemia as a survival response

For some researchers, the enhanced glucose production, uptake and utilisation by certain tissues and cells, and the insulin resistance with glucose intolerance in other body parts, are all mechanisms by which the higher energy demands of wounds and the immune response are satisfied. Hence, they believe that this adaptive response is beneficial, and mild to moderate hyperglycaemia should not normally be treated. Nonetheless, Marik et al. (2016; 2013) emphasise that hyperglycaemia may be harmful when it is severe, defined as glycaemic levels above 12.2mmol/L, or when it remains for prolonged periods, and therefore its treatment may be needed in these circumstances.

In their review, Marik & Bellomo (2013) provided a biological explanation about the protective role of hyperglycaemia and insulin resistance in hospitalised patients, which they supported with evidence from a number of *in vivo* experiments. They highlighted the lack of experimental studies that demonstrate causation between hyperglycaemia and poor outcomes. They also pointed out certain limitations of trials supporting approaches of tight glycaemic control (TGC) that target euglycaemic levels in critically ill patients, and they described the recommendations based on such trials as recommendations that lack scientific basis, and which can even be detrimental to patients (Marik & Bellomo, 2013).

2.2.5 Stress hyperglycaemia as a potentially detrimental response

Most of the studies published over the past 15 years, including observational studies and clinical trials, have challenged the traditional view of stress hyperglycaemia as a beneficial response, and have concluded that its treatment can improve patients' outcomes. Within this position are researchers that support TGC approaches that target euglycaemic levels using intensive insulin therapies (Gunst & Van den Berghe, 2016; Pittas et al., 2006; Van den Berghe, Wilmer, Hermans, et al., 2006; Van den Berghe et al., 2001); as well as others that support the need for treating stress hyperglycaemia, although with targets that are looser than euglycaemic levels (Stewart et al., 2016; Finfer et al., 2013; Kansagara, 2013; NICE-

SUGAR Study Investigators et al., 2009). Further details about the evidence supporting these different targets can be found in section 2.3.1.

The detrimental effects of the acute stress hyperglycaemia are thought to occur when BG exceeds 10mmol/L (Krinsley & Preiser, 2015). These suggested detrimental effects are different from those found as a consequence of the chronic high BG levels in patients with diabetes, such as nephropathy, neuropathy and retinopathy, which can take years to develop (Dungan et al., 2009).

2.2.5.1 Detrimental effects of stress hyperglycaemia

Early in the metabolic response to the critical insult, despite the reduced insulin-mediated glucose uptake, there are several factors that upregulate the entry of glucose in the cells through the GLUT-1 and GLUT-3 transporters (non-insulin mediated glucose uptake). As a result, cells where non-insulin mediated glucose uptake predominates, such as neurones and immune cells, may be more susceptible to increased glucose toxicity (Dungan et al., 2009).

Studies in *in vitro* systems and animal models have associated high BG concentrations with impairment of the normal functioning of a number of cells and molecules involved in the immune response. These included impairment functioning of neutrophils; reduction of phagocytic activity of macrophages; and decreased lymphocyte numbers, among others (Papak & Kansagara, 2012; Clement et al., 2004). Consequently, this impaired immune response increases the vulnerability of patients to infections, including surgical wound infections, and septicaemia or sepsis (Farrokhi et al., 2011; Dungan et al., 2009; Clement et al., 2004).

Hyperglycaemia has also been associated with exacerbation of the inflammation response through an excessive production of inflammation mediators such as IL-6, IL-18, C-reactive protein, and TNF-α, among others (Farrokhi et al., 2011; Dungan et al., 2009; Clement et al., 2004). This has been linked with a higher risk of detrimental vascular effects, such as ischemic renal injury, congestive heart failure, and, in patients with acute myocardial infarction, higher severity of cardiac dysfunction (Clement et al., 2004). At the same time, this exacerbation of the inflammatory response could lead to further increase in glycaemic levels, creating a vicious cycle in which hyperglycaemia leads to further hyperglycaemia (Dungan et al., 2009).

Acute hyperglycaemia has been associated with oxidative stress and endothelial dysfunction (Preiser et al., 2015; Clement et al., 2004). A number of cardiovascular dysfunction effects have been associated with stress hyperglycaemia, which could be related to the documented endothelial dysfunction, or cardiac myocyte death through apoptosis in response to the stress, among others (Clement et al., 2004). Among these are microvascular dysfunction,

increased systolic and diastolic blood pressure, increased heart rate, decreased myocardial contractility and increased oxygen demand (Papak & Kansagara, 2012).

Polyneuropathy has also been associated with stress hyperglycaemia, due to impairment in microcirculation to peripheral nerves, and to mitochondrial dysfunction caused by the increased oxidative stress (Confer et al., 2012).

Acute hyperglycaemia has been found to contribute to coagulation activation and hypofibrinolysis (Cohn et al., 2012). This, and the endothelial dysfunction, can leave patients at greater risk of developing thrombotic events such as venous thrombosis (Cohn et al., 2012), and acute cardiac syndrome (Mansour & Wanoose, 2011).

Higher risk of multiple organ failure have been associated with stress hyperglycaemia, which can be in part attributed to the endothelial dysfunction (Dungan et al., 2009; Clement et al., 2004).

Other effects of hyperglycaemia identified in the circulatory system are electrolyte loss and acid-base disturbances, which may affect the normal regulation of the myocardial and neurological function (Farrokhi et al., 2011).

Also, when glycaemic levels exceed the renal threshold, of approximately 10-11mmol/L (or higher in adults with diabetes), this could result in osmotic diuresis, leading to volume depletion and hypoperfusion, and, consequently, higher risk of dehydration, hypotension and eventual renal failure (Marik & Bellomo, 2013; Farrokhi et al., 2011).

2.2.5.2 Stress hyperglycaemia and mortality

Longer length of stay (LOS) in the ICU due to increased complications, and higher risk of death are the ultimate consequences of all the detrimental effects of stress hyperglycaemia mentioned above. Higher mortality rates in the ICU, associated with stress hyperglycaemia, are mainly due to an increased susceptibility to sepsis (Buchleitner et al., 2012; Kansagara et al., 2011; Kavanagh & McCowen, 2010).

One of the most influential studies associating stress hyperglycaemia with higher mortality risk was conducted in 2001 in a surgical ICU at the University Hospital of Leuven (Van den Berghe et al., 2001). This was a large single-centre, prospective RCT of surgical ICU patients who were receiving mechanical ventilation, recruited over a period of 12 months. A total of 1548 patients were randomised to receive either an intensive insulin therapy (IIT), targeting euglycaemic levels of 4.4-6.1mmol/L (treatment group); or a conventional treatment in which 11.9mmol/L triggered treatment with insulin and the target was 10-11.1mmol/L (control group). The authors found a reduction in ICU mortality from 8% in the control group to 4.6% in the IIT treatment group ($p<0.04$). The results were even more

pronounced among patients who stayed in the ICU for five or more days, who had mortality rates of 20.2% in the control group versus 10.6% in the treatment group (p=0.005).

The Leuven group repeated their RCT five years later, in the same centre but in the medical ICU. The trial was very similar to the previous RCT, although the glycaemic target in the control group was BG<10mmol/L, and the nutrition therapy was less intense (Kavanagh & McCowen, 2010). In this trial, Van den Berghe et al. (2006) found survival benefit only among patients who stayed in the ICU for at least three days, for whom mortality was reduced from 52.5% in the control group to 43% in the treatment group (p=0.009).

Since 2001, subsequent observational studies indicated that not only the occurrence of hyperglycaemia was detrimental, but also the duration of the hyperglycaemic status. Results from these studies indicated that the exposure to hyperglycaemic levels is inversely associated with survival (Kavanagh & McCowen, 2010). Benefits in reduction of mortality risk have also been found with targets that are higher than euglycaemic levels (Preiser & Straaten, 2016; Mesotten et al., 2009).

As described in section 2.2.6, glycaemic levels below normal (hypoglycaemic levels), have also been linked with higher mortality. The relationship between mean glucose levels and mortality can be described as a J-shaped association, with 5-8mmol/L (Mesotten et al., 2009) or 7-9mmol/L (Preiser & Straaten, 2016) showing the lowest mortality rates.

2.2.5.3 Factors influencing the association between stress hyperglycaemia and mortality

A number of factors have been found to influence the association between stress hyperglycaemia and mortality. A large retrospective study found that hyperlactatemia confounded the relationship between hyperglycaemia and mortality, which did not exist after controlling for patients' lactate levels (Kaukonen et al., 2014). Rady et al. (2005) found that the administration of large amounts of insulin (average cumulative insulin >100U/day) was an independent risk factor for hospital mortality, this effect being more pronounced in the group of patients without diabetes.

The admission diagnosis has also been found to moderate the relationship between glycaemic levels and outcomes. In their retrospective cohort study in 173 medical, surgical, and cardiac ICUs in the USA, Falciglia et al. (2009) found that the association between the likelihood of mortality, calculated as odds ratio (OR), and hyperglycaemia, varied with admission diagnosis, as well as with the severity of hyperglycaemia. In patients with mean glycaemia above 11.1mmol/L, the diagnoses with highest risk included intracerebral haemorrhage, ischaemic cerebral-vascular accident, pulmonary embolism, acute myocardial infarction, gastrointestinal bleed with ulcer and arrhythmia.

Amongst the most vulnerable patients mentioned in the literature are those with certain cardiac conditions (Papak & Kansagara, 2012; Falciglia et al., 2009; Capes et al., 2000). In their systematic overview, Capes et al. (2000) concluded that patients with acute myocardial infarction and stress hyperglycaemia had a higher mortality risk; and stress hyperglycaemia in patients without diabetes increased the risk of congestive heart failure or cardiogenic shock. Also, Papak & Kansagara (2012) found that, among patients with acute myocardial infarction, higher glycaemic levels on admission were associated with higher risks of congestive heart failure, as well as within-hospital 30-day and 1-year mortality rates. In their systematic review, Giakoumidakis et al. (2012) concluded that there was a clear association between peri-operative hyperglycaemia and increased mortality risk in patients with cardiac surgery.

Besides the documented evidence about a higher prevalence of stress hyperglycaemia amongst surgical ICU patients (Ljungqvist, 2010; Rady et al., 2005), evidence points at an association between stress hyperglycaemia and higher mortality risk among surgical patients, other than cardiac surgery. In the first of the Leuven RCTs, reducing glycaemic levels to normal levels showed a clear survival benefit among surgical patients, regardless of the parenteral glucose load (Van den Berghe, Wilmer, Milants, et al., 2006; Van den Berghe et al., 2001). In addition, most other similar RCTs concluded that surgical ICU patients had lower mortality risk with IIT approaches, as shown in the meta-analysis of RCTs of Griesdale et al. (2009). Among surgical patients, Vogelzang et al. (2006) found a stronger association between stress hyperglycaemia and mortality among trauma ICU patients, as compared with other surgical ICU patients.

Finally, in their systematic review on the effects of GC on neurocritical patients, Kramer et al. (2012) concluded that hyperglycaemia in these patients was detrimental but too tight GC targeting normal levels could also increase the mortality risk due to the higher risk of iatrogenic hypoglycaemia secondary to the intensive treatment.

2.2.5.4 Stress hyperglycaemia in the presence of comorbid diabetes

Comorbid diabetes has a high prevalence among patients admitted to hospital. In 2012, in UK NHS hospitals, more than 15% of inpatients had diabetes, with the figure being as high as 30% in some hospitals (HSCIC, 2013a). Barth et al. (2007) found even higher percentages of diabetes among critically ill patients, although there were large differences between patient types: 30% of Surgical-Trauma ICU patients, 47% of MICU patients and 61% of Coronary Care Unit patients.

Post hoc analyses of the data from the two landmark Leuven studies showed that patients with a previous diagnosis of diabetes did not have a survival benefit with IIT (Van den

Berghe, Wilmer, Milants, et al., 2006). In a subsequent Cochrane systematic review, Buchleitner et al. (2012) concluded that in surgical ICU patients with diabetes, IIT approaches can increase the risk of secondary hypoglycaemia, and hence the mortality risk (Buchleitner et al., 2012).

Large observational studies have also shown that a previous history of diabetes attenuated the detrimental effect of hyperglycaemia among critically ill patients (Krinsley & Preiser, 2015; Krinsley et al., 2013; Egi et al., 2008). These studies concluded that, in the presence of poor glycaemic control, measured with different metrics, patients with diabetes had lower mortality risk than those without diabetes. Also, hyperglycaemia has been found to be associated with larger increases in mortality rates among critically ill patients with unrecognised diabetes (or newly diagnosed diabetes), than in ICU patients who had been previously diagnosed with diabetes, especially if they had been previously treated with insulin (Kansagara, 2013; Papak & Kansagara, 2012; Kansagara et al., 2011; Umpierrez et al., 2002).

The reasons for the difference in mortality risk, depending on the presence of comorbid diabetes, have not been established with certainty. Given the chronic moderate hyperglycaemia of patients with diabetes, it is speculated that, with time, these patients may develop a relative tolerance to such moderate levels, which would otherwise be more toxic for patients without diabetes (Krinsley et al., 2013; Krinsley, 2009).

Despite important advances during the past years in building knowledge about the processes and consequences of the metabolic stress response, it has been argued that further studies are still required to improve current knowledge on glucose physiology during a critical condition, and what the impact of GC is (Preiser et al., 2016).

2.2.6 Hypoglycaemia and glycaemic variability

Two other important events of dysglycaemia in critically ill patients are hypoglycaemia and glycaemic variability (Krinsley, 2011). Multiple risk factors could lead to either of these types of dysregulation, with the kind of therapy used for GC having a great influence (Klonoff, 2011). Together with hyperglycaemia, hypoglycaemia and glycaemic variability are known as the three main domains of GC (Krinsley, 2011, 2013).

Hypoglycaemia in critically ill patients is often defined as glycaemic levels ≤4mmol/L, with severe hypoglycaemia occurring when glycaemic levels fall under 2.2mmol/L (Kansagara, 2013; Kansagara et al., 2011; American Diabetes Association, 2005). Other authors used different glycaemic thresholds to define hypoglycaemia, including 4.5mmol/L (Egi et al.,

2010), 4.4mmol/L (Shulman et al., 2007), 3.8mmol/L (Bagshaw et al., 2009), 3.5mmol/L (Vogelzang et al., 2005), and 3.3mmol/L (Oeyen et al., 2007).

Hypoglycaemia can occur as a consequence of certain critical conditions. For example, patients with end-stage kidney disease, liver disease, immune-compromised patients, or patients admitted for sepsis have higher odds of hypoglycaemia occurring (Bagshaw et al., 2009). In addition, hypoglycaemia is a potential unwanted side effect of the treatment of stress hyperglycaemia, especially if IIT approaches are implemented (Marik & Preiser, 2010; NICE-SUGAR Study Investigators et al., 2009; Van den Berghe, Wilmer, Milants, et al., 2006).

The association between hypoglycaemia, especially when it is severe, and the risk of mortality in critically ill patients has been suggested by numerous studies (Krinsley et al., 2013; Krinsley & Grover, 2007; Van den Berghe, Wilmer, Hermans, et al., 2006; Finney et al., 2004; Van den Berghe et al., 2001). Data pooled from the two single-centre Leuven RCTs, indicated a risk of mortality that was three times higher with severe hypoglycaemia (defined as BG<2.2mmol/L) (Kavanagh & McCowen, 2010). These associations were also confirmed in other studies with different BG definitions of hypoglycaemia. Ranges or threshold levels, within which or below which there was a higher risk of mortality include 3.5-4.5mmol/L (Egi et al., 2010), ≤3.9mmol/L (Krinsley et al., 2011, 2013), 2.2-3.8mmol/L (Bagshaw et al., 2009) and ≤2.2mmol/L (Krinsley et al., 2011; Krinsley & Grover, 2007). It has been suggested that there is a proportional increase of the risk of death with the degree of hypoglycaemia (Krinsley et al., 2011; Egi et al., 2010; Bagshaw et al., 2009).

Most RCTs comparing the effectiveness of IIT targeting euglycaemic levels, with an approach targeting ranges higher than euglycaemic levels (often referred to as “conventional approaches”), to treat stress hyperglycaemia, have found significant associations between the incidence of severe hypoglycaemia and mortality rates (NICE-SUGAR Study Investigators et al., 2012; Kansagara et al., 2011). Consequently, in these cases, the hypoglycaemic events are considered as iatrogenic hypoglycaemia, that is, hypoglycaemia secondary to the care provided.

The third domain of GC, glycaemic variability, has been evaluated using different metrics. Hermanides et al. (2010) used the Mean Absolute Glucose (MAG), which they calculated by dividing all absolute glucose changes in the ICU by the total time (in hours) in the ICU. These authors found lower mortality rates associated with lower MAG, even when mean glycaemic levels remained elevated. Egi et al. (2006) used the glucose standard deviation (SD) to assess the effect of glycaemic variability, and found that for every one unit (mmol/L) increase in the glucose SD the odds of ICU mortality was 1.2 to 1.3 times higher. Krinsley et

al. (2013), used the glucose coefficient of variation (CV) (which is calculated by dividing the glucose SD by the mean glucose level) to study glycaemic variability, and they found that higher survival rates were associated with lower glucose CV in patients without diabetes, but not in patients with diabetes.

2.3 Methods for glycaemic control of stress hyperglycaemia

The large body of evidence linking stress hyperglycaemia and other dysglycaemias with poor outcomes has led to the implementation of different strategies of GC in ICUs. The main aim of GC methods is to stabilise patients within a pre-defined safe glycaemic target range, for the largest proportion of the admission time possible, while avoiding hypoglycaemic events and high glycaemic variability (Preiser, 2013). This is achieved through a balanced combination of the treatment with insulin, and the provision of the required amount of exogenous glucose and nutritional energy, while being guided by the regular monitoring of BG levels (Mesotten et al., 2015). The administration of insulin and nutrition have to be fine-tuned to the progress of a patient's condition during the whole ICU stay, as well as to a number of relevant influential factors. These factors include patient-related ones, such as existing comorbidities, the reason for admission, sociodemographic characteristics and insulin sensitivity, as well as therapy-related factors, such as the administration of certain concomitant medications and the nutritional therapy (Rady et al., 2005). The various aspects of GC methods are described in this section.

2.3.1 Optimal glycaemic targets

The ideal glycaemic targets for each patient population group have not yet been agreed upon within the scientific and clinical communities. Current available evidence can be divided into two main groups: studies that propose TGC approaches with IIT targeting euglycaemic levels, and those that support flexible glycaemic targets and therapies.

2.3.1.1 Tight glycaemic control targets with intensive insulin therapy

TGC embraces those GC approaches that target the euglycaemic levels of a healthy individual. Compared with approaches that target higher glucose levels, TGC approaches use insulin therapies that are more intensive, referred to as IIT. The two landmark trials of Van den Berghe et al. (2006; 2001) are the most influential studies supporting TGC in ICUs. Besides the reduction in mortality amongst certain patient groups, as mentioned in section 2.2.5.2, these studies also found a reduction in morbidity among medical patients of the IIT

treatment arm who stayed in the ICU for at least three days (Van den Berghe, Wilmer, Hermans, et al., 2006; Van den Berghe, Wilmer, Milants, et al., 2006). Morbidity reductions in surgical and medical patients included the prevention of kidney injury, shorter duration of mechanical ventilation and shorter stay in ICU. Surgical patients also had lower rates of bloodstream infections and critical illness poly-neuropathy.

The Leuven studies were very influential and marked a shift in the management of stress hyperglycaemia towards TGC, in many ICUs worldwide (Niven et al., 2015; Paddle et al., 2011). Several subsequent studies obtained similar results supporting TGC, as summarised in various literature reviews and meta-analyses (Klonoff, 2011; Pittas et al., 2004, 2006).

The probable beneficial effects of TGC have been attributed to the anti-inflammatory effects of insulin and/or to the attenuation of the pro-inflammatory effects of stress hyperglycaemia (Preiser et al., 2015). The main argument against TGC with IIT has been the higher risks of hypoglycaemia with this approach, and its subsequent poor outcomes (Kansagara et al., 2011; NICE-SUGAR Study Investigators et al., 2009).

2.3.1.2 Loose glycaemic control targets with non-intensive insulin therapy

After 2001, numerous other experimental and observational studies in ICU comparing TGC with a conventional approach, concluded against TGC. Among these is the Glucontrol study, which was a multi-centre RCT in mixed medical and surgical ICUs, comparing the impact of a TGC with IIT approach targeting BG of 4.4-6.1mmol/L, with a conventional treatment targeting BG within 7.8–10.0mmol/L (Preiser et al., 2009). Although the trial had to be prematurely terminated due to unintended protocol violations, its findings from 1078 patients suggested that TGC did not provide clinical benefit, and increased significantly the incidence of hypoglycaemia. The VISEP study was a multi-centre RCT in which sepsis patients were randomised to receive either a TGC with IIT approach targeting BG of 4.4-6.1mmol/L, or a conventional treatment targeting BG of 10.0-11.1mmol/L (Brunkhorst et al., 2008). This trial found no significant difference between the two groups in the rate of death or the mean score for organ failure at 28 days. In addition, severe hypoglycaemia (BG<2.2mmol/L) had a significantly higher incidence in the TGC group, and was significantly more often associated with life-threatening adverse events, which led to the trial being prematurely terminated. Examples of other trials concluding against TCG are the RCTs on Surgical ICU and Medical ICU patients of Arabi et al. (2008) and of De la Rosa et al. (2008); as well as NICE SUGAR trial (NICE-SUGAR Study Investigators et al., 2009).

NICE SUGAR, which stands for Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation, has been the most influential study concluding against TGC. This was a large international multi-centre RCT, carried out in Australia, New Zealand

and Canada, with both medical and surgical ICU patients. In the trial, 6104 patients were randomised to receive either a conventional treatment targeting BG below 10mmol/L, or a tighter glycaemic control targeting 4.5-6mmol/L. Results showed significantly lower 90-day mortality rates in the conventional treatment group (24.9%) than in the IIT group (27.5%), mainly due to lower rates of hypoglycaemic events. Hence, the authors of the trial concluded that they could not recommend TGC approaches in ICU (NICE-SUGAR Study Investigators et al., 2009). Summaries of these and other trials testing TGC approaches can be found in a number of literature reviews and meta-analyses that come to similar conclusions about the risks of detrimental effects of TGC (Kansagara et al., 2011; Marik & Preiser, 2010; Griesdale et al., 2009; Wiener et al., 2008).

The meta-analyses of Wiener et al. (2008) and Griesdale et al. (2009) concluded that TGC might reduce the risk of sepsis in surgical patients but not in medical patients. In their meta-analysis on TGC, Marik et al. (2010) concluded that TGC generally does not provide a survival benefit and it might increase morbidity, unless most of the caloric intake is provided parenterally.

Some of the main reasons suggested to explain why IIT approaches failed to be successfully implemented in other studies or other ICUs are the insufficient nurse to patient ratios (Qaseem et al., 2011; Kelly et al., 2006) and the lack of accurate and reliable monitoring systems (Kavanagh & McCowen, 2010; Van den Berghe et al., 2009). Also, nurses' fear of hypoglycaemia (Kelly et al., 2006) and the central axiom in clinical practice of *primum non nocere* ("first do no harm") (Van den Berghe et al., 2009) have been mentioned as being important obstacles for the success of IIT approaches. Other authors argue that the differences in the characteristics of patients and the features of care used in each of the studies (Kavanagh & McCowen, 2010), as well as differences in the levels of quality of the investigations (Marik & Bellomo, 2013) are possible reasons why current evidence seems to be so conflicting. For example, Kavanagh & McCowen (2010) pointed out that in NICE SUGAR trial there were lower mortality rates in the conventional treatment group than it was expected from their APACHE II score, the conventional treatment arm did receive substantial amounts of insulin suggesting that the glycaemic control was "moderate" rather than "lax", and the nutrition regimen was mostly enteral and less aggressive than in the Leuven studies.

Despite the publication of these findings on the risks associated with TGC and the conflicting evidence on the benefits of this approach, there still are ICUs that implement TGC with IIT protocols (Niven et al., 2015; Tomlinson et al., 2012; Paddle et al., 2011). More recent RCTs have confirmed the advantages of TGC (Lanspa et al., 2013), and there are scientists and clinicians who believe that TGC is beneficial for certain patients if the

necessary resources and skills to implement it safely are available (Gunst & Van den Berghe, 2016).

In a mid-way between the two positions described above, there are many ICUs that have adopted approaches in which the glycaemic target is neither as low as in TGC, nor as high as the 10mmol/L threshold used in NICE SUGAR (Stewart et al., 2016; Tomlinson et al., 2012; Paddle et al., 2011). This type of targets has been referred to as "medioglycaemia" (Tomlinson et al., 2012). Also, more recently there has been a movement supporting the individualisation of glucose targets (Krinsley, 2014; Le et al., 2013). Preiser & Straaten (2016) have recommended that the lower limit of a glycaemic target range in ICU should be higher than 4mmol/L, and that the upper limit should be adapted to each specific ICU environment, and even individualised based on patient requirements.

2.3.2 Insulin therapy

Regardless of the BG levels targeted, insulin therapy is considered the most effective method of GC in ICU. It can be lifesaving and it is generally used in all proposed strategies or protocols for GC (Fowler & Rayman, 2010). On the other hand, insulin is also considered a high risk drug that requires specialised knowledge and skills for it to be safely prescribed, administered and monitored (National Patient Safety Agency, 2010). There are different types of insulin, routes of administration and regimens of insulin therapy, with varying effectiveness depending on the specific condition or situation to be treated.

The different types of insulin are commonly classified based on how quickly they work, when they reach their highest levels in blood, and how long they last (American Diabetes Association, 2016). Insulin can be administered subcutaneously (SC) or intravenously (IV), either as a bolus or continuously. When given IV, the effect of insulin occurs much faster. Fast-acting insulins administered via IV have a half-life of 4-5 minutes and they disappear within 45 minutes (European Medicines Agency, 2016). In ICUs, stress hyperglycaemia is generally treated with a fast-acting insulin, commonly prepared in a standardised form of one international unit per millilitre (U/mL), which is usually administered IV and continuously at pre-specified rates (units per hour) using a pump (Kansagara, 2013; Wilson et al., 2007). In addition, stat boluses of insulin may also be administered occasionally, based on BG levels (Fowler & Rayman, 2010). Sometimes basal insulin or oral hypoglycaemic agents are also used, in conjunction with the fast-acting insulin (Krinsley, 2004).

The insulin infusion rate (IIR) is determined from algorithms. Algorithm has been defined as "a formalized sequence of instructions for solving a complex problem in finite processing steps (…)" which in intensive care "(…) is used to standardize care, for quality assurance

and to avoid intuitive decision making" (Wernerman et al., 2014). Wernerman et al. (2014) pointed out that insulin algorithms need to be not only safe and effective, but also reliable, feasible and efficient, while accounting for the different profiles and needs of different patient populations, and other therapeutic interventions.

Frequently, the continuous IIR is titrated based on the BG levels at each BG measurement. This is known as Variable Rate Intravenous Insulin Infusion (VRIII) or sliding scale insulin (Mesotten et al., 2015). Since changes in insulin titrations are usually performed after a BG measurement, these changes are often done once every 1-4 hours, if needed (Krinsley et al., 2015). More comprehensive algorithms that take into account the rate of change or trend of glycaemic levels, the intake of nutritional carbohydrates, as well as the insulin IIR itself, in the insulin titrations have been recommended (Mesotten et al., 2015).

At the time of writing, there are no standardised guidelines on the use of evidence-based VRIII algorithms. Consequently, there is a high variability in the recommended insulin dosages across ICUs at each possible glycaemic scenario, with insulin dosages ranging from 27 to 115 units (Wernerman et al., 2014). Also, despite the higher risk of making errors when insulin is used as a reaction to, rather than as a prevention of, hyperglycaemia, in the ICU the VRIII is often started only when certain hyperglycaemic values have been reached (Fowler & Rayman, 2010).

2.3.3 Glucose Monitoring

Besides an effective and safe insulin therapy, frequent, accurate and reliable BG monitoring methods are essential for a safe and effective GC. Although not necessarily all available within an ICU, there are various options available to monitor BG levels, each of which has certain limitations.

2.3.3.1 Method for glucose monitoring

Glycaemic levels can be measured from arterial, venous or capillary blood. The first two are obtained with intravascular catheters, and can be analysed with the monitoring gas machine, with point of care (POC) glucometers, or in external laboratory departments.

Capillary samples are taken by finger-stick devices and analysed with POC glucometers (Kavanagh & McCowen, 2010). Capillary BG is more susceptible to patients' common conditions such as haemodynamic instability (Finfer et al., 2013), tissue oedema, hypoperfusion or anaemia (College of American Pathologists, 2013), and it is less accurate, especially when trying to assess the degree of hypoglycaemia (Kansagara, 2013; Corstjens et al., 2006). A larger time lag between the actual BG levels, at the moment of the

measurement, and the capillary results is also a limitation that should be taken into consideration when capillary blood is used (Van Herpe & Mesotten, 2012).

In their consensus recommendations on measurement of BG and reporting of GC, Finfer et al. (2013) recommended that the BG sample of choice should be arterial or venous blood, taken from indwelling catheters, and analysed either in the blood gas analyser or, if the turnaround time is not too long, in the hospital laboratory. In their opinion, capillary samples should be used only if patients' severity does not justify invasive vascular monitoring.

Due to the frequency of monitoring and the need for quick results, both venepuncture and laboratory analyses are often impractical. In their literature review, Inoue et al. (2013) found that arterial blood analysed in the gas machine was the most accurate and reliable BG POC testing method available within the ICU. The main arguments against the use of arterial blood, and the sampling from indwelling vascular catheters, are the increased risk of catheter-related bloodstream infections, and the need to discard large volumes of blood to obtain uncontaminated samples (Finfer et al., 2013). Nonetheless, in their RCT comparing two arterial catheter clearing-volume return setups for hourly blood extractions, Raurell Torredá et al. (2014) concluded that the use of arterial catheters to obtain blood samples for glucose monitoring was a reliable and safe method, as BG was measured with an acceptable accuracy and none of the patients had a catheter-related infection.

Another important aspect to take into consideration is the accuracy and reliability of the particular POC glucometers available in an ICU (Watkinson et al., 2012; Van Herpe & Mesotten, 2012; Van Herpe, Pelckmans, et al., 2008). Watkinson et al. (2012) compared different POC glucometers and concluded that most of the devices that they studied were affected by the haematocrit, acidity (pH) and partial pressure of oxygen (pO2), and one of them was even considered as too imprecise to be used to monitor critically ill patients. With this regard, Van Herpe et al. (2008) designed an online service (The GLYCENSIT Procedure) where anyone can assess the reliability of a time-discrete glycaemic sensor device. Also, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has a task force on POC testing that is focused on GC in the ICU (IFCC, 2016).

2.3.3.2 Frequency of glucose monitoring

As with the insulin algorithms, at present there is very little evidence on what are the safest and most effective glucose monitoring frequencies in each glycaemic status. In their Monte Carlo simulation study of 3000 patients, Krinsley et al. (2015) concluded that a minimum of 1-hourly measurements are safer than 2-hourly measurements and therefore are recommended. However, in busy ICUs such measurement frequency is often not possible to achieve as a general rule for all patients, and BG measurements are usually taken every two

to four hours when the BG is "stable" for a number of hours within the pre-set glucose target range (Aragon, 2006; Goldberg et al., 2004). Continuous glucose monitoring may solve this problem, when the technology for accurate BG measurements is finally developed and scientifically tested with real-life data from multiple ICUs. Not only would this help with a better GC but it would also reduce nursing workload (Preiser et al., 2016).

2.3.4 Nutritional management

Another important component of GC, often neglected in GC protocols (Kansagara, 2013), is the nutritional therapy given to patients. One of the consequences of the patients' metabolic response to the critical condition is an increase in the energy expenditure (EE) at rest and in protein use. Exogenous energy is administered to patients through nutritional support, to meet their nutritional requirements. This, especially the glucose calories, has a strong effect on patients' glucose levels and, therefore, is an important component of GC (Mesotten et al., 2015).

Given that during the early phase of the critical illness a part of the patients' EE at rest is covered by endogenous glucose production, patients' caloric need during this phase is probably lower than their EE (Fraipont & Preiser, 2013). Consequently, stress hyperglycaemia may result from over-feeding in these patients (Preiser et al., 2015). Also, insulin needs will increase or decrease depending on the amount of energy provided, as well as whether it is given parenterally or enterally (Preiser, 2013). It has been argued that it is crucial to control for the nutritional intake in insulin titrations, and not administer insulin based only on BG levels (Mesotten et al., 2015; Shaw et al., 2014).

An early initiation of enteral nutrition (EN) within 24-48 hours, when possible, and the avoidance or delay of total parenteral nutrition (TPN) for about the first week of admission, depending on the nutritional risk, have been recommended (Casaer & Van den Berghe, 2016; McClave et al., 2016). This may include the need for a hypocaloric strategy while awaiting for EN to be tolerated (Preiser & Straaten, 2016). Such strategies are associated with higher risk of hypoglycaemia (Mesotten et al., 2015), and therefore frequent BG monitoring, and the administration of rescue glucose if needed, are essential when following these strategies.

TPN may be needed in under-nourished patients or patients with nutritional risk, for whom either it is necessary to complement EN (when less than 60% of the energy and protein requirements are being met), or the administration of EN is not possible (McClave et al., 2016). If TPN is present, a tighter GC may be beneficial (Mesotten et al., 2015; Preiser, 2013). This means that the insulin dosages required to keep BG within range and prevent hyperglycaemia would be significantly higher during TPN. Conversely, when oral feeding is

resumed, the risk of hypoglycaemia is higher and it is recommended that low glycaemic targets are avoided and that the provision of continuous insulin is interrupted (Mesotten et al., 2015).

2.4 Guidelines and protocols for glycaemic control in intensive care

The methods for GC can be formalised in the shape of national and international guidelines developed by relevant associations or specialty societies, or as clinical protocols designed locally by each hospital. These guidelines or protocols would include the establishment of a glucose target, the regular monitoring of BG levels, the administration of insulin when needed, and, ideally, the management of nutritional intake, among others.

Clinical practice guidelines and protocols are aimed at aiding in clinical decision making, reducing variability of practice and improving clinical outcomes (Wilson et al., 2007). Clinical guidelines are considered as sets of recommendations, designed by experts in the field, and based on the best available evidence. They provide clinicians with a framework to guide their practice, which should then be tailored to each particular patient (Kavanagh & Nurok, 2016).

Protocols are dynamic sets of instructions that should be followed to care for and treat a patient (NHS Institute for Innovation and Improvement, 2008a). Protocols are usually developed by each hospital, locally, and are often based on a series of conditional or if-then statements (Kavanagh & Nurok, 2016). Indeed, in most NHS ICUs there are locally designed protocols with written instructions and recommendations on how to achieve GC (Paddle et al., 2011).

2.4.1 Guidelines for glycaemic control in intensive care

Current discrepancies about the glycaemic levels that should be targeted in the ICU, as well as about the most effective and safest GC approaches to achieve them, are an important barrier to the development of common standards for GC of the critically ill. At present, the recommendations of existing national and international guidelines about the management of stress hyperglycaemia in the ICU differ among each other. A list of relevant international guidelines and some examples of national ones, together with the different glucose targets they propose, are provided in Figure 2.1 and Table 2.3.

One example of the discrepancies between recommendations amongst these guidelines is the different targets suggested for neurocritical patients. The Neurocritical Care Society of USA recommends that the BG of patients following an aneurysmal subarachnoid haemorrhage should be below 11.1mmol/L (Diringer et al., 2011). Meanwhile, in Spain, a Consensus of the Spanish Society of Intensive Care Medicine and Coronary Units with the Spanish Society of Parenteral and Enteral Nutrition recommends that, in neurocritical patients, BG should be kept within 6.7-8.3mmol/L (Acosta Escribano et al., 2011). Moreover, in their systematic review of RCTs about the optimal methods for GC in neurologically injured patients, Kramer et al. (2012) concluded that "intermediate" glycaemic levels should be targeted, avoiding values above 10mmol/L but not sticking to tight normal BG values of 4.4-6.1mmol/L.

In the UK, during the past few years, a number of national documents and guidelines concerning the GC of hospitalised patients have been published. However, these either focus on non-ICU patients or they are designed for specific patient populations only. In 2014, the UK National Institute for Clinical Excellence (NICE) published a clinical guideline for the management of hyperglycaemia in patients with acute coronary syndrome (NICE, 2014). In the same year, the Joint British Diabetes Societies for inpatient care (JBDS-IP) published a VRIII guideline for the GC of medical inpatients. This guideline is intended for use with patients who either are unable to take oral fluid/food, or need to achieve GC target quickly, and it specifically states that it can be implemented in both diabetic and non-diabetic patients with acute hyperglycaemia (JBDS-IP, 2014). Although it is not stated in the text, one of the guideline's lead authors mentioned to the author of this thesis that it could also be implemented in medical ICU patients (S. George, personal communication via email, July 2015). Patients admitted with acute coronary syndrome (NICE, 2014), or with diabetes and admitted for surgery, diabetic emergencies or stroke, would be excluded from the JBDS-IP guideline, since NICE and the JBDS-IP have developed other guidelines for these patients (JBDS-IP, 2011, 2012b, 2012a, 2013b, 2013a, 2014; NICE, 2014).

2.4.2 Protocols for glycaemic control in intensive care

As a consequence of the discrepant evidence and the lack of common guidelines and standards for GC in intensive care, there are numerous local protocols for GC, developed by the ICUs where they are implemented (Niven et al., 2015; J. Orban et al., 2013; Tomlinson et al., 2012; Paddle et al., 2011; Cook et al., 2009; Wilson et al., 2007; Mackenzie et al., 2005). One can find wide variations in the instructions given in the different protocols.

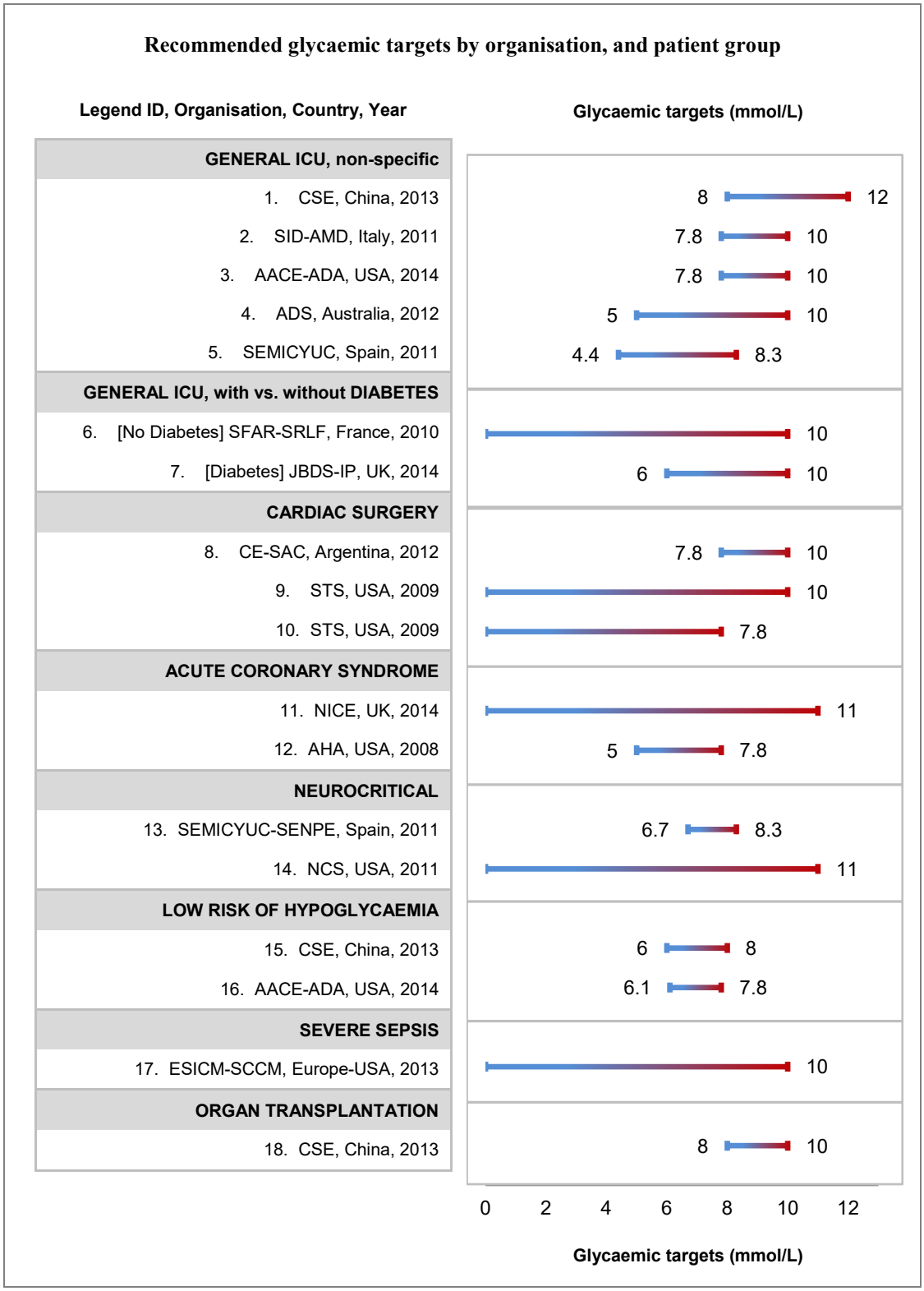


Figure 2.1 – Glycaemic targets recommended by national and international organisations (mmol/L), classified by patient group.
No lower limit is shown for targets which suggest an upper limit instead of a range. For full names of organisations and details on the target patients see Table 2.3

Table 2.3 – Main national and international organisations that provide guidelines for GC, and the target patients of these guidelines

ORGANISATION	TARGET PATIENTS
GENERAL ICU, non-specific	
1. Chinese Society of Endocrinology (CSE) (Lü & Tong, 2013)	Medical ICU and surgical patients (Postpandrial).
2. Societá Italiana di Diabetologia (SID) and Associazione Medici Diabetologi (AMD) (Bruno et al., 2011)	ICU patients, depending on the estimated risk of hypoglycaemia.
3. American Association of Clinical Endocrinologists (AACE) & American Diabetes Association (ADA) (American Diabetes Association, 2014; Moghissi et al., 2009)	ICU patients.
4. Australian Diabetes Society (ADS) (Australian Diabetes Society, 2012b, 2012a)	All hospitalised, including AMIa and stroke (Australian Diabetes Society, 2012a); diabetic patients with surgery, including if admitted to ICU (Australian Diabetes Society, 2012b).
5. Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC) (SEMICYUC, 2011)	ICU patients.
GENERAL ICU, with vs. without DIABETES	
6. Société Française d'Anesthésie-Réanimation (SFAR) & Société de Réanimation de Langue Française (SRLF) (Ichai & Preiser, 2010)	Non-diabetic ICU patients.
7. Joint British Diabetes Societies for Inpatient Care (JBDS-IP) (JBDS-IP, 2011, 2012b, 2014)	Diabetic hospitalised patients except ACS patients (JBDS-IP, 2012b); stroke patients with enteral feeding (JBDS-IP, 2011); and surgery patients (JBDS-IP, 2014).
CARDIAC SURGERY	
8. Consejo de Emergencias de las Sociedad Argentina de Cardiología (CE-SAC) (Benzadón et al., 2012)	Post cardiac surgery.
9. Society of Thoracic Surgeons (Lazar et al., 2009)	Cardiac surgery patients in ICU.
10. Society of Thoracic Surgeons (Lazar et al., 2009)	Cardiac surgery patients in ICU≥3 days & highly ill.
ACUTE CORONARY SYNDROME	
11. National Institute for Health and Care Excellence (NICE) (NICE, 2014)	Patients with ACS.
12. American Heart Association Diabetes Committee (AHA) (Deedwania et al., 2008)	ICU patients with ACS.
NEUROCRITICAL	
13. SEMICYUC & Sociedad Española de Nutrición Parenteral y Enteral (Acosta Escribano et al., 2011)	Neurocritical patients.
14. Neurocritical Care Society (Diringer et al., 2011)	ICU patients after ASH. Serum glucose.
LOW RISK OF HYPOGLYCAEMIA	
15. Chinese Society of Endocrinology (Lü & Tong, 2013)	Fine surgery without serious complications or risk of severe hypoglycaemia. Postpandrial.
16. American Association of Clinical Endocrinologists (AACE) & American Diabetes Association (ADA) (American Diabetes Association, 2014; Moghissi et al., 2009)	ICU "selected patients", without risk of "significant hypoglycaemia".
SEVERE SEPSIS	
17. European Society for Intensive Care Medicine & Society of Critical Care Medicine (ESICM & SCCM) (Dellinger et al., 2013)	ICU patients with severe sepsis.
ORGAN TRANSPLANTATION	
18. Chinese Society of Endocrinology (Lü & Tong, 2013)	Organ transplantation surgery Postpandrial.

ACS: acute cardiac syndrome; ASH: acute subarachnoid haemorrhage

In the UK, previous studies exploring written policies on GC in the ICU found important differences on whether ICUs had protocols for GC in place and, if they had any, when these had last been updated, as well as what the glucose target for their patients was (Paddle et al., 2011; Mackenzie et al., 2005). In their survey on the practice of GC in UK ICUs, Paddle et al. (2011) explored the update of protocols, their glucose targets, and they also included a number of closed questions on the monitoring technique and the insulin therapy, although they did not report their findings on the monitoring methods. From their findings on the insulin therapy, they concluded that practically all ICUs administered insulin as IV infusions, most often titrated following a sliding scale or an algorithm (92%). In about 70% of ICUs the upper limit of their glucose target range was 8.3mmol/L or less, and in more than 40% of ICUs the lower limit of the target range was 4.4mmol/L or higher (Paddle et al., 2011).

In their short cross-sectional telephone survey to 71 randomly selected ICUs from England, Mackenzie et al. (2005) explored whether the ICU had a protocol for GC in place and, if so, what the glycaemic target range was. In the 66 ICUs that had a protocol in place, the median (IQR) of the upper limit of their glycaemic ranges was 7.0 (6.1-8.0) mmol/L. Out of these 66 ICUs, 56 also had a lower limit for their glycaemic ranges, and the median (IQR) for this was 4.1 (4.0-4.5) mmol/L.

Although there have been various studies investigating the differences between GC protocols in ICUs, none of these have included detailed descriptions and comparisons between the individual protocol instructions at each glucose range in different ICUs. Such a comparison is likely to show significant differences in how each situation or scenario is being dealt with in different ICUs.

2.5 Adherence to protocols for glycaemic control in intensive care

Despite most ICUs having some written policy on the management of GC, there is evidence that protocols are often not adhered to (Leape et al., 2003). In order to avoid coming to wrong conclusions about the performance of a protocol, also known as “impact misattribution” to the protocol (Kavanagh & Nurok, 2016), the level of adherence to such protocol instructions has to be evaluated.

Previous quality evaluations of the methods for GC implemented in ICU have shown high levels of non-adherence to the protocol instructions (Kanji et al., 2010; Oeyen et al., 2007; M. M. Barth et al., 2007; Shulman et al., 2007; Rood et al., 2005). These studies have looked at different aspects, including: whether the insulin dose adjustments (Oeyen et al., 2007; M. M. Barth et al., 2007), or the monitoring time intervals (Shulman et al., 2007), or both (Kanji

et al., 2010; Rood et al., 2005), were carried out according to the protocol; what was the elapsed time between the actual and the recommended monitoring time intervals (Rood et al., 2005); and whether the treatment with insulin had been initiated at the BG threshold specified by the protocol (M. M. Barth et al., 2007).

In their retrospective-prospective, before-after intervention, observational study, Taylor et al. (2006) defined a number of protocol deviations, classified as minor or major deviations. Their classification was based on a *pre hoc* assessment of the likelihood that a defined deviation would cause severe or prolonged hypoglycaemia or hyperglycaemia, according to their clinical judgement (C. Coopersmith, personal communication via email, 2016). Minor deviations included: (a) BG check missed once; (b) insulin titration missed or done incorrectly once; (c) insulin infusion restarted two or less hours late; (d) insulin infusion inappropriately turned off for operating room; (e) incorrect "intravenous push" amount given; (f) failure to give "intravenous push"; (g) BG in "call House Officer" range and no intervention done or documented. Major deviations included: (a) BG check missed two or more consecutive times; (b) insulin titration missed or done incorrectly two or more consecutive times; (c) insulin infusion restarted more than two hours late; (d) insulin infusion off for unknown reason; (e) insulin infusion not turned off [according] to protocol; (f) none of these running: 5% Dextrose, EN, TPN; (g) titration of insulin infusion not adjusted to every three hours for creatinine of 1.5mg/dL or higher.

Taylor et al.(2006) found that, of the 550 patient-days studied, deviations occurred in almost half of the time, including minor deviations during 127 (23%) patient-days and major deviations during 132 (24%) patient-days. The most common minor deviations were (b) (85 occurrences) and (d) (35 occurrences). The most common major deviations were (b) (36 occurrences), (g) (34 occurrences), (e) (25 occurrences), and (d) (17 occurrences).

Kanji et al. (2010) explored the degree of adherence to a new protocol in the cohort of neurocritical patients receiving it (but not in the control group), and found a mean (SD) of 5.1 (2.2) late measurements per day. Late measurements were defined as an increase of the time between readings of 50% or more than specified on the order form. They also found a mean (SD) of 1.5 (1.2) deviations from the insulin dose adjustments per day.

Rood et al. (2005) compared four phases of implementation of a protocol and found that, depending on the study phase and the study cohort: 23-58% of the BG samples were followed by an insulin infusion titration that deviated from the protocol instructions; 59-71% of measurements were not compliant with the time-frame of the guideline (excluding deviations of 5% time or less); 26-35% were late measurements; and the mean (SD) elapsed time of such delayed measurements ranged between 71 (165) and 28 (118) minutes. Other

studies have also found high levels of non-adherence to GC protocols, including 47% of measurements not compliant with the time-frame of the protocol (Shulman et al., 2007), and 29% BG measurements followed by a titration of the IIR not compliant with the protocol (Oeyen et al., 2007).

In their retrospective study of the effectiveness and safety of a new protocol for GC in three ICUs, Barth et al. (2007) found that in 18% of patients there was one of the types of non-adherence they studied. The most common type of non-adherence (16% of patients) was starting the treatment with insulin in the wrong sliding-scale, of the four possible scales specified in the protocol. Another deviation (2% of patients) was starting the treatment with insulin when BG was below the recommended threshold (8.3mmol/L).

Francke et al. (2008) proposed that the factors influencing the level of professionals' adherence to clinical guidelines are classified in five groups, depending on which aspects they are related to: (1) characteristics of the guidelines; (2) characteristics of the implementation strategies; (3) characteristics of patients; (4) characteristics of the environment; (5) characteristics of professionals.

A number of characteristics of the guidelines or protocols, and of their implementation have been shown to improve adherence to the protocols. These include having a strong evidence base (Leape et al., 2003), being easy to understand and try out while consuming little resources (Francke et al., 2008), and allowing for some flexibility to adapt the instructions to what the clinicians find is more effective and feasible in each situation (Bland et al., 2005).

Characteristics of patients, such as high comorbidity, and characteristics of the environment, such as insufficient staff and time to implement the guidelines or protocols properly, are factors that are often more difficult to control, and which are likely to reduce the levels of adherence (Francke et al., 2008).

Characteristics of professionals, such as resistance to change and clinical inertia, have been identified as important barriers for the successful implementation of guidelines or protocols (Qaseem et al., 2011; Pérez Pérez et al., 2009). Factors identified as elements that can decrease the professional's resistance to change and increase adherence include increasing the awareness of and knowledge on existing protocols in the hospital or ward, as well as the provision of peers' and superiors' support (Francke et al., 2008).

2.6 Quality evaluation of glycaemic control of stress hyperglycaemia in intensive care

The design of evidence based protocols, even if they are adhered to, does not guarantee quality of care. The continuous quality evaluation of clinical practice in the ICU, exploring whether the desired improvement in patient outcomes is safely achieved, is essential for the quality improvement of critical care (Lugtenberg et al., 2009; Curtis et al., 2006).

Quality of healthcare can be defined as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" (IoM, 2001, p. 232). The three classic components of quality of care, originally proposed by Donabedian (1985), are the structure, the process and the outcome. Structure evaluations focus on how a health service is organised; process evaluations look at how healthcare is implemented, including what is not implemented; and outcomes evaluations measure the results achieved in patients or relatives (Curtis et al., 2006). For example, in intensive care, a structure evaluation could look at perceptions, knowledge or skill levels of ICU staff; a process evaluation could explore what care interventions are implemented and whether clinical protocols are being adhered to; and an outcomes evaluation could investigate infection rates or mortality rates, among others.

The structure, process and outcome can affect different dimensions of the quality of care. Effectiveness, efficiency and safety (EES) are three of the main dimensions that are frequently used in the quality evaluation of healthcare practice, together with patient centeredness, accessibility and equity (World Health Organization & WHO, 2006). Effectiveness refers to the extent to which the provision of evidence-based care results in the desired improved outcomes of individuals' or populations' health (World Health Organization & WHO, 2006). Efficiency measures to what degree a health care service or intervention delivers its care effectively, while using less resources, including lower costs due to less supplies, equipment and people, and also less workload or time from people (Hussey et al., 2009). Patient safety measures focus on the degree of risk or harm that the patients are exposed to as a direct or indirect result of the care provided to them (Mitchell, 2008).

One can find several metrics proposed in the literature to evaluate the EES of the methods for GC of stress hyperglycaemia in critically ill patients. Generally, these metrics are outcome measures of the extent to which the methods for GC achieve their aim of stabilising patients' BG within safe glucose levels.

2.6.1 Evaluation of effectiveness

The main metrics that have been used to describe the effectiveness of GC in different studies are discussed in this section. Some of them have important weaknesses, or they may not be suitable for use in the outcomes' evaluations. Also, due to the existing differences between the instructions of protocols, not all metrics can be used in comparison studies of GC.

The glucose mean, glucose median, and the hyperglycaemic index total (HIT) are measures of central tendency that have been associated with poor outcomes (Mackenzie et al., 2011). However, the mean and the median could result in an artificially normal BG, on average, if in reality the BG had both hyperglycaemic and hypoglycaemic events that cancelled each other (Van Herpe, De Brabanter, et al., 2008). Also, the mean is very sensitive to outlier values, and could be significantly increased or decreased by such values if there were either a few very high or a few very low outlier glycaemic events, respectively (Van Belle et al., 2004).

The HIT is the cumulative sum of the hyperglycaemic index (HI), where the HI is the area under the glucose curve and above the upper threshold of a euglycaemic range, divided by the LOS (Vogelzang et al., 2004). Van Herpe et al. (2008) argue that the HI is not a useful metric for the comparison of protocols in ICUs, since the two main conditions that the HI requires are not normally met by ICUs. First the calculation of the HI should be based on a sufficiently high number of BG measurements, which are ideally near-continuous, and, second, the frequencies of intermittent (non-continuous) BG monitoring should be comparable in all ICUs.

Based on these grounds, Van Herpe et al. (2008) designed the glycaemic penalty index (GPI) as a metric to compare ICU insulin titration algorithms, based on a penalty strategy. Using an optimised smooth penalty function, which they developed based on clinical expert knowledge, each BG measurement was given a score (penalty). Those within 4.4-6.1mmol/L were given a score of zero (no penalty), and any values above or below it were given a different score of up to 100 (the highest penalty). The GPI was the average of these scores, and it would be reported together with the distribution, in percentages, of the values that had been below and those that had been above the target, separately (Van Herpe, De Brabanter, et al., 2008).

The main limitation of the GPI is that it was designed to be calculated in the context of TGC targeting euglycaemic levels, and it is not applicable to ICUs implementing different approaches. Also, as with most summary metrics of GC, the GPI is affected by the monitoring frequency tending to be higher during hypoglycaemia. In this regard, the authors of the GPI emphasise the importance of designing studies such that both the monitoring

frequency and the duration of the insulin algorithm application are similar between patients, regardless of the metric used (Van Herpe, De Brabanter, et al., 2008). Two more weaknesses of the GPI are the facts that it ignores the severity and duration of the hypo- or hyperglycaemic events, as recognised by its own authors, and that it was developed based on "expertise" rather than on scientific grounds associating it with poor outcomes (Van Herpe, De Brabanter, et al., 2008).

Two other metrics that have also been widely used to assess the effectiveness of GC are the percentage of BG measurements that are within the glucose target range (M. M. Barth et al., 2007; Lonergan et al., 2006; Thomas et al., 2005), and the percentage of admission time spent within the glucose target range (time in range, TIR), also known as time in band (Krinsley & Preiser, 2015; Kanji et al., 2010; Preiser et al., 2009). The main limitation of the former metric, which is independent of time, is that it can only be used if the BG monitoring time intervals are always the same. It is not a useful metric to compare protocols that instruct different monitoring time intervals for the same glycaemic range, because more frequent monitoring would result in more data points for a particular range in some ICUs than in others, and therefore would bias the results. Moreover, within the same ICU, and for the same patient, BG is often monitored more frequently when BG is in hypoglycaemic ranges than for normal/high glycaemic statuses. If data points are weighted equally (independent of timing), this would decrease the mean BG among patients who had some BG measurements below a certain threshold, which would also result in a biased index (Finfer et al., 2013). This limitation is overcome by TIR, which is described in more detail below.

Percentage of time in range (TIR)

TIR, by definition, is a metric that is dependent of time, and it is usually possible to compare TIR between different protocols. If all original data points are available, TIR can be calculated for any glucose range and used to compare groups of patients or protocols for GC. Protocols with higher TIR would be considered as more effective than those with lower TIR, at a pre-specified glycaemic range. TIR is calculated as:

$$TIR = \frac{T_{in}}{T} \times 100\% \tag{2.1}$$

where T_{in} is the total length of time that the patient/s spent within the glucose range, and T is the length of the whole time period being considered.

Before this calculation is possible, it is necessary to impute BG values at the time intervals where BG was not measured. The time intervals are normally hourly but could also be different fractions of time. The imputation is often done assuming a linear change between

measurements. This assumption is considered to be a limitation of the metric (Preiser et al., 2016). However, the need to make such an assumption is due to the existing lack of fixed monitoring frequencies or continuous monitoring systems in most ICUs, which actually affects all proposed metrics that summarise GC.

Given the numerous factors that can affect glycaemic levels, and even the documented circadian rhythm of glycaemic levels in critically ill patients (Egi et al., 2007), it is likely that glycaemic levels have frequent changes, including peaks above the target range, which could be missed depending on the glycaemic monitoring frequency. Therefore, the less often glycaemic levels are measured, the more imputed values are required, and the less accurate TIR becomes. Studies about the accuracy of TIR in relation to monitoring frequencies are needed. Another limitation of TIR is that the frequency of exposure and severity of out-of-range events are not accounted for (Preiser et al., 2016), but again this is a common limitation of most other metrics.

The findings of several studies that have evaluated the effectiveness of GC in ICU using the TIR are summarised in Table 2.4. The majority of these studies were conducted in order to explore the level of effectiveness of a new protocol in an ICU, usually as compared with a different protocol, strategy, ICU or group of patients. Depending on the study, the protocol implemented, as well as the width of the target glucose range and how much higher above euglycaemic levels such target was, TIR values varied widely across these studies.

TIR values achieved by TGC protocols with euglycaemic target levels had mixed results, although they were often below 50%. These include median TIR values among medical/surgical patients that ranged from 23.1% (Shulman et al., 2007) to 39.3% (Preiser et al., 2009). Protocols targeting the BG range of 7-9mmol/L, which is a narrow but higher than normal range, also had TIR values that were often below 50%. On the other hand, protocols with a wider target range, but still higher than normal, achieved higher TIR levels, often over 50%. These included median TIR values of 55% in medical/surgical patients with diabetes and 80.6% in medical/surgical patients without diabetes (Krinsley & Preiser, 2015); and 78% in surgical patients, including both groups of patients with and without diabetes (Vogelzang et al., 2005). This might be because the wider the range the likelier it is for the patient's BG to fall within range, irrespective of the GC strategy. Hence, it is essential that when the effectiveness of protocols is compared, the TIR is calculated for the same glycaemic target range for all the protocols, irrespective of the actual target range of the protocols.

Table 2.4 - Results reported in the literature on the percentage of time spent within different BG target ranges, sorted by outcome measure and listed in reverse chronological order

Reference	Study setting and design	Sample size	BG target, mmol/L	Outcome measure: TIR (TIR calculated based on time in hours, unless specified otherwise)
				Median TIR
Krinsley & Preiser (2015)	Medical Surgical ICU Observational, retrospective. Post-hoc comparison of survival of patients with vs. without TIR>80%	n=3297	3.9-7.8	Median (IQR) TIR Patients without vs. with diabetes: **80.6%** (61.4-94.0%) vs. **55.0%** (35.3-71.1%) ***
Preiser et al. (2009)	Medical Surgical ICUs Multi-centre RCT (21 ICUs). Comparison IIT (Group-2) with intermediate GC (Group-1)	n=1101 (Group-1=542 Group-2=536)	7.8-10.0 (G-1) 4.4-6.1 (G-2)	Median (IQR) % time at: In range (TIR): **34.3%** (18.5-50.1%) (G-1) vs. **39.3%** (26.2-53.6%) (G-2) *** Above the range: **7.6%** (0.0-25.3%) (G-1) vs. **52.6%** (39.2-67.4%) (G-2) *** Below the range: **44.7%** (24.3-75.8%) (G-1) vs. **5.1%** (1.1-9.2%) (G-2) ***
Shulman et al.(2007)	Medical surgical ICU Observational, prospective. No comparison	n=50	4.4-6.1	Median (IQR) % time at: 4.4-6.1mmol/L (TIR): **23.1%** (15.4-29.8): **11.6%** (2.9-20.8%) (DM, n=6) vs. **23.9%** (18.4-30.7%) (No DM, n=44) 6.2-8.0mmol/L: **48.5%** (36.9-60.8): **36.3%** (15.3-43.5%) (DM, n=6) vs. **51.6%** (38.8-63.0%) (No DM, n=44)
Plank et al. (2006)	Cardiac surgery ICU patients Multi-centre RCT (three ICUs). Comparison of TGC vs. routine protocols	n=60 (30 per group, 10 per centre)	Intervention: 4.4-6.1 Control: routine GC and target	Median [range] TIR over first 24h: **52%** [17-92%] (New) vs. **19%** [0-71%] (Routine) ** Median [range] TIR over first 24h if LOS>48h (n=29): **50%** [17-71%] (New) vs. **21%** [6-67%] (Routine) * Median [range] TIR over 24-48 h if LOS>48h (n=29): **65%** [38-96%] (New) vs. **25%** [8-79%] (Routine) *
Vogelzang et al. (2005)	Surgical ICU Observational, prospective. No comparison	n=179	4-7.5	Median (IQR) TIR: 78 % (66 %-88 %)

Table 2.4 continued

				Mean TIR
Kanji et al. (2010)	Neuro ICU patients (neurovascular or head injury) Observational, retrospective and prospective. Comparison of previous vs. new protocol	n=100 (50 per cohort)	Target: 7-9 Acceptable range: 6-10	Mean±SD TIR at target: **36.4**±16.3% (intervention) vs. **27.1**±19.0% (conventional) *** Mean±SD TIR at acceptable range: **58.4**±21.5% (intervention) vs. NA (conventional)
De Block et al. (2006)	Medical ICU Observational, prospective. Comparison of two insulin regimes: SC vs. IV	n=50	4.5-6.1	Mean±SD TIR: **26%** ± 21% (IV) vs. **19%** ± 22% (SC) Mean±SD % time at <4.4mmol/L: **6**±9% (IV) vs. **4**±11% (SC) Mean±SD % time at >6.1 (target): **55**±22% (IV) vs. **71**±24% (SC) * Mean±SD % time at >7.8mmol/L: **35** ±24% (IV) vs. **42** ±29% (SC) Mean±SD % time at >11.1mmol/L: **13**±19% (IV) vs. **16**±23% (SC)
Kanji et al. (2004)	Medical surgical ICU Observational, retrospective and prospective. Comparison of "ad hoc" treatment vs. new protocol	n=100 (50 per cohort)	7-9	Mean±SD TIR: **47.9**±15.4% (intervention) vs. **29.6**±20.8% (control) ***
				Total TIR
Boord et al. (2007)	Surgical ICU. Observational, retrospective, before-after comparison study	n=351 (Pre=147 Post=204)	3.9-6.1	Total TIR (minutes) in target on <u>days 1-5</u> after ICU admission **29.1%** (Pre-implementation) vs. **39.3%** (Post-implementation) [a]
Chase et al. (2007)	Medical Surgical ICU Simulated virtual patient trials created from retrospective data	7358 patient-hours	Not specified (various ranges studied)	Total % time at: 4-6.1mmol/L: **59%** 4.0-7.0mmol/L: **84%** 4.0-7.75mmol/L: **92%**
Oeyen et al. (2007)	Medical surgical ICU Observational, prospective. No comparison	n=30	4.5-6.1	Total % time in: Target (TIR) (4.5-6.1): **42%** Acceptable (6.2-8.3): **36.9%** Hyperglycaemia (8.4-11.1): **8.2%** Severe hyperglycaemia (>11.1): **1.8%**

Table 2.4 continued

Scheuren et al. (2006)	Medical Surgical ICU Observational, prospective before-after study	n=58 (traditional=29, modified =29)	4.4-6.1	% Time in target: With modified protocol: **20.7%** (DM), and 24.3**%** (no DM) With traditional protocol: **7.0%** (DM) and **14.6%** (non DM) % Time within 6.2-8.3mmol/L: With modified protocol: **37.5%** (DM) and **38.7%** (no DM) With traditional protocol: **34%** (DM) and **37.6%** (no DM)
Chant et al. (2005)	Medical surgical ICU Observational, prospective before-after comparison	n=86 (Nomogram=44, Control=42)	5-8	Total TIR: 52% (nomogram) vs 20% (control) ***
Carr et al. (2005)	Cardiac Surgery ICU patients Observational, prospective. Comparison of three glycaemic thresholds triggering initiation of insulin	n=737	<7.2	Total TIR at: <8.3mmol/L: **44.8%** <6.9mmol/L: **57.4%** <6.1mmol/L: **75%** Total TIR <7.2mmol/L: **35%** (Without DM, 52%patients) vs. **42%** (With DM, 48%patients)
Rood et al. (2005)	Medical surgical ICU Observational, prospective before-after comparison. Intervention: Computerised new protocol.	n= 484 (Pre-impl.= 225, Paper-impl.=116, Intervention: Computerised=66, Control=54, Post-int=23)	4-7	Total TIR: **22.0%** (Pre); **44.3%** (paper); **54.2%** (Intervention, computerised); **52.9%** (Intervention, control); C) **42.3%** (Post) Total TIR at 4-8.5mmol/L **52.4%** (Pre); **72.2%** (paper); **80.8%** (Intervention, computerised **80.4%** (Intervention, control); C) **71.7%** (Post)
Zimmerman et al. (2004)	Cardiothoracic surgical patients Observational, prospective before-after comparison	n=342 (TGC=168 Control=174)	4.4-8.3	Total TIR **65.4%** (nurse driven TGC) vs. **54.6%** (control) ***

Pre-impl.: pre-implementation period; Paper-impl. = period in which the guideline was only available in its paper form; Post-int: period after the intervention; DM: Diabetes Mellitus.

*p<0.050; **p<0.010; ***p<0.001

[a] Significant on day-2 only, p=0.017

Several studies have confirmed associations between low values of TIR, at different ranges, and a number of poor outcomes, including mortality (Krinsley & Preiser, 2015; Penning et al., 2015; Omar et al., 2015; Signal et al., 2012; Chase et al., 2010). Krinsley & Preiser (2015) found that TIR>80% at BG within 3.9-7.8mmol/L was associated with increased survival in patients without diabetes. Omar et al. (2015) found that TIR>80% at BG within 6-8.1mmol/L was associated with better outcomes in all patients after cardiac surgery, in terms of less wound infections, shorter time with ventilation, and shorter stay.

A number of post-hoc analyses of data from patients under SPRINT protocol have looked at the impact of the cumulative time in band (cTIB), which measures the cumulative TIR of a patient up to a specific point in time (Penning et al., 2015; Signal et al., 2012; Chase et al., 2010). Amongst these post-hoc analyses, Chase et al. (2010) studied the effects of different values of cTIB at 4-7mmol/L and they concluded that cTIB>50% was associated with lower levels of organ failure, as measured by a significant reduction in the Sequential Organ Failure Assessment (SOFA) score. Signal et al. (2012) found that cTIB at 4-7mmol/L above 70% was independently associated with higher survival than lower cTIBs of 50% and 30%. Penning et al. (2015) combined data from the SPRINT and Glucontrol trials, and carried out post-hoc analyses looking at the effects of cTIB at several glycaemic bands (4-7mmol/L, 5-8mmol/L, and 4-8mmol/L) on the odds of survival. They found that cTIB higher than 80% in what they considered an "intermediate glycaemic band" of 4-7mmol/L, was associated with higher odds of survival than equal or lower cTIBs at other higher or wider glycaemic bands. This occurred regardless of how the GC was achieved, and as long as hypoglycaemia was avoided.

In conclusion, TIR has been described as a useful unifying metric that provides a quantitative description of dysglycaemic events (Machado Tironi, 2015). Recently, renowned experts in the field of GC in intensive care have emphasised the great importance of calculating the TIR for the quality and feasibility assessment of GC in the ICU (Preiser & Straaten, 2016).

2.6.2 Factors that can affect the effectiveness of glycaemic control

There are a number of factors inherent to the patient, or to the treatment or care provided, which have been found to be associated with the effectiveness of GC. Multivariate analyses that have explored the effects of these factors on the effectiveness of GC, as measured with TIR, or with pre-specified percentages of time spent within certain BG ranges, are reviewed in this section. A summary the findings from these studies is provided in Table 2.5.

Table 2.5 – Published evidence on factors affecting the time spent in specific glucose ranges

Reference	Outcome	Factors affecting outcome	Regression Coefficient $\hat{b}$ or OR, and (SE) or (95%CI)
Omar et al. (2015)	TIR>80% at 6-8.1mmol/L	Diabetes	OR(95%CI)=0.30 (0.12-0.75) *
Shulman et al. (2007)	TIR at 4.4-6.1mmol/L	Body Mass Index	NA
		APACHE II score	NA
		History of diabetes	NA
Oeyen et al. (2007)	TIR at 4.5-6.1mmol/L	Level of C-reactive protein	b(SE)=-0.31 (0.15) *
		Bilirubin	b(SE)=2.10 (0.59) ***
		Total insulin dose per day	b(SE)=-0.07 (0.02) **
		Adherence	b(SE)= 0.65 (0.06) ***
De Block et al. (2006)	TIR at 4.4-6.1mmol/L	Body Mass Index	b=0.73 ***
Carr et al. (2005)	Achievement of "good GC" defined as TIR>50% at BG<7.2mmol/L (Measured time)	Protocol with lower BG threshold triggering treatment	b(SE)=0.167(0.040), OR=1.18 ***
		Hours between 1st and last tests	b(SE)=-0.011(0.002), OR=0.99 ***
		Number of tests	b(SE)=0.012(0.003), OR=1.01 ***
		History of diabetes	b(SE)=-0.167(0.043), OR=0.85 ***
		First BG>11.1mmol/L	b(SE)=-0.225(0.080), OR=0.80 ***
		Inotropic agents on arrival [a]	b(SE)=0.100(0.042), OR=1.11 ***
Thomas et al. (2005)	Achievement of BG values <8mmol/L	Length of ICU Stay (days)	OR(95%CI)=1.04 (1.03-1.05) ***
		Use of TPN	OR(95%CI)=0.63 (0.51-0.77) ***
		Use of vasoactive drugs	OR(95%CI)=0.61 (0.52-0.71) ***
		Use of insulin	OR(95%CI)=0.64 (0.50-0.81) ***
Rady et al. (2005)	Poor GC defined as BG ≤8mmol/L for <5% of total hospital stay time	Age (per decade)	OR(95%CI)=3.2 (2.3-4.3) ***
		History of diabetes	OR(95%CI)=5.6 (4.7-6.9) ***
		Cardiac surgery	OR(95%CI)=6.1 (4.9-7.8) ***
		Catecholamine infusions	OR(95%CI)=1.8 (1.6-2.1) ***
		Propofol	OR(95%CI)=1.5 (1.3-1.7) ***
		Corticosteroids	OR(95%CI)=2.6 (2.3-3.0) ***
		Maximal daily SOFA score>8	OR(95%CI)=2.7 (2.1-3.5) ***
		Mechanical ventilation ≥96 h	OR(95%CI)=2.5 (1.6-4.1) ***
		Postoperative complications	OR(95%CI)=1.7 (1.4-2.0) ***
		Nosocomial infections	OR(95%CI)=1.6 (1.4-1.9) ***
Cely et al. (2004)	% time>8.3mmol/L, in patients who had normal baseline glucose control (NBGC)	HbA1c (%)	b(SE)0.1170 (0.0550)
		Age (years)	b(SE)0.0048 (0.0023)
		Corticosteroid dose (hydrocortisone equivalent)	b(SE)0.0002 (0.0001)
		IV dextrose (g/dL)	b(SE)0.0014 (0.0003)
		Enteral carbohydrate (g/dL)	b(SE)0.0021 (0.0006)
	% time>11.1mmol/L in patients with NBGC	HbA1c (%)	NA
		Noradrenaline dose (μ/kg/min)	NA
	%time>16.7mmol/L in patients with NBGC	BMI	NA
		Noradrenaline dose (μ/kg/min)	NA

b: beta coefficient; SE: Standard Error; 95CI: 95%Confidence Interval NA: Not Available; OR: Odds Ratio.
*p<0.050; **p<0.010; ***p<0.001
[a] Inotropic agents included milrinone, adrenaline, dobutamine, levophed, or dopamine.

2.6.2.1 Patient inherent factors

Among the patient inherent characteristics, the most commonly found factor associated with lower effectiveness of GC, or with shorter TIR, is a history of diabetes (Krinsley & Preiser, 2015; Omar et al., 2015; Shulman et al., 2007; Rady et al., 2005; Carr et al., 2005), or a high HbA1c (Cely et al., 2004). On the other hand, as described in section 2.2.5.4, a previous diagnosis of diabetes tends to attenuate the detrimental effect of hyperglycaemia on poor clinical outcomes.

In their large case-control study (n=2826), Rady et al. (2005) found that a history of diabetes mellitus increased the risk of having poor GC by 5.6 times, with poor GC defined as less than 5% of total hospital LOS with glycaemic levels ≤8mmol/L. They also concluded that, for each glycaemic range, patients with diabetes required higher doses of insulin to achieve glycaemic levels similar to those without diabetes. Cely et al. (2004) found statistically significant differences in the percentages of times spent over certain glycaemic thresholds depending on the levels of HbA1c. Among others, they found that for every one unit increase in the HbA1c (%) there was a 0.117 increase in the fraction of time spent with BG>8.3mmol/L. In their observational prospective studies on cardiac surgery patients, Omar et al. (2015) found that having diabetes decreased by about 70% the odds of having a TIR>80% at BG within 6.1-8mmol/L, while Carr et al. (2005) found that diabetes was associated with about 15% lower odds of having a TIR>50% at BG<7.2mmol/L.

A high BMI (Shulman et al., 2007; De Block et al., 2006; Cely et al., 2004), older age (Rady et al., 2005; Cely et al., 2004), high levels of C-reactive protein and low levels of bilirubin (Oeyen et al., 2007), and higher severity levels on admission as measured with the APACHE II score (Shulman et al., 2007), are all patient related factors that have also been associated with shorter TIR, at various glucose ranges. Other factors having a detrimental effect on the TIR include those indicating higher severity levels during patients' stay in the ICU, such as higher degree of organ failure (maximal daily SOFA score>8), the need for mechanical ventilation for 96 or more hours, and the development of post-operative complications or nosocomial infections (Rady et al., 2005). Also, being admitted for cardiac surgery (Rady et al., 2005), and, if so, having a BG on admission higher than 11.1mmol/L (Carr et al., 2005), have both been found to be predictors of lower TIR. Finally, a shorter stay in ICU was also found to have a negative effect on TIR (Thomas et al., 2005), indicating that TIR improves the longer a patient stays in the ICU.

Lower effectiveness of GC methods has been correlated with the presence of sepsis. Patients with a known infection and hypercytokinaemia can be diagnosed with sepsis. Hirasawa et al. (2009) used the threshold IL-6 levels in blood of 1000pg/mL to diagnose patients with

hypercytokinaemia. These authors found that the success rate of TGC (targeting BG of 6.1-8.3mmol/L) was significantly lower among patients with ICU admission IL-6 blood level higher than 1000pg/mL. Also, in their retrospective study with septic ICU patients, Nakamura et al. (2012) found that there was a significant positive correlation between admission blood IL-6 levels and admission BG levels ($p=0.01$), which was even larger in patients without diabetes ($p<0.01$). They also found that achieving a good GC, which they defined as at least six days with BG levels <8.3mmol/L, occurred less often in patients who had had hypercytokinaemia on admission, the rate of success decreasing with increasing blood IL-6 levels on admission ($p=0.01$). However, these correlation analyses did not control for other confounding, moderating or mediating factors, and therefore their conclusions must be interpreted with caution.

2.6.2.2 Therapeutic interventions

The nutritional therapy administered to a patient has potentially deleterious effects on the incidence and duration of hyperglycaemia, due to the administration of high amounts of energy, especially carbohydrate kilocalories (Mesotten et al., 2015; Preiser et al., 2015; Shaw et al., 2014; Preiser, 2013; Thomas et al., 2005; Cely et al., 2004). This has been described in detail in Section 2.3.4. In addition to the nutritional support, propofol has also been identified as a medication with detrimental effects on TIR, probably caused by its high content of lipid energy (Rady et al., 2005). Propofol is a sedative agent formulated in fat emulsion and it is commonly used in the ICU. Each millilitre of 1% propofol has 0.1g of fat, providing 1.1kcals. Findings on the link between exogenous energy administered as enteral or IV carbohydrates (Cely et al., 2004), as TPN support (Thomas et al., 2005), or through the administration of propofol (Rady et al., 2005), and poorer GC in terms of lower TIR, are summarised in Table 2.5.

Besides the type and amount of nutritional therapy, there are a number of commonly used medications that can induce hyperglycaemia as an adverse effect (Shulman et al., 2007). Among these are the exogenously administered catecholamines, which are commonly used as inotropes in the management of a number of cardiovascular conditions and septic shock (Kavanagh & McCowen, 2010; Dungan et al., 2009; Rady et al., 2005; Thomas et al., 2005; Cely et al., 2004), and exogenous glucocorticoids, which are medications widely used as vasopressors in the ICU. The ability of these medications to induce the same effects as the natural hormones (as described in Section 2.2.3), such as the stimulation of hepatic gluconeogenesis and glycogenolysis, can result in the exacerbation of stress hyperglycaemia in critically ill patients (Pretty et al., 2011). Findings on the detrimental effects on the TIR of vasoactive drugs in general (Thomas et al., 2005), and of certain specific catecholamines

(Rady et al., 2005; Cely et al., 2004), as well as of corticosteroids (Rady et al., 2005; Cely et al., 2004), are summarised in Table 2.5.

Finally, protocols that have a high BG threshold triggering the initiation of insulin treatment, longer time between the first and the last of all BG measurements in a patient, and having instructions that lead to fewer BG measurements have been found to be detrimental on TIR (Carr et al., 2005). Irrespective of the type of GC protocol, low adherence to the protocol instructions has also been related to a decrease in TIR (Oeyen et al., 2007) (Table 2.5).

2.6.3 Evaluation of efficiency

It is less common for studies to focus on the efficiency of GC, as compared to the effectiveness. By definition, efficiency measures the level to which a desired outcome, such as bringing patient glycaemic levels to a safe range, is achieved, as compared with the cost, workload and/or time that is required to achieve it.

Several studies have explored the costs associated with GC strategies or protocols. Krinsley & Jones (2006) carried out a before-after study to compare the costs of a new TGC protocol implemented in a medical-surgical ICU with a previous one. They found that the new protocol resulted in $1580 net savings per patient. This was due to decreases in: patients' ICU LOS; duration of advanced respiratory support; total laboratory, pharmacy and radiology costs; and post-ICU hospital LOS with the new protocol.

In a *post hoc* analysis of their first RCT on IIT in a surgical ICU, Van den Berghe, Wouters, et al. (2006) compared the costs of IIT versus the conventional treatment. They found an average of €2566 savings per patient with the IIT approach, due to lower LOS and fewer ICU complications. The latter included reductions in bloodstream infections, acute renal failure requiring dialysis or haemofiltration, red-cell transfusions, critical-illness polyneuropathy and prolonged mechanical ventilation. While Hilleman (2006) also concluded that IIT can be considered efficient based on financial savings. Investigators of the Control of Hyperglycaemia in Paediatric intensive care (CHiP) trial found both IIT and conventional treatment similar in terms of cost-effectiveness within the paediatric ICU environment (Macrae et al., 2014).

A few studies have explored the workload associated with GC strategies. In their two prospective before-and-after protocol implementation studies, Kanji et al. (2004, 2010) calculated different measures of the GC quality. They used the number of BG measurements required per patient as a metric of process quality, and found a significant increase in the number of measurements with the new protocol, in both of their studies. The mean (SD) number of BG measurements per patient required per day, for the previous vs. new protocol,

were 8.3 (3.0) and 11.3 (2.7), respectively, in the first study ($p<0.001$) (Kanji et al., 2004), and 8.8 (2.6) and 13.6 (3.2), respectively, in the second study ($p<0.001$) (Kanji et al., 2010). However, this cannot be considered as a measure of efficiency, unless both protocols had the same effectiveness, and in this case they didn't.

Aragon et al. (2006) analysed the workload of nurses with a new IIT strategy implemented in their ICU. They concluded that implementing TGC required up to two hours of nurse time per patient in a 24-hour period. However, they did not compare this with a different or previous GC approach having the same effectiveness, and therefore the efficiency of the new strategy could not be evaluated.

These metrics are important, as hospitals consider effects on cost and workload when deciding whether to implement a new approach. However, they do not measure direct effects on patients. Several studies have explored the metric "time needed to reach a specific target range (or time to range, TTR)", which is a time-efficiency measure that has a direct effect on patients. TTR is calculated as:

$$TTR = t_{controlled} - t_{1st\ BG>target} \tag{2.2}$$

where $t_{1st\ BG>target}$ is the time of the first occurrence of BG above the glycaemic target range, and $t_{controlled}$ is the time, after $t_{1st\ BG>target}$, when the BG is brought to the glycaemic target range. Higher TTR implies that it takes longer to bring a patient's BG back within the target range, and hence lower efficiency.

The results of some of the studies using this metric are summarised in Table 2.6. In these studies, TTR was explored mainly descriptively, usually comparing a new protocol with a different protocol or strategy, or comparing different groups of patients. In most studies, regardless of the glucose target, TTR had median values that were below 24 hours. Most TTR ranged from 5 hours in neurocritical patients receiving a new protocol of GC (Kanji et al., 2010) to 16.4 hours in MICU/SICU patients receiving an ad hoc treatment of GC (Kanji et al., 2004). However, some studies found TTR values in certain groups of patients that were either much lower, such as 2.1 hours in cardiothoracic surgical patients receiving a TGC protocol (Zimmerman et al., 2004), or much higher, such as 66 hours in the control group of a before-after intervention study in a MICU/SICU unit (Chant et al., 2005).

While TTR is an easy metric to calculate and useful to explore how time-efficiently a protocol or an ICU manages to achieve their target, the impact of this metric on poor outcomes, such as those associated with lower TIR, has not yet been confirmed in observational studies or RCTs. Therefore its clinical impact remains unknown (Preiser & Straaten, 2016).

Table 2.6 – Results reported in the literature on the evaluation of efficiency and safety of GC protocols, listed in reverse chronological order

Reference	Study setting and design	Sample size	BG target, mmol/L	Outcome measure of efficiency (TTR)	Outcome measure of safety (incidence of and percentage of time spent in hypoglycaemia)
Kurtz et al. (2014)	Neuro ICU patients after SAH [a] Observational, retrospective. No comparison	n=28	4.4-8.3	*NA*	Severe hypoglycaemia<2.3: 0% patients Hypoglycaemia<3.9: 57% patients
Kanji et al.(2010)	Neuro ICU patients (neurovascular or head injury) Observational, retrospective and prospective. Comparison of previous vs. new protocol	n=100 (50 per cohort)	7-9	Median [range] TTR: 5 [0.5-20.5] h (intervention) vs. 12.9 [1.3-90.3] h (control) ***	Median [range] measurements per day in: Moderate hypoglycaemia<3.9: 0 [0-0.55] (intervention) vs. 0 [0-1.25] (control) *** Severe Hypoglycaemia<2.2: 0 [0-0.55] (intervention) vs. 0 [0-0.01] (control)
Chase et al.(2008)	Medical surgical ICU Observational, before-after comparison	n=784 (Retrospective =413 SPRINT=371)	4-6	*NA*	Percentage of measurements less than 4.4mmol/L: 6.5% (Retrospective) 9.0% (SPRINT) ** 4.0mmol/L: 3.8% (Retrospective) 3.8% (SPRINT) 2.2mmol/L: 0.2% (Retrospective) 0.1% (SPRINT) **
Oeyen et al. (2007)	Medical surgical ICU Observational, prospective. No comparison	n=30	4.5–6.1	*NA*	Hypoglycaemia ≤3.3: 0.3% time 60% patients ≥1 event 37% patients ≥1 event plus rescue dextrose Severe Hypoglycaemia≤2.2: 2% patients ≥1 event
Shulman et al. (2007)	Medical surgical ICU Observational, prospective. No comparison	n=50	4.4-6.1	Median (IQR) TTR: 10.5 (4.8-14.5) h	Hypoglycaemia≤4.4: 1.7% time Severe Hypoglycaemia≤2.2: 10% patients ≥1 event 0.04% time

Table 2.6 continued

De Block et al. (2006)	Medical ICU Observational, prospective. Two insulin regimes: SC vs. IV	n=50	4.5–6.1	NA	Hypoglycaemia<3.3. Mean±SD: 6±9% time (IV) vs. 4±11% time (SC)
Chant et al. (2005)	Medical surgical ICU Before-after comparison	n=86 (Intervention=44 Control=42)	5-8	Median TTR for two consecutive measurements: 15h (intervention) vs. 66h (control) ***	Measurements in hypoglycaemia<4: 2.2% (Control) vs. 3.8% (Intervention) Measurements in Severe Hypoglycaemia<2.2: 0.4% (Control) vs. 0.2% (Intervention)
Vogelzang et al. (2005)	Surgical ICU Observational, prospective. No comparison	n=179	4-7.5	Median (IQR) TTR to first BG<7.5mmol/L: 5.7 (1.2-11.4) h	Hypoglycaemia≤3.5: 11.2% patients Severe Hypoglycaemia≤2.2: 0.6 % patients
Kanji et al. (2004)	Medical surgical ICU Observational, retrospective and prospective. Comparison of "*ad hoc*" treatment vs. new protocol	n=100 (50 per cohort)	7-9	Mean±SD TTR: 11.3±7.9 h (intervention) vs. 16.4±12.6 h (control) *	Severe Hypoglycaemia≤2.2: 4% patients (intervention) vs. 16% patients (control)
Zimmerman et al. (2004)	Cardiothoracic surgical patients Before-after comparison	n=342 (TGC=168 Control=174)	4.4-8.3	Median (IQR) TTR to first BG<8.3mmol/L: 2.1h (TGC group) vs. 9.4h (control group) ***	Measurements in hypoglycaemia<3.6: 16.7% (TGC group) vs. 9.8% (control group)

TGC: Tight Glycaemic Control

*p<0.050; **p<0.010; ***p<0.001

[a] Patients with Subarachnoid Haemorrhage (SAH) who underwent multimodality neuro-monitoring with intracranial pressure, cerebral microdialysis, and brain tissue oxygen pressure as part of their clinical care

2.6.4 Evaluation of safety

The main risk of GC methods is the development of iatrogenic hypoglycaemia. Given the strong association between hypoglycaemia and poor outcomes, including mortality (Krinsley et al., 2013; Krinsley & Grover, 2007; Van den Berghe, Wilmer, Hermans, et al., 2006; Finney et al., 2004; Van den Berghe et al., 2001), studies exploring the effectiveness of GC strategies or protocols, usually also explore their safety, with metrics related to the occurrence of hypoglycaemia. These metrics include the number of patients with at least one event of severe or moderate hypoglycaemia (Kanji et al., 2010), the proportions or the incidence of hypoglycaemic and severe hypoglycaemic events in a group of patients (Chant et al., 2005), as well as the time spent in the hypoglycaemic and severe hypoglycaemic ranges, and the frequency of administration of rescue dextrose (Oeyen et al., 2007).

The findings of some of studies on GC protocol safety are summarised in Table 2.6. Severe hypoglycaemia, defined as BG≤2.2mmol/L, occurred more often in studies of TGC protocols targeting euglycaemic levels, with 2% (Oeyen et al., 2007) to 10% (Shulman et al., 2007) of patients having at least one such event. In one study with a protocol targeting glycaemic levels that were above euglycaemic levels (target BG=7-9mmol/L), the number of patients with at least one event of severe hypoglycaemia was even higher (16%).

When hypoglycaemia was defined as BG below 4mmol/L or below 3.3mmol/L, the incidence of hypoglycaemia was higher in all studies. While Oeyen et al. (2007) reported that 60% of patients had at least one BG<3.3mmol/L, in other studies this prevalence was usually lower than 50% but still considerably high.

The percentage of time spent in hypoglycaemia (or time below range, TBR) can be used to assess safety, and is calculated as:

$$TBR = \frac{T_{hypo}}{T} \times 100\% \tag{2.3}$$

where T_{hypo} is the time spent with BG levels below a specified hypoglycaemic threshold, and T is the total admission time.

Literature using this metric also showed varying findings, even if the threshold used to define a hypoglycaemic event was the same (Table 2.6). For example, from two studies that used the threshold BG<3.3mmol/L to define hypoglycaemia, one found a TBR of 0.3% (Oeyen et al., 2007) while another found a mean (SD) TBR of 6% (9%), or 4% (11%), depending on the protocol implemented (De Block et al., 2006).

2.6.5 Other recommendations for evaluation of glycaemic control

Experts in the field of GC have proposed a number of recommendations regarding the measurement of BG and reporting of GC in critically ill adults (Finfer et al., 2013). Among these was that, until further RCTs confirm which is the optimal measure of the performance of GC strategies, trials and observational studies should calculate and report measures of GC that are simple and can be intuitively understood. They recommend reporting: (a) the median (interquartile range, IQR) of individual patients' mean BG levels, (b) the median (IQR) of the SD of the BG levels of each patient, and (c) the number and percentage of patients experiencing at least one episode of severe and moderate hypoglycaemia, defined as BG≤2.2mmol/L and BG of 2.3-3.9mmol/L, respectively. These expert recommendations also advise, when possible, the inclusion of details on the hypoglycaemic events, such as duration, associated symptoms, amount of glucose administered, time to next BG measurement, and possible iatrogenic aetiology. In addition, they recommend reporting: (1) the frequency of BG measurements, (2) the duration of monitoring, (3) the nature of blood sampling including capillary, peripheral-venous, central-venous and arterial samplings, and (4) the technology used to measure BG.

Nonetheless, these experts recognise in their report that these recommendations have a pragmatic nature, rather than scientific, and that further studies were needed to determine the optimal metric of GC. This optimal metric needs to be simple and associated with clinical outcome (Preiser et al., 2016; Finfer et al., 2013). TIR has been suggested as a metric that can meet both of these criteria (Preiser et al., 2016).

2.7 The role of clinical professionals in the quality evaluation of glycaemic control in intensive care

One of the key components in the continuous quality improvement of health services are stakeholders such as the health professionals. In quality evaluations of health services, their views can be crucial both as a source of information, and as instrumental agents in the implementation of quality improvement plans (EFQM, 2012).

The European Foundation for Quality Management (EFQM) model was developed in order to guide the design, structure and assessment of the quality of an organisation, and has been widely used across private and public health care organisations, including the NHS (NHS Scotland Quality Improvement Hub, 2012; NHS Wales SSP Procurement Services, 2011; NHS Institute for Innovation and Improvement, 2008b). It is based on a *total quality* or

excellence approach, which aims to achieve a continuous improvement of quality on all the organisation's activities and at all its levels.

The essence of the EFQM model's approach is its aim of meeting the expectations, needs and demands of all its stakeholders, in the long term (EFQM, 2012). Key stakeholders in all organisations are their employees. As key stakeholders in the ICU, critical care professionals must be considered in any evaluation or intervention development for the quality improvement of clinical practice in the ICU (Montpetit & Sessler, 2013). Professionals' views on their clinical practice affect the treatments and care they implement, their degree of adherence to protocol instructions and, ultimately, the clinical outcomes of the patients they care for. In this regard, the AGREE II (Appraisal of Guidelines for Research & Evaluation) instrument proposed that, in evaluations of guidelines' development, one of the six domains that are evaluated should be the involvement of stakeholders, which includes the whole multidisciplinary team (Brouwers et al., 2010).

Therefore, in a quality evaluation of a clinical service or a protocol, exploring the opinions of professionals regarding their clinical practice or the protocols they implement, is a key and essential element. Not only does this help with the identification of areas for quality improvement (Draper et al., 2008), but it also increases the probability of success of any recommendations for change arising from the evaluation (EFQM, 2012).

Despite the growing evidence on the prevalence of non-adherence to clinical protocols, as described in Section 2.5, and the relevance of involving stakeholders in the development of clinical guidelines (Brouwers et al., 2010), most studies on the EES of new protocols for GC do not report on the attitudes and views towards GC of the ICU professionals who had to implement them. However, there are a number of studies in which ICU professionals, usually nurses, were surveyed or interviewed about a number of aspects regarding GC, either as a standalone project or as part of a larger study on the impact of GC.

Mc Mullin et al. (2004) conducted a multi-centre survey on the beliefs and attitudes of ICU clinicians about several aspects of GC, although none of the five participating ICUs had a GC protocol in place. Of the 317 respondents, 74% were nurses. On average, participants considered 4mmol/L and 10mmol/L as thresholds for hypoglycaemia and hyperglycaemia, respectively, which were clinically important thresholds in their view. Among the participants, nurses suggested significantly higher thresholds for hyperglycaemia than physicians, on average. There were significant differences between the views of the two professional groups (nurses vs. physicians) also regarding the patient sub-groups in which, in their opinion, avoidance of hyperglycaemia was particularly beneficial. Patients with diabetes were the sub-group of highest concern for most professionals. However, more

physicians than nurses were concerned about hyperglycaemia in patients with acute myocardial infarction, while more nurses than physicians were concerned about hyperglycaemia in patients with severe liver disease. Participants were also asked about their concerns about using glucometers in the ICU. The accuracy of these instruments was the most frequently expressed concern for all professionals, and patients' discomfort and glucometer availability was of more concern for nurses than for physicians. Finally, they were also asked about strategies they would find most useful to help achieve optimal GC in the ICU. Apart from the need for more research, about which there was agreement amongst both nurses and physicians, the views of the two groups of respondents differed significantly. More effective sliding scales and faster laboratory turnaround were endorsed by nursing staff more often than by medical staff. On the other hand, a higher emphasis on GC in general, increased use of insulin infusion, increased use of glucometers and more frequent monitoring were endorsed by physicians more often than by nurses, as strategies to achieve optimal GC.

Aragon (2006) conducted a multi-methods study on the organisational and financial impacts of the implementation of a new TGC protocol targeting euglycaemic levels. The study included a survey of the nursing staff's perceptions about the TGC protocol, which 66 nurses completed. The study concluded that nurses were generally supportive of the benefits of TGC. However, they often expressed concern about having to perform multiple finger sticks per day to each patient, and most of them would have preferred if an automated system existed for BG monitoring. Also, about half of the respondent nurses thought that TGC required too much time, more than half of them did not think that TGC was a normal part of patients' care, and 10 nurses (more than one in seven) even thought that TGC should be done by someone else other than the nursing staff (Aragon, 2006). In their clinical review about strict vs. loose GC, Schultz et al. (2010) also remarked that the additional work load required for TGC, and the uncertainties about who should be primarily responsible for its implementation, can hamper the successful implementation of TGC strategies.

As part of a pilot study comparing a TGC with a conventional approach for GC, Bland et al. (2005) interviewed nurses about their perceptions of the new TGC protocol. As in Aragon's survey, respondents expressed concern about the need to take multiple capillary samples from the patients, and the increased workload with the introduction of the TGC protocol. In addition, they also provided some suggestions to make TGC successful, such as the possibility of titrating insulin infusions in steps of 0.1U/h rather than 0.5U/h, and the possibility of temporarily stopping the insulin infusion instead of giving rescue glucose when there was an event of moderate hypoglycaemia (BG within 3.3-3.9mmol/L).

This evidence confirms that there are important gaps between what protocols or guidelines recommend for the management of stress hyperglycaemia, and what the clinicians

implementing them can do, or think they should do, for the GC of their patients. In addition, the significant differences between the views of nurses and physicians points to a need for exploring both professional groups in any experimental or observational study on GC.

There remain several important questions regarding professionals' opinions. Their views on the aims of GC of stress hyperglycaemia defined by the patient's TIR, as well as the hypoglycaemic events that should be treated with rescue glucose, have not been explored thus far. Also, while previous findings showed that the need for GC is generally accepted, professionals' views on the relevance of adhering to protocols remain unknown. Finally, ICU professionals can have varied levels of experience, which can affect their perceptions, and this was not controlled for in previous studies (Kansagara, 2013; Schulz et al., 2010).

2.8 GlyCon study: aims and objectives

The design of GlyCon study was motivated by a number of important gaps in the current knowledge, which have been identified in this literature review. These are summarised below.

There is a vast amount of literature concluding that not treating or controlling stress hyperglycaemia could have potentially detrimental effects on ICU patients' clinical outcomes. However, current evidence about the most effective and safest glycaemic targets, and methods to achieve them, is discrepant. As a consequence of this inconsistent evidence, there is a lack of standardised recommendations to manage stress hyperglycaemia, agreed at the international or national levels, as well as a large variation between locally developed GC protocols. Numerous studies have demonstrated that the adoption of different protocols for GC can have a different impact on patients' outcomes, particularly in terms of the time that patients' BG is kept stable within certain target levels. However, there are also studies showing that protocols are frequently not adhered to. Therefore, the impact of adopting a particular GC protocol also depends on how much its instructions are adhered to. ICU professionals, who are in the front line of patients' care, are key stakeholders, highly influential in the success of any strategy for GC.

Among the main gaps identified in the current knowledge are the following:

- There is scarce evidence about the extent to which the monitoring and treatment methods for GC that are actually implemented in ICU, regardless of what the protocol instructs or recommends, affect the effectiveness of GC strategies.

- Previous descriptive studies on ICU protocols for GC have not investigated in detail what each of the instructions for GC to deal with each specific glycaemic scenario are, and how these differ between ICUs.
- Studies on the views of both nursing and medical staff about what they consider as "good" GC in the ICU, and how they perceive the adherence to protocols, while controlling for their level of experience, are lacking and would likely improve our understanding on the practice of GC.

Based on these grounds, one main study hypothesis and seven specific objectives were proposed, to be investigated in seven ICUs of a UK based ICU network that admit level-3 critically ill patients. The main hypothesis of GlyCon study was that the implementation of different protocols for GC in ICUs would result in different decisions and actions being taken to manage the same situation, and, consequently, they would have a different impact on patients' outcomes. Specifically, it was hypothesised that patients who are monitored more frequently and/or who receive insulin for longer periods during hyperglycaemia have better outcomes, in terms of more effective GC.

The study specific objectives were:

- To describe and compare each of the instructions to deal with each specific glycaemic scenario, stated in different ICU protocols for GC;
- To explore the opinions of ICU nursing and medical staff from different ICUs, on effective GC and on deviations from protocol instructions;
- To describe and compare the methods for GC implemented in different ICUs;
- To describe and compare the levels of adherence to protocol instructions of GC in different ICUs;
- To describe and compare the levels of effectiveness, efficiency and safety of GC in different ICUs using relevant metrics;
- To analyse the relationship between different methods for GC and their levels of effectiveness, efficiency and safety;
- To produce a series of recommendations for the quality improvement of GC in ICUs, based on GlyCon results.

TIR was chosen as the primary outcome measure of the effectiveness of GC, since it is easy to understand, comparable, and a meaningful metric that provides a quantitative description of effectiveness. TTR was used as a secondary outcome measure of time-efficiency, this metric being very closely related to TIR and also straightforward to calculate. Given the reported evidence on the risk of and the negative impact that the development of hypoglycaemia can have among critically ill patients, the incidences and durations of events

of moderate (<4mmol/L) and of severe (<2.2mmol/L) hypoglycaemia were calculated as secondary outcome measures of safety.

In order to meet the objectives of GlyCon, a multi-centre study (in seven ICUs) with a multi-methods design was developed, resulting in three sub-studies. These were:

1) a review of the protocols for GC implemented in the seven participating ICUs;
2) an online survey of ICU professionals working in the seven participating ICUs;
3) a retrospective review of methods and outcomes of GC in a random sample of 146 patients from the seven participating ICUs.

A summary of the overall methodology, and a description of the ICU network within which this study was carried out, are presented in the next chapter.

Chapter 3
Overall methodology

As outlined in the literature review (Chapter 2), numerous randomised controlled trials (RCT) and observational studies have been conducted about the management of stress hyperglycaemia in ICUs, and yet there is no clear answer about the optimal glycaemic targets and the most effective and safest methods for this in ICU. The questions that emerged from the GlyCon literature review required a research project that combined different methods. The overall methodology adopted for the GlyCon study is presented in this chapter, without going into the specific methods with which each of the sub-studies were conducted (these are dealt with in their respective chapters).

3.1 Philosophical considerations

The effect of medical treatments on potential outcomes is often investigated through studies that use quantitative methods, and are traditionally associated with the positivist paradigm (Benton & Craib, 2001). Positivists pursue a empiricist view about reality according to which each fact is a corresponding portion of reality (Benton & Craib, 2001). For them, reality has to be experienced through the senses, it is easy to capture, predictable and controllable, and can be measured and explained using quantitative research methods that are objective and value-free (Feilzer, 2010).

Qualitative research approaches, on the other hand, are usually associated with the interpretivist paradigm. For interpretivists social reality is not always directly observable; it is constructed in the human mind, and thus is multiple and flexible. Interpretivists pursue a view of truth according to which ideas and beliefs can be true if they cohere with other ideas and beliefs that we may have in our minds (Gray, 2014).

For research purists, since these two paradigms (positivism and interpretivism) hold incompatible ontological and epistemological assumptions, they should not be mixed in the same research. Pragmatists disagree with this incompatibility of paradigms, the so called "incompatibility thesis". Research pragmatists argue that, while extreme paradigms have contradictions that may have a logical basis, they should not be seen as prescriptive rules for

doing research but, rather, as descriptions of the research practice (Greene, J, Benjamin, L, Goodyear, 2001). Hence, they advocate that paradigms can either remain separate or be mixed in the same research project (Gray, 2014). For pragmatists, restricting oneself to the use of one type of data or research method on the basis of a longstanding unsolved philosophical debate, is a reductionist view of research, which limits the researcher's range of possibilities for answering the questions that are relevant for the real world (Feilzer, 2010).

In addition, the pragmatist paradigm also advocates the use of research methods or approaches in a way that best addresses the research problem, regardless of whether they are quantitative or qualitative (Creswell, 2003). Thus, it also tries to reconcile the two extreme philosophical paradigms, represented by the positivist and the interpretivist paradigms, in this case, in medical research.

The methodological design of the GlyCon study was underpinned by a pragmatic philosophy, as described by Teddlie & Tashakkori (2009). As such, rather than starting from a fixed, pure ontological and epistemological position, the GlyCon study began by finding relevant research questions that are important for patients and healthcare providers. This was followed by the selection of the most appropriate research methods to answer the questions. This resulted in a multi-method design, as defined by Brewer & Hunter (2006). For these authors, a multi-method study is a type of research in which different research methods are used, either in parallel or sequentially, and which are combined or integrated in different phases of the study. Although there is no common definition of multi-method research and mixed methods research, all researchers agree on one common feature: quantitative and qualitative approaches are mixed in the same research project (Johnson et al., 2007).

While quantitative data analyses were used to answer the main research question of the GlyCon study and other research objectives, qualitative data analyses were used with expansion, complementarity and development aims, as described by Greene et al. (1989, cited in Gray, 2014). More specifically, the qualitative data analyses and their results: (1) helped to obtain a broader look on the study topic; (2) informed the development of a subsequent study; and (3) reflected different but interrelated elements of the phenomena, which, in return, complemented and helped in the discussion of the results from other methods. A brief description of each of the methods is provided in Section 3.3, following an introduction to the study setting provided in the next section.

3.2 Study setting

A Critical Care Network has been defined as "a service that is provided across NHS Trusts, working to common standards and protocols, taking responsibility for all the critically ill in all specialties within a geographical area" (UK Department of Health, 2000). The Mid Trent Critical Care Network (MTCCN) is a collaborative partnership between providers and commissioners of critical care services, within a defined geographical area in the East Midlands of England (Figure 3.1).

Besides other sectors and organisations, the network comprises eight critical care units, in five acute Hospital Trusts. One of the units admits patients requiring up to level-2 of care, while seven of them admit medical and surgical level-3 critically ill patients (Mid Trent Critical Care Network, 2011). The GlyCon study was conducted in the latter seven NHS ICUs of the MTCCN (Figure 3.1), focusing in particular on patients admitted during 2012 and 2013.

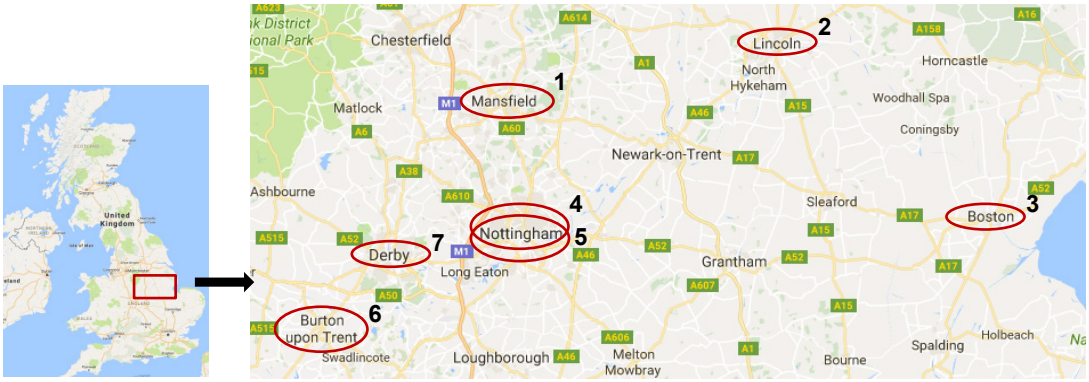


Figure ID - Hospital (Location)		Estimated populations [a]
1 -	Kings Mill Hospital (Mansfield)	103,000
2 -	Lincoln County Hospital (Lincoln)	92,000
3 -	Pilgrim Hospital (Boston)	62,000
4 -	Nottingham City Hospital (Nottingham)	306,000
5 -	Queen's Medical Centre (Nottingham)	
6 -	Queen's Hospital (Burton Upon Trent)	72,000
7 -	Royal Derby Hospital (Derby)	248,000

Figure 3.1 – Geographical location of the seven ICUs of Mid Trent Critical Care Network that admit level-3 critically ill patients and estimated populations of the areas they cover
Map Source: Google maps (2016)
[a] Estimated populations source: Association of Public Health Observatories, APHO (2012, 2013) and Office for National Statistics (2012)

Justification for the study setting selection

The MTCCN was formed in 2000 in order to "ensure equitable access and care for all critically ill patients within a defined geographical area" (Mid Trent Critical Care Network, 2011). In this area, the Network "reviews, plans, commissions and oversees" the clinical development of critical care services provided (NHS Networks, 2014).

The Network operates as a managed clinical network and is structured in different groups, all coordinated by the Network Board. Among others, the Network Clinical, Lead Nurse and Service Improvement Groups encourage and facilitate the sharing of local policies, procedures and guidelines among the staff (Mid Trent Critical Care Network, 2011). Despite this setup, a retrospective study carried out in two of the MTCCN ICUs in 2011 showed important differences in the methods for glycaemic control (GC) implemented in each of them (Tomlinson et al., 2012).

Based on these grounds, the MTCCN was considered an ideal setting to explore the practice, protocols and outcomes of the methods for GC of stress hyperglycaemia implemented in the ICU. While different approaches and protocols were expected between the ICUs (Tomlinson et al., 2012), the Network's aim is to reduce these differences, and this increases the probability of success in the implementation of recommendations for the quality improvement of GC, resulting from studies in their ICUs (Mid Trent Critical Care Network, 2011). In addition, studies within a defined geographical area minimise the possible geographical factors influencing clinical practice (Fox, 2003).

Health profile of the study setting

According to the UK Census of 2011, the population of East Midlands was 4,533,000 in 2011, of which 16.1% were aged 65 and over (Office for National Statistics, 2012). During 2012-2013, according to the 31 health indicators that Public Health England (PHE) explores and reports annually about the health of local authorities in England, the health profiles of most of the areas where the GlyCon participating ICUs were located were often significantly worse, on average, than the overall health profile of England (PHE, 2013). This included higher early mortality rates from cancer, heart disease and stroke; higher rates of road injuries with/without death; longer hospital stays for self-harm or alcohol related harm; and higher rates of hip fractures, among others (Table 3.1). Exceptions were East Staffordshire (area where Burton upon Trent is located) and Boston, in which those indicators were often not significantly different from the national figures, on average (PHE, 2013) (Table 3.1).

All areas covered by the GlyCon ICUs also had significantly higher percentages of hospital admissions that were emergencies, as compared to the overall national figures, again except

for East Staffordshire and Boston, where these percentages were significantly lower (PHE, 2013). Finally, the percentage of people with a recorded diagnosis of diabetes on GP registers was significantly lower in Nottingham and Lincoln, and significantly higher in Derby, East Staffordshire, Mansfield and Boston, than overall in England (PHE, 2013) (Table 3.1).

Table 3.1 – Relevant health indicators for 2013 in the local authorities where the ICUs of GlyCon are located, as compared with the average in England. Included are 11 of the 31 health indicators reported by Public Health England annually, which are relevant to this study

INDICATOR	(A)	(B)	(C)	(D)	(E)	(F)	(G)
People diagnosed with diabetes (%)	6.2	5.3	6.5	5.1	6.0	6.8	5.8
Obese adults (%)	25.6	23.6	26.8	22.7	25.7	24.2	24.2
Hospital stays for self-harm (per 100,000 population)	259.3	485.2	203.1	256.2	209.1	328.5	207.9
Hospital stays for alcohol related harm (per 100,000 population)	2290	2241	1805	2398	1805	2416	1895
Hip fracture in 65s and over (per 100,000 population)	459	620	507	567	442	450	457
Excess winter deaths, ratio[a]	17.7	15.6	16.2	18.0	18.0	17.7	19.1
Life expectancy for men (years)	77.9	77.2	78.1	76.2	78.0	78.2	78.9
Life expectancy for women (years)	81.6	81.9	82.0	81.6	83.0	82.5	82.9
Early deaths: heart disease and stroke (per 100,000 population)	69.4	71.9	81.3	83.8	62.9	72.4	60.9
Early deaths: cancer (per 100,000 population)	117.9	131.9	102.3	130.9	111.1	110.1	108.1
Road injuries and deaths (per 100,000 population)	49.0	34.7	53.8	48.7	30.1	40.5	41.9

Significantly worse than the average in England
Significantly better than the average in England
Not significantly different from the average in England

(A) Mansfield
(B) Lincoln
(C) Boston
(D) Nottingham
(E) East Staffordshire (Burton)
(F) Derby
(G) England average

Source: Public Health England (PHE, 2013)

[a] Ratio of excess winter deaths (observed winter deaths minus expected deaths based on non-winter deaths) to average non-winter deaths (PHE, 2013)

General characteristics of the Intensive Care Units

For confidentiality reasons, the hospitals participating in this study will be referred to with their study ID. This ID consisted of the letter H followed by three digits identifying the hospital, with a number ranging from 100 to 700, by hundreds.

All seven ICUs participating in GlyCon, except the ICU of H-100, were combined intensive care with high dependency units (ICU/HDU) that admit both level-3 and level-2 patients (Table 3.2). The ICU from H-100 participating in GlyCon admitted only patients who required level-3 care at some point, as patients requiring only level-2 and level-1 care were admitted to two separate HDUs.

The number of level-3 beds (i.e., beds dedicated to level-3 patients) in each of the seven ICUs ranged from four to 17 beds (Table 3.2). In 2013, the seven ICUs admitted a total of 2923 level-3 patients, ranging from 200 to 946 per ICU. The average [range] number of annual admissions of level-3 patients per level-3 bed in these ICUs was 48 [34-56] (Table 3.2).

All ICUs admitted both medical and surgical patients, except for cardiac surgery patients who are usually admitted to a specialised cardiac ICU, within the Trent Cardiac Centre, covering the Network's geographical area (D. Harvey, personal communication, 2014).

Table 3.2- Number of hospital beds, level-3 beds, and level-3 admissions in 2013 per hospital

Hospital ID	Number of hospital beds	Number of level-3 beds in ICU	Number of ICU level-3 admissions in 2013	Number of annual ICU level-3 admissions per level-3 bed in 2013
H-100[a]	1628[a]	17	946	56
H-200[a]		8	345	43
H-300	1157	11	614	56
H-400	580	6	201	34
H-500	705	8	357	45
H-600	500	5	260	52
H-700	420	4	200	50
Total:	4,990	59	2,923	48 (average)

Main source of information: personal communication with MTCCN Coordinator, 2014.
Source of information on Number ICU level 3 admissions 2013: HSCIC (2013b)
ICU: Intensive Care Unit
[a] The number of hospitals beds for H-100 and H-200 was only available for both hospitals combined.

3.3 Study design

The GlyCon study was comprised of three sub-studies (Figure 3.2):

1) a review and comparison of the protocols for GC implemented in all seven ICUs of the Network;
2) an online survey of professionals from the participating ICUs, about different aspects of GC;
3) a retrospective study based on different types of medical records.

Each sub-study was designed to address at least one of the GlyCon research objectives, and also to complement, expand or help develop the parts of the other sub-studies. This is illustrated in Figure 3.2. A brief description of the methods used in each of the sub-studies of GlyCon is provided below. Full details about each of the methods are provided in the chapters for each of the studies (Chapter 4 to Chapter 6).

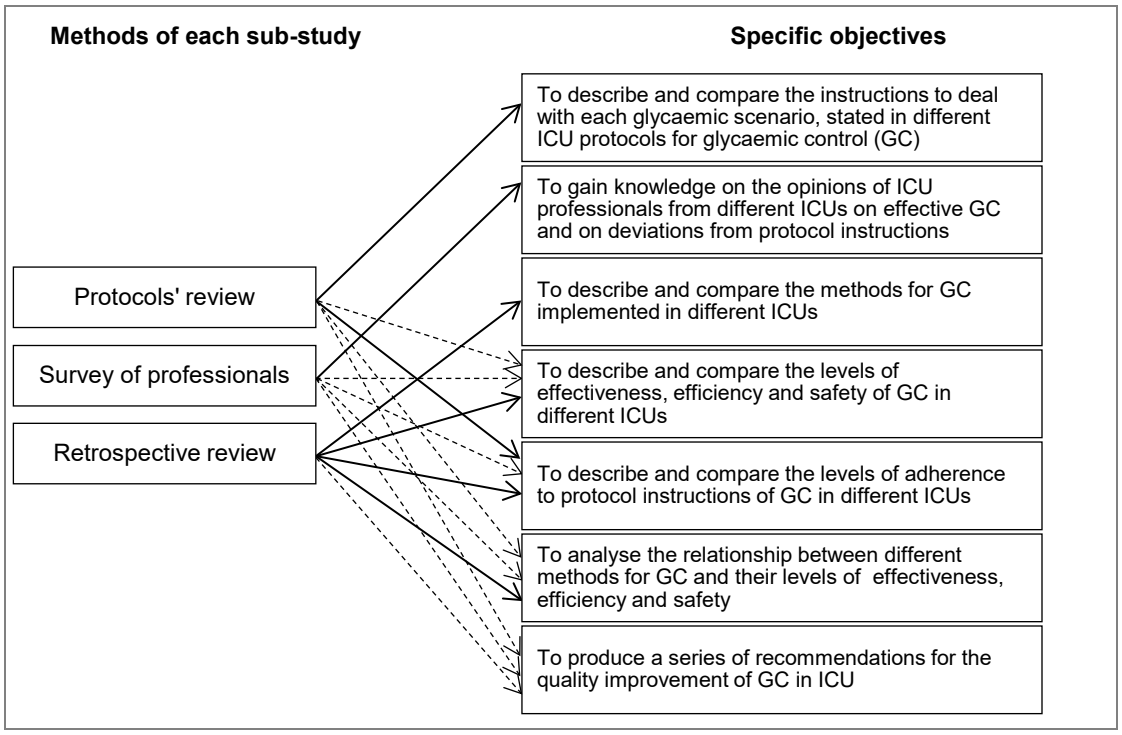


Figure 3.2 – Research methods of the three sub-studies of GlyCon and their relationship with the study specific objectives.
Solid lines represent relationships in which the method provided all or part of the data required to meet the objective. Dashed lines represent relationships in which the method helped with the analysis or interpretation of the data required to meet the objective

3.3.1 Review of protocols

Copies of protocols were gathered from each of the participating ICUs. Data from the protocols were extracted and analysed using techniques of inductive content analysis. Through an open coding process as described in Elo et al. (2008), different categories of instructions for GC, as well as a number of quantitative variables and qualitative themes were identified within each protocol. Each of these categories grouped all the relevant instructions stated in the protocols for the management of each glycaemic scenario. The quantitative variables and qualitative themes identified were used as a framework for the description and comparison of the GlyCon protocols. In the process, a generic method was developed that could be used in similar studies to describe and compare the content of protocols for GC.

The structure and complexity of the protocols were also analysed. For this, protocol flow-charts were built, illustrating all processes and decision steps identified for each possible glycaemic scenario. These were quantitatively analysed and qualitatively described.

3.3.2 Online survey

An online survey for ICU professionals was designed using an online service of the University of Bristol for the design and distribution of surveys. All medical and nursing staff of the GlyCon ICUs were invited to participate via email. The survey included mainly closed questions, organised in four domains, one for socio-demographical data, and three with questions about professionals' views on different aspects of GC. These aspects focused on professionals' opinions on the degree of GC achieved, in terms of the percentage of time that patients may spend within the glycaemic target of the ICU; the management of hypoglycaemia; and the adherence to protocol instructions.

The survey was self-administered, and password protected access was given to professionals via email. Data were analysed descriptively, and associations of the answers with the professionals' role and level of experience were also explored.

3.3.3 Retrospective study

A retrospective review of different types of medical records was carried out with a stratified random sample of 146 patients admitted to the participating ICUs during the study period of interest, which spanned over two years, from 1st January 2012 to 31st December 2013. The records reviewed consisted of both electronic records, such as data from the Case Mix Program of the Intensive Care National Audit and Research Centre (ICNARC), and manual records, including observation charts and medical notes.

The main data collected were relevant data about the methods for GC implemented, primarily in terms of monitoring and treatment with insulin, as well as the outcomes achieved. The study primary outcome measure was the percentage of time that each patient spent with glycaemic levels within 4-10mmol/L (referred to as time in range, TIR), as a measure of effectiveness. In the analyses, this was transformed into the odds of being within the glycaemic range 4-10mmol/L at any time (odds of IR). Other outcomes of interest were a number of metrics of efficiency and safety.

All results were analysed descriptively including summary statistics and graphs. Based on the results of the review of protocols, the levels of adherence to the protocols' instructions were calculated and analysed descriptively. In some instances, associations of the levels of adherence with the primary outcome were also analysed. Associations between the exposure variables and the study outcome measures of interest were explored using generalised estimating equations with autoregressive correlation structure, multiple log-linear regression with heteroskedasticity robust standard errors, as well as some univariate analyses. Results from the review of protocols and the survey of professionals were used in the discussion to complement and help interpret the findings of the retrospective review.

3.3.4 Timelines of data collection and analyses

Data collection for the three sub-studies was carried out in parallel, although the start and end dates of the data collection phases for each of them were different (Figure 3.3). Analyses were carried out sequentially, starting with the review of protocols, followed by the survey and culminating with the retrospective study. The findings from the study as a whole were distilled into a series of recommendations for the quality improvement of GC in ICU, to be disseminated to all the participating ICUs as well as the MTCCN.

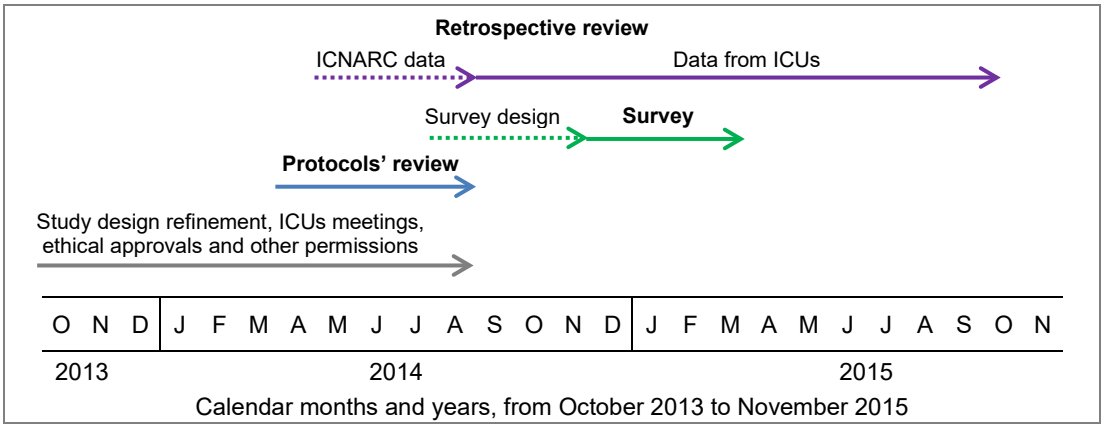


Figure 3.3 – Timeline of the multi-methods study design refinement and data collection of each sub-study.
The dotted green line represents the time of the survey design. The dotted purple line refers to the phase of data requests and related approvals to obtain the part of the study data required from ICNARC

3.3.5 Study management

The GlyCon study was initially presented to the director of the MTCCN, and the study was endorsed by the Network as a study for their Quality Improvement Group. Initial contacts and recruitment of ICUs to participate in GlyCon were carried out through the director of the MTCCN network. Following this, email correspondence and face to face meetings were held with clinicians, including lead medical and nurse clinicians, from all seven ICUs individually. During the meetings, the study was introduced to the ICU teams, and the board of directors of the MTCCN. All units accepted to participate in the study, with at least one clinician in each ICU acting as local collaborator for the study. The local collaborators helped with the provision of access to the ICU, and working space either in the ICU or other parts of the hospitals, as well as with other necessary resources for data collection. Collaborators were instrumental in the invitation to participate in the study survey, and in the distribution of the link and password to access the survey. Also, their support was essential for ethical approvals and other permissions required from relevant bodies (see Section 3.4).

ICU teams of the participating ICUs were involved in the study design, both during the meetings as well as via email correspondence. Their main input included the suggestion of some relevant data to be collected for the study, information about the sources of these data, advice for a smoother performance of the data collection, and the suggestion of the glycaemic range to be used in the primary objective and outcome measure of the study.

3.4 Ethical considerations

Ethical considerations for carrying out the GlyCon study, which were particularly important in the retrospective review study, are detailed in this section.

3.4.1 Retrospective study

While the GlyCon retrospective study was a review of medical data recorded in the past, and contact with patients was not needed, data collection required the access to medical records of patients, which included personal data and sensitive information about their medical history. This was to be carried out by the author of this thesis, who was not an NHS staff member, and seeking informed consent was considered impractical for the study (see Section 3.4.1.1). As a consequence, a number of strict and thorough strategies were required in order to ensure data protection and confidentiality of patients (see Section 3.4.1.2). Before commencement of the study, permissions and approvals for this from all relevant bodies were granted (see Section 3.4.1.3).

3.4.1.1 Informed consent

The following aspects, needed for seeking informed consent to access patients' records, were considered disproportionate to this retrospective study: the difficulty, or even impossibility, of locating and contacting all patients; the high costs and effort needed; the risk of bias (Al-Shahi et al., 2005; McKinney et al., 2005; Jousilahti et al., 2005); and the risk of breaching individuals' privacy. In addition, the British public has been found to be highly supportive of the use of personal medical data in non-commercial medical research that "has no effect on the individuals being studied and has been approved by an accredited research ethics committee" (Peto et al., 2004, p. 1030). Based on these grounds, permission to access personal data without consent was obtained from the UK Health Research Authority, under Section 251 of the NHS Act of 2006 (National Health Service Act 2006). For this, the data protection and confidentiality measures described below were instrumental.

3.4.1.2 Data protection and confidentiality

All study investigators endeavoured to protect the rights of the study patients to privacy, and adhered to the UK Data Protection Act of 1998 (British Parliament, 1998). Personal and medical information in the medical records was treated confidentially in accordance with regulations, held securely, and never shared with third parties. Access to the information was limited to the study staff and investigators, and any relevant regulatory authorities. Data generated as a result of the study were available for inspection on request by the participating collaborators, the University of Nottingham representatives, a NHS Research Ethics Committee, local Research and Development (R&D) Departments of all participating trusts, and the regulatory authorities. This access to the data was restricted by user names and passwords, and encrypted using a one-way encryption method.

Patient identifiers were necessary for sampling purposes of the retrospective study. These included patients' NHS and admission numbers. These direct identifiers were stored in a separate digital file, saved in an encrypted data storage container within a laptop provided by the University of Nottingham. This was separate from the encrypted container where the rest of the study data were saved. The file containing the identifiers was only opened for sampling purposes when records needed to be requested.

Electronically collected data were backed up every 24 hours to both local and remote media in encrypted format. The remote media consisted of a digital folder created within the University of Nottingham dedicated space for research data (called "R drive").

During the data collection for the retrospective study, the requested medical records were held securely, in a locked room or locked cabinet, within the premises of the hospitals.

The author of this thesis attended relevant training courses in data protection and confidentiality (Appendix F), including:

- Short-course on "Introduction to Good Clinical Practice", organised by the National Institute for Health Research, at Nottingham University Hospitals NHS Trust, 4th October 2013;
- Workshop on "Personal data in Research", organised by the Heath Research Authority, Manchester, 1st May 2014;
- Two modules of the Information Governance Training Tool of the Health and Social Care Information Centre, 28th February 2014: "Introduction to Information Governance"; and "Access to information and information sharing in the NHS".

3.4.1.3 Permissions and approvals

The following permissions and approvals were granted before commencement of the study (Appendix E), in chronological order as follows:

1) Permission from the Data Access Advisory Group of ICNARC for ICNARC to produce a data extract from their databases with essential information for GlyCon. This was followed by an application for, and acceptance by, the School of Health Sciences (ScHSc) of the University of Nottingham to cover the costs for the production of ICNARC data extract.
2) Waivers of confidentiality signed by each of the ICU designated consultants for ICNARC to provide with patient identifiable data.
3) Approval from The Research Governance Team of the University of Nottingham for the University to act as Research Sponsor of the study. This required prior application for a research passport, and preparation of a University laptop with two encrypted spaces for data collection and storage.
4) Permission from the Confidentiality Advisory Group (CAG) of the Health Research Authority to access personal data without consent, under Section 251 of the NHS Act 2006 (*National Health Service Act 2006*). This required prior training of the author of this thesis on data protection and confidentiality issues, and the completion of the CAG Information Governance toolkit by the University of Nottingham.
5) Approval by a NHS Research Ethics Committee.
6) Permissions from the R&D Departments of each of the participating NHS Trusts, which issued a "letter of access" allowing the author of this thesis to access and use NHS premises and pre-specified resources for research purposes described in the application.

Figure 3.4 outlines the time-lines for each of the applications, from start of the applications until the permission was granted.

Task Name	Start	Finish
ICNARC approvals and data production	**Mon 13/01/14**	**Fri 15/08/14**
ICNARC DAAG approval	Mon 13/01/14	Mon 03/02/14
ScHSc agreement to cover costs	Mon 03/02/14	Wed 19/02/14
ICNARC waivers of confidentiality	Wed 19/03/14	Tue 27/05/14
ICNARC data extract production	Fri 07/03/14	Fri 15/08/14
University Sponsorship and other procedures	**Fri 06/12/13**	**Tue 08/07/14**
Research passport	Fri 06/12/13	Tue 21/01/14
ScHSc Laptop prepared by MHS IT	Mon 20/01/14	Mon 10/03/14
University Sponsor Approval	Tue 11/03/14	Wed 09/04/14
CAG IG toolkit completed by the University	Tue 04/03/14	Tue 08/07/14
CAG approval	**Wed 09/04/14**	**Thu 10/07/14**
CAG of the HRA approval	Wed 09/04/14	Thu 10/07/14
REC approval	**Wed 09/04/14**	**Thu 12/06/14**
REC approval (conditional to CAG)	Wed 09/04/14	Thu 12/06/14
R&Ds Approvals	**Thu 10/04/14**	**Fri 31/10/14**
NUH R&D approval and LoA	Thu 10/04/14	Fri 11/07/14
Derby Hospital R&D approval and LoA	Thu 10/04/14	Wed 30/07/14
KM Hospital R&D approval and LoA	Thu 10/04/14	Thu 07/08/14
Burton Hospital R&D approval and LoA	Thu 10/04/14	Fri 31/10/14
ULHT R&D approval and LoA	Tue 22/04/14	Wed 30/07/14

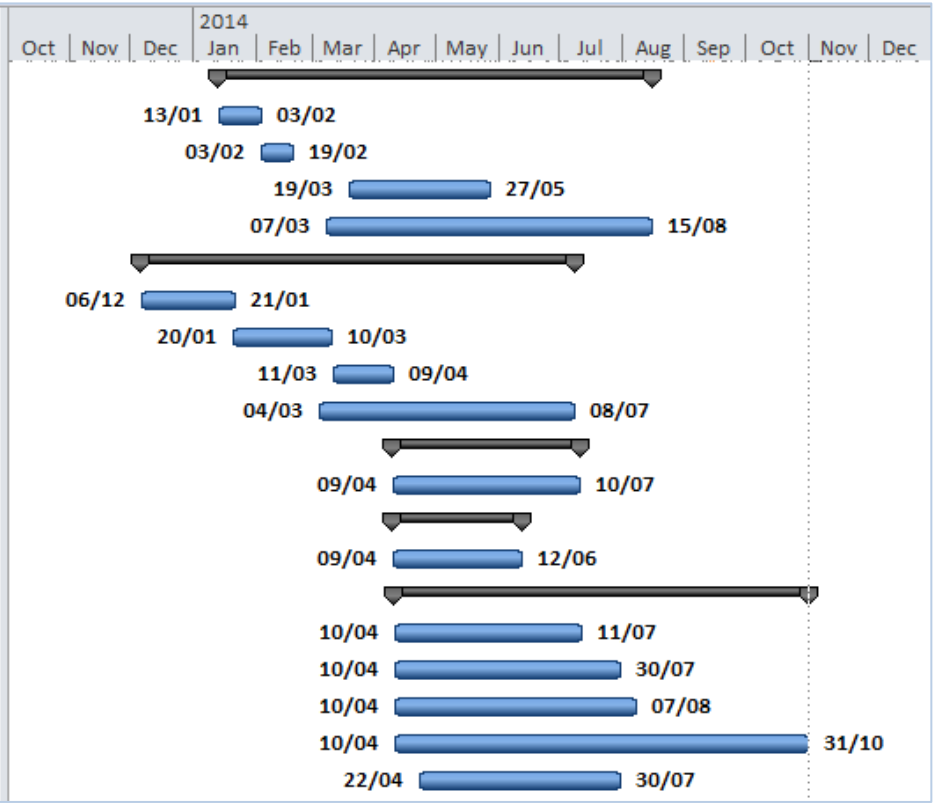


Figure 3.4 - Gantt-chart showing the timelines for relevant applications for approvals and permissions to carry out the study.
ICNARC: Intensive Care National Audit and Research Centre; DAAG: data access advisory group ; ScHSc: School of Health Sciences; CAG: confidentiality advisory group; IG: information governance; HRA: health research authority; REC: research ethics committee; LoA: letter of access

3.4.2 Protocols review and online survey

3.4.2.1 Informed consent and participant information

Informed consent and participant information did not apply to the protocols' review.

Professionals responding to the survey were told that participation was not obligatory, but by completing the survey they were consenting to their responses being used for research purposes. The introductory page of the online survey reminded participants that their answers would be held anonymously and securely, and that no personal data would be requested.

3.4.2.2 Permissions and approvals

Of the permissions and approvals listed in Section 3.4.1.3, number (3) was also granted for the review of protocols and the online survey; and numbers (5) and (6) were also required and granted for the survey study.

3.5 Justification of methodology

GlyCon study had one main aim and a number of specific objectives. While these objectives were closely inter-related and complementary, they could not be answered with a single type of study, and hence a multi-methods study was required.

The review of protocols provided essential information about what professionals recommended for the management of GC in each ICU. Given the lack of previous content analyses of these types of protocols, an inductive content analysis was instrumental as it allowed to systematically extract categories or concepts based on recorded data (Phil, 2008; Hsieh & Shannon, 2005).

The survey to professionals provided influential information about how professionals view the management of GC in the ICU. The aim was not to gain an in depth knowledge about professionals' perceptions, but rather to explore their opinions on the aspects of GC, which would be investigated in the subsequent retrospective review. As a PhD study with limited resources and a finite timeframe, a short survey was considered sufficient for this aim. The survey was carried out via an online platform, rather than face-to-face, in order to be able to reach the large and widely spread population (Evans & Mathur, 2005). In addition, it was short and included mainly closed questions in an attempt to increase the response rate (Evans & Mathur, 2005).

The main aim of GlyCon study was to investigate the impact of the actual clinical practice of GC of stress hyperglycaemia in critically ill patients. Findings from a RCT, which is ranked as the study with the highest level of evidence (OCEBM Levels of Evidence Working Group, 2013), can inform about the efficacy of an intervention in strictly controlled conditions. However, RCTs say little about the effectiveness of such clinical practice in real life situations. Study designs that allow for the investigation of actual clinical practice are observational studies. These can be conducted prospectively, or retrospectively. Awareness of their participation in a prospective study could have influenced the practice of ICUs, and hence biased the results. Since the main aim of GlyCon was to investigate the effectiveness of GC in real life settings, a retrospective study was considered to be the best study design to serve this purpose.

Chapter 4
Description and comparison of protocols for glycaemic control in ICU

4.1 Background

Clinical protocols can be defined as a set of steps that need to be taken to care for and treat a patient in particular circumstances (NHS Institute for Innovation and Improvement, 2008a). The aim of a protocol is to standardise the care that is delivered locally (Kavanagh & Nurok, 2016).

Currently, available evidence about ideal glycaemic target ranges in critically ill patients with stress hyperglycaemia, and the safest and most effective methods of glycaemic control (GC) to achieve these, is discrepant and conflicting (NICE-SUGAR Study Investigators et al., 2009; Preiser et al., 2009; Chase, Shaw, et al., 2008; Brunkhorst et al., 2008; Van den Berghe et al., 2001). International and national guidelines for the GC of critically ill patients have not yet been standardised and their recommendations differ among each other (Figure 2.1). Consequently, hospitals put in place their own locally developed protocols, and such protocols for GC are very numerous and varied, differing not only between countries (Wilson et al., 2007) but also between hospitals within the same country (Niven et al., 2015; J. Orban et al., 2013; Tomlinson et al., 2012; Paddle et al., 2011; Cook et al., 2009; Mackenzie et al., 2005). This can lead to inequitable access to healthcare across hospitals, and avoiding such inequities is amongst the commitments and responsibilities of NHS employees, as stated in the NHS Constitution of 2015 (Department of Health, 2015).

The studies cited above, which describe and compare protocols for GC, found important differences between these protocols. However, these studies dealt with general descriptions of the protocols' instructions, and most of them focused mainly on the protocols' insulin algorithms. There is a lack of studies that report detailed descriptions and comparisons of each of the GC instructions for each pre-specified glycaemic range, in the protocols of different intensive care units (ICU). Such studies ought to show the differences, if any, among the recommendations provided by different ICU protocols to deal with the same situation or scenario. In order to make these analyses comprehensive and comparable across

hospitals and internationally, a standardised, replicable and globally transferable method is required. This would allow for systematic descriptions and comparisons in future studies exploring the contents of ICU protocols for GC. At the time of GlyCon design, such a standardised method was not available.

Based on these grounds, the GlyCon study aimed to explore and compare each of the specific instructions for the management of stress hyperglycaemia, as stated in the protocols for GC of the seven participating ICUs belonging to the Mid-Trent Critical Care Network (MTCCN). For this, a specific method for the systematic qualitative and quantitative description and comparison of the protocols' contents was developed. The aim was for this method to be comprehensive, as well as flexible, so that it could be used in future studies with the same objectives, in a meaningful way.

4.2 Methods

4.2.1 Sample of ICUs and data sources

A purposive sample of the seven ICUs of the MTCCN that admit level-3 critically ill patients was recruited. Further details about the justification for the choice of this sample, the recruitment method and the characteristics of the ICUs can be found in the overall methodology chapter (Chapter 3). Soft copies of the protocols for GC, which had been in place in the participating ICUs during 2012 and 2013, were gathered from each of the participating ICUs.

4.2.2 Data extraction and analyses

In this study, the protocols for GC were the sources of data, whereas the data to be extracted (collected) were the contents of these protocols. Data extraction and analyses were carried out using techniques of inductive content analysis. Quantifiable data extracted through such analyses were also summarised using descriptive statistical analyses. Content analysis has been defined as a research method "used to determine the presence and meaning of concepts, terms, or words in one or more pieces of recorded communication" (Stan, 2010). Inductive content analysis is a type of content analysis through which concepts or categories of data and theories are systematically generated based on recorded data (Phil, 2008; Hsieh & Shannon, 2005). As opposed to deductive content analysis, inductive content analysis is not based on pre-conceived categories of data. Instead, the categories of data or themes emerge directly from the empirical text data (Phil, 2008; Hsieh & Shannon, 2005).

Protocol variables and themes

The selected units of analysis were each of the sentences, or clauses within sentences, written within the protocols. Through an open coding process as described by Elo & Kyngäs (2008), a heading or category was assigned to each unit of analysis, by writing notes in the margin of the protocols' text. The inferred categories were then used to code subsequent units of analysis. Two outputs were obtained:

1) different categories and sub-categories of the data provided within each protocol of the participating ICUs (see Section 4.3.1); and
2) a list of variables and themes for the structured and systematic extraction of qualitative and quantitative data provided in the protocols for GC (Appendix A).

Subsequently, the list of variables and themes were populated with the information pertaining to the GC protocols from the seven participating ICUs (see Section 4.4.1). These tables provided a clear and concise set of information that formed the basis for the descriptive and systematic comparison of the protocols (see Sections 4.4.1 to 4.4.7). Bar charts and box plots were used to illustrate the distribution of categorical and numerical data, respectively.

Protocol flow-charts

In addition to the tables of variables and themes, detailed flow-charts of the instructions contained within the protocols for GC were compiled. For this, a distinction was made between "processes", "decisions" and "scenarios" within the protocols. A process referred to any activity that should be carried out for the management of a patient's glycaemic status. A decision referred to any situation that would require thinking and judging what process should be carried out. For example, conditional instructions, such as "the insulin infusion may need to be modified after 12 hours *if* blood glucose levels are unstable", were considered as decision steps. A scenario referred to a possible loop comprising a sequence of processes and decisions.

In order to extract the information required to compile the protocol flow-charts, each of the glycaemic ranges considered by the protocol was identified. Subsequently, all the instructions dealing with each of these glycaemic ranges, for any given glycaemic measurement, were identified and classified as either a process or a decision. Finally, these processes and decisions were depicted schematically in closed-loop flow-charts, in a way that each loop (scenario) started and finished with a glycaemic measurement. Processes were represented with a rectangle and decisions were represented with a diamond, following the International Organization for Standardization (ISO) 5807 norm (ISO, 1985). The resulting flow-charts provided a graphical representation of the complexity and comprehensiveness of

the protocols (see Section 4.3.2 and Appendix B). The possible scenarios and the processes and decisions contained within each scenario, were counted and grouped by type of instruction, so that they could be analysed with descriptive statistics using counts, medians and ranges (see Section 4.4.8).

Finally, the structure of each protocol was analysed, based on its length and how detailed it was. For this, the total number of words per protocol, and the average number of words per page were calculated. Also, each protocol was classified, depending on its level of detail, into either a chart-type protocol, such as insulin sliding scale charts, or a protocol with detailed written descriptions of the instructions (see Section 4.4.8).

4.3 Development of a method for the review of protocols for glycaemic control

As stated above, the outcomes of the inductive content analysis through open coding were two generic tables containing lists of quantifiable variables and non-quantifiable themes that could be present in a protocol, as well as a technique for condensing a protocol into a single, comprehensive flow-chart from which the complexity and completeness of the protocol can be assessed. This section describes the iterative process that led to those two outcomes, which involved a number of rounds of data extraction and data analysis.

4.3.1 Protocol variables and themes

The two broadest categories of data that were identified in the protocols were the method used to develop the protocols, and the instructions for GC contained within the protocols (Figure 4.1). The data category relating to the protocol development included metadata about when, how and by whom the protocol was developed, as well as the evidence on which the protocol was based, and for which target patients it was meant to be used. These could be either quantifiable characteristics or non-quantifiable features of the protocols.

The protocol instructions were first divided into five sub-categories based on the aim of the instruction. These included diagnostic, monitoring, treatment, organisational and mixed instructions (Figure 4.1). Diagnostic instructions referred to those instructions related to the definition of the glycaemic status of the patient. Monitoring instructions referred to any indications on how or when BG should be monitored. Treatment instructions included any written directions on the administration of insulin, other medication or glucose solutions with the aim of affecting BG levels. Organisational instructions were indications related to the

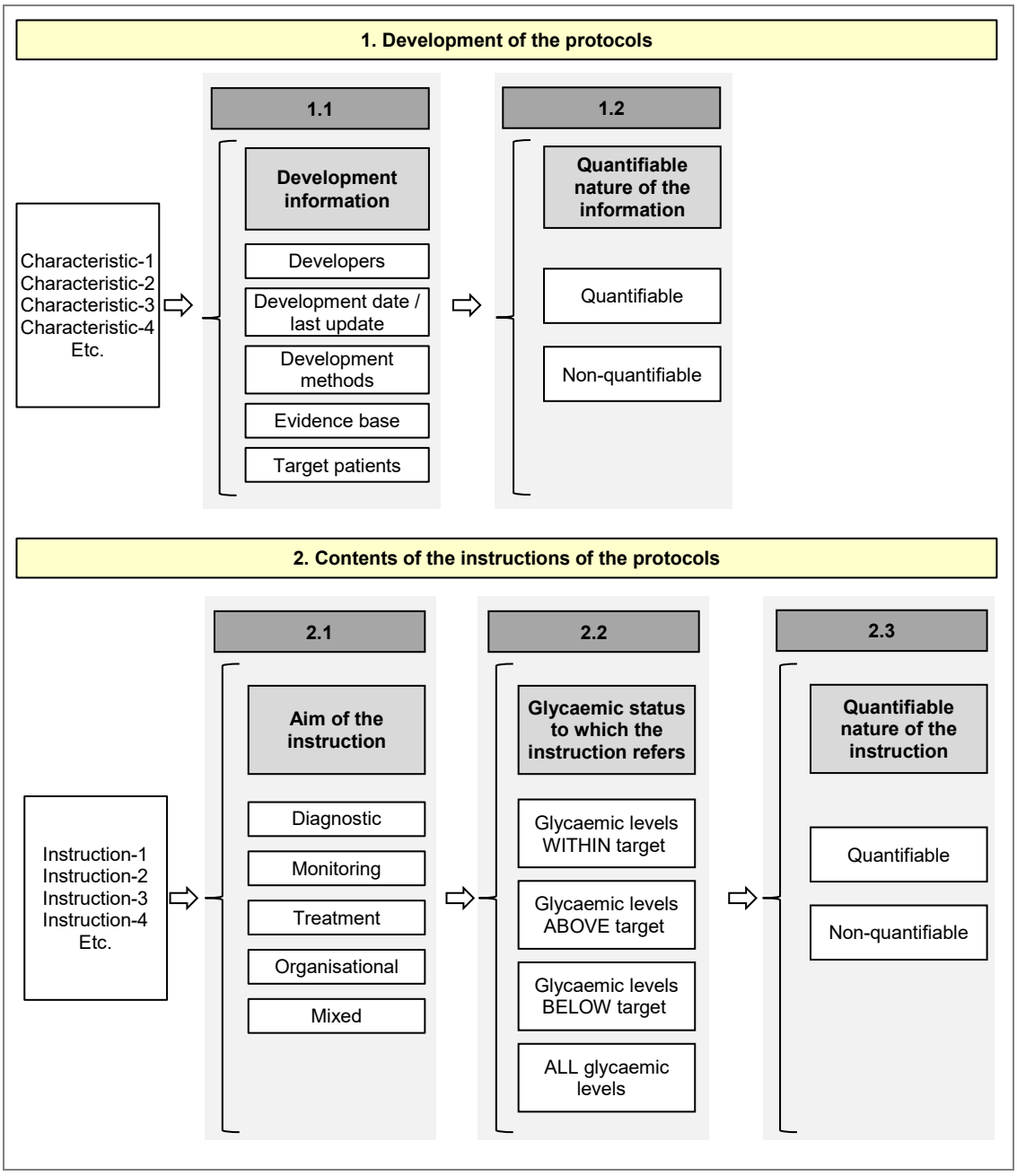


Figure 4.1 - Classification process of the broadest categories of data that were identified in the protocols: (1) development of the protocols; (2) contents of the instructions of the protocols

organisation of the ICU team, division of roles, or administrative activities, related to the management of GC in the ICU. Instructions that could be classified in more than one category were considered as mixed type of instructions.

Each of the five sub-categories of instructions was further divided into four sub-categories, depending on the glycaemic status to which the instructions related. These included instructions relevant to BG levels below, within or above the protocol's glycaemic target range, as well as a fourth category for instructions that were relevant at all glycaemic levels (Figure 4.1). All the sub-categories of instructions were finally classified as quantifiable data

(instructions that could be counted or transformed into categorical variables) or non-quantifiable information.

The following are some examples of this coding:

- "Consultation process: Senior ICU nursing staff and cross-town guidelines group", coded as: Development of the protocols → developers → non-quantifiable.
- "Date of submission: 01/07/2012. Date on which guideline must be reviewed: 01/09/2015", coded as: Development of the protocols → development date / last update → Non-quantifiable → Based on this information the numerical variable 'number of years since the last update' was generated.
- "Blood gas and glucometer readings are both acceptable", coded as: Monitoring instruction → relevant at any glycaemic level → non-quantifiable → based on this instruction the categorical variable 'preferred method for BG monitoring (blood gas analyser / glucose meter / laboratory)' was generated.
- "If BG is >20mmol/L, administer 8 units of insulin and call medical staff", included two clauses describing two instructions:
  - "Administer 8 units of insulin", coded as: Treatment instruction → relevant to the glycaemic status above the BG target → quantifiable.
  - "Call medical staff", coded as: Organisational instruction → relevant to the glycaemic status above the BG target → non-quantifiable → based on this instruction the categorical variable 'calling medical staff if severe hyperglycaemia is instructed (yes/no)' was generated.

The 35 quantifiable variables and 11 themes identified thought the open coding process are listed in Appendix A. The results of using these variables and themes for the descriptions and comparisons of the GlyCon protocols are included in Section 4.4.

4.3.2 Protocol flow-charts and scenarios

The flow-charts obtained by applying the procedure explained in Section 4.2.2 to the protocols in this study, are included in Appendix B. Figure 4.2 shows an example of the resulting flowchart for one of the protocols. Figure 4.3 illustrates how the scenarios, processes and decisions were identified from each flow-chart, for their quantitative description and classification. The results of these descriptions and comparisons are included in Section 4.4. In any protocol, decision steps always added at least one more scenario to the flow-chart analysis. Therefore, the more decision steps a protocol had, the more the number of scenarios that had to be considered.

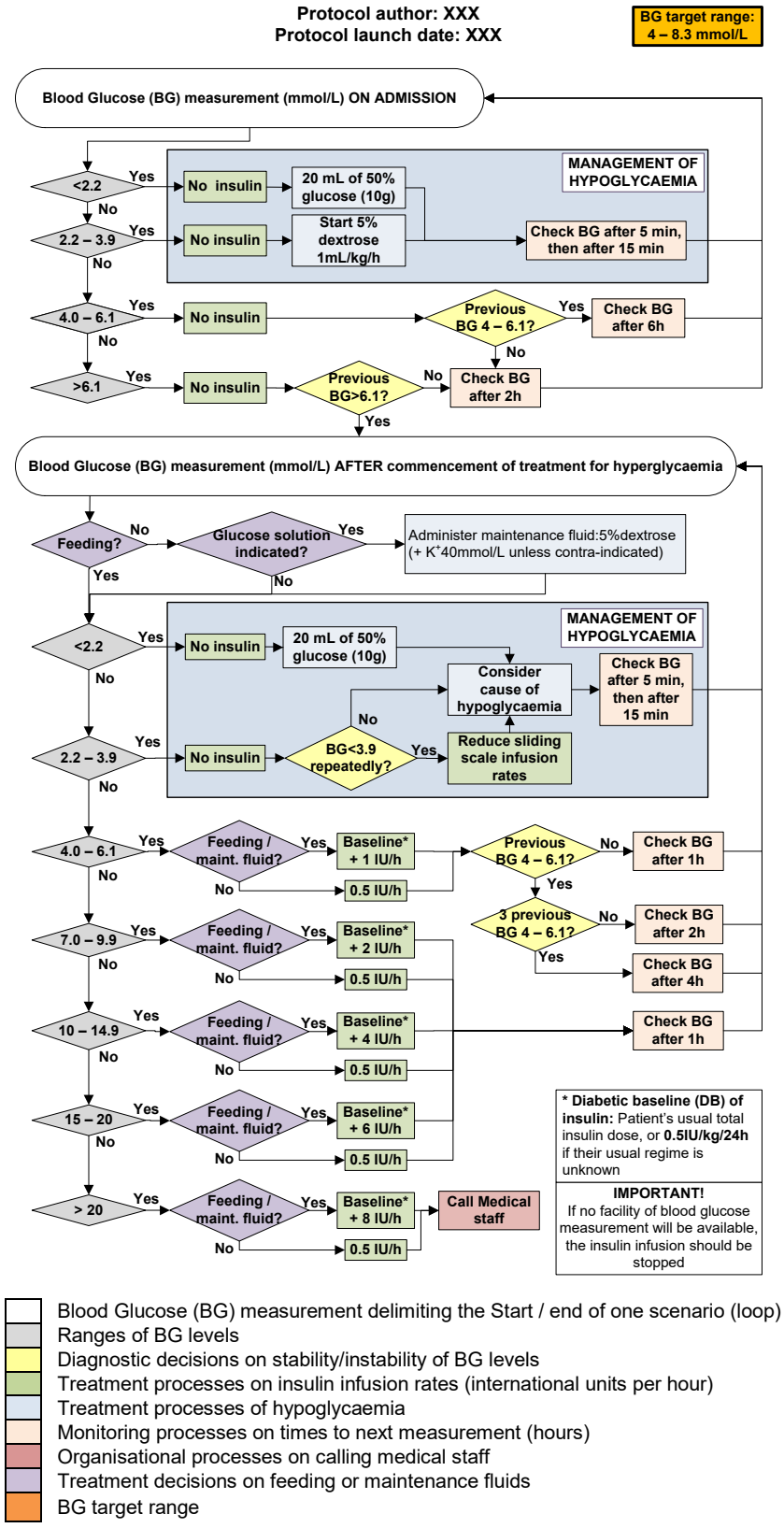


Figure 4.2 – Example of one of the resulting flowchart of protocol instructions. BG stands for blood glucose; IU stands for international units of insulin

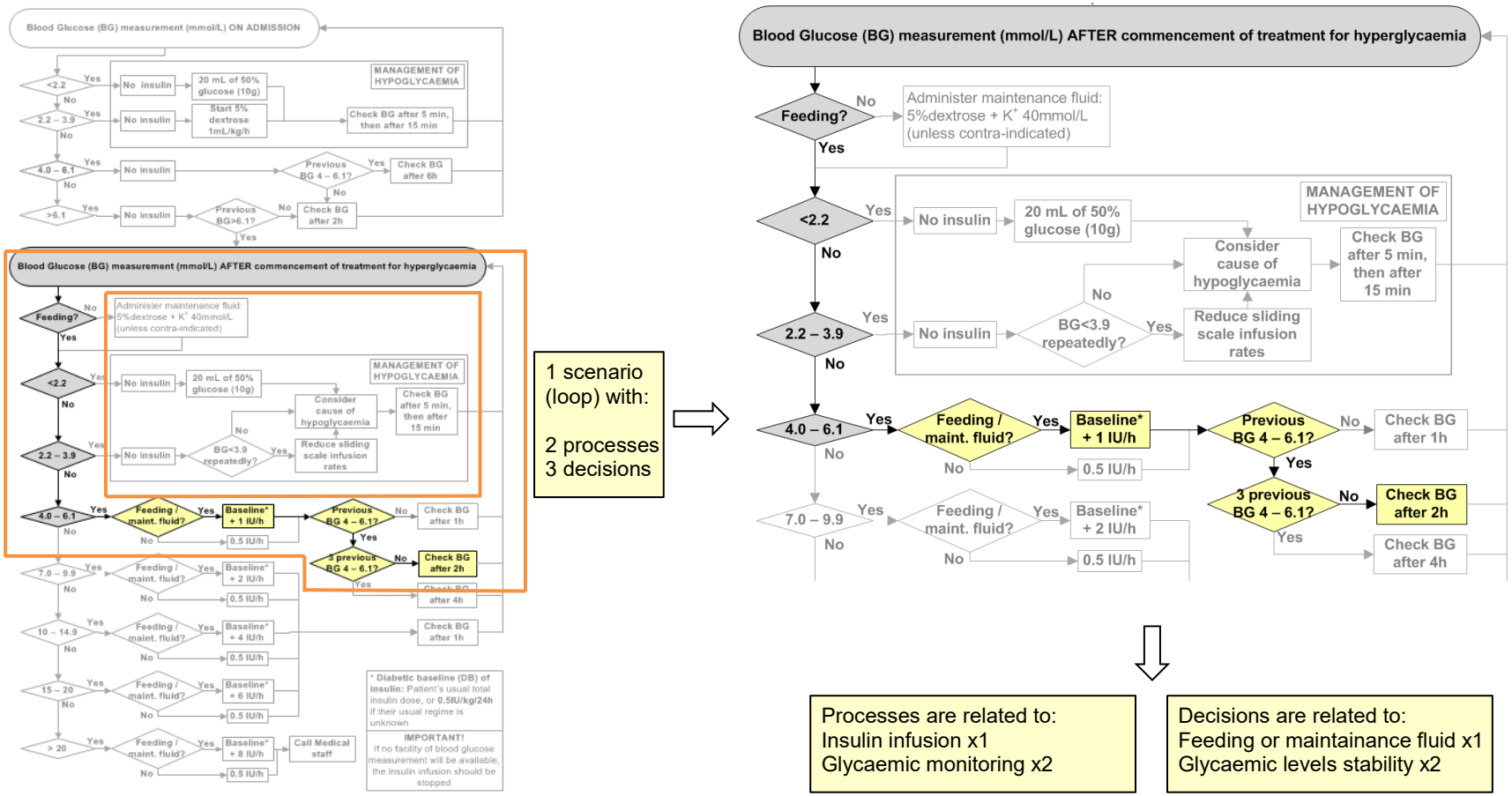


Figure 4.3 – Example of the scenario analysis of protocol flowcharts, identifying numbers and types of scenarios, processes and decisions. BG stands for blood glucose; IU stands for international units of insulin

4.4 Results of the review of protocols

In this section, the results of the description and comparison of the protocols, using the methodology developed, are presented. These include the results of the development characteristics of the protocols; the findings on the diagnostic, monitoring, treatment and organisational instructions, based on the relevant quantitative variables and qualitative themes identified; and the scenario analyses of the protocols, based on the quantitative and qualitative analysis of the flowcharts previously developed. Also, due to their relevance for GC, the management of hypoglycaemia as well as the differences in the management of patients with diabetes, are described in separate sub-sections.

4.4.1 Development of the protocols

Two of the seven ICUs (H-100 and H-200) shared the same clinical protocols. These two ICUs changed their protocol for GC in July 2012, which was during the period of interest of GlyCon study (January 2012 to December 2013). In addition, these two ICUs, together with a third ICU had different instructions for the GC of patients with diabetes (H-100, H-200 and H-500).

For the purpose of this study, the instructions for patients with diabetes were studied separately, and considered as a different protocol. As a result, a final sample of 10 protocols was included in this study as illustrated in Figure 4.4. As for hospitals, for confidentiality reasons, protocols will be referred to by their study ID, as listed in Table 4.1 and Figure 4.4.

Since some hospitals implemented more than one protocol, a new variable called protocol-hospital was generated to describe together the hospital of admission and the protocol implemented. For example, protocol P-1.1 in hospital H-100 corresponded to protocol-1.1_hospital-100 or P-1.1_H-100. The resulting 14 categories of protocol-hospital are listed in Table 4.1.

Four of the protocols (P-1.1, P-2.1, P-1.2 and P-2.2) mentioned explicitly that they should be regarded just as a guide in clinical practice, and that their interpretation and application should remain the responsibility of the attending physician.

Three protocols (P-1.2, P-2.2 and P-3) included information about how and by whom they were developed. All three involved ICU consultants and nurses, and consultation of topic experts. The remaining protocols did not provide this information (Table 4.1).

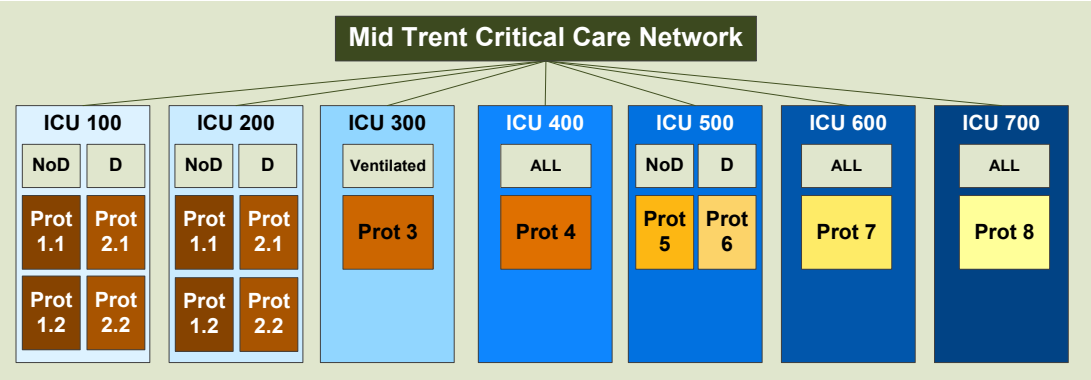


Figure 4.4 – Distribution of protocols in each ICU.
ICUs 100 and 200 shared all protocols, they changed their protocols during the study period of interest (from P-x.1 to x.2), and they had different protocols for patients with diabetes (P-2.x).
ICU 500 had a different protocol for patients with diabetes (P-6).
NoD stands for protocol targeting patients without diabetes and, in P-1.1, patients without total resection of the pancreas; D stands for protocol targeting patients with diabetes and, in P-2.1, patients with total resection of the pancreas.

All protocols except P-7 and P-8 specifically mentioned the evidence base behind their instructions, including recommendations from relevant societies and/or scientific papers. These included: Leuven studies in four protocols (P-1.1, P-2.1, P-5, P-6); Surviving Sepsis Campaign of 2004 in three protocols (P-1.1, P-2.1, P-3); Surviving Sepsis Campaign of 2012 in two protocols (P-1.2, P-2.2); and NICE SUGAR trial in three protocols (P-1.2, P-2.2, and P-4). During the study period of interest, P-1.1 and P-2.1 were replaced by P-1.2 and P-2.2 respectively, with the newer protocols including more recent evidence.

4.4.2 Diagnostic instructions

The protocol instructions relating to the diagnosis of the different glycaemic levels are summarised in Table 4.1 and illustrated graphically in Figure 4.5. These are described in the following sub-sections.

4.4.2.1 Glycaemic target range

In this chapter the upper and lower limits of the glycaemic target will be referred to as UL and LL, respectively. Glycaemic targets were defined as ranges in seven protocols (P-1.1, P-1.2, P-2.1, P-2.2, P-5, P-6 and P-8), and varied between 4-6mmol/L and 4-10mmol/L. Two of the remaining protocols mentioned a UL (8.3mmol/L in P-3, and 10mmol/L in P-4) but no LL. The remaining protocol, P-7, did not include a BG target, but the local collaborators of GlyCon study at the relevant ICU communicated that two consecutive BG measurements of 10mmol/L or more would trigger the commencement of the protocol for GC (D. Connolly, personal communication via email, 2014).

Table 4.1 – Description and comparison of the 10 protocols for glycaemic control participating in GlyCon using quantitative variables

		Protocol ID	1.1	1.2	2.1	2.2	3	4	5	6	7	8
		Hospital or ICU ID	100, 200	100, 200	100, 200	100, 200	300	400	500	500	600	700
		Protocol-Hospital ID	P1.1_H100, P1.1_H200	P1.2_H100, P1.2_H200	P2.1_H100, P2.1_H200	P2.2_H100, P2.2_H200	P3_H300	P4_H400	P5_H500	P6_H500	P7_H600	P8_H700
Gl. Status	Inst. Aim	Target patients (Pts)	All except if diabetes	All except if diabetes or TRP [p]	Pts with diabetes	Pts with diabetes or TRP [p]	Ventilated Pts	All	All except if diabetes	Pts with diabetes	All	All
WITHIN glycaemic target	D	Upper limit of glycaemic target range (mmol/L)	8.3	10	8.3	10	8.3	10	6.1	6.1	NM (10) [k]	8
	D	Lower limit of glycaemic target range (mmol/L)	4	4	4	4	NM	NM	4	4	NM	6
	M	Minimum time to next measurement (TNM) if within target ≥4h	1	1	1	1	1	1	1	1	1 [l]	1
	M	Maximum TNM if within target for ≥4h (h)	4	4	4	2	4	4	1	1	2 [l]	4
	T	Minimum Insulin Infusion Rate (IIR) if within target ≥4h (U/h) [a]	0	0	0.5	0	1	1	0	1	1 [m]	0.5
	T	Maximum IIR if within target for ≥4h (U/h)	2	0	4.5 (hyp.)[j]	0	2	2	NA [n]	NA [n]	NA [o]	NA [n]
ABOVE glycaemic target	O	Is there a threshold within hyperglycaemia indicating when to inform medical staff?	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
	X (D+O)	Glycaemic threshold, within hyperglycaemia, indicating when inform medical staff (mmol/L)	20	18	20	18	17	20	NM	NM	NM	NM
	M	Minimum TNM if above target (h)	1	1	1	1	1	1	1	1	1 [l]	1
	M	Maximum TNM if above target (h)	1	1	1	1	1	1	1	1	2 [l]	2
	T	Minimum IIR if above target (U/h)	0	1	0.5	2	2	4	0.5	1	1 [m]	0.5
	T	Maximum IIR if above target for ≥4h (U/h)	8	4	12.5(hyp.)[j]	5	4	6	NA [n]	NA [n]	8 [o]	NA [n]

Table 4.1 Continued

BELOW glycaemic target	O	Is there a hypoglycaemic threshold (i.e., threshold within hypoglycaemia), indicating when to inform medical staff?	No	Yes	No	Yes	No	Yes	No	No	No	Yes
	X (D+O)	Hypoglycaemic threshold indicating when to inform medical staff (mmol/L)	NM	4	NM	4	NM	2.5	NM	NM	NM	3
	X (D+T)	(Hypo)glycaemic threshold triggering the administration of rescue glucose always (mmol/L)	2.2	2.2	2.2	2.2	3	2.4	2.1	2.1	3	2.9
	M	Minimum TNM if severe hypoglycaemia [b] (h)	0.08	<0.25	0.08	<0.25	<0.25	0.5	<0.25	<0.25	1	<0.5
	M	Maximum TNM if severe hypoglycaemia (h)	0.25	0.25	0.25	0.25	0.25	0.5	0.25	0.25	1	0.5
	T	Minimum IIR if severe hypoglycaemia (U/h)	0	0	0	0	0	0	0	0	0.5	0.5
	T	Maximum IIR if severe hypoglycaemia (U/h)	0	0	0	0	0	0	0	0	0.5	0.5
	T	Minimum dose of rescue glucose if severe hypoglycaemia (grams, g)	10	10	10	10	10	10	10	10	NM	10
	T	Maximum dose of rescue glucose if severe hypoglycaemia (g)	10	16	10	16	10	10	10	10	NM	10
GENERAL INSTRUCTIONS / CHARACTERISTICS	X (D+T)	Glycaemic threshold triggering the start of insulin infusion (mmol/L)	4	10	4	6	4	3.9	3.9	3.9	0	0
	M	Preferred monitoring method [c]	BGA/GM	BGA	BGA/GM	BGA	BGA/GM	NM	BGA/GM	BGA/GM	GM	NM
	M	Preferred monitoring blood sample [d]	NM	A	NM	A	NM	NM	NM	NM	C	NM
	T	Preferred insulin type [e]	FA	FA	FA	FA	FA	FA	FA	FA	FA (+ B)	FA
	T	Preferred insulin administration route [f]	IV	IV	IV	IV	IV	IV	IV	IV	IV (+SC)	IV
	T	Insulin titration method during admission [g]	F	F	F	F	F	F	A	A+B	F	A
	T	Treatment actions depending on underlying condition/s and/or severity [h]	C	NM	C	NM	NM	C	C	C	NM	NM
	T	Treatment actions if on other medication [h]	C	C	C	C	NM	C	C	C	NM	NM
	T	Treatment actions if no feeding / glucose-based maintenance fluid [i]	Stop	Stop	Reduce	Stop	Stop	Stop	Stop	Reduce	Stop	Stop

Table 4.1 Continued

GEN. INSTRUCTIONS / CHARACTERISTICS	O	Is management after ICU discharge mentioned?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
	P	Are protocol development methods mentioned?	No	Yes	No	Yes	Yes	No	No	No	No	No
	P	Are protocol developers mentioned?	No	Yes	No	Yes	Yes	No	No	No	No	No
	P	Is protocol evidence base mentioned?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
	P	Launch date / date of last update	2007[q]	2012	2007[q]	2012	2005	2009	2001	2001	2012	NM

Gl. Status: glycaemic status; Inst. Aim: instruction aim; Pts: patients; TRP: total resection of the pancreas; NM: not mentioned; NA: not applicable; hyp: hypothetical

[a] All insulin infusion rates of intravenous fast-acting insulin in International Units per hour (U/h)

[b] Severe hypoglycaemia defined as a random blood glucose measurement ≤2.2mmol/L or symptomatic hypoglycaemia

[c] BGA: Blood Gas Analyser / GM: Glucose Meter / L: Laboratory / NM: Not Mentioned

[d] A:Arterial / V:Venous / C:Capillary / Not Mentioned

[e] FA: Fast-acting / FA+B: Fast-acting + Basal / Not mentioned

[f] IV: Intravenous / SC: Subcutaneous / IV + SC: IV for fast-acting insulin and SC for basal insulin (if applicable) / NM: Not mentioned

[g] F: fixed rates of fast-acting insulin / A: adjustments of previous rates of r fast-acting insulin / A+B: adjustments of previous rates of fast-acting insulin + basal insulin

[h] DI: Different insulin infusion rate / DMF: Different monitoring frequency / C: Mentioned as an aspect that should be considered / NM: Not mentioned

[i] Stop: stop insulin infusion / Reduce: reduce insulin infusion / NM: Not mentioned

[j] Besides the sliding scale recommended IIRs, P-2.1 recommends a fixed baseline IIR per hour, calculated with the formula 0.5*weight(kg)/24(hours). For this protocol, the highest IIRs in each glycaemic status was estimated based on a hypothetical 120kg adult.

[k] Protocol 7 did not have a glycaemic target specified in the protocol. In brackets is the glycaemic levels that local collaborators communicated as the "informal" threshold levels that triggered the commencement of the protocol if they were obtained in two consecutive measurements

[l] For protocol 7 (without a glycaemic target specified) the minimum and maximum TNMs included in sections "WITHIN" and "ABOVE" target are those recommended at "any time" except when the patient has severe hypoglycaemia

[m] For protocol 7 (without a glycaemic target specified), the minimum IIRs included in sections "WITHIN" and "ABOVE" target are the lowest IIRs recommended when patient is above its (hypo)glycaemic threshold (3mmol/L)

[n] For protocols 5, 6, 8 (with IIRs are adjusted based on previous rate) it is not possible to calculate maximum IIRs in sections "WITHIN" or "ABOVE" target

[o] For protocol 7 (without a glycaemic target specified), the maximum IIR in section "WITHIN" target cannot be calculated. The maximum IIR in section "ABOVE" target is the highest IIR recommended by the protocol

[p] Patients treated with insulin for hyperkalaemia, or those for whom it had been decided that only conservative management or palliative care was appropriate were excluded

[q] Protocols P-1.1 and P-2.1 were replaced by protocols P-1.2 and P-2.2, respectively, in 2012

4.4.2.2 Hyperglycaemia and severe hyperglycaemia

For the purpose of this study, glycaemic values above the protocols' glycaemic target ranges or thresholds are referred to as "hyperglycaemia". The hyperglycaemic values above which a protocol recommended that medical staff were informed, were considered as severe hyperglycaemic events. Six of the ten protocols (P-1.1, P-1.2, P-2.1, P-2.2, P-3 and P-4) specifically stated the need to inform medical staff when BG levels were above a particular threshold, while others did not mention this. These thresholds ranged from 17 to 20mmol/L (Table 4.1 and Figure 4.5).

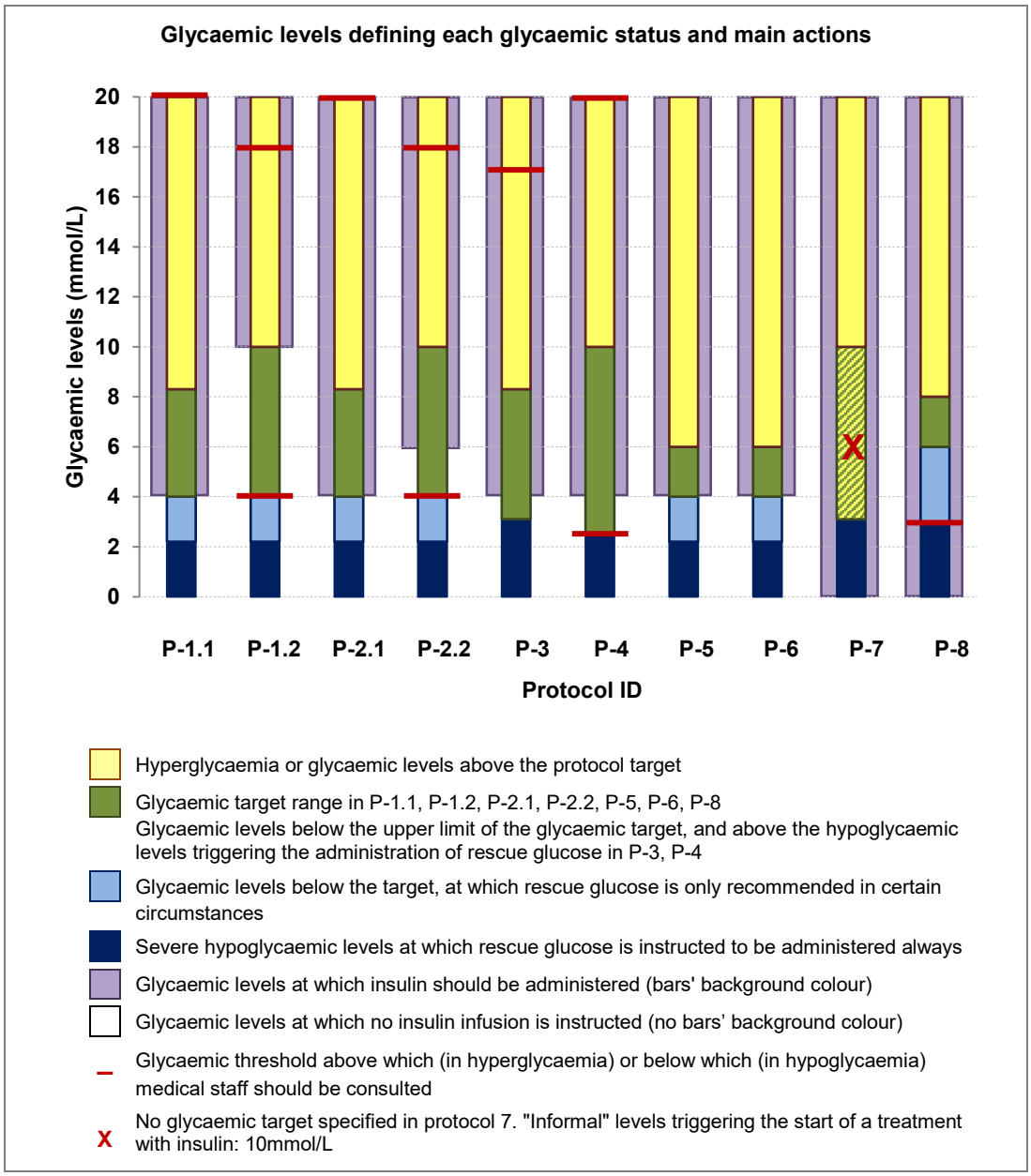


Figure 4.5 – Glycaemic values defining each glycaemic status, and when main actions are instructed

4.4.2.3 Hypoglycaemia and severe hypoglycaemia

Protocols P-1.2 and P-2.2 specifically defined hypoglycaemia and severe hypoglycaemia as any random glycaemic value below 4 and 2.2mmol/L, respectively. In the remaining eight protocols, glycaemic values below the glycaemic target range were considered as hypoglycaemia. Four of the 10 protocols (P-1.2, P-2.2, P-4, and P-8) specifically stated the need to inform medical staff in events of severe hypoglycaemia (Table 4.1 and Figure 4.5).

4.4.3 Monitoring instructions

The protocol instructions relating to the monitoring of patients' BG levels are summarised in Table 4.1 and illustrated graphically in Figure 4.6. These are described in the following sub-sections.

4.4.3.1 Blood sample and method for monitoring

In protocols P-1.2 and P-2.2 arterial samples (when an arterial line is available) analysed with the blood gas analyser were the preferred method for BG monitoring. Venous samples analysed with a point of care (POC) BG meter and laboratory analyses were also recommended in specific situations: to double check BG levels with a different technique before commencing an insulin regimen; after any BG<2.2mmol/L, in which case a blood sample should be sent to the hospital laboratory; or where BG results are "unexpected". In these two protocols capillary samples were described as a "last resort option".

Protocols P-1.1, P-2.1, P-3, P-5 and P-6 indicated that both the blood gas analyser and a POC BG meter were acceptable for BG monitoring, although they did not mention specifically a blood sample source of preference. Protocol P-7 recommended capillary samples, while P-4 and P-8 did not specify the blood sample source or the preferred device for monitoring.

4.4.3.2 Monitoring Time Intervals

The times to next measurement (TNM) instructed in the protocols ranged from five minutes to four hours. The lowest TNMs were recommended when patients were within lower glycaemic ranges. At hypoglycaemic statuses, during which rescue glucose was recommended, TNMs were 15 minutes or less in seven protocols (P-1.1, P-1.2, P-2.1, P-2.2, P-3, P-5 and P-6), 30 minutes or less in two protocols (P-4 and P-8), and one hour in one protocol (P-7).

The highest TNMs were recommended when patients were within their protocol target. In most protocols these varied within a range, depending on the time spent within the glycaemic target. These TNM ranges were of one to four hours in six protocols (P-1.1, P-1.2, P-2.1,

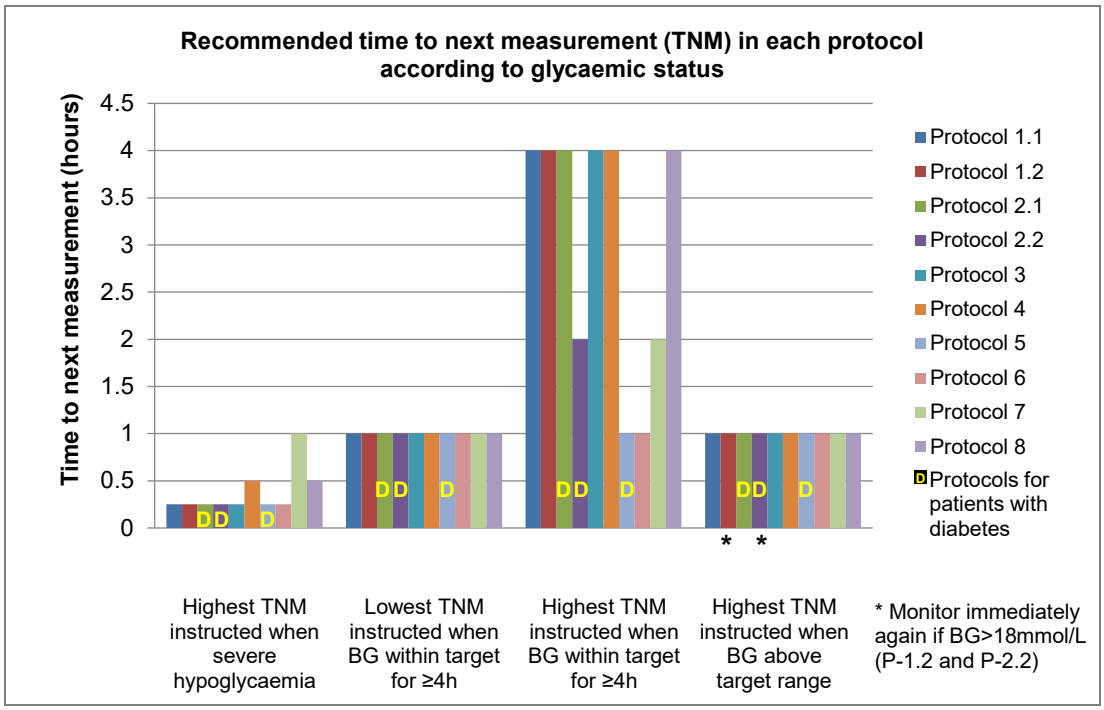


Figure 4.6 – Maximum and/or minimum time to next measurement (TNM) instructed in each protocol, depending on the glycaemic status and, when applicable, the time spent within target

P-3, P-4, P-8) and one to two hours in two protocols (P-2.2 and P-7). In protocols P-5 and P-6 hourly TNMs were recommended at any non-hypoglycaemic range.

Finally, when patients were above their glycaemic target all protocols instructed hourly TNMs, except for hyperglycaemia above 18mmol/L in protocols P-1.2 and P-2.2, where re-checking glucose levels "immediately" was instructed.

4.4.3.3 Rationale for adjusting the monitoring frequency

The rationale for adjusting the TNM was often different on admission than after initial admission. However, in both cases the main rationale for adjusting TNMs in all protocols were patient glycaemic levels at each measurement. Other reasons for these adjustments were:

- At the discretion of medical staff for events of severe hyperglycaemia (four protocols: P-1.2, P-2.2, P-3 and P-4) or severe hypoglycaemia (three protocols: P-1.2, P-2.2 and P-8);
- When feeding is started or stopped (seven protocols: P-1.1, P-1.2, P-2.1, P-2.2, P-3, P-5 and P-6), or when intravenous (IV) glucose infusion is started or stopped (six protocols: P-1.1, P-1.2, P-2.1, P-2.2, P-5 and P-6);
- Depending on the length of the time that patients are "stable" (four protocols: P-1.2, P-4, P-7 and P-8), or receiving insulin (two protocols: P-3 and P-7), or with hyperglycaemia (two protocols: P-1.1& P-2.1).

4.4.4 Treatment with insulin instructions

The protocol instructions relating to the administration of insulin are summarised in Table 4.1. These are described in the following sub-sections. All protocols except two (P-7 and P-8) recommended administering an insulin infusion only when certain glycaemic levels were recorded, ranging from 4 to 10mmol/L (Figure 4.5). In P-7 and P-8, once patients had been started on the insulin algorithm, it was instructed that insulin infusion was not stopped, irrespective of glycaemic levels.

4.4.4.1 Insulin type and route of administration

All protocols recommended the use of fast-acting soluble insulin, with Actrapid® being specifically indicated in all protocols except P-4. In one protocol (P-7), basal insulin (either glargine insulin or detemir insulin) could be used at the same time as the fast-acting insulin. In all protocols, insulin had to be intravenously administered in a solution with sodium chloride, with protocol P-7 also allowing the subcutaneous route for the administration of basal insulin.

4.4.4.2 Insulin dosage

On admission, all protocols had algorithms indicating VRIII (Variable Rate Intravenous Insulin Infusion) that were fixed for each pre-specified glycaemic range. After initial admission, three protocols (P-5, P-6 and P-8) specified adjustments to the insulin infusion rates (IIR) being administered before the BG measurement was taken (Table 4.1). Besides the IIR adjustment scale, two of the protocols for patients with diabetes (P-2.1 and P-6) recommended the infusion of a fixed baseline insulin or fast-acting insulin. This baseline was either the patient's usual insulin regime or, if this was unknown, calculated from the patient's weight using the formula:

$$Baseline\ isulin\ hourly\ rate\ (U/h) = \frac{0.5\ (U/kg) \times patient\ weight\ (kg)}{24\ hours} \qquad (4.1)$$

Table 4.2 illustrates the differences in the fixed IIRs (excluding the baseline insulin rates of P-2.1 and P-6) recommended on admission in each protocol, depending on patients' initial glycaemic levels. For glycaemic values above the protocol's glycaemic target, the highest fixed IIRs, measured in international units of insulin per hour (U/h), ranged from 4U/h to 8U/h, and the lowest fixed IIRs ranged from 0.5U/h to 4U/h. For glycaemic values within the target range, the highest fixed IIRs ranged from 0U/h to 2U/h and the lowest fixed IIRs ranged from 0U/h to 1U/h. In the two protocols that recommended that insulin was not stopped irrespective of glycaemic levels (P-7 and P-8), the recommended IIRs for glycaemic values at hypoglycaemic levels below 4mmol/L was 0.5U/h.

Table 4.2 – Insulin infusion rates (U/h) instructed on admission in each protocol depending on initial blood glucose levels. These rates were often different after admission. Darker shading indicates higher insulin infusion rates. Black shading indicates that no insulin dosage was recommended for that glycaemic range

Glycaemic levels	Protocol ID									
	P-1.1	P-1.2	P-2.1	P-2.2	P-3	P-4	P-5	P-6	P-7	P-8
20	8	4	8	5	4		4	4	8	4
19-19.9	6	4	6	5	4	6	4	4	8	4
18-18.9	6	3	6	4	4	6	4	4	8	4
17-17.9	6	3	6	4	3	6	4	4	8	4
16-16.9	6	3	6	4	3	6	4	4	4	4
15-15.9	6	2	6	3	3	6	4	4	4	4
14-14.9	4	2	4	3	3	4	4	4	4	4
13-13.9	4	2	4	3	3	4	4	4	4	2
12-12.9	4	1	4	2	3	4	4	4	2	2
11-11.9	4	1	4	2	2	4	2	2	2	2
10-10.9	4	0	4	1	2	4	2	2	2	2
9-9.9	2	0	2	1	2	2	2	2	2	0
8-8.9	2	0	2	1	2	2	2	2	1.5	0
7-7.9	2	0	2	1	1	2	2	2	1.5	0
6-6.9	1	0	1	0	1	1	2	2	1.5	0
5-5.9	1	0	1	0	1	1	1.5	1.5	1	0
4-4.9	1	0	1	0	0	1	1.5	1.5	1	0
3-3.9	0	0	0	0	0	0	0	0	0.5	0
2-2.9	0	0	0	0	0	0	0	0	0.5	0
1-1.9	0	0	0	0	0	0	0	0	0.5	0
0-0.9	0	0	0	0	0	0	0	0	0.5	0

4.4.4.3 Rationale for adjusting the rates of insulin infusion

The main rationale for adjusting IIRs in all protocols, on and after admission, was the glycaemic levels of patients. Other reasons for these adjustments were:

- At the discretion of medical staff for events of severe hyperglycaemia (four protocols: P-1.1, P-1.2, P-2.1 and P-4) or severe hypoglycaemia (one protocol: P-8);
- When feeding is started or stopped (seven protocols: P-1.1, P-1.2, P-2.1, P-2.2, P-3, P-5 and P-6), or when IV glucose infusion is started or stopped (six protocols: P-1.1, P-1.2, P-2.1, P-2.2, P-5 and P-6);
- Length of the time that patients were receiving insulin (one protocol: P-7);
- Patients' usual insulin regime (the three protocols for patients with diabetes: P-2.1, P-2.2 and P-6);
- Movement of BG within range (two protocols: P-5 and P-6).

All the protocols mentioned some factors which could influence insulin requirements. These are summarised in Table 4.1 and described below.

Nutritional support

Seven protocols (P-1.1, P-1.2, P-2.1, P-2.2, P-3, P-5 and P-6) instructed that either some type of nutritional support (enteral or parenteral nutrition) or a maintenance fluid with glucose should be given whenever insulin was administered. If none of these were being administered, five protocols indicated that insulin should be stopped (P-1.1, P-1.2, P-2.2, P-3 and P-5) and P-2.1 and P-6 indicated that the IIRs should be reduced to 0.5U/h. The possibility for adjusting IIRs depending on the type of nutrition administered was also mentioned in protocol P-4. Protocol P-7 recommended that "appropriate IV fluids according to clinical need" should be prescribed.

Diabetes

In the three ICUs implementing a different protocol for patients with diabetes (P-2.1, P-2.2 and P-6), insulin dosages were higher than those for patients without diabetes. Comorbid diabetes was also mentioned as a possible cause of the need for a higher dosage of insulin in protocols P-8 and P-4, although specific adjustments were not given.

Underlying condition and severity

Five of the protocols (P-1.1, P-2.1, P-4, P-5 and P-6) advised taking into account patients' underlying condition/s and/or their degree of severity.

Concomitant medication

The need for different IIRs depending on whether certain concomitant medications were being given was mentioned in seven protocols (P-1.1, P-1.2, P-2.1, P-2.2, P-4, P-5 and P-6), although the exact adjustments were not specified. Specifically, P-4 warned about the use of steroids in doses equivalent to more than 100mg per day of hydrocortisone, and the other six protocols stated that treatment with steroids was "likely" to increase insulin requirements by 20%.

Body temperature

Seven protocols (P-1.1, P-1.2, P-2.1, P-2.2, P-4, P-5 and P-6) described rises in body temperature, due to increases in the catabolism associated to the critical condition, particularly if they were due to infection, as a possible cause for higher insulin requirements.

Insulin sensitivity over time

Five protocols (P-1.1, P-2.1, P-4, P-5 and P-6) mentioned the possibility of changes in insulin sensitivity over time, which could increase or decrease the amounts of insulin needed.

Epileptic seizures

Epileptic seizures were described as a possible cause of increased needs for insulin in six protocols (P-1.1, P-1.2, P-2.1, P-2.2, P-5 and P-6).

4.4.5 Management of hypoglycaemia

All protocols stated that a bolus of a pre-specified amount of IV rescue glucose should be administered when patients were below certain hypoglycaemic thresholds. These thresholds varied from 2.2 to 3.1mmol/L (Table 4.1 Figure 4.5). Seven protocols (P-1.1, P-2.1, P-3, P-4, P-5, P-6 and P-8) recommended the administration of 10 grams of glucose per bolus. All of these protocols except for P-3 recommended that this bolus consists of 20mL of 50% weight/volume (w/v) glucose solutions, which are solutions having a concentration of 50 grams of glucose per 100mL (50g/100mL). P-3 recommended the administration of 50mL of 20% w/v glucose solutions, which are solutions having a glucose concentration of 20g/100mL. Protocols P-1.2 and P-2.2 recommended the administration of either 10 grams of glucose, using 20mL of 50% w/v glucose solution, or 15-16 grams of glucose using 75-80mL of 20% w/v glucose solution. P-7 mentioned that "increased glucose infusion" should be put in place, but it did not specify how much or which solutions should be used.

As mentioned previously, two protocols (P-7 and P-8) recommend administering insulin always, regardless of glycaemic levels. During hypoglycaemic events, these protocols recommend an insulin infusion of 0.5U/h. All the other eight protocols instructed that the insulin infusion should be stopped during hypoglycaemic and severe hypoglycaemic events. All protocols indicated the need to recheck glycaemic levels sometime after a moderate or severe hypoglycaemic level was recorded, ranging from "immediately" (P-1.2, P-2.2 and P-3) to one hour later (P-7).

Other instructions given by some protocols during events of hypoglycaemia or severe hypoglycaemia included: (1) calling medical staff; (2) reassessing feeding; (3) laboratory analysis of glucose levels; (4) checking whether nutrition or glucose infusions had been stopped; (5) considering any possible cause for the hypoglycaemic episode and (6) looking for symptoms of hypoglycaemia.

4.4.6 Organisational instructions

4.4.6.1 Informing medical staff

Seven of the protocols instructed that medical staff should be informed, either in events of severe hyperglycaemia (P-1.1, P-1.2, P-2.1, P-2.2, P-3 and P-4) and/or of severe

hypoglycaemia (P-1.2, P-2.2, P-4 and P-8) (Figure 4.5). In hyperglycaemic statuses, the levels above which medical staff had to be informed ranged from 17mmol/L (P-3), to 20mmol/L (P-1.1, P-2.1 and P-4). Also, three protocols advised calling medical staff when glycaemic levels were high for long periods, including within 10-18mmol/L for 6 or more hours (P-1.2 and P-2.2), or above 8.3mmol/L for six hours (P-3) (Figure 4.5). In hypoglycaemic statuses, the levels below which medical staff had to be informed were 4mmol/L (P-1.2 and P-2.2), 3.4mmol/L (P-8, on admission), 3mmol/L (P-8, after initial admission) and 2.4mmol/L (P-4).

One protocol (P-7) recommended discussing the insulin sliding scale with the prescriber if the patient had been "stable" for more than 12 hours, and to contact the diabetes team if a patient had been receiving insulin infusion for more than 48 hours. However, the protocol did not specify what "stable" meant.

4.4.6.2 Other organisational instructions

Documenting and recording of treatment

One protocol (P-7) instructed that insulin syringe changes had to be documented, and that the IIR had to be checked at change of shifts or handover, or if a patient was moved.

Management at discharge

Instructions for the management of patient glycaemic levels on or after discharge from ICU were mentioned in six protocols (P-1.1, P-1.2, P-2.1, P-2.2, P-3, P-5 and P-6) (Table 4.1). These instructions referred mainly to the need to either prescribe an insulin sliding scale before discharge for insulin-dependent patients with diabetes (P-2.1, P-2.2 and P-6); or, in patients whose GC had been difficult during the ICU admission, discussing or making arrangements about his/her subsequent GC management in the ward to which the patient was being admitted (P-1.1, P-1.2, P-3 and P-5).

4.4.7 Patients with vs. without comorbid diabetes: differences and similarities

The ICUs H-100, H-200 and H-500 implemented different protocols for patients with diabetes. The main differences between protocols for patients with vs. without diabetes are described below.

ICUs H-100 and H-200 implemented the same general protocol for most patients (P-1.1 before July 2012 and P-1.2 from July 2012 onwards), and a protocol with a different set of instructions for patients with diabetes (P-2.1 before July 2012 and P-2.2 from July 2012 onwards). Most instructions were the same in each of the pairs of protocols (the pair

implemented before July 2012 and the pair implemented after), including the target blood glucose. The main differences between them were their insulin titration algorithms and their monitoring frequencies.

When comparing the pair of protocols implemented from July 2012 onwards in ICUs H-100 and H-200 (P-1.2 and P-2.2 for patients without and with diabetes, respectively), the glycaemic threshold determining when insulin infusion should be commenced were 10mmol/L in patients without diabetes (P-1.2) and 6mmol/L in patients with diabetes (P-2.2). In each pre-specified glycaemic range, patients with diabetes had to be administered 1U/h more than patients without diabetes. The TNMs were sometimes shorter for patients with diabetes (Table 4.1 and Figure 4.6). For example, patients with diabetes who were stable for some time and not receiving high concentration glucose infusions could be monitored every two hours, while for patients without diabetes four-hourly measurements were instructed. On the other hand, calling medical staff when a patient had been above 10mmol/L for six hours or more, after commencement of the treatment, was advised only in protocol P-1.2 for patients without diabetes.

When comparing the pair of protocols implemented before July 2012 in ICUs H-100 and H-200 (P-1.1 and P-2.1 for patients without and with diabetes, respectively), as well as when comparing the two protocols implemented in ICU 500 (P-5 and P-6 for patients without and with diabetes, respectively), the main differences were the IIRs instructed. For patients with diabetes (P-2.1 and P-6), it was instructed that a baseline amount of insulin should be added to the insulin rate specified in the sliding scale for patients without diabetes (P-1.1 and P-5). The baseline was to be equivalent to the patient's usual treatment, or, if this was not known, based on the patient's weight (using equation (4.1)). In addition, if feeding was stopped, P-1.1 and P-5 (for patients without diabetes) recommended that insulin was stopped, while P-2.1 and P-6 (for patients with diabetes) indicated that insulin should not be stopped but reduced to 0.5U/h. No differences regarding the TNMs were found between these protocols for patients with vs. without diabetes.

4.4.8 Protocol structure and scenarios considered

4.4.8.1 Length and structure

The length and structure of each of the protocols are summarised in Table 4.3. Two of the protocols (P-7 and P-8) were mainly chart-type protocols, containing insulin infusion algorithms and monitoring frequencies, with minimal written instructions. The remaining eight protocols included more detailed descriptions and/or instructions, in addition to the charts.

Table 4.3 - Protocol structure, and number of scenarios, processes and decisions, considered in each protocol, on and after initial admission

Protocol ID	P-1.1	P-2.1	P-1.2	P-2.2	P-3	P-4	P-5	P-6	P-7	P-8
Type of protocol [a]	D+C	D+C	D+C	D+C	D+C	D+C	D+C	D+C	C	C
Protocol word count: Total (mean words/page)	1012 (337)	1012 (337)	2783 (186)	2783 (186)	655 (218)	425 (213)	620 (310)	620 (310)	431 (216)	239 (239)
TOTAL number of scenarios per protocol	59	59	74	68	9	11	14	14	48	16
Median [range] number of "processes" per scenario	2 [2-5]	2 [2-5]	3 [1-9]	3 [2-9]	2 [1-3]	2 [1-4]	2 [2-4]	2 [2-4]	4 [2-7]	2 [2-7]
Median [range] number of "decisions" per scenario	2 [0-5]	2 [2-5]	3 [0-5]	3 [0-4]	1 [1-2]	1 [0-2]	0 [0-2]	0 [0-2]	4 [3-5]	0 [3-5]

[a] C: Chart-type protocol with sliding scale insulin and monitoring interval instructions, and only minimal other written instructions; D+C: Protocol with descriptions of instructions and chart

The longest protocol had a total of 2,783 words in 15 pages (186 words per page); and the shortest had a total of 239 words in one page. Seven of the 10 protocols (P-1.1, P-2.1, P-1.2, P-2.2, P-5, P-6 and P-8) indicated different instructions on admission and after initial admission, while the remaining protocols (P-3, P-4 and P-7) gave the same instructions for the whole stay.

4.4.8.2 Protocol scenarios

The resulting flow charts of all the protocols are included in Appendix B. The number of scenarios per protocol ranged from nine (P-3) to 74 (P-1.2). The amounts and types of decisions and processes included in each scenario are summarised in Table 4.3, Table 4.4 and Figure 4.7. The three protocols with the highest median numbers of processes and of decision steps included in their scenarios (P-1.2, P-2.2 and P-7) also had high numbers of possible scenarios, ranging from 48 to 74 scenarios per protocol. Two of these three protocols (P-1.2 and P-2.2) were the longest, in terms of word count, while the remaining protocol (P-7) was the third shortest (Table 4.3 and Figure 4.7). The latter was a chart-type protocol with minimal written details, but among the few details included were several conditional instructions which, as decision steps, added scenarios to the flow-charts. Two other protocols (P-1.1 and P-2.1) also considered a large number of possible scenarios, but their median numbers of processes and decisions were lower than the previous three protocols (Table 4.3 and Figure 4.7).

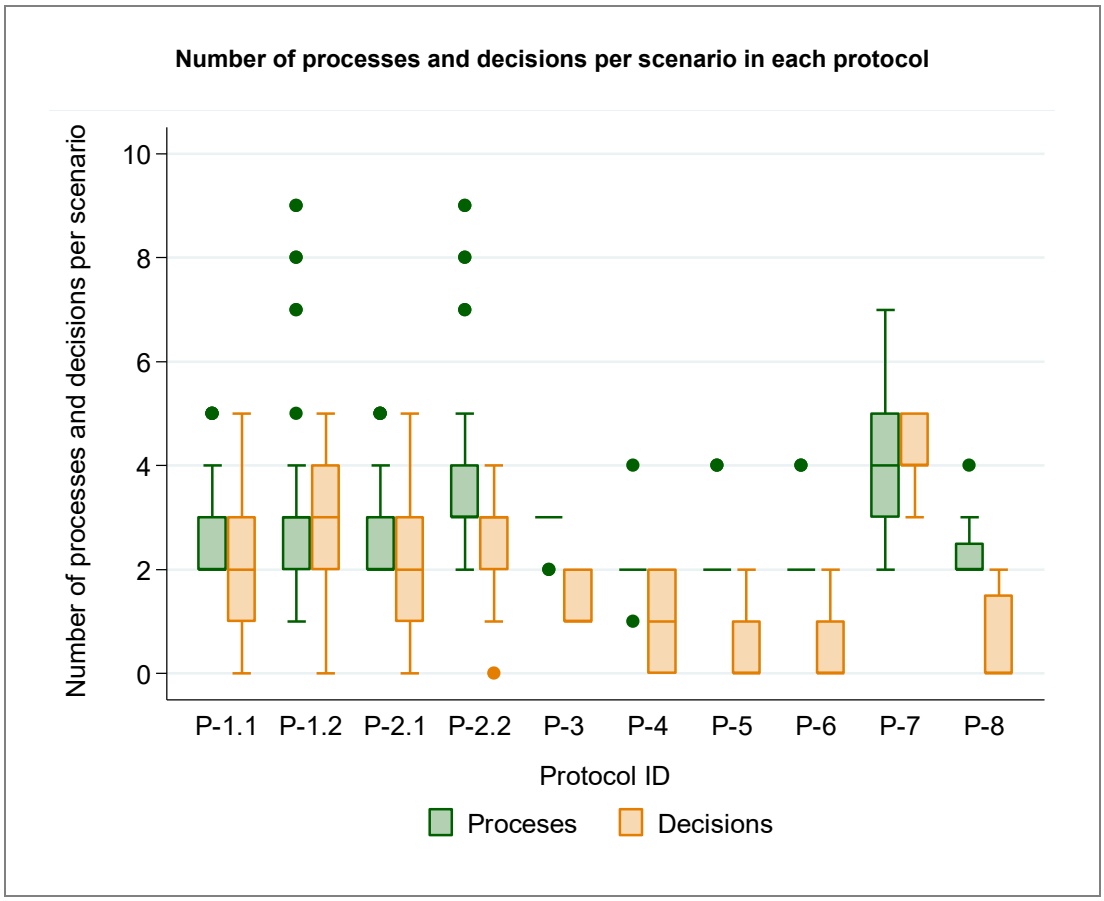


Figure 4.7 – Distribution of the number of processes and decisions per scenario in each protocol

Most protocols had a median of two processes per scenario (P-1.1, P-2.1, P-3, P-4, P-5, P-6 and P-8), although the highest number of processes in a single scenario was found to be nine. Similarly, while the median number of decisions in a scenario was two or less in seven of the protocols (P-1.1, P-2.1, P-3, P-4, P-5, P-6 and P-8), there were scenarios with up to five decisions to make (Table 4.3).

All protocols considered processes related to monitoring, insulin infusion and rescue glucose infusion, and all of them except two (P-5 and P-6) mentioned processes regarding calling medical staff or a specialist team in particular situations. The types or themes of processes considered by each protocol are listed in Table 4.4. The protocols with the highest number of themes of processes considered were P-1.2 and P-2.2 (both eight themes).

Table 4.4 – Themes to which processes and decisions related to

Protocol ID	1.1	2.1	1.2	2.2	3	4	5	6	7	8
PROCESSES related to:										
Glycaemic monitoring	√	√	√	√	√	√	√	√	√	√
Insulin infusion	√	√	√	√	√	√	√	√	√	√
Rescue glucose infusion	√	√	√	√	√	√	√	√	√	√
Calling medical staff / prescriber	√	√	√	√	√	√			√	√
Identify cause of hypoglycaemia	√	√	√	√						
Send blood sample to laboratory			√	√						
Check if feeding has been stopped			√	√						
Check urine ketones			√	√						
Reassess feeding							√	√		
Assess movement in range							√	√		
Contact diabetes team									√	
Total number of themes considered in the processes per protocol	5	5	8	8	4	4	5	5	5	4
DECISIONS related to:										
Glycaemic stability/instability	√	√	√	√	√	√	√	√	√	√
Feeding /maintenance fluid	√	√	√	√	√		√	√		
Insulin infusion			√	√		√			√	
Treat for hypoglycaemia			√	√						
Rescue glucose infusion			√	√						
Change of syringe of infusion pump									√	
Comorbid diabetes	NA[a]	√	NA[a]	√			NA[a]	√		√
Total number of themes considered in the decisions per protocol	2	3	5	6	2	2	2	3	3	2
TOTAL number of themes considered in processes or decisions per protocol	7	8	13	14	6	6	7	8	8	6

NA: Not Applicable

[a] Protocols P-1.1, P-1.2 and P-5 were for patients without diabetes only

All protocols considered decisions related to monitoring. Most of these concerned the length of time that patients' glycaemic levels had been too high, too low, or within target or stable. Decisions related to patient's feeding, or the administration of other sources of glucose, were the second most common type of decisions. These were mainly about whether feeding had been stopped (P-1.1, P-2.1, P-1.2, P-2.2, P-3, P-5 and P-6), or whether high concentration glucose infusions were being simultaneously administered (P-1.2, P-2.2). The themes of decisions considered by each protocol are listed in Table 4.4. The protocols with the highest number of themes of decisions considered were once again P-1.2 and P-2.2 (five and six themes, respectively).

4.5 Discussion

Three national surveys conducted across the UK between five and eleven years before GlyCon study, showed important differences in several aspects of GC. These included the number of ICUs that had protocols or standardised care approaches for GC in place, and their glycaemic targets (Paddle et al., 2011; Mackenzie et al., 2005), as well as some aspects of the insulin therapy they implemented (Paddle et al., 2011). However, these studies did not perform a detailed research of the contents of the protocols in place. One of the aims of GlyCon study was to decrease this gap in the evidence, through a thorough analysis of the specific instructions that ICUs propose for GC.

The network under study was a well organised and collaborative network, which had been in place for more than a decade when GlyCon was conducted. The network aimed to provide equitable access and care for all its critically ill patients. Its seven ICUs were located in a defined geographical area within the UK, with relatively short distances between each other, which should help to minimise the possible influence of geographical factors on clinical practice (Fox, 2003). Yet, the ICUs' protocols for GC showed important differences among each other, not only in their form but, more importantly, in their content.

4.5.1 Protocol development, structure and scenarios considered

The strength of the evidence base supporting protocols' instructions (Lugtenberg et al., 2009), their up-to-datedness (NICE, 2015), transparency about the method of their development (Brouwers et al., 2010), as well as the complexity and clarity of their instructions (Francke et al., 2008), are factors that can affect the level of adherence to them. These aspects varied between the protocols reviewed in GlyCon study, as discussed below.

4.5.1.1 Protocol development

At the time of the GlyCon study data collection for this protocol analysis in 2014, four of the seven ICUs had reviewed their protocols within the previous two to five years, while the protocols of two other ICUs were eight or more years old, and there was one ICU that did not mention its launch or update dates in the protocol (Table 4.1). In addition, of the ten protocols reviewed, only three mentioned the people involved and the method used for developing them. As a consequence of these differences in the protocols' update, the evidence base supporting their instructions differed among each other too.

Of the five ICUs with protocols that mentioned their evidence base, two cited evidence that was at least seven years old, and which supported either the tight glycaemic targets proposed the Leuven studies (Van den Berghe, Wilmer, Hermans, et al., 2006; Van den Berghe et al.,

2001), or the glycaemic targets below 8.3mmol/L proposed by the Surviving Sepsis campaign of 2004 (Dellinger et al., 2004). More recent evidence supporting looser targets (NICE-SUGAR Study Investigators et al., 2009; Dellinger et al., 2008) were cited in the protocols of the remaining three ICUs, representing just 43% of the whole sample of ICUs studied.

This is largely in line with the findings by Paddle et al. (2011), who reported that less than half of the 232 ICUs participating in their UK national survey had updated their policies for GC following the publication of relevant studies on GC. Also, a recent retrospective analysis of a large national database in the USA, concluded that the updating of clinical practice of GC to match the latest evidence is rather slow, and approaches based on older evidence were still present in more than 25% of admissions (Niven et al., 2015).

These findings are counter to the recommendations of the UK National Institute for Health and Care Excellence (NICE) (NICE, 2015). For NICE, it is very important to perform regular updates of guidelines, so that the most accurate and up-to-date evidence is used in their recommendations. These regular updates should include relatively frequent checks, such as at two, six and 10-year time points, with methods that are "less resource intensive", as well as more thorough reviews performed less often, such as at four and eight years after the guideline is launched (NICE, 2015). While this may be a difficult endeavour to be performed by busy clinicians working in the ICU, protocol updating is an important task that should not be neglected by the ICUs as it is essential for the provision of high quality care.

The method of development and transparency of a healthcare guideline (Brouwers et al., 2010), as well as the strength of the evidence behind its recommendations (Lugtenberg et al., 2009), are factors that have been found to influence the levels of adherence to the guideline. As a consequence, protocols that do not provide details about how they had been developed, and what evidence they were based on, could have lower adherence to their instructions.

4.5.1.2 Protocol structure and scenarios considered

Length of protocols

The four longest protocols considered more scenarios than most of the shortest protocols. However, there was one short chart-type protocol, with minimal written instructions (P-7), which considered three to five times more scenarios than the other short protocols (Table 4.3 and Figure 4.7). Rather than the length of the protocol, it was the type of instructions that was determinant in the amount of scenarios considered by the protocol. In other words, protocols could consider different possible scenarios with fewer words, depending on how they were expressed.

Similarly, the numbers of processes and decisions included per scenario was not always higher in longer protocols. For example, the maximum numbers of processes and decisions per scenario of the two chart-type protocols, with minimal written instructions (P-7 and P-8) were very close to those of the two longest and most detailed protocols (P-1.2 and P-2.2) (Table 4.3 and Figure 4.7). In addition, the comprehensiveness of the protocols, in terms of the number of different themes considered in their instructions, did not seem to be associated with a longer protocol either (Table 4.4). For example, two of the shortest protocols (P-6 and P-7) considered the same number of themes in their instructions as two of the longest protocols (P-1.1 and P-2.1) (Table 4.4).

In summary, the number of possible scenarios considered per protocol, the numbers of process and decision steps included per scenario, and the number of different themes covered by these steps, were not necessarily associated with the length of the protocols. This is important to consider as concrete and concise guidelines have been found to be adhered to more often than more vague and lengthy ones (Francke et al., 2008; Grol et al., 1998a).

Complexity of protocols

An instruction or recommendation has been described as complex when it is composed of numerous different interacting elements, and includes a complex decision tree, besides other factors that could affect these elements (Grol et al., 1998a). In GlyCon study, the most complex protocols, defined as those with the highest median numbers of processes per scenario and decisions per scenario, were P-1.2, P-2.2 and P-7. The structural characteristics of these protocols differed from each other (Table 4.3). However, they had in common that they were all updated in 2012, they were influenced by the same evidence base, and the UL was 10mmol/L in all three (although in P-7 the target was not formally written in the protocol) (Table 4.1). This is also an important finding to consider as the complexity of a protocol is one of the most commonly mentioned characteristics of guidelines that can affect the level of adherence to them (Francke et al., 2008).

4.5.2 Protocol instructions

As a consequence of these differences in the protocols' evidence base, their instructions differed among each other too.

4.5.2.1 Diagnostic instructions

The ULs of the glycaemic targets of the protocols were very varied. On the other hand, all the protocols except one had the same LL for the glycaemic target range (when this was stated) (Figure 4.5).

Upper limit of the glycaemic target range

The UL was either 8.3mmol/L or lower in six (60%) of the protocols reviewed. In the remaining four (40%) protocols, this UL was 10mmol/L. The latter included the ICU implementing a protocol (P-7) without a written target but, rather, a threshold level that was informally accepted by the ICU team as the level triggering the commencement of the protocol. This represents a higher prevalence of protocols with a UL higher than 8.3mmol/L than that found in previous years. About 11 years before GlyCon study, Mackenzie et al. (2005) found that 11.3% of ICUs had UL of more than 8.5mmol/L. Also, about eight and six years before GlyCon study, Paddle et al. found that 4% and 28% of ICUs, respectively, had a UL greater than 8.3mmol/L (Paddle et al., 2011). A higher UL implies a wider glycaemic target range (assuming the same lower target limit), hence a looser target. The reason for this trend, where more ICUs seem to be adopting higher UL, could be related to the increasing evidence supporting looser glycaemic targets, as opposed to the evidence supporting tighter targets that was prevalent in the early 2000s.

Lower limit of the glycaemic target range

Of the protocols that specified a LL, all except one took this to be 4mmol/L. However, three (30%) of the protocols failed to specify any LL. The lack of this written information in the protocols could be a risk for the safety of patients, as hypoglycaemia has been widely associated with poor outcomes in ICU patients (Ancona et al., 2011; Krinsley & Grover, 2007; Van den Berghe, Wilmer, Hermans, et al., 2006; Finney et al., 2004; Van den Berghe et al., 2001). BG ranges of 3.5-4.5mmol/L (Egi et al., 2010), 2.2-3.8mmol/L (Bagshaw et al., 2009), and below 3.9mmol/L (Krinsley et al., 2011, 2013), have all been associated with a higher risk of mortality in intensive care. While all GlyCon protocols specified a hypoglycaemic level triggering the administration of rescue glucose, these levels were even lower than the ones suggested by the cited evidence. The hypoglycaemic trigger levels were 2.1-2.2mmol/L in seven (70%) protocols and 2.9-3mmol/L in three (30%) protocols.

The findings of the GlyCon study, regarding the ICUs' glycaemic targets, reflect the current discrepant evidence about the optimal glycaemic targets for patients admitted in ICU. While some researchers support tight, normal, glycaemic levels of 4-6.1mmol/L, when the resources to achieve them safely are available (Gunst & Van den Berghe, 2016), others believe that stress hyperglycaemia should not be treated unless it reaches high values of 12-13mmol/L (Marik, 2016). Then there are others who advocate glycaemic targets that are in between these two extremes, such as 4.4-8mmol/L (Stewart et al., 2016) or 3.9-7.8mmol/L (Krinsley & Preiser, 2015).

Irrespective of the glycaemic target range adopted by an ICU, it is essential that it is stated clearly in any protocol for GC, in order to avoid inequities in the care provided. Also, while there are more discrepant opinions about the UL, it is generally agreed that glycaemic levels below 4mmol/L are to be avoided. Therefore, the LL should not be lower than 4mmol/L. In fact, based on some of the latest evidence, it has been proposed that the UL is individualised and adapted to the ICU environment and patient needs, but the LL is always 4mmol/L (Preiser & Straaten, 2016).

4.5.2.2 Instructions for the treatment with insulin

Insulin type and route of administration

As well as aiming for different glycaemic targets, the GlyCon protocols also differed in their methods for achieving these targets. In this study, the narrower and lower glycaemic targets of 4-6mmol/L (P-5 and P-6) and 6-8mmol/L (P-8) were accompanied by the use of charts where the IIRs were given as adjustments to previous rates, rather than as fixed rates for each glycaemic range, as was the case in the other seven protocols.

The insulin type of choice in all protocols was fast-acting soluble insulin administered intravenously. In all protocols except one, Actrapid® was specifically mentioned as the insulin to use. Actrapid® (Novo Nordisk pharmaceutical) is a fast-acting human insulin, also known as regular insulin, which, when administered intravenously, has a lifetime of a few minutes (European Medicines Agency, 2016). The reasons for the choice of this insulin are not specified in the protocols, and it is not clear from the evidence whether Actrapid® is more effective than other insulins in the treatment of stress hyperglycaemia.

There is, however, evidence that human insulin analogues can be more effective than human regular insulins (such as Actrapid®) for the complementary treatment of type 2 diabetes mellitus (Cucinotta et al., 2012; Chlup et al., 2007). In addition, while most adverse reactions to Actrapid® are rare, iatrogenic hypoglycaemia, defined as hypoglycaemia as a result of a treatment with insulin such as Actrapid®, is very common and occurs in 10% or more patients treated with this drug (European Medicines Agency, 2016). On the other hand, in their pilot study simulating the glucose-insulin feedback system of 200 virtual patients with stress hyperglycaemia, Strilka et al. (2014) found an inferior performance of the human insulin analogue insulin lispro (Humalog®), as compared with regular insulin (such as Actrapid®) due to a higher risk of iatrogenic hypoglycaemia. Nonetheless, this was a mathematical simulation study, and the authors concluded with the need to confirm these results with clinical trials on real patients.

Cost-effectiveness is another factor that could be associated with the prevalent use of Actrapid®. This regular insulin costs considerably less than other fast-acting insulins, including both regular human insulins such as Humulin® (Lilly pharmaceutical) and Insuman Rapid® (Sanofi-Aventis pharmaceutical), and human insulin analogues such as NovoRapid® (Novo Nordisk pharmaceutical) and Humalog® (Lilly pharmaceutical) (British National Formulary, 2014). All of these cost at least twice as much as Actrapid® (British National Formulary, 2014).

Further studies are therefore currently needed to help answer this question about the most effective and safest type/s of insulin to manage stress hyperglycaemia. In the meantime, including in the protocols a description of the rationale for choosing Actrapid® as their insulin type of choice would increase their completeness.

Insulin dosage

Most of the protocols of this study recommended starting the administration of insulin before the UL was reached. However there were two protocols (P-7 and P-8) that recommended that insulin was administered even at hypoglycaemic and severe hypoglycaemic levels (Figure 4.5). These protocols do not specify the reasons for this instruction, which seems to contrast with their higher than normal UL of 10mmol/L (P-7) and 8mmol/L (P-8). Temporarily stopping the administration of insulin when glycaemic levels are below 4mmol/L, and monitoring glycaemic levels more frequently, is the approach of all other protocols of this study, and has been suggested by nursing staff as a better strategy for a successful GC (Bland et al., 2005).

The VRIII of the protocols of the participating ICUs instructed changes in the insulin dosages as a function of the current BG, and in some of them the BG rate of change was also considered. While this approach is widely used for GC in ICU, it has been argued that also incorporating some estimation of the insulin sensitivity of a patient can increase the protocol's safety and effectiveness (Kansagara, 2013).

The dosages of insulin recommended for each glycaemic range in the protocols varied widely (Table 4.2). For example, for admission glycaemic levels of 19mmol/L or higher, the IIR recommended in the protocols ranged from 4 to 8U/h; and when admission glycaemic levels were within 10-11mmol/L, the recommended IIRs ranged from 0 to 4U/h (Table 4.2). This translates into large differences in the treatment of patients admitted to the ICUs of the same ICU network.

These large differences are likely to represent the general situation across ICUs in the UK and even worldwide, and they have also been pointed out by Wernerman et al. (2014). This can be associated with the fact that insulin titration charts are developed by individual

hospitals based on their own in-house expertise. Examples of other locally developed protocols for GC in hospitals from across the world have been shared through numerous journal publications (Chant et al., 2012; Chase, Shaw, et al., 2008; Wilson et al., 2007; Kelly et al., 2006). Consequently, international guidelines with validated optimal IV insulin titration rates for the management of stress hyperglycaemia in ICU, based on high quality evidence, are currently needed.

4.5.2.3 Management of hypoglycaemia

Most of the reviewed protocols recommended the use of 50%w/v glucose solutions for the management of hypoglycaemia, either as the only glucose solution (P-1.1, P-2.1, P-4, P-5, P-6 and P-8) or as one of two possible solutions (P-1.2 and P-2.2). While the response to 50%w/v glucose solutions is faster than to lower concentrations ones, this comes with a higher risk of overcorrection of glycaemic levels and of glucose variability (Arnold et al., 2013). For this reason, organisations such as the Joint British Diabetes Societies for inpatient care Group (JBDS-IP) currently recommends 20%w/v and 10%w/v solutions for treating hypoglycaemia (JBDS-IP, 2013a). In addition, 50%w/v glucose solutions are strongly hypertonic and more likely to cause thrombophlebitis (JBDS-IP, 2013a). The JBDS-IP recommends that, if a 50%w/v solution is used, this should be infused in a central line (JBDS-IP, 2013a). None of the protocols specifically mentioned the need for this route of administration, and thus mentioning this is another of the opportunities for the quality improvement identified in this study.

One outstanding finding in the instructions regarding the management of severe hypoglycaemia was the fact that only four of the ten protocols (P-1.2, P-2.2, P-4, and P-8) specifically stated the need to inform medical staff in events of severe hypoglycaemia. This is in stark contrast with the large body of evidence demonstrating the detrimental effects of hypoglycaemia, especially when this is severe, as has been discussed earlier. Including this written instruction in a protocol is highly recommended as it is likely to improve the safety, and therefore the quality, of the protocol.

4.5.2.4 Factors affecting glycaemic control

Current evidence shows that there are numerous factors that can affect the effectiveness of GC methods, including treatment-related factors and patient-inherent factors (see Section 2.6.2). While it may not be practical or even possible to take into account each of these factors in the instructions of a clinical protocol, at least the most influencing factors should be included in them, in order to improve their quality.

Treatment-related factors

Most protocols mentioned the need to coordinate insulin dosing with patient nutrition, or at least with the administration of some type of glucose-based maintenance fluid. However, the protocols only instructed to stop insulin if no source of glucose was being administered to the patients, and none of them provided a detailed nutritional guidance. This is notwithstanding the fact that the types and rates of nutrition provided have been shown to be an effective component in the management of GC (Kansagara, 2013). For example, STAR protocol (Stewart et al., 2016) and its predecessor SPRINT protocol (Chase, Shaw, et al., 2008), are protocols that modulate both insulin dosages and nutritional intake, and both of them have been found to be highly effective, achieving 83-87% of time within the target range 4.4-8mmol/L and just 0.002-0.004% of time in severe hypoglycaemia (Stewart et al., 2016).

Other treatment-related factors influencing GC include the administration of concomitant medications such as catecholamines, glucocorticoids and propofol (Pretty et al., 2011; Rady et al., 2005). Of the ten GlyCon study protocols, seven (P-1.1, P-1.2, P-2.1, P-2.2, P-4, P-5 and P-6) warned about the possibility that concomitant steroids increase insulin requirements, although none of them mentioned specific adjustments to be made based on these. None of the protocols mentioned the possible effects of other medications such as adrenaline, noradrenaline or propofol. Including the consideration of relevant concomitant medication in insulin adjustments would improve the protocols by making them more comprehensive, as well as potentially more effective and safer (Kansagara, 2013).

Patient-inherent factors

Among the seven ICUs participating in GlyCon, five (H-100, H-200, H-400, H-500, and H-700) mentioned in their protocols the need to take comorbid diabetes into consideration, and only three of them gave specific instructions for these patients (H-100, H-200 and H-500). This is of special concern given the available evidence about the different responses to GC methods between patients with and without diabetes. Among patients with stress hyperglycaemia, comorbid diabetes has been found to increase the proportion of time that they spend in hyperglycaemia (Krinsley & Preiser, 2015; Omar et al., 2015; Shulman et al., 2007; Rady et al., 2005; Carr et al., 2005) and the dosages of insulin needed to achieve pre-specified glycaemic levels (Rady et al., 2005). Based on these grounds, it is critical that protocols for GC make different recommendations for patients with a history of diabetes or chronic hyperglycaemia. This may include higher dosages of insulin for each pre-specified glycaemic range (Rady et al., 2005), as well as a different upper limit of the glycaemic target range (Preiser & Straaten, 2016).

4.5.2.5 Monitoring instructions

Most protocols agreed on both the blood gas machine and POG BG meters being acceptable monitoring devices, and in most of them the ideal blood sample of choice was not mentioned. Two of them (P-1.2 and P-2.2) mentioned arterial blood as the first blood sample of choice, although they also accepted capillary samples analysed in POC BG meters. In addition, in one of the protocols (P-7) such capillary blood was the preferred blood sample. This is also of special concern in the ICU, as POC glucometers can be significantly inaccurate, even by more than 20% (Corstjens et al., 2006). Their accuracy can be even more affected when the sample is capillary and there is tissue hypoperfusion, as this can change the usual relationship between the subcutaneous and circulatory glucose (Klonoff et al., 2011). In ICU there are certain commonly used medications and common conditions, such as acidosis, hypothermia and hypotension (Klonoff et al., 2011), and oedema and anaemia (College of American Pathologists, 2013), which have a hypoperfusion effect.

While blood plasma analyses in hospital laboratories are the most accurate method to estimate BG levels, this approach is too lengthy to be used routinely in the ICU. POC blood gas analysers are the next best method, as they have been found to be more accurate than POC bedside glucometers (Finfer et al., 2013; Corstjens et al., 2006). Based on these grounds, experts in the field have recommended that arterial or venous blood, taken from indwelling catheters, are the sample of choice, and that they are analysed in the blood gas analyser or, if turnaround time is not too long, in the hospital laboratory (Finfer et al., 2013).

Instructions about the TNM, at each glycaemic status, varied amongst the different protocols (Figure 4.6). While when patients were hyperglycaemic, all protocols recommended hourly measurements, when patients were within the target range, TNM instructions ranged from one to four hourly measurements. The latter contrasts with the widely documented need for frequent monitoring of BG levels in ICU patients, ideally through continuous monitoring technology (Preiser et al., 2016; Finfer et al., 2013; Van den Berghe et al., 2009). Since safe, reliable continuous glycaemic monitoring systems are still under development or under evaluations, until this technology is available, intermittent monitoring will still be the most frequently used method for monitoring BG in ICU. With this method, Krinsley et al. (2015) have concluded that hourly or shorter intervals are safer than 2-hourly measurements and therefore these are recommended when possible.

4.5.3 Methodological considerations

The Appraisal of Guidelines for Research & Evaluation (AGREE) collaboration of researchers and policy makers, developed the AGREE II instrument as a tool to assess the

quality of clinical guidelines, and whether they should be recommended for use in practice. It rates the level to which guidelines deal with relevant aspects, including the scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. This tool has not been used in GlyCon, as the aim of the study was not to assess the protocols' quality, but rather to perform a thorough description and comparison of the form and contents of the specific instructions for glycaemic control.

This description of protocols content and structure was done though inductive content analysis. Inductive content analysis uses a methodology in which the values of the researcher could affect the results. For this type of research, contingent validity, rather than internal validity, has been proposed as a quality criteria of research (Healy & Perry, 2000). Contingent validity can be assessed through triangulation of data from different data sources, and through the interpretation of those triangulations by different peer researchers (Healy & Perry, 2000). In this study, the only sources of other information to perform such triangulations were the ICU professionals, and the protocol developers. However, the aim of the GlyCon review of protocols was not to describe what should be understood from a protocol according to its authors, but what is actually understood by an external clinician who has never used or seen the protocol before. The interpretation of the protocols according to their developers and the professionals who use them on a daily basis, was not considered or sought, as their views would have been affected by informally accepted practices, not included in written in the protocols. Therefore, results of this review were not triangulated with information from another source such as the protocols' designers.

The strengths of the methods used include the use of graphical representation and summary of protocols through flow charts; using techniques of inductive content analysis leading to the identification of categories of instructions for GC which had not been identified before; and the consideration of both quantifiable and non-quantifiable data. The flow-charts provided a visual representation of the events sequence, which can help to gain a shared understanding of the processes and decisions involved in the management of patients with stress hyperglycaemia among the ICUs. Including qualitative data enriched the quantifiable summaries and helped to understand the rationale for instructions and other types of data that cannot be quantified. Separating instructions according to the glycaemic status, rather than on narrower glycaemic ranges, as well as according to the recommendation type, provided a framework within which the instructions of all protocols could be fitted and compared. Finally, this also made the method universally applicable to the analysis of other protocols for GC, which was one of the objectives in the development of this method.

4.6 Summary of results and conclusions

Most protocols reviewed in GlyCon study specified a glycaemic target range, or at least an upper limit that should not be exceeded, with the exception of one protocol, which did not explicitly state any glycaemic target. The recommended target levels ranged from as wide as 4-10mmol/L, to as narrow and low as 4-6.1mmol/L. The glycaemic levels triggering the start of the insulin treatment could be as high as 10mmol/L while other protocols recommended insulin treatment at all BG levels. The maximum recommended insulin dosage per protocol, in the seven protocols that had fixed insulin titration rates, ranged from 4 to 8U/h.

Most protocols mentioned a preferred glycaemic monitoring device, often either the gas machine or POC glucometer, but only three mentioned a preferred blood sample, either arterial or capillary samples. Recommended monitoring frequency at each glycaemic status differed between protocols, and ranged from "immediately" to four hourly. Hypoglycaemia triggered the shortest monitoring time intervals, followed by hyperglycaemia. Besides monitoring BG more closely, during hypoglycaemia all except two out of ten protocols instructed to stop insulin, and all protocols instructed to administer a bolus of intravenous glucose if hypoglycaemia was severe or symptomatic.

There were no specific recommendations regarding the management of the nutritional support of patients in any of the protocols, apart from instructions to stop insulin if no feeding or intravenous glucose fluids were in place. Also, only three ICUs had a protocol that made different recommendations for patients with diabetes, which consisted mainly of higher recommended dosages of insulin.

Some of the protocol instructions were not in line with current evidence about optimal monitoring methods (Finfer et al., 2013) and frequency (Krinsley et al., 2015), the seriousness of hypoglycaemia (NICE-SUGAR Study Investigators et al., 2012; Egi et al., 2010), the need to consider the nutritional support as an important component in the management of GC (Kansagara, 2013), the risks of high average cumulative insulin per day (Rady et al., 2005), or the need to treat patients with diabetes differently (Krinsley et al., 2013; Rady et al., 2005). These could affect the protocols' impact on patients' outcomes, including on patient safety (Lugtenberg et al., 2009).

In conclusion, the ten protocols under study differed not only in their size and structure, but, more importantly, in their glycaemic targets and the instructions they give for the GC of their patients. These disparities are likely to be reflected throughout the rest of the ICUs within the UK, and even worldwide (Niven et al., 2015; J.-C. Orban et al., 2013; Paddle et al., 2011). Changing this is proving challenging, not only due to contextual differences between ICUs (Qaseem et al., 2011; Rycroft-Malone et al., 2010; Pérez Pérez et al., 2009), but also due to

the existing conflicting evidence (Gunst & Van den Berghe, 2016; Marik, 2016), and the consequent lack of national or international agreements, about the most effective and safest methods for GC of stress hyperglycaemia.

Besides the implementation of evidence-based, feasible local protocols, there are other factors which could also affect the performance of such protocols. One important factor is the views of ICU professionals, who have a key role in both the development of these protocols for GC, as well as in the subsequent implementation of their instructions or recommendations (Rycroft-Malone et al., 2010). As part of GlyCon study, a survey to ICU professionals was conducted, in order to explore their views on the aims of GC, and on the implementation of protocols' instructions. The results of this survey are presented in the next chapter (Chapter 5).

Chapter 5
Opinion of intensive care professionals on methods for glycaemic control

5.1 Background and aims

The quality evaluation of intensive care services, on a regular basis, ensures the continuous quality improvement of the healthcare provided in intensive care units (ICU) (Lugtenberg et al., 2009; Curtis et al., 2006). Clinical protocols implemented in ICU, which are intended to support professionals in their decisions and actions, must also be continuously evaluated (Kavanagh & Nurok, 2016). As the primary users of such protocols, and key stakeholders in the ICU, in the quality evaluation of protocols it is crucial to account for professionals' opinions about the aims of the protocol and the instructions to achieve them (Brouwers et al., 2010). This provides with essential information for the identification of areas for quality improvement (Draper et al., 2008), and increases the probability of success of any recommendations for change resulting from the evaluation (EFQM, 2012).

As part of the GlyCon study, a short survey of professionals was conducted in the seven participating ICUs of the MTCCN network. There are several aspects of GC for which no standardised or agreed definitions have yet been proposed. These aspects include the level of effectiveness of GC, as defined by the percentage of time spent within a protocol's glycaemic target (TIR); the management of hypoglycaemia; and the adherence to protocols' instructions. With the survey, the GlyCon study aimed to gain knowledge about the views of the ICU professionals about such aspects. This information would complement the analyses and discussion of the subsequent study of GlyCon, which explored the effectiveness, time-efficiency and safety of the methods for GC implemented in intensive care. Finally, while it was not the main aim of the survey, the possible effects of the professionals' role and their level of experience on their opinions were also explored.

5.2 Methods

An online survey was specifically designed for GlyCon study using the Bristol Online Surveys (BOS) service (https://nottingham.onlinesurveys.ac.uk/glycon). The survey mainly included closed questions, organised in four domains, one with two questions about the professional's role and number of years of experience, and three with questions about professionals' views on three aspects of GC (Table 5.1). One of these aspects focused on the degree of GC achieved, in terms of the TIR of patients, which was the primary outcome measure of the subsequent sub-study of GlyCon. For this, professionals were asked to rate several ranges of TIR as poor or good or "other" GC (Table 5.1). If they answered "other" they were asked to specify.

The second aspect of GC in the survey addressed the management of hypoglycaemia. Professionals were asked about when, in their opinion, three possible ranges defining hypoglycaemia should be treated (Table 5.1). Of the three thresholds defining the possible ranges of hypoglycaemia, two were commonly used thresholds defining moderate (4mmol/L) and severe (2.2mmol/L) hypoglycaemia (Finfer et al., 2013; Krinsley et al., 2011; Egi et al., 2010; Krinsley & Grover, 2007; Van den Berghe et al., 2001). The last threshold of 1.5mmol/L defined an even more severe range that is associated with severe neuroglycopaenia (shortage of glucose in the brain), which can lead to coma and death (Frier, 2007).

The last section of the survey focussed on adherence to protocols for GC (Table 5.1). Professionals were asked whether they would rate possible deviations from protocol instructions as major or minor (or "other"). These deviations were mainly based on those proposed by Taylor et al. (2006). In their before-after observational study about the efficacy and safety of nurse-driven insulin infusion protocol, Taylor et al. (2006) had classified their proposed deviations as major or minor based on their clinical judgement (C. Coopersmith, personal communication via email, 2016) about the "likelihood that deviations would cause a severe or prolonged hypoglycaemia or hyperglycaemia". It is unknown whether professionals within a different context and expertise, would judge them differently, and the GlyCon survey aimed to explore this in order to better understand the results of its subsequent study. Thus, the GlyCon survey used all deviations that were relevant for the study, in a way that can be applied to most ICU protocols.

Face validity checks of the survey were carried out by three investigators, of whom two were clinicians (including the author of this thesis), through pretesting and reviewing the content and structure of the survey. These were discussed, reformulated and reassessed, until consensus was reached that questions were clearly stated, formatted and organised, and that

they measured the three aspects of interest for GlyCon study. Questions were formulated so that they could be used to check for the consistency of the answers. For example, within the section on the degree of GC, if a specific range of TIR was rated as poor, all subsequent questions about higher ranges of TIR, should be rated as poor too.

Table 5.1 – Summary of the sections of GlyCon online survey to ICU professionals

(Q.1) Socio-demographic information
(Q.1.1) Role **(Q.1.2)** Years working in intensive care: ≤5; 6–15 ; 16–30; >30
(Q.2) Degree of glycaemic control
Rate the following percentages of time spent within the target glycaemic range as "poor" or "good" glycaemic control, or "other (specify)"
(Q.2.1) 0-24% **(Q.2.2)** 25-49% **(Q.2.3)** 50-74% **(Q.2.4)** 75-94% **(Q.2.5)** ≥95%
(Q.3) Treatment of hypoglycaemia
Specify when these hypoglycaemic ranges should be treated with glucose: "always" vs. "depending on underlying condition" vs. "never", or "other (specify)" (plus optional comments for each item)
(Q.3.1) <4mmol/L **(Q.3.2)** <2.2mmol/L **(Q.3.3)** <1.5mmol/L
(Q.4) Deviations from protocol instructions
Rate the following deviations from instructions of an ICU protocol for glycaemic control as: "minor" vs. "major" (plus optional comments for each item)
(Q.4.1) Blood glucose measurement missed x1
(Q.4.2) Insulin titration missed or done incorrectly x1
(Q.4.3) Insulin infusion restarted 2 or less hours late
(Q.4.4) Blood glucose measurement missed 2 or more consecutive times
(Q.4.5) Insulin titration missed/done incorrectly 2 or more consecutive times
(Q.4.6) Insulin infusion restarted more than 2 hours late
(Q.4.7) Insulin infusion not turned off
(Q.4.8) Rescue glucose infusion dose done incorrectly x1
(Q.4.9) Rescue glucose infusion administered 15 or less minutes late
(Q.4.10) Rescue glucose infusion administered more than 15 minutes late
(Q.4.11) Open question (optional): other events considered as minor and/or major deviations

The relevance of the study for the quality improvement of ICU healthcare was emphasised in the survey introduction in an attempt to increase professionals' motivation to complete the survey (Evans & Mathur, 2005). Also, the survey was designed so that it required approximately just five minutes to be completed, in order to increase the response rate (Evans & Mathur, 2005). Since the survey was self-administered, it reduced the costs and resources required (Fowler, 2009). In addition, this self-administration increased the internal validity of the answers as compared to those from interviewer-administered surveys, by minimising interviewer bias (Fowler, 2009). In order to reduce survey bias, the questions had to be answered in the described order and respondents could not look ahead to later questions (Evans & Mathur, 2005).

The Research Governance Team of the University of Nottingham, as GlyCon's Research Sponsor, reviewed and approved the survey before it was distributed. Ethical approval from a NHS Research Ethics Committee and permissions from the R&D department of each of the hospitals were obtained before commencement of the study. Further details about the study ethical approvals are described in the overall methodology chapter (Chapter 3).

The survey was launched on 1st December 2014 and closed on 31st March 2015. The local collaborators of GlyCon study at each of the ICUs invited via email all the ICU medical and nursing staff of their respective ICUs to complete the survey. The email included the BOS link to the online survey, which was password protected. A reminder about the survey was sent by the author of this thesis to the local collaborators one month before closing the survey, with the aim of increasing the response rate (Evans & Mathur, 2005). Participants were told that they did not need to participate but by completing the survey they were consenting to participate. The introductory page to the survey reminded participants that their answers would be held anonymously and securely, and that no personal data would be asked for.

5.2.1 Sample

Since the population of interest was a finite population, random sampling techniques were not utilised, and the survey was sent to all eligible professionals via email. All nursing and medical staff working at the seven ICUs participating in GlyCon were eligible to participate in the survey. Since the purpose of the survey was not to compare groups, but rather to describe the opinions of the professionals, sample size estimations using power-based calculations were not performed.

For descriptive studies such as the GlyCon survey, and when the interest is on proportions rather than means, the minimum sample size, n, can be calculated as (Eng, 2003):

$$n \geq \frac{4Z_{\alpha/2}^2 P(1-P)}{D^2} \tag{5.1}$$

where P is the proportion of the variable of interest in the population (for example, the proportion of professionals rating something as good), D is the maximum marginal error of the estimates that the researcher is ready to accept (i.e., the width of the 95% confidence interval, CI), and $Z_{\alpha/2}$ is the value of the standard normal deviate corresponding to the chosen significance level, which for a 95% confidence level is approximately equal to 1.96.

The proportions of the variables of interest of GlyCon in the population were unknown. For some questions it was expected that a higher proportion of professionals would agree. For example, it was expected that a high proportion of respondents would rate spending 95% or higher TIR ((Q.2.5) in Table 5.1) as good GC. However, for most of the questions it was expected that there would be more variability of opinions, and thus lower proportions of professionals agreeing on the same answer (i.e., higher D).

From Equation (5.1), for questions with high expected proportion of professionals agreeing, such as a proportion of 0.9 (i.e., 90% professionals would give one answer, and 10% professionals the other possible answers), with 0.2 width of the 95% CI, a minimum sample size of 35 would be required. For questions with the lowest possible proportion of p=0.5 professionals agreeing to the same answer (i.e., 50% professionals would give one answer, and 50% professionals the other possible answers), with 0.3 width of the 95% CI, a minimum sample size of 43 would be required. Therefore a minimum sample size of 43 professionals was expected.

5.2.2 Analyses

Quantifiable variables were summarised using counts and percentages, and presented graphically as bar charts. Values of the percentages were rounded to the nearest integer, as the final sample size was lower than 100.

Chi-squared tests, or Fisher's exact tests when Chi-squared tests are not recommended, were used for the comparison of proportions. All statistical tests were two-tailed and the level of statistical significance was set at α=0.05. This level of significance meant that the confidence level was 95%, meaning that if the study was repeated 100 times, in 95 of them the

confidence interval would contain the true population value of interest. Given that this study was not investigating the effects of a new drug that could have serious effects on the patient, but rather, it was exploring whether there were differences in professionals' opinions, depending on a number of factors, 95% was considered a reasonable level of confidence.

Multiple logistic regression analysis was used to explore how the professionals' role and experience affected their answers to the survey's categorical questions. The interest was on their likelihood to rate pre-specified TIR ranges as poor GC, and to rate pre-specified deviations as major.

In order to have dummy variables as the outcome variables in logistic regression analyses, new variables were generated from the original variables. In these new variables, depending on the question, "poor" and "major" answers were coded as 1, and "good" and "minor" answers were coded as 0. All "other" answers were recoded as missing values in the regression analyses except for one "other" answer to the question on rating a TIR of 95% or more as good or poor. This answer included the comment "excellent", hence it was recoded as good GC.

Results from these logistic regression analyses were presented as ORs and adjusted OR, with their 95% CI and *p*-values. ORs, adjusted ORs and their 95% CI were given to one decimal place, as, given their wide CI, estimates to more decimal places would have given a false sense of precision (Cole, 2015). Following the American Psychological Association (APA) standards for scientific communication, *p*-values of 0.001 and above were rounded to three decimal places, while *p*-values below 0.001 were reported as $p<0.001$ (APA, 2010).

The term significant is used throughout the remainder of this chapter to refer to "statistically" significant differences. For greater fluidity in reading, the word "statistically" is sometimes omitted.

Qualitative information, including the open question and the comments to closed questions, were used mainly as anecdotal material for illustrative purposes, rather than as quantitative measures (Fowler, 2009). In one occasion it was possible to use them to recode one of the answers for the regression analyses, as described above.

5.3 Results

5.3.1 Sample

Forty professionals completed the survey. Amongst these, 11 (28%) were nurses and 29 (72%) were medical staff; 13 (33%) had five or less years of experience in intensive care, and 26 (65%) had more than five years of experience (one person answered "other" to this question about experience) (Figure 5.1).

The proportion of nurses who had more than five years' experience (82%) was higher than the proportion of medical staff who had more than five years' experience (62%), but this difference was not statistically significant at the 95% confidence level.

5.3.2 Degree of glycaemic control

Most professionals (83-85%) considered a TIR≥75% as good GC, while most of them (75-83%) considered a TIR<50% as poor GC (Figure 5.2). Opinions were more divided regarding a TIR of 50-74%, which was rated as poor by 22 (55%) professionals, as good by 15 (38%) and as "other" by three (8%) professionals. Of these three, two added comments in the free text provided to rate this range as "fair" rather than good or poor. One of these two professionals also pointed out the need to consider the patient's reason for admission and the different patient groups.

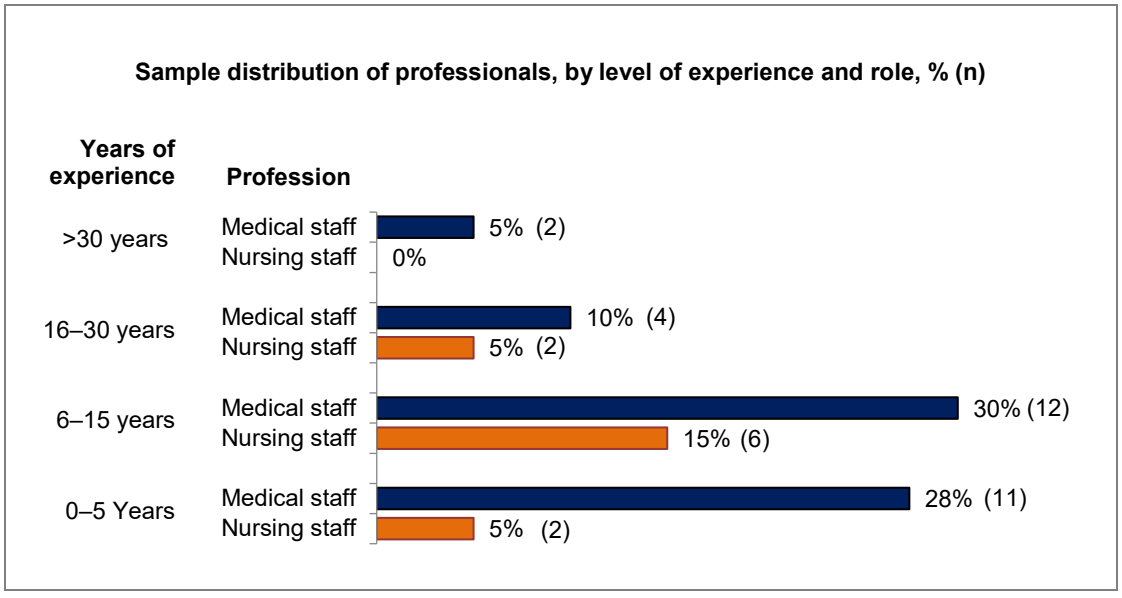


Figure 5.1 – Sample distribution, by level of experience and professional group (n=40)

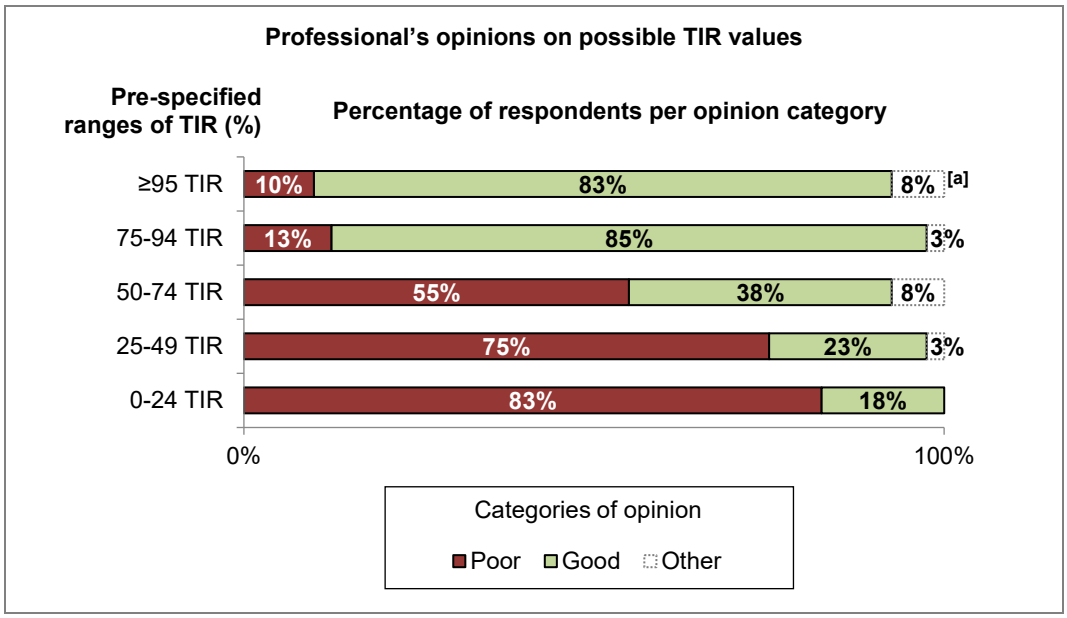


Figure 5.2 – Distribution of opinions on whether pre-specified percentages of admission time spent within the target glycaemic range (TIR) constitute poor or good glycaemic control.
[a]Among the "other" answers to the question on TIR≥95%, one medical doctor with 6-15 years' experience used the free text comments to rate this as "excellent".

5.3.2.1 Opinion on degree of glycaemic control by profession

For all pre-specified ranges of TIR that were below 75%, there was a higher proportion of medical doctors than of nurses who rated them as poor GC. For these ranges, nurses' opinions were more divided than those of medical doctors, with 45-55% nurses in each option of answer (either poor or good GC). For TIR ranges that were higher than 75% there was a higher proportion of nurses than medical doctors who rated them as poor GC (Figure 5.3).

There were five nurses (45%) who considered a TIR lower than 25% as a good GC, while only two medical doctors (7%) rated this as good GC (p=0.011) (Figure 5.3). The distribution of these proportions were similar regarding the respondents' opinion about a TIR within 25-49%: 55% of nurses and 10% of medical doctors considered this as good GC (p=0.008) (Figure 5.3). On the other hand, all medical staff except two (93%) rated a TIR of 95% or more as good GC, or even as "excellent" (as stated in a free text comment to this question), while only seven nurses (64%) rated this TIR as good GC (p=0.004) (Figure 5.3). The difference in the proportions of answers about the TIR ranges 50-74% and 75-94% were not statistically significant (p>0.050), showing a higher agreement between the professional groups.

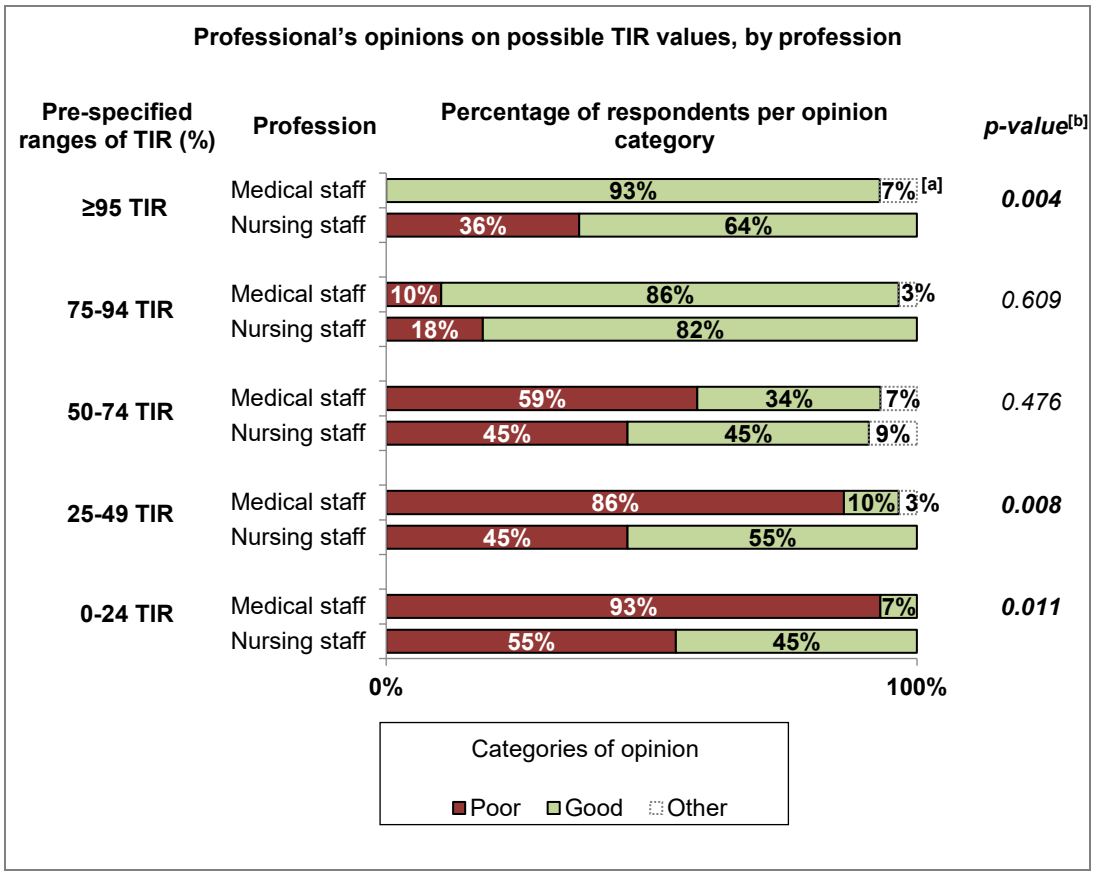


Figure 5.3 – Distribution of opinions on whether pre-specified percentages of admission time spent within the target glycaemic range (TIR) constitute poor or good glycaemic control, by professional role.
[a] Among the "other" answers to the question on TIR≥95%, one medical doctor with 6-15 years' experience used the free text comments to rate this as "excellent"
[b] The proportion of professionals who considered ≥95% TIR as poor GC was significantly higher among Nursing staff; and the proportions of professionals who considered 25-49% TIR and <25%TIR as poor GC were higher amongst medical staff.

5.3.2.2 Opinion on degree of glycaemic control by level of experience

For all pre-specified ranges of TIR, there were always higher proportions of professionals with more than five years' experience than of less experienced professionals who rated them as poor GC (Figure 5.4). However, there was only one statistically significant difference in the answers of these two groups of professionals, and it concerned TIRs within 50-74%. Among the more experienced professionals, 18 of them (67%) considered this range as poor GC, while among professionals with five or less years' experience only four (31%) rated this TIR range as poor GC (p=0.036) (Figure 5.4).

There were four nurses, with different levels of experience, who rated a TIR<25% as good GC while they rated a TIR≥95% as poor GC, and two of them also rated a 75-94% TIR as poor GC. These answers did not follow a logical trend and hence may not reflect consistent opinions of these four nurses. Possible reasons and potential solutions for this are described in Section 5.4.5.

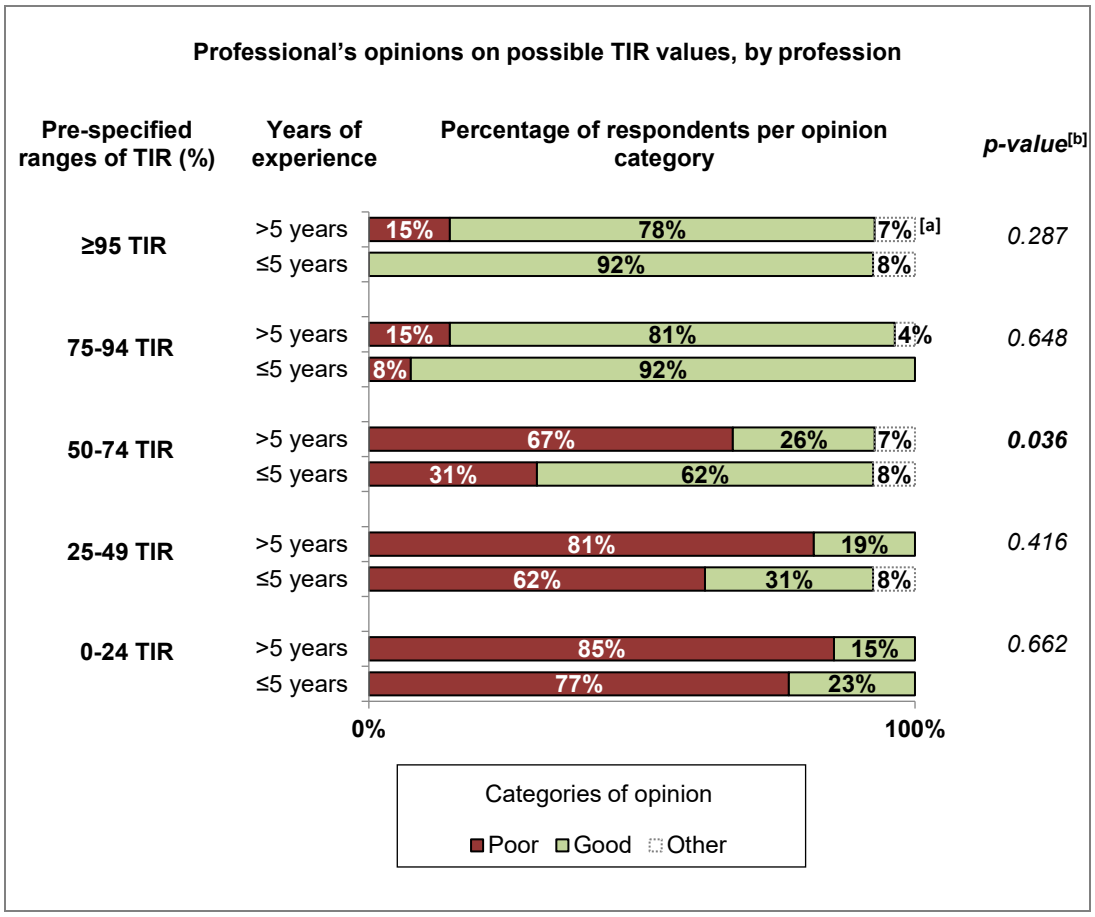


Figure 5.4 – Distribution of opinions on whether pre-specified percentages of admission time spent within the target glycaemic range (TIR) constitute poor or good glycaemic control, by level of experience.
[a] Among the "other" answers to the question on TIR≥95%, one medical doctor with 6-15 years' experience used the free text comments to rate this as "excellent"
[b] The proportion of professionals who considered 50-74% TIR as poor GC was significantly higher amongst those with more than five years' experience.

5.3.2.3 Likelihood for rating a TIR range as poor glycaemic control

Findings from the logistic regression analyses revealed that medical doctors were more likely to rate a TIR of less than 50% as poor GC than their nursing colleagues, even after controlling for their level of experience (Table 5.2). Also, professionals with more than five years' experience in intensive care were more likely to rate a TIR within 50-74% as poor than their less experienced colleagues, even after controlling for their profession (Table 5.2). Nonetheless, while these estimates were statistically significant at the 95% confidence level, the estimates of the coefficients also had very large confident intervals, and therefore there was some uncertainty about the actual effect sizes.

Table 5.2 – Effect of professionals' role and number of years of experience in intensive care, on their likelihood for rating pre-specified ranges of TIR as poor glycaemic control

	OR (95% CI)	*p-value*	Adj OR (95% CI)	*p-value*
Rating these TIR (%) ranges as <u>poor</u> glycaemic control				
0-24 TIR				
Medical staff [a]	11.3 (1.7, 72.5)	*0.011*	20.9 (2.0, 219.3)	***0.011***
>5 years' experience [b]	1.7 (0.3, 9.2)	*0.522*	5.1 (0.5, 55.9)	*0.179*
25-49 TIR				
Medical staff [a]	10 (1.9, 54)	*0.007*	21.5 (2.2, 209.7)	***0.008***
>5 years' experience [b]	2.2 (0.5, 10.3)	*0.317*	7.0 (0.7, 71.3)	*0.101*
50-74 TIR				
Medical staff [a]	1.7 (0.4, 7.4)	*0.478*	2.6 (0.5, 13.7)	*0.246*
>5 years' experience [b]	5.1 (1.2, 22.7)	*0.031*	6.4 (1.3, 31.1)	***0.022***
75-94 TIR				
Medical staff [a]	0.5 (0.1, 3.8)	*0.535*	0.6 (0.1, 4.4)	*0.626*
>5 years' experience [b]	2.2 (0.2, 21.8)	*0.506*	2.0 (0.2, 20.1)	*0.569*
≥95 TIR				
Medical staff [a]	1	*N/A*	1	*N/A*
>5 years' experience [b]	1	*N/A*	1	*N/A*

OR: odds ratio; Adj OR: adjusted odds ratio

[a] Medical staff as compared with Nursing staff

[b] Professionals with more than five years' experience as compared with professionals with five or less years' experience

5.3.3 Treatment of hypoglycaemic events

Of the 40 survey respondents, 18% indicated that they would always treat moderate hypoglycaemia with rescue glucose, 78% professionals stated that they would do it only depending on the patient's underlying condition, and two professionals, one nurse and one medical doctor, both with 6 to 15 years' experience, said that they would never treat these hypoglycaemias with glucose (Figure 5.5). No statistically significant differences in the respondents' opinions were found between the groups of profession and of level of experience.

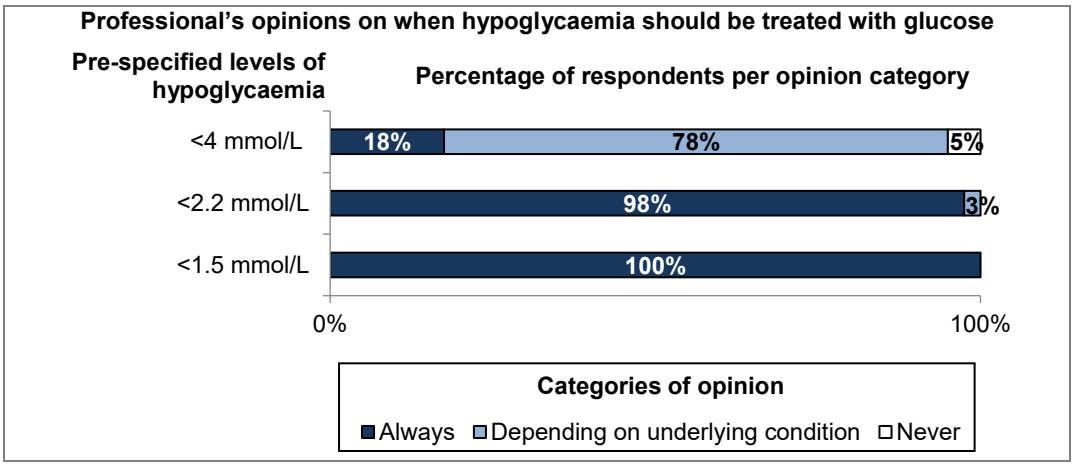


Figure 5.5 – Distribution of opinions on when pre-specified levels of hypoglycaemia should be treated with glucose

All professionals agreed with the need to administer glucose to any patient with a severe hypoglycaemia of 1.5mmol/L (Figure 5.5). Also, all professionals except one stated that they would always treat any severe hypoglycaemic event of 2.2mmol/L or less with rescue glucose. The professional with a different opinion was a medical doctor with 6 to 15 years' experience, who indicated that he/she would use rescue glucose to treat this level of hypoglycaemia only depending on the underlying condition of the patient (Figure 5.5).

5.3.4 Deviations from instructions of protocols for glycaemic control

Eight out of the ten pre-specified deviations from protocol instructions were rated as major by at least half of the respondents (Figure 5.6). In the free text spaces provided for these questions, professionals often commented on the need to take into account the context and patients' situation. All the comments registered in these free text spaces are listed in Table 5.3. Most professionals (90%) considered missing a BG measurement twice or more as a major deviation, but most of them (85%) regarded missing a BG measurement only once as a minor deviation (Figure 5.6). In the free text space provided for these questions, respondents stated that the level of stability of patients' glycaemic levels, whether the patient was receiving insulin, and any situation that would make BG monitoring difficult at a specific moment, were contextual factors that could justify the need to deviate from protocol instructions (Table 5.3).

Deviations from instructions related to the administration of insulin were rated as major by higher proportions of professionals than the other types of instructions. Not turning an insulin infusion off when it is recommended to do so; missing/doing a titration incorrectly twice or more; and an insulin infusion restarted more than two hours late, were regarded as major deviations by 95%, 90% and 80% of respondents, respectively. An insulin infusion

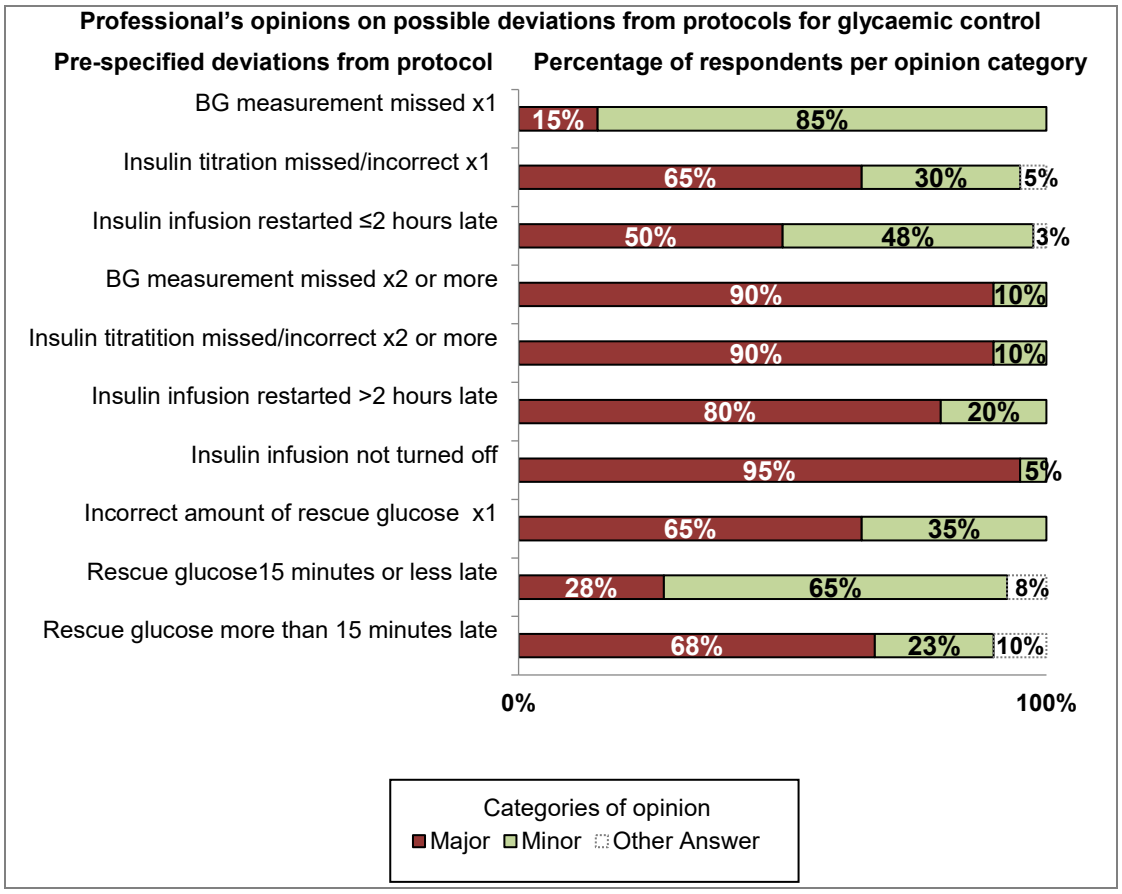


Figure 5.6 – Distribution of opinions on whether pre-specified deviations from the instructions of protocols for glycaemic control constitute major or minor deviations

missed or done incorrectly once, and an insulin infusion restarted two or less hours late were also considered major deviations by at least half of the respondents (Figure 5.6). In the free text space provided, professionals also mentioned a number of contextual factors that may justify these deviations. These factors included the status of the patient, a lack of a central venous catheter, a medical history of insulin dependent diabetes, or the lack of feed or glucose-containing fluids. One of the nurses specifically stated that incorrect insulin titrations are "drug errors" (Table 5.3). Some professionals also mentioned that the glycaemic levels of the patient, and how large the incorrect insulin dosage was, were also aspects that would affect how they would rate the deviation.

Administering a rescue glucose bolus more than 15 minutes late and administering an incorrect dose of rescue glucose were rated as major deviations by 68% and 65% of professionals, respectively. Administering a rescue bolus less than 15 minutes late was rated as major by only 28% of professionals (Figure 5.6). In the free-text comments, contextual factors that were described as possible justifications for these deviations, included whether the patient was receiving insulin, whether there were other priorities, and whether the hypoglycaemia was severe (Table 5.3).

Table 5.3 - Comments on opinions of major or minor deviations from protocol instructions

Deviations	Comments
Blood glucose measurement missed x1	"Minor if BMS stable. Major if on slide scale" (medical doctor, MD, 0-5 years' experience, study participant ID, ID, 204) "All context specific" (MD, 6-15 years' experience, ID 209) "Depends a bit on the previous stability of glycaemic control" (MD, 6-15 years' experience, ID 210) "All context specific" (MD, 6-15 years' experience, ID 220) "Depending on stability of glycaemic control at that time" (MD, 6-15 years' experience, ID 223)
An insulin titration missed or done incorrectly x1	"Depends on the blood glucose level, incorrect changes are obviously a drug error" (registered nurse, RN, 16-30 years' experience, ID 102) "Depends on level of incorrect!" (RN, 6-15 years' experience, ID 103) "All context specific" (MD, 6-15 years' experience, ID 209) "All context specific" (MD, 6-15 years' experience, ID 220)
An insulin infusion restarted 2 or less hours late	"Deviation of protocol, however depends on what was occurring with the patient, i.e.: were they having a cardiac arrest, were they having a CVC inserted and had no access, if neither of these or any other good reason I would call this a major deviation" (RN, 16-30 years' experience, ID 102) "All context specific" (MD, 6-15 years' experience, ID 209) "Depends if a IDDM [insulin dependent diabetes mellitus] or not" (MD, 16-30 years' experience, ID 218) "Depending on glucose level" (MD, 6-15 years' experience, ID 223)
A blood glucose measurement missed x2 or more	"Again depends on what is occurring with the patient" (RN, 16-30 years' experience, ID 102) "All context specific" (MD, 6-15 years' experience, ID 209) "Especially if on insulin" (MD, 6-15 years' experience, ID 210) "All context specific" (MD, 6-15 years' experience, ID 220)
An insulin titration missed or done incorrectly x2 or more	"Any incorrect dosing is a drug error" (RN, 16-30 years' experience, ID 102) "All context specific" (MD, 6-15 years' experience, ID 209) "All context specific" (MD, 6-15 years' experience, ID 220)
An insulin infusion restarted more than 2 hours late	"Could potentially cause a problem, however it would be worse to leave the insulin running and not checking the BM due to hypoglycaemia"(RN, 16-30 years' experience, ID 102) "All context specific" (MD, 6-15 years' experience, ID 209) "All context specific" (MD, 6-15 years' experience, ID 220)

Table 5.3 Continued

An insulin infusion not turned off	"Potentially very dangerous especially if feed/fluid containing glucose is not running" (RN, 16-30 years' experience, ID 102) "All context specific" (MD, 6-15 years' experience, ID 209) "Circumstances vary, but often of limited severity" (MD, >30 years' experience, ID 212)
Amount of rescue glucose infusion given incorrectly x1	"Any incorrect dosage is a drug error. Nurses should ALWAYS be second checking infusion doses/rates" (RN, 16-30 years' experience, ID 102) "All context specific" (MD, 6-15 years' experience, ID 209) "All context specific" (MD, 6-15 years' experience, ID 220)
A rescue glucose infusion administered 15 or less minutes late	"Major if insulin started without glucose" (MD, 0-5 years' experience, ID 204) "Unfortunately this could potentially happen on a busy shift" (RN, 16-30 years' experience, ID 102) "All context specific" (MD, 6-15 years' experience, ID 209) "What do you mean by late?" (MD, 16-30 years' experience, ID 218) "All context specific" (MD, 6-15 years' experience, ID 220) "This depends on the context - for correction of severe hypoglycaemia then it's definitely a major error, if someone have a relatively high /high normal glucose then it's less significant; the context of the omission has to be taken into account" (MD, 0-5 years' experience, ID 229)
A rescue glucose infusion administered more than 15 minutes late	"Potentially major problem with hypoglycaemia, should not really occur within an ICU" (RN, 16-30 years' experience, ID 102) "All context specific" (MD, 6-15 years' experience, ID 209) "Unclear is the insulin running [?]" (MD, 16-30 years' experience, ID 218)

All the "other events" that professionals described as potential deviations from their ICU protocol for GC, in the final optional open question of the survey, are included in Table 5.4. In these, many of the professionals commented on the need to maintain a safe balance between the administration of insulin and the input of nutrition and/or fluids with glucose. Other deviations proposed are related to the treatment with insulin, including incorrect interpretations of the sliding scale, incorrect concentration of the insulin preparation, or "too intensive" insulin therapies. Deviations related to monitoring include the contamination of the blood sample with a glucose solution, and a failure to double-check unexpectedly abnormal glycaemic levels with a different monitoring method.

Table 5.4 – Answers to the "open" question on deviations from protocol instructions

Are there any other events that you would consider as minor and/or major deviations from your ICU protocol for glycaemic control?
"Incorrect interpretation of escalation of sliding scale insulin doses - we have moved to fixed rates for DKA, but not for sepsis" (Medical doctor, MD, 16-30 years' experience, ID 201)
"Insulin administered without glucose" (MD, 6-15 years' experience, ID 203)
"Arterial line flush bag containing glucose" (MD, 6-15 years' experience, ID 203)
"Insulin infusion concentration not correct" (MD, 6-15 years' experience, ID 203)
"Failure to double check an "abnormal" result using a second sampling method (i.e. Failure to identify that a high or low glucose measurement is actually an artefact, rather than a true result)" (MD, 6-15 years' experience, ID 205)
"Using a glucose-containing solution in an arterial or central line flush bag (thus contaminating results)" (MD, 6-15 years' experience, ID 205)
"Insulin infusion without nutrition input with BM below 10 mmol/L" (MD, 6-15 years' experience, ID 206)
"Failure to stop / start nutrition" (MD, 6-15 years' experience, ID 207)
"Recurrent episodes of hypoglycaemia from excessive or overenthusiastic insulin regimes - this is major and has a significant negative impact on outcomes" (MD, >30 years' experience, ID 212)
"Focus on less of paperwork and more of actual work" (MD, 0-5 years' experience, ID 215)
"In our ICU we don't put the patients on glucose infusion when the patients on sliding scale insulin as they might be on enteral/parenteral feed and we check the BM's strictly every two hours or more if needed" (Registered Nurse, RN 6-15 years' experience, ID 111)
"Adjusting or stopping feed without consideration of insulin regime" (MD, 6-15 years' experience, ID 223)

5.3.4.1 Opinion on deviations from protocols by profession

In every category of deviations from protocols' instructions considered, there were higher proportions of nurses than medical doctors who regarded the deviations as major (Figure 5.7). The largest and the only statistically significant differences between these two groups of professions were found in two of the pre-specified deviations. An insulin infusion restarted two or less hours late was rated as major by 82% of nurses but by only 38% of medical doctors (p=0.031). An amount of rescue glucose given incorrectly once was considered as major by 91% of nurses and by 55% of medical doctors, a difference that was important but borderline not significant (p=0.061) (Figure 5.7).

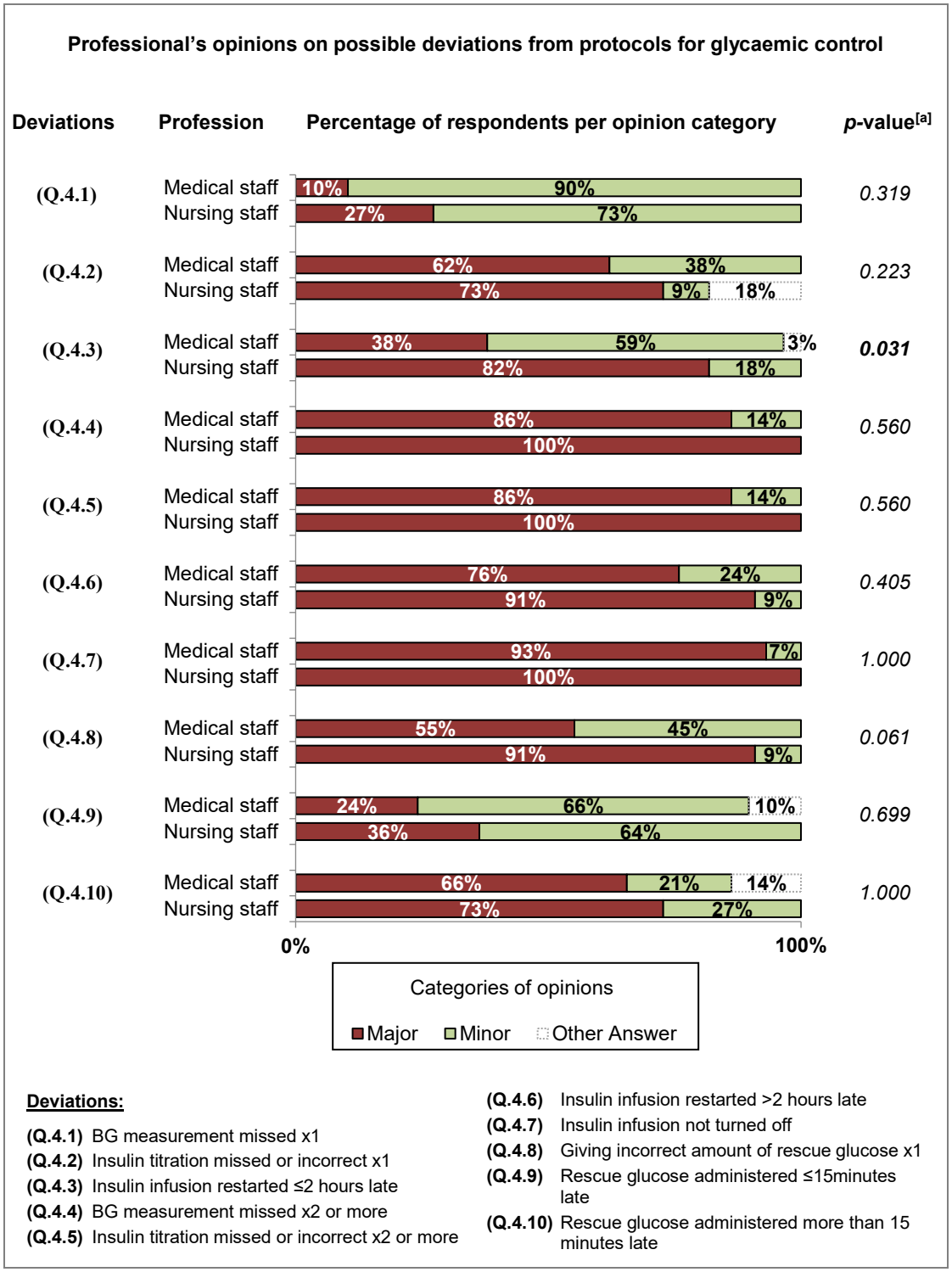


Figure 5.7 – Distribution of opinions on whether pre-specified deviations from protocols for glycaemic control are major or minor deviations, by profession (nursing or medical staff).
[a] The proportion of professionals who considered "An insulin infusion restarted ≤2 hours late" a major deviation was significantly higher among Nursing staff

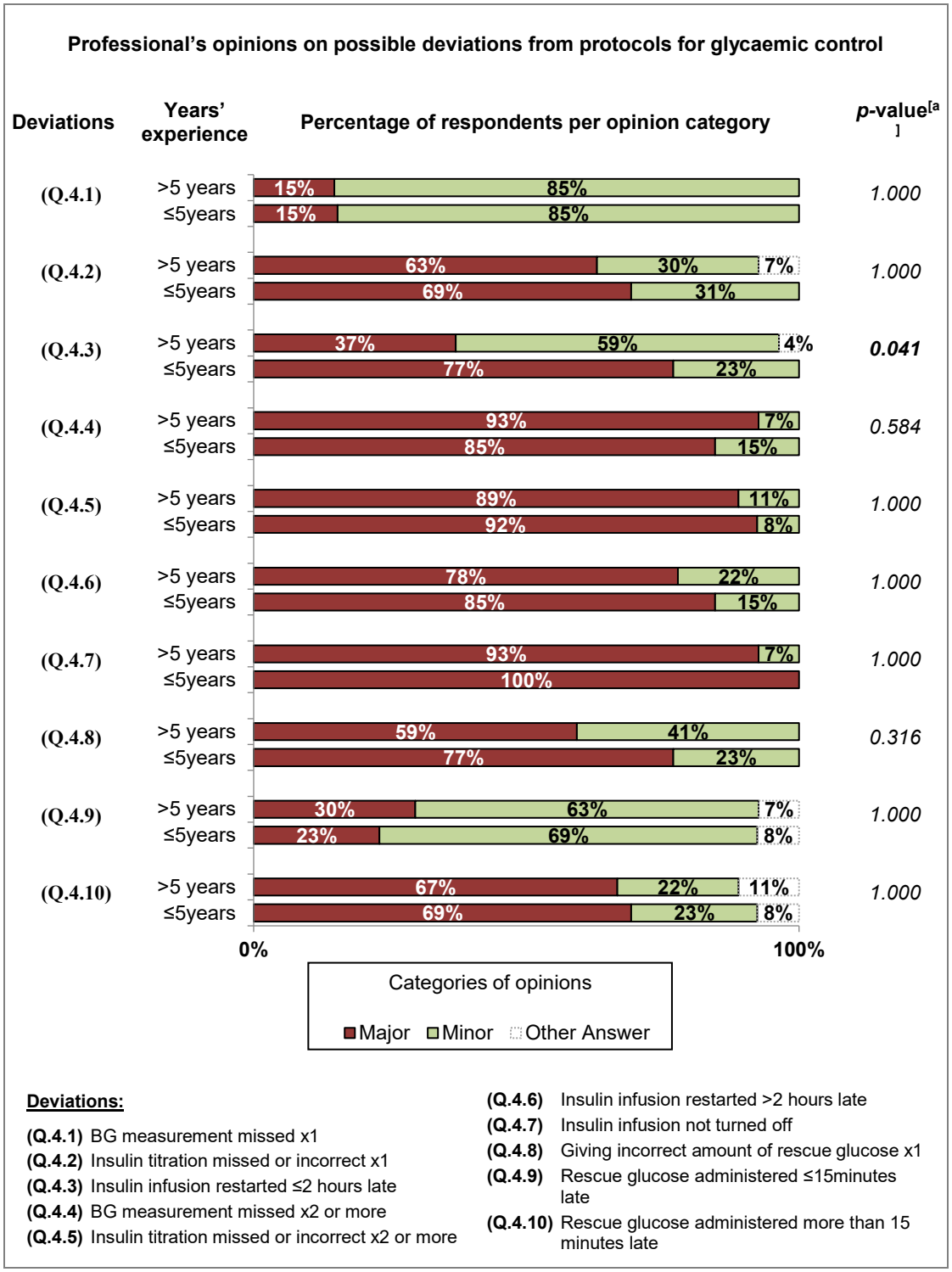
5.3.4.2 Opinion on deviations from protocols *by level of experience*

For seven out of the ten protocol deviations considered, there were higher proportions of professionals with five or less years' experience than of more experienced professionals who regarded them as major (Figure 5.8). However, the only statistically significant difference between the two groups was found in the pre-specified deviation of an insulin infusion restarted two or less hours late, which was rated as major by 77% of professionals with five or less years' experience, and by 37% of the more experienced professionals (p=0.041) (Figure 5.8).

There was one medical doctor with five or less years' experience who rated an insulin infusion restarted two or less hours late as major, while he/she rated an insulin infusion restarted more than two hours late as minor. There was also one medical doctor with 16-30 years' experience who rated an insulin titration missed or done incorrectly once as major, while he/she rated insulin titration missed or done incorrectly twice or more consecutive times as minor. These answers did not follow a logical trend and hence may not reflect consistent opinions of these two medical doctors. Possible reasons and potential solutions for this are described in Section 5.4.5

5.3.4.3 Likelihood for rating a deviation as major

Results from the logistic regression analyses showed that nurses were more likely to rate an insulin infusion restarted two or less hours late and an amount of rescue glucose given incorrectly once as major, as compared with medical doctors, even after controlling for their level of experience (Table 5.5). Also, professionals with five or less years' experience were more likely to rate an insulin infusion restarted two or less hours late as major, as compared with more experienced staff, even after controlling for their profession (Table 5.5). However, the estimates of the ORs had very large CI so, while they were statistically significant, there was some uncertainty about the actual size of the effect. All other results from the logistic regression analyses were not statistically significant.



Deviations:

(Q.4.1) BG measurement missed x1
(Q.4.2) Insulin titration missed or incorrect x1
(Q.4.3) Insulin infusion restarted ≤2 hours late
(Q.4.4) BG measurement missed x2 or more
(Q.4.5) Insulin titration missed or incorrect x2 or more
(Q.4.6) Insulin infusion restarted >2 hours late
(Q.4.7) Insulin infusion not turned off
(Q.4.8) Giving incorrect amount of rescue glucose x1
(Q.4.9) Rescue glucose administered ≤15minutes late
(Q.4.10) Rescue glucose administered more than 15 minutes late

Figure 5.8 – Distribution of opinions on whether pre-specified deviations from protocols for glycaemic control are major or minor deviations, by level of experience.
[a] The proportion of professionals who considered "An insulin infusion restarted ≤2 hours late" a major deviation was significantly higher amongst professionals with five of less years' experience

Table 5.5 - Effect of professionals' role and number of years' experience in intensive care on their likelihood for rating pre-specified deviations from the protocol as major deviations

	OR (95% CI)	*p-value*	Adj OR (95% CI)	*p-value*
Rating these deviations are <u>major</u>:				
BG measurement missed x1				
Nursing staff	3.3 (0.5, 19.4)	*0.196*	3.5 (0.5, 22.1)	*0.158*
≤5 years' experience	1.0 (0.2, 6.6)	*0.962*	1.4 (0.2. 9.7)	*0.747*
Insulin titration missed/incorrect x1				
Nursing staff	4.9 (0.5, 44.6)	*0.159*	5.1 (0.5, 47.0)	*0.153*
≤5 years' experience	1.0 (0.2, 4.5)	*0.938*	1.3 (0.3, 5.6)	*0.766*
Insulin infusion restarted ≤2 hours late				
Nursing staff	6.7 (1.3, 38.4)	*0.026*	17.1 (2.4, 123.4)	***0.005***
≤5 years' experience	5.3 (1.2, 24.2)	*0.030*	12.9 (2.1, 78.0)	***0.005***
BG measurement missed x2 or more				
Nursing staff	1	*N/A*	1	*N/A*
≤5 years' experience	0.4 (0.1, 3.5)	*0.440*	0.6 (0.1, 4.7)	*0.595*
Insulin titration missed/incorrect x2 or more				
Nursing staff	1	*N/A*	1	*N/A*
≤5 years' experience	1.5 (0.1, 16.0)	*0.737*	2 (0.2, 22.1)	*0.571*
Insulin infusion restarted >2 hours late				
Nursing staff	3.2 (0.3, 29.4)	*0.308*	3.6 (0.4, 34.4)	*0.265*
≤5 years' experience	1.6 (0.3, 9.1)	*0.614*	1.9 (0.3, 11.5)	*0.481*
Insulin infusion not turned off				
Nursing staff	1	*N/A*	1	*N/A*
≤5 years' experience	1	*N/A*	1	*N/A*
Incorrect amount of rescue glucose x1				
Nursing staff	8.1 (0.9, 72)	*0.060*	10.9 (1.2, 102.7)	***0.036***
≤5 years' experience	2.3 (0.5, 10.3)	*0.279*	3.5 (0.7, 17.2)	*0.125*
Rescue glucose administered ≤15 minutes late				
Nursing staff	1.5 (0.3, 7.0)	*0.567*	1.5 (0.3, 6.8)	*0.621*
≤5 years' experience	0.7 (0.1, 3.3)	*0.664*	0.7 (0.2, 3.7)	*0.740*
Rescue glucose administered >15 minutes late				
Nursing staff	0.8 (0.2, 4.2)	*0.835*	0.8 (0.2, 4.4)	*0.831*
≤5 years' experience	1.0 (0.2, 5.0)	*1.000*	1.0 (0.2, 5.0)	*0.963*

BG: blood glucose; OR: odds ratio; Adj OR: adjusted odds ratio

[a] Nursing staff as compared with Medical staff

[b] Professionals with five or less years' experience as compared with professionals with more than five years' experience

5.4 Discussion

Professionals' attitudes towards, and perceptions about, the aims and methods for GC of protocols, are rarely reported in studies on the effectiveness of these protocols. Bland et al. (2005) and Aragon (2006) surveyed nursing staff about their perceptions on GC, although they only focused on TGC and its management, and medical staff were not included. In a larger study, Mc Mullin et al. (2004) surveyed both nurses (74%) and physicians (26%), although they were mainly concerned about professionals' beliefs and attitudes towards a number of practicalities and strategies of GC. None of these surveys looked at professionals' views on the aims of GC as measured by the TIR, the treatment of hypoglycaemic events, or about not adhering to protocol instructions. The GlyCon study aimed to decrease these gaps in the current evidence by exploring the opinions of nursing and medical staff from the seven ICUs of the MTCCN network, on these important aspects of GC.

5.4.1 Degree of glycaemic control

Currently there are no standards agreed about the minimum optimal TIRs that should be targeted, within a safe BG. For example, Carr et al. (2005) defined good GC as more than 50% TIR at BG<7.2mmol/L, while Rady et al. (2005) defined poor GC as less than 5% TIR at BG<8mmol/L. A number of studies proposed different TIR thresholds to define good GC, based on the impact on clinical outcomes. The following TIR thresholds have been associated with higher survival: 80% TIR at BG within 3.9-7.8mmol/L (Krinsley & Preiser, 2015), 80% TIR at BG within 4-7mmol/L (Penning et al., 2015), and 70% TIR at BG within 4-7mmol/L (Signal et al., 2012). Also, TIR≥80% at BG within 6-8.1mmol/L has been associated with less wound infections, shorter length of ventilation, and shorter ICU stay in patients after cardiac surgery (Omar et al., 2015); and cumulative TIR>50% at BG within 4-7mmol/L has been associated with lower levels of organ failure (Chase et al., 2010).

The findings of the GlyCon survey are broadly in line with the publications cited above: over half of the respondents stated that a patient spending less than 75% of the admission time within a targeted glycaemic range constituted poor GC. This opinion was even more prevalent among medical doctors and professionals who had more than five years' experience. However, TIR≥75% has proven to be difficult to achieve amongst critically ill patients, at various glycaemic target ranges. Previous studies rarely reported median or mean TIR higher than 75%, especially when the glycaemic targets were normal or narrow ranges (see Table 2.4).

Despite being difficult to achieve TIR≥75%, over half of the GlyCon survey participants agreed that TIR<75% constitutes poor GC. This indicates that professionals seemed to be

aware about the evidence associating lower TIR with poor outcomes, and were responding to this. It could be that either TIR≥75% was actually being achieved in their units, or that such level of TIR was not being achieved, but they still had the "evidence-based" aspiration for achieving it. The subsequent retrospective study of GlyCon, which looked at the outcomes of these participating ICUs, in terms of TIR values, clarified whether the ICUs managed to achieve such TIR of at least 75% on average. This is described in Chapter 6.

Nonetheless, regardless of whether the ICUs considered for GlyCon study achieved a higher TIR than reported in previous studies or not, there were still seven (18%) to 15 (38%) of professionals who rated different ranges of TIR, which were lower than 75% TIR, as good GC (Figure 5.2).

Factors that may have affected these opinions, besides the profession and level of experience, are discussed in Section 5.4.4.

5.4.2 Treatment of hypoglycaemic events

Severe hypoglycaemia has been largely associated with higher risk of neurological damage and mortality (Ancona et al., 2011; Krinsley & Grover, 2007; Van den Berghe, Wilmer, Hermans, et al., 2006; Finney et al., 2004; Van den Berghe et al., 2001). Professionals who responded to this survey seemed to be aware of these associations as all of them except one stated that they would always treat hypoglycaemias below 2.2mmol/L with rescue glucose.

One medical doctor with more than five years' experience answered that a hypoglycaemia of 1.5-2.2mmol/L should be treated with glucose only depending on the underlying condition of the patient. He/she could be referring to cases in which patients are particularly vulnerable to hyperglycaemia, such as surgical patients or patients with certain cardiovascular conditions (Buchleitner et al., 2012; Mesotten et al., 2009; Griesdale et al., 2009) and, therefore, he/she could decide to not administer any glucose even if BG is within 1.5-2.1mmol/L. However, since this respondent did not specify which underlying conditions he/she was referring to, it remains unclear which situations he/she would consider as not warranting the administration of rescue glucose.

Most professionals stated that they would only administer rescue glucose to patients with hypoglycaemia below 4mmol/L (but higher than 2.2mmol/L) depending on the underlying condition of the patients. This also shows existing concerns about the development of hyperglycaemic events. In fact, none of the protocols of the participating ICUs recommended the administration of rescue glucose for the treatment of hypoglycaemia when the BG was more than 3.1mmol/L (Figure 4.5). Hence, regardless of the profession and level

of experience, there was a clear agreement amongst professionals on this particular GC protocol instruction.

5.4.3 Deviations from instructions of protocols for glycaemic control

Most of the survey respondents agreed in their rating of the pre-specified deviations from protocol as major or minor with the ratings proposed by Taylor et al. (2006) (Figure 5.6). On the other hand, there were three deviations categorised as minor by Taylor et al. (2006), which the majority of the professionals of the GlyCon survey considered as major. These included an insulin infusion not turned off (major for 95% of respondents), an insulin titration missed or done incorrectly once (major for 65% of respondents), and an insulin infusion restarted two or less hours late (major for 50% of respondents) (Figure 5.6).

Given that Taylor et al. (2006) had done the classification based on their clinical judgement (C. Coopersmith, personal communication via email, 2016), and that 33% of the GlyCon professionals had five or less years' experience in intensive care (Figure 5.1), the survey respondent's experience and expertise could be behind these divergent opinions. For example, professionals with more than five years' experience were significantly more likely to agree with Taylor et al. (2006) in rating an insulin infusion restarted two or less hours late as minor than their less experienced colleagues, even after controlling for their profession (Table 5.5). Contextual differences, including institutional and geographical factors (single ICU in USA vs several ICUs in UK), as well as temporal factors (2005 vs. 2015), could also be part of the reason for these differences in opinion. Temporal factors are related to the availability of different evidence guiding clinical practice. From the time that the publication by Taylor et al. (2006) was accepted in September 2005, until the launch of the GlyCon survey in December 2014, the evidence about the effects of GC in ICU increased greatly, including the publication of at least 25 systematic reviews and meta-analyses on different aspects of glycaemic control in the ICU, as indexed in PubMed.

Most of the pre-specified deviations from protocol instructions included in this survey were rated as major by the majority of professionals, especially those deviations related to the administration of IV insulin (Figure 5.6). On the other hand, two of the deviations related to BG monitoring (a BG measurement missed once) and administration of rescue glucose (a rescue glucose infusion administered 15 or less minutes late) were rated as minor by 85% and 65% of the professionals, respectively. In addition, two of the insulin related deviations were rated as minor by 30% (an insulin infusion titrated or done incorrectly once) and 48% (an insulin infusion restarted two or less hours late) of the professionals (Figure 5.6).

A BG missed once may mean that a patient spends several hours without being monitored, during which dysglycaemic events could be missed. However, in the free text comments to this question professionals point out the need to consider the situation, such as when the BG is "stable" or when the patient is not receiving insulin (Table 5.3). Similarly, while a late rescue glucose in a patient with severe hypoglycaemia could have detrimental effects, including increasing the risk of mortality (Krinsley et al., 2011; Bagshaw et al., 2009), professionals emphasise the need to consider the context of the deviation, such as the BG levels or whether insulin is being administered (Table 5.3).

There are significant risks associated with the treatment with insulin of critically ill patients (Fowler & Rayman, 2010; Chase, Shaw, et al., 2008), and late or incorrect titrations of insulin infusions could make these worse. Insulin resistance in critically ill patients often requires that insulin is administered in very high concentrations for its effect to saturate, which in turn increases the risk for iatrogenic hypoglycaemia (Chase, Shaw, et al., 2008). In addition, insulin treatment in ICUs is often used reactively rather than to prevent hyperglycaemia, and this increases the probability of making errors (Fowler & Rayman, 2010). Consequently, the risks associated with late or wrong titrations of insulin infusions in critically ill patients should not be underestimated. On the other hand, insulin needs are affected by a multitude of factors, including patient related and treatment related ones. This makes the determination of insulin needs even more complex, and may result in fixed insulin sliding scales not being followed by clinicians (Chase, Hann, et al., 2007).

Factors that may have affected the survey respondents' opinions, besides their profession and level of experience, are discussed in Section 5.4.4.

5.4.4 Factors associated with professionals' views

The survey responses indicate that medical doctors and more experienced staff seemed more concerned about maintaining patients within the glycaemic target so as to achieve high TIR values, while nurses and less experienced professionals seemed more concerned about adhering to what they are supposed to do according to their protocol instructions. Similar observations have been reported in other studies. In their large survey on GC, Mc Mullin et al. (2004) found that more physicians were concerned about hyperglycaemia, while more nurses were concerned about aspects that can affect their practice, which would in turn affect their adherence to instructions, such as the glucometer availability, duration of laboratory turnaround, and taking BG measurements too often. The same study also found that significantly higher proportions of physicians than of nursing staff endorsed the need to put different strategies in place to achieve optimal GC. In an observation study about critical care nurses' decision-making activities in routine clinical practice, Bucknall (2000) found

that nurses carried out so-called "old" intervention decisions (following directions from other nurses, doctors or protocols and policies) two to seven times more often, on average, than "new" intervention decisions (initiating a new therapy or new changes to existing patient care).

The different opinions found in GlyCon depending on professionals' role and experience could lead to different practice, and therefore different outcomes. Previous studies have shown that professionals' experience can affect how medication is prescribed (Peters-Klimm et al., 2012; Fehrenbach et al., 2001), and even patients' outcomes, such as length of stay and mortality rates (Southern et al., 2011). It seems necessary that a higher awareness about the impact of poor GC, defined by a low TIR, is promoted especially amongst nursing and less experienced staff.

Other than the professionals' role and level of experience, there are a number of other factors that could affect professionals' views, including lack of knowledge or unawareness about the latest evidence, resistance to change established ways of practice, and a tendency to overemphasise successful personal clinical decisions over successful decisions based on rules, among others (Blakey et al., 2015). Since exploring these factors was not the aim of the GlyCon survey, they were not included in the questionnaire. Future studies investigating a more comprehensive group of variables affecting professionals' opinions may be able to determine other factors, as well as to confirm the effects of the profession and level of experience found in GlyCon. While these factors will not be easy to investigate in future studies, whether any of these or other reasons are behind the differences found in the GlyCon survey should be investigated, and qualitative research approaches may be the best way forward for this.

Finally, another important factor that could be related to why some professionals were less concerned about straying from protocols, is the type of protocols for GC that were in place in their ICUs. As described in Chapter 4 all the protocols for GC implemented in the ICUs participating in GlyCon, were a "one size fits all" set of recommendations and the same instructions were given for all patients, without considering sub-populations that may benefit from different management approaches. For example, patients with diabetes may require a different glucose target (Krinsley et al., 2013), and/or higher dosages of insulin to achieve the same glucose levels (Rady et al., 2005). In the GlyCon study, none of the ICUs had protocols with different targets for patients with diabetes, and only three ICUs made different recommendations for patients with diabetes, which were mainly a higher insulin dosage for any glycaemic range. Also, patients with acute cardiac syndrome (Deedwania et al., 2008) or with cardiac surgery and ICU length of stay above three days (Lazar et al., 2009) may benefit from lower glycaemic target ranges. In such cases, a more personalised

approach in the management of ICU patients' GC has been proposed in the past few years by experts in the field (Preiser & Straaten, 2016; Krinsley, 2014; Le et al., 2013). However, none of these sub-populations were mentioned in the protocols for GC of the GlyCon participating ICUs.

5.4.5 Methodological considerations

The results from this survey show important findings, which help to understand how GC is being implemented in ICUs. Among the strengths of this survey is the fact that it can be completed online, which allows for the inclusion of large and widely spread populations (Evans & Mathur, 2005). The survey was designed as a very short questionnaire in an attempt to improve the response rate (Evans & Mathur, 2005). Another factor that increased the participation rate was the endorsement of the study by the ICU network as a study for their quality improvement group. In addition, the invitations to participate in the survey were sent by the ICU collaborators for the study in each ICU, who were senior colleagues of those invited to participate, rather than an external researcher unknown to them.

Some of the answers to the survey questions had a distribution that did not show a logical trend. Also some of the comments included in the free text spaces, indicated that some questions may need further clarifications. As a consequence of being an online self-administered questionnaire, it could be that some of the questions were not sufficiently self-explanatory for some respondents, and occasional misunderstandings may have occurred. Also, as an anonymous self-administered online survey, inter-rater reliability and test-retest reliability did not apply to this survey. Future studies could build on and amend the GlyCon survey in order to improve its reliability and internal validity, and to reduce the possibility of misunderstandings in the survey questions, which could have affected the results obtained in the GlyCon survey. Suggestions in this regard are provided below.

Recommendations for future studies using this survey

The questions included in this survey were designed so that it was applicable to most ICUs. However, due to protocol differences, future studies using this survey in different settings may need to review the protocols for GC in place in the participating ICUs in order to confirm or adapt any questions that may not be applicable to particular ICUs.

In the section on degree of GC, a description of the meaning of the two extremes of TIR (0% and 100%) should be added to help with the clarity of these questions. In questions on deviations from instructions, more detailed descriptions of the pre-specified deviations may help to avoid misunderstandings. Also, it should be stated at the beginning of the survey that the questions refer to involuntary omissions, rather than to voluntary decisions.

5.5 Summary of results and conclusions

When surveyed on various aspects of GC in intensive care, ICU professionals often agreed, although there were certain areas of disagreement in which their profession and level of experience seemed to play a role.

Professionals often agreed that TIR≥75% is good GC and TIR<50% is poor GC. Opinions were divided on an intermediate level of TIR, and professionals having more experience in intensive care tended to rate such intermediate TIR as poor GC more often than their less experienced colleagues. When their professional role was considered, opinions seemed more divided amongst nurses, and nurses rated lower levels of TIR as good GC more often than medical staff. Nonetheless, there were some nurses whose answers did not follow a logical trend, which may mean that there were some misunderstandings about the survey questions amongst them.

Most professionals agreed on the need to treat severe hypoglycaemia with rescue glucose, but opinions were more divided regarding the treatment of moderate hypoglycaemia.

Professionals also often agreed on how to rate pre-specified deviations from their protocols. There were only a few deviations where there was general disagreement in opinion, and both professionals' role and level of experience seemed to play a part in these disagreements. Also, respondents often commented on the possibility that a number of patient-related factors and other contextual factors could justify the need to deviate from protocols.

Given that professionals' views can affect their clinical practice, considering their opinions is essential in research studies on the impact of the implemented methods for GC. The findings of this survey helped in the interpretation and discussion of the results of the GlyCon retrospective study, which is the topic of the next chapter.

Chapter 6
Glycaemic control of stress hyperglycaemia in intensive care: a multi-centre retrospective study

6.1 Background

Current evidence suggests that untreated events of stress hyperglycaemia are associated with higher morbidity and mortality than if strategies are implemented to control those events (Dungan et al., 2009). However, there is also evidence that too strict methods for glycaemic control (GC) can actually be detrimental. The aim of GC strategies is to keep patients within a safe glycaemic range for as long as possible, while avoiding any type of dysglycaemia. The evaluation of currently implemented methods for GC in intensive care units (ICU) is essential for the determination of which are the optimal methods, or methods with the highest quality.

In this study, effectiveness, efficiency and safety are three indicators of quality, collectively referred to as EES. Previous studies on associations between methods for GC and metrics of EES have generally focused on the effect of protocols as a whole, for example a previous vs. a new protocol, on the levels of EES (see Table 2.4). However, there is evidence that protocols are often not adhered to (Kanji et al., 2010; Oeyen et al., 2007; M. M. Barth et al., 2007; Shulman et al., 2007; Rood et al., 2005). In order to avoid an impact misattribution to the protocol (Kavanagh & Nurok, 2016), the actual practice must be evaluated. Therefore, studies looking at how the actual methods for GC affect their effectiveness are currently needed.

Several metrics have been used in previous studies to evaluate the effectiveness of protocols for glycaemic control (GC) of stress hyperglycaemia in ICU, as well as their efficiency and safety (see Section 2.7). Due to differences in the instructions for GC given in protocols from different ICUs, not all metrics can be used to compare approaches used in different ICUs. Amongst the metrics that allow a comparison across ICUs are the following:

a) the percentage of time spent within a specified safe glycaemic target range (time in range, TIR), to evaluate the effectiveness;

b) the time from the first BG measurement above the glycaemic target range to the first time when glycaemic levels return to within range (time to range, TTR), to assess time-efficiency; and
c) the presence and duration of at least one event of moderate or of severe hypoglycaemia, as a measure of safety.

Higher TIR, lower TTR and less incidence and lower duration of moderate/severe hypoglycaemic events represent better GC. Low values of TIR (Krinsley & Preiser, 2015; Penning et al., 2015; Omar et al., 2015; Signal et al., 2012; Chase et al., 2010) and high incidence and duration of moderate/severe hypoglycaemic events (Krinsley et al., 2011, 2013; NICE-SUGAR Study Investigators et al., 2012; Egi et al., 2010; Hermanides et al., 2010; Bagshaw et al., 2009; Krinsley & Grover, 2007) have been associated with poor clinical outcomes, including higher mortality risk.

Main aim and hypothesis of the study

The main aim of the GlyCon study was to investigate the relationship between the different methods for GC implemented in critically ill patients admitted to the ICUs of the Mid Trent Critical Care Network (MTCCN), and the levels of effectiveness of these methods. Effectiveness was assessed based on the TIR at BG within 4-10mmol/L, which was the primary outcome measure of the study. In addition, the time-efficiency and safety of the methods for GC implemented were also explored. The primary and secondary outcome measures are described in Section 6.2.6.3.

The main study hypothesis was that monitoring patients more frequently and/or administering them with insulin for longer periods, during hyperglycaemia, result in more effective GC as measured by higher TIR.

The proposed glycaemic range (4-10mmol/L) was chosen as the study target to calculate the outcome measures because it included the glycaemic targets of all participating ICUs (see Figure 4.5). In addition, this range was discussed, and agreed as being the optimal study range, in a meeting with the representatives of the ICUs in the MTCCN. The upper threshold of 10mmol/L is also significant because it is the upper limit that is currently accepted by most international critical care societies for general ICU patients (see Figure 2.1) and because it is the level above which the toxic effects of hyperglycaemia are thought to occur (Preiser et al., 2009).

6.2 Methods

6.2.1 Study Design

A multi-centre retrospective study, with a repeated measures design, was carried out, based on the review of different types of medical records. Retrospective studies are observational studies in which both the exposures and the outcomes occurred in the past (Song & Chung, 2010). A group of subjects are selected based on their past exposure status, and a subsequent outcome of interest is reconstructed and analysed. Repeated measures designs use repeated measurements of one variable of interest, on the same experimental unit, over time or space (Sullivan, 2008). Medical records reviews are studies that use patient-focused data that are registered in patient records, as the primary source of information (Worster, 2004).

The study setting included the seven NHS ICUs of the MTCCN that admit level-3 critically ill patients, and the study period of interest spanned two years, from 1st January 2012 to 31st December 2013.

6.2.1.1 Sample

General characteristics of the MTCCN and the seven ICUs included in the study can be found in the overall methodology chapter (Section 3.2). The population of interest included all eligible patients admitted to the ICUs of the MTCCN, excluding one ICU of this network, which does not admit level-3 critically ill patients.

Inclusion criteria included all of the following:

a) received level-3 of care;
b) length of stay in intensive care of at least 48 hours;
c) had at least one glycaemic measurement above 10mmol/L during the first 24 hours of admission.

These criteria ensured that the most severely ill patients who survived the first two days of admission were included. Also during the study design phase, the only electronic data available about all the patients' glycaemic levels were the highest glycaemic levels recorded during the first 24 hours of admission. Consequently, the inclusion criterion (c) was chosen to ensure that all sampled patients had at least one event of hyperglycaemia.

Exclusion criteria included any of the following:

a) age below 18 years;
b) readmissions of the same patient during the period considered;
c) pregnant women;

d) patients with any of the following primary or secondary reasons for admission: cardiac surgery; insulinoma; islet cell transplant; diabetic emergencies including diabetic ketoacidosis, hyperosmolar coma, and hypoglycaemia due to the insulin therapy.

Patients meeting the exclusion criteria could have biased the study sample for the following reasons:

- Patients who were younger than 18 years old were sometimes admitted to paediatric ICUs in hospitals that had those services;
- Readmissions were excluded so that only one admission per patient was covered;
- Glycaemic metabolism changes occurring during pregnancy can lead to gestational diabetes, where hyperglycaemia is caused by reasons other than stress hyperglycaemia;
- Patients undergoing cardiac surgery in the Mid Trent area were usually admitted in a cardiac ICU, which is not part of the MTCCN;
- In "diabetic emergencies", insulinomas and islet cell transplants, glycaemic levels are affected for reasons other than stress hyperglycaemia;

6.2.1.2 Sample size

A priori calculations were performed in order to determine the minimum sample size required to test the main study hypothesis. For this, it was required to pre-determine: (a) an expected effect size or difference between the means of TIR (which is considered a continuous variable) of the two groups of patients compared (lower vs. higher monitoring frequency; and lower vs. higher percentage of time receiving insulin); (b) the variances of TIR in these groups; (c) the values of α (probability of rejecting the null hypothesis when it is true) and of $1-\beta$ or power (the probability of rejecting the null hypothesis if it is not true) of the tests (Van Belle et al., 2004).

In previous studies comparing the TIR of several groups, there was often a difference between the means of TIR in each group of at least 7%, and the SDs of TIR in each group had values ranging between 15% and 22% (see Table 2.4). Since the target glycaemic range proposed for the GlyCon study (4-10mmol/L) was broader than the ranges used in most of the previous studies, it was expected that the percentages of time spent within this range would be higher than in these previous studies. Higher percentages would have smaller SDs as they become closer to 100%. Given that critically ill patients have a median (IQR) ICU length of stay (LOS) of 4 (2-10) days (Soares et al., 2012, p. 149), 5% difference in TIR would represent a median (IQR) of 5 (2-12) hours difference in the total LOS, and 7% difference in TIR would represent 7 (3-17) hours difference in the total LOS. Since higher TIR has been associated with survival benefit in critically ill patients (Krinsley & Preiser,

2015; Penning et al., 2015; Signal et al., 2012; Chase et al., 2010), these differences were considered as clinically important in this study.

Consequently, pre-study power calculations, using GPower®, yielded the following results. A sample size of 150 patients would provide over 80% power (1–β), to detect a difference in the means of two equally sized groups (e.g. groups with monitoring frequencies above and below the median) of 5% assuming a SD of 10%, or of 7% assuming a SD of 15%, using a significance level of 0.05, in two-tailed tests (Figure 6.1). For planning purposes, equal sample sizes and equal variances per group were assumed (Van Belle, 2002). The final sample size of 150 selected for the study was also higher than the exact sample sizes obtained with the parameters chosen for these calculations (Figure 6.1) to account for potential inter-group variability (Van Belle et al., 2004).

For the sample selection, a stratified random sampling with allocation proportional to two levels of strata was used. Strata included the ICU and the type of admission (surgical vs. medical). As a result, the sample size of each stratum was proportional to the number of annual medical and the annual surgical eligible admissions in each of the ICUs of the population. This sampling technique was used in order to get a more representative random sample of the population of interest (Malec, 2005).

6.2.2 Data sources and acquisition

Data were acquired for GlyCon study from various sources. These sources and the procedure followed to extract and record the required data from them are described in this section.

6.2.2.1 Data sources

Data sources used in GlyCon included the Case Mix Program (CMP) database of the Intensive Care National Audit & Research Centre (ICNARC), observation charts, medical notes and a number of other databases, which varied in each hospital.

Case Mix Program database of ICNARC

ICNARC is an independent registered charity that carries out national clinical audits and research about the quality of care provided in UK NHS ICUs (ICNARC, 2014). The CMP is one of the national audits that ICNARC has in place. It is focused on patient outcomes derived from adult critical care provided by ICUs and high dependency units (HDU). Most of the data collected for the CMP is about the first 24 hours of admission (ICNARC, 2009).

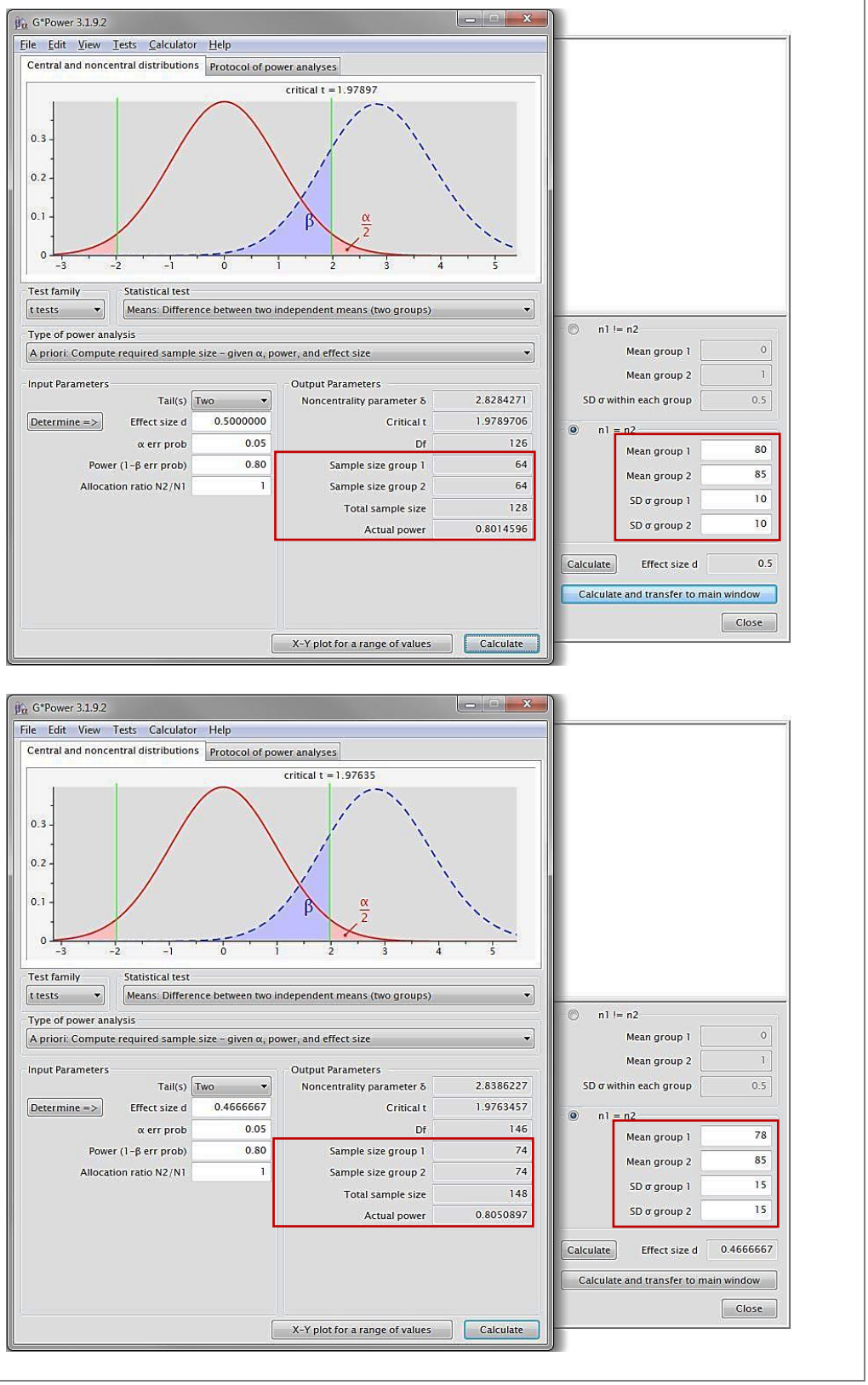


Figure 6.1– Sample size calculations in order to ensure 80% power, using a α=0.05 significance level (two-tailed), to detect a difference in the mean TIR of two equally divided groups of 5% with a SD of 10% in both groups (top), or 7% with a SD of 15% in both groups (bottom)

The ICNARC CMP database was used in this study to identify eligible patients and obtain a random sample from them as described earlier. It also provided important demographic and clinical baseline data, as well as treatment-related data (Table 6.1).

Observation charts

Observation charts were used by nursing and medical staff to record hourly and daily physiological and treatment data of each patient. There was one observation chart per natural day of admission per patient. Most charts were recorded manually. In 2013, electronic charts were introduced in the ICU of one of the hospitals (H-600), and the study sample included four patients with these charts.

Essential clinical and treatment-related data were obtained for each patient from these observation charts, including glycaemic levels, glycaemic monitoring frequencies and insulin titrations (Table 6.1). Based on these data, the primary and secondary outcome measures of this study, exposures of interest, and measures of the degree of staff adherence to the protocol's instructions, were calculated. Other information collected from these charts is listed in Table 6.1.

Medical notes

Each patient had one or more personal files with manually or electronically recorded clinical and treatment data, and printed copies of test results, resulting from all their hospital admissions and specialist appointments occurring within the same trust. From these, important clinical and treatment data were obtained (Table 6.1). Whether the patient had a previous diagnosis of diabetes was often found in manually written notes about their past medical history, or in GP or specialist letters filed within these notes. Enteral nutrition (EN) and total parenteral nutrition (TPN) prescriptions were usually filed within the notes too.

Other electronic records

In two hospitals (H-100 and H-200), belonging to one trust, a trust-specific electronic platform was used to collect data on the patients' previous diagnosis of diabetes and type.

6.2.2.2 Data acquisition procedure and instrument

In this study, the acquisition of data was divided into two phases. The first was the data collection phase, which entailed requesting, reviewing, anonymising and taking photographs of the manual and electronic medical records. This was followed by the data entry phase, consisting of the extraction of information from the photographs, storing the data in a database and carrying out quality checks on these data. A flow-chart with a summary of these and subsequent steps is shown in Figure 6.2.

A case report form (CRF) was designed, containing variables for each of the data listed in Table 6.1. The CRF guided the data request and data collection, and was the database where the study data were inputted during the data entry phase. There was one CRF per patient. The structure was set in long format, meaning that each patient had multiple observations (rows) of data, per time-dependent variable. Time-constant data (e.g., previous diagnosis of diabetes) had the same value in all the rows for that variable in the same patient. Example extracts of the CRF can be found in Section 6.2.5.

Table 6.1 – Data sources and data collected from each source

CMP database
a) Demographic data: age on admission; sex and ethnic group; b) Anthropometric data: height, weight; c) Clinical data: type of admission; primary reason for admission; highest glycaemic levels during the first 24h; ICNARC and APACHE II physiology scores, and their model predicted mortality risk scores (ICNARC 2013 recalibration); ICU and in-hospital mortality (any cause); ICU and hospital length of stay; ICU-acquired infections (any); presence of blood stream infections; d) Treatment data: Organs needing support, type and duration (days) of support; antimicrobial use during ICU admission.
Observation charts
a) Recorded glycaemic levels and most probable blood source and analysis method; b) Time at each measurement; c) Hourly insulin dosage; d) Nutritional support administration rate, via enteral and/or parenteral nutrition; e) Dosage of glucocorticoids, catecholamines, propofol.
Medical notes
a) Previous diagnosis of diabetes and type; b) Dosage of glucocorticoids, catecholamines, propofol; c) Hypoglycaemic agents (for diabetes treatment) type and dosage; d) Type of enteral and/or parenteral nutrition prescribed.

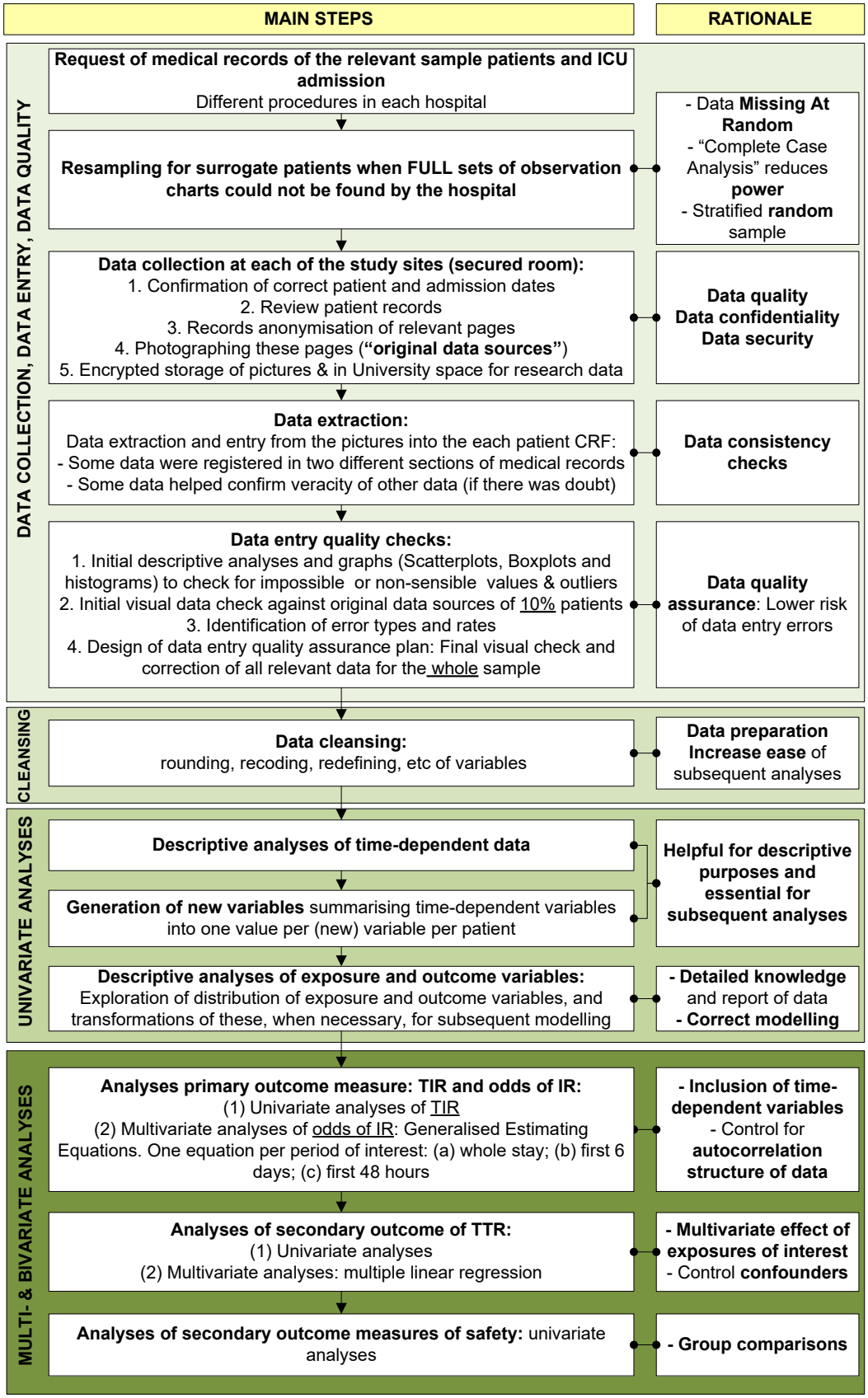


Figure 6.2 – Flow-chart of the steps followed for data collection, entry and analyses, and the main rationale for each of the steps

6.2.3 Data collection

All relevant permissions and ethical approvals were granted before the start of data collection. Further details are described in the overall methodology chapter (Section 3.4.1).

6.2.3.1 Data requests and data collection

A request for data from the CMP database of ICNARC was submitted. After their approval, ICNARC sent a data extract in encrypted format via email. This contained all the relevant data from the CMP database for all eligible patients, including two personal identifiers: NHS and ICNARC CMP numbers. Before randomisation, each patient was allocated a study specific identifier (ID). This ID had two parts: the first three digits identified the hospital, with a number ranging from 100 to 700, in hundreds; the subsequent digits were the patient unique ID number, which ranged from 1 to N, where N was the total number of all eligible patients at each hospital. From this list of patients, the stratified random sample of 150 patients was obtained using Stata®. The corresponding patient identifiers were subsequently used to request the relevant medical records at each of the participating hospitals, in succession. These requests where done through intermediary administrative or managerial staff in each of the hospitals (Figure 6.3).

Collection of the data of interest from the medical records took place in observed rooms within the premises of the participating hospitals (Figure 6.3). For this, relevant sections of the patients' medical records were anonymised and photographed. Anonymisation consisted of covering personal identifiers with note papers on which was written the study-specific ID and, often, the admission day to which the record belonged (an example can be seen in Figure 6.5).

6.2.3.2 Feasibility study

The feasibility study phase explored the data collection duration and methods, including the CRF format and contents. This was carried out in two of the participating ICUs with a subsample of 15 (10%) patients. Based on the results of this phase, the CRF was reorganised and adapted to facilitate the data entry; and the option of scanning medical records was replaced by photographing them.

6.2.3.3 Quality of data collection

A number of measures were taken to ensure that the data collection was of good quality:

- Before the start of data collection for each patient, dates and identifiers were used to confirm that the records belonged to the correct patient and for the relevant admission.

- A check-list with the main fields to review and photograph helped to ensure that all relevant data were recorded. A data collection field notebook was used to keep notes on incidences, remarks, and any actions needed.
- During the data collection phase at each ICU, data entry (in the database) was carried out for the first patient before proceeding with data collection for the remaining cases, in order to assess the ease of data entry and amend the CRF if required.

6.2.4 Missing data

During data collection, three types of missing data were encountered in this study:

a) some full sets of observation charts could not be found, resulting in all the essential data about both the outcome and the exposure variables of interest being missing;
b) several sets of observation charts had one or more pages missing, resulting in some of the essential data about both the outcome and the exposure variables of interest during the admission time corresponding to these chart/s being missing;
c) some of the medical notes were either incomplete or could not be found.

Figure 6.3 – Illustrative images of the data collection phase: (a) Storage of the requested boxes of records within an ICU (yellow rectangles), and hospital staff doing the records' request; (b) Storage of the requested records within an ICU; (c,d) Requested records on desk during data collection within the hospital

In addition, as expected, BG levels were usually not recorded in the observation charts on an hourly basis, even if other hourly data were present.

Missing data can be classified into three types depending on the mechanism causing the missingness (Ibrahim & Molenberghs, 2009). Data missing completely at random (MCAR) refers to situations when the probability that data of interest (among the outcome and/or the exposures or other covariates) are missing is unrelated to the values of such data. Data missing at random (MAR) refers to cases when the probability that data in a variable of interest are missing does not depend on its values, once other observed variables have been controlled for. When data are MCAR, they are also MAR. Finally, data missing not at random (MNAR) occurs when the probability of being missing depends on the values of the missing or unobserved parameters of interest, even after controlling for observed data.

Depending on the mechanism causing the missingness, there are different approaches to deal with missing data (Ibrahim & Molenberghs, 2009). When it can be assumed that data are MAR, and the factors determining the missing data mechanism are different from the parameters to be estimated, the missing data mechanism is said to be ignorable. When missing data are ignorable there is no need for modelling the missing data mechanism, but procedures to improve the efficiency of the available data need to be put in place.

The approaches followed for dealing with each type of missing or unavailable data in this study are described below.

6.2.4.1 Completely and partly missing records

Full sets of charts missing

All hospitals except H-400 and H-500 had some patients with full sets of charts missing. In H-200, a large number of full sets of observation charts had been destroyed during recent years due to limited storage space. The remaining hospitals were unable to explain why their missing charts could not be located, other than they had been accidentally lost or filed elsewhere but the location was unknown. There was no reason to believe that the fact that the sets of charts were missing was related to the values of any of the variables of interest within them. Therefore, the possibility that their information was MNAR was discarded.

The reasons why H-400 and H-500 did not have any charts missing could be due to their different storage systems. In H-400 charts were stored within the medical notes which were kept within the hospital (rather than off site), and in H-500 charts were stored within the ICU itself.

Given that all the essential data needed to calculate both the outcome and the exposure variables of interest were missing in patients whose full sets of observation charts were

missing, these patients could not be included in any of the analyses of interest. A complete case analysis approach, where only patients with available data are included, without replacing those patients with full sets of missing charts, would have reduced the sample size, leading to less efficient analyses. In the classical (frequentist) view, "every subject in a randomly chosen sample can be replaced by a new subject that is randomly chosen from the same source population as the original subject, without compromising the conclusions" (Donders et al., 2006). Therefore, through the same stratified random sampling procedures as for the initial sample, surrogate patients were randomly selected to replace those patients in the sample who had full sets of charts missing.

Incomplete sets of observation charts

Hospital staff explained that some pages within a set of observation charts often go missing as they are accidentally lost or filed elsewhere. There was no reason to believe that the values of the variables of interest in these charts were among the factors causing the charts to be missing. Therefore, the possibility that their information was MNAR was discarded. However, in cases when a high proportion of charts were missing from a patient's file, a high percentage of essential data required to calculate the outcome and exposure variables of interest were also missing. In these cases, there was a high risk that the data were insufficient to represent the patient's ICU stay. Hence there was a high risk that the values of those outcome and exposure variables were inaccurate, and therefore biased.

Consequently, even though data from missing parts of observation charts was not considered as MNAR, in order to handle the risk of biased results, patients who met either or both of the following conditions were excluded from the analyses: (a) data from the charts were missing for more than 50% of the first 48 hours of a patient's ICU stay; (b) data from the charts were missing for more than 50% of a patient's whole ICU stay. In such cases the whole patient was removed from the analyses, and sensitivity analyses were performed with and without the removed patients, so as to determine the effect of including those patients. Patients who did not meet any of these criteria were included, and analyses were performed on their available data.

Missing data within medical notes

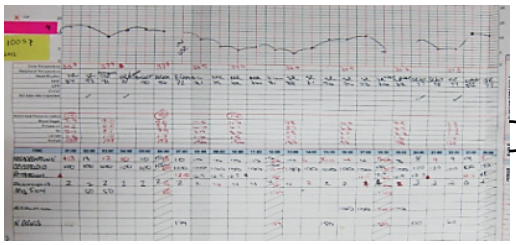
The main pieces of information that were frequently missing within the notes were the nutritional preparations prescription sheets, and the type and amount of glucose-based fluids administered, including rescue glucose prescriptions for the management of hypoglycaemia. In most ICUs, fluids administered were usually registered in the observation charts as crystalloids, in which other non-glucose-based fluids were included.

The reasons why medical notes were either incomplete, with some pages missing, or even completely missing (impossible to locate), were also unknown by the hospital staff. Thus, the possibility that their information was MNAR was discarded. Since the missing information was not essential for the calculation of the outcome or the main exposure variables of interest, all patients were included regardless of the amount of missing information from the medical notes.

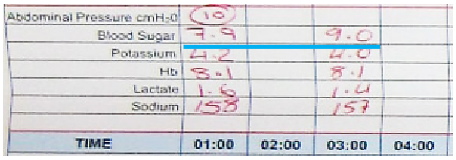
6.2.4.2 Unrecorded glycaemic levels, blood source and analysis method

While unrecorded BG levels are not strictly missing data, given the outcome measures of this study, the BG levels had to be imputed (filled in) for the hourly intervals where measurements were not recorded. Linear interpolation at hourly intervals was the method used to impute the BG levels between recorded measurements, assuming a linear progression between two measurements. This approach is the most commonly used approach in these types of studies (Krinsley & Preiser, 2015; Chase, Hann, et al., 2007; Rood et al., 2005). During the hours before the first and after the last BG available, BG levels were not extrapolated. Also, during the time covered by a missing chart, interpolation was not carried out. In order to check for the effect of spending more than eight hours without a glycaemic measurement, on the values of the outcome measure, sensitivity analyses were conducted including and excluding the observations when the patient had spent more than eight hours without any measurement performed in ICU (i.e. when at least two BG measurements had been missed, as the maximum interval time between measurements recommended in the protocols of the ICUs of this study was four hours).

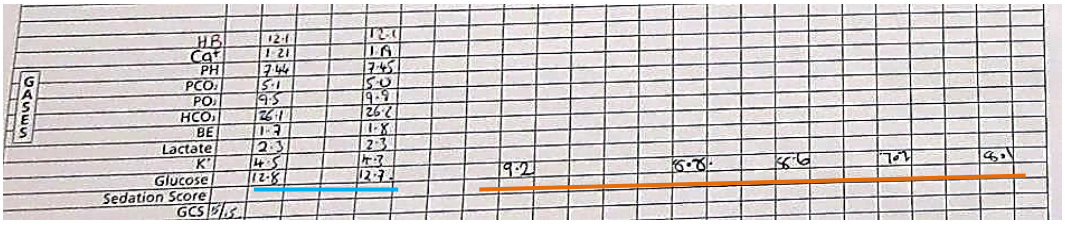
The blood source and analysis method of each glycaemic result were not recorded within the available records. The ICU staff of three ICUs informally communicated that in the case of ventilated patients it was common for arterial samples to be taken and analysed in the gas machine. Patients meeting the inclusion criteria of GlyCon were often ventilated patients. However, due to the retrospective nature of the study, it could not be confirmed what the actual blood analysis methods were. Therefore, glycaemic levels were analysed all together, irrespective of the blood analysis method. This was the approach taken in a previous large study by Krinsley & Preiser (2015). Nonetheless, for each glycaemic value, the "most probable" blood source (arterial, venous or capillary) and analysis method (blood gas analyser, glucose meter or other) were noted during the data entry, and used for descriptive purposes. This was done based on the instructions written in the protocols and verbal information obtained from the staff working in the participant ICUs. Figure 6.4 shows an example of how the most probable blood source and analysis method was arrived at.



Half a page of an observation chart



Other physiological parameters given by the gas machine were registered. Therefore most probable type of glucose measurement: arterial blood analysed in gas machine



Most probable type of measurements:

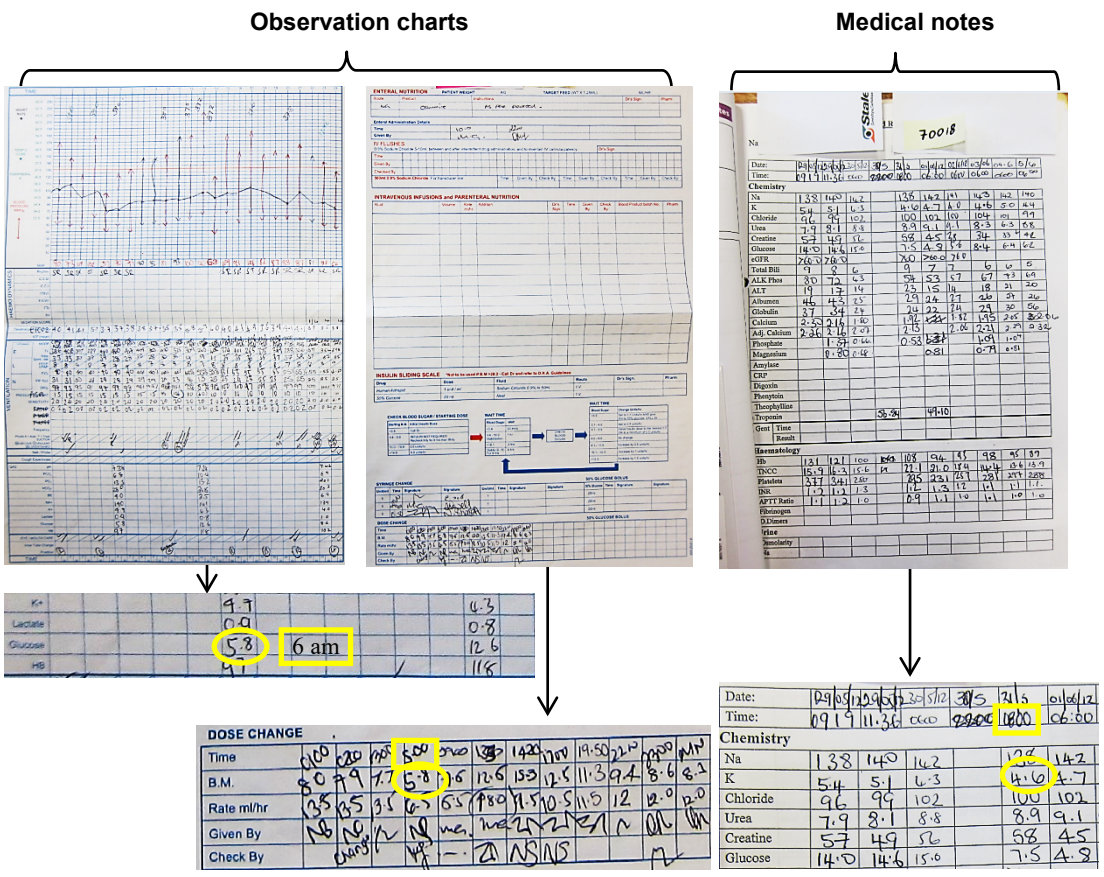
- Blue line: Arterial blood analysed in gas machine, as other physiological parameters given by the gas machine were registered
- Orange line: Other physiological parameters given by the gas machine were not registered. Depending on protocol instructions, the most probable blood sample and analysis method assigned to these values would be either "unknown" or "capillary blood analysed in a point of care glucose meter"

Figure 6.4 – Example of recorded glycaemic levels within the observation charts, and the logic followed to determine the probably blood source and analysis method

6.2.5 Data entry

The data entry of the data collected from the medical records (charts and notes) involved the lengthy process of visually identifying all relevant data from the photographs, and entering them in the CRF of each patient using Microsoft Excel®. This took place within the premises of the research team. Figure 6.5 illustrates an example of data sources and how data were entered in the database.

In the observation charts there was usually one value for each relevant treatment administration rates recorded every hour. From these, one observation per hour per variable was entered in the database. Since the exact time of administration was not recorded in the charts, the time of all rates was rounded to the next lower hour. Glycaemic values recorded in the charts were usually not hourly. Hours without recorded values were left empty. Occasionally two BG measurements were recorded in the same hour. In these cases, the average of the two values was entered in the study database.



Yellow circles: glycaemic levels; yellow squares: time of the glycaemic measurement.

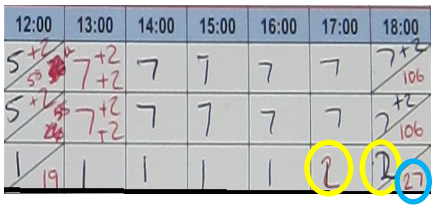
Section of the database when the BG levels above were entered:

Patient ID	Diabetes	Diabetes type	Day	Time	BG levels (mmol/L)	Blood source	Analysis method	Insulin (U/h)
70018	Yes	2	3	05:00	5.8	Unknown	Unknown	6.5
70018	Yes	2	3	06:00	5.8	Arterial	Gas machine	6.5
70018	Yes	2	3	07:00	.	.	.	6.5
70018	Yes	2	3	08:00	4.6	Venous	Lab	6.5
…	…	…	…	…	…	…	…	…

Figure 6.5 – Extract illustrating the location of glycaemic levels in different data sources and how they were entered in the database

The time of each measurement was used to generate the variable on glycaemic monitoring frequency, recorded as the time to next measurement (TNM). This was calculated as the time difference (in hours) from a measurement to the next one.

Occasionally there were data that were not understandable, or that were contradictory with other data sources. When the value of any data was not sufficiently clear, this was entered as "missing", or "not measured", depending on the nature of the data. Often, a second data source could be checked in order to determine the actual value, as shown by the example in Figure 6.6.



Unclear insulin infusion rate: 1 or 2? (Yellow circles)
Total amount infused (blue circle) helped to determine this

Figure 6.6 – Extract of an observation chart showing examples of unclear information, and how this was clarified during data extraction

6.2.5.1 Quality of data entry

The digital CRF was designed to give warning messages for logical errors in the data as they were entered. Also, when information in the original data sources did not look sensible or realistic, other data sources were used in order to try to ascertain whether it had been a human error of the person recording the information, or whether it was actually a possible value. A CRF codebook with an easily understandable and clearly defined list of variables was available during the entire data entry phase in order to minimise possible confusions about the relevant variables, as recommended by Latha et al. (2014).

After completing the data entry, a careful check was performed with a random sub-sample of 10% of the study patients, by visually comparing their database entries against the photographs of the original data sources. Error types were identified and the frequency of their occurrences were calculated. Three types of errors were found:

a) error in the total number of entries in a field or variable;
b) error in the recorded measurement time;
c) error in the value of the entry.

The frequencies of each error type were summarised in tables using counts and percentages. A thorough report on the data entry quality results was prepared so as to decide whether further checks were necessary. Table 6.2 shows an extract of this report, summarising the data entry quality results for glycaemic levels and monitoring frequency. All the tables of the report are included in Appendix C. Due to the clinical importance, relevance to the study aims, and distribution of the errors that were found in certain variables, the visual check was extended to cover the whole sample of patients for these variables, namely:

a) Glycaemic levels and monitoring frequency;
b) Insulin infusion rates (IIR);
c) Rescue glucose infusions rates;
d) EN and TPN types and rates.

Errors found during the full sample check of these variables were corrected in the database.

Table 6.2 – Data entry errors in the glycaemic levels and monitoring frequency of the sub-sample of 10% of study patients

Hospital	**100**	**100**	**200**	**200**	**300**	**300**	**400**	**500**	**TOTAL**	
Patient study ID no. (showing only cases with at least one entry error)	**10028**	**100175**	**2002**	**20075**	**30042**	**30061**	**40020**	**50054**	**All-8[a]**	**All[b]**
Total entries CRF-1	39	16	45	92	68	21	41	5	327	671
Total entries CRF-2	39	18	45	93	68	21	41	5	330	674
Mismatch in number of entries between CRF-1 and CRF-2										
Number (%) of occurrences	0	2(11.1)	0	1(1.1)	0	0	0	0	3 (0.9)	3 (0.4)
Range of values of the missing entries (mmol/L)	0	9.8-11.8	0	13.2	0	0	0	0	9.8-13.2	
Mean value of the missing entries (mmol/L)	0	10.8	0	13.2	0	0	0	0	12	
Wrong measurement time in CRF-1										
n (%)	0	1(5.6)	0	1(1.1)	1(1.5)	1(4.8)	2(4.9)	1(20)	7 (2.1)	7 (1)
Range of values of the Errors in time (h)	0	1	0	1	1	1	1	2	1–2	
Mean error in time (h)	0	1	0	1	1	1	1	2	1.2	
Wrong value of entries in CRF-1										
n (%)	1(2.6)	0	1(2.2)	0	1(1.5)	1(4.8)	0	0	4 (1.2)	4 (0.6)
Range of values of the errors (mmol/L)	0.6	0	0.5	0	0.3	3.4	0	0	0.3-3.4	
Mean error (mmol/L)	0.6	0	0.5	0	0.3	3.4	0	0	1.2	

CRF: Case Report Form; CRF-1: CRF of first entry, CRF-2: corrected CRF
[a] Out of the eight patients with at least one type of entry error in BG levels.
[b] Out of the sub-sample of 15 (10%) reviewed patients.

The size of the errors found during the sub-sample check of the data on the treatment with propofol, catecholamines and glucocorticoids were not large enough as to justify the time costs of checking these variables in the whole sample (Appendix C). The errors found in the sub-sample during the data check of these variables were not corrected so as not to bias the data.

6.2.5.2 Data cleansing

Frequency tables, box-plots and histograms of the data were examined visually in order to check for missing data, errors in the data such as outliers due to incorrect data entry, and data consistency.

As suggested by Aguinis et al. (2013), unexpected data points that were candidate error outliers were checked and corrected if they were found to be data entry errors. Those that were not data entry errors could have been errors made by the person completing the medical

record, during or after the clinical encounter. Since there was no way of confirming this, it was assumed that they were correct, and were kept in the database. Data points that were considered as interesting outliers, as defined by Aguinis et al. (2013), were studied in depth during the analyses. Influential and model fit outliers were dealt with during the analyses of association, as described in Section 6.2.7.2.

All variables were renamed for consistency and recoded. Empty observations were recoded to differentiate between missing data due to missing charts, not applicable data, and unrecorded glycaemic levels.

6.2.6 Variable definitions

The types of variables used in this retrospective study, and how they were defined and calculated are described in this section.

6.2.6.1 Clarification of key terms used in the study

Data on the glycaemic levels were recorded in two variables:

1) the variable containing the actual glycaemic levels that were measured and recorded in the observation charts, referred to as "recorded glycaemic (or BG) levels" in this study; and
2) the variable containing the recorded glycaemic levels as well as the linearly interpolated glycaemic values on the hours when glycaemic levels had not been measured (as described in Section 6.2.4.2), which are referred to as "interpolated glycaemic (or BG) levels".

As described in Section 6.2.4.2, in the interpolated glycaemic levels variable, values were not extrapolated before the first and after the last BG value available for each patient. Also, interpolation was not carried out during the time covered by a missing chart.

Three glycaemic statuses were considered in the analyses of this study:

1) hypoglycaemia of BG<4mmol/L, which is referred to as "hypoglycaemia" in this study;
2) glycaemia within the study target range of 4-10mmol/L, referred to as "glycaemia at BG=4-10mmol/L" or "glycaemia within the study target range"; and
3) hyperglycaemia of BG>10mmol/L, referred to as "hyperglycaemia>10".

The term "diabetic status" refers to patients' status regarding whether they had previously diagnosed diabetes or not.

6.2.6.2 Types of variables

Two main types of variables were used in this study: time-dependent and time-constant variables. An extract of the database with some of these variables is illustrated in Table 6.3.

Time-dependent variables

Time-dependent variables were those that changed over time (hourly). These included all the repeated measures of glycaemic levels, during the whole patient stay in the ICU, obtained from the observation charts. They also included hourly treatment data collected from both the observation charts and the medical notes.

Time-constant variables

Time-constant variables are those that remained constant over time. Hence, each patient had only one value for each time-constant variable. These included:

a) Clinical and baseline demographic characteristics of patients. Most of these were collected from the CMP database of ICNARC.
b) New variables, which described a relevant summary of a time-dependent variable over a period of time. These summary variables were calculated based on the first two days of ICU stay, the first six days of ICU stay and on the whole ICU stay. For example, the time-dependent variable on glycaemic levels at each hour was used to calculate the primary outcome measure TIR at BG within 4-10mmol/L, which was a time-constant variable.

Table 6.3 – Section of the database for one patient – time-dependent and time-constant (newly generated) variables

			Time-dependent		**Time-constant (summary of time-dependent)**		
Patient ID	**Day**	**Time**	**BG**	**BGi**	**TIR**	**TIR-2**	**TIR-6**
10025	1	22:00	6	6	70	50	65
10025	1	23:00	.	10*	70	50	65
10025	2	00:00	14	14	70	50	65
10025	2	01:00	12	12	70	50	65
10025	2	02:00	.	11*	70	50	65

BG: blood glucose; BGi: BG levels with values imputed using linear interpolation (* indicates imputed values);
TIR: Percentage of whole admission time spent with BG=4-10mmol/L
TIR-2: Percentage of the first two days of admission spent with BG=4-10mmol/L
TIR-6: Percentage of the first six days of admission spent with BG=4-10mmol/L

6.2.6.3 Outcome measures

The study outcome measures included time-constant variables, which represented meaningful summaries of the time-dependent variable of interpolated glycaemic levels, and one time-dependent variable (Table 6.4).

For the calculation or the outcome measures, first, it was necessary to generate a new binary variable indicating whether interpolated glycaemic values were within the range 4-10mmol/L or not. From this, TIR was calculated as:

$$TIR = \frac{T_{4-10}}{T} \times 100\% \tag{6.1}$$

where $T_{4\text{-}10}$ is the number of hours with BG values within 4-10mmol/L, and T is the total number of hours with available BG levels, including imputed values (i.e., excluding the hours before the first and after the last BG value, and excluding the hours with missing charts).

Similarly, TB4 and TB22, the metrics of safety that considered time, were calculated as:

$$TB4 = \frac{T_{<4}}{T} \times 100\% \tag{6.2}$$

$$TB22 = \frac{T_{<2.2}}{T} \times 100\% \tag{6.3}$$

where $T_{<4}$ and $T_{<2.2}$ are the number of hours with BG levels below 4mmol/L and below 2.2mmol/L, respectively, and T is the total number of hours with available BG levels.

TTR was calculated as:

$$TTR = t_{controlled} - t_{1st\ BG>10} \tag{6.4}$$

where $t_{1st\ BG>10}$ is the time of the first occurrence of BG>10mmol/L and $t_{controlled}$ is the time, after $t_{1st\ BG>10}$, when the BG is brought back to range (4-10mmol/L) and kept within this range for at least two consecutive hours.

In addition to TIR, which was the primary outcome measure initially proposed at the study design stage, with the progress of the study it became necessary to generate one more outcome measure. Specifically, for statistical reasons that will be explained in Section 6.2.7.2, in the analyses of association TIR had to be transformed into the outcome measure of "odds of being within the range 4-10mmol/L at any time" (odds of in range, referred to as "odds of IR").

Table 6.4 – Primary and secondary outcome measures of EES

Primary outcome measures of effectiveness
a) Percentage of admission time with glycaemic levels within the range 4–10mmol/L (TIR) b) Odds for being within the range 4–10mmol/L at any time (Odds of IR)
Secondary outcome measures of time-efficiency
c) Time between the first occurrence of BG>10mmol/L and the moment when the BG level was brought back to range (4–10mmol/L) and kept within this range for two consecutive hours (TTR)
Secondary outcome measures of safety
d) Number of patients experiencing at least one episode of severe hypoglycaemia ≤2.2mmol/L and number of patients experiencing at least one episode of moderate hypoglycaemia ≤4mmol/L e) Percentage of admission time spent with severe hypoglycaemia ≤2.2mmol/L (TB22), and percentage of admission time spent with moderate hypoglycaemia ≤4mmol/L (TB4)

While the metric odds of IR comes directly from the transformation of TIR, TIR is simpler and can be more intuitively understood than the odds of IR. Since it is important that the metric of effectiveness is simple and associated with clinical outcomes (Preiser et al., 2016; Finfer et al., 2013), TIR was used in all the other parts of the analyses, including descriptive and univariate analyses. This was also intended to allow the findings to be compared to previous studies, most of which used TIR as their outcome measure.

6.2.6.4 Exposure variables and other covariates

The exposure variables of interest were three categorical time-constant variables, two of which were generated based on time-dependent variables (Table 6.5):

a) The protocol-hospital (P-x_H-x) of the patient was a variable defining the hospital (H-x) of admission and the protocol (P-x) implemented for that patient. This variable was generated because there were three hospitals that implemented different protocols for patients with diabetes, and there were two hospitals that changed their protocol during the period of interest of this study (see Section 4.4.1).
b) The exposure variable summarising the monitoring frequency defined whether the median TNM of each patient during hyperglycaemia>10 was above or below the median of the sample.
c) The exposure variable summarising the treatment with insulin defined whether the percentage of time that each patient spent receiving insulin while in hyperglycaemia>10 was above the median of the sample.

Table 6.5 – Variables potentially affecting the primary outcomes and explored in the analyses

Variables	Description: types, units, categories	
Main exposures (Time-constant)		
a) Protocol-hospital (categorical)	Without diabetes	With diabetes
	P-1.1_H-100	P-2.1_H-100
	P-1.1_H-200	P-2.1_H-200
	P-1.2_H-100	P-2.2_H-100
	P-1.2_H-200	P-2.2_H-200
	P-3_H-300	P-3_H-300
	P-4_H-400	P-4_H-400
	P-5_H-500	P-6_H-500
	P-7 _H-600	P-7_H-600
	P-8_H-700	P-8_H-700
b) The % hours receiving insulin during hyperglycaemia>10mmol/L was above the threshold close to the sample median	Categorical, binary: yes/no	
c) The median time to next measurement during hyperglycaemia>10mmol/L was below or equal to the threshold close to the sample median	Categorical, binary: yes/no	
Other covariates		
Time-dependent		
With a lag of 1 h (value in the previous hour):		
Glycaemic exceedance above 10mmol/L	Numerical. Unit: mmol/L	
Dosage of noradrenaline; adrenaline; dobutamine	Numerical. Unit: mcg/kg/h	
Dosage of hydrocortisone	Numerical. Unit: mg/h	
Energy from: Propofol	Numerical. Unit: kcal/h	
No-protein energy from: EN, TPN	Numerical. Unit: kcal/h	
No lag, one of these two:		
Number of hours from admission	Numerical/discrete. Unit: h	
Number of days from admission	Numerical/discrete. Unit: days	
Time-constant		
Age	Numerical. Unit: years	
Sex	Categorical, binary: female/male	
Asian ethic group	Categorical, binary: Asian/non-Asian	
One of these four as a measure of severity:		
ICNARC physiology score	Numerical. Range: 0-100	
APACHE II score	Numerical. Range: 0-71	
Highest BG on admission	Numerical. Unit: mmol/L	
% time with mechanical ventilation	Numerical. Unit: days	

BG: Blood glucose; EN: Enteral Nutrition; TPN: Total Parenteral Nutrition

Patients were considered to have been monitored more frequently during hyperglycaemia when their monitoring frequency, during periods with BG >10mmol/L, was, on average, higher than a threshold value. This threshold was the value of the group median or close to the group median. This way, the sample was divided into two groups equally, or close to equally, sized to compare.

Patients were considered as having received insulin for longer periods during hyperglycaemia, when their percentage of time receiving insulin, during periods with BG >10mmol/L, was, on average, higher than a threshold value close to the group median, as above.

The remaining covariates that were controlled for in analyses of association included patient inherent characteristics and treatment or care related factors (Table 6.5). Some were time-constant and some were time-dependent variables. All time-dependent confounders except one were analysed with 1-hour lag, i.e. using their value to analyse their effect on the odds of IR in the following hour. The time-dependent covariate, analysed without lag, was the time since admission (in either hours or days, depending on the analyses).

Among the time-dependent covariates was a newly created variable indicating how high a hyperglycaemic event was, referred to as "glycaemic exceedance" in mmol/L. This was defined as by how much the BG values exceeded the threshold of 10mmol/L. For BG values of 10mmol/L or less, the glycaemic exceedance was zero.

Two new exposure dummy variables, describing two relevant aspects of the protocols that have been described in the protocols review chapter, were generated to be used in univariate analyses. One of them classified the protocols into two groups, depending on whether the upper limit of their glycaemic target range was 10mmol/L (UL10) or ≤8.3mmol/L (UL83) (Table 6.6). The other variable classified the protocol in two groups depending on whether it instructed the administration of insulin during hypoglycaemia or not (Table 6.7).

6.2.6.5 Degree of staff adherence to protocol instructions

GC flowcharts describing the GC methods to be implemented in each ICU, according to the ICU's protocol instructions, were drawn, as described in the protocols review chapter (see Section 4.3.2 and Appendix B). A software tool called *Glycad* was designed and programmed using an algorithm based on these flowcharts. *Glycad* automatically determined the expected actions after each BG measurement of each patient, according to the Protocol-Hospital instructions relevant to that patient. These included instructions on monitoring frequency, insulin dosages and amounts of rescue glucose bolus. Since these instructions could often lead to a range of possible values, *Glycad* output the maximum and minimum values for each of expected actions.

Table 6.6 – Protocol classification depending on the upper limit of the glycaemic target range

Upper limit of glycaemic target	Group	Protocol
8.3mmol/L or lower	UL83:	P-1.1, P-2.1, P-3, P-5, P-6, P-8
10mmol/L	UL10 :	P-1.2, P-2.2, P-4, P-7[a]
[a] P-7 did not indicate target in protocol, but had an "accepted" threshold for initiating treatment with insulin of 10mmol/L		

Table 6.7 – Protocol classification depending on insulin instructions during hypoglycaemia

Insulin during hypoglycaemia	Group	Protocol
Administer insulin	Yes:	P-7, P-8
Stop or do not start insulin	No:	P-1.1, P-1.2, P-2.1, P-2.2, P-3, P-5, P-6

The author of this thesis designed and administered the algorithm on which *Glycad* was based. The technical programming of the tool was undertaken by an independent technical implementer using Matlab®, under the supervision of the author. At no time did the implementer have access to any confidential information.

The output of the *Glycad* tool was compared to the actual actions (or inactions) or the ICU staff, according to the data retrieved from the medical records. Where the staff actions did not correspond to the protocol instruction, this will be referred to as non-adherence, and where the staff actions matched what the protocol indicated, this will be referred to as adherence. Due to the retrospective nature of the study, it was not possible to identify whether non-adherences were a voluntary decision, or an involuntary omission.

A number of time-dependent variables on the levels of staff adherence to the treatment with insulin and the monitoring frequency, were explored in the study, for descriptive purposes (Table 6.8). Adherence to the insulin dosage was assessed at every hour, based on the interpolated glycaemic levels, while adherence to TNM was only assessed at each recorded BG measurement.

Table 6.8 – Time-dependent variables on adherence to protocol instructions

Variable	Description
Type of non-adherence to insulin dosage	Categorical. Categories: a) Insulin not needed and not given; b) Insulin given as specified; c) Given less insulin than specified; d) Given more insulin than specified.
Deviation above the specified insulin dosage	Numerical. Unit: U/h
Deviation below the specified insulin dosage	Numerical. Unit: U/h
Type of non-adherence to monitoring frequency: Time to Next Measurement (TNM) (Categorical)	Categorical. Categories: a) TNM as specified; b) TNM less than specified; c) TNM more than specified; d) Not applicable: Call medical staff
Deviation above the specified TNM	Numerical. Unit: hours
Deviation below the specified TNM	Numerical. Unit: hours

6.2.7 Data analyses

The analyses were carried out using Stata®. All the analyses were carried out separately on patients with diabetes and on patients without or with unknown diagnosis of diabetes. When applicable, sensitivity analyses were used to check for the effect of extreme values, and significant effects were reported throughout the results sections of this chapter.

All statistical tests were two-tailed and the level of statistical significance was set at $\alpha=0.05$. This level of significance meant that the confidence level was 95%, meaning that if the study was repeated 100 times, in 100 different samples, in 95 of them the confidence interval (CI) would contain the true population value of interest. Given that this study was not investigating the effects of a new drug that could have serious effects on the patient, but rather, whether existing clinical practice is having different outcomes, 95% was considered a reasonable level of confidence.

Following the American Psychological Association (APA) standards for scientific communication, *p*-values of 0.001 and above were rounded to three decimal places, while *p*-values below 0.001 were reported as $p<0.001$ (APA, 2010). In tables and figures, when displaying the exact *p* value would have made it difficult to follow or comprehend, asterisks were used to denote ranges of *p* values as: $*p<0.050$; $**p<0.010$; $***p<0.001$ (APA, 2010).

Odds Ratios (OR) were presented with their 95% CI, and they were reported to one decimal place since, given their wide CI, having more decimal places could have given a false sense of precision (Cole, 2015). For some data, such as the coefficients of certain medication dosages that were measured in small increments (e.g. in mcg/kg/h) in the modelling analyses, results were presented to two decimal places.

The term "significant" is used to refer to statistically significant differences throughout the text of this thesis. For ease of legibility, the word "statistically" is sometimes omitted in the results.

6.2.7.1 Descriptive analyses

Descriptive analyses were carried out with all variables of interest. Time-dependent data were described first overall at the hour level, and, subsequently, using individual summary variables calculated at the patient level.

Continuous variables were summarised using measures of central tendency and dispersion. Normally or near normally distributed variables were reported as means with standard deviations (SD). Not normally distributed variables were summarised as medians with Inter-Quartile Ranges (IQR), 10^{th}-90^{th} deciles, or ranges of minimum-maximum values. Categorical variables were summarised using counts and percentages or proportions.

In addition to these descriptive statistics, specific descriptive analyses were carried out with some of the variables as described below.

Glycaemic levels

Due to the log-normal distribution of glycaemic levels, summary statistics of these were performed in normal and log-normal statistics formats. In order to provide data that are easier to understand, the mean and SD of log-normal BG data were reverse-transformed, resulting in the BG geometric mean and multiplicative standard deviation (MSD), respectively (Braithwaite et al., 2013; Chase, LeCompte, et al., 2008).

At the patient level, the measures of central tendency and of dispersion recommended in a consensus by experts in the field (Finfer et al., 2013), were calculated, including the glycaemic metrics recommended by Mackenzie et al. (2011). Among the measures of dispersion of BG at the patient level were the SD, which describes the absolute value of excursions from the mean, and the coefficient of variation (CV), which is calculated as the SD divided by the mean, and therefore describes the relative excursions of the data, in proportion to the mean.

Other metrics of location of the BG levels per patient calculated included the time-weighted BG mean as suggested by Egi et al. (Egi et al., 2010) and Finney et al. (2003), and the minimum and maximum BG values per patient as suggested by Egi et al. (2010) and Preiser et al. (2009).

Methods for glycaemic control and other treatment related data

Both the TNM and the IIRs could have very high values that were explored using descriptive statistics and graphs.

The percentages of time spent receiving insulin were calculated for each patient in the following conditions: (a) at any time; (b) at each glycaemic status; and (c) when no nutrition of any type was administered at the same time.

Other treatment related data, which includes the nutritional support administered, and the treatment with propofol, catecholamines and glucocorticoids, were described using their dosages and the percentage of time receiving them.

Level of staff adherence

The percentage of hours with each type of non-adherence to the protocol instructions, on both monitoring frequency and treatment with insulin, were explored. For the glycaemic status of hyperglycaemia>10, the deviations above or below the protocol instructions were described.

Group comparisons

Mean values of continuous normally, or near normally, distributed variables were compared using:

a) student's t-tests (with Welch's approximation when groups had unequal variances) for two-group comparisons; or
b) single-factor analysis of variance models, one-way ANOVA, for more than two groups.

Medians and/or distributions of not-normally distributed variables were compared using:

a) The non-parametric test of the median (number of points above median), Mann-Whitney U-test (or Wilcoxon-Mann-Whitney rank-sum test) for two-group comparisons of unmatched data; and the Wilcoxon matched-pairs signed-ranks test for matched data; or
b) Kruskal-Wallis tests, for more than two groups.

Proportions of categorical data between two or more groups were compared using Pearson chi-squared (χ^2) tests. For pair-wise comparisons, for which χ^2 tests are not recommended, Fisher's exact test was used instead.

Graphical presentation of data

Box-plots and histograms were used to visualise and describe quantitative variables. In the box-plots, the ends of whiskers represent the lowest data point within 1.5×IQR below the lower quartile, and the highest data point within 1.5×IQR above upper quartile. Values outside the whiskers are represented as circles.

Pie charts and bar charts were used to visualise and describe proportions and counts of categorical variables.

Kaplan-Meier survival curves were used to visualise and describe the TTR by Protocol-Hospital, and by group of UL83 vs. UL10 target.

6.2.7.2 Analyses of association

Repeated measures data can be analysed using different approaches, depending on the study aims and the nature of the data. Measurements that are taken from the same individual are usually correlated with each other. This means that the assumption of independence of the error terms in linear regression would not hold and results of this type of analyses could be misleading (Burton et al., 1998). Analysing such data as if they were independent would result in biased estimates, with artificially small standard errors and *p*-values. This is often referred to as naïve analysis. One valid and safe approach to analyse repeated measurements, taken from the same individual, is to create a single meaningful metric that optimally summarises the repeated outcome for each patient (Burton et al., 1998). These type of variables are often referred to as indexes (Preiser et al., 2016).

The index, or summary statistic of the repeated BG measures (time-dependent variable), chosen for GlyCon study as its primary outcome measure, was the percentage of hours spent with BG levels of 4-10mmol/L (TIR), calculated as described in Section 6.2.6.3. Since this is a bounded outcome, linear regression on the untransformed variable is often not an appropriate approach, as it can make predictions outside the variable interval. It would have been a valid approach if there had not been any extreme values and the outcome had always been located in the middle (i.e. values at least within 20% and 80%) (Grace-Martin, 2013). However, in GlyCon study the distribution of the TIR was heavily negatively skewed, with most of its values being above 60%, and a long tail towards zero. To overcome this, the method proposed by Baum (2008) was followed, whereby the outcomes that are proportions (or percentages) are transformed into their logit and analysed in the logit space. The logit transformation of a proportion p is calculated using the natural logarithm (ln) as:

$$logit = \ln\left(\frac{p}{1-p}\right) \tag{6.5}$$

Baum (2008) also suggested using a generalised linear model (GLM) with a logit link and robust standard errors, as proposed by Papke & Wooldridge (1996, cited in Baum, 2008). GLMs are the broader group of linear models, which include ordinary least-squares linear regression as well as other linear models that do not meet the condition of normality of the errors, such as logistic or logit regression. The interpretation of the coefficients of a logistic or logit model can be done in the logit space. Alternatively, the model equation can be exponentiated, transforming the outcome into its odds. In addition, when the value of the denominator of the proportion differs between patients, it is important to account for this, something which is possible with GLMs. While the outcome measure for GlyCon is the summary metric TIR, when it is transformed into its logit the interpretation of the exponentiated coefficients of the GLM becomes "how the independent variables affect the odds of being in range (odds of IR) at any time".

This approach of modelling a summary metric of numerous observations has the disadvantage that all the data points (in this case all the data points of a patient) are reduced to a single value, and therefore only part of the information is being used. This is still a correct approach but it can be less efficient than other methods. Among the main statistical techniques that are available for the analyses of repeated measures data, which can extract more information from the data without exaggerating the apparent sample size, are generalised estimating equations (GEE). The primary outcome measure of GlyCon was analysed using GEE with logit link as described below.

Generalised Estimation Equations (GEE)

GEEs use the same estimation methods as in GLMs, but GEEs are more specialised. As with GLMs, the focus of GEEs is on modelling the expected values of a dependent variable in relation to independent variables. However, while GLMs are based on the maximum likelihood theory, GEEs are based on the quasi-likelihood theory, in which no assumption is made about the distribution of the outcome measures. The outcome observations do not need to be independent, and can be correlated *within* each individual (Cui & Qian, 2007), although the assumptions of independence *between* individuals still holds.

Consequently, GEEs of repeated measures account for the possible correlation between measurements that come from the same patient, while using all data points (Cui & Qian, 2007). The correlation structure underlying the data is not a parameter of interest in itself, but rather some nuisance that needs to be accounted for. While a misspecification of this working correlation structure is not so important in a GEE analysis, because the estimated regression coefficients would still be consistent (Cui & Qian, 2007), its correct specification helps in the calculation of more efficient coefficient estimators.

Autoregressive correlation structure is the most commonly used structure for data that are correlated within clusters (or individuals) over time, with a lag period (Ballinger, 2004). In order to visualise the autocorrelations in the data and help to determine a suitable lag, correlograms with pointwise confidence intervals were plotted for 14 randomly chosen patients, two from each of the participating ICUs (see Appendix D). In GlyCon study, an autoregressive correlation structure with lag one was used, implying that each observation within a cluster is correlated with the adjacent previous observation.

Coefficients derived from a GEE model have a population-averaged interpretation. This means that the interpretation of the coefficients would be that "for every one-unit increase in one particular covariate in a population, the average response across that population would change by *b,* where *b* is the value of the coefficient" (Ballinger, 2004). Another advantage of GEEs is that they allow for the calculation of robust estimates for the standard error of the coefficients (Burton et al., 1998).

Model selection was performed following a step-wise selection approach, adding one variable at a time. The variable protocol-hospital was always kept in the model. Exposures of interest, followed by potential confounders, were added one at a time, and they were kept if they had a statistically significant effect on the outcome. The effects of the degree of adherence to instructions, on the primary outcome of interest, were explored only in cases when there was a significantly different performance between two of the hospitals that implemented the same protocol. Clinically plausible interactions were explored.

The model fit methods that are normally used with maximum likelihood theory cannot be used in GEE, due to the non-independence of the residuals mentioned earlier. The quasi-likelihood under the independence model criterion (QIC) was proposed by Pan (2001, cited in Cui & Qian, 2007) as a criterion for selecting an optimal subset of covariates in a GEE model, as well as the best working correlation structure. The model with the smallest QIC value is the most parsimonious model (Cui & Qian, 2007), i.e., the "best", simplest model that achieves a desired level of explanation or prediction with as few exposure variables as possible (Van Belle et al., 2004); and has the best correlation structure (Cui & Qian, 2007). In GlyCon study, the choice of the correlation structure was theory based as suggested by Twisk et al. (2004) and the QIC value was used for the comparison of models.

The components that need to be defined in the specification of a GEE, and how these were defined in the analyses of GlyCon, are listed in Table 6.9.

Table 6.9 – GEE model specification

GEE model specification components	Specifications in GlyCon
1) Distribution of the dependent variable	Bernoulli distribution
2) Link function	Logit link
3) Dependent and independent variables	Dependent: Binary variable on whether BG was in range (4-10mmol/L) at each hour. Independent: protocol-hospital and significant exposures and confounders
4) The covariance structure of the repeated measurements	Autoregressive with lag one

Linear regression

The secondary outcome measure of TTR had a log-normal distribution both among patients with diabetes and among patients without diabetes. A variable has a log-normal distribution when its distribution becomes closer to the normal when it is transformed to its log. Linear regression of a log-transformed dependent variable is referred to as log-linear regression. For the modelling of TTR, multiple log-linear regression, with heteroskedasticity robust standard errors, was used.

Ordinary Least-Squares linear regression assumptions were explored for all final models.

Outliers

Influential outliers have been defined as "accurate data points that lie at a distance from other data points, are not error or interesting outliers, and also affect substantive conclusions" (Aguinis et al., 2013). These can be of two types: model fit or predictor outliers. Model fit outliers are those whose presence influences the fit of the model, (e.g. R-squared), either increasing or decreasing it, depending on their location. Prediction outliers are those that affect the parameter estimates of the model. Often, model fit are also predictor outliers (Aguinis et al., 2013).

In order to deal with important or significant model fit outliers, analyses were performed with and without the influential outliers, as recommended by Aguinis et al. (2013), and results from both models were presented. In order to deal with important or significant predictor outliers, in regression analyses, robust multiple linear regression was carried out in addition to standard multiple linear regression with robust SE, as recommended by Aguinis et al. (2013), and the results from both models were presented.

6.2.8 Ethical considerations

Permissions from relevant bodies and institutions were granted before commencement of the GlyCon study. These included the Confidentiality Advisory Group of the UK Health Research Authority; a NHS Research Ethics Committee; the R&D Departments of each of the participating NHS Trusts; ICNARC; each of the participating ICUs; as well as the University of Nottingham. Strict and thorough measures to ensure data protection and confidentiality were implemented. Further details about these permissions and measures have been described in the overall methodology chapter (see Chapter 3).

6.3 Results: missing data, demographics and implemented methods for glycaemic control

Between 1st January 2012 and 31st December 2013, the total number of admissions to adult, general critical care units in the MTCCN was 10695. Of these, 9735 (91%) admissions were not eligible for GlyCon study for the reasons listed below, leaving 960 (9%) eligible patients for this study:

- 51: age <18 years at admission;
- 5805: no level 3 care following admission to critical care;
- 1645: ICU length of stay <48 hours;
- 2092: reported highest glycaemic levels <10mmol/L or no reported glycaemic levels in the first 24 hours following admission;
- 3: pregnant women on admission;
- 29: any of the excluded primary or secondary reasons for admission;
- 107: the admission was not the first admission to critical care in the same hospital stay.

The study random sample of 150 patients represented 15.6% of the 960 eligible patients. These 150 patients resulted in a total of 30142 patient-hours of data. The numbers and percentages of patients included in each of the 14 proportional strata of the sample, chosen as described in Section 6.2.1.1, are listed in Table 6.10.

None of the comparisons of the study variables between surgical vs. non-surgical patients were statistically significant or clinically important, and therefore these comparisons are not presented in this chapter.

Table 6.10 – Eligible and non-eligible patients, and distribution of GlyCon stratified random sample, by hospital and type of admission

Hosp. ID	Total population size, n (%)			GlyCon final sample size, n (%)		
	All	Non-eligible for GlyCon	Eligible for GlyCon	All:	Medical;	Surgical
100	1365	1153 (84.5%)	212 (15.5%)	34 (22%):	17 (50%);	17 (50%)
200	1527	1414 (92.6%)	113 (7.4%)	18 (12%):	15 (83%);	3 (17%)
300	2230	2015 (90.4%)	215 (9.6%)	33 (22%):	26 (82%);	7 (18%)
400	1332	1224 (91.9%)	108 (8.1%)	17 (11%):	14 (82%);	3 (18%)
500	1968	1863 (94.7%)	105 (5.3%)	16 (11%):	11 (69%);	5 (31%)
600	1321	1186 (89.8%)	135 (10.2%)	21 (14%):	16 (76%);	5 (24%)
700	952	880 (92.4%)	72 (7.6%)	11 (8%):	8 (73%);	3 (27%)
Total	10695	9735 (91.0%)	960 (9.0%)	150 (100%):	107 (71%);	43 (29%)

Hosp. ID: Hospital ID

6.3.1 Missing data

6.3.1.1 Full sets of charts missing

Of the 150 patients selected in the first sample, 124 (83%) had complete or partly complete observation charts and were kept in the final sample, while 26 (17%) had to be excluded and replaced by surrogate patients because their full sets of charts were missing. Of the subsequent random sampling selections of surrogate patients, as outlined in Section 6.2.4.1, 9 (6%) further patients had to be excluded and replaced by other surrogates because their full sets of charts were also missing. Therefore, a total of 35 patients had to be excluded from the first and subsequent samples because their full sets of charts were missing. The distribution of the groups of patients from the first sample versus surrogate patients differed by hospital, as shown in Figure 6.7.

6.3.1.2 Incomplete sets of observation charts

In all hospitals at least two sampled patients had incomplete sets of observation charts. There were a total of 1388 patient-hours (4.6%) in 39 patients in which the glycaemic monitoring data and related treatment data from observation charts were completely (1262 [4.2%] hours)

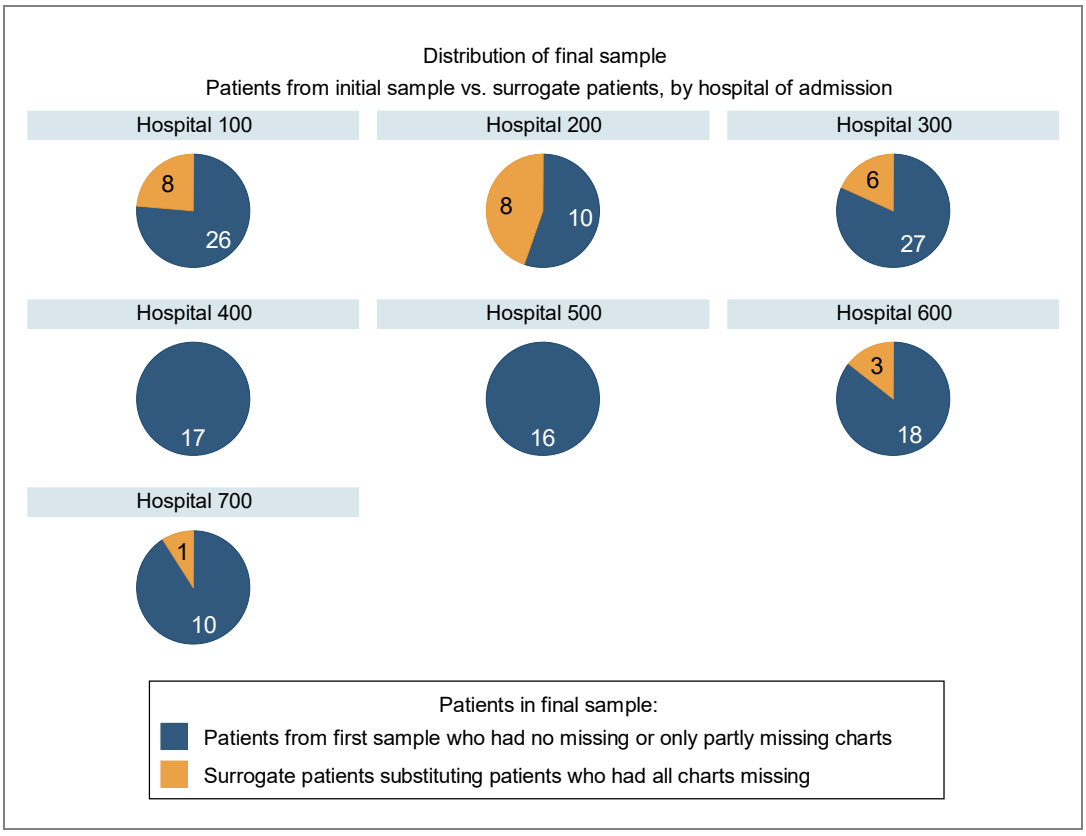


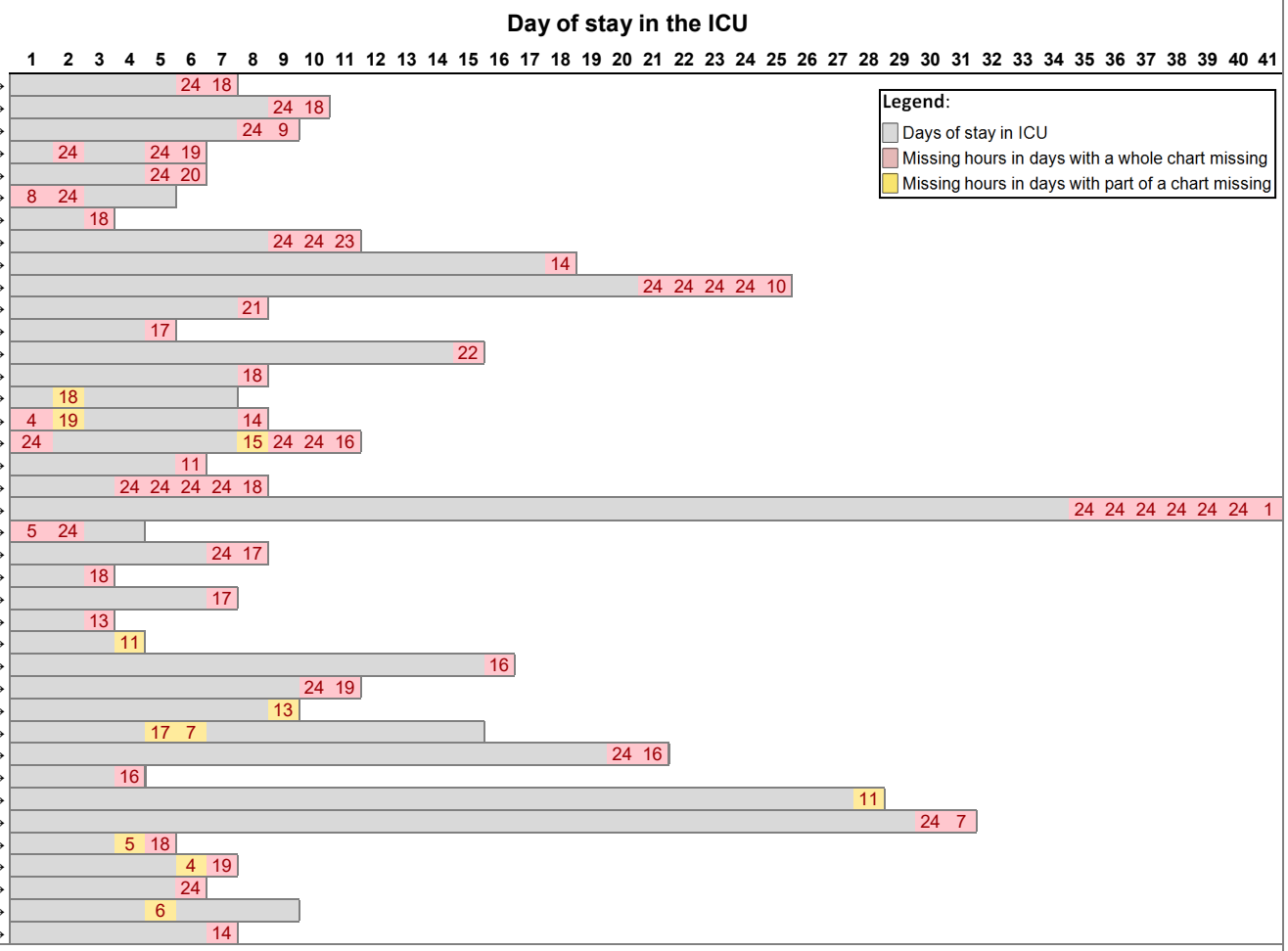
Figure 6.7 – Number of patients per hospital in the final sample by group of selection: selected in the first sampling round vs. selected in subsequent sampling rounds

or partly (126 [0.4%] hours) missing (Figure 6.8). Among these 39 patients, the mean (SD) missing hours per patient was 28 (30) hours. Usually, the charts that were missing corresponded to the last day/s of admission. H-500 had the highest percentage of patients with at least one chart missing (75% of its patients), followed by H-400 and H-100, but H-400 had the highest percentage of missing charts per patient.

Four patients (two from H-100 and two from H-400) met at least one of the criteria for exclusion from the analyses, as they presented a high risk of bias due to missing data, as described in Section 6.2.4.1, and therefore were excluded from the analyses (Figure 6.8). All four were women, not Asian, and none of them had diabetes. None of them was admitted for surgery and all of them survived hospital admission. No statistically significant differences in the demographic and clinical data were found between these four excluded patients without diabetes and the other included patients without diabetes, except for their sex, as 100% of the four excluded patients were female.

Consequently, the final sample size of patients included in the analyses was 146, representing a total of 29672 patient-hours, or 2136 patient-days included in the final analyses. Sensitivity analyses with and without the four excluded patients were carried out and are presented in Section 6.4.8.

Patient ID	LOS (h)	% miss	% miss48
10028	147	29%	0%
10031	232.7	17%	0%
10036	181.6	18%	0%
10090	119.3	56%	50%
100149	119.8	37%	0%
100175	102.4	31%	65%
100191	52.7	33%	27%
100204	259.8	27%	0%
20043	409	3%	0%
20047	570.1	19%	0%
30035	176.7	8%	0%
300107	95.2	10%	0%
300130	349.2	4%	0%
40016	172	11%	0%
40020	155.5	12%	38%
40032	162.3	23%	49%
40036	255.6	40%	50%
40047	118	10%	0%
40053	175.3	65%	0%
40087	953.7	15%	0%
40089	72.7	33%	59%
5008	165.7	20%	0%
50037	55.5	19%	6%
50050	138.8	12%	0%
50054	48	27%	27%
50055	72.8	15%	0%
50058	372.3	4%	0%
50062	255.3	17%	0%
50068	194.9	7%	0%
50074	353.5	7%	0%
50085	473.4	8%	0%
50092	75.4	21%	0%
50095	663.8	2%	0%
50096	726	4%	0%
600132	101.4	23%	0%
600134	157.6	15%	0%
7007	141.6	17%	0%
70024	196.6	3%	0%
70054	142.5	10%	0%



Patient ID: First 3 digits=Hospital identifier, in red excluded patients; LOS: length of stay (h); % miss: %missing hours; %miss48: % missing hours during first 48 h

Figure 6.8 – Hours with missing data due to missing chart/s: proportions, counts and their timing during the whole ICU stay

6.3.1.3 Time with no recorded glycaemic levels

Glycaemic levels were rarely measured hourly. Within the available records, corresponding to a total of 28797 patient-hours of admission without missing data due to the chart being completely/partly missing, there were 18461 (64.1%) patient-hours without BG levels being measured. Of these, 169 (0.6%) and 940 (3.1%) were hours before the first and after the last BG measurement of each patient, respectively. Since these hours before the first and after the last BG measurements were not extrapolated, this left 17352 (60.3%) patient-hours which were imputed using linear interpolation. The distribution of these patient-hours differed between hospitals, as shown in Figure 6.9.

6.3.1.4 Medical notes missing or incomplete

Three patients, one from each of H-100, H-300 and H-600, had their full sets of medical notes missing. Incomplete sets of medical notes included sets with one or more of the following being totally or partially missing:

- the enteral/parenteral nutrition prescriptions, missing in 100 (67%) patients;
- medication prescription charts, missing in four (3%) patients;
- nursing or medical notes with information on diabetic status, missing in six (4%) patients.

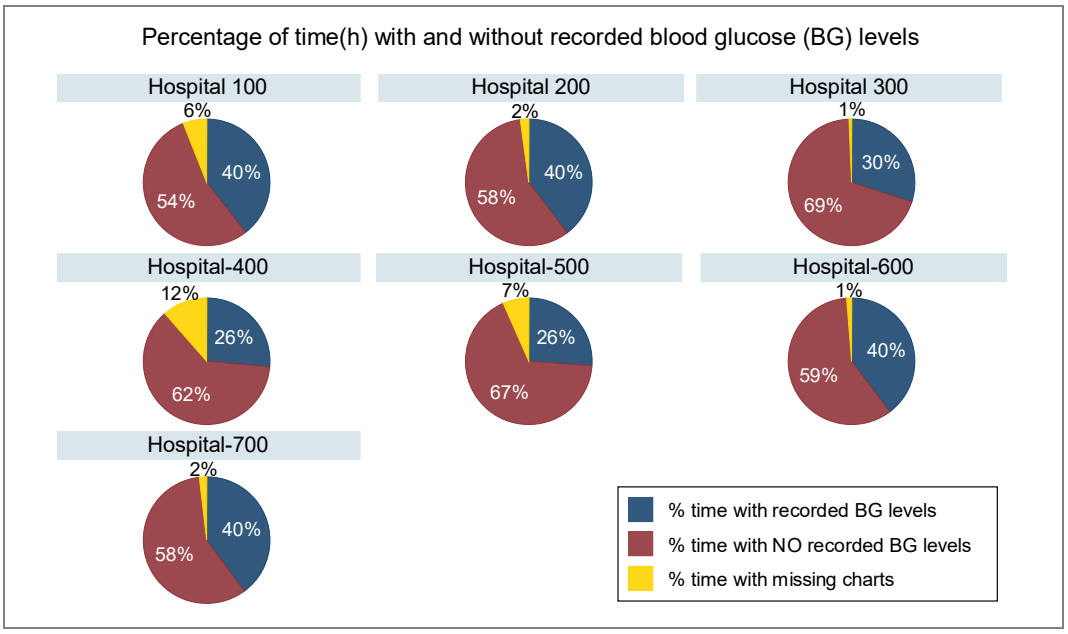


Figure 6.9 – Percentage of time (hours) with and without recorded BG values, by hospital

6.3.2 Demographic and clinical characteristics

Over half of the patients in the final sample of GlyCon study were between 50 and 75 years old (Figure 6.10); 42% were females; 33% were obese (defined as a body mass index, BMI>30kg/m^2); and 3% were Asian (Table 6.11).

On admission, patients' severity scores, based on ICNARC's 2013-calibrated scores, had median values that were in the lowest quarter of two scales: 17 out of 71 (Apache II score), and 22 out of 100 (ICNARC's model score). Their corresponding predicted mortality probability scores according to ICNARC's model had median values four points higher than according to the Apache II model, although this difference was not statistically significant (Table 6.11).

More than three quarters of the sample patients needed organ support of at least four organs during their ICU stay. All except six patients required advanced respiratory support, of whom 82% needed it for at least half of their stay (Table 6.11). Most patients (84%) stayed in the ICU for more than three days, and over 70% of patients stayed in the ICU for less than 10 days. The majority of patients spent most of their LOS receiving level-3 care. Fifty (34%) patients died in the hospital, 62% of whom having passed away while in the ICU (Table 6.11).

6.3.2.1 Sample vs. eligible not sampled patients

No statistically significant differences between the final study sample (n=146) and the rest of eligible patients (n=814) were found in any of the relevant demographic and clinical characteristics available before the start of the study (Table 6.11).

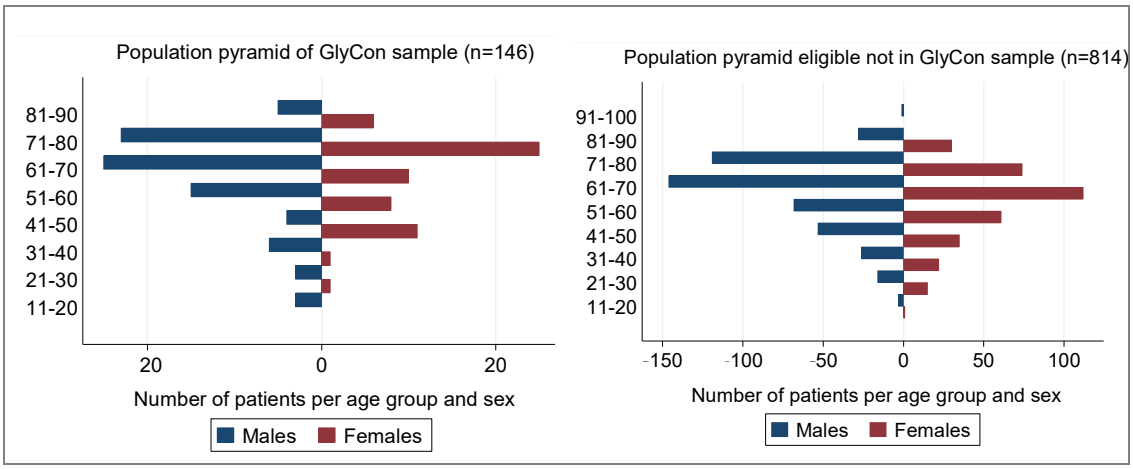


Figure 6.10 – Population pyramids: group of GlyCon patients vs. all eligible patients

Table 6.11 – Demographic and clinical characteristics of GlyCon versus all eligible patients

Characteristics Median (IQR) and number (%)	Final sample of GlyCon (n=146)	Eligible patients not in final sample (n=814)[a]
Age (years)	65 (54–73)	65 (54–73)
Females	64 (42%)	354 (44%)
Asians	5 (3%)	29 (4%)
BMI (kg/m^2)	26 (24–31)	27 (24–32) [b]
Previous diagnosis of diabetes	54 (37%)	NA
Highest glycaemic levels on admission (mmol/L)	11.8 (10.9–14.7)	12.3 (10.9–14.9) [c]
Maximum number of organs supported	4 (4–5)	4 (3–5)
ICU LOS (days)	6.0 (3.6–11.4)	6.1 (3.6–11.2)
Hospital LOS (days)	19.5 (10–36)	20 (9–39)
Number of days with level-3 care	5 (3-8)	5 (3-10)
ICNARC physiology score[g]	22 (18–28)	22 (18–27)
APACHE II score[g]	17 (14–21)	17 (13–22)
ICNARC predicted mortality probability score[g] (%)	33% (16–53%)	32% (14–55%)
APACHE II predicted mortality probability score[g] (%)	29% (14–45%)	25% (12–45%)[d]
ICU mortality	31 (21%)	194 (24%)
Hospital mortality	50 (34%)	262 (33%)[e]
28-day mortality	41 (28%)	217 (27%)[f]

**p<0.05; **p<0.01; ***p<0.001*

BMI: Body Mass Index; LOS: Length of Stay; NA: Not available.

[a] 810 (patients eligible but not in GlyCon sample) + 4 (patients excluded due to missing data criteria)

In comparisons within individual hospitals, there were significant differences between groups (GlyCon sample vs. eligible not in sample) in the following factors:

[b] The BMI, in H-200 was higher in GlyCon sample: 30 (24-36) vs 27 (22-31) (p=0.035)

[c] The highest BG on admission in:

H-300 was lower in GlyCon sample: 11.3 (11.0-11.7) vs. 12.6 (11.1-14.8) (p=0.007)

H-500 was higher in GlyCon sample:13.5 (11.9-17.8) vs. 11.4 (10.4-14.0)] (p=0.044)

[d] APACHE II predicted mortality probability score in H-200 was lower in GlyCon sample: 34 (14-50) vs. 52 (35-64) (p=0.034)

[e] Hospital mortality in H-400 was higher in GlyCon sample: 9 (60%) vs. 21 (23%) (p=0.003)

[f] 28-day mortality in H-400 was higher in GlyCon sample: 8 (53%) vs.19 (20%) (p=0.006)

[g] 2013 ICNARC recalibration

In comparisons within individual hospitals, the following variables were found to be significantly different between GlyCon sample and the rest of eligible patients in certain hospitals, as noted in Table 6.11:

- the BMI in H-200 was higher in GlyCon;
- the highest BG on admission in H-300 was lower in GlyCon, and in H-500 was higher in GlyCon;
- the APACHE II predicted mortality probability score in H-200 was lower in GlyCon;
- the in-hospital mortality and 28-day mortality rates in H-400 were higher in GlyCon.

6.3.2.2 Previous diagnosis of diabetes

Of the 146 patients included in the analyses, 54 (37%) had a previous diagnosis of diabetes, 86 (59%) did not have diabetes and for six (4%) patients this was unknown. Of the patients with diabetes, 47 (87%) had type II diabetes, four (7%) had type I diabetes, and for three patients the diabetes type was not available in the records. In proportion to the number of admissions, there were significantly less patients with a previous diagnosis of diabetes in H-300 (15%) than in the other six hospitals (H-100: 36%, H-200: 53%, H-400: 47%, H-500: 50%, H-600: 33%, H-700: 54%).

As will be described in Sections 6.3.3 and 6.4, there were significant differences in all exposures of interest, as well as in the outcome measures of interest in the GlyCon study, depending on whether patients had a previous diagnosis of diabetes. Hence, all the analyses were carried out separately for groups with and without a previous diagnosis of diabetes. It was also found that patients without diabetes and patients for whom it was unknown whether they had history of diabetes, had very similar BG summary statistics and distributions (see Section 6.4.1). Therefore, these 92 patients were placed in the same group of "no/unknown diabetes" for the purpose of the analyses.

There were no statistically significant differences between patients with a previous diagnosis of diabetes versus patients without (or with unknown) diagnosis of diabetes, in any the relevant demographic and clinical characteristics, except for their BMI and APACHE II score on admission (Table 6.12), both of which were higher for patients with diabetes. The higher APACHE II scores were caused by the APACHE II scores in patients with diabetes from H-300 and H-600.

No significant differences were found between hospitals in the demographic and clinical characteristics available before the start of the study, in any of the groups of diabetes.

Table 6.12 – Demographic and clinical characteristics of the sample by diabetes diagnosis

Characteristics Median (IQR) and number (%)	Previous diagnosis of diabetes No/unknown	 Yes
No. patients	92 (63%)	54 (37%)
Age (years)	66 (53–74)	70 (59–77)
Females	37 (40%)	25 (46%)
Asians	3(3%)	2(4%)
BMI (kg/m^2)***	26 (22–30)	29 (25–35)
Maximum no. of organs supported	4 (4–5)	4 (3–5)
ICU LOS (days)	6 (4–11)	6 (4–13)
Hospital LOS (days)	18 (7–32)	25 (13–41)
Number of days with level-3 care	6 (3-9)	5 (3-8)
ICNARC physiology score [a]	23 (21–24)	24 (22–26)
APACHE II score[a] *	16 (13–21)	18 (15–23)
ICNARC predicted mortality probability score (%)[a]	30% (15–52%)	38% (17–60%)
APACHE II predicted mortality probability score (%)[a]	27% (14–41%)	33% (16–52%)
ICU mortality	22 (24%)	9 (17%)
Hospital mortality	32 (35%)	18 (33%)
28-day mortality	26 (28%)	15 (28%)

*p<0.05; **p<0.01; ***p<0.001

BMI: Body Mass Index; ICNARC: Intensive Care National Audit & Research Centre; LOS: Length of Stay

[a] 2013 ICNARC-recalibration

6.3.2.3 Reasons for admission

Among patients without diabetes, the most common primary reasons for admission were pneumonia without organism isolated, with 11 (12%) patients being admitted for this (range: 0% [H-400, H-500, H-600, H-700] to 65% [H-200]). This was followed by ventricular tachycardia or fibrillation (9%), and acute myocardial infarction (AMI) (4%). Patients with diabetes were also primarily admitted for pneumonia without organism isolated, with seven (13%) patients admitted for this (range: 0% [H-400] to 20% [H-300]). This was

followed by acute renal failure due to infection (6%), left ventricular failure (6%), and supra-ventricular tachycardia, atrial fibrillation or flutter (6%). Patients were classified into five main population groups: neurosurgery and trauma, cardiac, hepatobiliary-pancreatic, surgical (general), and medical (other) (Figure 6.11).

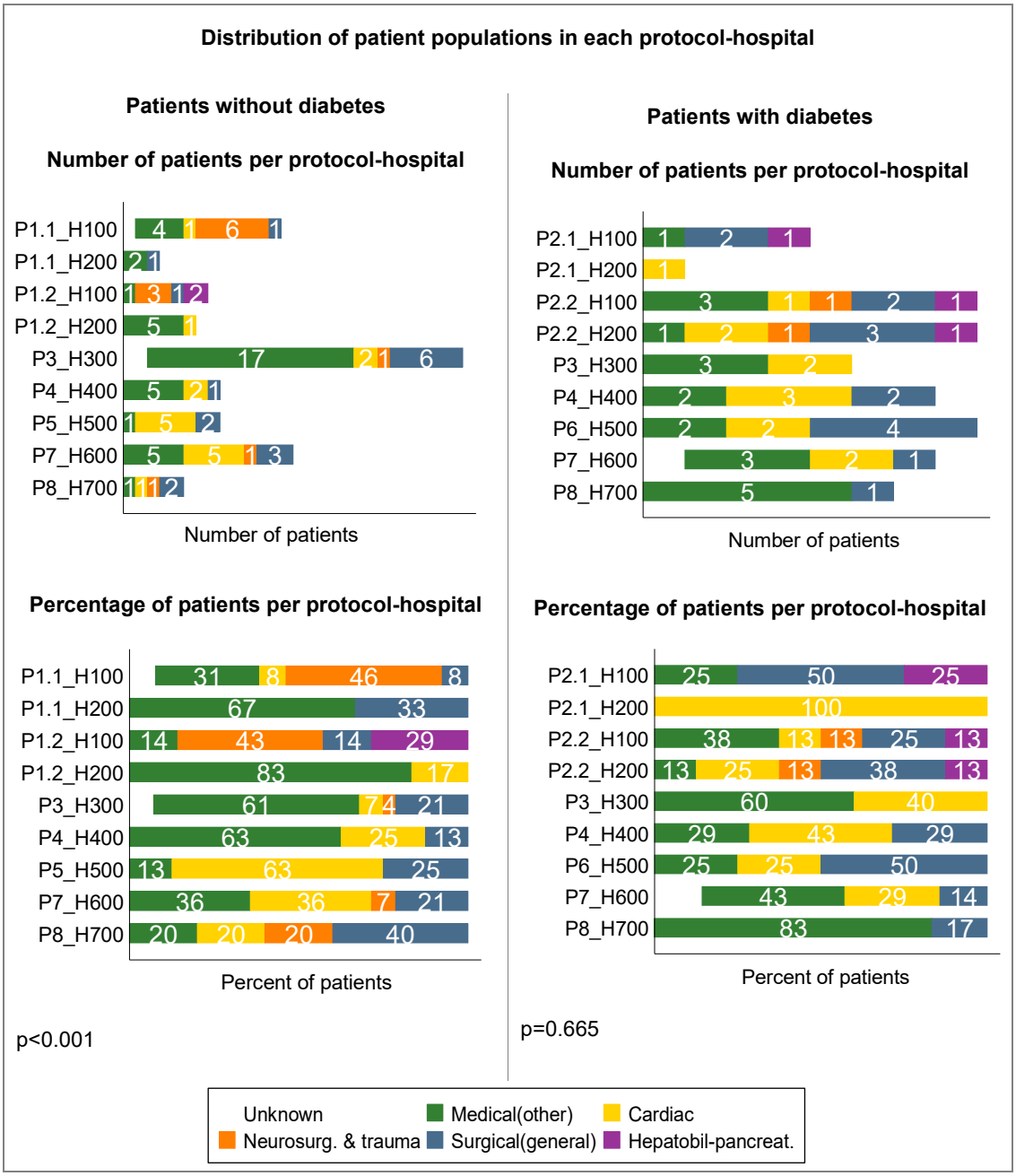


Figure 6.11 – Number and percentage of patient populations, by protocol-hospital and previous diagnosis of diabetes

Among patients without diabetes, the following percentages of admissions differed significantly between protocol-hospitals:

- admissions for neurosurgery and trauma, which were more common in P-1.1_H-100 and P-1.2_H-100 (p=0.003);
- admissions for cardiac reasons, which were more common in P-5_H-500 and P-7_H-600 (p=0.016);
- the two admissions for hepatobiliary-pancreatic conditions, which occurred in P-1.2_H-100 only (p=0.025); and
- admissions for (other) medical reasons, which were more common in P-1.1_H-200, P-1.2_ H-200, P-3_H-300 and P-4_H-400 (p=0.028) (Figure 6.11).

Among patients with diabetes, none of the percentages of admissions differed significantly between protocol-hospitals, although the few hepatobiliary-pancreatic and neurosurgery and trauma admissions occurred in H-100 and H-200 only (Figure 6.11).

6.3.3 Glycaemic control methods implemented

6.3.3.1 Glycaemic monitoring

Monitoring method

As described in Section 6.2.4.2, only the most probable method for measuring BG could be identified. Overall, the most probable method was arterial blood analysed in the gas machine (65% measurements), followed by capillary blood analysed in the point of care BG meter (28%). H-300, H-500, and H-400 had the highest percentages of arterial samples, while H-600, H-200 and H-100 had the highest proportions of capillary samples (Figure 6.12). While these were the "most probable" methods, the probability that these were the actual method was unknown.

Overall frequency of monitoring

Most glycaemic measurements (90.5%) were carried out with a frequency of every one to four hours. Hourly glycaemic measurements represented 13.0% and 36.8% of all measurements among patients without and with diabetes, respectively; and 2-hourly measurements represented 32.0% and 31.6% of all measurements among patients without and with diabetes, respectively (Figure 6.13).

However, the spread of the TNM was large, and there were several very high TNM values of up to 80 hours. Of all TNM values, 1.3% were above eight hours, and on 14 (0.1%) occasions they were above 24 hours (Figure 6.13). Most (99.9%) of the TNMs that were

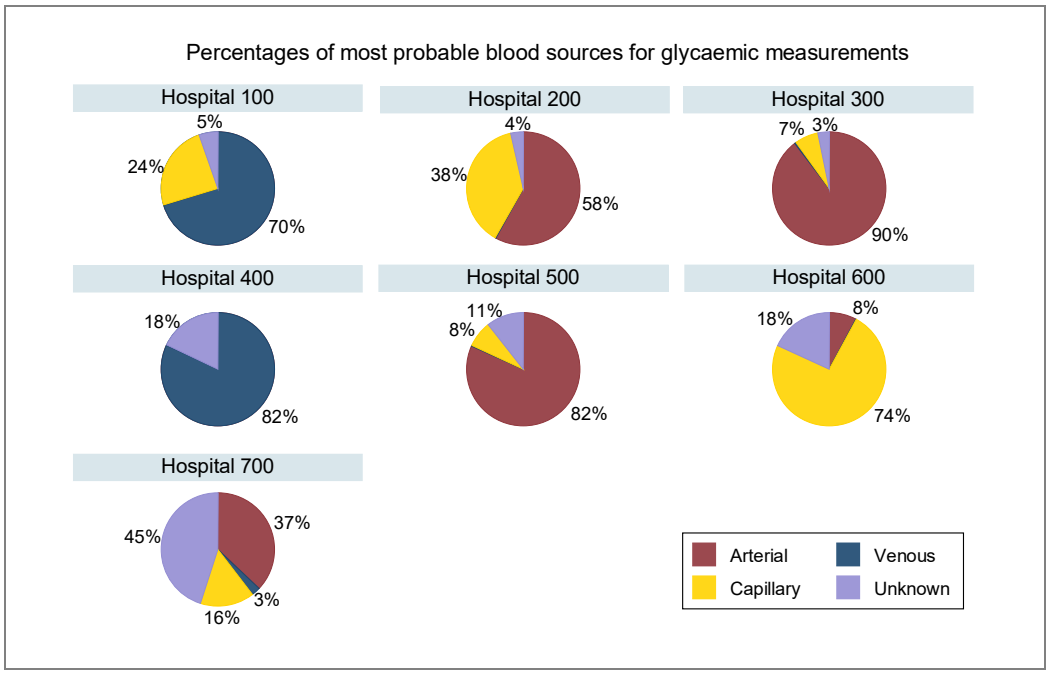


Figure 6.12 – Distribution of the most probable blood source for glycaemic measurements, by hospital

above eight hours, including those above 24 hours, were not due to a chart being missing following a measurement, and more than half (55.0%) of these very high values occurred in the last third of the patients' total stay. H-500 had the highest percentages of very high TNM, with 3.6% 8-hourly BG measurements; and H-100 had the lowest, with 0.5% 8-hourly BG measurements.

The distribution of the TNM varied significantly depending on the glycaemic status, in all groups of diabetic status (all with $p<0.001$) (Figure 6.13). On average, glycaemic measurements were taken less frequently during periods when the patient's glycaemic levels were within the study target range of 4-10mmol/L (Figure 6.13).

Overall, the TNM was significantly different between protocol-hospitals (Figure 6.14) during hours of hyperglycaemia ($p<0.001$) and during hours of glycaemia within the study target range ($p<0.001$), in both groups of diabetic status. During hypoglycaemic events, differences between protocol-hospital were significant only among patients with diabetes ($p=0.020$). In most protocol-hospitals, the TNM variability within protocol-hospital was larger during hours when BG was within the study target range (Figure 6.14).

P-5_H-500 in patients without diabetes and P-6_H-500 in patients with diabetes had the highest overall median TNM during hyperglycaemia (median of three hours); while P-1.2_H-100 in patients without diabetes and P-2.2_H-100 in patients with diabetes had the lowest median TNM (median of one hour) (Figure 6.14).

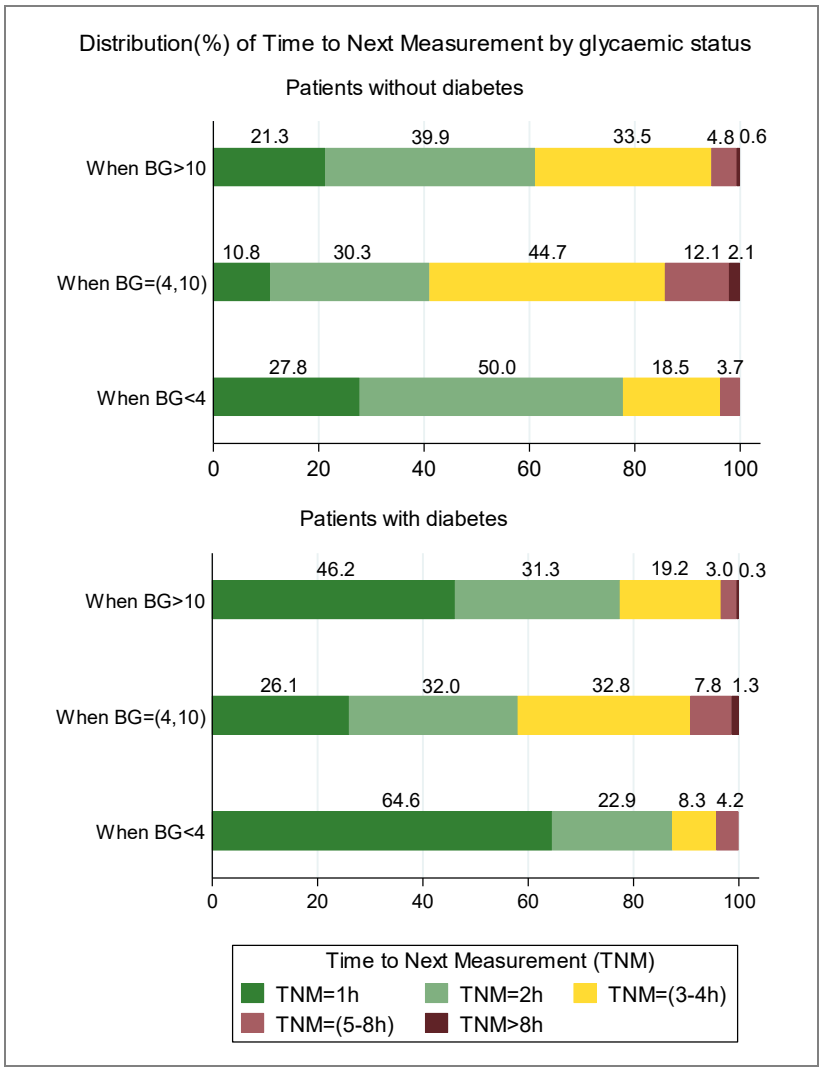


Figure 6.13 – Distribution (%) of times to next measurement (hours), by glycaemic status

Frequency of monitoring in each patient

The TNM for each patient individually will be referred to as patient-TNM. More than 50% of the patients had a mean patient-TNM of three hours or higher during their whole ICU stay, although the spread of these values was large and 35% of the patients had at least one TNM above eight hours (Table 6.13). The median of the mean patient-TNM, for the whole sample, was significantly higher during the periods of BG within the study target range (median of three hours), followed by during hyperglycaemia>10 (median of 2.5 hours), the lowest occurring during hypoglycaemia (median of two hours) ($p<0.001$) (Table 6.13).

Patients with diabetes had a significantly lower mean and SD of patient-TNM during the glycaemic status of 4-10mmol/L, meaning that they were monitored more frequently, and with less variability of frequency, than patients without diabetes, during this glycaemic status (Table 6.13).

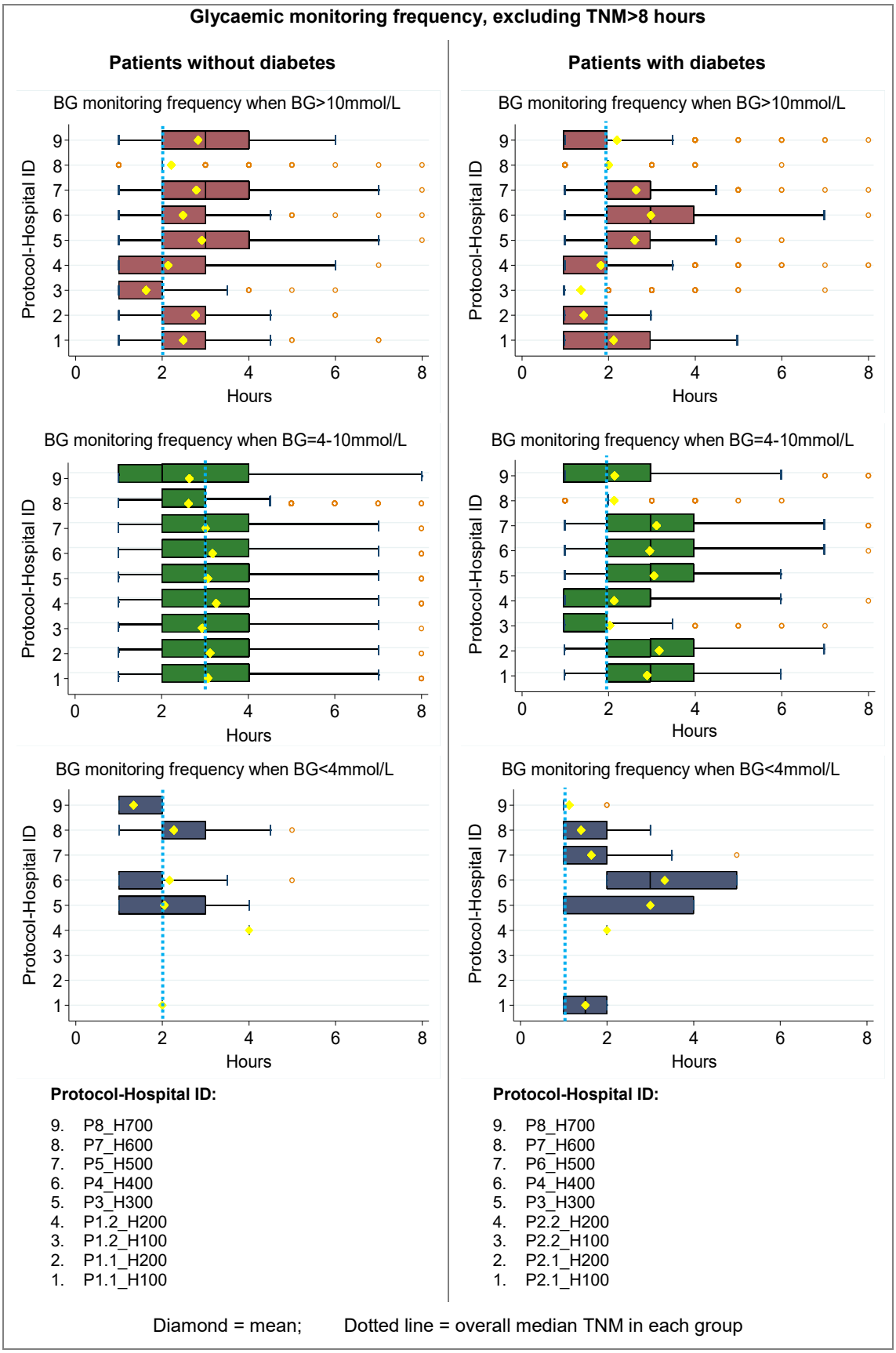


Figure 6.14 – Box-plot of overall time to next measurement (excluding very high TNM>8h), at each glycaemic status, by protocol-hospital.
BG: blood glucose.

Table 6.13 – Summary statistics on time to next measurement (h) for each patient, in each glycaemic status

		Diabetes previously diagnosed	
	All	**No/Unknown**	**Yes**
At any time			
No.(%) patients with 1 or more TNM>8	51 (35%)	36 (39%)	15 (28%)
No.(%) patients with 1 or more TNM>24	9 (6%)	6 (7%)	3 (6%)
During hours of hyperglycaemia>10			
Median(IQR) of mean patient-TNM	2.5 (2-3)	2.6 (2-3)	2.2 (1.9-2.8)
Median(IQR) of SD patient-TNM	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.0 (0.7-1.3)
During hours within range 4-10mmol/L			
Median(IQR) of mean patient-TNM ***	3 (2.5-3.4)	3.1 (2.7-3.6)	2.6 (1.9-3.1)
Median(IQR) of SD patient-TNM **	1.3 (1.1-1.7)	1.4 (1.1-1.9)	1.1 (0.8-1.6)
During hypoglycaemia			
Median(IQR) of mean patient-TNM	2 (1.2-2.3)	2 (1.9-2.3)	1.5 (1-2.3)
Median(IQR) of SD patient-TNM	0.7 (0.4-1.0)	0.7 (0.4-1.4)	0.6 (0.0-0.7)

Differences by diabetic status:

** $p<0.050$; ** $p<0.010$; *** $p<0.001$*

BG: blood glucose; TNM: time to next measurement; SD: standard deviation

Among patients without diabetes, the median patient-TNM did not differ significantly by protocol-hospital, in any of the glycaemic statuses. On the other hand, among patients with diabetes, there were significant differences in the median patient-TNM between the different protocol-hospitals, in all glycaemic statuses: during hyperglycaemia>10 ($p<0.001$), at the study target glycaemic range ($p=0.002$), and at hypoglycaemia ($p=0.043$). This means that patients with diabetes were monitored with significantly different frequency depending on where they were admitted and with what protocol they were treated.

During the period from the first BG>10mmol/L to the time when the BG is within 4-10mmol/L for two consecutive hours, which is referred to as the TTR period in this study, the median (IQR) of the median patient-TNM was 2.0 (2.0-3.0) hours and 2.0 (1.5-3.0) hours among patients without and with diabetes, respectively.

There was one outlying patient who did not have any BG measurement for nine hours during his TTR period. Hence, his mean and median TNM during the TTR period were nine hours. This patient was a 66-year-old male, without diagnosed diabetes, admitted after surgery of laryngeal tumour, and assigned to protocol-hospital P-5_H-500. During this TTR period, this patient did not receive any insulin.

6.3.3.2 Treatment with insulin

All the participating ICUs used intravenous rapid acting insulin (Actrapid ®) to manage hyperglycaemia, administered continuously and intravenously at rates that were intermittently titrated based on patients' BG levels.

Of the 146 participating patients, 31 (21%) patients from all hospitals did not receive any insulin during their whole ICU stay. Of these 31 patients, 24 (77%) spent more than three hours with hyperglycaemia>10, and two (6%) had diabetes. Of these two, one received 500mg of Metformin for three hours.

Overall insulin dosage

The frequency and dispersion of the IIR varied depending on whether patients had diabetes, on the glycaemic status (Table 6.14, Figure 6.15), and on the hospital of admission (Figure 6.16). Approximately half of the IIRs (50.6%) were 2U/h or lower, and 89.6% of all the rates given were within 1-6U/h. There were often very high IIR values, with IIRs ranging from 0.5 to 21U/h.

Insulin was usually administered when glycaemic levels were above or within the study target range and, on average, the dosages were higher during hyperglycaemia>10 (Figure 6.15). There were 954 events in which no insulin was given during hyperglycaemia>10 for at least two hours, despite feeding being in place. There were 45 occasions with insulin administration during hypoglycaemia (Figure 6.15), in 27 of which there was no feeding in place.

There were significant differences in the IIRs between protocol-hospitals, in both groups of patients with/without diabetes, and in all glycaemic statuses (all with $p<0.001$) (Figure 6.16), except for during hypoglycaemia when the differences between protocol-hospitals were not statistically significant. During hyperglycaemia>10, patients with diabetes received significantly higher IIRs, on average, than patients without diabetes (Figure 6.16). The dispersion of IIRs during hyperglycaemia>10 was also higher among patients with diabetes than among patients without diabetes, both within and between protocol-hospitals (Figure 6.16).

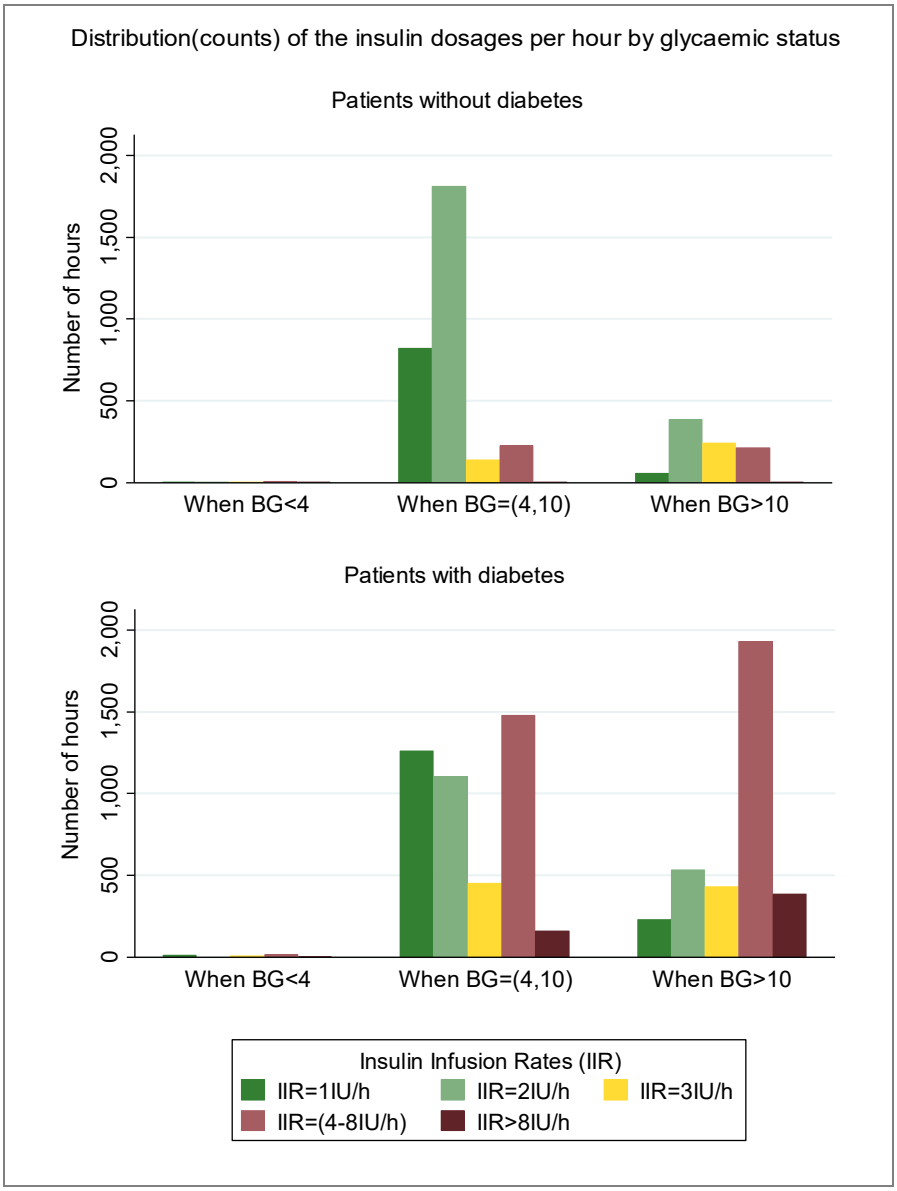


Figure 6.15 – Distribution of Insulin Infusion Rates (U/h), by glycaemic status

In 556 (5%) occasions, in 31 (21%) patients, the IIR administered was above 8U/h (Figure 6.15). 99% (549) of these occasions occurred in 25 (80%) patients who had a previous diagnosis of diabetes. In 163 (29%) of the 556 occasions, BG levels were below 10mmol/L, two of them being below 4mmol/L. These 163 events occurred in 16 patients, of whom all except for one had diabetes. All ICUs except for H-100 had at least three of these 163 events, although 50% of them occurred in P-8_H-700.

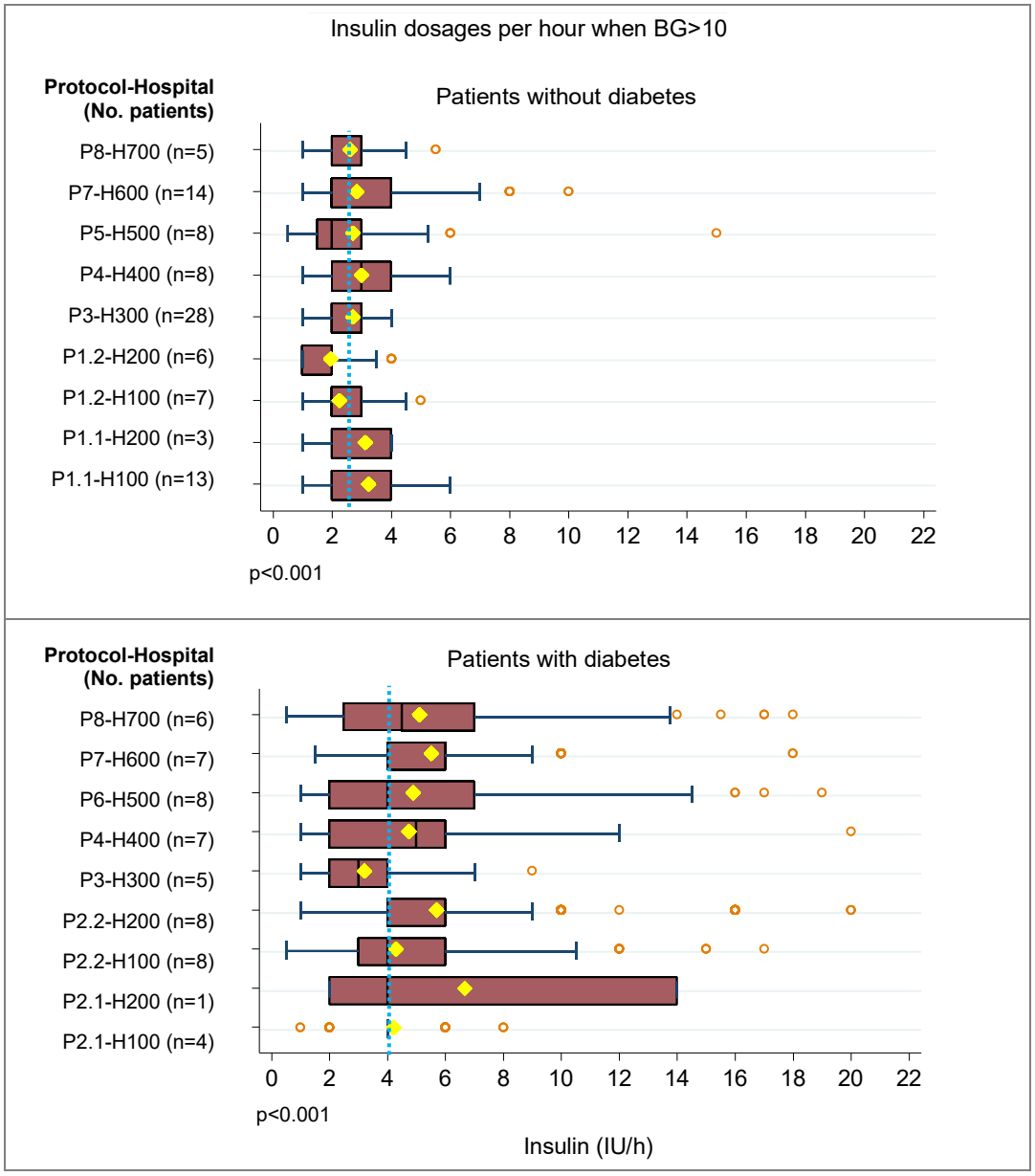


Figure 6.16 – Box-plot of the insulin dosages per hour during hyperglycaemia above 10mmol/L, by hospital. The hours with no insulin are excluded from the calculations

Insulin dosage in each patient

The IIR for each patient individually will be referred to as patient-IIR. The mean patient-IIR ranged from 1 to 15U/h, although for 91% patients of the 115 patients who received insulin their mean patient-IIR was below 5U/h. All metrics of frequency and dispersion of the mean patient-IIR were significantly higher among patients with diabetes, except during hypoglycaemia when this difference was not statistically significant (Table 6.14).

Table 6.14 – Summary statistics of Insulin Infusion Rates (U/h) per patient, at each glycaemic status

		Diabetes previously diagnosed	
	All	**No/Unknown**	**Yes**
At any time			
n (%) patients who received insulin***	115 (79%)	63 (69%)	52 (96%)
n (%) patients with ≥1dosage >8U/h***	31 (27%)	6 (7%)	25 (46%)
n (%) patients with ≥1dosage >15U/h**	8 (7%)	1 (1%)	7 (13%)
During hours of hyperglycaemia>10			
n (%) patients with insulin***	105 (72%)	54 (59%)	51 (94%)
Median (IQR) mean patient-IIR***	1.0 (0.0-2.4)	0.5 (0-1.4)	2.5 (1.3-4.3)
Median (IQR) SD patient-IIR***	1.3 (0.2-2.0)	0.9 (0.0-1.4)	2.0 (1.4-2.7)
During hours within range 4-10mmol/L			
n (%) patients with insulin***	112 (77%)	62 (67%)	50 (93%)
Median (IQR) mean patient-IIR***	0.6 (0-1.5)	0.2 (0.0-1.0)	1.6 (0.8-2.8)
Median (IQR) SD patient-IIR***	0.8 (0.1-1.3)	0.5 (0.0-0.9)	1.4 (0.8-1.9)
During hypoglycaemia			
n (%) patients with insulin	21 (14%)	10 (11%)	11 (20%)
Median (IQR) mean patient-IIR	0.4 (0.0-2.3)	0.0 (0.0-2.0)	0.5 (0.0-3.0)
Median (IQR) SD patient-IIR	0.0 (0.0-2.0)	0.0 (0.0-0.5)	0.0 (0.4-2.0)

Differences by diabetic status:

* p<0.050; ** p<0.010; *** p<0.001 v

BG: blood glucose; IIR: insulin infusion rate; SD: standard deviation

Patients with higher insulin dosages during lower glycaemic statuses and other unexpected results

The number of patients receiving insulin when they were within the study target range was higher than the number of patients receiving insulin during hyperglycaemia>10 (Table 6.14). Also, 30 (26%) of the 115 patients who received insulin had a higher mean patient-IIR when they were below than when they were above 10mmol/L. All hospitals had at least one of these cases, although most of them belonged to H-100 (27%), H-300 (23%) and H-700

(20%). The median (IQR) number of hours that these 30 patients spent in hyperglycaemia>10 was 17 (3-45) hours, but nine (30%) of these 30 patients spent three or less hours in hyperglycaemia>10, and seven (78%) of these nine patients did not receive any insulin during those hours of hyperglycaemia>10. In 29 of the 30 cases, the difference between the mean patient-IIR during hyperglycaemia>10 and the mean patient-IIR during the study target glycaemia was lower than 1U/h. Of the 30 patients, nine (30%) had diabetes.

The 954 events of no insulin administration during hyperglycaemia>10 for at least two hours, despite feeding being in place, occurred in 49 (53%) patients without and 23 (44%) patients with diabetes, from all protocol-hospitals. The highest percentages of patients with at least one of these events occurred in P-2.2_H-200 (63%) among patients with diabetes, and in P-8_H-700 (100%) among patients without diabetes.

The 45 events of insulin administration during hypoglycaemia occurred in 21 patients: 11 (12%) without and 10 (19%) with diabetes (Table 6.14). They were spread amongst the seven participating ICUs, but not amongst all protocol-hospitals. Most of these patients received P-8_H-700 (six patients) and P-4_H-400 (five patients); followed by P-6_H-500 and P-7_H-600 (three patients each); P-1.1_H-100 (two patients); and P-1.2_H-200 and P-3_H-300 (one patient each).

Of these 21 patients, eight patients with diabetes (73%) and two without diabetes (20%) received the insulin during hypoglycaemia when no feeding was in place (p=0.016). This occurred for 28 patient-hours in total, and with a median insulin dosage of 3U/h. Five of them (50%) received P-8_H-700, and the other five received P-4_H-400, P-6_H-500, and P-7_H-600. Also, 13 of the 21 patients (62%) had a higher mean patient-IIR during hypoglycaemia than during the study glycaemic target. Three of these 13 patients spent more than three hours in hypoglycaemia. Seven of the 13 patients (54%) had diabetes.

Duration of insulin treatment per patient

The percentage of admission time spent receiving insulin ranged from 0% to 100% (Figure 6.17), although in half of the patients this percentage was 38% or less (Table 6.15). In 65 (71%) patients without diabetes and 17 (31%) patients with diabetes, the percentage of time with hyperglycaemia>10 and receiving insulin was lower than 50% (Figure 6.17).

The percentages of time spent receiving insulin were significantly higher among patients with diabetes than among patients without diabetes, in all glycaemic statuses (Table 6.15). In comparisons between glycaemic statuses, the percentages of time spent receiving insulin did not differ significantly when comparing the glycaemic status in the study target range and

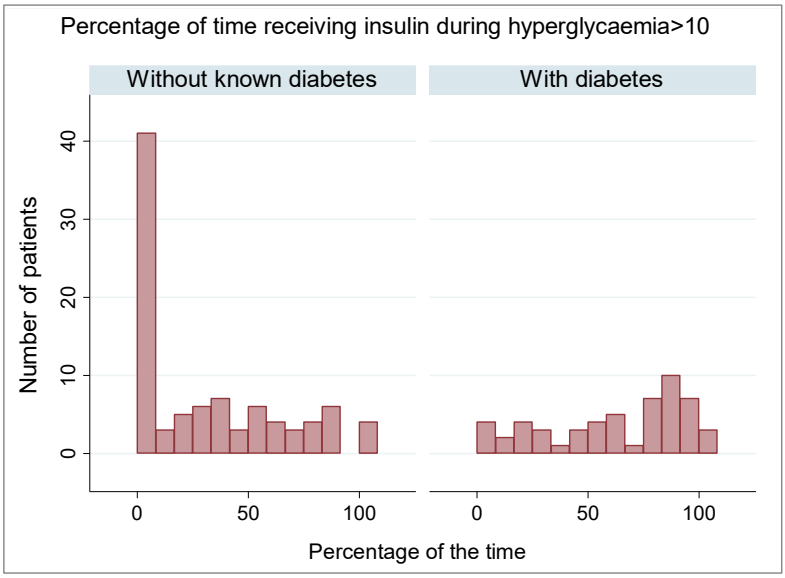


Figure 6.17 – Percentage of time that each patient spent receiving insulin during periods of hyperglycaemia>10, by previous diagnosis of diabetes

Table 6.15 – Percentage of admission hours receiving insulin per patient

		Diabetes previously diagnosed	
	All	**No/Unknown**	**Yes**
At any time			
Median (IQR) percentage hours receiving insulin, per patient ***	38% (2-73%)	10% (0-54%)	73% (40-91%)
During hours of hyperglycaemia>10			
Median (IQR) percentage hours with insulin **	37% (0-79%)	21% (0-56%)	74% (42-90%)
When BG=4–10mmol/L			
Median (IQR) percentage hours with insulin ***	32% (1-72%)	7% (0-50%)	70% (22-94%)
When BG<4mmol/L			
Ratio of patient median hours receiving insulin during hypoglycaemia to patient median hours spent in hypoglycaemia [a]	2:3	1:2	2:3

* p<0.050; ** p<0.010; *** p<0.001

EN: Enteral Nutrition; TPN: Total Parenteral Nutrition

[a] Including only the 21 patients who received insulin during hypoglycaemia at least once

the glycaemic status at hyperglycaemia>10, both for patients without and with diabetes. On the other hand, in both groups of diabetic status, the percentage of time receiving insulin was significantly higher during periods of glycaemia within target range ($p<0.001$), and during periods of hyperglycaemia>10 ($p<0.001$), than during hypoglycaemia.

Among patients with diabetes, there were no statistically significant differences between protocol-hospitals in the percentage of time receiving insulin per patient, in any of the study glycaemic statuses. Among patients without diabetes, there were significant differences between protocol-hospitals in the percentage of time that patients spent receiving insulin during hours within the study target glycaemia ($p=0.027$), and during hypoglycaemia ($p=0.049$), but not during hyperglycaemia>10.

Table 6.16 summarises the results on the percentage of time per patient receiving insulin, and the median TNM per patient, during hyperglycaemia>10, for each group of diabetic status, at each of the study periods of admission considered.

Table 6.16 – Duration of insulin treatment and median monitoring frequency during hyperglycaemia>10, and during the TTR period

		Patients without diabetes	Patients with diabetes
Median (IQR) of the percentage of hours that each patient spent receiving insulin during hyperglycaemia>10	**During full stay**	21% (0-56%)	74% (42-90%)
	During first 6 days	21% (0-56%)	76% (42-90%)
	During first 2 days	0% (0-46%)	64% (33-85%)
	During the TTR period[a]	0% (0-33%)	50% (0-85%)
Median (IQR) of the median time (hours) to next measurement of each patient during hyperglycaemia>10	**During full stay**	2.5 (2.0-3.0)	2.0 (1.5-3.0)
	During first 6 days	2.3 (2.0-3.0)	2.0 (1.0-3.0)
	During first 2 days	2.0 (2.0-3.0)	2.0 (1.0-2.5)
	During the TTR period[a]	2.0 (2.0-3.0)	2.0 (1.5-3.0)

BG: blood glucose

[a] TTR period: time from first BG>10mmol/L to next (subsequent) BG=4-10mmol/L for two consecutive hours

6.3.3.3 Nutrition

Enteral nutrition

Of the 146 patients, 11 (20%) patients with diabetes and 11 (12%) patients without diabetes did not receive any EN during their ICU stay. Three of these patients, of whom one had diabetes, received TPN.

Of the 17483 patient-hours with available data on the EN rates (excluding when no EN was in place), only 7078 (40.3%) patient-hours were accompanied by information about the EN preparation type prescribed, and therefore the non-protein kcal administered per hour (npkcal/h) could only be calculated for this time. During these hours, there were four EN preparations that represented more than 55% of all those patient-hours (Figure 6.18), including: Nutrison Standard, used in four hospitals; Nutrison Concentrated, used by three hospitals; Fresubin Original, used two hospitals; and Osmolite 1.0, used in one hospital. The remaining types were used in one or two hospitals only and each of them were given during less than 10% of the hours with available data about this (Figure 6.18).

Some EN types had concentrations as high as 170npkcal/100mL, with concentrations above 125npkcal/100mL accounting for slightly over 29% of the total patient-hours with available data on EN prescriptions (Figure 6.19). EN types with 82-102npkcal/100mL represented more than 70% of all patient-hours (Figure 6.19).

During the hours for which there were nutritional prescriptions available, the median npkcal/h was significantly higher during hours when high concentration EN preparations

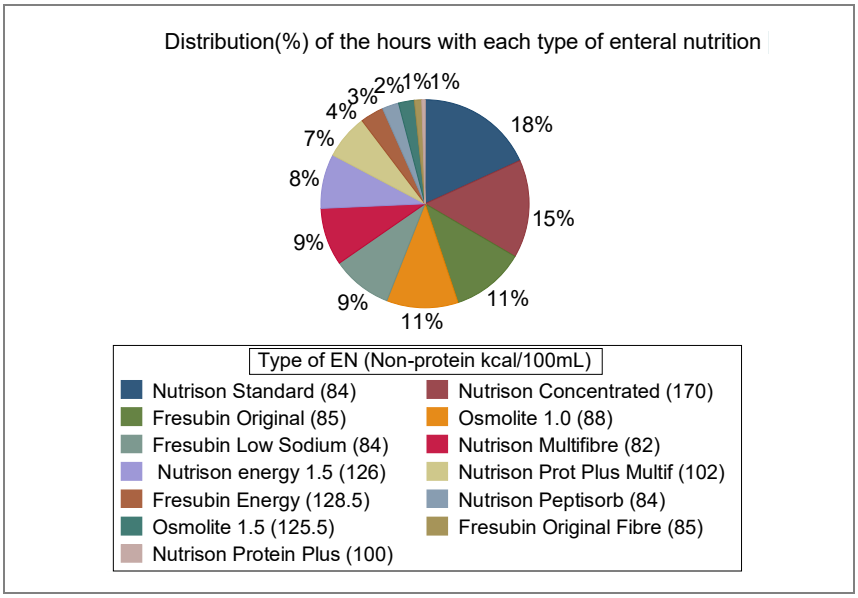


Figure 6.18 – Distribution (%) of the time (hours) administering each type of enteral nutrition during the hours for which there was information on the prescribed enteral nutrition available from the medical notes

(>125npkcal/100mL) were given, than when lower concentration EN preparations were administered, at all glycaemic statuses (p<0.001) (Table 6.17). Also, the median npkcal/h was significantly higher during hyperglycaemia>10 than during the study glycaemic target (*p*<0.001) (Table 6.17).

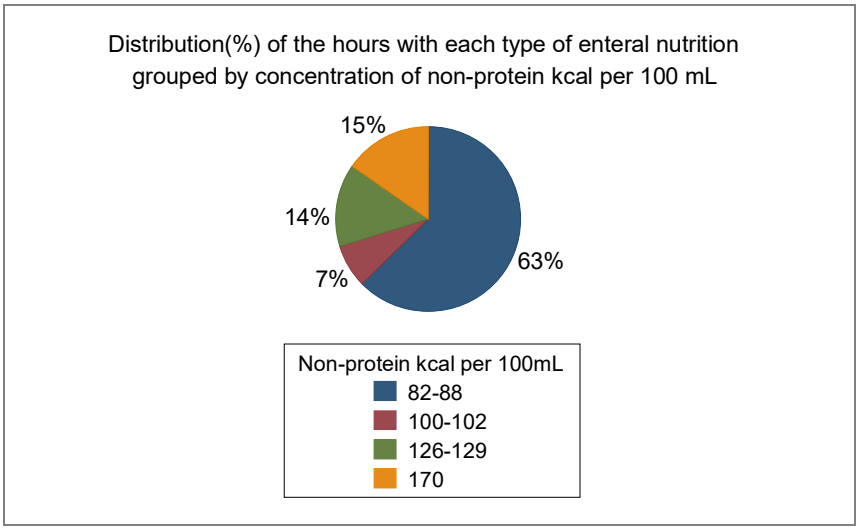


Figure 6.19 – Distribution(%) of the time (hours) administering each group of types of enteral nutrition, grouped depending on the amount of non-protein kcal per 100mL (among the hours for which there was information on the prescribed enteral nutrition available from the notes)

Table 6.17 – Non-protein kcal/h given through enteral nutrition, excluding the hours when no enteral feeding was in place

	During each glycaemic Status		
Median (IQR)	**BG>10**	**BG=4-10**	**BG<4**
Overall npkcal/h	65 (53–79)	57 (49–74)***	68 (34–75)
Overall npkcal/h of patient-hours with **high**[a] concentration (>125npkcal/100mL) EN only	66 (64–90)	68 (56–75)***	72 (68–75)[b]
Overall npkcal/h of patient-hours with **non-high** concentration (<125npkcal/100mL) EN only	56 (53–79)	56 (42–73)***	34 (8–69)[b]

Comparison of hours with **BG>10mmol/L** with each of the other two glycaemic statuses:

*p<0.050; **p<0.010; ***p<0.001

No significant difference in any of the metrics between hyperglycaemia>10 and hypoglycaemia

EN: Enteral Nutrition; npkcal/h: non-protein kcal/h

All metrics are expressed in median (IQR)

[a] High concentration EN preparations included: Nutrison Concentrated, Nutrison Energy 1.5, Fresubin Energy and Osmolite 1.5

[b] Based on the only 4 hours with available data on EN prescriptions during hypoglycaemia

Enteral nutrition at the patient level

At the individual patient level, there were no significant differences in the patient mean npkcal/h, between patients with and without diabetes, in any of the glycaemic statuses. Also, the patient mean npkcal/h did not differ between protocol-hospitals, at all the glycaemic statuses, and all the groups of diabetic status.

On average, the patient mean npkcal/h was significantly higher during hours of hyperglycaemia>10 than during periods within the study target range (p=0.048); and the dispersion of the npkcal/h data per patient, as measured by the SD, was significantly lower during hours of hyperglycaemia>10 (p=0.026) (Table 6.18).

However, when analyses were done by groups of diabetes separately, the difference in the mean npkcal/h per patient at each glycaemic status was not statistically significant, and the difference in the SD of the npkcal/h per patient was significant only among patients without diabetes (p=0.018).

This means that hyperglycaemia>10 did not seem associated with higher EN energy input than when BG was within the study target range, and that for patients without diabetes there was a higher variability in these energy rates during periods within the study target range than during hyperglycaemia>10.

Table 6.18 – Non-protein kcal/h given through enteral nutrition per patient, excluding the hours when no enteral feeding was in place

	During each glycaemic Status		
Median (IQR)	**BG>10**	**BG=4-10**	**BG<4**
n (%)[a] **patients** who received EN	100 (68%)	124 (85%)	16 (40%)
n (%)[a] **patients** who received EN and for whom there were data on the EN preparation type	36 (25%)	43 (29%)	6 (15%)
Median (IQR) of patient mean npkcal/h	59 (48–75)	52 (49–69)*	63 (8–75)
Median (IQR) of patient SD npkcal/h	11 (7–18)	15 (11–20)*	NA[b]

Comparison of hours with **BG>10mmol/L** with each of the other two glycaemic statuses:

*p<0.050; **p<0.010; ***p<0.001

No significant differences in any of the metrics between hyperglycaemia>10 and hypoglycaemia

EN: Enteral Nutrition; npkcal/h: non-protein kcal/h;

[a] Percentages of patients with EN out of the whole sample (146) or out of the 40 patients who had hypoglycaemia at least once

[b] One or two values per patient only

Parenteral Nutrition

TPN was administered to nine (6%) patients from four hospitals (H-300, H-400, H-500 and H-600) at least once. Of these, five patients had diabetes, and four patients belonged to H-600.

The types of TPN preparations prescribed were known for 84.4% patient-hours. These included Kabiven-9 (32%), Kabiven-11 (18%), Kabiven-14 (17%), Kabiven-5 (13%), and two personalised preparations of TPN for the same patient (21%).

Five patients, from H-400, H-500 and H-600, received both EN and TPN at the same time, for 12h, 21h, 27h, 32h, and 71h. Four of these five patients had diabetes.

Parenteral nutrition at the patient level

At the individual level, there were no statistically significant differences in the patient mean npkcal/h via TPN, between the different glycaemic statuses, regardless of the diabetic status, nor between patients with and without diabetes, regardless of the glycaemic status. The patient mean npkcal/h via TPN did not differ significantly between the three protocol-hospitals where TPN was administered, neither overall nor in each of the glycaemic statuses separately.

6.3.3.4 Medication

Propofol

Propofol was administered to 116 (79%) patients at least once. The percentage of time during which these patients received propofol ranged from 0 to 91% of admission time, although more than 85% patients spent less than 50% of the time with propofol (Table 6.19).

Among patients without diabetes, there were no statistically significant differences in the mean dosage, as well as in the mean duration of propofol treatment, when comparing the different glycaemic statuses. Among patients with diabetes the mean dosage of propofol was significantly lower during hypoglycaemia than during both hyperglycaemia>10 ($p=0.003$), and during glycaemia within the study target ($p=0.048$). Among these patients, the mean duration of propofol treatment was also lower during hypoglycaemia than both during hyperglycaemia>10 ($p=0.005$), and during glycaemia within the study target ($p=0.014$).

Catecholamines

Catecholamines were administered to 121 (83%) patients at least once, of whom 46 (85%) had diabetes and 75 (82%) did not have diabetes. Noradrenaline was administered to 114 (78%) patients, adrenaline to 23 (16%) patients, and dobutamine to 17 (12%) patients.

Among patients who received them, treatment with catecholamines was in place for 3% to 100% of the admission time (Table 6.19), but for half of the patients this proportion was below 36% of the admission time. Noradrenaline was in place for a median (IQR) 33% (17-61%) time, and adrenaline for a median (IQR) 8% (4-18%) time.

There were no statistically significant differences between patients with and without diabetes in the mean dosages of each of the catecholamines given, at all the glycaemic statuses. The proportion of time spent receiving catecholamines, and the mean dosage of noradrenaline per patient, were higher during hours of hyperglycaemia>10 than during hours within the study glycaemic target range (Table 6.19), but this was statistically significant only among patients

Table 6.19 – Dosages and proportion time per patient with propofol, catecholamines or glucocorticoids

	During time at each glycaemic Status		
	BG>10mmol/L	**BG4-10mmol/L**	**BG<4mmol/L**
Propofol			
Median (10-90dec) proportion hours per patient	11% (0–100%)	18% (0–54%)	0 (0–100%)
Median (10-90dec) of patient mean dosage (mg/h)	8 (0–110)	19 (0–59)	0 (0–78)
Catecholamines			
Median(10-90dec) percentage hours per patient with any catecholamine	37% (0–100%)	24% (0–88%)***	0% (0–100%)
Noradrenaline median(10-90dec) of patient mean dosage (mcg/kg/h)	2 (0–15)	1 (0–9)***	0 (0–11)*
Adrenaline median(10-90dec) of patient mean dosage (mcg/kg/h)	0 (0–1)	0 (0–0)**	0 (0–0)
Dobutamine median(10-90dec) of patient mean dosage (mcg/kg/h)	0 (0–0)	0.0 (0–13)	0 (0–0)
Glucocorticoids			
Median(10-90dec) percentage hours per patient with any corticoid	0% (0–8%)	0% (0–7%)	0% (0–0%)
Hydrocortisone median(10-90dec) of patient mean dosage (mg/h)	0 (0–3)	0 (0–5)	0 (0–0)

Comparison of hours with BG>10mmol/L vs. each of the other two glycaemic statuses:

*p<0.050; **p<0.010; ***p<0.001

No significant difference in any of the metrics between hyperglycaemia>10 and hypoglycaemia

The median(10^{th}-90^{th}deciles), instead of the median(IQR) is shown, as the IQR was often 0–0%

BG: Blood Glucose; LOS: Length of Stay

without diabetes. The mean dosage of adrenaline was higher during hours of hyperglycaemia>10 than during hours in the study target range (Table 6.19), but this was statistically significant only among patients with diabetes.

Glucocorticoids

Of the study patients, 16 (30%) patients with diabetes and 32 (35%) without diabetes, received treatment with a glucocorticoid at least once (Table 6.19). The most commonly used was hydrocortisone (39 patients), followed by prednisolone (15 patients), dexamethasone (two patients), methylprednisolone (two patients), and fludrocortisone (one patient).

There were no statistically significant differences between patients with and without diabetes neither in the mean dosages of glucocorticoids given, regardless of the glycaemic status, nor between glycaemic statuses, regardless of the diabetic group.

6.3.3.5 Hypoglycaemic agents (diabetes treatment)

Of the 54 patients with diabetes, 15 (28%) patients, from all ICUs except one (H-300), were given some type of treatment for diabetes, other than Actrapid®, during their ICU stay. These were mostly oral Metformin® (83%), and in 17% of the occasions some type of intermediate or long-acting insulin administered subcutaneously (Figure 6.20). One patient was given a fast-acting insulin (Apidra®) combined with a long-acting insulin (Levemir®), subcutaneously, on three occasions; and one patient was administered another rapid-acting insulin (Novorapid®) subcutaneously on one occasion.

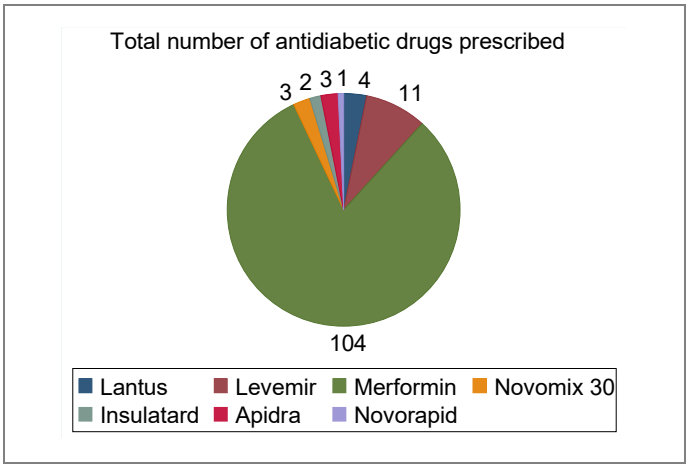


Figure 6.20 – Total number of each hypoglycaemic agent administered to patients with diabetes, other than Actrapid®

6.3.4 Comparison of implemented glycaemic control methods with protocol instructions: level of staff adherence

The level to which the methods for GC implemented matched with what the pertinent protocol recommended, depended on the type of protocol-instruction, the protocol-hospital concerned, and whether the patient had a previous diagnosis of diabetes. The findings on the staff's adherence to protocol instructions are described in the following sections.

6.3.4.1 Adherence to instructions on insulin titration

The differences in the percentages of each type of non-adherence to insulin instructions (giving more or giving less than specified), depending on the protocol-hospital, were all statistically significant in both groups of diabetes (all with $p<0.001$). In each of the hospitals that implemented the same protocol for all patients regardless of their diabetic status (H-300, H-400, H-600 and H-700) the percentages of each type of non-adherence to insulin instructions were significantly different between patients with and without diabetes, in all those hospitals (all with $p<0.001$).

Patients without diabetes

Among patients without diabetes, according to protocol-hospitals instructions, insulin was often not needed and not given. In this group of patients, giving less insulin than specified in the protocol occurred in 0% to 76% of admission time, and giving more than specified occurred in 2% to 13% of admission time, depending on the protocol-hospital (Figure 6.21). The percentage of patients without diabetes per protocol-hospital, with at least one occasion during hyperglycaemia>10 in which the insulin dosage was lower than specified, ranged from 0% to 100% patients (Table 6.20). In these occasions, deviations below the dosage specified had medians of the patient-mean, per protocol-hospital, ranging from 0 to 3.6U/h. The percentage of patients without diabetes with at least one occasion during hyperglycaemia>10 with an insulin dosage higher than specified ranged from 0% to 50% patients, depending on the protocol-hospital (Table 6.20). In these occasions, deviations above the dosage specified had medians of the patient-mean, per protocol-hospital, ranging from 0 to 4U/h.

Patients with diabetes

Among patients with diabetes, according to protocol-hospital instructions, insulin was often needed but the dosages given were often either higher or lower than specified in each particular protocol-hospital (Figure 6.21). Depending on the protocol-hospital, the percentages of hours when patients were given less insulin dosage than specified ranged

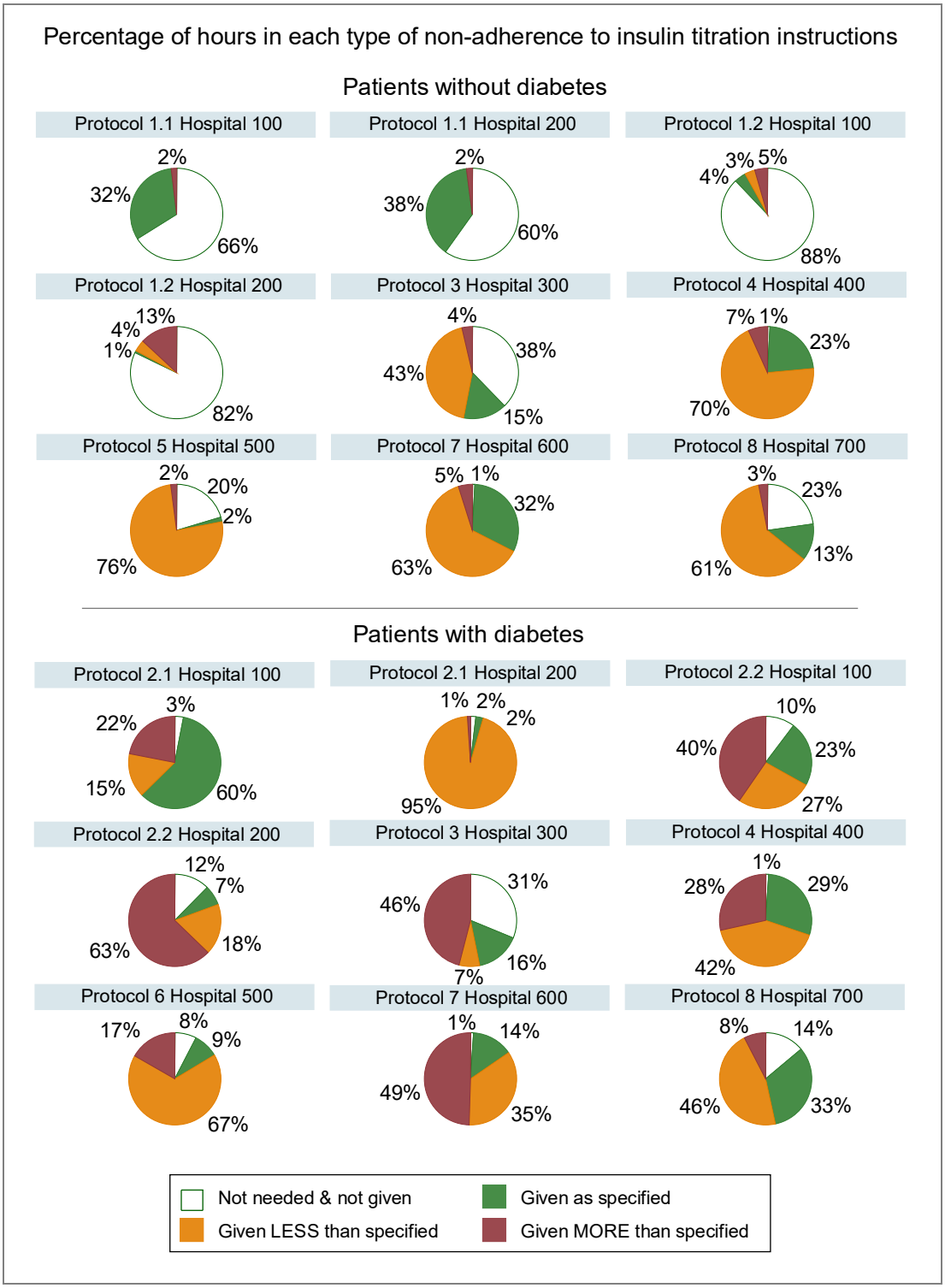


Figure 6.21 – Percentage of hours in each type of non-adherence to insulin titration instructions, by protocol-hospital and diabetic status

from 7% to 95%, and the percentage of hours in which they were administered more than specified ranged from 8% to 63% (Figure 6.21).

Giving less insulin than specified during hours of hyperglycaemia>10 occurred at least once in all patients with diabetes of all protocol-hospitals, except P-3_H-300 where it occurred in 60% patients (Table 6.20). In these occasions, deviations below the dosage specified had medians of the patient-mean, per protocol-hospital, ranging from 0.5 to 3.3U/h, although in most protocol-hospitals this was 2U/h or lower (Table 6.20).

Administering a higher dosage than specified during hyperglycaemia>10 occurred at least once in 60% to 100% patients, depending on the protocol-hospital. Deviations over the specified dosage had medians of the patient-mean, per protocol-hospital, ranging from 0.7 to 8.3U/h (Table 6.20).

6.3.4.2 Adherence to instructions on monitoring frequency

There were statistically significant differences in the percentages of each type of non-adherence to monitoring frequency instructions between protocol-hospitals, both among patient with and without diabetes (all with $p<0.001$).

Patients without diabetes

Among patients without diabetes, the percentages of BG measurements taken later than specified, per protocol-hospital, ranged from 20% to 91%. Early BG measurements occurred in five protocol-hospitals, ranging from 2% to 6% of occasions. In three protocol-hospitals there were 4% to 12% measurements in which adherence could not be assessed as the protocols would have not specified a TNM, but instead specified that "medical staff should be called" (Figure 6.22).

In all protocol-hospitals except two, all the patients had at least one late BG measurement during hours of hyperglycaemia>10. During hours of hyperglycaemia>10, deviations over the specified TNM had medians of the patient-mean, per protocol-hospital, ranging from 1.3 to 2.4 hours (Table 6.20). Only two protocol-hospitals had occasions when BG measurements were taken earlier than specified during hyperglycaemia>10. This happened at least once in 21% of patients in P-1.1_H-100 and in 60% of patients in P-8_H-700. The median of the patient-mean deviation was of 1 hour for both protocol-hospitals (Table 6.20).

Patients with diabetes

Among patients with diabetes, late BG measurements occurred in all protocol-hospitals, ranging from 26% to 86% of occasions. Early BG measurements occurred in four protocol-hospitals, ranging from 1% to 11% of occasions. In one protocol-hospital

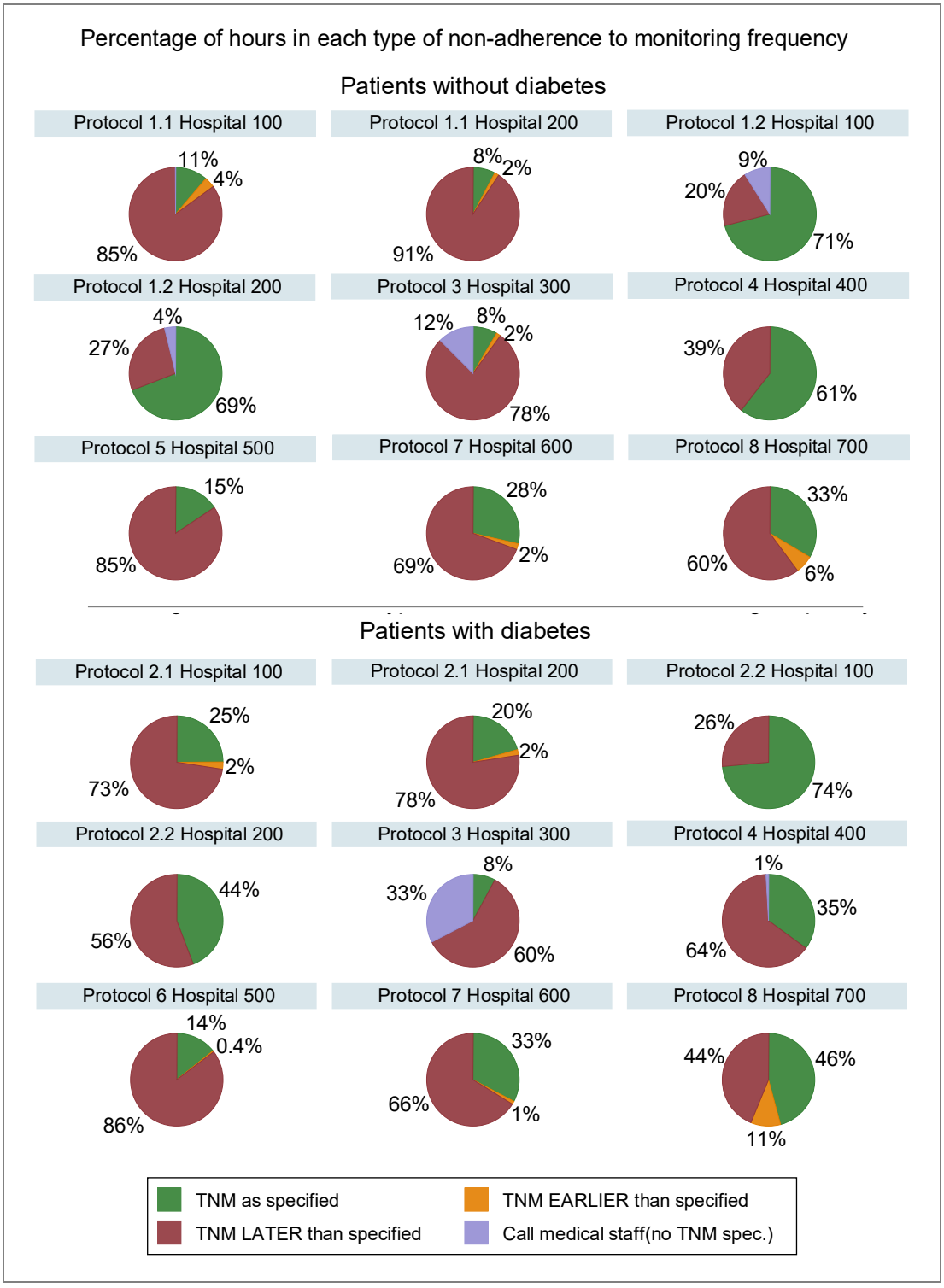


Figure 6.22 – Percentage of hours in each type of non-adherence to monitoring frequency, by protocol-hospital and diabetic status

(P-3_H-300), 33% of measurement timings could not be assessed for adherence as the protocol did not specify a TNM (Figure 6.22).

In all protocol-hospitals except P-3_H-300, all patients had at least one late BG measurement during hours of hyperglycaemia>10. During hyperglycaemia>10, deviations over the specified TNM were similar to those among patients without diabetes, with medians of the patient-mean, per protocol-hospital, ranging from 1.2 to 2.0 hours (Table 6.20). Also, the same two hospitals as for patients without diabetes (P-2.1_H-100 and P-8_H-700) had some patients (25% and 83%, respectively) with at least one measurement taken earlier than specified, during hyperglycaemia>10, with patient-means that were always of 1 hour (Table 6.20).

6.3.4.3 Adherence to instructions of the same protocols implemented in different ICU

P-1.1 and P-1.2 for patients without diabetes, and P-2.1 and P-2.2 for patients with diabetes, were all implemented in H-100 and H-200 in two different periods. This allowed a comparison to be made between the adherence of the two ICUs to the same protocols.

Patients without diabetes

Among patients without diabetes treated with P-1.2, patients were given a higher insulin dosage than the specified significantly more often in H-200 than in H-100 ($p=0.002$); and they were monitored later than specified significantly more often in H-200 than in H-100 ($p=0.021$). On the other hand, there was no significant difference in the adherence of the two ICUs when P-1.1 was implemented (Figure 6.21 and Figure 6.22).

Patients with diabetes

Among patients with diabetes treated with P-2.1, patients were administered a lower insulin dosage than specified significantly more often in H-200 than in H-100 ($p<0.001$); while they were given a higher insulin dosage than specified significantly more often in H-100 ($p<0.001$) (Figure 6.21). However, there was only one patient receiving P-2.1_H-200, and therefore these results may not be representative of that protocol-hospital. The adherence to monitoring instructions of P-2.1 did not differ significantly between H-100 and H-200 (Figure 6.22).

When P-2.2 was implemented, patients were administered a lower insulin dosage than specified significantly more often in H-100 ($p<0.001$); while they were given a higher insulin dosage than the specified significantly more often in H-200 ($p<0.001$) (Figure 6.21). Also, when P-2.2 was implemented, late BG monitoring occurred significantly more often in H-200 than in H-100 ($p<0.001$) (Figure 6.22).

Table 6.20 – Deviations from protocol instructions on insulin titrations and on monitoring frequency during hyperglycaemia>10, by protocol-hospital

	Median(IQR) of the mean deviations from IIR per patient				Median(IQR) of the mean deviations from TNM per patient			
	U/h ABOVE that specified		U/h BELOW that specified		Hours ABOVE that specified		Hours BELOW that specified	
Patients without diabetes	**% patients[a]**	**median (IQR)**	**% patients[a]**	**median (IQR)**	**% patients[a]**	**median (IQR)**	**% patients[a]**	**median (IQR)**
P-1.1_H-100	21%	4.0 (2.0–4.0)	0%		93%	1.8 (1.1–2.0)	21%	1.0 (1.0–1.0)
P-1.1_H-200	0%		0%		100%	2.0 (2.0–2.0)	0%	
P-1.2_ H-100	43%	1.0 (1.0–1.2)	57%	1.5 (1.3–1.8)	100%	1.6 (1.0–2.3)	0%	
P-1.2_H-200	50%	1.4 (.3–2.4)	33%	1.3 (1.3–1.3)	83%	1.4 (1.0–1.5)	0%	
P-3_H-300	25%	2.0 (1.0–3.0)	43%	2.0 (1.9–2.2)	100%	2.0 (1.8–2.4)	0%	
P-4_H-400	38%	1.0 (1.0–1.3)	100%	3.6 (3.1–3.9)	88%	1.7 (1.2–2.9)	0%	
P-5_H-500	50%	1.7 (1.2–4.5)	88%	2.0 (1.6–2.2)	100%	2.4 (1.6–5.5)	0%	
P-7_H-600	21%	2.7 (2.0–2.7)	100%	2.4 (2.0–3.1)	100%	1.3 (1.0–1.7)	0%	
P-8_H-700	40%	1.0 (0.5–1.5)	100%	1.1 (1.0–1.4)	100%	1.5 (1.5–2.5)	60%	1.0 (1.0–1.0)
Patients with diabetes	**% patients[a]**	**median (IQR)**	**% patients[a]**	**median (IQR)**	**% patients[a]**	**median (IQR)**	**% patients[a]**	**median (IQR)**
P-2.1_H-100	75%	0.7(0.7–0.8)	100%	0.5(0.5–0.5)	100%	1.9 (1.9–2.1)	25%	1.0[b]
P-2.1_H-200	100%	8.3[b]	100%	0.5[b]	100%	1.5[b]	0%	
P-2.2_ H-100	100%	2.1 (1.3–3.7)	100%	1.5 (1.2–1.8)	100%	1.3 (1.2–1.6)	0%	
P-2.2_H-200	100%	2.2(1.3–2.6)	100%	2.0 (1.7–2.5)	100%	1.6 (1.3–2.1)	0%	
P-3_H-300	60%	1.7 (1.1–4.6)	60%	1.5 (1.0–1.9)	80%	2.0 (1.5–2.4)	0%	
P-4_H-400	71%	2.2 (2.0–2.8)	100%	3.3 (2.5–4.6)	100%	2.2 (2.0–2.5)	0%	
P-6_H-500	88%	3.8 (2.8–4.7)	100%	1.8 (1.6–2.2)	100%	2.0 (1.6–2.8)	0%	
P-7_H-600	71%	3.1 (2.1–4.9)	100%	2.4 (2.2–3.7)	100%	1.2 (1.1–1.5)	0%	
P-8_H-700	83%	1.1 (1.0–1.3)	100%	1.2 (1.2–1.3)	100%	1.8 (1.3–2.5)	83%	1.0 (1.0–1.0)

IIR: insulin infusion rate; TNM: time to next measurement

[a] Percentage of patients with at least one event of non-adherence

[b] Only one patient with this non-adherence, hence only the median is reported, and the IQR is not applicable

6.4 Results: outcomes of glycaemic control

In this section results on the primary and secondary outcomes measures are presented, including the results of the analyses of association between the outcome measures and the exposures of interest. Relevant metrics of glycaemic levels are also included.

6.4.1 Glycaemic levels

6.4.1.1 Overall recorded glycaemic levels

As stated previously (see section 6.3.2.2), the overall BG levels of patients without and patients with unknown history of diabetes had very similar summary statistics and distributions (Table 6.21 and Figure 6.23), so they were placed in the same group of "no/unknown diabetes" for the purpose of the analyses. BG data had a log-normal distribution with a positive skew and positive kurtosis (Figure 6.24). Statistics were calculated both in the original and the log-transformed spaces (Table 6.21).

As per the inclusion criteria, all patients had at least one BG measurement above 10mmol/L during the first 24 hours of admission. On average, both the mean and the median of the overall untransformed BG, as well as the geometric mean (calculated using the anti-log of the mean of log-transformed data), were 2.1-2.4mmol/L higher among patients with diabetes than amongst patients without or with unknown history of diabetes ($p<0.001$) (Table 6.21).

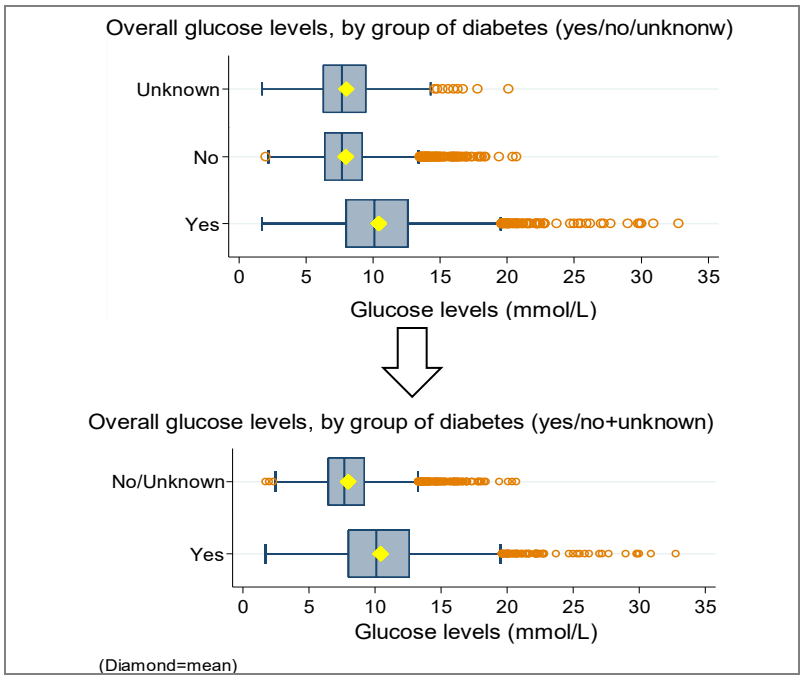


Figure 6.23 – Box-plot of the distribution of overall glucose levels by group of diabetes. Top: separating "no" from "unknown" diagnosis of diabetes. Bottom: grouping no/unknown diagnosis of diabetes together

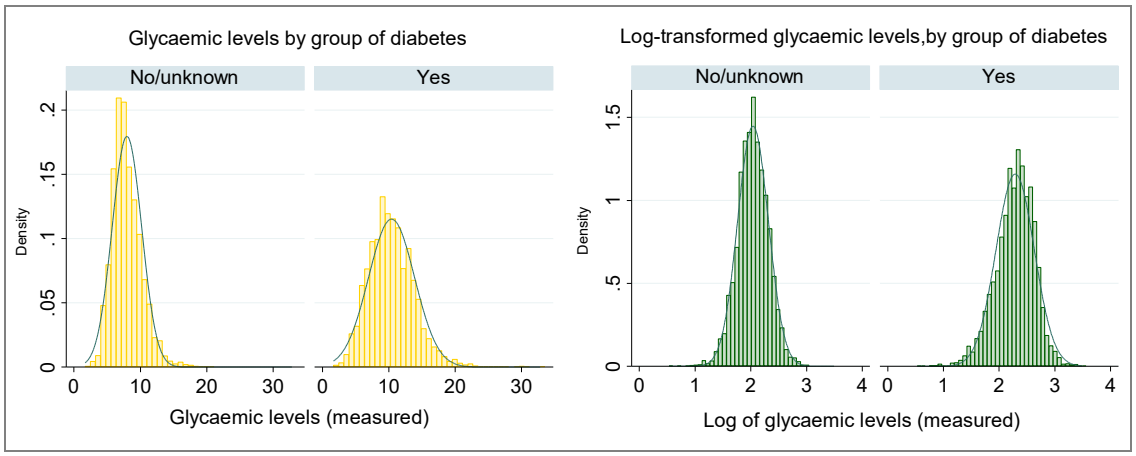


Figure 6.24 – Overall recorded glycaemic levels, in original and log-transformed spaces, by previous diagnosis of diabetes

The geometric mean was lower than the arithmetic mean in all groups. This was expected, as this is what usually happens with geometric means of positively skewed data (Braithwaite et al., 2013). The values of the geometric mean were closer to the untransformed median than to the untransformed mean.

The values of glycaemic levels for the whole sample fluctuated throughout the ICU stay, and tended to be less variable and slightly lower towards the end of the stay (Figure 6.25). BG levels of patients with diabetes showed larger fluctuations than those of patients without known diabetes, especially during the first 24 hours of admission.

6.4.1.2 Glycaemic levels per patient

Patients with diabetes had higher medians of all metrics of location and dispersion of BG levels than patients without diabetes (all with $p<0.001$), except for the minimum BG per patient (Figure 6.26 and Table 6.22). These show that patients with diabetes not only had higher glycaemic levels, on average, but also higher variability, as shown by the higher median values of the patient SD and patient CV (Table 6.22), and illustrated in Figure 6.26.

In addition, episodes of hyperglycaemia>10 were of higher severity among patients with diabetes, as shown by a glycaemic exceedance above 10mmol/L that was, on average, more than twice as high as in patients without diabetes (Table 6.22). Nonetheless, while the maximum BG among patients with diabetes was, on average, more than 5mmol/L higher than among patients without diabetes, their minimum BG was actually lower, on average, although the difference in the latter was not statistically significant (Table 6.22). This also shows the wider fluctuations in glycaemic levels among patients with diabetes, and indicates that the BG during hypoglycaemic events among these patients could be as low, or even lower, than among patients without diabetes.

Table 6.21 – Summary statistics of overall recorded glycaemic levels

		Diabetes previously diagnosed		
	All	**No**	**Unknown**	**Yes**
Patients, no. (%)	146	86 (58.9%)	6 (4.1%)	54 (37.0%)
BG measurements, no. (%)	10253	5010 (48.9%)	327 (3.2%)	4916 (47.9%)
Untransformed blood glucose (BG) data (mmol/L)				
Mean BG (SD)***	9.1 (3.1)	8.0 (2.2)	8.0 (2.7)	10.4 (3.5)
Median BG (IQR)***	8.6 (6.9–10.9)	7.7 (6.5–9.3)	7.7 (6.3–9.5)	10.1 (8.0–12.6)
Reverse-transformed from logarithmically-transformed BG data (mmol/L)				
Geometric mean BG ÷/× overall MSD***	8.7 (÷/×1.4)	7.7 (÷/×1.3)	7.6 (÷/×1.4)	9.8 (÷/×1.4)

Differences between patients with diabetes and each of the other two groups without and with unknown diabetes diagnosis:

*p<0.050; **p<0.010; ***p<0.001

No significant differences between patients without vs. patients with unknown diagnosis of diabetes were found in any of the metrics of this table

MSD: Multiplicative Standard Deviation

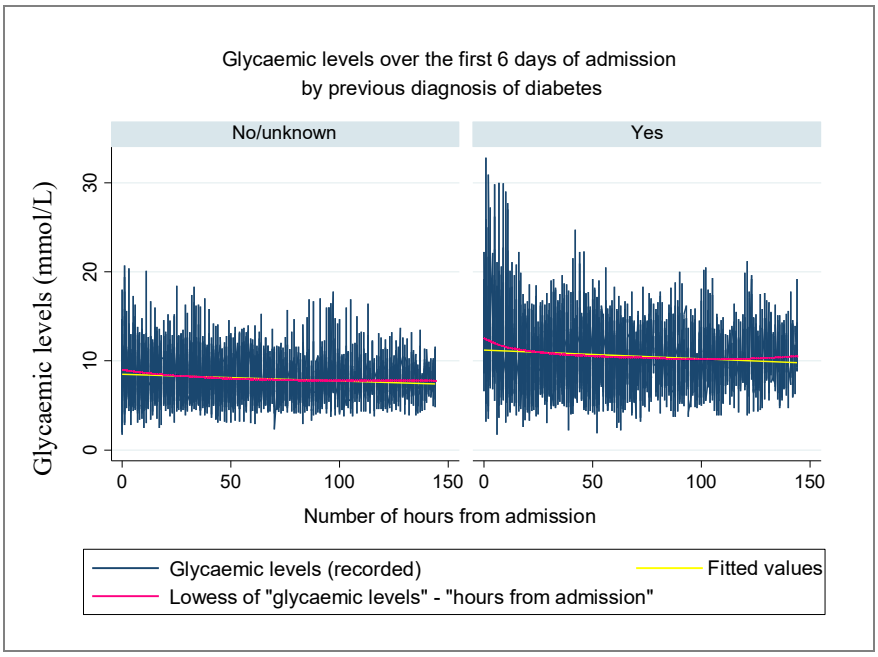


Figure 6.25 - Recorded glycaemic levels of all patients, over time, during the first six days of admission, by previous diagnosis of diabetes

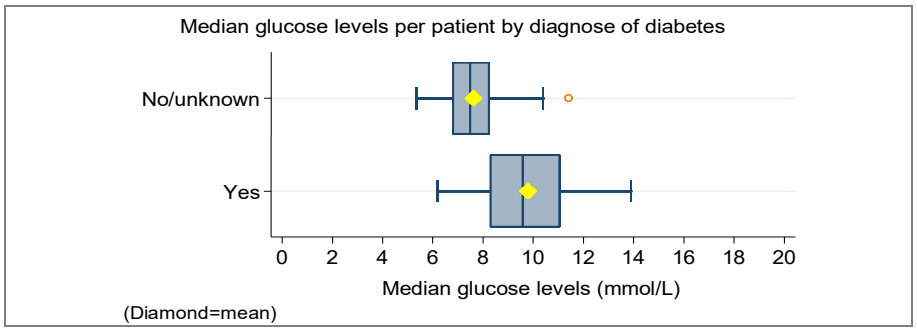


Figure 6.26 – Box-plot of the median glycaemic levels per patient, by diagnosis of diabetes

Table 6.22 – Summary statistics on recorded glycaemic levels (mmol/L) for each pa tient: Metrics from untransformed BG data

		Diabetes previously diagnosed	
	All	**No/Unknown**	**Yes**
Median (IQR) of time-weighted patient mean* **	8.2 (7.3-9.4)	7.7 (7.1-8.5)	9.8 (9.1-11.5)
Median (IQR) of patient mean* **	8.3 (7.4-9.6)	7.8 (7.2-8.7)	9.8 (8.6-11.2)
Median (IQR) of patient SD* **	2.1 (1.7-2.6)	1.9 (1.5-2.2)	2.8 (2.3-3.5)
Median (IQR) of patient CV* **	25% (20-30%)	24% (19-28%)	28% (21-36%)
Median (IQR) of patient mean BG exceedance above 10mmol/L* **	1.4 (0.8-2.3)	0.9 (0.6-1.4)	2.3 (1.7-3.1)
Median (IQR) of maximum BG per patient* **	13.6 (11.5-17.8)	12.5 (11.2-14.2)	17.9 (15.4-20.5)
Median (IQR) of minimum BG per patient	4.8 (4.1-5.4)	4.8 (4.1-5.4)	4.6 (3.5-6.4)
Differences by diabetic status: *p<0.050; **p<0.010; ***p<0.001 BG: Blood Glucose; CV: Coefficient of Variation			

When looking at one patient at a time, glycaemic levels over time also showed fluctuations throughout the ICU stay, and for some of the patients the BG levels had a trend that tended to be lower towards the end of the ICU stay. The time-series plot of recorded glycaemic levels for the first six days of admission of 14 randomly chosen patients (two per ICU) are included in Figure 6.27 for illustration. Each of the peaks in the plots represents an actual BG measurement point, and the lines connecting them span the time in which there was no actual measurement. Shorter horizontal distances between each two consecutive peaks (measurements) represent more frequent monitoring (less imputed values), and shorter vertical distances between peaks represent lower glycaemic variability between measurements. The plots of some of the patients, such as 1002, 20031 and 60030, show that, despite achieving the target range for a great part of their first six days of admission, patients could go back out of range, entering the glycaemic status of hyperglycaemia>10, in the last day or two of these first six days (Figure 6.27).

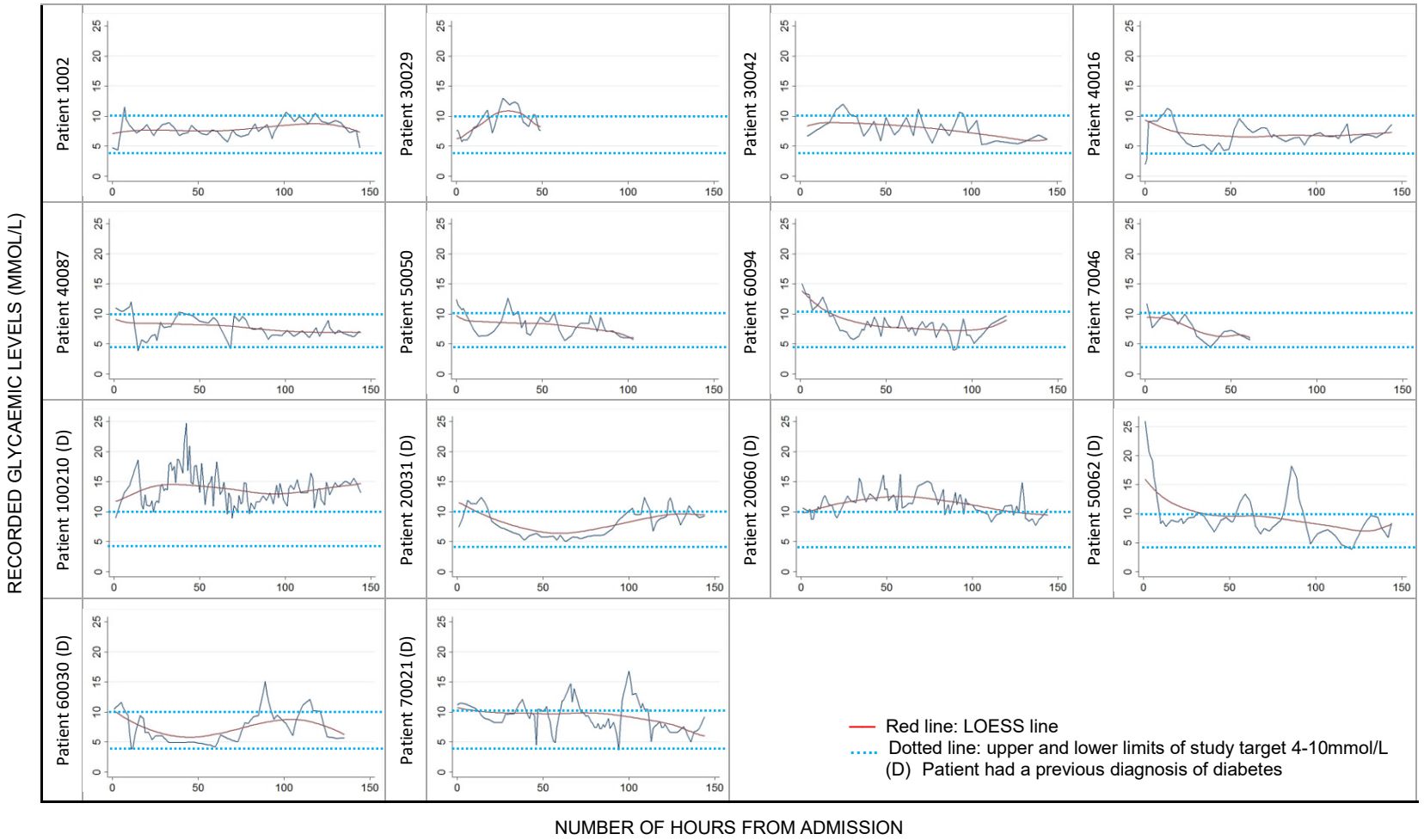


Figure 6.27 - Time-series plot of recorded glycaemic levels for the first six days of admission of 14 randomly chosen patients (two per ICU)

Glycaemic levels per patient by protocol-hospital

Among patients with diabetes, on average, protocol-hospitals differed significantly in the patient-median glycaemic levels (p=0.002) as well as in the patient-CV glycaemic levels (p=0.002) (Figure 6.28). Among these patients with diabetes, the median of the patient-median BG ranged from 8.6mmol/L (P-8_H-700) to 12.7mmol/L (P-2.2_H-100); while among patients without diabetes this median ranged from 7.1mmol/L (P-3_H-300) to 8.6mmol/L (P-1.2_H-100).

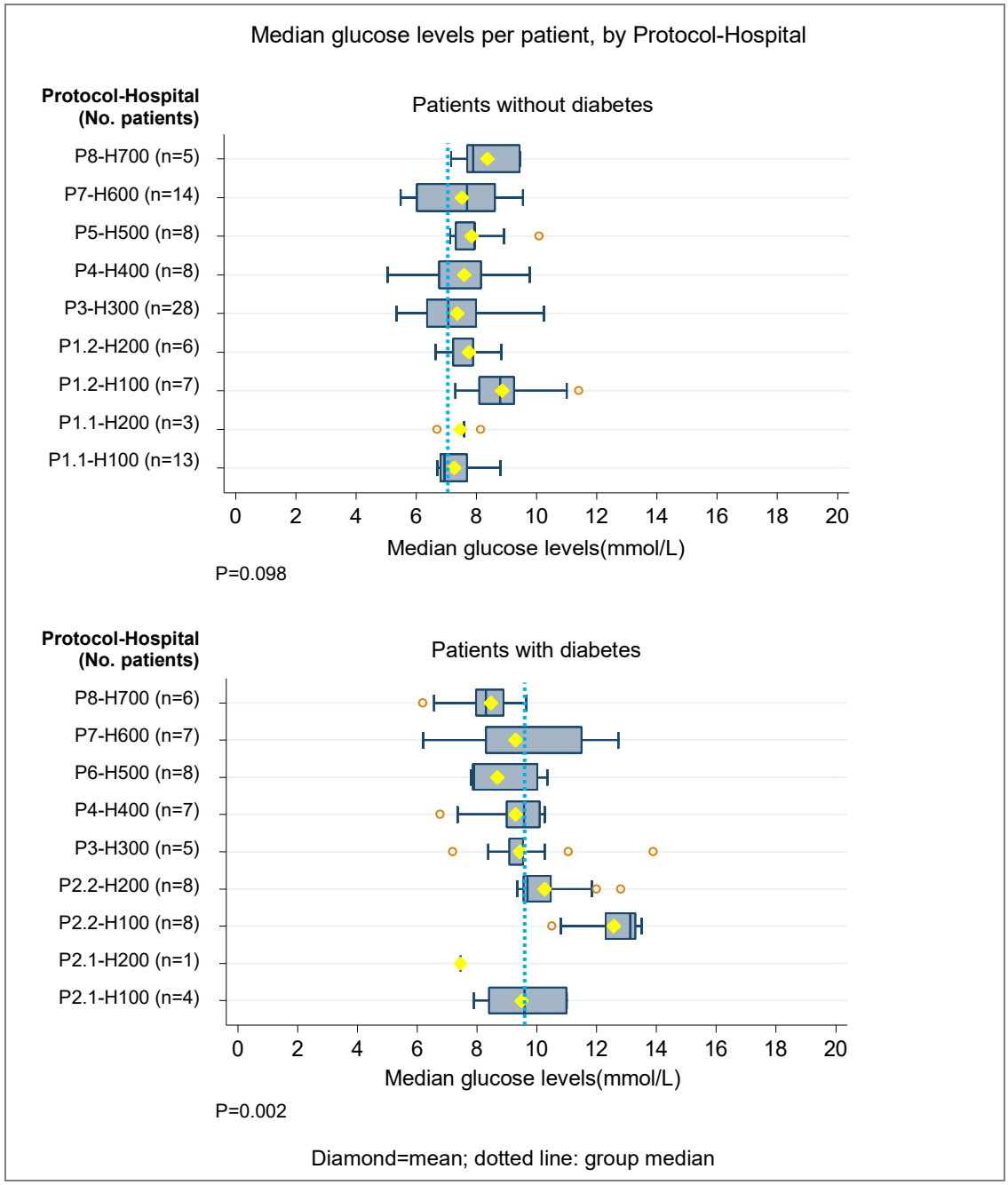


Figure 6.28 – Box-plot of the median glycaemic levels per patient, by protocol-hospital
P: Protocol; H: Hospital

One patient with diabetes from P-3_H-300 had very high glycaemic levels during all the ICU stay, resulting in a median (IQR) of 13.9 (9.6-26)mmol/L (Figure 6.28). She was a 69-year-old female with diabetes, admitted primarily for left ventricular failure, and with a secondary diagnosis of cardiogenic shock. Her treatment was both withheld and withdrawn, and she died in the ICU after 2.1 days.

6.4.2 Effectiveness: percentage of time in range

6.4.2.1 Overall percentage of time in range

Overall, 74% of the patient-hours (with measured and interpolated glycaemic values) were within the study range 4-10mmol/L, and 25.3% and 0.5% were above and below that range, respectively. The variability between protocol-hospitals, in the percentage of patient-hours with glycaemic values within 4-10mmol/L, was larger among patients with diabetes. Depending on the protocol-hospital, this ranged from 77.9% to 93.1% of patient-hours among patients without diabetes, and from 10% to 92.5% of patient-hours among patients with diabetes (Figure 6.29). Among patients with diabetes, the percentage of patient-hours with glycaemic values within 4-10mmol/L were lower in all protocol-hospitals that adopted an upper BG target limit of 10mmol/L (UL10) (P2.2_H100, P2.2_H200, P4_H400, P7_H600) than in protocol-hospitals that adopted an upper BG target limit of 8.3mmol/L (UL83) (P2.1_H100, P2.1_H200, P3_H300, P6_H500, P8_H700) (Figure 6.29).

Among patients without diabetes, when the ICU's own protocol definitions to classify the glycaemic status were used, there was higher inter protocol-hospital variability in the percentage of patient-hours with glycaemic values within each protocols' target, than when the same study glycaemic target range (4-10mmol/L) was used (Figure 6.29). This confirms that effectiveness metrics based on the percentage of patient-hours spent within the protocols' glycaemic targets would have not been appropriate to compare the effectiveness between protocols.

6.4.2.2 Percentage of time in range per patient

Of the 146 patients, the total time spent in hyperglycaemia>10 was four or less hours in 25 (17%) patients, and it was one hour in eight (5%) patients. Only one of these 25 patients had a previous diagnosis of diabetes.

TIR per individual patient ranged from 1.0% to 99.7%, but the median TIR was higher than 80% (Table 6.23). Nonetheless, the median of the TIR per patient was significantly higher among patients without known diabetes (91%) than among patients with diabetes (56%) ($p<0.001$) (Table 6.23 and Figure 6.30). Also, the TIR among patients with diabetes had

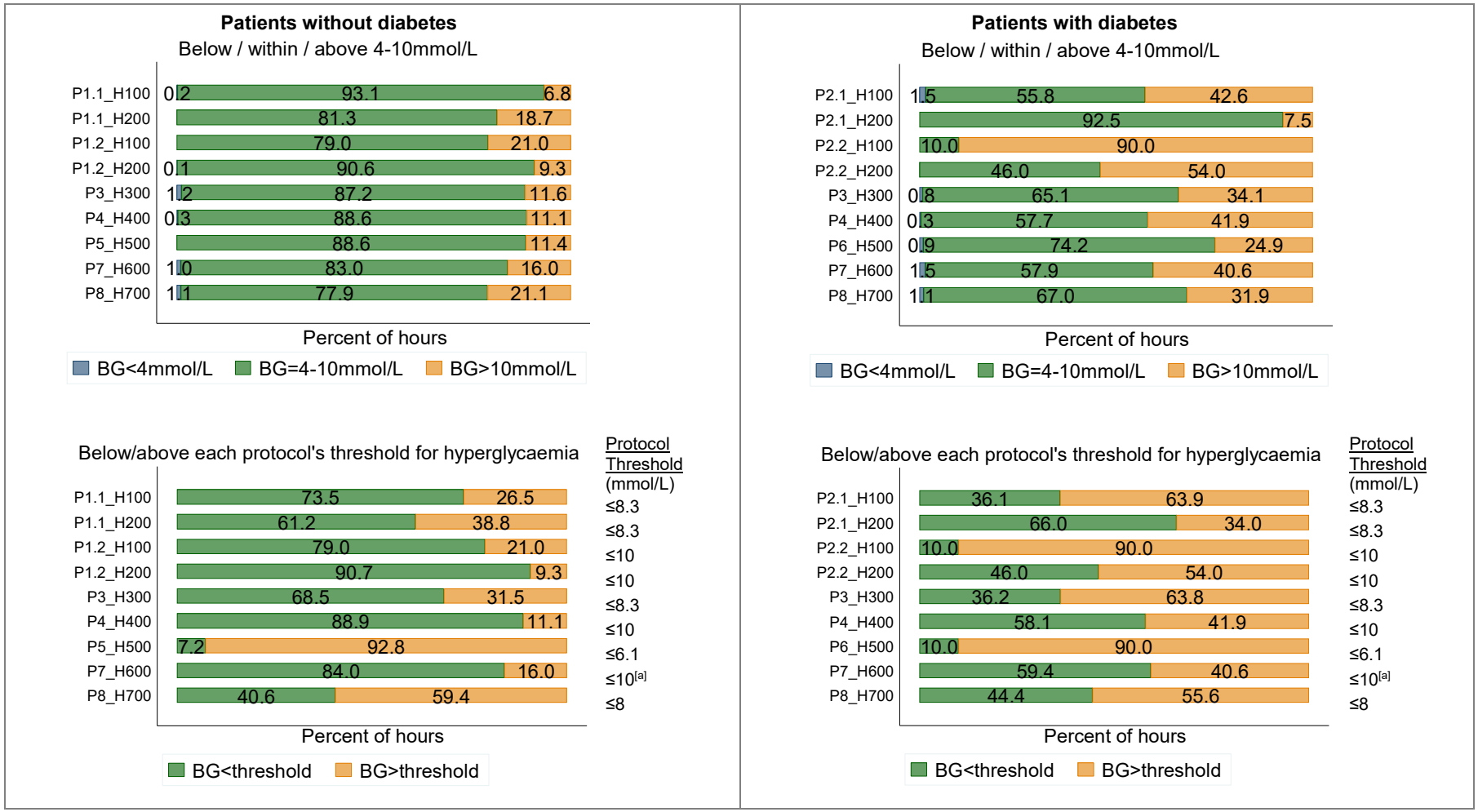


Figure 6.29 – Overall percentage of hours with recorded blood glucose (BG) levels in each glycaemic status, by hospital and diabetic status. Top: based on GlyCon BG target range 4-10mmol/L; Bottom: based on each protocol's BG target range.
[a] Informally accepted BG threshold levels, not stated in protocol.

higher variability, with an IQR distance (i.e., the distance between the first and the third quartiles) of 38%, as compared with the IQR distance of 15% among patients without diabetes (Table 6.23).

Among patients without diabetes, the median TIR decreased slightly by about one 1% when all the imputed BG values corresponding to monitoring frequencies of TNM>8h (i.e., the hours when the patient spent more than eight consecutive hours without being monitored) were excluded (p=0.001) (Table 6.23). The TIR of these patients without diabetes was, on average, significantly lower during the first two days (TIR-2d) (p<0.001), and the first six days of admission (TIR-6d) (p<0.001), than during the whole length of stay. Also, TIR-2d was significantly lower than TIR-6d (p<0.001) (Table 6.23).

Among patients with diabetes, the median TIR did not change significantly when the imputed BG values corresponding to TNM>8h were excluded. Within this group, the total TIR did not differ significantly from TIR-6d or TIR-2d, but TIR-2d was significantly lower than TIR-6d (p=0.019) (Table 6.23).

6.4.2.3 TIR and the protocol-hospital

TIR by protocol-hospital was less dispersed among patients without diabetes than in patients with diabetes (Figure 6.30), although there were no statistically significant differences between protocol-hospitals. Nonetheless, there were some outlying patients without diabetes, who had markedly lower TIRs than the majority of patients in their protocol-hospital, especially in P-3_H-300 (Figure 6.30).

Table 6.23 – Primary outcome measure of effectiveness

		Previous diagnosis of diabetes	
	All	**No/Unknown**	**Yes**
n (%)	146	92 (63%)	54 (37%)
Percentage time within 4-10mmol/L per patient (TIR), during the whole stay***	82% (59–93%)	91% (81–96%)	56% (34–72%)
TIR–excluding–TNM>8 (excluding hours with no glycaemic measurement for >8h)***	81% (60–93%)	90% (80–95%)	57% (34–71%)
TIR–2 (TIR during 2 first days)***	75% (55–90%)	85% (70–95%)	53% (26–72%)
TIR–6 (TIR during ≤6 first days)***	80% (62–93%)	89% (80–95%)	59% (31–75%)

Differences by diabetic status:
**p<0.050; **p<0.010; ***p<0.001*
All metrics are expressed in median(IQR) unless otherwise specified
TNM: time to next measurement

The values of TIR among patients with diabetes were very dispersed in each protocol-hospital (Figure 6.30). P-2.2_H-100 had a significantly lower TIR than all other protocol-hospitals (all with p<0.001) among patients with diabetes (Figure 6.30). The same protocol (P-2.2), which was implemented in two hospitals, was associated with significantly lower TIR per patient when it was implemented in H-100 than when it was implemented in H-200 (p=0.004). Most patients without diabetes had a TIR higher than 75%, while for most patients with diabetes TIR was lower than 75%. A TIR of more than 75% at a protocol's glycaemic target was considered as constituting "good" GC by most of the professionals (83-85% professionals) who responded to the GlyCon survey; whereas more than half of the surveyed professionals (55% professionals) rated a TIR of less than 75% as "poor" GC.

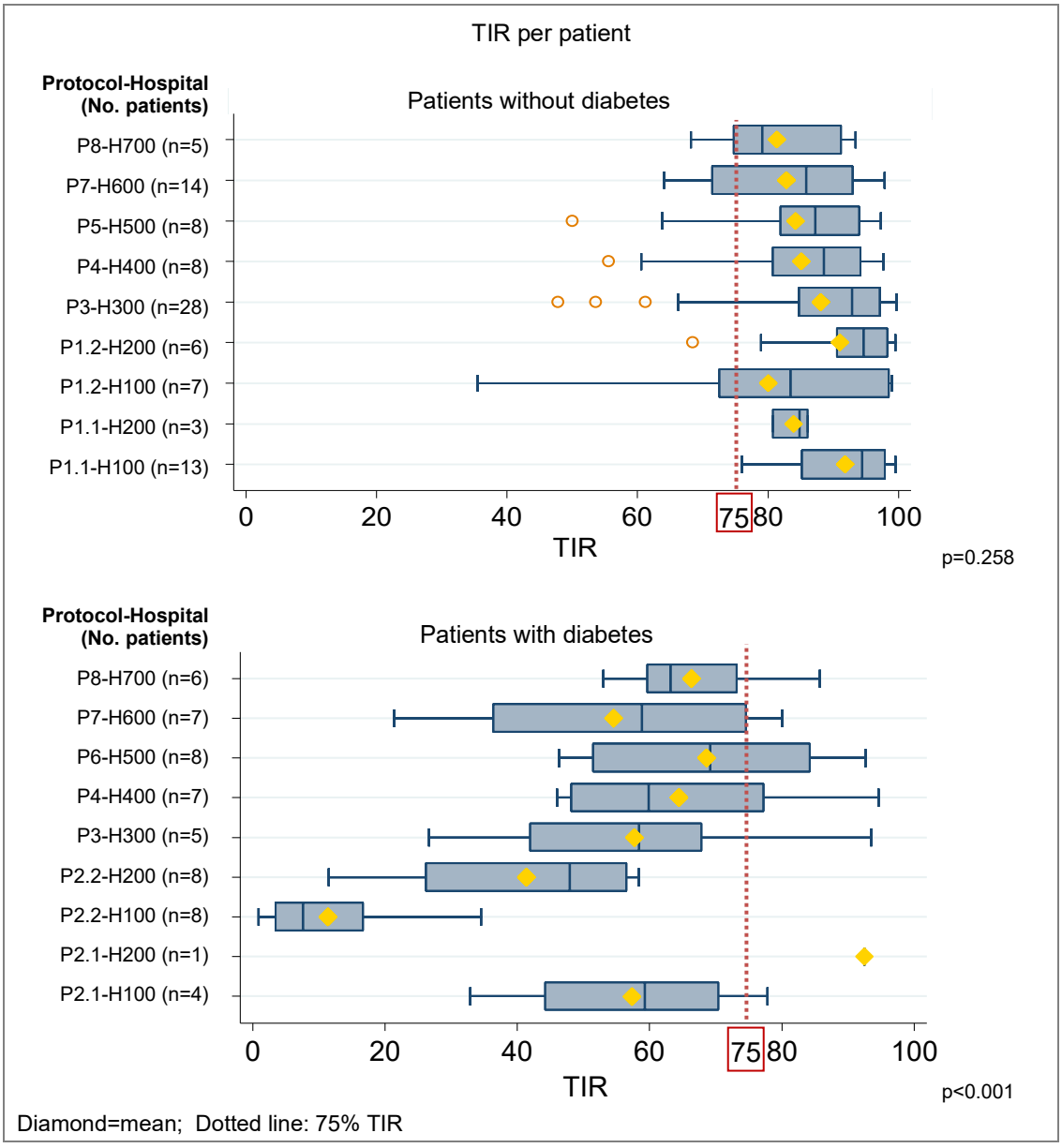


Figure 6.30 – Box-plot of the TIR per patient, by protocol-hospital and diagnosis of diabetes. 75% TIR was the threshold percentage time defining "good" glycaemic control by most professionals of the GlyCon survey.
TIR: percentage of time spent with BG=4-10mmol/L per patient. P: Protocol; H: Hospital

6.4.2.4 TIR and the target range of the individual protocols

The classification of protocol-hospitals depending on the upper limit of their glycaemic target range is explained in Section 6.2.6.4 and listed in Table 6.6. Figure 6.31 and Figure 6.32 show how protocol-hospitals with a UL83 target and a UL10 target performed in terms of TIR.

Among patients with diabetes, TIR was significantly higher among those admitted to a UL83 protocol-hospital as compared to those admitted to a UL10 protocol-hospital (p=0.002) (Figure 6.31). However, when P-2.2_H-100 was excluded from the analyses, the difference remained but it was not statistically significant (p=0.062). The median TIR of P-2.2_H-100 and P-2.2_H-200 were below the group median for patients with diabetes, while the median TIR for the remaining protocol-hospitals was above the group median (Figure 6.32).

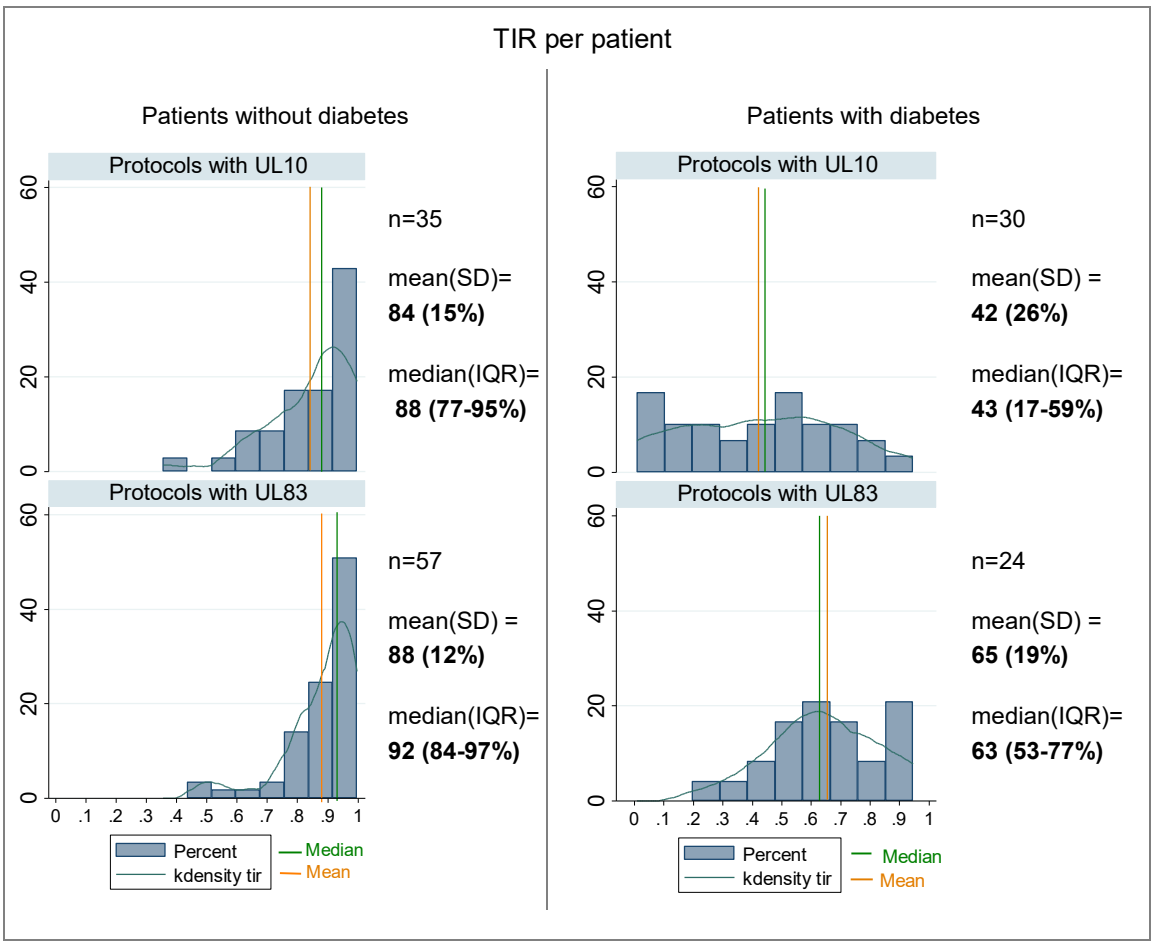


Figure 6.31 – TIR (%) by group of upper limit of the protocol glycaemic target and diabetic status.
UL10: upper limit of glycaemic target=10mmol/L; UL83: upper limit of glycaemic target≤8.3mmol/L

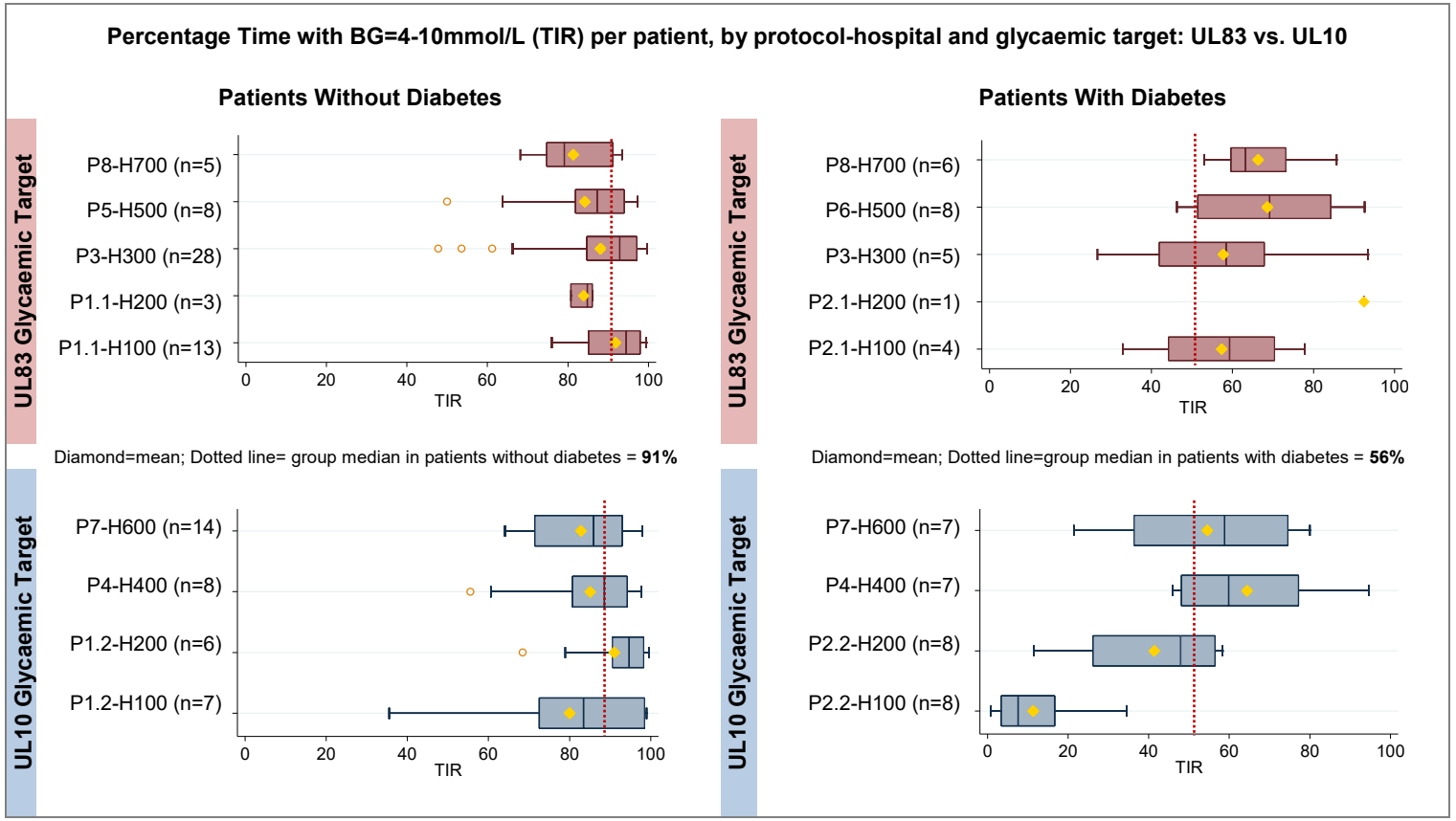


Figure 6.32 – Box-plot of the TIR by protocol-hospital, upper limit of glycaemic target and diabetic status.
P: Protocol; H: Hospital.

6.4.3 Exposure variables

The exposure variables of interest on the monitoring frequency and treatment with insulin of each patient, to be used in the analyses of association with the outcome measures, were generated based on the results obtained from the assessment of the implemented methods for GC (see Table 6.16), as described in Section 6.2.6.4. In this section, a description of these exposure variables is provided, before proceeding to the subsequent sections describing the results on the analyses of association. These variables were generated for each group of diabetic status, and at each period of time considered (Table 6.24), and included:

- Four dummy variables (binary), one for each part of the admission considered, defining whether a patient's percentage of time receiving insulin during hyperglycaemia>10 was above (=1) or below (=0) the threshold values given in Table 6.24.
- Four dummy variables (binary), one for each part of the admission considered, defining whether a patient's median TNM during hyperglycaemia>10 was below or equal to (=1) or above (=0) the threshold values given in Table 6.24.

The threshold values were chosen such that they divided the sample of patients into two equally sized (or as close to equally sized as possible) groups.

Table 6.24 – Threshold values used to define the main exposure variables relating to the monitoring frequency and percentage of time receiving insulin during hyperglycaemia

PARAMETER	THRESHOLD VALUES	
Patient's percentage of time receiving insulin during hyperglycaemia>10	**Patients without diabetes**	**Patients with diabetes**
	During full stay: 20%time	**During full stay**: 75%time
	During first 6 days: 20%time	**During first 6 days**: 75%time
	During first 2 days: 10%time	**During first 2 days**: 65%time
	During TTR period[a]: 0%time	**During TTR period**: 50%time
Patient's median time to next measurement (TNM) during hyperglycaemia>10	**Patients with and without diabetes**	
	During the full stay / first 6 days / first 2 days: 2h	
	During TTR period: 2h	

[a] TTR period: time from first BG>10mmol/L to next (subsequent) BG=4-10mmol/L for two consecutive hours

6.4.4 Multivariate analyses of effectiveness

Results from GEE analyses on the factors that affected the effectiveness of the methods for GC, by increasing or decreasing the odds of being within the study glycaemic range 4-10mmol/L (odds of IR) at any time are presented in this section. Higher odds of IR represent more effective GC.

The results are presented in tabular format in terms of the unadjusted (one variable at a time) and adjusted (all relevant variables included in the final model) odds ratios (OR). The OR is the ratio of the odds of IR when the exposure is present to the odds of IR when the exposure is not present. In addition to the tabulated results, significant effects are highlighted in the text.

Since patients belonged to different clusters (protocol-hospitals), regardless of its significance, the variable protocol-hospital was always kept in the final model. For cases when one protocol was implemented in two different hospitals (H-100 and H-200), and the protocol had different and significant effects on the outcome in each of these hospitals, the effects of non-adherence to protocol instructions are reported. These results are also presented for the analyses carried out separately for each of the three periods of interest.

6.4.4.1 Odds of being in range during the whole ICU stay

Patients without diabetes

After controlling for relevant covariates, patients without diabetes who received insulin for more than 20% of the time while they were at hyperglycaemia>10 had, on average, approximately twice the odds of IR than patients who spent less time receiving insulin (p=0.005) (Table 6.25). Having a median monitoring frequency of two hours or less during hyperglycaemia did not show a significant effect on outcome in the multivariate analyses. Neither did the protocol-hospital for patients without diabetes. On average, for every one unit increase in the ICNARC severity score, there was about 2% (1-4%) decrease in the odds of IR at any time. With every one more day of stay in the ICU, patients' odds of IR increased, on average, by about 7% (3-11%) (Table 6.25).

Of the time-dependent covariates, in patients without diabetes, the adrenaline hourly dosage (mcg/kg/h) decreased the patients' expected odds of IR in the following hour by about 4% (1-7%), while the dobutamine dosage (mcg/kg/h), slightly increased the patients' expected odds of IR in the following hour by about 0.3% (0.02-0.48%)(Table 6.25). All these significant associations were found even after controlling for the glycaemic exceedance, which had a strong and significant negative effect on the odds of IR in the following hour (Table 6.25).

Table 6.25 – Effect of time-dependent and time-constant variables on the odds of IR at any time, during the whole ICU stay, in patients without diabetes

Exposure variables	OR (95%CI)	Adjusted OR (95%CI)
Spent >20% time with insulin during hyperglycaemia>10	2.09 (1.26–3.47) **	1.98 (1.14–3.43)*
≤2hourly median TNM during hyperglycaemia>10	1.06 (0.63–1.78)	–
Protocol-hospital (Reference category: P-1.2_H-100)		
P-1.1_H-100	3.23 (1.50–6.99)**	1.58 (0.91–2.74)
P-1.1_H-200	1.12 (0.59–2.13)	0.78 (0.41–1.47)
P-1.2_H-200	2.45 (0.66–9.17)	1.63 (0.69–3.87)
P-3_H-300	1.69 (0.69–4.17)	1.02 (0.57–1.83)
P-4_H-400	1.91 (0.66–5.52)	0.99 (0.46–2.11)
P-5_H-500	1.94 (0.78–4.80)	1.05 (0.54–2.04)
P-7_H-600	1.17 (0.54–2.56)	1.03 (0.55–1.92)
P-8_H-700	0.80 (0.38–1.71)	0.98 (0.58–1.66)
ICNARC physiol. score on admission	0.97 (0.95–0.99) *	0.98 (0.96–0.99)*
Highest BG on admission (in mmol/L)	0.91 (0.84–0.98) *	–
Day (number of full 24h from admission time)	1.10 (1.04–1.17) ***	1.07 (1.03–1.11)***
Time-dependent exposures with 1 hour lag:		
Insulin dosage (in U/h)	1.01 (0.92–1.12)	–
Adrenaline dosage (in mcg/kg/h)[a]	0.02 (0.00–0.32)	0.96 (0.93–0.99)*
Dobutamine dosage (in mcg/kg/h)[b]	0.999 (1.000–1.000)	1.003(1.0002–1.0048)*
Glycaemic exceedance	0.01 (0.00–0.01)***	0.01 (0.0004–0.016)***

**p<0.050; **p<0.010; ***p<0.001*

Odds of IR: Odds of being within range 4-10mmol/L at any time

BG: Blood Glucose (mmol/L); TNM: Time to Next Measurement

[a] 13 of 92 patients received adrenaline at some point, with durations ranging from 2 to 79h

[b] 9 of 92 patients received dobutamine at some point, with durations ranging from 10 to 65h

The GEE analyses were repeated including each of the variables on the EN and TPN energy administered per hour in the previous model, one at a time. This reduced the number of observations included in the models as the EN and TPN energy were only available for part of the sample. Nevertheless, the models showed that both the EN and TPN npkcal/h given had a significant detrimental effect on the expected odds of IR in the following hour. Specifically, for every one unit increase in the npkcal/h administered via EN, there was a 1% (1-3%) decrease in the odds of IR in the following hour ($p=0.005$); and for every one unit increase in the npkcal/h administered via TPN, there was a 2% (1-3%) decrease in the odds of IR in the following hour ($p<0.001$). This effect of the EN and TPN energy remained even when the 32 hours during which both EN and TPN were given at the same time were excluded from the analyses.

Patients with diabetes

Neither having received insulin for more than 75% of the time during hyperglycaemia>10, nor having a median TNM of at least 2h during hyperglycaemia, had a significant effect on the odds of IR at any time among patients with diabetes (Table 6.26). Compared to P-2.2_ H-100 (reference category in the model), the other protocol-hospitals had an odds of IR 2.5 to 16.3 times higher. P-2.1_H-200 had the highest odds of IR (16.3) followed by P-6_H-500 (8.7). Also, P-2.2 had 2 to 4 times higher odds of IR at any hour, when it was implemented in H-200 than when it was implemented in H-100 ($p<0.001$) (Table 6.26).

Analyses were also performed using each of the other protocol-hospitals as the reference category to compare with. Based on these, P-2.1_ H-200 had the highest expected odds of IR at any time, of all the protocol-hospitals. Also, P-6_H-500 had, on average, higher expected odds of IR at any time than all other protocol-hospitals (all with $p<0.001$) except for P-2.1_H-200.

Among the time-dependent covariates, in patients with diabetes, the insulin hourly dosage (U/h) increased patients' expected odds of IR in the following hour by about 8% (1-17%), and the hourly hydrocortisone dosage (mg/h) slightly but significantly decreased patients' expected odds of IR in the following hour by about 0.5% (0.2-0.8%) (Table 6.26). The glycaemic exceedance in the previous hour had a strong and significant effect on the outcome in the following hour (Table 6.26).

Table 6.26 – Effect of time-dependent and time-constant variables on the odds of IR at any time, during the whole ICU stay, in patients with diabetes

Exposure variables	OR (95%CI)	Adjusted OR (95%CI)
Spent >75% time receiving insulin during hyperglycaemia>10	0.68 (0.37–1.26)	–
≤2 hourly median TNM during hyperglycaemia>10	0.58 (0.44–0.75)***	–
Protocol-hospital (Reference category: P-2.2_H-100)		
P-2.1_H-100	10.45(3.40–32.13)***	2.45 (1.27–4.73)**
P-2.1_H-200	107.1(43.0–266.4)*** [a]	16.3(10.3–25.64)*** [a]
P-2.2_H-200	6.20 (2.23–17.26)***	2.69 (1.71–4.24)***
P-3_H-300	14.74(5.06–42.91)***	3.71 (2.10–6.57)***
P-4_H-400	11.30(4.14–30.87)***	4.19 (2.17–8.11)***
P-6_H-500	23.04(6.38–83.16)***	8.69 (4.38–17.28)***
P-7_H-600	10.73(3.50–32.90)***	4.50 (2.36–8.59)***
P-8_H-700	15.97(6.12–41.68)***	4.24 (2.58–7.00)***
Age	1.02 (1.00–1.05)*	–
Highest BG on admission (in mmol/L)	0.93(0.87–0.99)*	0.95(0.92–0.97)***
Time-dependent exposures with 1 hour lag:		
Insulin dosage (in U/h)	1.04 (1.01–1.06)**	1.08 (1.01–1.17)*
Adrenaline dosage (in mcg/kg/h)[b]	0.02(0.00–0.33)**	–
Hydrocortisone dosage (in mg/h)[c]	0.997 (0.998–0.999)***	0.995 (0.992–0.998)**
Glycaemic exceedance	0.07 (0.04–0.13)***	0.08 (0.04–0.15)***

**p<0.050; **p<0.010; ***p<0.001*

Odds of IR: Odds of being within range 4-10mmol/L at any time

BG: Blood Glucose (mmol/L); TNM: Time to Next Measurement;

[a] Represents one patient only

[b] 10 of 54 patients received adrenaline at some point, with durations ranging from 4 to 76h

[c] 13 of 54 patients received hydrocortisone at some point, with durations ranging from 1 to 33h

Patients with diabetes receiving protocol-2.2 in hospital-100 and hospital-200

Given the lower performance of H-100 as compared to H-200 when they both implemented P-2.2 in patients with diabetes, demographic and clinical characteristics of the patients admitted to these two hospitals were explored. Significant differences between the hospitals were found in three aspects: patients admitted to H-200 had significantly higher BMI (p=0.021), longer LOS (p=0.006) in the ICU, and higher in-hospital mortality rates (p=0.039) than those admitted to H-100.

After controlling for relevant and significant covariates, giving less insulin than specified in the protocol (P-2.2), showed a negative effect on the outcome by decreasing the expected odds of IR in the following hour, on average, by 53% (4-77%) (Table 6.27). Also, patients admitted to H-100 had lower odds of IR at any time than those admitted to H-200, on average, by 62% (22-81%) (Table 6.27). The detrimental effect of the glycaemic exceedance remained highly significant (Table 6.27).

6.4.4.2 Odds of being in range during the first six days

Patients without diabetes

Among patients without diabetes, all variables that had a statistically significant effect on the outcome, when the whole stay was considered, were also significant when only the first six days were analysed, except for the following covariates: spending more than 20% of the time in hyperglycaemia receiving insulin; ICNARC severity score on admission; and the hourly dobutamine intravenous dosage of the previous hour (Table 6.28).

Table 6.27 – Effect of non-adherence to P-2.2 instructions on the odds of IR at any time, during the whole ICU stay, in patients with diabetes admitted to H-100 and H-200

	OR (95%CI)	Adjusted OR (95%CI)
Hospital (Reference category: H-200)		
H-100	0.16 (0.05–0.46)***	0.38 (0.19–0.78)**
Adherence to insulin dosage in previous hour (Reference category: insulin given as specified)		
Insulin required but dosage given lower than specified	0.69 (0.56–0.86)***	0.47 (0.23–0.96)*
Glycaemic exceedance	0.17 (0.09–0.32)***	0.19 (0.11–0.35)***

**p<0.050; **p<0.010; ***p<0.001*

Odds of IR: Odds of being within range 4-10mmol/L at any time

In the analyses with the sub-section of patients with information on EN and TPN energy, only the hourly non-protein energy given via EN showed a significant effect on the outcome of the first six days, by decreasing the odds of IR by 2% (1-4%) (p=0.035). This effect remained the same when the 32 hours during which both EN and TPN were given at the same time were excluded from the analyses.

Table 6.28 – Effect of time-dependent and time-constant variables on the odds of IR at any time, during the first six days, in patients without diabetes.

	OR (95%CI)	Adjusted OR (95%CI)
Spent >20% time receiving insulin during hyperglycaemia>10	0.42 (0.30–0.62)***	–
≤2hourly median TNM during hyperglycaemia>10	0.62 (0.46–0.84)**	–
Protocol-hospital (Reference category: P-1.2_H-100)		
P-1.1_H-100	2.19 (0.93–5.17)	1.28 (0.68–2.41)
P-1.1_H-200	0.72 (0.29–1.79)	0.77 (0.41–1.47)
P-1.2_H-200	1.61 (0.52–4.99)	1.27 (0.47–3.41)
P-3_H-300	1.48 (0.61–3.62)	1.04 (0.54–2.01)
P-4_H-400	0.92 (0.36–2.38)	0.69 (0.35–1.37)
P-5_H-500	1.18 (0.47–2.99)	1.00 (0.49–2.05)
P-7_H-600	0.76 (0.33–1.80)	0.73 (0.37–1.41)
P-8_H-700	1.03 (0.44–2.39)	0.84 (0.42–1.67)
Highest BG on admission (in mmol/L)	0.89 (0.84–0.97)**	–
Day (Number of full 24h from admission time)	1.27 (1.14–1.43)***	1.16 (1.03–1.30)*
Time-dependent exposures with 1 hour lag:		
Adrenaline dosage (in mcg/kg/h)[a]	0.94 (0.90–0.99)**	0.95 (0.92–0.99)*
Glycaemic exceedance	0.01 (0.01–0.02)***	0.01 (0.01–0.02)***

**p<0.050; **p<0.010; ***p<0.001*

Odds of IR: Odds of being within range 4-10mmol/L at any time

BG: Blood Glucose (mmol/L); TNM: Time to Next Measurement;

[a] 12 of 92 patients received adrenaline at some point during first 6days, with durations of 2-79 h

Patients with diabetes

The highest BG on admission and the insulin dosages did not have a statistically significant effect on the outcome when only the first six days of admission were considered among patients with diabetes (Table 6.29), while they had been found significant when modelling

Table 6.29– Effect of time-dependent and time-constant variables on the odds of IR at any time during the first six days, in patients with diabetes.

	OR (95%CI)	Adjusted OR (95%CI)
Spent >75% time receiving insulin during hyperglycaemia>10	0.48 (0.28–0.85)*	–
≤2hourly median TNM during hyperglycaemia>10	0.43 (0.30–0.61)***	–
Protocol-hospital (Reference category: P-2.2_ H-100)		
P-2.1, H-100	8.39 (2.47–28.45)***	2.77 (1.51–5.10)***
P-2.1, H-200	77.87 (29.75–203.84)*** [a]	19.70 (14.59–26.60)***
P-2.2, H-200	5.40 (1.55–18.82)**	2.87 (1.91–4.32)***
P-3, H-300	9.42 (2.75–32.18)***	3.04 (1.84–5.01)***
P-4, H-400	12.04 (3.94–36.80)***	5.07 (3.18–8.07)***
P-6, H-500	17.68 (6.31–49.56)***	4.93 (2.86–8.50)***
P-7, H-600	7.42 (2.31– 23.80)***	3.36 (1.82–6.22)***
P-8, H-700	10.00 (3.74–26.70)***	4.29 (2.86–6.44)***
Highest BG on admission (in mmol/L)	0.92 (0.85–0.98)*	–
Day (No. full 24h from admission time)	1.14 (1.04–1.25)**	–
Time-dependent exposures with 1 hour lag:		
Adrenaline dosage (in mcg/kg/h)[b]	0.92 (0.87–0.97)**	0.68 (0.62–0.76)***
Hydrocortisone dosage (in mg/h)[c]	0.998 (0.997–0.999)***	0.994 (0.989–0.999)*
Glycaemic exceedance	0.06 (0.03–0.12)***	0.07 (0.03–0.14)***

**p<0.050; **p<0.010; ***p<0.001*

Odds of IR: Odds of being within range 4-10mmol/L at any time

BG: Blood Glucose (mmol/L); TNM: Time to Next Measurement;

[a] Represents one patient only

[b] 7 of 54 patients received adrenaline at some point during first 6days, with durations of 6-76 h

[c] 13 of 54 patients received hydrocortisone at some point in first six days, with durations of 1-18h

their effect on the outcome for the whole ICU stay (Table 6.27). On the other hand, during the first six days the adrenaline dosages had a statistically significant negative effect decreasing the odds of IR by about 5% (1-8%) in the following hour (Table 6.29), which was not the case when analysing the whole stay in the ICU. In addition, the protocol-hospital, as well as the hourly hydrocortisone dose, and the glycaemic exceedance, all remained having a significant negative effect on the outcome when analysing the first six days, as was the case when analysing the whole LOS (Table 6.29). When comparing the effect of each protocol-hospital with P-2.2_H-100, in some of them the OR was higher or lower than when the whole LOS was considered, but still greater than 1 in all cases. For P-6_H-500 the OR during the first six days (4.9) was almost half of its OR during the whole stay (8.7), implying that its effect on the odds of IR was twice as much when considering the whole stay (Table 6.29).

Patients with diabetes receiving protocol-2.2 in hospital-100 and hospital-200

During the first six days of admission the effects of P-2.2 were also significantly different depending on whether patients were admitted to H-100 or H-200 (Table 6.30). However, after controlling for relevant covariates, giving less insulin than specified in P-2.2, as compared with giving the insulin dosage as specified, decreased the expected odds of IR in the following hour but not at a statistically significant level [Adjusted OR(95%CI)=0.36(0.12-1.07)].

Table 6.30– Effect of non-adherence to P-2.2 instructions on the odds of IR at any time, during the first six days of stay, in patients with diabetes admitted to H-100 and H-200

	OR (95%CI)	Adjusted OR (95%CI)
Hospital (Reference category: H-200)		
H-100	0.18 (0.05–0.67)*	0.33 (0.19–0.56)***
Adherence to insulin dosage in the previous hour (Reference category: insulin given as specified)		
Insulin required but dosage given *lower* than specified	0.64 (0.46–0.88)**	–
Glycaemic exceedance	0.14 (0.05–0.36)***	0.16 (0.06–0.39)***

**p<0.050; **p<0.010; ***p<0.001*

Odds of IR: Odds of being within range 4-10mmol/L at any time

6.4.4.3 Odds of being in range during the first two days

Patients without diabetes

Among patients without diabetes, of the variables that had a statistically significant effect on the outcome when the whole stay was considered, only three variables remained statistically significant in their relationship with the odds of IR when considering just the first two days (Table 6.31). The adrenaline dosage and the glycaemic exceedance in the previous hour still showed a significant negative effect on the patient's odds of IR in the following hour. The time from admission still had a significant positive effect on the outcome, but in this case, the number hours from admission were used in the analyses rather than the number of days.

Patients with diabetes

Among patients with diabetes, of the variables with a significant effect on the outcome when the whole ICU stay was studied, only the hydrocortisone dosage and glycaemic exceedance remained with statistically a significant negative effect on the outcome during the first two days of admission (Table 6.32). None of the other covariates, including the protocol-hospital, remained significant in this period. On the other hand, the same as during the first six days, the adrenaline dosages had a statistically significant negative effect on the outcome in the following hour in this period (Table 6.32). This had not been significantly associated with the outcome when the whole stay in ICU was considered (Table 6.26).

Since there were no statistically significant differences in the effect of P-2.2 between H-200 and H-100, the effect of non-adherence to the instructions of this protocol during the first two days was not explored.

6.4.4.4 Odds of being in range depending on the protocol's target range

Patients with diabetes being cared for with a protocol having a UL83 glycaemic target had two to three times higher odds of IR (study glycaemic range), depending on the period of ICU stay considered, than patients with protocols having a UL10 target (Table 6.33). This difference was statistically significant in all periods considered.

Patients without diabetes had about 1.5 times higher odds of IR at any time if they were treated with a protocol having a UL83 target, but this difference was statistically significant only during the first two days and the first six days of admission (Table 6.33).

Table 6.31 – Effect of time-dependent and time-constant variables on the odds of IR at any time during the first two days, in patients without diabetes.

	OR (95%CI)	Adjusted OR (95%CI)
Spent >10% time receiving insulin during hyperglycaemia>10	0.46 (0.32–0.67)***	–
≤2hourly median TNM during hyperglycaemia>10	0.77 (0.52–1.13)	–
Protocol-hospital (Reference category: P-1.2_H-100)		
P-1.1_H-100	1.15 (0.45–2.96)	1.12 (0.53–2.36)
P-1.1_H-200	0.88 (0.35–2.25)	0.99 (0.56–1.73)
P-1.2_H-200	0.66 (0.17–2.53)	0.80 (0.23–2.78)
P-3_H-300	1.18 (0.49–2.85)	1.09 (0.57–2.07)
P-4_H-400	0.89 (0.30–2.60)	0.92 (0.41–2.07)
P-5_H-500	0.89 (0.30–2.68)	0.81 (0.39–1.71)
P-7_H-600	0.58 (0.23–1.46)	0.70 (0.36–1.38)
P-8_H-700	1.04 (0.44–2.48)	1.07 (0.58–1.98)
Highest BG on admission (in mmol/L)	0.85 (0.80–0.91)	–
Hour (Number of hours from admission)	1.04 (1.02–1.05)***	1.02 (1.01–1.03)**
Time-dependent exposures with 1 hour lag:		
Adrenaline dosage (in mcg/kg/h)[a]	0.03 (0.00–0.57)*	0.94 (0.89–0.99) *
Glycaemic exceedance	0.02 (0.01–0.04)***	0.03 (0.02–0.04)***

**p<0.050; **p<0.010; ***p<0.001*

Odds of IR: Odds of being within range 4-10mmol/L at any time

BG: Blood Glucose (mmol/L); TNM: Time to Next Measurement;

[a] 12 of 92 patients received adrenaline at some point during first 2 days, with durations of 2-46h

Table 6.32 – Effect of time-dependent and time-constant variables on the odds of IR at any time during the first two days, in patients with diabetes.

	OR (95%CI)	Adjusted OR (95%CI)
Spent >65% time receiving insulin during hyperglycaemia>10	0.31 (0.20–0.49)***	–
≤2hourly median TNM during hyperglycaemia>10	0.29 (0.17–0.47)***	–
Protocol-hospital (Reference category: P-2.2_ H-100)		
P-2.1_H-100	1.48 (0.42–5.19)	1.09 (0.42–2.87)
P-2.1_H-200	7.00(3.09–15.86)***[a]	3.36 (1.56–7.25)**[a]
P-2.2_H-200	0.41 (0.09–1.84)	0.84 (0.28–2.54)
P-3_H-300	2.41 (0.72–8.09)	1.46 (0.58–3.65)
P-4_H-400	2.11 (0.74–6.01)	2.09 (0.78–5.61)
P-6_H-500	3.46 (1.42–8.40)**	1.94 (0.82–4.60)
P-7_H-600	2.07 (0.66–6.42)	1.87 (0.70–5.01)
Prot8_H-700	2.18 (0.83–6.42)	1.51 (0.64–3.53)
Highest BG on admission (in mmol/L)	0.94 (0.89–0.99)*	–
Hour (Number of hours from admission)	1.02 (1.01–1.03)**	–
Time-dependent exposures with 1 hour lag:		
Adrenaline dosage (in mcg/kg/h)[b]	0.01 (0.00–0.28)**	0.81 (0.70–0.94)**
Hydrocortisone dosage (in mg/h)[c]	0.997 (0.996–0.999)**	0.992 (0.985–0.999)*
Glycaemic exceedance	0.06 (0.03–0.11)***	0.07 (0.04–0.12)***

**p<0.050; **p<0.010; ***p<0.001*

Odds of IR: Odds of being within range 4-10mmol/L at any time

BG: Blood Glucose (mmol/L); TNM: Time to Next Measurement;

[a] Represents one patient only

[b] 7 of 54 patients received adrenaline at some point during first 2 days, with durations of 6-46h

[c] 12 of 54 patients received hydrocortisone at some point during first 2 days, with durations of 1-8h

Table 6.33 – Effect of having a protocol with UL83 glycaemic target range as opposed to a UL10 glycaemic target range, on the odds of IR at any time

	OR (95%CI)	
	No/Unknown diabetes and UL83 glycaemic target	**Diagnosed diabetes and UL83 glycaemic target**
n(%)	57 (62%)	24 (44%)
During the whole stay	1.2 (0.7–2.0)	2.9 (1.7–5.0)***
During first six days	1.6 (1.1–2.4)*	2.4 (1.4–4.1)***
During first two days	1.5 (1.0–2.3)*	2.1 (1.2–3.7)**

Difference between group of patients with a UL83 as compared with those with a UL10 of the glycaemic target:

**p<0.050; **p<0.010; ***p<0.001*

Odds of IR: Odds of being within range 4-10mmol/L at any time

6.4.5 Efficiency: time to return to range

The period of time from the first BG>10mmol/L to the subsequent first two hours with BG within the study glycaemic range 4-10mmol/L, is referred to as the TTR period. The first event of BG>10mmol/L was available from the ICNARC database for all patients. For two of the 146 patients in the study sample, this BG value could not be verified from the observation charts, as the chart for the first 24h of admission was completely/partially missing. Also, there were two other patients who did not have two consecutive hourly BG values within 4-10mmol/L after the first BG>10mmol/L. Consequently, the TTR could not be calculated for these four patients, who were excluded from the analyses on TTR, leaving a sample size of 142. One of these four did not have diabetes.

The TTR per patient ranged from 1 to 132 hours, but in 90% of the patients TTR was 22 hours or less. The first hyperglycaemic value >10mmol/L occurred significantly earlier among patients with diabetes ($p<0.001$), who also had a significantly longer TTR period ($p<0.001$) (Table 6.34).

Table 6.34 – Secondary outcome measure of time-efficiency

		Previous diagnosis of diabetes	
	All	**No/Unknown**	**Yes**
n (%) [a]	142	91 (64%)	51 (36%)
Number hours from admission to first BG>10mmol/L, per patient* **	2 (1–7)	4 (1–13)	1(1–4)
Number hours from first BG>10mmol/L to first BG in range in 2 consecutive hours, per patient* **	5 (3–12)	4 (2–8)	11 (4–19)

Differences of by diabetic status:

** p<0.05, ** p<0.01, *** p<0.001*

All metrics are expressed in median(IQR) unless otherwise specified

[a] Excluding four patients: two patients whose first chart was missing, causing that the first event of BG>10mmol/L was missing; and two patients who did not have two consecutive BG=4-10mmol/L after the first BG>10mmol/L

6.4.5.1 TTR and the protocol-hospital

There were no statistically significant differences between protocol-hospitals in their median TTR, in either group of diabetic status. Generally, in all protocol-hospitals there was a larger variability in the TTR among patients with diabetes, particularly in the protocol-hospitals implemented in H-100 and H-200 (Table 6.34 and Figure 6.33). Among patients without diabetes, the median (IQR) TTR ranged from 2 (2-2) (in P-8_H-700) to 6 (1-13) (in P-7_H-600). Among patients with diabetes, excluding P-2.1_H-200 which only had one patient (with TTR=4hours), the median (IQR) TTR ranged from 6 (3.5-8) (in P-6_H-500) to 41 (4-75) (in P-2.2_H-100).

Kaplan-Meier graphs for TTR, by protocol-hospital and diabetic status, are presented in Figure 6.34. In this plot, narrower steps of each line indicate a better outcome, as the event of interest is achieving the study glycaemic target range (rather than death, as it is often plotted in this type of graphs). Among patients without diabetes, their often shorter TTR is illustrated by markedly narrower steps than in patients with diabetes. Among patients with diabetes, excluding three outliers, the line for P-2.2_H-100 was above the lines of all other protocol-hospitals for most of the time after the first 12 hours (Figure 6.34). This means that P-2.2_H-100 was less time-efficient than the remaining protocol-hospitals.

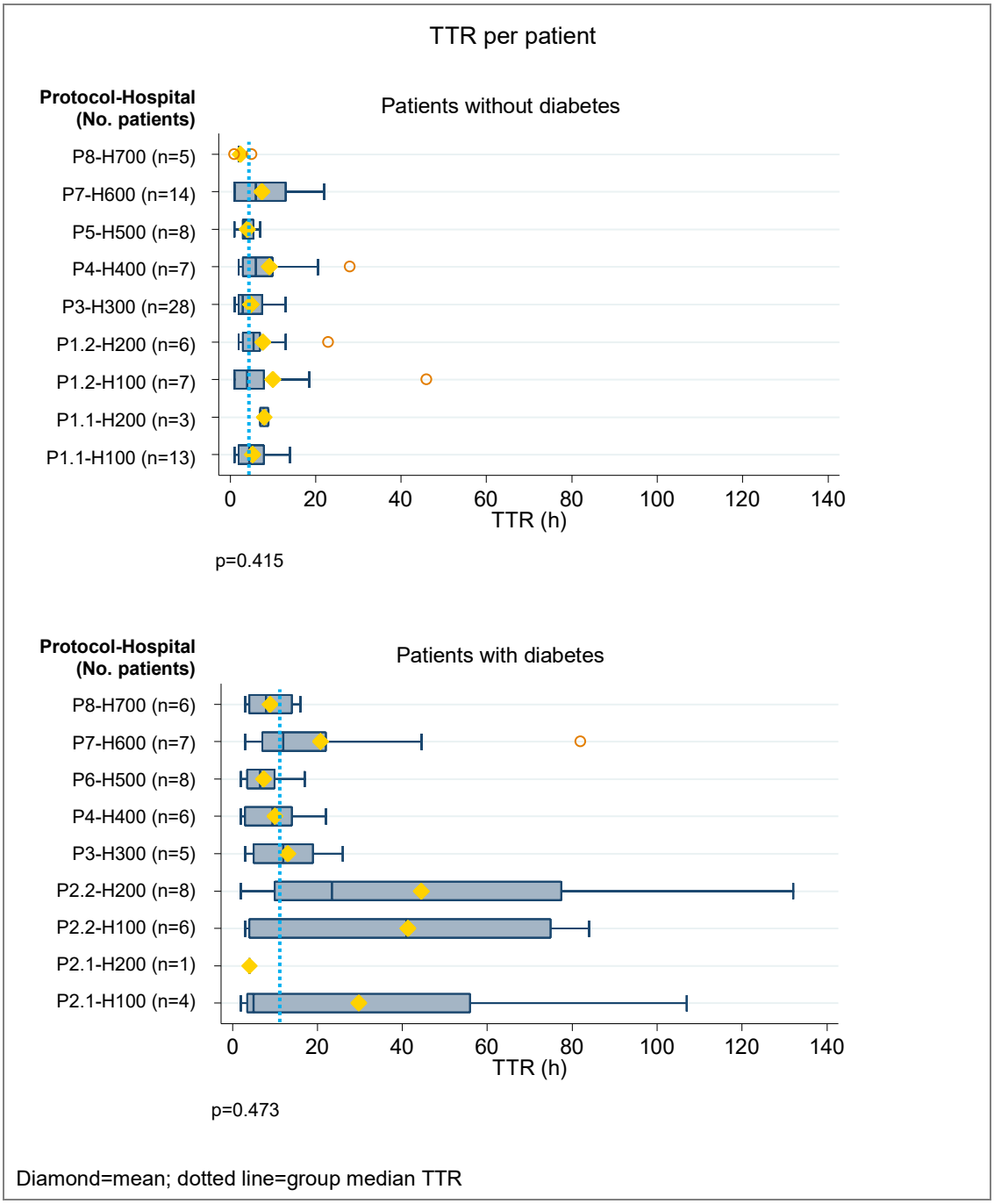


Figure 6.33 – Box-plot of the TTR per patient, by protocol-hospital and diagnosis of diabetes. P: Protocol; H: Hospital

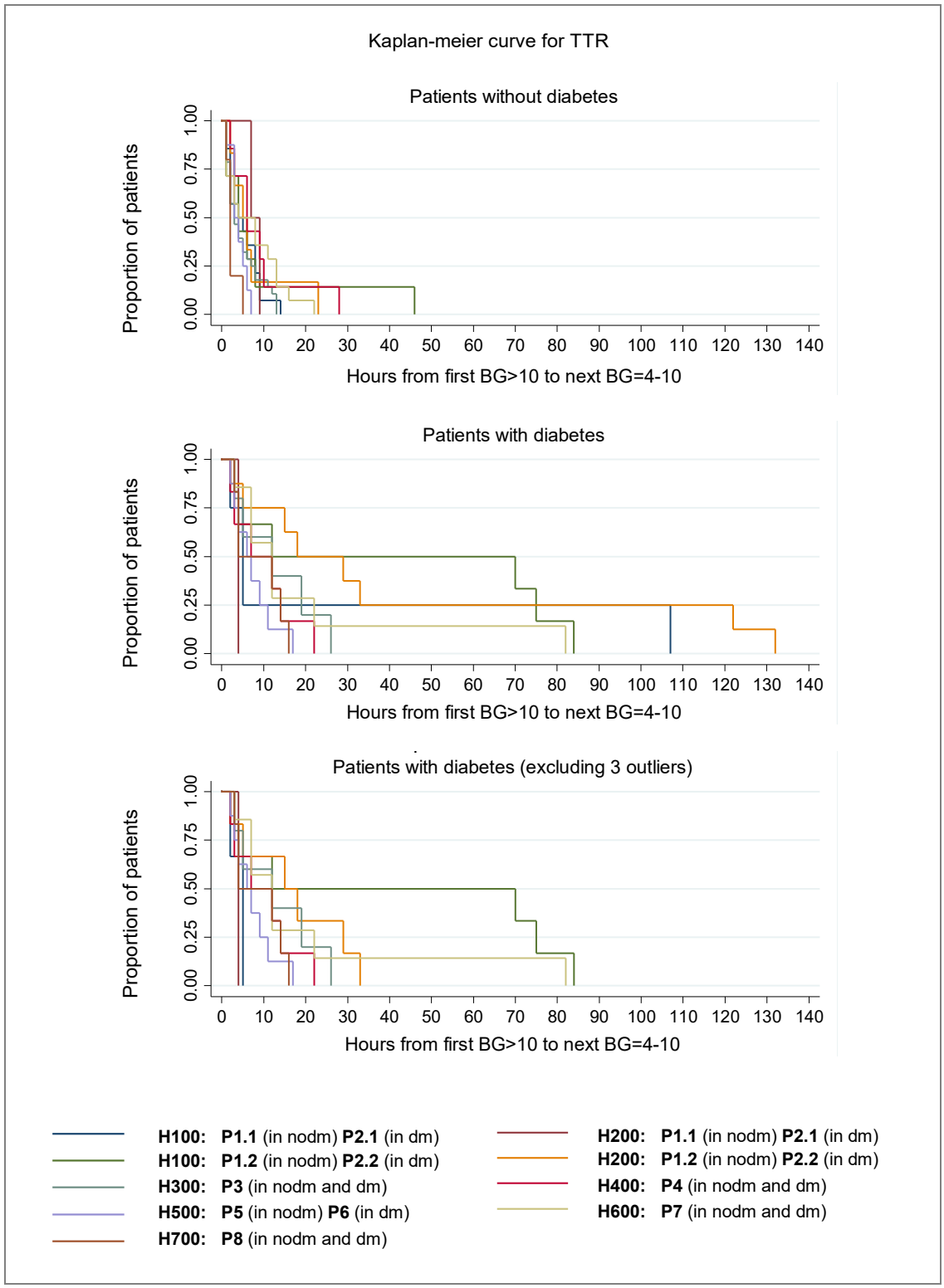


Figure 6.34 – Kaplan-Meier graph for TTR by protocol-hospital and diabetic status: (top) patients without or with unknown diabetes, (middle) all patients with diabetes, (bottom) patients without diabetes excluding three identified model fit outliers.
H: Hospital; P: Protocol; nodm: patients without diabetes; dm: patients with diabetes.

6.4.5.2 TTR and the target range of the protocol

In protocol-hospitals with UL83 glycaemic target, the median TTR per patient was significantly shorter than protocol-hospitals with a UL10 glycaemic target (p=0.002) (Figure 6.36 and Figure 6.35). Excluding three outliers, the steps of the Kaplan-Meier line for patients in the UL83 group were narrower than those in the line for the UL10 group, and the former were always above the line for the UL10 group (Figure 6.36). These indicate that protocols with UL83 were more time-efficient than those with UL10.

However, when the comparison of groups by protocol target range was done separately for each group of diabetic status, the difference in the median TTR was not statistically significant for patients without diabetes (p=0.081). Among patients with diabetes the difference was also borderline not significant, both when outliers were included (p=0.051) and when they were excluded (p=0.058).

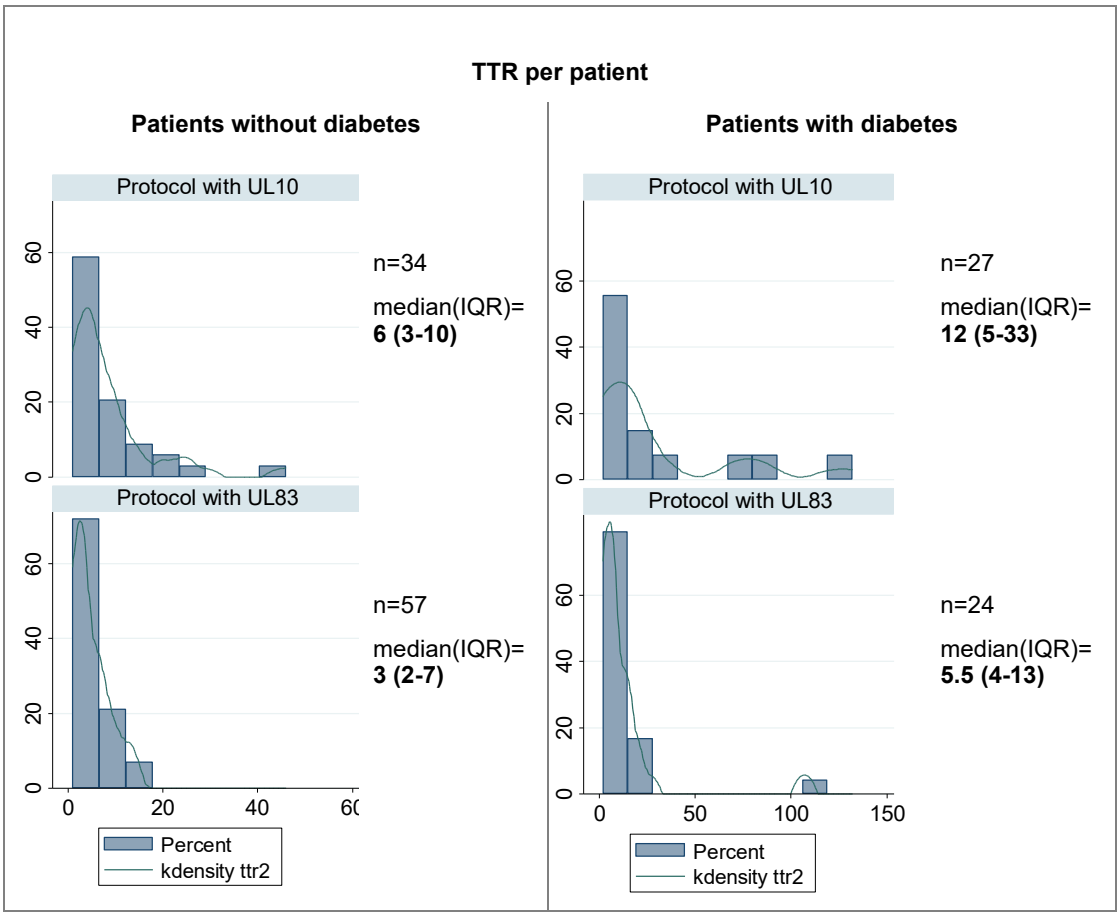


Figure 6.35 – Number of hours from first BG>10mmol/l to first BG within the study target range (4-10mmol/) for two consecutive hours (TTR), by upper limit of glycaemic target (UL 83 vs UL 10) and diabetic status.

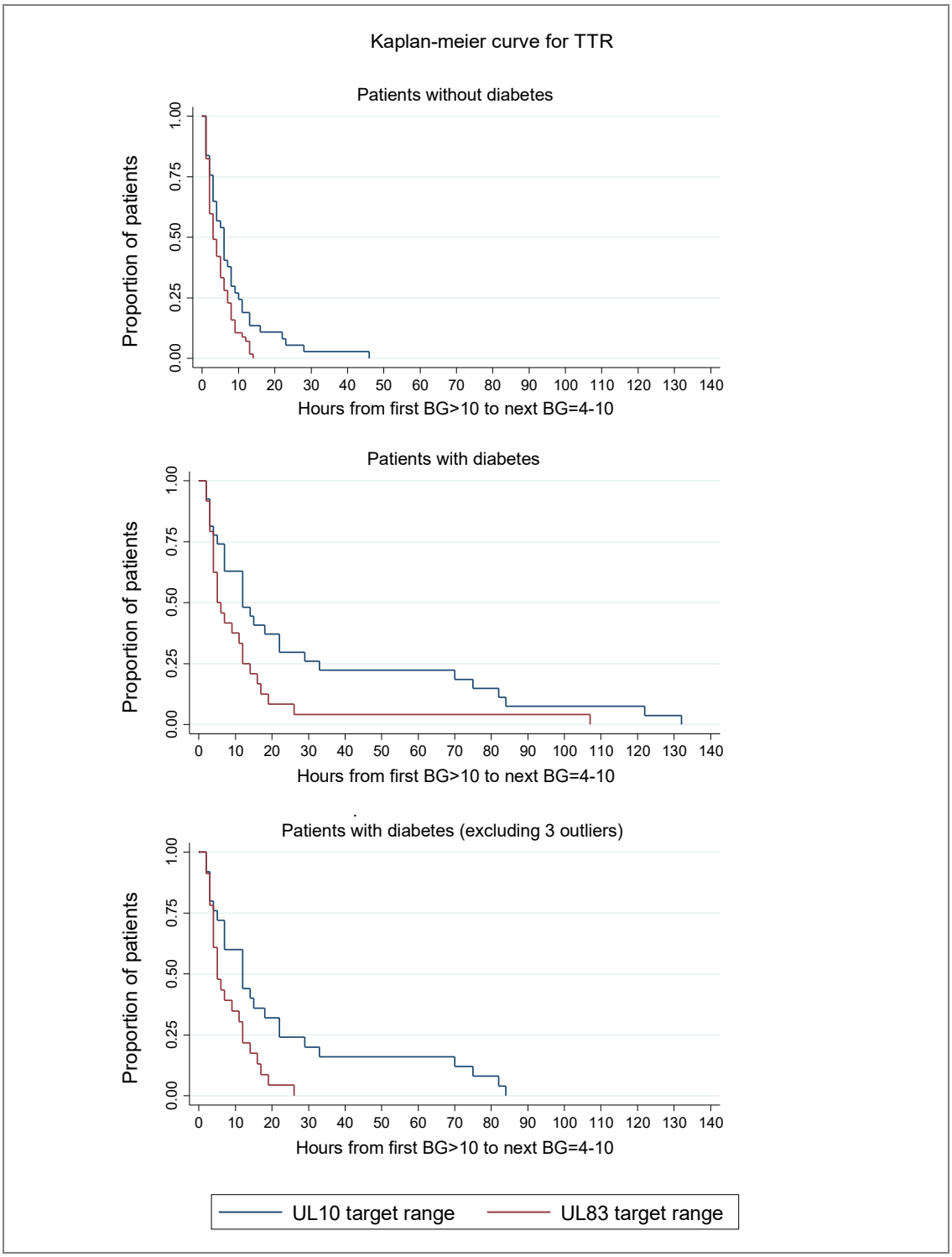


Figure 6.36 – Kaplan-Meier graph for TTR by UL83 vs. UL10 glycaemic target and diabetic status: (top) patients without or with unknown diabetes, (middle) all patients with diabetes, (bottom) patients without diabetes excluding three identified model fit outliers. TTR: time from first BG>10mmol/L to next BG=4-10mmol/L for two consecutive hours

6.4.6 Multivariate analyses of time-efficiency

6.4.6.1 Patients without diabetes

Outlying patients

Among patients without diabetes, analyses on the existence and impact of outliers revealed that there were two (2%) patients with a mean TTR more than two SDs from the sample mean, and three (3%) patients with a high leverage. While these were considered model fit outliers, the R-squared did not improve when these were excluded, and therefore they were kept in the analyses.

There were also five (6%) and seven (8%) predictor outliers affecting the linear regression model, with a high Cook's distance and a high DfFit, respectively. Excluding these predictor outliers had a significant effect in the coefficient for one of the protocol-hospitals. In order to handle this, robust regression was carried out. Results from the standard Log-linear regression with robust standard errors, and of the robust Log-linear regression are summarised in Table 6.35. The significant effects that were found are mentioned below.

Log-linear regression analyses

After controlling for relevant covariates, a median monitoring frequency during TTR period of two or less hours was associated with approximately 37% shorter TTR, on average. Giving insulin to the patients without diabetes at some point during the TTR period was associated with longer TTR (Table 6.35). The glycaemic exceedance had to be log-transformed to improve the linear relationship with the outcome. A 10% increase in the glycaemic exceedance significantly increased TTR by approximately 1.6% on average (Table 6.35).

While none of protocol-hospitals had a significantly different effect when compared to P-1.2_H-100, this was kept as the reference category in the results shown in Table 6.35 for consistency with other results tables. Analyses were also performed with each of the other protocol-hospitals as the reference category. Based on these, TTR was, on average, two to four times longer in patients with P-4_H-400 than those with P-5_H-500 (p=0.037), P-3_H-300 (p=0.022) and P-8_H-700 (p=0.009).

Table 6.35 – Factors affecting Time To Range (TTR) among patients without diabetes – Robust Log-linear Regression and Log-linear regression with robust SE

	e^Coeff. from *Robust* Log-linear regression[a]	***Robust* Log-linear Regression Coefficient (95%CI)[b]**	***Standard* Log-linear Regression with robust SE Coefficient (95%CI)**
R-squared[c]		NA	44%
Received insulin at some point during TTR (Y/N)	1.94***	0.66 (0.26 – 1.06)***	0.68 (0.32 – 1.04)***
≤2hourly median Time to Next Measurement during TTR (Y/N)	0.63*	-0.45 (-0.83 – -0.09)*	-0.45 (-0.78 – -0.11)**
Log of median glycaemic exceedance >10 during TTR[d]	1.016***[d]	0.37 (0.17 – 0.58)***	0.37 (0.20 – 0.53)***
Protocol-hospital (Ref. category: P-1.2_H-100)			
P-1.1_H-100	0.74	-0.30 (-1.04 – 0.45)	-0.40 (-1.14 – 0.34)
P-1.1_H-200	1.25	0.22 (-1.06 – 1.51)	0.19 (-0.93 – 1.31)
P-1.2_H-200	1.04	0.04 (-0.85 – 0.93)	0.06 (-0.77 – 0.88)
P-3_H-300	0.63	-0.47 (-1.15 – 0.22)	-0.48 (-1.17 – 0.21)
P-4_H-400	1.42	0.35 (-0.51 – 1.21)	0.31 (-0.39 – 1.02)
P-5_H-500	0.58	-0.54 (-1.38 – 0.29)	-0.56 (-1.36 – 0.25)
P-7_H-600	0.70	-0.36 (-1.11 – 0.39)	-0.43 (-1.21 – 0.35)
P-8_H-700	0.39*	-0.95 (-1.91 – 0.00)	-0.98 (-1.72 – -0.24)**

** p<0.05, ** p<0.01, *** p<0.001*

Outcome measure: Log transformation of Time To Range (TTR)

TTR: Time from first BG>10 to next (subsequent) BG=4-10mmol/L for two consecutive hours

[a] Coefficients are presented as natural exponentials of the coefficients from **robust regression** analyses, b (e^b) to show the effect of X_i on the *un*transformed Y

[b] Coefficients are presented with their 95% CI to show the effect of X_i on the log-transformed Y

[c] Neither R-squared or adjusted R-squared can be calculated with *robust* regression. Adjusted R-squared cannot be calculated with *standard* regression with *robust SE*

[d] Both the outcome and the independent variable are log transformed: A **10%** increase in the glycaemic exceedance>10mmol/L multiplies TTR by e^[0.37*log(1.1)]=**1.016**

6.4.6.2 Patients with diabetes

Outlying patients

Among patients with diabetes, analyses on the existence and impact of outliers revealed that there was one (2%) patient with high leverage due to a very low TTR, and three (6%) patients with at very high TTR, more than two SDs above the mean. The effect of the three model fit outliers with high TTR can be seen in the Box-plots by hospital in Figure 6.33, and in the Kaplan-Meier curves for TTR in Figure 6.34. These three outlying patients were explored in depth and it was concluded that they were not a data entry error but they were "interesting cases" that were important to keep in the sample(Aguinis et al., 2013). None of the three long TTRs were caused by a missing chart. One of these patients received insulin for 50% of the TTR time, with a median (IQR) IIR of 3 (3-4) U/h. The other two patients received insulin for more than 95% TTR time with median (IQR) IIRs of 3 (1-4) and 4 (4-6) U/h. One had a cardiac related primary reason for admission, one respiratory and one hepatic. They stayed in the ICU for 7-18 days and they all survived ICU and the first 28 days after admission. Regression analyses were performed with and without these three outliers (Table 6.36).

There were also three (6%) predictor outliers with a high Cook's distance and four (7%) predictor outliers with a high DfFit. Excluding these predictor outliers did not cause a large change (by at least 10%) in the coefficients of the significant independent variables in the linear regression model and, therefore, robust regression was not performed. Instead standard Log-linear regression with robust standard errors was used.

Log-linear regression

Among patients with diabetes, the exposures of interest regarding the monitoring frequency did not show a significant effect on the TTR, regardless of whether the three model fit outliers had been excluded or not. After controlling for relevant covariates, giving insulin to these patients with diabetes for at least 50% of the TTR period was associated with longer TTR (Table 6.36). The glycaemic exceedance was not significantly associated with the length of TTR.

While none of protocol-hospitals had a significantly different effect when compared to P-2.2_H-100, this has been kept as the reference category in Table 6.36 for consistency with other tables. Analyses were also performed with each of the other protocol-hospitals as the reference category. Based on these, on average, P-2.2_H-200 and P-3_H-300 had five (p=0.037) and three (p=0.006) times higher expected TTR than P-6_H-500, respectively.

Table 6.36 – Factors affecting Time To Range (TTR) among patients with diabetes – Log-linear regression with robust SE

	e^Coeff. from Log-linear regression with robust SE excluding 3 outliers[a]	***Standard* Log-linear Regression with robust SE, EXCLUDING 3 influential outliers Coefficient (95%CI)[b]**	***Standard* Log-linear Regression with robust SE Coefficient (95%CI)**
R-squared[c]		41%	NA
Received insulin for >50% time during TTR (Y/N)	2.71**	1.31 (0.63 – 2.00)***	1.00 (0.26 - 1.73)**
Protocol-hospital (Ref. category: P-2.2_H-100)			
P-2.1, H-100	0.60	-0.29 (-1.30 – 1.89)	-0.52 (-2.56 – 1.53)
P-2.1, H-200	0.46	-0.51 (-1.69 – 0.66)	-0.78 (-2.03 – 0.48)
P-2.2, H-200	1.68	0.34 (-1.03 – 1.72)	0.52 (-0.95 – 1.99)
P-3, H-300	0.92	0.11 (-1.17 – 1.40)	-0.08 (-1.43 – 1.26)
P-4, H-400	0.43	-0.51 (-1.82 – 0.79)	-0.84 (-2.20 – 0.52)
P-6, H-500	0.33	-1.10 (-2.34 – 0.15)	-1.12 (-2.37 – 0.13)
P-7, H-600	0.79	-0.16 (-1.45 – 1.14)	-0.24 (-1.57 – 1.09)
P-8, H-700	0.82	0.06 (-1.27 – 1.40)	-0.20 (-1.61 – 1.20)

** $p<0.05$, ** $p<0.01$, *** $p<0.001$*

CI: Coefficient Interval; SE: Standard Error; Y/N: Yes/No

Outcome measure: Log transformation of Time To Range (TTR)

TTR: Time from first BG>10 to next (subsequent) BG=4-10mmol/L for two consecutive hours

[a] Coefficients are presented as natural exponentials of the coefficients from **regression analyses with robust SE** excluding three influential outliers, b (e^b) to show the effect of X_i on the *un*transformed Y

[b] Coefficients are presented with their 95%CI to show the effect of X_i on the transformed Y

[c] Adjusted R-squared cannot be calculated with *standard* regression with *robust SE*

Adjusted R-squared calculated from standard regression without robust SE, but the (95CI) of the coefficients shown in this table are based on regression with robust SE

6.4.7 Safety: outcomes on hypoglycaemia

Of the 40 patients who had at least one episode of moderate hypoglycaemia (defined as a BG measurement of 2.3-3.9mmol/L), almost half (n=19) had diabetes (Table 6.37). Thus the incidence of patients who had moderate hypoglycaemia at least once was 23% among patients without diabetes and 35% among patients with diabetes. In 50% of the 40 patients who had at least one event of moderate hypoglycaemia, the duration of these events was of two hours or less (Table 6.37).

Among patients without known diabetes, there were two patients who spent 18 and 23 hours in moderate hypoglycaemia. The remaining patients spent eight hours or less in moderate hypoglycaemia. Among patients with diabetes, the median duration of hypoglycaemia was higher than for patients without known diabetes, but this difference was not statistically significant, and all patients in this group spent a maximum of eight hours in moderate hypoglycaemia (Table 6.37). These durations represented percentages of the admission time ranging from 0.1% to 15.3% in patients without diabetes, and 0. 2% to 11.0% in patients with diabetes.

Table 6.37 – Secondary outcome measures on safety

	Previous diagnosis of diabetes		
	All	**No/Unknown**	**Yes**
Patients with ≥1 event moderate hypoglycaemia (BG=2.3–3.9mmol/L), No. (%)	40 (27%)	21 (23%)	19 (35%)
Patients with ≥1 event severe hypoglycaemia (BG≤2.2mmol/L), No. (%)	4 (2.7%)	2 (2%)	2 (4%)
Percentage of admission time with moderate hypoglycaemia per patient, median (Range) [a]	1.0% (0.5-3.0%)	0.9% (0.5-2.8%)	1.0% (0.6-3.3%)
Percentage of admission time with severe hypoglycaemia per patient, median (Range) [b]	1.3% (0.8-1.7%)	0.8% (0.7-0.9%)	1.7% (1.6-1.8%)
Duration (h) of events of moderate hypoglycaemia per patient, median (Range) [a]	3 (1–23)	2 (1–23)	3 (1–8)
Duration (h) of events of severe hypoglycaemia per patient, median (Range) [b]	1 (1–1)	1 (1–1)	1 (1–1)

All metrics are expressed in median(IQR) unless otherwise specified

[a] Excluding patients without any event of moderate hypoglycaemia

[b] Excluding patients without any event of severe hypoglycaemia

Severe hypoglycaemic events (defined as a BG measurement of ≤2.2mmol/L) occurred once (one measurement) in four patients, two of whom had diabetes (Table 6.37). These durations represented percentages of the admission time ranging from 0.7% and 0.9% in the two patients without diabetes, and 1.6% and 1.8% in the two patients with diabetes.

6.4.7.1 Safety and the protocol-hospital

Most patients experiencing at least one episode of severe or moderate hypoglycaemia were from P-7_H-600 and P-8_H-700, which had 12 (57%) and 7 (64%) patients with at least one event of moderate hypoglycaemia, respectively, and two (10%) and 1 (9%) patients with one event of severe hypoglycaemia, respectively (Figure 6.37). These were followed by P-4_H-400 which had five (33%) patients who experienced moderate hypoglycaemia at least once and one (7%) patient with one event of severe hypoglycaemia. The remaining hospitals had two to six patients with at least one event of moderate hypoglycaemia, and no events of severe hypoglycaemia (Figure 6.37). These differences in the proportions of patients experiencing moderate hypoglycaemia depending on the protocol-hospital were statistically significant (Figure 6.37).

6.4.7.2 Safety, protocol target and insulin instructions during hypoglycaemia

Amongst the 40 patients who had at least one episode of moderate hypoglycaemia, 21 (52%) had protocols with a UL83 glycaemic target, 19 (48%) had protocols that recommended insulin even during hypoglycaemia (P-7_H-600 and P-8_H700). Among patients without diabetes, there was a lower proportion of patients experiencing moderate hypoglycaemia from those receiving a protocol with a UL83 glycaemic target (16%) than if they had a UL10 glycaemic target (34%) (p=0.040). Similarly, a lower proportion of patients without diabetes experienced moderate hypoglycaemia if their protocol did not recommend insulin during hypoglycaemia (15%) than if it did (52%) (p=0.001). One patient from a protocol-hospital that recommended insulin during hypoglycaemia (5%), and one from a protocol-hospital that did not recommend this (1%) had one event of severe hypoglycaemia (p=0.372).

Among patients with diabetes, there were lower proportions of patients experiencing moderate hypoglycaemia if they received a protocol with a UL10 glycaemic target (23%) than if it had a UL83 glycaemic target (50%) (p=0.040); and if their protocol did not recommend insulin during hypoglycaemia (24%) than if it did (69%) (p=0.003). The two patients with diabetes who had an event of severe hypoglycaemia were both from protocol-hospitals that recommended insulin during hypoglycaemia (15%), while there were no patients with severe hypoglycaemia in the other protocol-hospitals that did not recommend this (0%) (p=0.055).

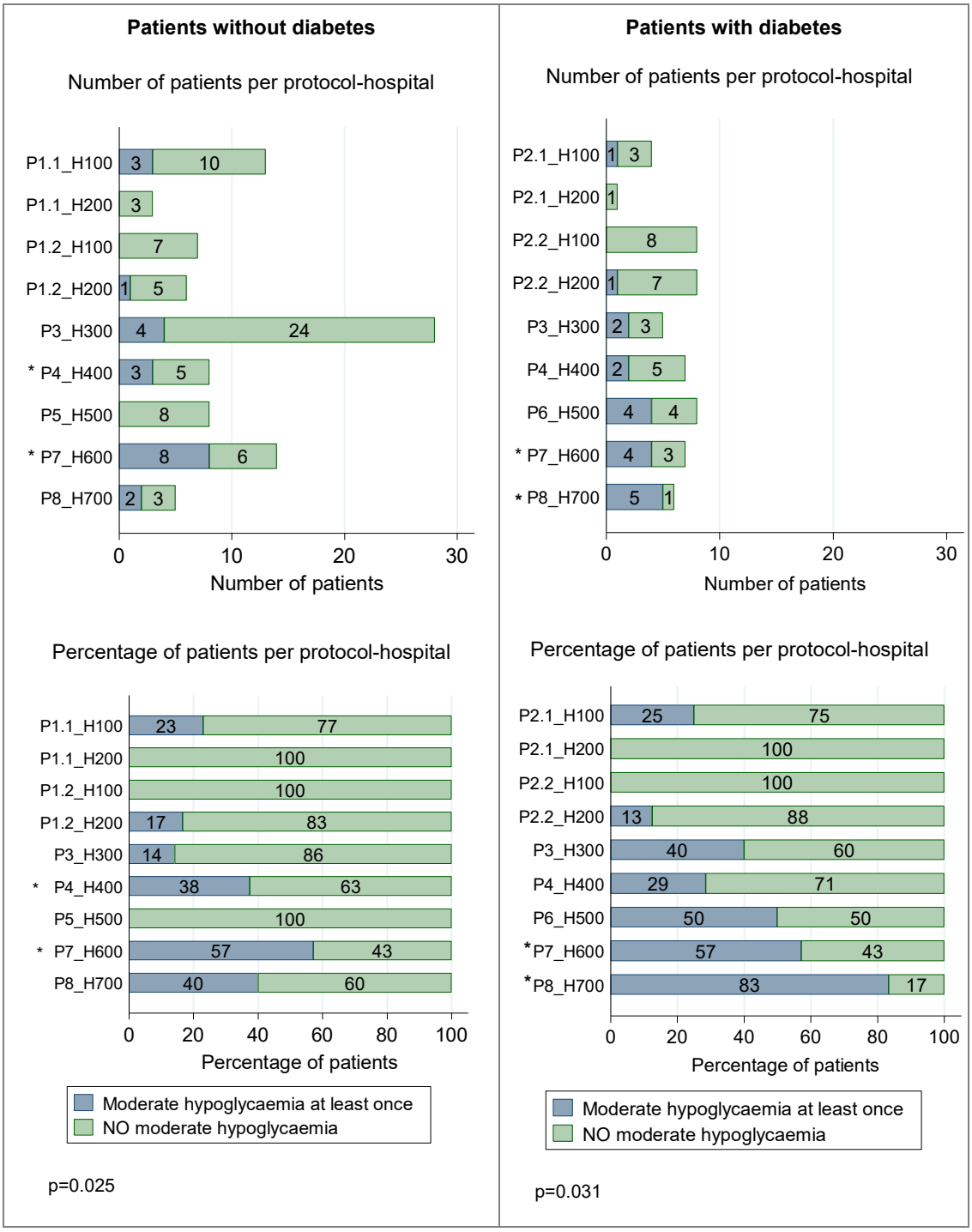


Figure 6.37 – Number and percentage of patients with at least one episode of moderate hypoglycaemia, by hospital and previous diagnosis of diabetes.
*** One patient had one event of severe hypoglycaemia**

Of the 40 patients who had moderate hypoglycaemia at least once, 10 (48%) patients without diabetes and 11 (58%) with diabetes received insulin while they were in hypoglycaemia. Of these 21, only four (40%) patients without diabetes and five (46%) patients with diabetes belonged to protocol-hospitals that recommended the administration of insulin during hypoglycaemia (Figure 6.38).

Among patients without diabetes, the proportion of patients who had at least one event of hypoglycaemia and received insulin during at least one hour within hypoglycaemia differed significantly by protocol-hospital (p=0.012) (Figure 6.38).

The percentage of time and the median time spent in moderate hypoglycaemia per patient did not show statistically significant differences by protocol-hospital, by the upper limit of the protocol glycaemic target, or by whether protocols recommended insulin during moderate or severe hypoglycaemia, in any of the groups of diabetic status.

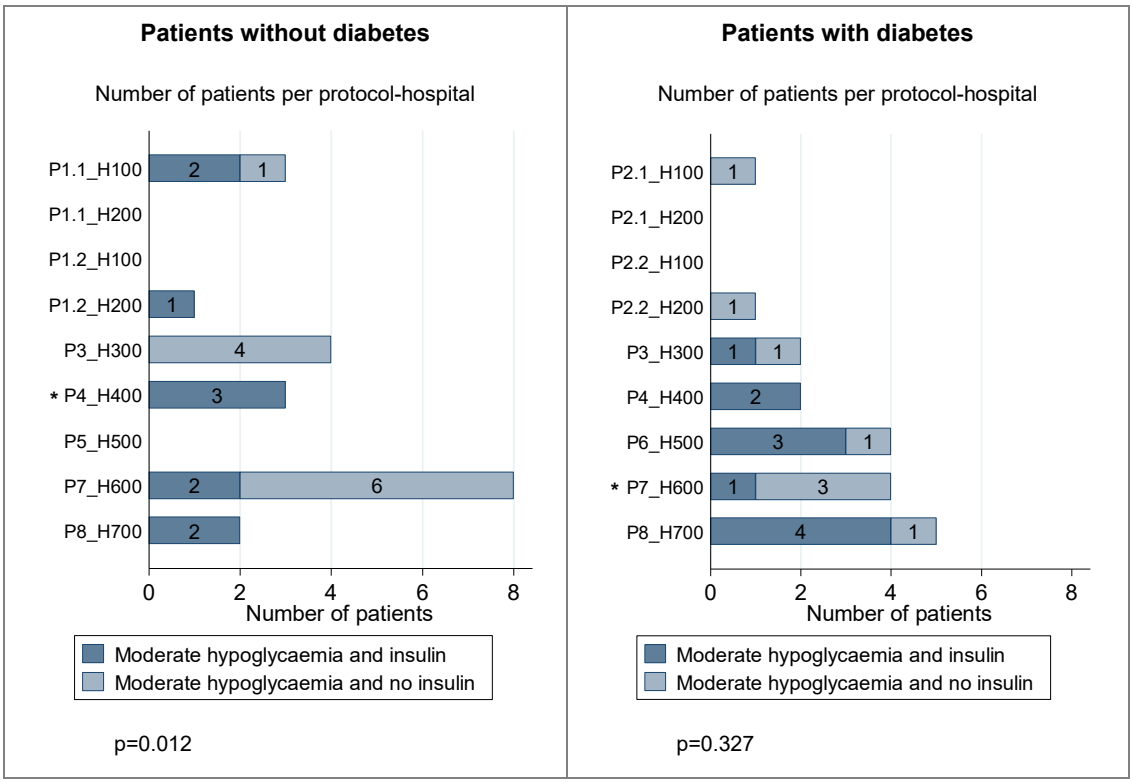


Figure 6.38 – Number of patients with at least one episode of insulin administration during moderate hypoglycaemia, by hospital and previous diagnosis of diabetes.
*** One patient had one event of severe hypoglycaemia while receiving insulin**

6.4.8 Sensitivity analyses

The effect of including the four patients that had been initially excluded from the analyses, due to a high risk of bias caused by the large relative amount of missing data from the charts, was explored (Table 6.38 and Table 6.39). None of these patients had a previous history of diabetes and all four patients received a protocol-hospital with a UL10 glycaemic target. None of the summary statistics of TIR and events of hypoglycaemia were significantly different when these four patients were included in the sample (Table 6.38).

Analyses of association and comparisons of the outcome measures, showed different results only in one of the univariate analyses when the excluded patients were included (Table 6.39). When these were included, having received a protocol-hospital with a UL83 glycaemic target was no longer statistically significantly associated with a lower percentage of patients that had at least one event of moderate hypoglycaemia (Table 6.39).

Table 6.38 – Summary statistics of TIR, TTR and hypoglycaemic events among patients without diabetes: including vs. excluding the four patients who had high risk of biasing results because of the amount of missing data they had

	Excluding patients with large amounts of missing data	Including all patients
Median (IQR) TIR	91% (81-96%)	91% (80-96%)
Median (IQR) TIR-6	89% (80-95%)	90% (80-96%)
Median (IQR) TIR-2	85% (70-95%)	85% (70-96%)
% of patients with moderate hypoglycaemia	21 (23%)	21 (22%)
Median(range) time with moderate hypoglycaemia (excluding patients without any hypoglycaemic event)	2 (1-23)	2 (1-23)

TIR: % time in range 4-10mmol/L; TIR-6: TIR during first six days; TIR-2: TIR during first two days; TTR: time(h) between first BG>10mmol/L and subsequent BG=4-10mmol/L for two consecutive hours

Table 6.39 – Modelling analyses and univariate analyses of the outcome measures among patients without diabetes: including vs. excluding the four patients who had high risk of biasing results because of the amount of missing data they had

	All patients without diabetes excluding patients with large amounts of missing data	All patients without diabetes	Are there significant or important differences in: a) modelling analyses or b) univariate analyses?
Multivariate analyses			
Odds of IR GEE model	-	-	No
Odds of IR-6 GEE model	-	-	No
Odds of IR-2 GEE model	-	-	No
Univariate analyses (group comparisons)			
Odds of IR ↔ UL of target	-	-	No
Odds of IR-6 ↔ UL of target	-	-	No
Odds of IR-2↔ UL of target	-	-	No
TIR ↔ protocol-hospital	-	-	No
TIR ↔ UL of target	-	-	No
TTR ↔ UL of target	-	-	No
% patients with hypoglycaemia ↔ protocol-hospital	-	-	No
% patients with hypoglycaemia ↔ UL83 target	% hypo and: a) UL83: 16% b) UL10: 34% *	% hypo and: a) UL83: 16% b) UL10: 31%	Yes. After including patients with large amounts of missing data, the difference between groups of target (UL83 vs. UL10) is not statistically significant
Hypo time ↔ protocol-hospital	-	-	No
Hypo time ↔ UL of target	-	-	No

* p<0.05, ** p<0.01, *** p<0.001

Odds of IR, Odds of IR-6, Odds of IR-2: Odds of being In Range at any time during the full ICU stay, or the first six days, or the first two days, respectively; GEE: Generalised Estimating Equations; TIR: % time in range 4-10mmol/L; UL: upper limit of the glycaemic target range: UL83 (upper limit ≤8.3mmol/L) and UL10 (upper limit = 10mmol/L)

6.5 Discussion

The GlyCon study was designed to help answer the question of how to manage the glycaemic control of stress induced hyperglycaemia, in the real critical care setting, effectively, as well as efficiently and safely. This is a pertinent question, which is still being widely debated (Preiser & Straaten, 2016; Gunst & Van den Berghe, 2016; Marik, 2016). GlyCon study has produced several novel findings, which add to the current body of knowledge on this topic. Some of these findings confirm previous evidence but the study has also produced results that seem to contradict, or at least call into question previous evidence. As with any study, GlyCon has some limitations, and the study results must be put into context.

Before proceeding to a discussion of the results, important issues concerning the selection of outcome measures are first described (section 6.5.1). The discussion starts with an interpretation of the study results regarding the levels of effectiveness, efficiency and safety of GC in the GlyCon ICUs, and how these results relate to previous evidence (sections 6.5.2 to 6.5.4). This is followed by a discussion of how the outcome measures were associated with the protocols and hospitals (section 6.5.5), the GC methods implemented (sections 6.5.6 and 6.5.7), and the nutritional strategy and other covariates (section 6.5.8).

6.5.1 Study aims and outcome measures

A common challenge in studies carried out in intensive care is the selection of outcomes that can actually measure the impact of an intervention or treatment, given the high complexity of the conditions and therapeutic interventions that critically ill patients usually have (Corwin, 2005). The decision on which intermediate outcomes to use in this study, to assess the effectiveness of GC, as well as its time-efficiency and safety, was based on the aims of GlyCon, the most up-to-date literature, and the best, feasible study design. The metrics had to be relevant, as well as measurable and meaningful.

The primary outcome measure of effectiveness chosen, time in range/band or TIR, had been used in numerous studies before to describe the performance of an ICU or a protocol as a whole (Table 2.4), to investigate its effects on clinical outcomes (Krinsley & Preiser, 2015; Penning et al., 2015; Omar et al., 2015; Signal et al., 2012; Chase et al., 2010). One of the novel contributions of GlyCon was its main aim of investigating which methods for GC implemented in different ICUs were the most effective (i.e., had the highest TIR), while controlling for relevant covariates. This was done by using TIR as an outcome rather than as a risk factor of other outcomes. In GlyCon study, it was hypothesised that the different protocols for GC of the participating ICUs would guide different decisions and actions, for

the same situation, and consequently they would have a different impact, as measured by the TIR of critically ill patients. As the study progressed, and due to the results on the distribution of TIR, the intermediate outcome measure to use in the analyses of association was transformed into the odds of IR (odds of being in the study target range at any time).

One of the main complications of evaluating the performance of the specific components of a GC protocol is due to the dynamics of their bidirectional relationship with the outcome. BG levels determine the measurement frequency (measured as the time to next measurement, TNM) and insulin titration, if any, at each measurement, while, at the same time, such BG levels would have been strongly affected by the previous insulin dosage and the time passed since the previous measurement. At higher glycaemic ranges, patients are likely to be monitored more closely and to receive insulin at higher rates and for longer periods, than when BG is stable within a particular target range. Therefore, analyses on the effects of the GC methods implemented in a particular ICU, could show, for example, that more frequent BG monitoring and giving higher insulin dosages or for longer, are associated with higher BG ranges, i.e. with lower effectiveness.

On the other hand, different ICUs implement different protocols for GC (Niven et al., 2015; J. Orban et al., 2013; Tomlinson et al., 2012; Paddle et al., 2011; Cook et al., 2009; Wilson et al., 2007; Mackenzie et al., 2005). These differ in their diagnostic, monitoring and treatment instructions at each particular scenario. Thus, it was expected that the same glycaemic scenario would be dealt with differently by each of the seven participating ICUs in the GlyCon study. Based on these grounds, it was hypothesised that patients who are monitored more frequently and who receive insulin for longer periods during hyperglycaemia would have a better (more effective) glycaemic control.

6.5.2 Effectiveness of glycaemic control

6.5.2.1 Glycaemic levels

In this study, the overall arithmetic mean (10.4mmol/L), geometric mean (9.8mmol/L) and median of the patient BG means (9.8mmol/L) among patients with diabetes were higher than most values reported in previous studies. Examples of previously reported mean BG include 9.5mmol/L (Egi et al., 2008), 8mmol/L (Sechterberger et al., 2013), or 7.1mmol/L (Krinsley, 2009); and Krinsley & Preiser (2015) found a median of the patient mean BG of 7.7mmol/L. On the other hand, among patients without diabetes the overall arithmetic mean (8mmol/L), geometric mean (7.7mmol/L) and median of the patient BG means (7.8mmol/L), were similar or perhaps only slightly higher than previously reported values. Examples of previously reported mean BG include 8mmol/L (Sechterberger et al., 2013), 7.8mmol/L (Egi

et al., 2008), and 6.4mmol/L (Krinsley, 2009); and Krinsley & Preiser (2015) found a median of the patient mean BG of 6.6mmol/L. In both groups of diabetes, the glycaemic variability, as measured by the SD and the CV, was generally higher among GlyCon patients than in the cited studies (Krinsley & Preiser, 2015; Sechterberger et al., 2013; Krinsley, 2009; Egi et al., 2008).

The higher average BG values and variability could be due to the fact that patients from GlyCon study were treated with protocol-hospitals that differed in their glycaemic targets, and that most of these target ranges had an upper limit (8, 8.3 or 10mmol/L), which was often higher than those in previous studies. In fact, amongst patients with diabetes, protocol-hospitals differed significantly in their measures of location and dispersion of the BG levels per patient, indicating that different GC methods and glycaemic targets may lead to different measures of location of glycaemic levels (Figure 6.28).

The markedly and statistically significant higher summary measures of location and dispersion of glycaemic levels found in GlyCon study among patients with diabetes, as compared to those without diabetes, have also been reported in previous studies (Krinsley & Preiser, 2015; Krinsley, 2009; Egi et al., 2008). In GlyCon, such differences were also found in the higher degree of hyperglycaemia>10 among patients with diabetes. This was measured by a newly introduced metric on the glycaemic exceedance above 10mmol/L.

Physiologically, these differences between patients with and without diabetes are plausible. The already existing insulin resistance and/or the defective secretion of insulin by the pancreas among patients with diabetes (Dungan et al., 2009) may have increased the degree of hyperglycaemia resulting from the metabolic response to the critical acute condition in these patients. However, in their large single-centre retrospective study of 10320 medical and surgical ICU patients, Sechterberger et al. (2013) did not find significant differences in the mean BG glycaemic levels depending on the diabetic status (mean BG of 8mmol/L in both groups), indicating that it may be possible to achieve similar outcomes in both groups of diabetes.

Unit transformation of glycaemic levels

It has been suggested that BG levels are transformed so that their probability distribution, which is usually positively skewed, becomes closer to the Gaussian distribution and thus parametric tests in the new unit space can be performed (Braithwaite et al., 2013). In the GlyCon study, the median of the patient-mean of untransformed glycaemic levels was relatively close to the geometric mean, calculated from the antilog of the log-transformed glycaemic levels. This suggests that, for clinical purposes, when faster, less specialised statistical summaries of the BG profiles of an ICU are necessary, the simpler metric of

untransformed data may suffice to provide acceptable measures of location. Further studies are needed to investigate whether the use of either type of metric could make an important difference in clinical decisions, or in the results of evaluation studies.

6.5.2.2 Percentage of time spent within the range 4-10mmol/L: TIR

There is still no standardised definition for what constitutes effective or good GC, in terms of the percentage of time spent within a particular target range (time in range, TIR). Some studies pre-specified what they believed was poor or good GC a priori, before conducting their research, but they did not justify the scientific basis for their choice (Rady et al., 2005; Carr et al., 2005). Three more recent studies have concluded that spending 80% or more of the admission time within certain glycaemic ranges had a positive impact on clinical outcomes, and hence can be considered as good or effective GC (Krinsley & Preiser, 2015; Penning et al., 2015; Omar et al., 2015).

In this study, it was expected that the TIR at 4-10mmol/L would, on average, be larger than the TIR at the narrower ranges found by previous studies. However, the median TIR of 82% found in GlyCon (for the whole sample) seemed lower than those identified by a recent study analysing TIR at 4-10mmol/L (Stewart et al., 2016). Such study was a retrospective analysis of the STAR GC protocol in two ICUs, and it reported that most of the 314 analysed patients spent 90% or more of the admission time with BG within 4-10mmol/L. Nonetheless, GlyCon found significant differences depending on the previous history of diabetes of patients, and patients without diabetes had in fact a median TIR of 91%.

TIR in patients without diabetes

According many of the professionals who participated in GlyCon survey, the results on the TIR of patients without diabetes, which was higher than 80% in at least three quarters of these patients (Table 6.23), should be considered as good results for a protocol with a glycaemic target like the one used in GlyCon study (4-10mmol/L). Specifically, most professionals indicated that, in their opinion, 75% of the time spent within a protocol's glycaemic target constituted good GC. However, this may not necessarily translate into better actual benefits in terms of patients' lower mortality risk.

In their recent single-centre retrospective study of 3247 medical and surgical ICU patients, Krinsley & Preiser (2015) concluded that patients without diabetes who spent more than 20% of admission time with BG outside the range 4.4-7.8mmol/L were less likely to survive. Although survival was not assessed in GlyCon study, the group overall median of the recorded BG of patients without diabetes was 7.7mmol/L (Table 6.21). This means that 50% of the BG measurements were 7.7mmol/L or higher and, therefore, it is likely that numerous

patients spent more than 20% of their admission time above the range assessed by Krinsley & Preiser (2015). Penning et al. (2015) have recently re-analysed data from two previous studies, and concluded that spending more than 80% of the cumulative time with BG within 4-7mmol/L or 4-8mmol/L were both associated with higher odds of survival, although the longer the patient stayed in ICU the more beneficial the former range was. Thus, until further studies on the effects of TIR at 4-10mmol/L on the mortality risk and other outcomes are conducted, it is not clear whether the threshold of 75% TIR at 4-10mmol/L could define an effective or good GC.

TIR in patients with diabetes

As for the results on glycaemic levels, patients with diabetes in GlyCon study had a markedly and significantly lower TIR than patients without diabetes. This occurrence had also been reported in previous studies, although with different glycaemic target ranges (Krinsley & Preiser, 2015; Omar et al., 2015; Shulman et al., 2007; Rady et al., 2005; Carr et al., 2005; Zimmerman et al., 2004).

Given the glycaemic target defining TIR in GlyCon, the results suggest that the protocols that were assessed had a less effective GC, as compared with other studies. Krinsley & Preiser (2015) had found a median TIR of 55% (35-71%) at 4-7.8mmol/L among patients with diabetes. Although they are difficult to compare with GlyCon findings, due to the different glycaemic ranges defining the target, their results suggest better outcomes in their patients with diabetes, as compared to those of GlyCon study, which had a similar median (IQR) TIR of 56% (34-72%), but within a wider glycaemic range of 4-10mmol/L. In their prospective study on patients after cardiac surgery, Omar et al. reported that 32% of their patients with diabetes had spent more than 80% of the admission time within 6-8.1mmol/L. In GlyCon study, only about 20% patients with diabetes spent 80% or more of the time within the wider glycaemic range of 4-10mmol/L (Figure 6.31), which means that GlyCon patients' percentage of time spent at the narrower range of 6-8.1mmol/L was, on average, even lower.

The results confirm that GC is significantly less effective in patients with diabetes. On the other hand, diabetes has been shown to attenuate the relationships between intermediate outcomes, such as low TIR or low mean BG, and poor clinical outcomes, such as mortality (Krinsley & Preiser, 2015; Krinsley et al., 2013; Egi et al., 2008).

These results re-emphasise the importance of stratifying analyses based on diabetic status in any studies of the effectiveness of GC in ICU. Equally, clinical decisions on the aims of GC, as measured with TIR, should take into account patients' history of diabetes.

Another important finding of the GlyCon study concerns the large inter-patient variability found in the TIR (Figure 6.30 and Figure 6.32). TIR had large IQR distances in all groups, but more so amongst patients with diabetes, who had TIRs with IQR distances of up to 45%, depending on the admission period of interest (Table 6.23). Krinsley et al. (2015) had also found wide IQR distances of TIR, but at the narrower glycaemic range of 4-7.8mmol/L, both in patients without diabetes (IQR distance of 33%) and in patients with diabetes (36%). This variability of the TIR among patients treated with the same protocol is also an indication that "one size may not fit all" (Abdelmalak & Lansang, 2013; Krinsley, 2013), i.e. that methods for GC can be more effective for some patients than for others. It has been suggested that the main reason why providing safe and effective GC is proving difficult comes from the need for addressing the inter- and intra-patient variability (Shaw et al., 2014). Thus, a formalised degree of flexibility stated in the protocols, with evidence-based recommendations, may help with the individualisation of care, while, at the same time, avoiding inequalities of care.

TIR as an indicator of effectiveness

With TIR increasingly being used as an outcome measure, there is a need for evidence-based definitions for effective GC, based on TIR, to be agreed among the scientific community and clinical organisations. These could include a list of desirable TIRs for different glycaemic targets, where the TIRs are different for patients with or without a previous history of diabetes.

6.5.3 Efficiency of glycaemic control

Excluding the three cases that were considered as outliers (and were explored in depth and analysed accordingly), patients from GlyCon study returned to the glycaemic study target after their first hypoglycaemia>10 episode (time to range, TTR) within a median (IQR) of 5 (3-12) hours. Also, in most patients, regardless of their diabetic status, TTR occurred within the first 24 hours after the first BG value above 10mmol/L. For protocols that stated that the aim was to achieve the target within the first 24 hours, this would be considered a good result.

It is difficult to determine how this time-efficiency compared with other studies, because their glycaemic targets were narrower than the 4-10mmol/L of GlyCon, and often they focused on certain population groups only. Among those that focused on mixed medical-surgical ICUs, like those included in GlyCon, there was one study (Chant et al., 2005) in which patients were considered as having "reached the target" when two consecutive measurements had been within target, as in GlyCon. In such study, the median TTR at 5-8mmol/L (for two consecutive measurements) was 15 hours in the intervention

group and 66 hours in the control group (Chant et al., 2005). In other studies that focused on medical-surgical ICUs (Kanji et al., 2004, 2010; M. M. Barth et al., 2007; Shulman et al., 2007; Vogelzang et al., 2005; Zimmerman et al., 2004), TTR was usually lower than that in Chant et al.'s study, despite having even narrower glycaemic targets. This indicates that the condition of two consecutive measurements could have played an important role. Given that GlyCon also found shorter TTR, on average, the width of the reference target range may also have influenced the results of this study.

The lower time-efficiency found among patients with diabetes, as compared to those without diabetes, is another indication of a poorer response of these patients to the methods for GC. Also, the considerable inter-patient variability, especially within some protocol-hospitals (Figure 6.33), could indicate that GC methods were more time-efficient in some patients than in others.

It is important to mention that, while this metric of TTR is easily measured and calculated, it has not yet been associated with clinical outcomes and it is unknown whether it really has a clinical impact (Preiser et al., 2016). However, being closely related to the metric of percentage of time in range (TIR), any associations of poor outcomes with the TIR during the first one to two days of admission, would probably affect TTR too. Hence, further studies exploring the effects of the time-efficiency of GC on poor outcomes are still needed.

6.5.4 Safety of glycaemic control

Moderate hypoglycaemia (defined as any BG=2.3-3.9mmol/L) in GlyCon patients was not uncommon, as it occurred at least once in more than one quarter of the patients (23% patients without diabetes and 35% patients with diabetes), but these seemed lower than the figures reported in previous studies. For example, in the NICE SUGAR trial, Finfer et al. (2012) found an incidence of 45% patients who experienced moderate hypoglycaemia at least once. Oeyen et al. (2007) found that 60% patients in their medical-surgical ICU had at least one event of BG<3.3mmol/L; and, among patients after subarachnoid haemorrhage, Kurtz et al. (2014) found an incidence of at least one event of BG<3.9mmol/L in 57% of patients. On the other hand, while the average duration of the events of moderate hypoglycaemia found in GlyCon were of 2-3 hours, representing 1% of the admission time on average, some lasted as much as 15% of admission time. Given the detrimental effects of hypoglycaemia, the importance of these findings should not be underestimated.

Events of severe hypoglycaemia (defined as any BG≤2.2mmol/L) occurred only once in each of four patients in GlyCon study (in 2% and 4% patients without and with diabetes, respectively). These events represented a maximum of 2% of the individual patients' total

admission time. Some studies have reported similar incidences of patients with at least one episode of severe hypoglycaemia<2.2mmol/L, such as the 2% out of 5365 medical, surgical, and cardiac ICU patients identified by Krinsley & Grover (2007). In other studies, the incidence was higher, depending on the treatment provided. Among these is NICE SUGAR trial, which reported an incidence of 6.9% and 0.5% patients who experienced severe hypoglycaemia, depending on whether they were treated with an IIT or a conventional approach, respectively (NICE-SUGAR Study Investigators et al., 2012). Also, Kanji et al. (2004) reported severe hypoglycaemia in 4% and 16% patients in their before-after observational study, depending on whether patients were in the intervention or the control group, respectively.

Despite the generally lower incidence of hypoglycaemia found in GlyCon, given that in some patients they represented a considerable percentage of their admission time, and that even a single event of hypoglycaemia has been associated with poor outcomes in critically ill patients with and without diabetes (Krinsley et al., 2013; NICE-SUGAR Study Investigators et al., 2012; Hermanides et al., 2010; Bagshaw et al., 2009; Krinsley, 2008; Finney et al., 2004), it seems necessary that the GlyCon ICUs put further emphasis on avoiding hypoglycaemia altogether.

6.5.5 Association between the outcomes of glycaemic control and the protocol and hospital

6.5.5.1 Protocol-hospital and effectiveness of glycaemic control

Patients without diabetes

Among patients without diabetes, the differences in TIR between protocol-hospitals were not statistically significant. Equally, multivariate analyses showed that none of the protocol-hospitals had a significantly higher effectiveness (as measured by the odds of being within the study target range, the odds of IR) in any of the study periods of interest for patients without diabetes. On the other hand, the odds of IR of patients without diabetes was higher, on average, when the protocol had a UL83 target (upper limit 8.3mmol/L) as opposed to a UL10 target (upper limit 10mmol/L), although this became not significant as the stay became longer than six days. This indicates that, regardless of the protocol and the hospital, having a glycaemic target with a lower upper threshold could be beneficial for these patients, especially during the first six days of admission, by increasing their likelihood of being controlled within the target BG range at any time.

Patients with diabetes

Among patients with diabetes, the protocol and the hospital of admission did seem to have had a role in the effectiveness of glycaemic control, both in univariate analyses (using TIR), as well as after controlling for relevant covariates in multivariate analyses (using odds of IR). In the univariate analyses, the odds of IR was higher, on average, when the protocol had a UL83 than when it had a UL10, at all periods of considered, and this became more significant as the length of stay increased. In addition, when the protocol-hospitals were ranked from highest to lowest percentages of patient-hours spent within 4-10mmol/L, those protocol-hospitals with a narrower glycaemic target (UL83) occupied the first four places in the ranking, while those with a wider glycaemic target (UL10) occupied the last five places of the ranking (Figure 6.32). These results suggest that some protocols and certain ICUs managed GC more effectively than others for patients with diabetes. The results also indicate that an established glycaemic target plays an important role in a GC protocol, and that it may be more effective to establish a glycaemic target range that is lower than what would be the "acceptable" target. In this regard, in the *post hoc* analyses of two previous studies, Stewart et al. (2016) found that patients under the protocol of one of the studies (SPRINT protocol), which targeted 4-6.1mmol/L, achieved a higher percentage of time within the glycaemic target of the protocol of the other study (STAR protocol) of 4.4-8mmol/L (87.2%) than the patients who had actually been treated with STAR protocol (82.6%). Finally, the GlyCon study findings also suggest that the effect of having a protocol with a UL83 target is stronger during the first six days of admission among patients without diabetes, and regardless of the period considered among patients with diabetes.

Protocol-hospitals with highest and lowest effectiveness among patients with diabetes

Among the protocols with a UL10 target there was one protocol (P-2.2) for patients with diabetes, which was implemented in two hospitals (H-100 and H-200), and which had a markedly and significantly lower performance than all other protocol-hospitals, in terms of lower TIR and lower odds of IR. This protocol's performance was even lower when it was implemented in H-100 than when it was implemented in H-200, even after controlling for relevant covariates.

Among the possible reasons behind the different levels of effectiveness between these two hospitals, despite implementing the same protocol, could be the fact that H-100 administered less insulin than specified in the protocol more often than H-200. In fact, one of the most important findings of GlyCon was that, in the multivariate analyses, giving less insulin than specified in P-2.2 showed a detrimental effect in both hospitals where it was implemented, by decreasing the odds of IR in the following hour, as compared to giving the specified

dosage. This was significant only when the whole ICU stay was considered in the analyses. This finding suggests that protocols' insulin dosage recommendations can have an important role in GC, and that following the insulin instructions can improve the effectiveness of the care provided, as an overall benefit during the whole ICU stay. Similar conclusions were made by Omar et al. (2015), who found that increased general adherence of nurses with their protocol was associated with patients spending more than 80% of the whole ICU stay in their target range 6-8.1mmol/L. Also, Oeyen et al. (2007) found that the TIR at 4.5-6.1mmol/L increased from 28% during hours of general non-adherence to the protocol, to 65% during hours of compliance with their protocol.

Even after controlling for the level of adherence to insulin instructions, patients from H-200 had significantly higher odds of IR at any time than patients from H-100, when both hospitals were implementing P-2.2. Patients' population groups, based on their primary diagnosis, did not seem to have played a role, as the distributions of the patient population groups were very similar between P-2.2_H-100 and P-2.2_H-200. Also, as compared to patients with P-2.2_H-200, those with P-2.2_H-100 did not seem to have become significantly more severe during their admission, as they died in hospital significantly less often. These patients with P-2.2_H-100 also stayed in the ICU for significantly shorter times, and it could be argued that the length of stay could have played a role in the different effectiveness outcome of the two hospitals. This is because longer stayers (in H-200) could have had their BG better controlled towards the end of their stay, which in the analyses could have increased their odds of IR at any time. With this regard, Thomas et al. (2005) found that the odds of having a BG<8mmol/L increased by 4% with every one day increase in patients' ICU stay. Nonetheless, in GlyCon study the cumulative time spent in the ICU was found to have a significant effect on the odds of IR only among patients without diabetes, as will be discussed in section 6.5.8.3. In addition, when looking at the first six days of admission only, the significantly better performance of patients from H-200, as compared to H-100, was still evident.

Another possible factor affecting these results could be related to fact that in H-100 there were two high dependency units (HDU), separate from the GlyCon ICU, to which patients from the ICU could be transferred when their condition was less severe and they required lower levels of care. A lower severity could coincide with a stabilisation of the glycaemic response. It is therefore possible that the periods when patients had more stable glycaemic levels were included in H-200, which was a combined ICU/HDU, but not in H-100, which was only an ICU (with a separate HDU). On the other hand, the number of days requiring level-3 care per patient had not shown significant differences between hospitals, so it is unclear whether such possible patient transfers did actually affect the results.

In conclusion, while it was not possible to determine all the actual causes for the lower effectiveness of P-2.2 when it was implemented in H-100 as compared with when it was implemented in H-200, it is clear that giving less insulin than indicated in the protocol was detrimental for patients. This important and novel finding indicates that adhering to the insulin treatment instructions of evidence-based protocols (as is P-2.2) can be beneficial to patients. Nonetheless, one should also consider other factors related to the professionals, the hospital, or characteristics of the patients, which were not available for this study. For this, a larger study is required to build on and confirm the findings of GlyCon.

At the other extreme, P-6_H-500, which had a UL83 glycaemic target and was implemented for patients with diabetes, had, on average, higher odds of IR than most other protocol-hospital (all except for one). Since no significant differences between hospitals were found in the demographic and clinical characteristics of their patients, it is unlikely that the type of patients admitted to H-500 played a role in the higher effectiveness of P-6_H-500. Interestingly, P-6_H-500 had the highest percentages of non-adherences to the protocol instructions on monitoring frequency and insulin titrations. Therefore, it is not clear to what extent the protocol itself contributed to the better performance of this protocol-hospital.

At face value, such low levels of adherence could be interpreted as contradicting the earlier finding of higher effectiveness being associated with higher adherence to insulin dosages. However, this is not necessarily the case since, as was described in the protocols' review chapter, the insulin instructions differed greatly between protocol-hospitals. Hence it can be argued that, while the insulin instructions of P-2.2 were shown to be effective (better outcomes when adhered to), the effectiveness of these instructions in P-6 could not be determined due to the low levels of adherence to them. These results further emphasise the importance that studies on effectiveness of protocols for GC control for levels of adherence to their instructions.

Based on the results of GlyCon, it cannot be concluded that the protocol implemented can, on its own, be associated with the evaluated outcomes. As was recently emphasised by Kavanagh & Nurok (2016), attributing any harmful or beneficial outcomes to the protocol implemented, without considering the actual reasons that resulted in such outcomes, could result in an "impact misattribution" to the protocol. Impact evaluations of protocols for GC require that the levels of adherence, as well as other professional-related and ICU-related factors, which could affect the effectiveness of GC, are controlled for. Ideally, the actual GC methods implemented would be analysed too, as was done in GlyCon.

6.5.5.2 Protocol-hospital and efficiency of glycaemic control

In GlyCon study there was a clear variability between the time-efficiency of the different protocol-hospitals (Figure 6.33 and Figure 6.34). In the multivariate analyses, certain protocol-hospitals were found to have a significantly shorter TTR (i.e., better time-efficiency) than others.

The protocol-hospital with the worst time-efficiency among patients with diabetes (P-2.2_H-100) had admissions from all patient population groups, and no statistically significant differences had been found in the proportions of admissions at each patient population group among patients with diabetes. The protocol-hospital with the worst time-efficiency among patients without diabetes (P-7_H-600) had admissions from all patient population groups except for hepatobiliary-pancreatic admissions (Figure 6.11), and one third of them were cardiac admissions. Being admitted for cardiac surgery (Rady et al., 2005; Carr et al., 2005) has been found to be a predictor of lower TIR, which could also mean that it is also a predictor of higher TTR. However, cardiac surgery patients were excluded from GlyCon sample. Consequently, it did not seem likely that the case mix of P-7_H-600 (in patients without diabetes) and P-2.2_H-100 (in patients with diabetes) were related to their lower TTR, and the actual reasons for this remain unclear.

Among patients without diabetes, the protocol-hospital (P-4_H-400) that had a significantly worse time-efficiency than three other protocol-hospitals (P-5_H-500, P-3_H-300 and P-8_H-700) had a UL10 glycaemic target, while the latter three had a UL83 glycaemic target. Among patients with diabetes, the only protocol-hospital (P-6_H-500) that had a significantly better time-efficiency than two other protocols (P-2.2_H-200 and P-3_H-300), had the narrowest and lowest glycaemic target (4-6.1mmol/L), while the latter two protocols had wider and higher targets (<8.3mmol/L, and 4-10mmol/L). While these results show a trend indicating that the target of the protocols may have had a role, in the univariate analyses of TTR by group of UL83 vs. UL10 glycaemic target, TTR differed between groups but not at a statistically significant level. Thus larger studies covering more ICUs are needed to confirm whether having a lower upper limit of the glycaemic target is more time-efficient than having a higher one, in terms of the time needed to achieve a common glycaemic range.

6.5.5.3 Protocol-hospital and safety of glycaemic control

Univariate analyses showed that protocol-hospitals differed significantly in their incidences of moderate hypoglycaemia. H-600 and H-700, which were the hospitals with the lowest safety levels (highest incidence of hypoglycaemia), had admissions from all patient population groups, except for hepatobiliary-pancreatic admissions. With this regard, admissions for surgery, trauma, severe sepsis and cardiovascular failure have been identified

as determinants of higher risk for hypoglycaemia (NICE-SUGAR Study Investigators et al., 2012). However, the proportions of admissions of these groups were not significantly higher in H-600 and H-700 than in all other hospitals, and therefore it seemed that the patient population group did not have a strong effect on the higher incidence of hypoglycaemia in H-600 and H-700.

Having a protocol-hospital with a UL83 glycaemic target seemed beneficial for the safety of patients without diabetes, as indicated by a lower incidence of moderate hypoglycaemia. However, in the sensitivity analyses, when the four patients who had been excluded in all analyses (because of the large amount of missing charts they had) were included, the effect of having a protocol-hospital with a UL83 glycaemic target was not statistically significant. The four patients that had been excluded had protocols with a UL10 target and, based on their available charts, these patients did not have any event of hypoglycaemia (Table 6.38). Although they could have had a hypoglycaemic event during those hours of missing data, given these results, and that the calculations on the effects of a UL83 target were done using univariate analyses, the suggested beneficial effect of a UL83 target should be interpreted with caution. Among patients with diabetes, meanwhile, there was no doubt that a UL83 target seemed detrimental, as the incidence of both moderate and severe hypoglycaemia was higher among patients treated with a UL83 target.

In the multivariate analyses of NICE SUGAR trial, having been treated with an IIT approach (targeting 4.5-6mmol/L), having diabetes and having been previously treated with insulin were all identified as factors that increased the odds of developing moderate hypoglycaemia (NICE-SUGAR Study Investigators et al., 2012). In their review of the literature on IIT and safety, Kansagara et al. (2013) concluded that protocols targeting higher glycaemic ranges were generally associated with lower rates of hypoglycaemia. Based on this previous evidence, in GlyCon patients, the combination of history of diabetes and being treated with a UL83 glycaemic target (which, although often higher than the IIT target of NICE SUGAR, was lower than UL10 targets) could have been behind the higher incidence of moderate and severe hypoglycaemia among these patients. Thus it is likely that protocols with a UL83 target were less safe for patients with diabetes and, therefore, being treated with a target having a higher upper limit could be beneficial for these patients, in terms of safety (i.e., avoidance of hypoglycaemia).

The GlyCon results indicated that having a protocol that recommended the administration of insulin during hypoglycaemia had a potentially detrimental effect regarding safety. In both groups of diabetic status, there were significantly higher rates of moderate hypoglycaemia among the patients treated with a protocol that instructed the use of insulin at all times,

regardless of glycaemic levels, and including during hypoglycaemia (P-7_H-600 and P-8_H-700) (Figure 6.37).

From this, it could be inferred that GC is less safe if insulin is administered during hypoglycaemia. However, given the high levels of non-adherence found in this study, such a conclusion could be another example of impact misattribution to the protocol, unless the actual clinical practice is examined. In fact, there were 21 patients who received insulin at some point during hypoglycaemia and they belonged to all ICUs, including those with a protocol-hospital that instructed that no insulin should be administered during hypoglycaemia.

Due to the low sample of patients with hypoglycaemia, it was not possible to carry out multivariate analyses in this study. Therefore, since the results on safety of GlyCon were based in univariate analyses, there may have been other factors affecting the higher incidence of moderate and severe hypoglycaemia in the groups described above, which could not be controlled for. Future studies with a larger sample to include more patients with hypoglycaemic events are encouraged, in order to look at what specific aspects of the GC methods implemented can increase the odds of developing hypoglycaemia at any time during a patient's admission in the ICU, while controlling for relevant confounders.

6.5.6 Association between outcomes of glycaemic control and glycaemic monitoring frequency

6.5.6.1 Monitoring methods implemented

The monitoring of glycaemic levels constitutes the basis of any strategy for GC. The values of glycaemic levels are used to make judgements on patients' status, and to determine their management. Poor glycaemic monitoring can lead to an incorrect assessment of patients and, therefore, to an incorrect management of these patients. Thus, it is paramount for GC that the method for monitoring is reliable, and it is done with a frequency that allows detection of events of dysglycaemia, including hyperglycaemia, hypoglycaemia or high glycaemic variability.

Monitoring technique and blood sample

In this study, it was not possible to determine the actual monitoring technique and blood samples that had been used at each measurement, because of the lack of systematic registration of this information. Such a lack is of special concern in ICU, firstly, for clinical reasons. As it has been discussed in the protocols' review chapter, certain monitoring techniques can be very inaccurate (Inoue et al., 2013; Finfer et al., 2013; Van den Berghe,

2012). For example, results from POC glucometers can be considerably inaccurate in critically ill patients, by even more than 20%, especially when the blood sample is capillary (Van Herpe & Mesotten, 2012). If the glucometers overestimate or underestimate glycaemic levels, hypoglycaemic and hyperglycaemic events could pass undetected and become more severe. Without knowing the blood source and glycaemic monitoring technique, intensivists cannot take into account the (in)accuracy of the measurement when deciding on a treatment plan for a patient.

Knowing the blood source and analysis technique are also important for research purposes, so as to be able to analyse separately BG values obtained with different monitoring methods, as has been recommended by experts in the field (Finfer et al., 2013). This was not possible in GlyCon study, and one of the limitations was that all BG values had to be analysed together, regardless of the blood source. This approach was also taken in a number of previous studies on GC, although the BG measurement technique used is often not reported in the literature (Wahl, 2009). For example, in a recent large retrospective study on the detrimental effects of low TIR on survival (Krinsley & Preiser, 2015), different blood sources were analysed together with this approximate distribution of 80% capillary, 10% venous and 10% arterial (J. Krinsley, personal communication via email, 2016).

Being a limitation encountered early on in this study, the lack of registration of monitoring technique and blood sample source was also one of the first opportunities of GlyCon study to make recommendations for improvement. Recording this information in the patients' medical records will, not only increase the quality of future observational studies on GC such as GlyCon, but it will also improve clinical judgements potentially leading to better effectiveness and safety of GC, and therefore the quality of care provided.

Monitoring intervals

The monitoring time intervals identified in GlyCon were often large and, frequently, they did not reflect what was recommended by the protocol. This resulted in rates of non-adherence to monitoring intervals, often in the form of delayed measurements, which occurred in up to 93% and 86% of the total hours per protocol-hospital, among patients without and with diabetes, respectively (Figure 6.22). To put this into clinical context, in the GlyCon survey of professionals, 85% of respondents rated a BG missed once as a minor deviation from their protocol. They also pointed out that level of stability of patients' glycaemic levels, whether the patient was receiving insulin, and any situation that would make BG monitoring difficult at a specific moment, were contextual factors that could justify the need to deviate from protocol instructions. Also, nursing ICU staff tend to be concerned about patients' discomfort during GC, and about having to perform multiple finger sticks per day to each

patient (Aragon, 2006; Bland et al., 2005). This could have contributed to the lower monitoring frequency than specified, as found in GlyCon study.

As expected, patients' BG was monitored more frequently following measurements outside the study glycaemic target range (4-10mmol/L), especially during hypoglycaemia, followed by the periods of hyperglycaemia>10. However, even when they were outside this target range, monitoring was often done every two or more hours, in all ICUs, and regardless of whether patients had a history of diabetes. In addition, in all ICUs there were some occasions where patients spent more than eight hours without being monitored. While none of these occasions followed a BG measurement in hypoglycaemia, some of them happened after a measurement of hyperglycaemia>10mmol/L.

These results suggest a higher fear for hypoglycaemia than for hyperglycaemia>10, probably influenced by the increasing evidence about the detrimental effects of hypoglycaemia during recent years (Goto et al., 2013; NICE-SUGAR Study Investigators et al., 2012). However, it is not right to neglect hyperglycaemia, as the negative effects of this condition are also well documented, particularly when BG exceeds 10mmol/L (Krinsley & Preiser, 2015). Also, an assumed stability of glycaemic levels, once they have reached certain levels, is probably the main reason behind the decrease in the monitoring frequency following a measurement within the study target range. In addition, this decrease relieves nurses from some of their high workload, and also reduces some costs (Preiser et al., 2016). However, as has been illustrated in the BG time-history plots of some of the patients of this study (Figure 6.27), hyperglycaemia can occur even after periods of stability. Moreover, stress hyperglycaemia can occur during both the acute and the chronic phases (Vanhorebeek et al., 2006). Therefore, it is risky to assume glycaemic stability and relax the monitoring frequency before the critical condition has been resolved.

GlyCon study results also indicate a higher concern among ICU staff for keeping patients with diabetes monitored more closely, as these patients were monitored significantly more often than patients without diabetes, in all glycaemic statuses. Similarly, in a multi-centre survey on the opinions of ICU clinicians, patients with diabetes were identified as the sub-group of highest concern regarding the need to avoid hyperglycaemia (McMullin et al., 2004). Also, in two of the GlyCon ICUs (H-100 and H-200), P-2.1 for patients with diabetes recommended a more frequent monitoring than protocol P-1.1 for patients without diabetes, in certain situations (Table 4.1 and Figure 4.6). However, it is known that patients without diabetes are more vulnerable to events of hyperglycaemia (Krinsley et al., 2013; Egi et al., 2008) and to lower TIR (Krinsley & Preiser, 2015), than patients with diabetes. Therefore, the approach of monitoring patients' BG more frequently if they have a known history of diabetes is not necessarily justified and deserves further investigation. Protocols for GC

should emphasise the clinical importance for monitoring glycaemic levels for all patients, regardless of whether they have diabetes. This should help to reduce these differences in monitoring frequencies, and thus improve the quality of the care provided.

6.5.6.2 Monitoring frequency and effectiveness of glycaemic control

The effects of the monitoring frequency on the effectiveness of GC was analysed by looking at the effect of having had a median TNM during hyperglycaemia>10 of two hours or less. Results of the multivariate analyses did not show a significant effect on the odds of IR, for both groups of diabetic status, and for all the periods of interest considered. As described at the beginning of this discussion, due to the double role of BG levels as both determinants and consequences of the monitoring frequency, the risk of not being able to confirm the study hypothesis that more frequent monitoring during hyperglycaemia would be associated with better glycaemic control, was known before the analyses were conducted. Future studies may be able to confirm this GlyCon study hypothesis, regarding the frequency of monitoring, if they have larger sample sizes, and they can stratify patients by admission diagnosis. This would require a larger research team, and, if possible a prospective design.

6.5.6.3 Monitoring frequency and efficiency of glycaemic control

One of the key and novel findings of the analyses was the positive effect that a more frequent monitoring had on time-efficiency among patients without diabetes. A median TNM of two hours or less during the TTR period significantly reduced TTR among these patients, bringing them back to range faster. As with other results in this and any study using linear interpolation to impute glycaemic data, this result could have been affected by the imputation. Nonetheless, the median patient-TNM in patients without diabetes was 2.0 (2.0-3.0), which means that they were often monitored every two or three hours. Hence the risk of bias on the time-efficiency results due to the imputation method was not considered as high, since actual measured BG values were fairly frequent and periods with imputed BG were consequently shorter during the TTR period than in other periods.

Among patients with diabetes, on the other hand, the median monitoring frequency did not show a significant effect on the outcome. This suggests that, regardless of how often these patients were monitored, it was equally challenging to bring their BG back to range.

6.5.7 Association between outcomes of glycaemic control and the treatment with insulin

6.5.7.1 The treatment with insulin implemented

Insulin can be lifesaving for patients with stress hyperglycaemia (Van den Berghe, 2013) but it is also a high risk drug that can cause hypoglycaemia which, if severe, could even be fatal (Marik & Preiser, 2010). Therefore, it is crucial to implement an insulin algorithm that is both safe and effective in each patient. Among the main findings of GlyCon were the incidence of a number of unexpected results regarding the dosages and duration of the insulin treatment, which were difficult to explain with the available data. There were also significant differences in the dosages and duration of the insulin treatment within the same glycaemic status, depending on the protocol-hospital and on the patients' history of diabetes.

Insulin type

All ICUs used a fast-acting or regular insulin (Actrapid®), administered continuously and intravenously. Whether Actrapid® is the optimal insulin type to treat stress hyperglycaemia in critically ill patients has not been investigated, and thus further studies are currently needed. This issue has been discussed in the protocols' review chapter.

Insulin during hyperglycaemia>10

Among the unexpected results emerging from this study, was the high incidence of patients (in 53% patients without diabetes and 44% patients with diabetes) who did not receive insulin for two or more hours during hyperglycaemia>10, despite some type of feeding being in place. Based on the ICUs' protocols, insulin should have been administered in all these cases. On average, when insulin was under-administered, the deviation from the doses specified in the protocols ranged from 1.1U/h to 3.6U/h among patients without diabetes, and from 0.5U/h to 3.3U/h among patients with diabetes (see Section 6.5.7.2 for a more detailed discussion on adherence to insulin instructions). It is possible that the need to prioritise other interventions led to insulin not being administered in these cases of hyperglycaemia>10. However, the professionals' views obtained from the GlyCon survey are also telling. Just under half of the survey respondents considered that "an insulin infusion restarted two or less hours late" constituted only a minor deviation from protocol instructions. This calls for future prospective or survey studies to ascertain whether such professionals' views could be affecting their practice in not adhering to protocol instructions on insulin administration.

It also seemed counter-intuitive that in a number of instances the average insulin dosages per patient, and the percentage of time receiving insulin, were lower during hyperglycaemia>10

than during hours at lower glycaemic levels. The reason for this could be related to the fact that the BG levels triggering the start of the treatment with insulin were lower than 10mmol/L in most protocols, and in about half of the protocol-hospitals the upper limit of their glycaemic target was lower than the GlyCon study target's upper limit (10mmol/L). Since periods of BG<10mmol/L were longer that periods of hyperglycaemia>10, *ad hoc* increases in the insulin dosages, to reach the protocol-hospital's own target, could have resulted in higher mean dosage and/or duration of insulin treatment during periods of BG<10mmol/L than during periods of hyperglycaemia>10.

The GlyCon results indicate that ICU staff often delayed the start of a treatment with insulin, especially among patients without diabetes, which according to protocols should either not occur, or occur for a maximum of one hour (when they are waiting for a second BG that confirms hyperglycaemia). However, they may also indicate a possible occurrence of incorrect insulin titrations which, as highlighted by one of the professionals in the GlyCon survey, is considered as a "drug error". Regardless of whether these are voluntary decisions or involuntary errors, taking into account the detrimental effects of TIR in all patients (Penning et al., 2015; Omar et al., 2015), and particularly in those who do not have a previous diagnosis of diabetes (Krinsley & Preiser, 2015), these results are of some concern and deserve further investigation.

Insulin during hypoglycaemia

The administration of insulin during hypoglycaemia was an unexpected result among the cases from protocol-hospitals that do not recommend insulin during hypoglycaemia. Moreover, there were 10 patients (including eight with diabetes) who, besides receiving insulin during hypoglycaemia, often with dosages of 3U/h or higher, had no nutritional support in place for some time. These could have been cases of iatrogenic hypoglycaemia. For patients with diabetes these events are of even higher concern as even moderate hypoglycaemia would represent a larger drop from their usual BG levels than for patients without diabetes.

On one hand, these patients may have been receiving some type of glucose-based fluid during those hours, information that in GlyCon study was not possible to control for. However, given the high dosages of insulin often administered, the fact that there was more than one occasion per patient, including from hospitals where insulin is instructed to be stopped during hypoglycaemia, and the potentially highly detrimental effects of hypoglycaemia (Ancona et al., 2011; Krinsley & Grover, 2007; Van den Berghe, Wilmer, Hermans, et al., 2006; Finney et al., 2004; Van den Berghe et al., 2001), these results raised some concern about the occurrence of protocol deviations that may be unsafe for patients. As

above, these issues could not be explored with GlyCon study and need further research focused on trying to understand the reasons for these types of cases, and whether they are justified.

Insulin treatment and diabetes

Among patients with diabetes, most insulin dosages when they were in hyperglycaemia>10, and a great part of dosages when they were in the study target glycaemia, were higher than 4U/h. This increases the risk of having a very high average cumulative insulin level, and average cumulative insulin that exceeds 100U/day has been associated with higher hospital mortality risk (Rady et al., 2005). GC methods that could reduce the need for very high insulin infusion rates are recommended. Among these are the implementation of algorithms that are based on the prediction of BG, rather than on reactions to BG levels (Amrein et al., 2014), or algorithms that estimate patients' insulin sensitivity and consider the trend of BG levels over time (Le et al., 2013); as well as better synchronisation of insulin dosages with the rates of exogenously administered glucose (Mesotten et al., 2015; Shaw et al., 2014).

Although only three GlyCon ICUs implemented different protocol instructions for patients with and without diabetes, the significantly higher IIRs among patients with diabetes, during all glycaemic statuses, were not unexpected, as patients with diabetes have been found to require higher doses of insulin to achieve similar glycaemic levels, as compared with those without diabetes (Rady et al., 2005). Also, insulin dosages had a markedly higher variability among patients with than those without diabetes. This was also expected as patients with diabetes spent considerably higher percentages of time in hyperglycaemia, and they had higher and more varied BG values, than patients without diabetes.

Nonetheless, patients with diabetes also spent significantly higher percentages of time in hyperglycaemia>10 receiving insulin, than patients without diabetes. This again suggests a higher concern about the treatment of stress hyperglycaemia in patients with diabetes, despite the documented higher vulnerability to the negative effects of stress hyperglycaemia of patients without diabetes (Krinsley & Preiser, 2015; Krinsley et al., 2013; Egi et al., 2008).

The significant differences in the insulin dosages between protocol-hospitals, regardless of the presence of diabetes, were also expected, as all protocols differed greatly in their insulin titration algorithms. However, the durations of the insulin treatment during hours within the study target differed significantly between protocol-hospitals only among patients without diabetes. This suggests that diabetes may trigger a more constant concern for the need to administer insulin, regardless of the protocol-hospital.

Hypoglycaemic agents

Despite the fact that only the protocols of three ICUs instructed staff to consider the treatment that individual patients with diabetes normally received, hypoglycaemic agents other than Actrapid® were given to at least one patient with diabetes in each of six out of the seven ICUs. Nonetheless, less than a third of the patients with diabetes received these drugs, and in most cases only in a small number of hours. Including instructions about how to deal with the usual treatment of patients with diabetes would increase the completeness of protocols, and help with the provision of equal care among these patients.

6.5.7.2 Insulin treatment implemented vs. protocol instructions

Adherence to insulin instructions in patients without diabetes

Among patients without diabetes, the proportion of hours with some type of non-adherence to insulin instructions ranged from 2% to 78%, depending on the protocol-hospital. In all protocol-hospitals, it was more common to find lower dosages than specified rather than higher dosages (Figure 6.21) and, if the protocol dosage was exceeded, the difference was small. This is in line with the general concerns of ICU professionals, who tend to have a greater fear of hypoglycaemia than of prolonged hyperglycaemia (NICE-SUGAR Study Investigators et al., 2012; Faust et al., 2011; Ancona et al., 2011; Krinsley & Keegan, 2010). The fact that in most GlyCon protocols titration adjustments are based on 0.5 or 1U/h steps might also increase nurses' fear of hypoglycaemic events. Protocols that permit insulin dosage adjustment in smaller steps, such as 0.1U/h, have been suggested as a means for improving adherence (Bland et al., 2005). With this regard, one of the respondents to the GlyCon survey described recurrent iatrogenic hypoglycaemia caused by "excessive or overenthusiastic insulin regimes" as a major issue that has "significant negative impact on outcomes". Also, 48% professionals rated an insulin titration missed or done incorrectly once as "minor" non-adherence, and 30% professionals rated an insulin infusion restarted two or less hours late also as "minor" non-adherence. This indicates a degree of flexibility among some professionals' approach with regard to adhering to the insulin instructions. Nonetheless, many professionals also pointed out the importance of considering the context and a number of patient-related factors, which could make the deviation less serious, or simply unavoidable.

Adherence to insulin instructions in patients with diabetes

Among patients with diabetes, the proportion of hours with some type of non-adherence to insulin instructions was generally higher than among patients without diabetes, ranging from 37% to 96%, depending on the protocol-hospital. Among these there were high percentages

of hours (1-49%) in which higher insulin dosages than specified were administered, although this did not lead to a significantly higher incidence of hypoglycaemia, as compared with patients without diabetes. Moreover, given that most ICUs do not have different protocols for patients with diabetes, and since patients with diabetes need more insulin to achieve the same effect as those without diabetes (Rady et al., 2005), it was not surprising that ICU staff often did not adhere to their protocol's insulin dosages instructions for these patients. In fact, some of the professionals answering the GlyCon survey indicated a history of insulin dependent diabetes mellitus as a possible justification for deviating from the protocols' instructions.

This finding supports the idea that a "one fits all" algorithm is not sensible in patients with diabetes, and that, as has been suggested by Wernerman et al. (2014), insulin algorithms should account for the different patient profiles and needs of different patient populations, as well as for other therapeutic interventions.

Adherence to insulin instructions in patients with diabetes in hospital 100

In H-100, the incidence of non-adherence to the insulin dosages indicated in P-2.2 were almost twice as large as those in P-2.1, including either giving more or giving less insulin than specified. Both protocols were for patients with diabetes. P-2.1 had been implemented in H-100 for more than six years up until June 2012. P-2.2 was newly introduced in July 2012 (six months after commencement of the GlyCon study 2-year period of interest). Compared with P-2.2, the earlier P-2.1 had a lower glycaemic target, infusion of insulin started at lower BG levels, and the insulin dosages recommended had higher maximum rates. Therefore, the higher incidence of over-administration of insulin in P-2.2 could be due to a phase of adaptation of the ICU staff, as they moved from P-2.1 to the lower dosage P-2.2. Nonetheless, the elapsed time since the release of a set of recommendations has been found to not significantly affect the level of compliance to them (Grilli & Lomas, 1994). In addition, there was also a higher percentages of hours in which less insulin than specified was administered when the new protocol (P-2.2) was implemented. Another possible explanation for the significantly higher percentage of non-adherences to insulin administration with the new protocol could be the emergence of a more flexible view of GC among the ICU staff of H-100, triggered by the implementation of a protocol with a looser glycaemic target and insulin algorithm.

Adherence and characteristics of the protocols

Among patients without diabetes, the highest levels of adherence to insulin instructions occurred with two protocols (P-1.1 and P-1.2), both implemented in two of the largest ICUs (H-100 and H-200). One of these protocols (P-1.1) was based on older evidence and did not

describe its development methods, while the other was based on more recent evidence and provided details about its development methods (Table 4.1). They were the two longest protocols, in terms of word count, and they considered the highest total numbers of scenarios. In addition, they were among the most complex protocols, in terms of the average number of processes and decisions that each of their glycaemic scenarios had; and the scenarios of P-1.2 covered a wide variety of themes (Table 4.3 and Table 4.4).

Although the association of these protocol characteristics with adherence was not studied in GlyCon, it is possible that the level of complexity and comprehensiveness of the protocols played a role in increasing the level of staff adherence to their instructions, while the up-to-datedness of their evidence base was not so influential. This would be worth investigating in future studies, by comparing different protocols implemented in the same ICU, since this suggestion seems to counter previous evidence concluding that recommendations of clinical guidelines that are evidence based, concrete and precise, easy to follow, and not complex, could improve adherence (Francke et al., 2008; Burgers et al., 2003; Grol et al., 1998).

Adherence in the context of the ICU

The ICU is a very specialised and complex hospital service, where patients are admitted with very severe conditions, usually life-threatening (Mitchell, 2010). Clinical protocols are developed to help clinicians with the decisions they make about the treatment and care of a patient, and to avoid inequality of care. However, such protocols should not constrain clinical judgements, and individual clinical expertise should be integrated with evidence-based protocols, so that the care can be adapted to each patient's particular needs (NHS Institute for Innovation and Improvement, 2008). Indeed, as mentioned in the protocols review Chapter 4, some of the GlyCon study protocols specifically stated that it was the clinician's responsibility to decide how to interpret and apply the protocol. Moreover, most protocols indicated that the insulin or other instructions should be modified if needed, for example, depending on the patient's underlying condition, severity, or the treatment provided. In fact, these were also factors that respondents to the GlyCon survey described as possible reasons that would justify the need to deviate from protocols' instructions.

Due to the retrospective nature of the study, it was not possible to identify which non-adherences were a voluntary decision, or which were an involuntary omission. However, as discussed earlier (see section 6.5.5.1), not adhering to the insulin dosages instructed by one of the protocols was found to be detrimental for its patients with diabetes, by decreasing their odds of being controlled within the study glycaemic target range in the

following hour. This is an important and novel finding of GlyCon study that demonstrates the positive impact that instructions of protocols for GC can have.

6.5.7.3 Insulin treatment and effectiveness of glycaemic control

Percentage of time receiving insulin during hyperglycaemia>10

One of the key findings in this study about the effectiveness of GC was that having received insulin for more than the group median 20% of the time spent in hyperglycaemia>10 had a beneficial effect, among patients without diabetes. Patients without diabetes who received insulin for less than 20% of the time in hyperglycaemia>10 had lower odds of IR at any time, when the whole LOS in ICU was considered. Similarly, in their prospective study on GC in cardiac surgery patients, Carr et al. (2005) had also found the percentage of time that patients spent with BG<7.2mmol/L increased when the threshold for initiation of insulin was lower, which means that the time spent receiving insulin during hyperglycaemia would probably have increased.

On the other hand, when considering only the first two to six days of admission, receiving insulin for more than 20% of the time in hyperglycaemia>10 was not significantly associated with the odds of IR. This suggests that the benefits of receiving insulin during hyperglycaemia for longer percentages of time may be more relevant in long-stay patients, and only after the first few (six in the case of GlyCon) days of admission. A different effect of the insulin therapy depending on the history of diabetes and the length of stay in the ICU was suggested by Van den Berghe, Wilmer, Millants et al. (2006) based on data from their two landmark trials on IIT (Van den Berghe, Wilmer, Hermans, et al., 2006; Van den Berghe et al., 2001). These authors concluded that the benefits of IIT (in terms of lower mortality and morbidity) occurred only among patients without diabetes and only if they had a long stay, which they defined as a LOS≥3days. Future studies could explore how and why the effect of the percentage of time receiving insulin on the odds of IR may change over time, as suggested by GlyCon results.

Among patients with diabetes, being in the group of patients who received insulin during hyperglycaemia>10 for a percentage of time higher than the group median 75% did not have a significant effect in any of the periods of interest considered. On the other hand, the time-dependent variable on the hourly dosage of insulin increased the odds of IR in the following hour, when the whole length of stay was considered. Hence, in these patients, the dosage of insulin played a role, while the duration of the treatment, in terms of the percentage of hours spent under treatment, did not.

While it was not unexpected, the positive effect that higher insulin dosages had by increasing the odds of bringing the patient back to range, was also an important finding of GlyCon. Previous studies have reported results that were opposite to this finding (Oeyen et al., 2007; Thomas et al., 2005). In particular, Thomas et al. (2005) used a mixed model to analyse the effect of different factors on the odds of IR, and found that the use of insulin actually reduced the odds of having a BG below 8mmol/L at each available BG. However, these authors did not specify whether they had considered a minimum time lag between the time of insulin use and the available BG value. Similarly, Oeyen et al. (2007) found that the total insulin dose per day was negatively associated with the TIR at BG levels within 4.5-6.1mmol/L.

Although the half-life of insulin in the blood stream is of a few minutes (European Medicines Agency, 2016), dosages are usually administered over one hour. This could be the reason why in the GlyCon study it was possible to identify a positive effect of the insulin rate administered on the odds of IR one hour after the start of titration. Therefore, the GlyCon approach of including a one-hour lag between the time of insulin administration and the available BG value is recommended for future studies with the same aim of exploring the effects of the hourly insulin dosage on bringing or keeping the patient within the glycaemic target.

The reason why patients without diabetes had a different result from patients with diabetes could be related to their higher insulin sensitivity. Given their existing co-morbid insulin resistance, in patients with type-2 diabetes (which represented most of the patients with diabetes in this study) it may be the last insulin dose, rather than the relative duration of the treatment, that actually makes a difference in bringing or keeping the patient within the glycaemic target. In long-stay patients without diabetes, meanwhile, receiving insulin for at least 20% time while they had hyperglycaemia>10, could have been enough to improve their likelihood of being within the target after the first few days of admission. With this regard, in their large retrospective study of 10320 patients, Sechterberger et al. (2013) found that, while both groups of diabetes achieved the same overall mean BG, almost all (98%) patients with diabetes required insulin during their stay and with significantly higher dosages (median[IQR]=2.8[2-4]U/h), while only 77% patients without diabetes needed insulin during their stay, and at lower dosages (median[IQR]=2.2[1.7-3.1]U/h).

6.5.7.4 Insulin treatment and efficiency of glycaemic control

Patients without diabetes who were given insulin at some point during TTR, and patients with diabetes who received insulin for more than half of the TTR period, had significantly longer TTRs (i.e., lower time-efficiency), on average. These results do not confirm the study

hypothesis associating longer periods receiving insulin during TTR with shorter TTR durations. The risk of not being able to confirm this hypothesis was known in advance, due to the bidirectional relationship between exposure and outcome, as has been discussed earlier.

6.5.8 Association between outcomes of glycaemic control and nutrition, relevant medications and other covariates

6.5.8.1 Nutrition and effectiveness of glycaemic control

In each ICU, there were different types of enteral and parenteral nutritional preparations that could be prescribed depending on the patient needs, some of the preparations having a higher caloric content than others. The amount of energy given to patients, especially in the form of glucose calories, has a direct strong effect on their BG levels, and is an influential aspect that should ideally be controlled for (Mesotten et al., 2015).

The frequent missing information in the medical records about the EN (missing in 59.7% of the hours) and TPN (missing in 15.6% of the hours) preparation types that were administered to the patients of this study, meant that the food energy administered to patients often could not be calculated. Since some types of nutrition could have considerably higher kilocalories per millilitre, the volume of nutrition administered per hour was not a good surrogate for the hourly energy given. In addition, information on the amounts of glucose-based fluids administered, which are also an important source of energy through the direct infusion of glucose, was also unavailable for most of the time.

As a consequence of this lack of information, including the variables about the EN and TPN non-protein kcal/h in the final multivariate model of the effectiveness of GC would have caused that all the observations occurring during the 59.7% and 15.6% hours of missing data were dropped. Hence, these variables were not included in the final model. However, their effect was explored in sub-analyses including only the hours with available data, so as to have an indication of the effects of the EN and TPN energy, while controlling for other covariates.

Results from these sub-analyses indicated that in patients without diabetes, the amount of non-protein energy given at each hour via EN can have a significant negative effect on the odds of IR in the following hour, in all periods considered except for the first 48 hours after admission. In these first two days, associations were not statistically significant. The TPN energy also seemed to have a detrimental effect on the odds of IR, but only when the whole ICU stay was considered. These results were expected, as it is known that the nutritional support provided to ICU patients has a strong direct effect on their glycaemic levels

(Mesotten et al., 2015). Thomas et al. (2005) had also found that the administration of TPN was associated with a decrease in the odds of having a BG below 8mmol/L.

Among patients with diabetes, EN and TPN nutrition did not show a significant effect on the outcome in any of the periods considered. This may indicate that, as opposed to what happened in patients without diabetes, a decrease in the amount of energy administered hourly did not seem to make it easier to bring patients with diabetes back to range in the following hour. However, given the large amount of missing data, these results could have been biased, and hence they must be interpreted with caution.

The lack of information about the EN and TPN preparation types was a critical limitation in the analyses of association, but this also presented an important opportunity for suggesting improvements for the quality of GC. The documentation and storage of this information within the records is recommended as it would not only benefit future studies like GlyCon, but, more importantly, it would facilitate the clinical use of this information by ICU professionals to provide better GC of their patients. What is clear is that it is important that the amount of non-protein calories is taken into account by GC protocols when recommending insulin titration levels.

6.5.8.2 Propofol, catecholamines and glucocorticoids, and effectiveness of glycaemic control

Propofol

Four out of every five patients were sedated with propofol, for different durations, although sometimes it was for most of their stay. Given that propofol provides 1.1 lipid kcals per mL of infusion, and that it had been previously associated with higher odds of poor GC (Rady et al., 2005), it was a factor that had to be controlled for in the analyses. However, in the multivariate analyses the hourly propofol energy provided was not found significantly associated with the odds of IR in the following hour. These results indicate that the effect of the dosage of propofol may not be as strong as previously suggested. However, given its caloric content, and the fact that there were other factors that could not be controlled for in this study and could have compensated for the effect of propofol (for example, higher nutritional calories in patients with lower propofol dosages), it cannot be concluded that the dosage of propofol should be disregarded in future studies, or in clinical practice.

Catecholamines

Exogenously administered catecholamines, including adrenaline, noradrenaline, or dopamine (Rady et al., 2005; Thomas et al., 2005; Cely et al., 2004) have been found to affect

glycaemic levels, and hence the TIR, by inducing the same effects as the natural hormones (Pretty et al., 2011).

In GlyCon, exogenous catecholamines were administered to more than 80% patients, with variable durations that could be of up to the whole ICU stay. In the multivariate analyses the dosage of noradrenaline did not show a significant effect on the odds of IR in the following hour, while the dosage of adrenaline was found to decrease the odds of IR in the following hour, in both groups of diabetic status. Among patients without diabetes this association between adrenaline and outcome was found in all periods of interest, while amongst the patients with diabetes this was found only during the first six days and the first two days of admission.

The increase in BG levels associated with the treatment with adrenaline was expected due to the adrenaline mediated insulin resistance, gluconeogenesis and glycogenolysis (Preiser & Straaten, 2016; E. Barth et al., 2007). The hepatic and renal endogenous production of glucose, stimulated by the adrenaline infusion, have been identified as the major source of endogenous glucose during critical illness (Mazeraud et al., 2014). The reason why the noradrenaline dosage was not associated with the odds of IR while adrenaline was, could be related to the stronger hyperglycaemic effect of adrenaline, as suggested by Levy (2005). Cely et al. (2004) had found that the dosages of noradrenaline were an independent determinant factor of poor GC, but they had related them to the time spent at very high hyperglycaemic levels, which were higher than the 10mmol/L threshold for hyperglycaemia used in GlyCon study.

The dosage of dobutamine showed a small but significant beneficial effect on the odds of IR in the following hour, among patients without diabetes only, and only when the whole ICU stay was included. Although this finding has not been reported in previous literature on the effectiveness of GC, this result was not surprising, as dobutamine metabolic effects are moderate (E. Barth et al., 2007), and they can even decrease glycaemic levels by reducing the rate of endogenous gluconeogenesis (Smith et al., 2011).

The GlyCon results suggest that considering the administration of adrenaline, but not of noradrenaline, in the adjustment of insulin dosages can make GC more effective. On the other hand, although the effect of the dobutamine dosage was significant, it was small and, thus, controlling such dosage in insulin titrations might not be worth the effort. Nonetheless, the potential hypoglycaemic effect of dobutamine should be kept in mind and, particularly when BG is low, the monitoring frequency should be increased if dobutamine is being administered.

Glucocorticoids

As for catecholamines, glucocorticoids administered to critically ill patients have been found to affect glycaemic levels (Rady et al., 2005; Cely et al., 2004), and hence the TIR, by inducing the same effects as the natural hormones (Pretty et al., 2011). In GlyCon study, the dosage of hydrocortisone showed a small but significant negative effect on the odds of IR in the following hour, in all periods of interest considered in this study, although only among patients with diabetes. This confirms the findings of previous studies which also associated the administration of corticoids with higher risk of developing hyperglycaemia (Annane et al., 2015), and with poorer GC in terms of the time spent in different glycaemic targets (Rady et al., 2005; Cely et al., 2004; Zimmerman et al., 2004).

It is not clear why among patients without diabetes the dosage of hydrocortisone did not affect the odds of IR. Previous studies that associated the treatment with corticoids with lower percentages of time spent within the target range, had thresholds defining hyperglycaemia (8 or 8.3mmol/L) which were lower than the threshold used in GlyCon study (10mmol/L). It could be that hydrocortisone had a hyperglycaemic effect in patients without diabetes, but at lower glycaemic levels than 10mmol/L. Future studies exploring the effect of these drugs on different levels of hyperglycaemia are suggested to clarify this finding. Nonetheless, given their negative effect found among patients with diabetes of GlyCon study, as well as their detrimental effect on all patients found in previous studies, it is still advisable to consider concomitant administration of hydrocortisone and other glucocorticoids when managing GC.

In conclusion, GlyCon findings confirmed that the concomitant treatment of patients should be taken into account when planning and implementing methods for GC of stress hyperglycaemia in intensive care. This should involve not only *ad hoc* increases in the BG monitoring frequency and insulin dosages, but also a formalisation in the protocols suggesting adjustments to insulin dosages if glycaemic levels increase following the start of a new treatment with adrenaline, hydrocortisone and, possibly, noradrenaline, propofol and other glucocorticoids.

6.5.8.3 Other covariates and effectiveness of glycaemic control

Severity of each hyperglycaemic event

As expected, in all periods of interest, and all groups of patients, the severity of each hyperglycaemic event, as measured by the glycaemic exceedance above 10mmol/L, had a strong significant negative effect on the odds of IR in the following hour. Controlling for this exceedance was fundamental, as not all hyperglycaemias are the same, and too high

hyperglycaemias may be an indication of higher levels of severity. It is recommended that in events of high hyperglycaemic exceedances, an even stronger emphasis is put in the methods for GC implemented in the ICU. Similarly, future similar longitudinal studies should use this metric to control for the severity of hyperglycaemic events.

Level of severity on admission

Among the potential confounders included in this study, two indicators of the level of severity on admission showed a significant negative effect on the odds of IR at any time, when the whole admission time was considered. On average, the higher the ICNARC severity score on admission in patients without diabetes, and the higher the "highest BG on admission" among patients with diabetes, the lower was the odds of IR at any time. When only the first two days or the first six days of admission where considered, none of these indicators of severity showed a significant effect on the odds of IR at any time, in any of the patient groups. This suggests that, on average, patients were doing better towards the end of their ICU stay if, on admission, they had lower severity scores. Similarly, other studies have found that a high APACHE II score on admission (Shulman et al., 2007), or a first BG on admission higher than 11.1mmol/L (Carr et al., 2005) were significantly associated with lower TIRs at each of the study's respective glycaemic targets. Moreover, different studies have shown that high glycaemic levels on admission are associated with worse outcomes, including higher risks of congestive heart failure among patients with AMI (Papak & Kansagara, 2012); and higher mortality risks in patients with AMI (Papak & Kansagara, 2012) and in sepsis patients (van Vught et al., 2016). This indicates that implementing effective methods for GC can be more challenging among patients who are more severe on admission, but given their potentially detrimental effects, special attention should be given to the GC of these patients.

Length of stay

Patients without diabetes improved their odds of IR with time (7% [95%CI=3-11%] higher odds of IR with every additional day), in all periods of interest considered in this study. On the other hand, among patients with diabetes time did not have a significant effect on the outcome. Similarly, Thomas et al. (2005) found that for every additional day in the ICU, the odds for achieving BG<8mmol/L increased by 4% (95%CI=3-5%), but their analyses were not stratified by diabetic status.

The reason why in patients with diabetes the cumulative time spent in the ICU did not seem to affect the effectiveness of GC is not clear. Patients with diabetes were significantly more severe on admission, as indicated by their higher APACHE II score (Table 6.12). This, combined with their existing permanent insulin resistance, could be related to their worse

response to GC methods. Therefore, it seems necessary that a sustained GC strategy is implemented during the whole ICU stay, including at later stages.

6.5.9 Protocol adherence: actual practice vs. protocol instructions

The low levels of adherence found in this study, and their possible implications in protocol evaluations, have been emphasised several times throughout this discussion.

Previous studies have also found that full adherence with guidelines is rare and not easy to achieve (J.-C. Orban et al., 2013; Kanji et al., 2010; Malesker et al., 2007; Shulman et al., 2007). Malesker et al. (2007) found that approximately 75% BG measurements were associated with some protocol deviation, including deviations from the monitoring timing (which was the most frequent deviation) and the insulin dosages, among others. Kanji et al. (2010) found 0.1 to 9.6% hours of non-adherence to IIRs, and 12% to 92% delayed BG measurements per day. Shulman et al. (2007) found a median percentage of non-adherence to the monitoring time intervals of 47.0% (32.9% to 59.0%) of the measurements. The relative non-adherence levels found in GlyCon study were similar or higher to those cited here.

The existing discrepant evidence, the lack of standardised guidelines, and the existence of numerous protocols for GC, which vary between hospitals, may be among the factors causing a low adherence of professionals to protocol instructions for GC (Evans et al., 2011). However, the responses to the GlyCon survey also indicates that professionals consider it appropriate, or even necessary, to deviate from protocol instructions under certain circumstances. Studying the reasons for these non-adherences, and whether they were intentional or accidental errors, was beyond the scope of this study, but are important aims to be considered for future studies.

Besides confirming previous evidence regarding low levels of adherence to clinical protocols in the ICU, these GlyCon findings reinforce the relevance of the study, in which the main exposures of interest investigated were directly derived from the actual clinical practice, rather than just considering the impact of the protocol implementation as a whole.

6.5.10 Methodological considerations

6.5.10.1 Study sample

The final sample of the GlyCon study represented 16% of the population of eligible individuals, and it did not differ significantly in any of the demographic and clinical variables from the rest of eligible patients who were not in the final sample. This made the

sample a good representation of the population of interest in the study, which was the eligible patients admitted to a delimited geographical area within the UK (Mid Trent area). It was not possible to determine whether the patients included in GlyCon study were representative of the population at the national or larger levels, due to unavailability of such data.

Information on the diabetic status of the target population was not available at the time of the sample selection for this study. These data had to be retrieved from patients' medical records, once the sample had been chosen and the records had been received. Consequently, the sample could not be selected stratified by previous diagnosis of diabetes. Previous studies have reported very varied values of the prevalence of diabetes among critically ill patients. In a large study involving 44,964 patients admitted to 23 ICUs from nine countries, Krinsley et al. (2013) found a prevalence of 28.6% patients with a history of diabetes. Barth et al. (2007) found percentages of diabetes among surgical, medical and cardiac critically ill patients ranging from 30% to 61%, depending on the patient population group. In addition, different geographical areas have different prevalence of diabetes (Shaw et al., 2010) and, hence, it was not possible to determine whether the prevalence of diabetes of 37% found in GlyCon differs significantly from that of the target population in the UK.

The main inclusion criterion of the study was having had BG measurement above 10mmol/L at least once during the first 24 hours of admission. There may have been patients who developed stress hyperglycaemia after the first 24 hours of admission. However, for methodological reasons that have been discussed earlier (section 6.2.1.1), those patients could not be represented in this study.

In the GlyCon sample, patients from H-400 had lower mortality rates than in the rest of eligible (not sampled) patients from the same ICU (Table 6.11). Given that all patients included in the sample from this ICU were those selected in the first round of sampling, and no surrogate patients were needed, this difference in the mortality rates was considered a random result, not caused by the sampling technique. In addition, the mortality rate of the final non-stratified sample for the whole cohort was almost identical to the rest of eligible patients who were not the in the final sample. Therefore, these differences have been described and acknowledged, but no statistical procedures, such as giving different weights to deceased patients, were carried out.

Finally, the population group of patients admitted at each of the hospitals was found to differ significantly among patients without diabetes. This is important to consider, because the reason for admission has been found to moderate relationship between stress hyperglycaemia and mortality, with patients admitted for cardiac or cardiovascular reasons being the most

vulnerable patients to stress hyperglycaemia, in terms of a higher mortality risk (Falciglia et al., 2009). While the sample size of this study did not allow stratified analyses by reason for admission, these differences between hospitals were explored descriptively and, when relevant, used in the interpretation of the study results.

6.5.10.2 Missing data

Missing data is a common issue in retrospective studies. The proportions of missing data found in the GlyCon study varied depending on the type of missing data, and looked similar to those found in previous studies (Jones & Farnell, 2007). In GlyCon, the possible reasons for these missing records were explored, and it was concluded that medical charts and notes were missing at random. Investigating these reasons in depth was beyond the scope of this study. Nonetheless, the proportions of incomplete charts (26%) and medical notes (67%) were high, and this raises the question of why this is happening, something which ICUs are encouraged to investigate. Completeness is important for research purposes, but it is even more paramount in clinical practice, as the medical history of patients is often used to make important clinical decisions.

The irregular glycaemic monitoring frequencies in the ICUs of the study showed shorter time-lapses between glycaemic measurements during hypoglycaemia, followed by hyperglycaemia>10. Consequently, there were larger proportions of hours in which BG values were missing and linearly interpolated when the actual measurements were within the study target range, than in the other two glycaemic statuses. These may have led to peaks or nadirs of BG, causing changes to/from different glycaemic statuses, to be missed during those hours when the patient was assumed to be within a safe glycaemic range and BG was not measured (Braithwaite et al., 2013). Thus, it is possible that BG trends were not accurately represented by the linear interpolation (Preiser et al., 2016), especially during such periods of assumed stability. Also, due to the different monitoring frequencies between protocol-hospitals among patients with diabetes, for the same glycaemic scenario, the comparison of the performance between protocol-hospitals could have been biased in these patients by such assumption of linear constant change of BG between measurements.

Among patients with diabetes, P-2.2_H-100 had the highest monitoring frequencies (Figure 6.14). Thus, the lower effectiveness of this protocol-hospital could have been affected by its more frequent monitoring of BG, which would have given it more opportunities for capturing changes to/from glycaemic statuses than other protocol-hospitals. Preiser et al. (2016) have recently described this strong dependency of TIR on the measurement frequency and interpolation method as one of the main limitations of this outcome measure. Nonetheless, until continuous glycaemic monitoring is available and tested in “real life”

conditions, and in the different types of patients and ICUs, the calculations of the outcome measures of time in band/range will inevitably require some sort of imputation of BG values during the non-monitored time. Thus, numerous studies on GC have used linear interpolation of glycaemic levels in their analyses, including for the calculation of the time in band (Krinsley & Preiser, 2015; Signal et al., 2010; Keene et al., 2010; Van Herpe et al., 2008; Boord et al., 2007; Rady et al., 2005), making it possible for GlyCon study results to be directly compared with those of previous studies.

In order to assess the effect of long periods of imputed BG values on the calculated TIR, sensitivity analyses were carried out calculating TIR excluding the hours without any glycaemic measurement for more than eight consecutive hours (TIR-excluding-TNM>8, in Table 6.23). Results showed that, among patients without diabetes, the median TIR-excluding-TNM>8 was only 1% lower than TIR, but the difference was statistically significant. While this was a small reduction of about 1%, it indicates that the calculation of TIR is sensitive to monitoring intervals longer than eight hours and, thus, that it is important to interpret TIR values considering monitoring frequencies.

Among patients with diabetes, meanwhile, TIR-excluding-TNM>8 was actually 1% higher than TIR, and this difference was not statistically significant. Hence it can be concluded that this outcome measure did to seem to be very strongly affected by the occurrences of large monitoring intervals of more than eight hours in these patients. Future studies comparing the TIR calculated from intermittently measured BG at different monitoring frequencies are needed. These should show the level of accuracy of TIR depending on the monitoring frequency. Also, future studies using TIR in their analyses should report the monitoring frequencies along with the results on TIR.

6.5.10.3 Risks of data errors

Data errors, either during their original documentation, or during the data entry of the study, could be behind some of the unexpected results identified. Despite the numerous data quality measures put into place in this study, including a second review of the records and correction of errors, further human errors cannot be excluded. Such human errors during the phases of data collection or extraction are common in these types of studies (Barchard & Pace, 2011).

Errors in the documentation of data during the original clinical encounter, i.e., the data arising out of each unique patient-clinician interaction (Logan et al., 2001), could also be among the causes of some of the unexpected results. These can include errors in registered glycaemic levels, insulin dosages or even in the timing of any of these. For example, Malesker et al. (2007) found that BG results indicating hyperglycaemia and the need for initiating an insulin infusion, were recorded, on average, 52 minutes after the BG meter was

picked up by the hospital staff. Such a delay in documentation, if present, could have affected the results of GlyCon study. For Logan et al. (2001) the clinical encounter data are the data that have the greatest risks for being incorrect, inaccurate or incomplete.

Given the retrospective nature of the study, it was not possible to investigate whether there were errors in the original documentation of data. However, a common adage in clinical practice is "what is not documented is work not done". Assuming that all data were documented correctly, the GlyCon results that were unexpected deserve further investigation.

6.5.10.4 Analyses

The analyses of association between the methods for GC and the odds of IR in this study were novel both in their aim and in the type of analysis. The use of GEEs increased the efficiency of the data, because all data points of the outcome could be used. In addition, it allowed for the inclusion of some time-dependent covariates. Consequently, it also allowed accounting for the frequency of exposure to some of the covariates considered in this study, which is something that often cannot be done with other methods (Preiser et al., 2016), certainly not with a standard linear regression model. This control for potential important confounders, including time-dependent and time-constant ones, increased the internal validity of the study.

On the other hand, GEEs have been found to behave unpredictably, and it has been suggested that their results should be interpreted cautiously (Twisk, 2004). Nonetheless, analyses were performed for six different situations (three periods of interest in two groups of patients, with/without diabetes). While the analyses focusing on shorter periods lost data efficiency and were able to find less statistically significant associations, none of the models contradicted each other, and all results were sensible, as well as, directly or indirectly, in line with previous literature.

It is worth mentioning that, in the multivariate analyses, the standard errors were sometimes high and, hence, the 95% CI of their estimates were wide. Thus, while there is no doubt about the direction of the effects and their statistical significance identified in GlyCon, the sizes of the effects of exposure variables and other covariates found in this study can only be confirmed by studies on larger samples.

The approach followed in GlyCon to analyse the effect of the exposure variables of interest, of monitoring frequency and duration of insulin treatment, used the full history of these exposures summarised in a single value, rather than each of their hourly values, to predict the outcome. This is among the approaches proposed for this type of study (Heagerty & Comstock, 2013). In their manuscript on analysis methods of lagged associations using

longitudinal data, Heagerty et al. (2013) provided a detailed overview of the challenges of this type of data, possible analysis methods depending on the nature of the data and their relationships, as well as the necessary assumptions for them. Among the statistical approaches that the authors describe is that used in GlyCon, which, due to the previously described bidirectional relationship of the methods for GC with the outcome, was considered a plausible approach for this study.

Other available statistical techniques for the analysis of repeated measures, and their association with other covariates, are multilevel or random effects models (MLM). The main focus of MLM is the patient, and MLM of repeated measures usually describe how the outcome changes over time in each patient. This was not the aim of GlyCon. In addition, the study had numerous repeated measures per patient, such that there were often more data points per patient than patients in the sample. According to experts in the field, this would have not been possible to handle with a MLM (I. Burton, personal communication at NCRM course on "Applied Multilevel Modelling", 2015).

In the linear regression models built in this study, between 4.5 and 8 subjects (patients) for every independent variable included in a model. Ten subjects per independent variable is a rule of thumb often advised for assuring the stability of the models (Peduzzi et al., 1996). However, Austin et al. (2015) have recently investigated this topic and have concluded that a minimum of two subjects per variable are enough for adequate estimation of regression coefficients, standard errors, and confidence intervals in linear regression.

6.6 Summary of results and conclusions

The GlyCon retrospective study focused on the actual clinical practice of GC implemented in the study ICUs, and the measurable glycaemic outcomes that may result from this. Broadly, it was hypothesised that different methods for GC implemented in the ICU, mainly in terms of monitoring frequency, treatment with insulin and protocol implemented, would have a different impact on patients' outcomes, in terms of effectiveness, as well as of time-efficiency and safety (EES). The salient findings from this study are summarised in this section.

6.6.1 Glycaemic control methods implemented

GC methods implemented in the participating ICUs often differed significantly between patients with and without diabetes, between the different glycaemic statuses, and between the different protocol-hospitals. In addition, there were some unexpected results that were

difficult to explain based on the data. All these suggested a number of opportunities for the quality improvement of GC in the ICU, as well as the need for further studies.

Glycaemic monitoring

The glycaemic monitoring frequency was usually of 1-4 hours, although there were about one tenth of the occasions when this was higher, of which some were even higher than eight hours. Monitoring was, on average, more frequent during periods of hypoglycaemia followed by during periods of hyperglycaemia>10; and it was also more frequent among patients with diabetes during periods of BG within the study target range. Protocol-hospitals differed in their monitoring frequencies, but the differences were statistically significant only among patients with diabetes.

Treatment with insulin

The treatment with insulin consisted of the intravenous, continuous infusion of a solution prepared with fast-acting insulin (Actrapid®), at rates that were titrated intermittently. Most rates were within the range 1-6U/h of insulin, but some patients received rates higher than 8U/h, even when their BG was below 10mmol/L. The latter occurred mainly among patients with diabetes. There were 38 patients without diabetes and four with diabetes who did not receive any insulin during hyperglycaemia>10, of whom half had spent more than three hours in hyperglycaemia>10. On the other extreme, there were 21 patients who received insulin at some point while they were in hypoglycaemia (BG<4mmol/L), of whom more than half had diabetes. The percentage of time spent receiving insulin was significantly and markedly higher (3 to 10 times higher) among patients with diabetes, than patients without diabetes. In both groups with and without diabetes, these percentages of time with an insulin drip differed significantly between protocol-hospitals.

Nutritional support

Most patients received some type of nutritional support during their stay, usually enteral. The mean non-protein energy per hour given did not differ by diabetic status, or by protocol-hospital, in any of the glycaemic statuses. Both patients with and without diabetes received, on average, higher non-protein energy rates via enteral nutrition during hours of hyperglycaemia>10.

Adherence

Protocol instructions on monitoring frequency and insulin titrations were not followed more often than they were followed. The distributions of each type of non-adherence differed significantly between protocol-hospitals. The most common types of non-adherence in all

protocol-hospitals were giving less insulin than specified, and BG measurements performed later than specified. Patients with diabetes had higher incidence of non-adherences in which more insulin than specified was given, than patients without diabetes. The high levels of non-adherence found in this study stress the importance of controlling for adherence to protocol instructions in evaluation studies, and reinforce the relevance of GlyCon study, in which the effect of actual practice (rather than protocol implementation) was investigated.

6.6.2 Outcomes of glycaemic control

Findings on the outcomes of GC often differed significantly between patients with and without diabetes, and between the different protocol-hospitals.

Glycaemic levels

Measures of location and dispersion of glycaemic levels were usually significantly higher among patients with diabetes. There was a high variability both between and within the ICUs. In order to describe and control for the different levels of hyperglycaemia, the new metric "glycaemic exceedance above 10mmol/L" was introduced. Using this metric, it was shown that the degree of hyperglycaemia>10 was usually higher among patients with diabetes.

6.6.2.2 Effectiveness

Effectiveness was analysed using TIR (percentage of time with BG within 4-10mmol/L) as the main outcome measure, and odds of IR (odds of being with glycaemic range 4-10mmol/L, at any time) as the outcome measure used in the analyses of association.

Patients with diabetes had markedly and significantly lower TIR than patients without diabetes. TIR was lower in both groups of with/without diabetes than what was reported in several previous studies, although given the different glycaemic targets defining TIR, direct comparisons between studies are difficult. Also, TIR had a high inter-patient variability, within both groups with/without diabetes, and in all protocol-hospitals, indicating that GC was more effective in some patients than in others. Nonetheless, most patients without diabetes had a TIR higher than 75%, which is the threshold defining a good GC according to most of the surveyed professionals of the participating ICUs. On the other hand, most patients with diabetes had a TIR below 75%. This indicates that what most professionals consider as good GC was not being achieved among patients with diabetes.

The TIR of patients without diabetes did not differ significantly by protocol-hospital, but they had, on average, higher odds of IR at any time if they were treated with a protocol that had a UL83 target than if it had a UL10 target. Among patients with diabetes, meanwhile,

TIR and the odds of IR differed significantly between protocol-hospitals, and their odds of IR was also significantly higher if they were treated with a protocol that had a UL83 target.

Among patients without diabetes, higher percentages of time with insulin while at hyperglycaemia>10 significantly improved effectiveness by increasing the odds of IR at any time, during the whole stay in ICU. This association did not remain when only the first two or six days of admission were considered, and therefore it seems that the protective effect of this factor may benefit mainly long stayers. Among patients with diabetes, a higher percentage of time with insulin while at hyperglycaemia>10 did not show a significant positive effect, but at the hourly level, the insulin dosage given at each hour showed a significant association with increased expected odds of IR in the following hour. In two hospitals, not adhering to their protocols' instructions on insulin titrations for patients with diabetes, by giving a lower insulin dosage than specified, had a significant negative effect, decreasing the expected odds of IR in the following hour.

A higher level of severity on admission was detrimental in both groups of diabetic status, when the full stay was considered. GC effectiveness improved with time among patients without diabetes, but not among those with diabetes. Various hourly-dependent variables were significantly associated with higher or lower odds of IR in the following hour, although they differed depending on the period of interest considered. The adrenaline dosage and the glycaemic exceedance were negatively associated with the odds of IR in the following hour, among both groups of diabetic status. Among patients without diabetes the non-protein energy given enterally or parenterally were also negatively associated with the odds of IR in the following hour, while the dobutamine dosage was positively associated with this outcome. Among patients with diabetes, the dosage of hydrocortisone was negatively associated with the odds of IR in the following hour, while the insulin dosage was positively associated with this outcome.

6.6.2.3 Efficiency

TTR (time from the first BG>10mmol/L to the next two consecutive BG within the range 4-10mmol/L) was the outcome measure used to assess time-efficiency. Most patients were brought to range within the first 24 hours, although it took significantly longer among patients with diabetes. Within ICUs variability was higher among patients with diabetes. Analyses of association showed that monitoring patients without diabetes more frequently made GC, on average, more time-efficient. Among patients with diabetes this factor did not have a significant effect. Higher glycaemic exceedance, made bringing patients to range more challenging, but only among patients without diabetes. In both groups of diabetic status

there were some protocol-hospitals that performed better than others in terms of time-efficiency.

6.6.2.4 Safety

The proportions of patients developing moderate hypoglycaemia (2.2-3.9mmol/L) or severe hypoglycaemia (<2.2mmol/L) were calculated to study safety. More than one quarter of the patients had at least one event of moderate hypoglycaemia, although the durations were generally short. Four patients, of whom two had diabetes, had one episode of severe hypoglycaemia each.

ICUs differed significantly in their proportions of patients with hypoglycaemic events. Having a protocol with a glycaemic target of 8.3mmol/L or less, seemed protective for patients without diabetes, while it seemed detrimental for patients with diabetes, in terms of safety. Having a protocol that recommends insulin during moderate and/or severe hypoglycaemia, seemed detrimental to both groups with/without diabetes, in terms of safety. However, data on actual practice showed that the administration of insulin during hypoglycaemia did not affect its incidence.

6.6.3 Conclusions

Protocols for GC, practice of GC, and outcomes of GC, all differed significantly across hospitals. Some protocols seemed more effective, efficient or safe than others but there was a high incidence of non-adherence to protocol instructions in all ICUs. Regardless of the protocols implemented, among patients without diabetes, longer proportions of time with an insulin drip, and lower rates of energy given through nutritional support were all associated with higher effectiveness; while a more frequent monitoring was associated with higher time-efficiency. Effectiveness improved with time among patients without diabetes, but not among those with diabetes.

Among patients with diabetes, administering the appropriate insulin dosage, for the whole duration of their stay increased the effectiveness. Having a protocol with a glycaemic target of 8.3mmol/L or less seemed associated with higher effectiveness, but lower safety in patients with diabetes.

In all patients, there were other factors related to the patient's condition or to other therapeutic interventions administered, that could be detrimental or protective for a good GC of these patients, during the whole duration of the ICU stay. These should, therefore, always be taken into consideration by the ICU staff caring for them.

Finally, the different outcomes and the markedly different actual practice of GC for patients with diabetes found in this study, corroborate the results of other studies, and endorse the need for new protocols that formalise these different methods for GC depending on the diabetic status of a patient. This and several other recommendations for the quality improvement of GC in ICUs, are the practical outcome of the GlyCon study. These recommendations are listed in the concluding chapter of this thesis.

Chapter 7
Conclusions and recommendations

The assessment of current methods for glycaemic control (GC) of stress-induced hyperglycaemia implemented in critically ill patients admitted to intensive care units (ICU) is paramount for the quality improvement of such methods, including their effectiveness, efficiency and safety (EES). Despite numerous studies carried out about this, further standardisation of glucose targets and definitions, insulin titrations, and of methods for blood glucose (BG) monitoring are still needed (Cook et al., 2012), without undermining the importance of allowing for the adaptation of GC targets and approaches to individual patients' conditions and needs at different stages (Krinsley, 2014; Abdelmalak & Lansang, 2013). The GlyCon study was designed with the aim of improving the current understanding about what ICUs recommended for the GC of their patients, what ICU professionals think about GC, and what is the impact of the GC methods currently implemented in ICU.

In order to address these different but interrelated research objectives, GlyCon was designed as a multi-centre, multi-method study, comprised of three sub-studies, which were carried out in seven ICUs on the Mid Trent Critical Care Network (MTCCN). These three sub-studies included: (1) a document review of the local protocols for GC implemented at each of the participating ICUs; (2) an online survey of ICU medical and nursing staff, on their opinion about effective GC, and deviations from protocol instructions; and (3) a retrospective study about the methods and outcomes of GC, based on a review of electronic and manual medical records, in a random sample of 146 patients from the seven ICUs.

The retrospective study was designed to address the main aim of GlyCon, which was to investigate the effectiveness of the monitoring and insulin treatment methods for GC implemented in ICU. The review of the protocols enabled the impact of the recommendations guiding these GC methods to also be explored. As key stakeholders in the ICU, the views of professionals on the aims of their protocols and methods for GC, explored in the survey sub-study was critical, both to understand such methods and their outcomes, and to consider ICU professionals' opinions in the quality improvement suggestions derived from the study.

The findings derived from each of the GlyCon sub-studies have been discussed in detail in their corresponding chapters. In this chapter, the main conclusions derived from the entire

study are presented, followed by a series of recommendations drawn from the GlyCon findings and complemented with previous evidence.

7.1 Summary of the main conclusions

Results from this study confirmed an expected but still important finding that, despite belonging to the same ICU network, the written instructions of the protocols for GC implemented in the seven participating ICUs differed widely among each other. The different evidence supporting their recommendations had a direct effect on their recommended glycaemic targets which, in turn, affected their insulin infusion algorithms and other instructions.

In practice, however, there was a low adherence to all protocols, including their monitoring and insulin treatment instructions, and this complicated the evaluation of their impact. This contrasted with the views of the GlyCon surveyed professionals, who often rated non-adherences from protocols as major, particularly those related to the insulin treatment, and especially if they occurred more than once consecutively. While the reasons for these deviations from protocols' instructions could not be determined due to the retrospective nature of the study, it is likely that at least some of them were driven by the needs of particular patients at certain stages of their treatment. Patient-specific needs and other contextual factors were highlighted by professionals in the GlyCon survey as possible justifications for deviating from protocol instructions. Nonetheless, this did not translate into similar clinical practice between ICUs. Indeed, there were still significant differences in practice both between and within the ICUs.

From the GlyCon survey, it emerged that more experienced medical staff tended to have a less strict view about adhering to protocols than nurses or less experienced clinicians. This, however, did not mean that the former were not concerned about the relevance of GC. In fact, senior staff often showed a more rigid view about what they considered as good GC.

Interestingly, GlyCon study indicated that not adhering to the insulin instructions of one of the protocols (implemented in two ICUs), by giving less insulin than specified, led to worse outcomes among patients with diabetes. This showed that following the recommendations of a local protocol for GC can have a positive impact. This is an important finding that suggests that locally developed protocols can actually be effective tools supporting clinical decision in the GC of critically ill patients. While further studies are needed to confirm these results in a larger sample, they indicate that protocols for GC should put further emphasis on the importance of following the suggested insulin dosing for each glycaemic range, unless it is

consciously and judiciously decided that specific needs of the patient require a change in the treatment.

Patients with diabetes

Another indication that the protocol followed in each ICU may play a role in patients' outcomes was the fact that, after controlling for relevant confounders, patients with diabetes seemed to do better with certain protocols than with others, in terms of effectiveness and safety outcomes, when considering the whole ICU stay, or at least the first six days of admission. For these patients, there was a trend indicating that protocols with an upper limit of the glycaemic target of 8.3mmol/L or lower, were more effective (kept patients within a desired glycaemic range for longer) but less safe (had more events of hypoglycaemia) than those with an upper limit of the glycaemic target of 10mmol/L. This occurred even if most of the protocols did not have specific recommendations for the management of patients with diabetes.

During the first two days of admission, however, neither the protocol received nor the GC methods studied in GlyCon seemed to play a role in the outcomes of patients with diabetes. Although the effectiveness of GC in such patients did not improve with time, it was when considering the first six days, and, even more markedly, the whole ICU stay, that certain factors were found to affect the outcomes of these patients: the insulin dosage, and certain protocols, showed a significant protective effect, and medications such as hydrocortisone had a negative effect, on average, throughout the whole stay. These findings highlight the importance of maintaining a close watch on the management of ICU patients' glycaemia, not only during the first few days of admission, but during the entire stay, especially with patients having a history of diabetes.

Patients without diabetes

On the other hand, patients without diabetes in GlyCon study did significantly better than patients with diabetes, in terms of effectiveness and efficiency outcomes. The protocol they were treated with did not seem to have had any effect on patients without diabetes. However, in these patients too, univariate analyses indicated that protocols with an upper limit of the glycaemic target of 8.3mmol/L or lower, were more effective, and even safer. Again, there were high levels of non-adherence to protocol instructions amongst these patients, so it was unclear to what extent the protocols may have played a role in the outcomes of these patients. But, given the effect of the upper limit of the glycaemic target, and the fact that patients with diabetes did actually have a more effective GC with certain protocols and ICUs, especially when the protocol instructions were adhered to, the role of the protocol should not be underestimated.

Patients without diabetes also differed from those with diabetes in the effect that time had on their outcomes. In the former, glycaemic levels were better controlled as days, and even hours, passed. With this regard, one of the most notable findings of GlyCon study arises. The glycaemic levels of patients without diabetes were better controlled after the first six days of admission if they had received insulin for higher percentages of time (>20% of the whole ICU stay) when they were in hyperglycaemia (blood glucose above 10mmol/L). This, in fact, is in line with what the protocols recommend (the insulin infusion should be started immediately, or at most one hour after the first event of hyperglycaemia), as well as with what professionals opined (delaying the start of an insulin infusion more than two hours, and wrong or missed insulin dosages twice or more, are major non-adherences). This critical finding suggests that (1) delaying the start of a treatment with insulin can reduce the effectiveness of GC for patients without diabetes, and (2) as above, there are instances when adhering to the protocols' instructions on the administration of insulin leads to better outcomes.

Another important finding of this study was that patients without diabetes who were monitored more frequently during the first event of hyperglycaemia, were brought back to the study target glycaemic range (4-10mmol/L) more quickly. Therefore, it is advisable that, during hyperglycaemic events, patients' BG is monitored at least hourly, as the GlyCon study protocols in fact recommend. Although most of the surveyed professionals opined that missing a glycaemic measurement twice or more was a major non-adherence, this specific protocol instruction was often not adhered to. Once again, this finding points out the beneficial impact of specific GC methods, in this case a more frequent glycaemic monitoring, in the glycaemic management of critically ill patients, and it reinforces the positive value of adhering to protocols' instructions about the glycaemic monitoring frequency of critically ill patients.

Patients without diabetes who received lower rates of non-protein calories per hour through enteral or parenteral nutrition, seemed to be better controlled, on average. Also, while the identified detrimental effect of the administration of adrenaline and hydrocortisone were expected, noradrenaline and propofol did not show a negative effect in this study, regardless of the diabetic status, while dobutamine was actually associated with better GC control in patients without diabetes. These findings highlight the importance that GC protocols also take into account the nutritional support and drugs being administered to patients.

It is worth mentioning that, despite being well-documented that patients without diabetes are more vulnerable than patients with diabetes to events of hyperglycaemia (Krinsley et al., 2013; Egi et al., 2008) and to lower time in range (Krinsley & Preiser, 2015), on average, patients with diabetes were monitored more frequently when their BG was within the study

target (4-10mmol/L), and received insulin for higher percentages of time, regardless of the glycaemic status, than patients without diabetes. This contrasted with the fact that only three ICUs had a protocol that made different recommendations for patients with diabetes, and these consisted mainly of higher dosages of insulin.

These findings showing different glycaemic management and different outcomes in patients with diabetes, reinforce the need to formalise different recommendations for the glycaemic management of patients with diabetes within the protocols. In addition, they indicate a clear need to increase awareness amongst ICU professionals about the potentially worse impact of stress hyperglycaemia on patients without diabetes.

Based on the results of GlyCon, a number of ICU professionals may be disappointed that GC is having a low effectiveness among their patients with diabetes, and that there is a high incidence of major deviations found in their ICUs. However, findings of GlyCon also show that practice and outcomes could be improved by taking certain measures. In this respect, the following section lists a number of recommendations for the quality improvement of GC in ICUs, that arose from the GlyCon findings, and which are also backed-up by the most up-to-date evidence.

7.2 Recommendations for the quality improvement of glycaemic control

The following recommendations were developed as a proposal for the quality improvement of GC in the ICUs of the NHS network studied in GlyCon. While clinical judgement in the treatment and care of patients should be guided, but not constrained, by the instructions of a clinical protocol (NHS Institute for Innovation and Improvement, 2008a), the proposed recommendations are based on data obtained directly from the targeted ICUs, and therefore will have the potential to increase the EES of the methods for GC implemented in these ICUs. As with any clinical protocol, these should be regarded as recommendations to improve protocols that are designed to support the decision making for the care of patients, reduce variability of practice, assure the same quality of treatment for all patients and, ultimately, improve patients' clinical outcomes.

The list of recommendations is divided into six relevant components of GC. For each component, the recommendations are preceded by a brief summary of the GlyCon findings, as well as of the relevant current evidence that has been detailed throughout this thesis. For clarity, this evidence is not accompanied by citations as these have been provided in the preceding chapters, particularly in the literature review (Chapter 2).

7.2.1 Glycaemic target

Summary of current evidence from literature

Glycaemic targets within normal levels (4-6.1mmol/L) might reduce the risk of sepsis in surgical ICU patients but not in medical ICU patients. In medical ICU patients, targeting normal levels does not decrease the mortality risk among patients with diabetes, while it is not clear whether targeting normal levels may provide a survival benefit in patients without a history of diabetes. The risk of hypoglycaemia increases when normal levels are targeted. Hypoglycaemic levels below 3.9mmol/L are associated with higher morbidity and mortality in ICU. High glycaemic variability is associated with higher mortality risk. Glycaemic targets of 3.9-7.8mmol/L are associated with higher survival among patients without diabetes if they are achieved for at least 80% of the time spent in ICU.

Summary of GlyCon findings

The main aim of GlyCon was to investigate the associations of the methods for glycaemic control implemented, with the primary outcomes of interest: the percentage of time spent with, and the likelihood of being within, the glycaemic range 4-10mmol/L. The glycaemic target stated in the protocols did not seem to have an effect on the outcomes among patients without diabetes, when considering their whole LOS. Among patients with diabetes, glycaemic targets with an upper limit of 8.3mmol/L or lower resulted in better glycaemic control, both when considering their whole LOS and when looking their first days of admission only,- but higher risk of hypoglycaemia.

Recommendations

Protocols should:

- Define a lower limit of the acceptable glycaemic target range of **4mmol/L or higher**. Higher levels may benefit patients with diabetes.
- Set an upper limit of the glycaemic target range, ideally, **not higher than 8.3mmol/L** but individualise this upper limit based on patients' condition.
- Stress the importance of avoiding hyperglycaemia, glycaemic variability and hypoglycaemia in all patients, including patients without diabetes.

7.2.2 Glycaemic monitoring

Summary of current evidence from literature

Both arterial and venous blood, analysed either in the gas machine or in point-of-care glucose meters, have been found to be more accurate and reliable point-of-care testing methods than when capillary blood is used, particularly to detect hypoglycaemia. Haemodynamic instability, tissue oedema, hypoperfusion or anaemia, may make capillary samples even more inaccurate. Hourly monitoring time intervals have been found to be safer than two-hourly intervals.

Summary of GlyCon findings

Capillary blood is the sample of choice in one protocol, and is accepted in some other protocols of the participating ICUs in GlyCon study. The blood source and method of analysis was rarely recorded in the observation charts. Without knowing the blood source and glycaemic monitoring technique, clinicians cannot consider what level of inaccuracy the measurement may have, and therefore cannot plan accordingly. The glycaemic monitoring frequency was usually of 1-4 hours, although there were about one tenth of the occasions when this was higher, of which some were even higher than eight hours. Patients with diabetes were monitored more frequently than patients without diabetes, even during similar glycaemic statuses. During the first hours of hyperglycaemia>10mmol/L, monitoring patients without diabetes every two or less hours helped to bring them back to 4-10mmol/L more quickly. Most surveyed professionals rated a glycaemic measurement missed twice or more as a major non-adherence.

Recommendations

- If indwelling arterial/venous catheters are available, use blood obtained from them analysed in the gas machine (first option) or point-of-care glucose meter (alternative option).
- If available, use blood conservation devices to reduce blood loss associated with glycaemic monitoring.
- When measuring and recording glycaemic levels:
    - Record the blood sample and analysis technique of each measurement in the observation charts, or
    - Identify in the charts which values are obtained from capillary samples.
    - Be aware that capillary blood analysed in glucometers can be more than 20% inaccurate, which is particularly critical to detect hypoglycaemia, and especially in haemodynamic instability, tissue oedema, hypoperfusion or anaemia.

- Be aware of the time lapse between whole blood concentration and capillary blood concentration.
- Record the measurement at the correct time it was taken.

Protocols should:

- Recommend taking hourly measurements when possible, especially during hyperglycaemia.
- Increase monitoring frequency further during hypoglycaemia.
- Emphasise the need to monitor glycaemic levels even during periods of assumed stability.
- Emphasise the need to monitor glycaemic levels regardless of patients' history of diabetes.

7.2.3 Insulin treatment

Summary of current evidence from literature

Patients with diabetes need higher insulin dosages than patients without diabetes to achieve the same glycaemic levels. Insulin infusion algorithms coupled with concomitant nutritional support can help avoiding hypoglycaemia. Catecholamines, glucocorticoids and propofol can increase glycaemic levels. Considering the rate of change or trend of glycaemic levels may help for an effective glycaemic control. Titrating insulin infusions in steps of 0.1U/h rather than 1 or 0.5U/h may decrease the fears for hypoglycaemia among nursing staff.

Summary of GlyCon findings

Patients without diabetes who received insulin during hyperglycaemia >10mmol/L for at least 20% of the time had a higher likelihood of being controlled within 4-10mmol/L at any time.

Patients with diabetes received insulin for significantly higher percentages of time, and significantly higher dosages, on average, than patients without diabetes, regardless of the glycaemic status. Among patients with diabetes there was a proportional increase of the likelihood of being controlled within 4-10mmol/L with the increase in the dosage of insulin administered in the previous hour. Giving less insulin than specified in the protocol decreased this likelihood in two of the ICUs.

There was a proportional decrease of the likelihood of being controlled within 4-10mmol/L with the increase in the dosage of adrenaline (in all patients), hydrocortisone (only in patients with diabetes) and non-protein kilocalories (only in patients without diabetes), administered

in the previous hour. Such likelihood increased with the increase in the dosage of dobutamine given in the previous hour among patients without diabetes.

Most of the surveyed professionals rated deviations from insulin instructions of their protocols as major non-adherences, particularly when they occurred for two or more consecutive hours.

Recommendations

Protocols should:

- Set different insulin algorithms, with higher dosages for each glycaemic range considered, for patients with diabetes, particularly if they are insulin dependent.
- Emphasise the need to administer insulin for as long as needed, even if the patient does not have diabetes.
- Ideally allow insulin dosage adjustments of 0.1U/h.
- In the adjustments of insulin dosages, mention that the following should be considered:
    - The hourly rates of the following can increase glycaemic levels: adrenaline, hydrocortisone and non-protein kilocalories and, possibly, noradrenaline and propofol.
    - The hourly rates of dobutamine can decrease glycaemic levels.
- Consider incorporating some estimate of individual patients' insulin sensitivity.

7.2.4 Management of hypoglycaemia

Summary of current evidence from literature

Solutions of 50%w/v glucose increase the risk of overcorrection of glycaemic levels and of glucose variability, and they are strongly hypertonic and more likely to cause thrombophlebitis than 20%w/v and 10%w/v solutions. Temporarily stopping the insulin infusion instead of giving rescue glucose to treat moderate hypoglycaemia may decrease the fears for hypoglycaemia among nursing staff.

Summary of GlyCon findings

Glycaemic targets with an upper limit of 8.3mmol/L were associated with higher risk of moderate hypoglycaemia among patients with diabetes, but with lower risk in patients without diabetes, as compared to targets with upper limits of 10mmol/L. It was not possible to infer from the data of the observation charts or the medical notes whether rescue glucose boluses had been administered to treat hypoglycaemic events. Only four of the ten protocols

reviewed in GlyCon specifically stated the need to inform medical staff in events of severe hypoglycaemia.

Most surveyed professionals opined that any severe hypoglycaemic event <2.2mmol/L should be treated with rescue glucose, and that the treatment of moderate hypoglycaemias of 2.2-4mmol/L should depend on the underlying condition of the patient.

Recommendations

- Use 20%w/v or 10%w/v solutions to treat hypoglycaemia. If 50%w/v solutions are used, administer through a central line.
- Record administration of rescue glucose boluses in the charts.

Protocols should:

- Recommend that insulin is temporarily stopped during hypoglycaemia, especially if it is severe (<2.2mmol/L).
- Describe under what conditions moderate hypoglycaemia (2.2-4mmol/L) should be treated with rescue glucose.
- Instruct that all events of severe hypoglycaemia (<2.2mmol/L), confirmed with a glycaemic measurement that is not from capillary blood, should be treated with a bolus of rescue glucose.
- Instruct that medical staff are to be informed if severe hypoglycaemia (<2.2mmol/L) occurs.

7.2.5 Nutritional considerations

Summary of current evidence from literature

During the early phase of the critical illness, part of the patients' energy expenditure at rest is covered by endogenous glucose production, and thus patients' caloric need is probably lower than such energy expenditure. Stress hyperglycaemia may result from over-feeding in ICU patients.

Summary of GlyCon findings

None of the protocols of the participating ICUs mention recommendations on the nutritional management of patients. Some of these protocols instruct to stop insulin if no feeding is in place. Notwithstanding this, some patients received insulin when no feeding was in place, including during hypoglycaemia, although it was not possible to determine whether glucose-based fluids were in place.

The type of nutritional preparation being administered to patients was not recorded in the charts and was often missing in the notes. All crystalloids, including glucose-based fluids, were recorded all together as one type of fluid. Based on the data during which there was information in the notes about the nutritional preparation type, among patients without diabetes there was a proportional decrease of the likelihood of being controlled within 4-10mmol/L with the increase in the hourly non-protein kilocalories administered in the previous hour.

Recommendations

- Record the type of nutrition administered in the charts.
- Distinguish between glucose-based fluids and other crystalloids in the charts.

Protocols should:

- Mention the need to stop insulin if no feed or glucose-based fluids are in place.
- Recommend decreasing the amount of non-protein kilocalories administered per hour during hyperglycaemia, when possible, particularly among patients without diabetes.
- Include recommendations on the nutritional management of patients.

7.2.6 Indicators of effectiveness

Summary of current evidence from literature

The following percentages of the admission time spent within a pre-specified glycaemic target have been found to decrease the mortality and/or morbidity risk: >80% within 3.9-7.8mmol/L in patients without diabetes; and >80% or >70% or >50% (depending on the study) within 4-7mmol/L, although findings were not stratified by diabetic status. Transparent, informative and timely data reporting, showing the direct and indirect clinical outcomes achieved with the implementation of a protocol, help with the successful implementation of protocols for GC. Involvement of the ICU multidisciplinary team in defining targets and in the development of protocols for GC, increase the probability of the successful implementation of the protocol.

Summary of GlyCon findings

GC methods were significantly less effective in patients with diabetes, in terms of the percentage of time that they spent within 4-10mmol/L, despite having received insulin for longer and having been monitored more frequently, on average, than patients without diabetes. Most of the surveyed professionals considered a patient spending 75% or more of

the admission time within a protocol's target as good GC. Nurses with all levels of experience and medical professionals with five or less years' experience viewed a patient spending 50-74% of the admission time within a protocols' target as good glycaemic control more often than more experienced medical staff.

Recommendations

- Define the target minimum percentage of time that a patient should spend within the protocol's glycaemic target range, as an indicator of the quality of GC. This minimum target can be lower for patients with a previous history of diabetes, to account for their worse response to GC methods, and to avoid too tight GC strategies that could increase the risk of iatrogenic hypoglycaemia.
- Inform the ICU multidisciplinary team of the continuous quality improvement of the process, including performance and areas for quality improvement;
- Involve the ICU multidisciplinary team in defining targets, as well as in the development of protocols for GC.

7.3 Novel contributions of this research and future outlook

The GlyCon study has highlighted that, although GC in patients with diabetes can be much more challenging than in patients without diabetes, appropriate insulin dosages for the whole duration of their ICU stay can increase the effectiveness of GC, regardless of the protocol implemented. The study has also pointed out that patients with diabetes can have a more effective and safer GC when their treatment follows certain types of protocols.

The findings of GlyCon have shown that GC in patients without diabetes is often managed more flexibly than in patients with diabetes, and this could affect their outcomes. This study has shed light on the detrimental effect of delaying the start of the insulin treatment in patients without diabetes, when they develop high hyperglycaemic levels above 10mmol/L, as well as on the positive effect of closely monitoring these patients when they develop their first event of hyperglycaemia.

The GlyCon results show that certain methods for GC, which were in line with protocol recommendations, were more effective. The opinion of the ICU professionals also supported these protocol recommendations. Nevertheless, there was a high incidence of non-adherence to protocols, which raises the question of why protocol instructions were not being adhered to more often than not, and what can be done about it.

The GlyCon study has confirmed that there is a large variability in instructions given by different GC protocols, as well as in the actual practice of GC in ICUs. In addition, the study has also shown that ICU professionals tend to have significantly different views about certain important aspects of GC, depending on whether they are nurses or doctors, and on their level of experience.

The differences found in protocol instructions for, implementation of, and views on GC could potentially affect the quality and equity of care. Based on this, and on the associations found between certain aspects of clinical practice and patients' outcomes, a number of areas for the quality improvement of GC in ICUs have been identified. These findings have been distilled into a series of proposed recommendations that can potentially improve such quality of care.

Future outlook

The GlyCon study has also opened new doors for future research. A prospective study investigating the effects of implementing the recommendations of GlyCon in a number of ICUs, on the EES of GC, would be the next logical step to follow on from GlyCon. This could perhaps take the form of an intervention study, where the effect of implementing the GlyCon recommendations on a group of patients (in one or, ideally, more ICUs) is compared with the outcomes of patients treated with current GC methods. Such a prospective study would be faced with less missing data, and it would allow the recording of, and controlling for, certain important information that was not available for the GlyCon retrospective study. Among these are the BG measurement technique and blood source, the type of nutrition administered, and the amount of glucose-based fluids administered, including the boluses of rescue glucose.

This prospective study should also investigate whether changing clinical practice and improving EES does actually reduce the mortality and morbidity risk of patients in the ICU, as compared with usual practice. This would demonstrate whether feasible changes in the real ICU setting regarding their GC methods, can have a direct effect on patients in terms of less/shorter organ failure and lower mortality risk, among others.

The findings of GlyCon about the impact of not adhering to protocols should also serve as a basis for further research. This needs to focus primarily on the effects that the levels of adherence to written instructions in protocols for GC have on the outcomes of EES. It would be worthwhile to investigate the reasons behind non-adherences, and to determine how often protocol instructions are actually deviated from voluntarily by ICU staff in order to cater for patient-specific needs.

Current studies on the effectiveness of GC, such as GlyCon, are mostly based on data obtained from intermittent BG measurements, which are often linearly imputed assuming stability of glycaemic levels (which is also the assumption made in the actual clinical practice). There is a need for future studies investigating whether more frequent monitoring could affect the results of these studies, which in turn would have implications on clinical decision making in routine practice.

Importantly, any future studies on the EES of GC should consider the views of ICU professionals. The findings of GlyCon have raised the question of whether the different views could affect clinical practice, and hence clinical outcomes. Observational studies addressing this question are needed.

The GlyCon study has produced several important and novel findings, which undoubtedly improve the current knowledge about glycaemic control in ICUs. In the context of highly variable evidence, international guidelines, and local protocol recommendations regarding the treatment of stress hyperglycaemia, the results of GlyCon study, and the recommendations derived from them, are an important step towards improving the management and quality of glycaemic control in ICUs. In this respect, GlyCon has made an incremental contribution towards achieving the ultimate goal of providing equitable, safer and more effective healthcare to critically ill patients.

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Appendix A

Variables for the description and comparison of protocols for GC

Table A.1 – Quantifiable Variables			Protocol ID		
Gl. Status	**Inst. Aim**	**Variables**	**1**	**2**	**Etc.**
WITHIN glycaemic target	**D**	Upper limit of glycaemic target range			
	D	Lower limit of glycaemic target range			
	M	Minimum time to next measurement (TNM)			
	M	Maximum TNM			
	T	Minimum insulin infusion rate (IIR) [a]			
	T	Maximum IIR			
ABOVE glycaemic target	**O**	Is there a Hyperglycaemic threshold instructing to inform medical staff?			
	X (D+O)	Hyperglycaemic threshold indicating when to inform medical staff			
	M	Minimum TNM (h)			
	M	Maximum TNM (h)			
	T	Minimum IIR (U/h)			
	T	Maximum IIR			
BELOW glycaemic target	**O**	Is there a hypoglycaemic threshold instructing to inform medical staff?			
	X (D+O)	Hypoglycaemic threshold indicating when to call medical staff			
	X (D+T)	Hypoglycaemic threshold indicating administration of rescue glucose always			
	M	Minimum TNM if severe hypoglycaemia (h) [b]			
	M	Maximum TNM if severe hypoglycaemia (h)			
	T	Minimum IIR if severe hypoglycaemia (U/h)			
	T	Maximum IIR if severe hypoglycaemia (U/h)			
	T	Minimum dose of rescue glucose if severe hypoglycaemia (grams, g)			
	T	Maximum dose of rescue glucose if severe hypoglycaemia (g)			
GENERAL INSTRUCTIONS AT ANY GLYCAEMIC LEVEL	**X (D+T)**	Glycaemic threshold determining start of insulin infusion			
	M	Preferred monitoring method [c]			
	M	Preferred monitoring blood sample [d]			
	T	Preferred insulin type [e]			
	T	Preferred insulin administration route [f]			
	T	Insulin titration method during admission [g]			
	T	Treatment actions depending on underlying condition/s and/or severity [h]			
	T	Treatment actions depending on concomitant medication[h]			
	T	Treatment actions if no feeding/glucose-based maintenance fluid			
	O	Is management after ICU discharge mentioned?			
DEVELOP-MENT CHARAC-TERISTICS	**P**	Are protocol development methods mentioned?			
	P	Are protocol developers mentioned?			
	P	Is protocol evidence base mentioned?			
	P	Launch date / date of last update			

***Instruction aim codes legend*:**

D: Diagnostic instructions
M: Monitoring instructions
T: Treatment instructions
O: Organisational instructions
X: Mixed types of instructions
P: Protocol development characteristics

Gl. Status: Glycaemic Status; Inst. Aim: Instruction aim

[a] All insulin infusion rates of intravenous fast acting insulin in International Units per hour (U/h)
[b] Severe hypoglycaemia defined as random blood glucose ≤2.2 mmol/L or symptomatic hypoglycaemia
[c] Blood Gas Analyser / Glucose Meter / Laboratory / Not Mentioned
[d] Arterial / Venous / Capillary / Not Mentioned
[e] Fast-acting / Fast-acting + Basal / Not mentioned
[f] Intravenous / Subcutaneous / Both intravenous and subcutaneous are accepted / Not mentioned
[g] Fixed rates / Adjustments of previous rates
[h] Different IIR / Different TNM/ Mentioned as an aspect that should be considered / Not mentioned

Table A.2 – Themes		Protocol ID		
Inst. Aim	**Themes**	**1**	**2**	**Etc.**
P	Target patients			
P	Evidence base supporting the protocol instructions			
P	Development methods			
T	Recommended insulin/s			
T	Rationale for adjusting insulin infusion rates (IIR) on admission			
T	Rationale for adjusting IIR during admission			
T	Instructions on feeding management			
M	Rationale for adjusting the times to next meausrement (TNMs) on admission			
M	Rationale for adjusting TNMs during admission			
X	Differences in diagnostic, monitoring and treatment instructions for patients with diabetes			
X	Diagnosis, monitoring and treatment of "severe" and "moderate" hypoglycaemia			

Inst. Aim: Instruction aim

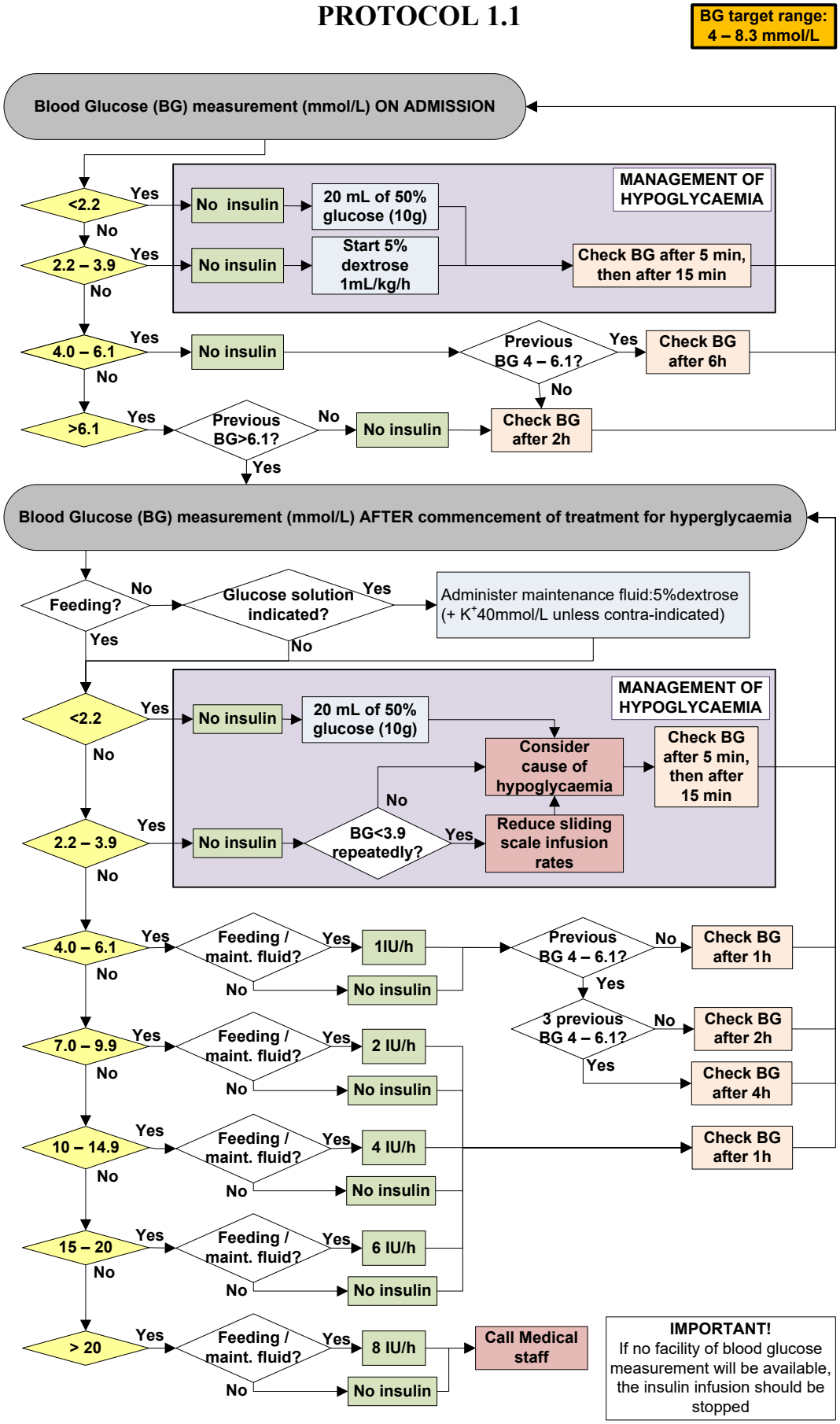
*Instruction aim codes legend:***:**

P: Protocol development characteristics
T: Treatment instructions
M: Monitoring instructions
X: Mixed types of instructions

Appendix B
Protocols flow-charts

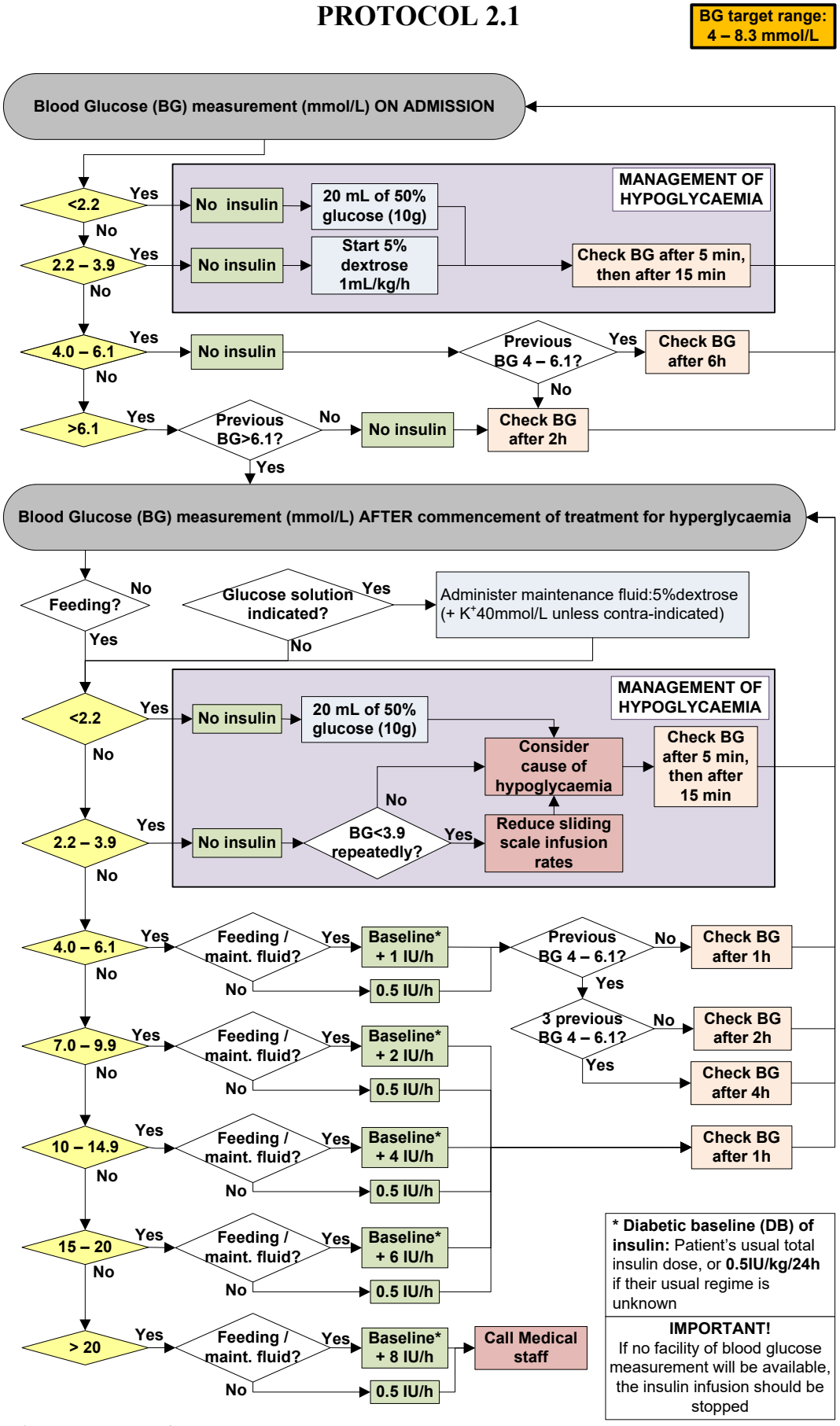
In this appendix the protocols' flow-charts built for each of the protocols reviewed in the GlyCon study are included. These flow-charts depict the instructions considered by the protocols for the management of each of the glycaemic scenarios.

PROTOCOL 1.1



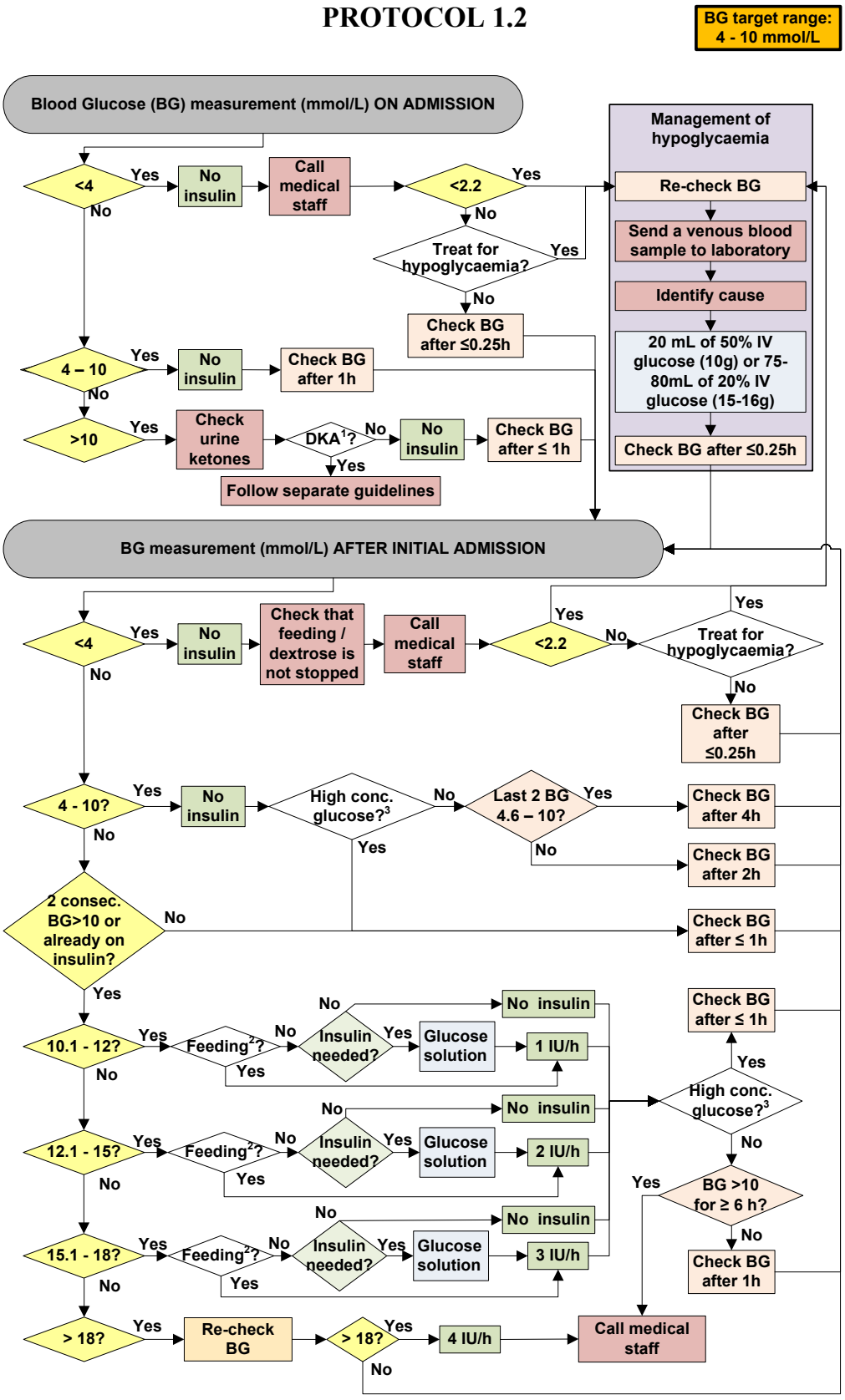
IU/h: International Units of insulin per hour

PROTOCOL 2.1



IU/h: International Units of insulin per hour

PROTOCOL 1.2

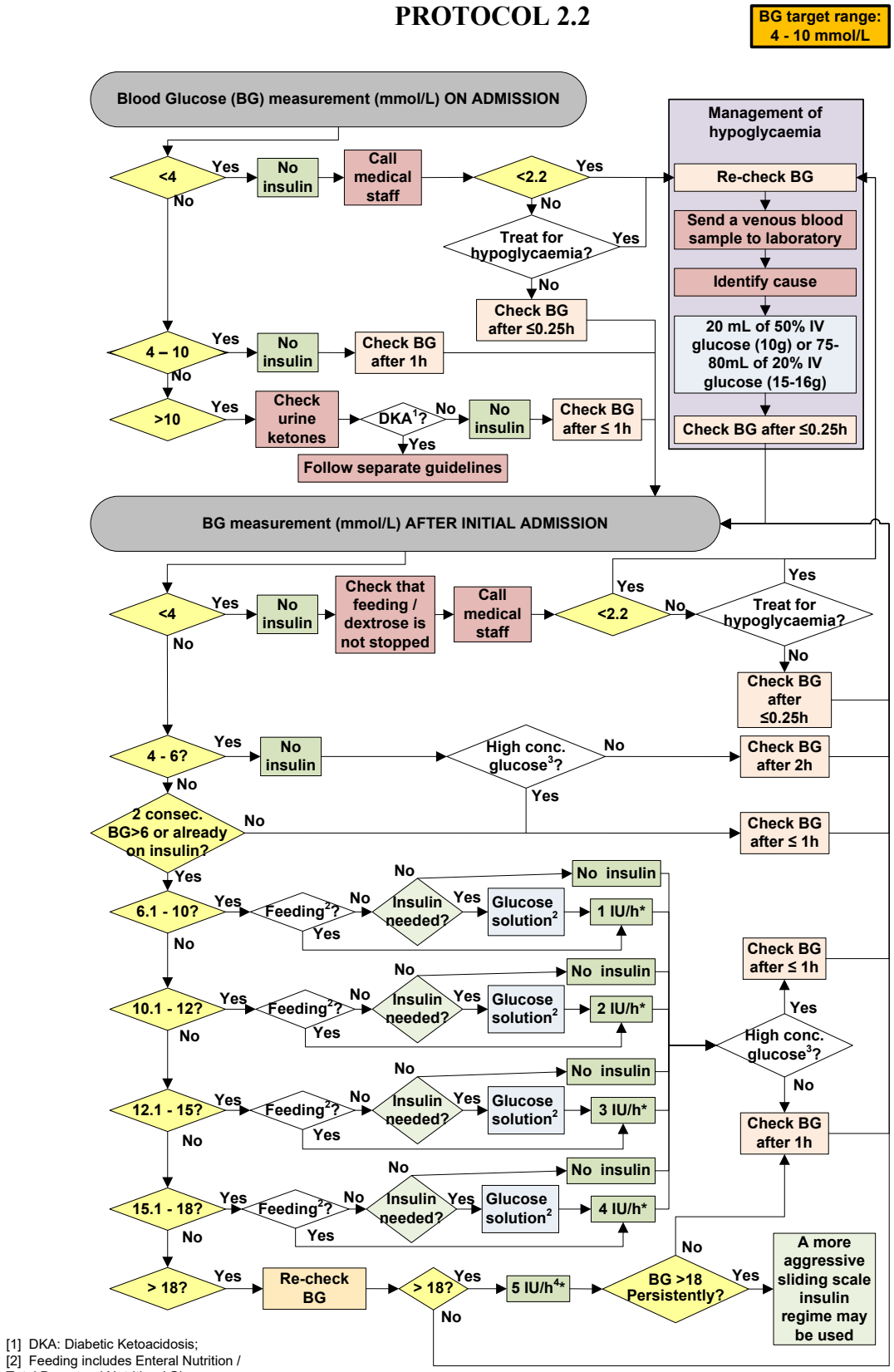


[1] DKA: Diabetic Ketoacidosis;
[2] Feeding includes Enteral Nutrition / Total Parenteral Nutrition / Glucose Solution
[3] High concentration glucose infusions for treatment of conditions other than hypoglycaemia, e.g. treatment for hypokalaemia

IU/h: International Units of insulin per hour

IMPORTANT!
IF NEW SWEATING, LOSS OF CONSCIOUSNESS, TACHYCARDIA, OR HYPOTENSION CHECK BLOOD GLUCOSE LEVEL IMMEDIATELY

PROTOCOL 2.2



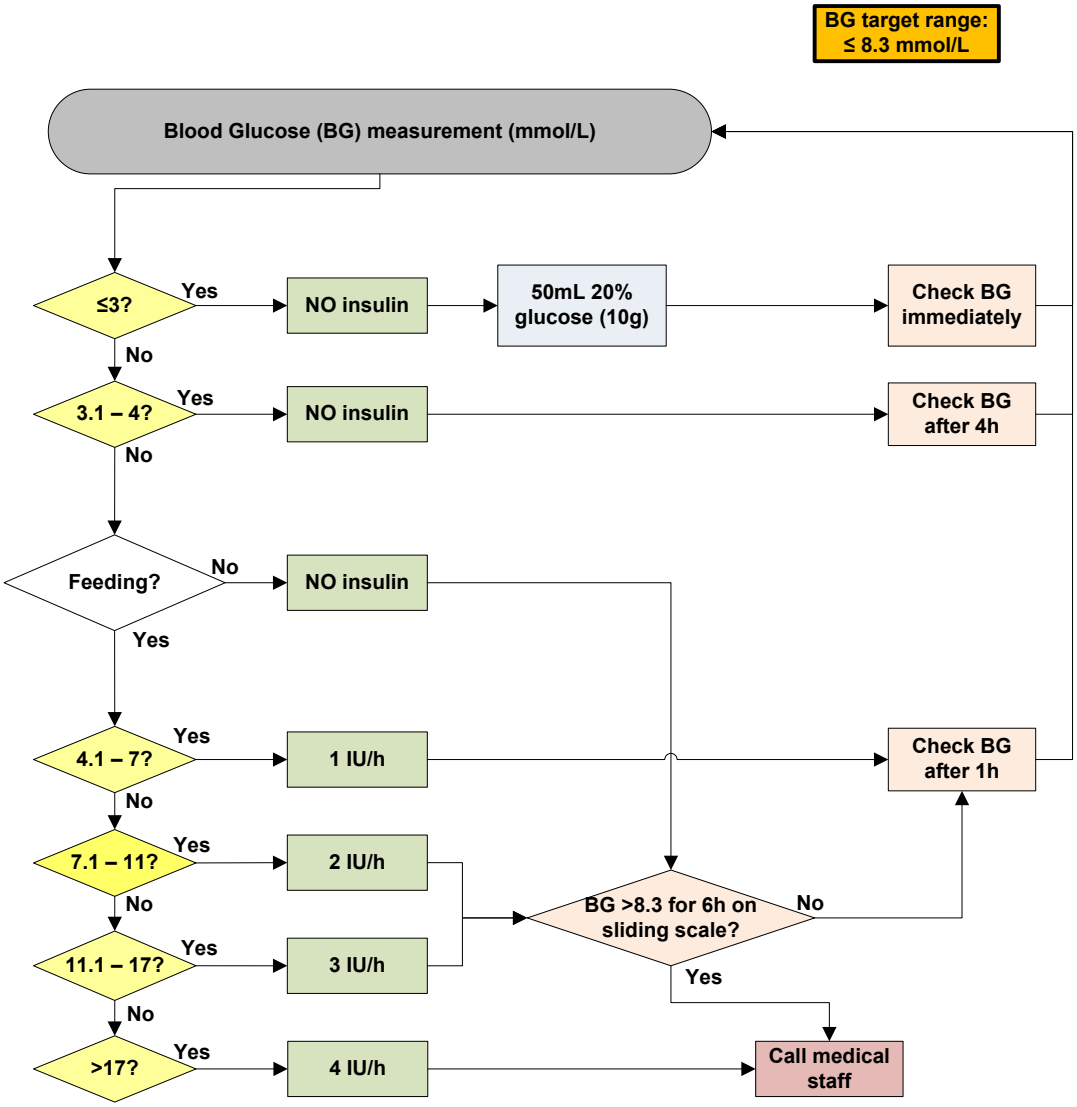
[1] DKA: Diabetic Ketoacidosis;
[2] Feeding includes Enteral Nutrition / Total Parenteral Nutrition / Glucose Solution
[3] High concentration glucose infusions for treatment of conditions other than hypoglycaemia, e.g. treatment for hypokalaemia

IU/h: International Units of insulin per hour

* If usual treatment is with high doses of insulin, a more aggressive sliding insulin scale regime may be used.

IMPORTANT!
IF NEW SWEATING, LOSS OF CONSCIOUSNESS, TACHYCARDIA, OR HYPOTENSION CHECK BLOOD GLUCOSE LEVEL IMMEDIATELY

PROTOCOL 3

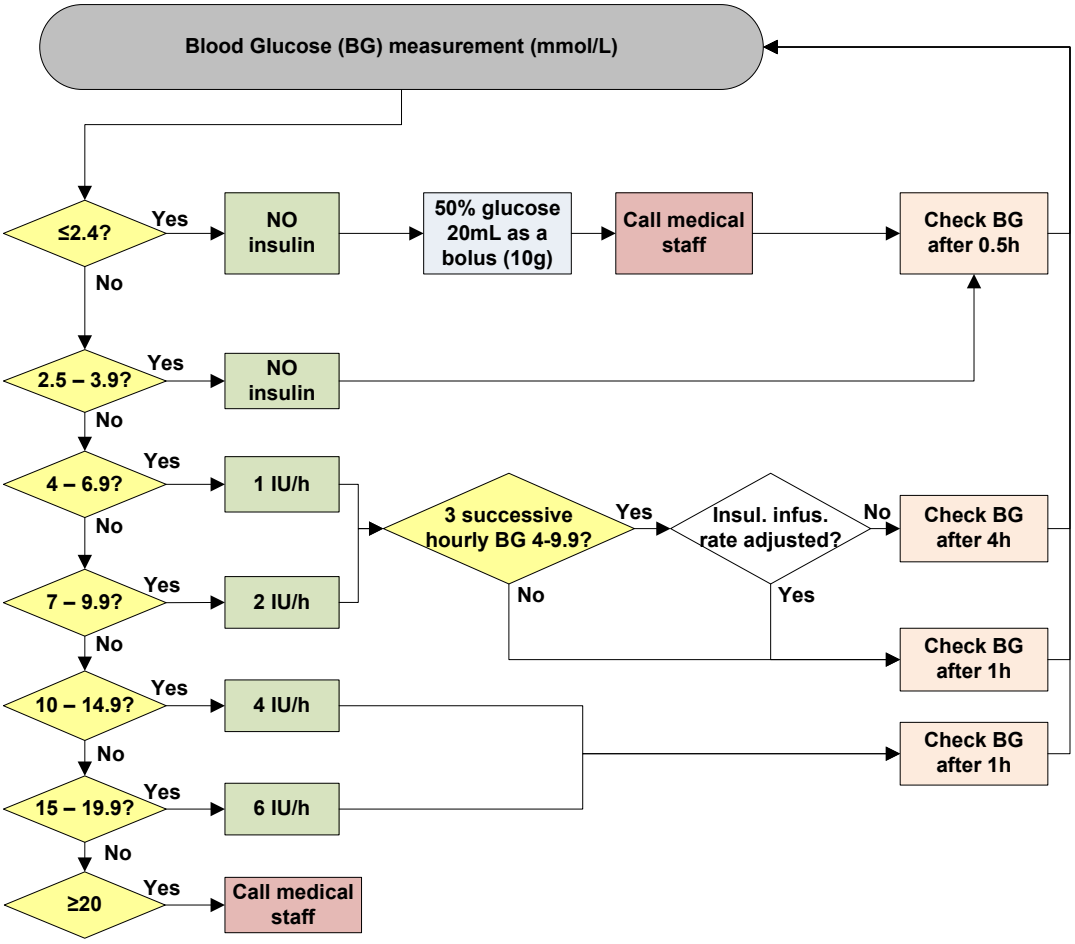


IU/h: International Units of insulin per hour

IMPORTANT:
Do not interrupt enteral feeding during rest periods

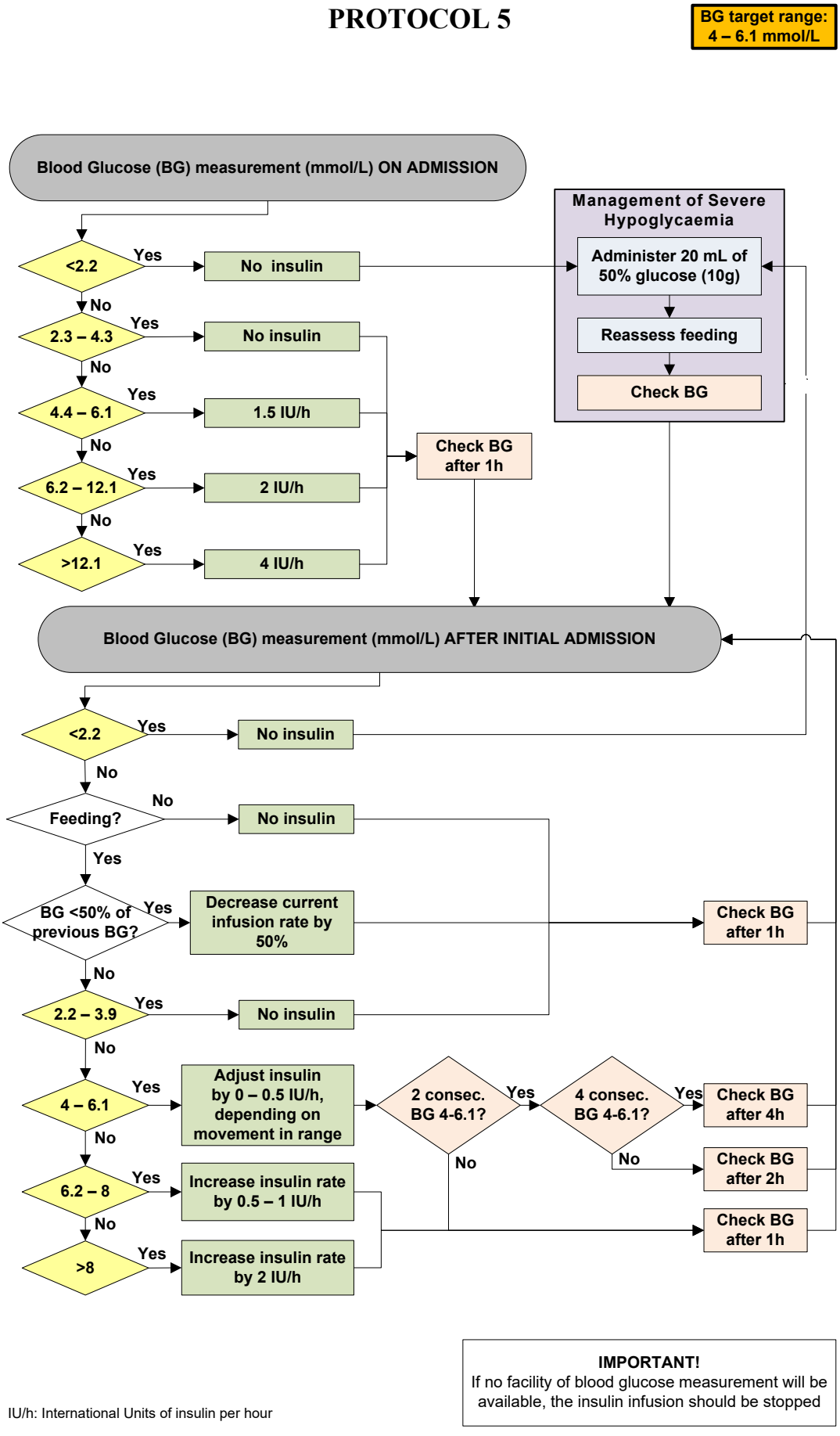
PROTOCOL 4

BG target range: ≤ 10 mmol/L



IU/h: International Units of insulin per hour

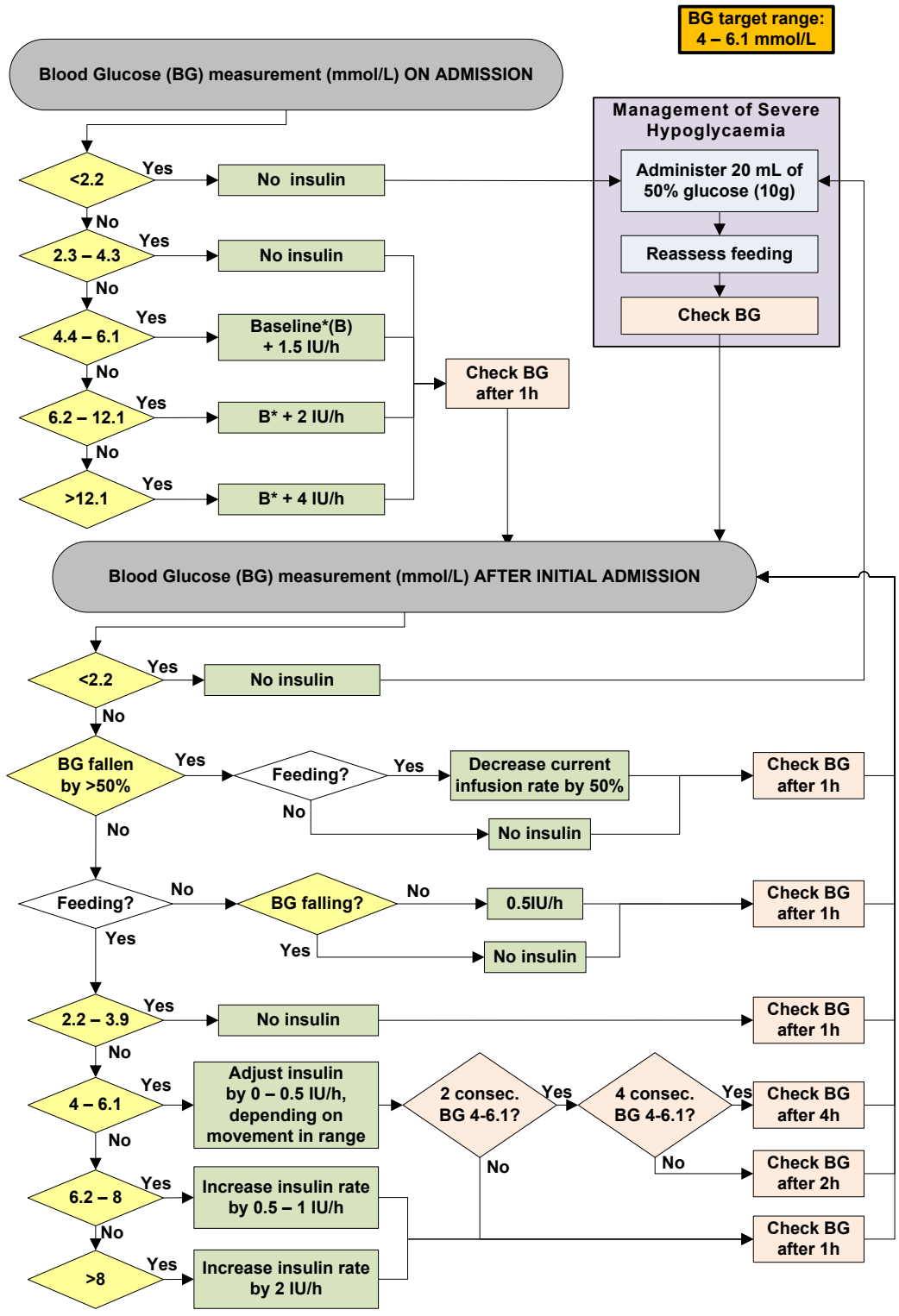
PROTOCOL 5



IMPORTANT!
If no facility of blood glucose measurement will be available, the insulin infusion should be stopped

IU/h: International Units of insulin per hour

PROTOCOL 6



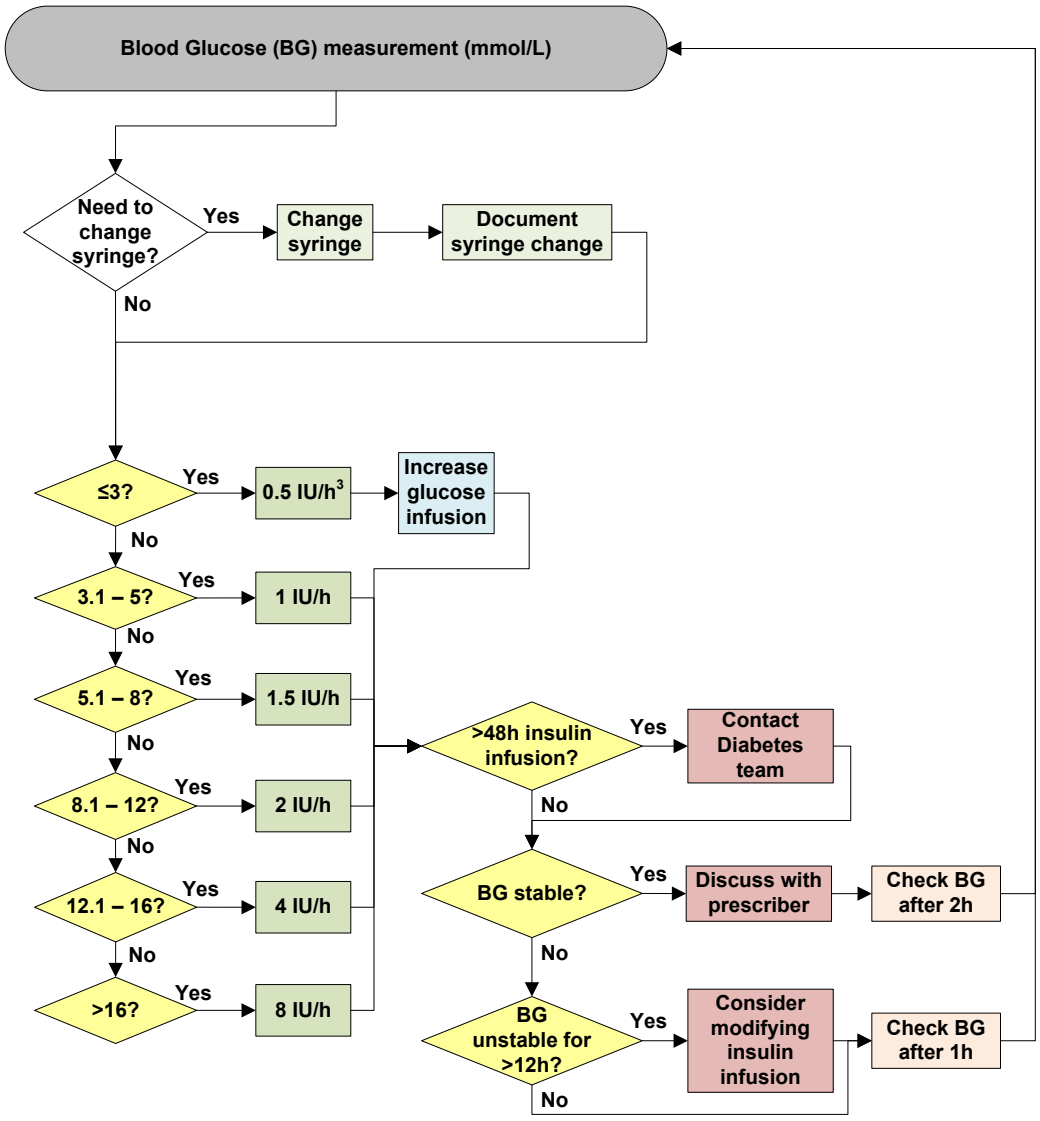
*** Diabetic baseline (DB) of insulin:** Patient's usual total insulin dose, or 0.5IU/kg/24h if their usual regime is unknown

IMPORTANT!
If no facility of blood glucose measurement will be available, the insulin infusion should be stopped

IU/h: International Units of insulin per hour

PROTOCOL 7

BG target range: *not specified*

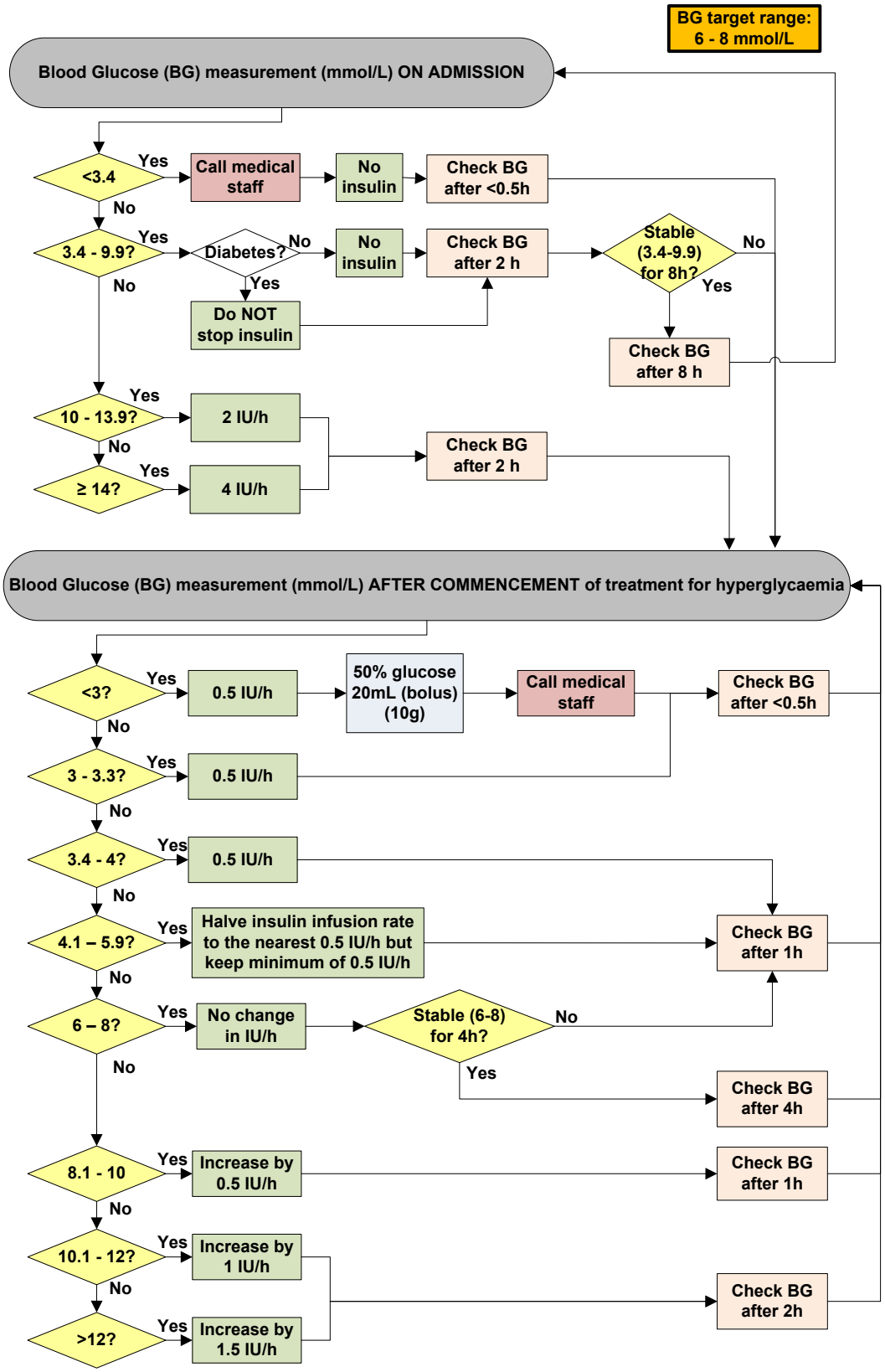


IMPORTANT: Always check insulin infusion rate at change of shift/handover or if patient is being moved

Prepare insulin infusion accordingly depending on route of administration:
A. Pump if IV[1] infusion
B. SC syringe if SC[2] administration (30-60' before stopping insulin administration)

IU/h: International Units of insulin per hour

Protocol 8



IU/h: International Units of insulin per hour

Appendix C

Results of the data entry quality checks: summary tables

Table C.1 - Data entry errors in the glycaemic levels and monitoring frequency of the sub-sample of 10% of study patients

Hospital	**100**	**100**	**200**	**200**	**300**	**300**	**400**	**500**	**TOTAL**	
Patient study ID no. (showing only cases with at least one entry error)	**10028**	**100175**	**2002**	**20075**	**30042**	**30061**	**40020**	**50054**	**All-8[a]**	**All[b]**
Total entries CRF-1	39	16	45	92	68	21	41	5	**327**	**671**
Total entries CRF-2	39	18	45	93	68	21	41	5	**330**	**674**
Mismatch in number of entries between CRF-1 and CRF-2										
Number (%) of occurrences	0	2(11.1)	0	1(1.1)	0	0	0	0	**3 (0.9)**	**3 (0.4)**
Range of values of the missing entries (mmol/L)	0	9.8-11.8	0	13.2	0	0	0	0	**9.8-13.2**	
Mean value of the missing entries (mmol/L)	0	10.8	0	13.2	0	0	0	0	**12**	
Wrong measurement time in CRF-1										
n (%)	0	1(5.6)	0	1(1.1)	1(1.5)	1(4.8)	2(4.9)	1(20)	**7 (2.1)**	**7 (1)**
Range of values of the Errors in time (h)	0	1	0	1	1	1	1	2	**1–2**	
Mean error in time (h)	0	1	0	1	1	1	1	2	**1.2**	
Wrong value of entries in CRF-1										
n (%)	1(2.6)	0	1(2.2)	0	1(1.5)	1(4.8)	0	0	**4 (1.2)**	**4 (0.6)**
Range of values of the errors (mmol/L)	0.6	0	0.5	0	0.3	3.4	0	0	**0.3-3.4**	
Mean error (mmol/L)	0.6	0	0.5	0	0.3	3.4	0	0	**1.2**	

CRF: Case Report Form; CRF-1: CRF of first entry, CRF-2: corrected CRF

[a] Out of the eight patients with at least one type of entry error in BG levels.

[b] Out of the sub-sample of 15 (10%) reviewed patients.

Table C.2 – Data entry errors in the insulin infusion rates (Units per hour) of the sub-sample of 10% of study patients

Hospital	100	100	300	400	500	600	TOTAL	
Patient study ID no. (showing only cases with at least one entry error)	**10028**	**10057**	**30042**	**40020**	**50068**	**600100**	**All-8[a]**	**All[b]**
Total entries CRF-1	89	134	19	112	181	48	583	683
Total entries CRF-2	86	136	49	113	181	67	632	732
Mismatch in number of entries of CRF-1 & 2								
n (%)	3 (3.4)	2 (1.5)	30 (61)	1 (0.9)	0	19 (28.4)	55 (8.7)	55 (7.5)
Range of values of the missing entries (U/h)	0.5 – 1	2	1 – 3	2 – 4	0	2	0.5 – 4	
Mean value of the missing entries (U/h)	0.75	2	2	2.667	0	2	1.9	
Wrong value of entries in CRF-1								
n (%)	3 (3.4)	2 (1.2)	0	2 (1.8)	1 (0.6)	0	8 (1.3)	8 (1.1)
Range of values of the errors (U/h)	0.5 – 1	1 – 2	0	1 – 4	2	0	0.5 – 4	
Mean error (U/h)	0.7	1.5	0	2.5	2	0	1.7	

CRF: Case Report Form; CRF-1: CRF of first entry, CRF-2: corrected CRF; U/h: Units of insulin per hour
[a] Out of the eight patients with at least one type of entry error in BG levels.
[b] Out of the 15 reviewed patients.

Table C.3 – Data entry errors in the basal insulin dosage of the sub-sample of 10% of study patients

Hospital	100	400	TOTAL	
Patient study ID no. (showing only cases with at least one entry error)	**10057**	**40020**	**All-8[a]**	**All[b]**
Total entries CRF-1	0	4	4	40
Total entries CRF-2	3	5	8	44
Mismatch in number of entries of CRF1 & 2				
n (%)	3 (100)	1 (20)	4 (50)	4 (9)
Range of values of the missing entries (mg)	1000 – 1000	500	500 - 1000	
Mean value of the missing entries (mg)	1000	500	750	

CRF: Case Report Form; CRF-1: CRF of first entry, CRF-2: corrected CRF
[a] Out of the eight patients with at least one type of entry error in BG levels.
[b] Out of the 15 reviewed patients.

Table C.4 – Data entry errors in the enteral nutrition administration rate (mL/h) of the sub-sample of 10% of study patients

Hospital	300	400	500	600	TOTAL	
Patient study ID no. (showing only cases with at least one entry error)	**30040**	**40020**	**50068**	**600100**	**All-8 [a]**	**All [b]**
Total entries CRF-1	61	133	132	132	458	1149
Total entries CRF-2	61	133	132	145	471	1162
Mismatch in number of entries of CRF-1 & 2						
n (%)	0	0	0	13 (9)	13 (2.8)	13 (1.1)
Range of values of the missing entries (mL/h)	0	0	0	45 – 290	45 – 290	
Man value of the missing entries (mL/h)	0	0	0	102.3	102.3	
Wrong value of entries in CRF-1						
n (%)	1 (1.6)	2 (1.5)	1 (0.8)	0	4 (4.8)	4 (0.3)
Range of values of the errors (mL/h)	30	84 – 84	7	0	7 – 84	
Mean error (mL/h)	30	84	7	0	40.3	

CRF: Case Report Form; CRF-1: CRF of first entry, CRF-2: corrected CRF

[a] Out of the eight patients with at least one type of entry error in BG levels.

[b] Out of the 15 reviewed patients.

Table C.5 – Data entry errors in the propofol infusion rates (mg/h) of the sub-sample of 10% of study patients

Hospital	100	300	300	400	500	600	700	TOTAL	
Patient study ID no. (showing only cases with at least one entry error)	**10028**	**30040**	**30061**	**40020**	**50068**	**600100**	**70024**	**All-8 [a]**	**All [b]**
Total entries CRF-1 [c]	42	81	7	36	24	62	76	328	552
Total entries CRF-2	42	83	10	45	24	62	82	348	572
Mismatch in number of entries of CRF-1 & 2									
n (%)	0	2 (2.4)	3 (30)	9 (20)	0	0	6 (7.3)	20 (5.7)	20 (3.5)
Range of values of the missing entries (mg/h)	0	20 – 20	20 – 25	1 – 1	0	0	15 – 15	1 – 25	
Mean value of the missing entries (mg/h)	0	20	23	1	0	0	15	14.8	
Wrong value of entries in CRF-1									
n (%)	1 (2.4)	0	0	0	1 (4.2)	1 (1.6)	0	3 (0.9)	3 (0.5)
Value of errors (mg/h)	2	0	0	0	3	5	0	2 – 5	
Mean error (mg/h)	2	0	0	0	3	5	0	3.3	

CRF: Case Report Form; CRF-1: CRF of first entry, CRF-2: corrected CRF

[a] Out of the eight patients with at least one type of entry error in BG levels.

[b] Out of the 15 reviewed patients.

Table C.6 – Data entry errors in the noradrenaline infusion rates (mL/h) of the sub-sample of 10% of study patients

Hospital	100	200	400	700	TOTAL	
Patient study ID no. (showing only cases with at least one entry error)	10028	2002	40020	70024	**All-8** [a]	**All** [b]
Total entries CRF-1	105	38	84	113	340	702
Total entries CRF-2	106	38	87	113	344	706
Mismatch in number of entries of CRF-1 & 2						
n (%)	1 (0.9)	0	3 (3.4)	0	4 (1.2)	4 (0.6)
Range of values of the missing entries (mL/h)	7	0	3 – 3	0	3 – 7	
Mean value of the missing entries (mL/h)	7	0	3	0	5	
Wrong value of entries in CRF-1						
n (%)	2 (1.9)	1 (2.6)	0	2 (1.8)	5 (1.5)	5 (0.7)
Range of values of the errors (mL/h)	1 – 7	1	0	0.2 – 0.2	0.2 – 7	
Mean error (mL/h)	4	1	0	0.2	1.7	

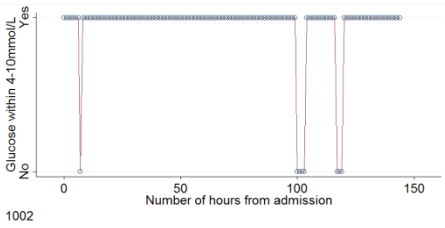
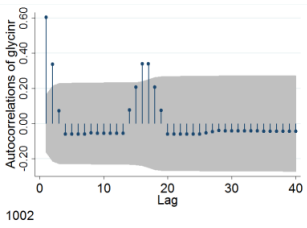
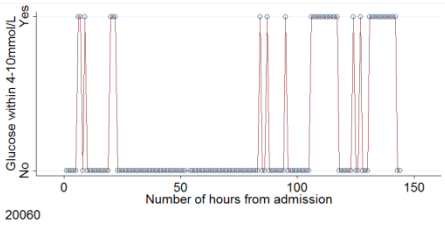
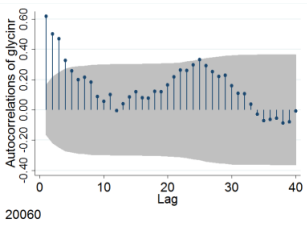
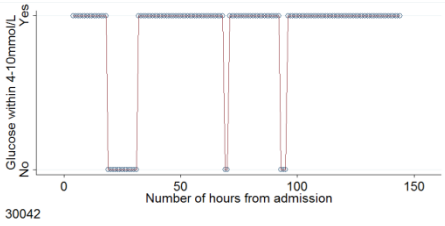
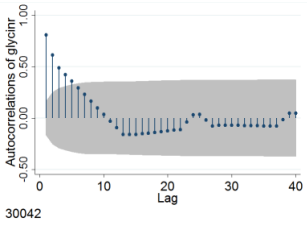
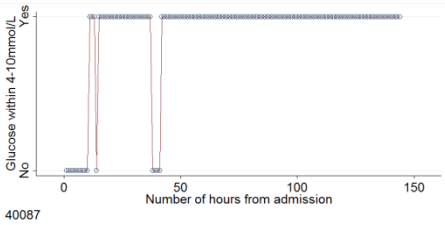
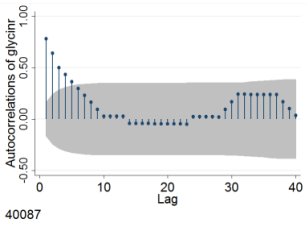
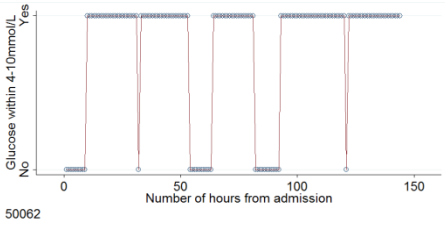
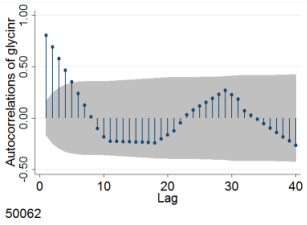
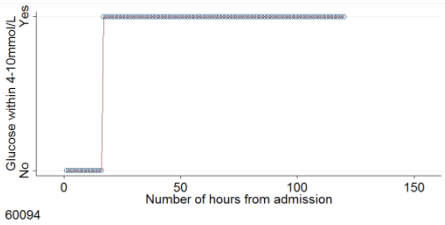
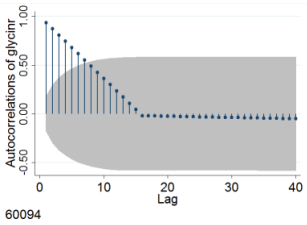
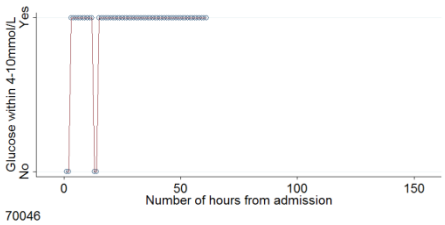
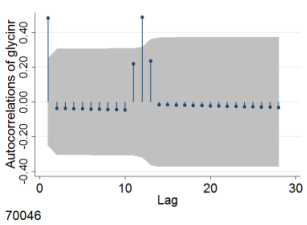
CRF: Case Report Form; CRF-1: CRF of first entry, CRF-2: corrected CRF
[a] Out of the eight patients with at least one type of entry error in BG levels.
[b] Out of the 15 reviewed patients.

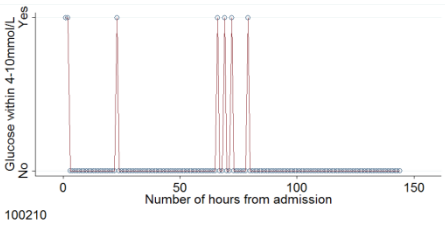
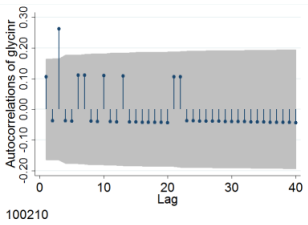
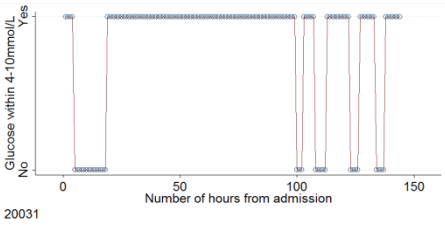
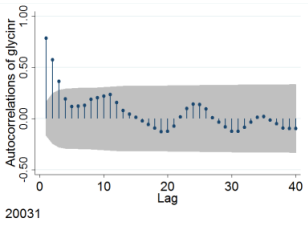
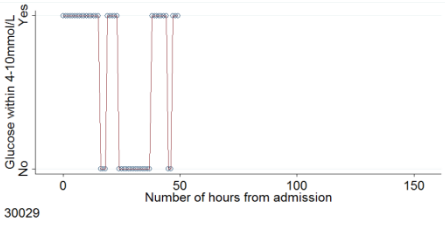
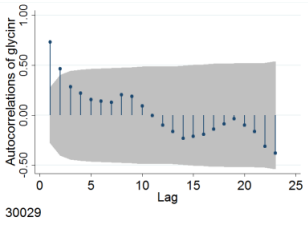
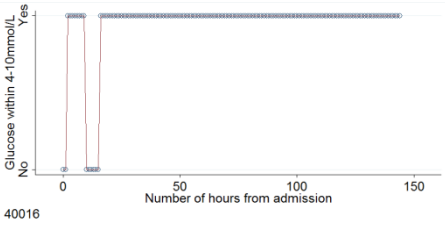
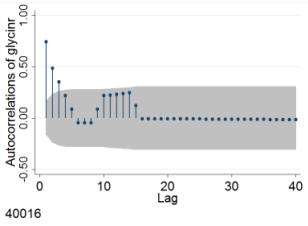
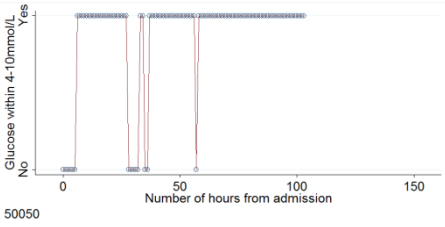
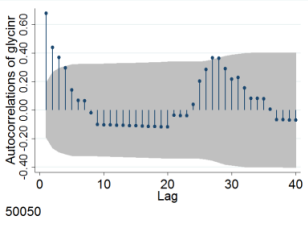
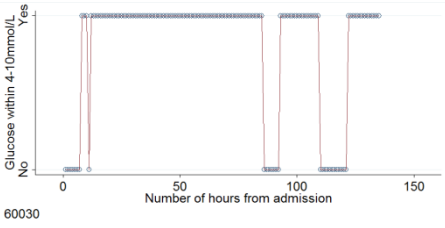
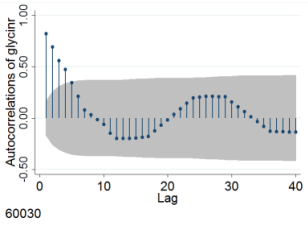
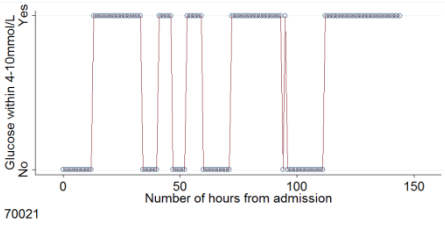
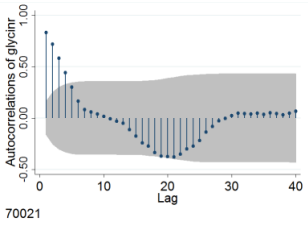
Glucocorticoids:

There was one entry error in the administration time of one of the dexamethasone dosages administered to one of the patients. The time lag was 2 hours, and the error represented 20% of the entries for that patient, and 2.7% of the entries for all 15 patients. No other errors were found.

Appendix D

Auto-correlations of glycaemic data: correlograms of 14 patients

Patient ID	Glycaemic levels: within 4-10mmol/L, yes/no	Correlograms
1002		
20060		
30042		
40087		
50062		
60094		
70046		

Patient ID	Glycaemic levels: within 4-10mmol/L, yes/no	Correlograms
100210	 100210	 100210
20031	 20031	 20031
30029	 30029	 30029
40016	 40016	 40016
50050	 50050	 50050
60030	 60030	 60030
70021	 70021	 70021

Appendix E

Permissions and Ethical approvals

Sponsor letters of sponsorship of GlyCon: letter for the REC and for the CAG

The University of Nottingham
UNITED KINGDOM • CHINA • MALAYSIA

Our reference:
RGS 14042
NRES REC reference:
14/EM/0177

Research and Graduate Services
University of Nottingham
King's Meadow Campus
Lenton Lane Nottingham
NG7 2NR

0115 9515679
sponsor@nottingham.ac.uk

Confidentiality Advisory Group (CAG)

Dr Gary Adams
Associate Professor in Diabetes Health and
Therapeutics at the School of Health Sciences
C44, C Floor, School of Health Sciences
The University of Nottingham
Queen's Medical Centre
Nottingham
NG7 2HA

09 April 2014

Dear Sir or Madam,

Sponsorship Statement

Re: GlyCon: Glycaemic Control of Stress Hyperglycaemia Implemented in NHS Intensive Care Units

I can confirm that this research proposal has been discussed with the Chief Investigator and agreement to sponsor the research is in place.

The University of Nottingham is in the process of completing the IG Toolkit.

The research proposal will be conducted in accordance with Caldicott principles and the Data Protection Act.

I can confirm that prior to the research commencing in any NHS organisation, the local Caldicott Guardian will be made aware of this research proposal and approval for the study to be conducted will be sought as part of the NHS R&D approval process.

Should you have any queries please do not hesitate to contact me

Yours faithfully

Angela Shone
Head of Research Governance
University of Nottingham

world-changing research
from the University of Nottingham

The University of Nottingham
UNITED KINGDOM • CHINA • MALAYSIA

Our reference:
RGS 14042
Your reference:
14/EM/0177

Research and Graduate Services
University of Nottingham
King's Meadow Campus
Lenton Lane Nottingham
NG7 2NR

0115 9515679
sponsor@nottingham.ac.uk

Nottingham 1 REC

East Midlands REC centre
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Dr Gary Adams
Associate Professor in Diabetes Health and
Therapeutics at the School of Health Sciences
C44, C Floor, School of Health Sciences
The University of Nottingham
Queen's Medical Centre
Nottingham
NG7 2HA

9th April 2014

Dear Sir or Madam,

Sponsorship Statement

Re: GlyCon: Glycaemic Control of Stress Hyperglycaemia Implemented in NHS Intensive Care Units

I can confirm that this research proposal has been discussed with the Chief Investigator and agreement to sponsor the research is in place.

An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.*

Any necessary indemnity or insurance arrangements will be in place before this research starts. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

The duties of sponsors set out in the NHS Research Governance Framework for Health and Social Care will be undertaken in relation to this research.**

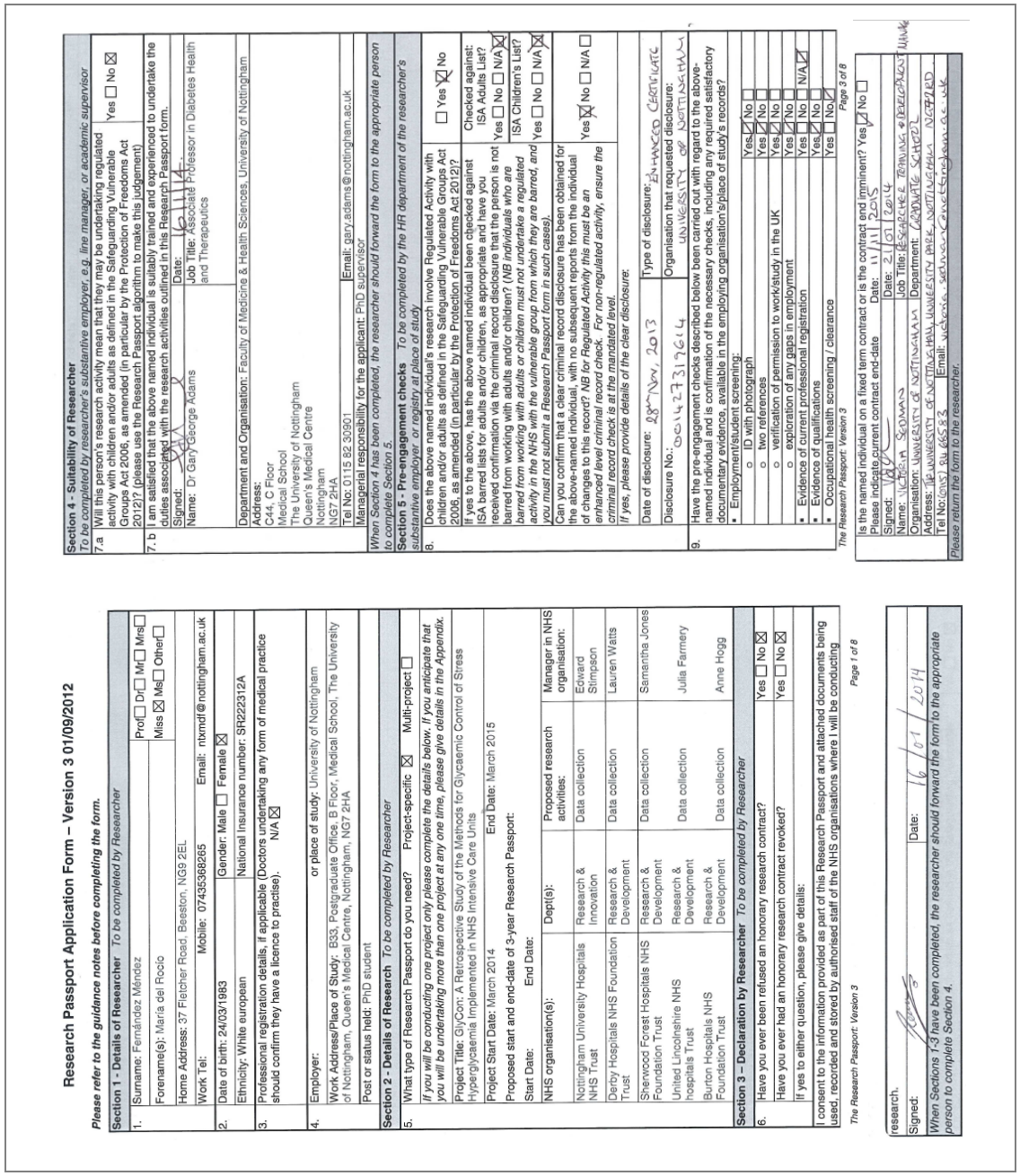
* Not applicable to student research (except doctoral research).
** Not applicable to research outside the scope of the Research Governance Framework.

Yours faithfully

Angela Shone
Head of Research Governance
University of Nottingham

world-changing research
from the University of Nottingham

Research passport



Research Passport Application Form – Version 3 01/09/2012

Please refer to the guidance notes before completing the form.

Section 1 - Details of Researcher *To be completed by Researcher*

1. Surname: Fernández Méndez — Prof☐ Dr☐ Mr☐ Mrs☐
   Forename(s): María del Rocío — Miss ☒ Ms☐ Other☐
   Home Address: 37 Fletcher Road, Beeston, NG9 2EL
   Work Tel: Mobile: 07435368265 Email: mkmdf@nottingham.ac.uk
2. Date of birth: 24/03/1983 Gender: Male ☐ Female ☒
   Ethnicity: White european National Insurance number: SR222312A
3. Professional registration details, if applicable (Doctors undertaking any form of medical practice should confirm they have a licence to practise). N/A ☒
4. Employer: or place of study: University of Nottingham
   Work Address/Place of Study: B33, Postgraduate Office, B Floor, Medical School, The University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2HA
   Post or status held: PhD student

Section 2 - Details of Research *To be completed by Researcher*

5. What type of Research Passport do you need? Project-specific ☒ Multi-project ☐

If you will be conducting one project only please complete the details below. If you anticipate that you will be undertaking more than one project at any one time, please give details in the Appendix.

Project Title: GlyCon: A Retrospective Study of the Methods for Glycaemic Control of Stress Hyperglycaemia Implemented in NHS Intensive Care Units
Project Start Date: March 2014 End Date: March 2015
Proposed start and end-date of 3-year Research Passport:
Start Date: End Date:

NHS organisation(s):	Dept(s):	Proposed research activities:	Manager in NHS organisation:
Nottingham University Hospitals NHS Trust	Research & Innovation	Data collection	Edward Stimpson
Derby Hospitals NHS Foundation Trust	Research & Development	Data collection	Lauren Watts
Sherwood Forest Hospitals NHS Foundation Trust	Research & Development	Data collection	Samantha Jones
United Lincolnshire NHS hospitals Trust	Research & Development	Data collection	Julia Farmery
Burton Hospitals NHS Foundation Trust	Research & Development	Data collection	Anne Hogg

Section 3 – Declaration by Researcher *To be completed by Researcher*

6. Have you ever been refused an honorary research contract? Yes ☐ No ☒
   Have you ever had an honorary research contract revoked? Yes ☐ No ☒
   If yes to either question, please give details:

I consent to the information provided as part of this Research Passport and attached documents being used, recorded and stored by authorised staff of the NHS organisations where I will be conducting research.

Signed: Date: 16/01/2014

When Sections 1-3 have been completed, the researcher should forward the form to the appropriate person to complete Section 4.

The Research Passport: Version 3 *Page 1 of 8*

Section 4 - Suitability of Researcher
To be completed by researcher's substantive employer, e.g. line manager, or academic supervisor

7.a Will this person's research activity mean that they may be undertaking regulated activity with children and/or adults as defined in the Safeguarding Vulnerable Groups Act 2006, as amended (in particular by the Protection of Freedoms Act 2012)? *(please use the Research Passport algorithm to make this judgement)* Yes ☐ No ☒

7. b I am satisfied that the above named individual is suitably trained and experienced to undertake the duties associated with the research activities outlined in this Research Passport form.
Signed: Date: 16/1/14
Name: Dr Gary George Adams Job Title: Associate Professor in Diabetes Health and Therapeutics

Department and Organisation: Faculty of Medicine & Health Sciences, University of Nottingham
Address:
C44, C Floor
Medical School
The University of Nottingham
Queen's Medical Centre
Nottingham
NG7 2HA
Tel No: 0115 82 30901 Email: gary.adams@nottingham.ac.uk
Managerial responsibility for the applicant: PhD supervisor

When Section 4 has been completed, the researcher should forward the form to the appropriate person to complete Section 5.

Section 5 - Pre-engagement checks *To be completed by the HR department of the researcher's substantive employer, or registry at place of study*

8. Does the above named individual's research involve Regulated Activity with children and/or adults as defined in the Safeguarding Vulnerable Groups Act 2006, as amended (in particular by the Protection of Freedoms Act 2012)? ☐ Yes ☒ No
   If yes to the above, has the above named individual been checked against ISA barred lists for adults and/or children, as appropriate and have you received confirmation via the criminal record disclosure that the person is not barred from working with adults and/or children? *(NB individuals who are barred from working with adults or children must not undertake a regulated activity in the NHS with the vulnerable group from which they are barred, and you must not submit a Research Passport form in such cases).* Checked against: ISA Adults List? Yes ☐ No ☐ N/A ☒ ISA Children's List? Yes ☐ No ☐ N/A ☒
   Can you confirm that a clear criminal record disclosure has been obtained for the above-named individual, with no subsequent reports from the individual of changes to this record? *NB for Regulated Activity this must be an enhanced level criminal record check. For non-regulated activity, ensure the criminal record check is at the mandated level.* Yes ☒ No ☐ N/A ☐
   If yes, please provide details of the clear disclosure:
   Date of disclosure: 28th Nov, 2013 Type of disclosure: Enhanced Certificate
   Disclosure No.: 041273196 14 Organisation that requested disclosure: University of Nottingham
9. Have the pre-engagement checks described below been carried out with regard to the above-named individual and is confirmation of the necessary checks, including any required satisfactory documentary evidence, available in the employing organisation's/place of study's records?

▪ Employment/student screening:		
○ ID with photograph	Yes ☑	No ☐
○ two references	Yes ☑	No ☐
○ verification of permission to work/study in the UK	Yes ☑	No ☐
○ exploration of any gaps in employment	Yes ☐	No ☐
▪ Evidence of current professional registration	Yes ☐	No ☐ N/A ☑
▪ Evidence of qualifications	Yes ☑	No ☐
▪ Occupational health screening / clearance	Yes ☐	No ☑

The Research Passport: Version 3 *Page 3 of 8*

Is the named individual on a fixed term contract or is the contract end imminent? Yes ☑ No ☐
Please indicate current contract end-date Date: 11/11/2015
Signed: Date: 21/01/2014
Name: Victoria Seddon Job Title: Research Technician & Postdoctoral Fellow
Organisation: University of Nottingham Department: Graduate School
Address: The University of Nottingham, University Park, Nottingham, NG7 2RD
Tel No: 0115 84 66582 Email: victoria.seddon1@nottingham.ac.uk

Please return the form to the researcher.

Research passport continued

Section 6 - Instructions to applicants *To be completed by Researcher* *Please indicate which of the following documents are attached to this Research Passport:*	
Current curriculum vitae, including details of qualifications, training and professional registration (please use the template C.V. at http://www.rdforum.nhs.uk/docs/template_cv.doc)	Yes ☒ No ☐
Researcher's copy of criminal record disclosure. NB where research involves regulated activity with children and/or adults as defined in the Safeguarding Vulnerable Groups Act 2006, as amended (in particular by the Protection of Freedoms Act 2012), the disclosure must include confirmation of a check against the appropriate ISA barred list(s).	Yes ☐ No ☐ N/A ☒
Evidence of occupational health screening / clearance	Yes ☐ No ☐ N/A ☒
Appendix – List of projects and amendments	Appendix numbers: N/A ☒

Please send the completed form and original documents to the Lead R&D office. The completed form and original documents will be returned to you. This package of documents will be used to validate your completed Research Passport form. You may then, and where relevant, provide the Research Passport to other NHS organisations.

You must inform all NHS organisations that have received this Research Passport of any changes to the information supplied above. Failure to do so may result in withdrawal of your honorary research contract or letter of access. As part of the quality control procedures for the Research Passport, random checks on the accuracy of the information held on this Research Passport may be made.

Section 7 **This section should be completed by HR in the Lead NHS organisation, only if additional checks are undertaken**			
The following additional checks have been completed:			
Having confirmed that the necessary additional pre-engagement checks have been completed, I am satisfied that the above named researcher is suitable to carry out the duties associated with their research activity outlined in this Research Passport.			
Signed:	Date:		
Name:	Job Title:		
Organisation:	Department:		
Email:			
Section 8 - For Office Use Only			
This section should be completed by the NHS R&D office that received the initial application. The NHS R&D office must countersign and date retained photocopies of the documents. The grey section must be completed before the form is returned to the applicant.			
CV reviewed?	Yes ☑ No ☐	Training?	Yes ☐ No ☑
Evidence of qualifications?	Yes ☐ No ☑	Appendix pages reviewed?	Numbers:
Professional registration details reviewed?	Yes ☐ No ☐ N/A ☑	Occupational health clearance reviewed?	Yes ☐ No ☐ N/A ☑
Criminal record disclosure reviewed?	Yes ☐ No ☐ N/A ☑	Date of disclosure: Disclosure No:	
For regulated activity as defined in the Safeguarding Vulnerable Groups Act 2006, as amended (in particular by the Protection of Freedoms Act 2012), did the criminal record disclosure confirm a satisfactory check against the appropriate ISA barred list(s)			Yes ☐ No ☐ N/A ☑
Enter Electronic Staff Record Number (if issued): RSCH 514			
Confirmation of valid Research Passport: Project specific ☑ Three-year ☐ Other End date ☐ Date:			
Signed: [signature]		Date: 23/07/11	
Name: Alison Steel (Head of Research & Development)			
NHS Organisation Name and contact details: Research Nurses Nottingham University Hospitals Trust alison.steel@nuh.nhs.uk CAMLCITE. DAVIES			
Date Honorary Research Contract/letter of access issued *(delete as appropriate)*			23/07/11

NHS
Health Research Authority
Confidentiality Advisory Group

Ms María del Rocío Fernández Méndez
B33, Postgraduate Office, B Floor, Medical School
The University of Nottingham, Queen's Medical Centre
Nottingham
NG7 2HA

ntxmdf@nottingham.ac.uk

Skipton House
80 London Road
London
SE1 6LH

Tel: 020 797 22557
Email: HRA.CAG@nhs.net

10 July 2014

Dear Applicant

Study title: **GlyCon: Glycaemic Control of Stress Hyperglycaemia Implemented in NHS Intensive Care Units**
CAG reference: **CAG 4-03(PR3)/2014**
Protocol number: **1.0**
IRAS Project ID: **129360**
REC number: **14/EM/0177**

Thank you for your research application, submitted for approval under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality, although other relevant legislative provisions will still be applicable.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether an application should be approved, and if so, any relevant conditions. This application was considered on 2 May 2014.

Health Research Authority approval decision

The Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, has determined the following:

1. The application is approved, subject to compliance with the standard and specific conditions of approval.

This letter should be read in conjunction with the outcome letter dated 19 May 2014.

Context

Purpose of application

This application from the University of Nottingham set out the purpose of a retrospective review of medical records and anonymised data extraction from seven sites based a selection of patients identified from the Intensive Care National Audit & Research Centre database.

Records will include observation charts, patients' notes, and the Case Mix Programme (CMP) database of the Intensive Care National Audit & Research Centre (ICNARC), among others. Data collected will include baseline characteristics, data about glycaemic monitoring and treatment, and outcome data. The primary outcome measure will be the effectiveness of the methods for glycaemic control implemented, measured as the proportion of time spent within the glycaemic range 4-10 mmol/L. Secondary outcomes will be other measures of effectiveness, efficiency and safety. The degree of staff adherence to the specific recommendations of the protocols will also be explored.

The main aim of GlyCon is to explore the associations between the methods for glycaemic control of stress hyperglycaemia implemented in 7 NHS ICUs of a network of ICUs, and the time that their patients spend within pre-specified glycaemic ranges.

A recommendation for class 4 and 6 support is being requested to link identifiable data to facilitate the review of medical records.

Confidential patient information requested

Access was requested to NHS number, hospital number, date of birth (as age), date of death (as survival time from admission), ethnicity, admission and discharge dates and sex.

CAG advice conclusion

The CAG agreed that the minimum criteria under the Regulations appeared to have been met, and therefore advised recommending support to the Health Research Authority, subject to compliance with the specific and standard conditions of support as set out below.

Specific conditions of support

1. Favourable opinion from REC **Received 08/07/2014.**
2. Confirmation of suitable security arrangements via IG Toolkit submission. **Confirmed 08/07/2014.**

As the above conditions have been accepted and/or met, this letter provides confirmation of final approval. I will arrange for the register of approved applications on the HRA website to be updated with this information.

Annual review

Please note that your approval is subject to submission of an annual review report to show how you have met the conditions or report plans, and action towards meeting them. It is also your responsibility to submit this report on the anniversary of your final approval and to report any changes such as to the purpose or design of the proposed activity, or to security and confidentiality arrangements. We are also streamlining the process to facilitate the service we provide to applicants. This means that annual reviews will be batched and reviewed on the last day of the preceding month before the date of approval. An annual review should therefore be provided no later than 30 June 2015 and preferably 4 weeks before this date.

Please do not hesitate to contact me if you have any queries following this letter. I would be grateful if you could quote the above reference number in all future correspondence.

Reviewed documents

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Covering Letter		09/04/2014
IRAS application form		09/04/2014

Confidentiality Advisory Group: final approval letter continued

NHS
Health Research Authority
Confidentiality Advisory Group

Protocol	1.0	07/04/2014
Data Flow diagram	1.0	09/04/2014
Leaflet		
Letter from Caldicott Guardian equivalent		09/04/2014
Response to CAG Queries Sheet		25/04/2014
REC Favourable Opinion Letter		12/06/2014
IGT submission confirmation		08/07/2014

Membership of the Committee

The members of the Confidentiality Advisory Group who were present at the consideration of this item are listed below.

There were *no* declarations of interest in relation to this item.

Feedback

You are invited to give your view of the service provided by the Confidentiality Advice Team and the application procedure in general by completion of this survey http://www.hra.nhs.uk/about-the-hralgovernance/quality-assurance/ We would be grateful if you could take some time to provide your feedback.

With the Group's best wishes for the success of this project.

Yours sincerely

John Robinson
Confidentiality Advisor

Email: HRA.CAG@nhs.net

Enclosures: *List of members who were present at the meeting and those who submitted written comments*

Standard conditions of approval

Copy to: NRESCommittee.eastmidlandsnottingham1@nhs.net

Standard conditions of approval

The approval provided by the Health Research Authority is subject to the following standard conditions.

The applicant will ensure that:

1. The specified patient identifiable information is only used for the purpose(s) set out in the application.
2. Confidentiality is preserved and there are no disclosures of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.
3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant.
4. All staff with access to patient identifiable information have contractual obligations of confidentiality, enforceable through disciplinary procedures.
5. All staff with access to patient identifiable information have received appropriate ongoing training to ensure they are aware of their responsibilities.
6. Activities are consistent with the Data Protection Act 1998.
7. Audit of data processing by a designated agent is facilitated and supported.
8. The wishes of patients who have withheld or withdrawn their consent are respected.
9. The Confidentiality Advice Team is notified of any significant changes (purpose, data flows, data items, security arrangements) prior to the change occurring.
10. An annual report is provided no later than 12 months from the date of your final confirmation letter.
11. Any breaches of confidentiality / security around this particular flow of data should be reported to CAG within 10 working days, along with remedial actions taken / to be taken.

Confidentiality Advisory Group
Sub Committee Meeting 02/05/2014

Group members

Name	Capacity
Dr Tony Calland (Vice Chair)	
Dr Patrick Coyle (Chair)	
Dr Murat Soncul	

NHS
Health Research Authority

NRES Committee East Midlands - Nottingham 1
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839695

12 June 2014

Dr Gary Adams
Lecturer
The University of Nottingham
Room B59b, School of Nursing
Queens Medical Centre, Derby Road
Nottingham
NG7 2UH

Dear Dr Adams

Study title:	**GlyCon: Glycaemic Control of Stress Hyperglycaemia Implemented in NHS Intensive Care Units**
REC reference:	**14/EM/0177**
Protocol number:	**14042**
IRAS project ID:	**129360**

Thank you for your letter of 29 May 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Helen Wakefield,at NRESCommittee.EastMidlands-Nottingham1@nhs.net

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Research Ethics Committee approval letter continued

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper	09 April 2014	09 April 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)	01 Aug 2013 - 31 July 2014 (Henderson Corporate)	31 July 2013
Letter from sponsor	University of Nottingham	09 April 2014
Other [Certificate of Attendance - Introduction to Good Clinical Practice]	Maria del Rocio Fernandez Mendez	10 April 2013
Other [MPhil/PhD Confirmation of Transfer Form]	Maria Del Rocio Fernandez Mendez	11 July 2013
Other [Certificate - Access to information and information sharing in the NHS (e-learning module)]	Maria del Rocio Fernandez Mendez	28 February 2014
Other [Data Flow Diagram During Data Collection]	1.0	09 April 2014
Other [Certificate - Introduction to Information Governance (e-learning module)]	Maria del Rocio Fernandez Mendez	28 February 2014
Other [Investigator's CV]	Maria del Rocio Fernandez Mendez	07 April 2014
Other [GlyCon - File with Identifiers]	1.0	09 April 2014
Other [Letter from CAG]		19 May 2014
Other [Investigator's CV]	Dr Gary George Adams	22 January 2014
Other [Glycaemic Control Treatment Data - Hourly Data/Variable Labels and Coding]	1.0	09 April 2014
Other [Certificate - 17th Annual Meeting of the Case Mix Programme]	Maria del Rocio Fernandez Mendez	03 April 2014
Other [Investigator's CV]	Dr Richard Windle	22 January 2014
Other [Data Extract from the CMP Database of ICNARC]	3.1.0	
Other [GlyCon Study Protocol Leaflet]	1.0	19 March 2014
REC Application Form	129360/593344/1/640	09 April 2014
Research protocol or project proposal	1.0	07 April 2014
Response to Request for Further Information		29 May 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/EM/0177 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp

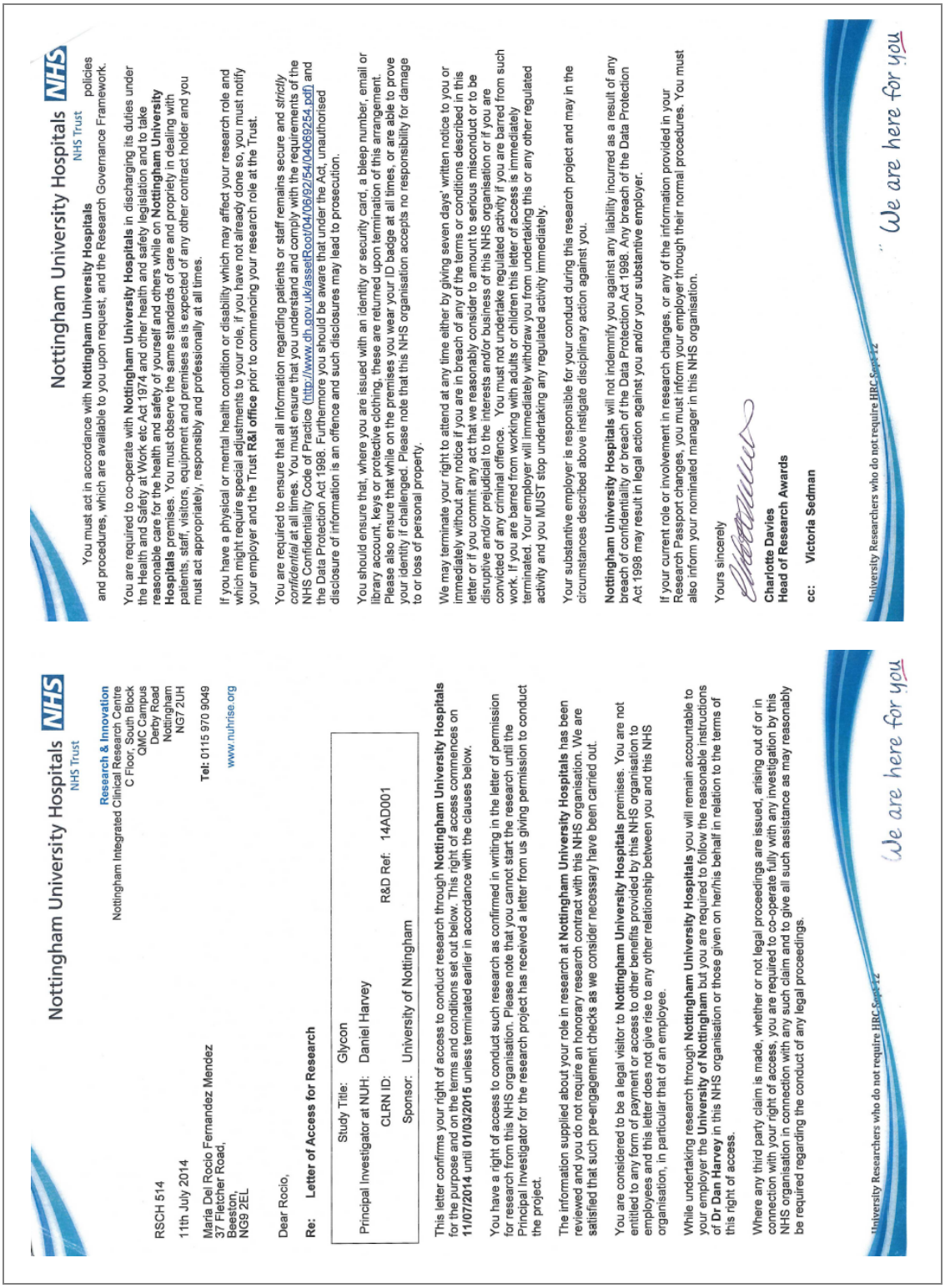
Dr Carl Edwards
Chair

Email:NRESCommittee.EastMidlands-Nottingham1@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Angela Shone*
Mr Edward Stimpson, Nottingham University Hospitals NHS Trust

Letter of Access from Nottingham University Hospitals Trust



Nottingham University Hospitals NHS
NHS Trust

Research & Innovation
Nottingham Integrated Clinical Research Centre
C Floor, South Block
QMC Campus
Derby Road
Nottingham
NG7 2UH

Tel: 0115 970 9049

www.nuhrise.org

RSCH 514

11th July 2014

Maria Del Rocio Fernandez Mendez
37 Fletcher Road,
Beeston,
NG9 2EL

Dear Rocio,

Re: Letter of Access for Research

Study Title:	Glycon
Principal Investigator at NUH:	Daniel Harvey
CLRN ID:	R&D Ref: 14AD001
Sponsor:	University of Nottingham

This letter confirms your right of access to conduct research through **Nottingham University Hospitals** for the purpose and on the terms and conditions set out below. This right of access commences on **11/07/2014** until **01/03/2015** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at **Nottingham University Hospitals** has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to **Nottingham University Hospitals** premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through **Nottingham University Hospitals** you will remain accountable to your employer the **University of Nottingham** but you are required to follow the reasonable instructions of **Dr Dan Harvey** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

University Researchers who do not require HRC Sept 12

We are here for you

Nottingham University Hospitals NHS
NHS Trust

You must act in accordance with **Nottingham University Hospitals** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with **Nottingham University Hospitals** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on **Nottingham University Hospitals** premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and the Trust **R&I office** prior to commencing your research role at the Trust.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/asset/Root/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Nottingham University Hospitals will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Charlotte Davies
Head of Research Awards

cc: Victoria Sedman

University Researchers who do not require HRC Sept 12

We are here for you

Letter of Access from United Lincolnshire Hospitals NHS Trust

United Lincolnshire Hospitals NHS
NHS Trust

RESEARCH & DEVELOPMENT DEPARTMENT
Telephone: 01522 512512 Ext 2059
Fax: 01522 597845
Email: Tanweer.Ahmed@ulh.nhs.uk

María del Rocío Fernández Méndez
37 Fletcher Road
Beeston
NG9 2EL

Lincolnshire Clinical Research Facility
Lincoln County Hospital
Greetwell Road
Lincoln
LN2 5QY

Our ref: HA

30th July 2014

Dear Rocío,

Letter of access for research

This letter should be presented to each participating organisation] before you commence your research at that site. The participating organisation(s) is/are:

United Lincolnshire Hospitals NHS Trust – *Lincoln County Hospital and Pilgrim Hospital*.

In accepting this letter, each participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. This right of access commences on **30th July 2014** and ends on **1st May 2015** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from **United Lincolnshire Hospitals NHS Trust**. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving confirmation from the individual organisation(s) of their agreement to conduct the research.

The information supplied about your role in research at the organisation(s) has been reviewed and you do not require an honorary research contract with the organisation(s). We are satisfied that such pre-engagement checks as we consider necessary have been carried out however the final decision rests with the University of Nottingham. Evidence of checks should be available on request to the organisation(s).

You are considered to be a legal visitor to the organisations premises. You are not entitled to any form of payment or access to other benefits provided by the organisation(s) or this organisation to employees and this letter does not give rise to any other relationship between you and the organisation(s), in particular that of an employee.

While undertaking research through United Lincolnshire Hospitals NHS Trust, you will remain accountable to your employer but you are required to follow the reasonable instructions of your nominated manager, **Alan Liddle (Lincoln County Hospital) and Yvonna Plesnikova (Pilgrim Hospital, Boston)**, in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by the organisation(s) in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with the organisations policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with the organisation(s) in discharging its/their duties under the Health and Safety at Work etc. Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on the organisations premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and each organisation prior to commencing your research role at that organisation.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the **Data Protection Act 1998**. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the organisations premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that the organisation(s) do not accept responsibility for damage to or loss of personal property.

This organisation may revoke this letter and any organisation(s) may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of the organisation(s) or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

No organisation will indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in each participating organisation and Helen Ayre – Research Governance & Quality Manager in this organisation.

Yours sincerely

Dr Tanweer Ahmed
Director of Lincolnshire Clinical Research Facility, Head of R&D & IP lead
United Lincolnshire Hospitals NHS Trust

cc: **ULHT Human Resources Dept.**
HR Dept. of the substantive employer

Letter of Access from Derby Hospitals NHS Foundation Trust

Derby Hospitals NHS
NHS Foundation Trust

Royal Derby Hospital
Uttoxeter Road
Derby
DE22 3NE

Tel: 01332 340131
Minicom: 01332 254944
www.derbyhospitals.nhs.uk

Ref No: Glycaemic control of stress

Ms. Maria del Rocio Fernandez Mendez,
PhD Student
B33, Postgraduate Office, B-Floor,
Medical School, Queens Medical Centre,
University of Nottingham
NG7 2HA

30 July 2014

Dear Ms. Maria del Rocio Fernandez Mendez

Letter of access for research – Data Collection

This letter confirms your right of access to conduct research through Derby Hospitals NHS Foundation Trust for the purpose and on the terms and conditions set out below. This right of access commences on **1/3/2014** and ends on **31/3/2015** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at Derby Hospitals NHS Foundation Trust has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to Derby Hospitals NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through Derby Hospitals NHS Foundation Trust, you will remain accountable to your employer **University of Nottingham** but you are required to follow the reasonable instructions of **Dr G Adams** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with Derby Hospitals NHS Foundation Trust policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with Derby Hospitals NHS Foundation Trust in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on Derby Hospitals NHS Foundation Trust premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Derby Hospitals NHS Foundation Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

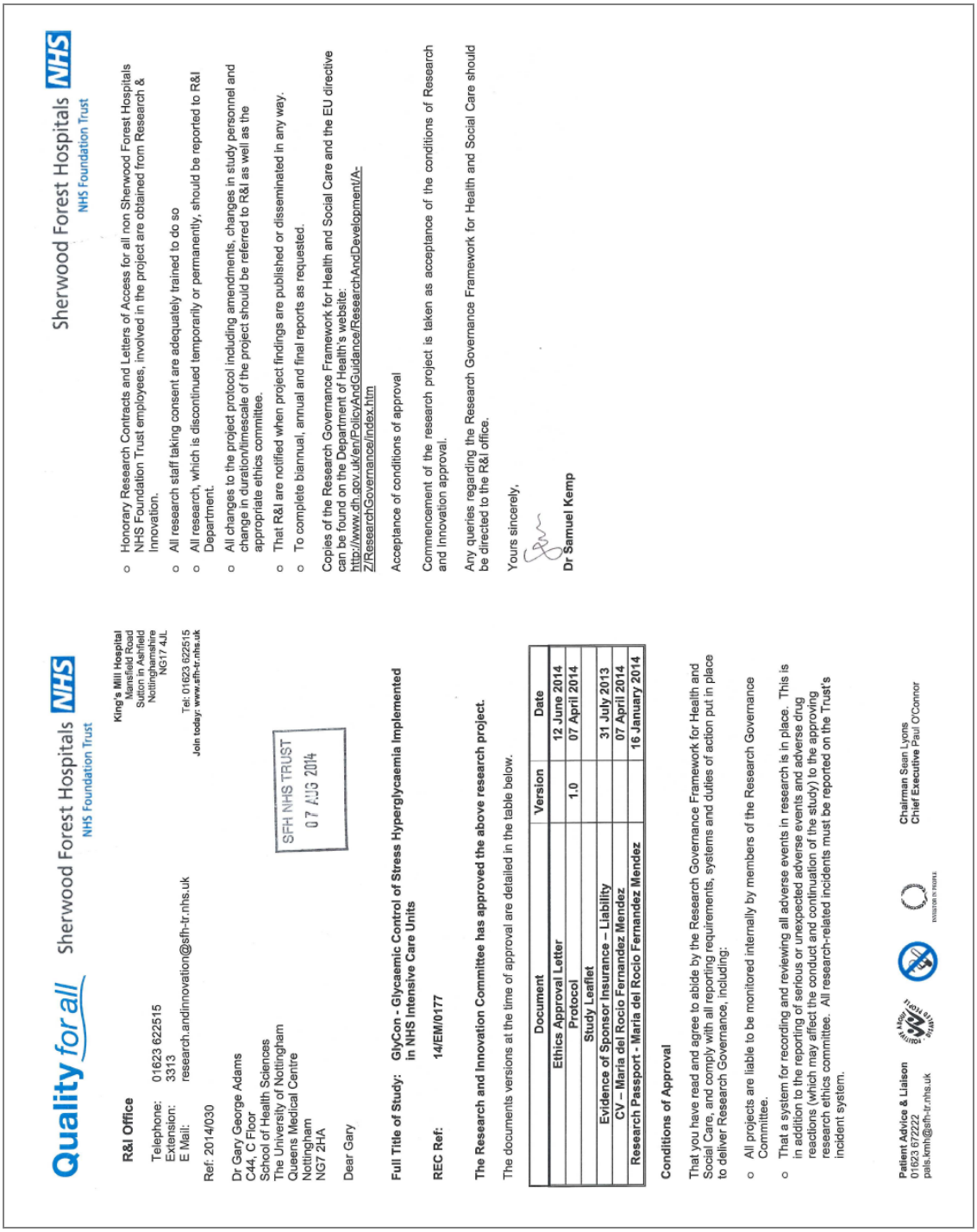
Claire Nourigan
for Recruitment & Retention Advisor
Derby Hospitals NHS Foundation Trust

cc: **R&D office at Derby Hospitals NHS Foundation Trust**
HR department of the substantive employer

Smoking is not permitted anywhere in the buildings and grounds of Derby's Hospitals. For advice and support about giving up smoking please call Free Phone 0800 707 6870.

Chief Executive: Sue James
Chair: John Rivers

Letter of Access from Sherwood Forest Hospitals NHS Foundation Trust



Quality for all — Sherwood Forest Hospitals NHS Foundation Trust

Sherwood Forest Hospitals NHS Foundation Trust

R&I Office

King's Mill Hospital
Mansfield Road
Sutton-in-Ashfield
Nottinghamshire
NG17 4JL

Telephone: 01623 622515
Extension: 3313
E Mail: research.andinnovation@sfh-tr.nhs.uk

Tel: 01623 622515
Join today: www.sfh-tr.nhs.uk

Ref: 2014/030

Dr Gary George Adams
C44, C Floor
School of Health Sciences
The University of Nottingham
Queens Medical Centre
Nottingham
NG7 2HA

SFH NHS TRUST
07 AUG 2014

Dear Gary

Full Title of Study: **GlyCon - Glycaemic Control of Stress Hyperglycaemia Implemented in NHS Intensive Care Units**

REC Ref: **14/EM/0177**

The Research and Innovation Committee has approved the above research project.

The documents versions at the time of approval are detailed in the table below.

Document	Version	Date
Ethics Approval Letter		12 June 2014
Protocol	1.0	07 April 2014
Study Leaflet		
Evidence of Sponsor Insurance – Liability		31 July 2013
CV – Maria del Rocio Fernandez Mendez		07 April 2014
Research Passport - Maria del Rocio Fernandez Mendez		16 January 2014

Conditions of Approval

That you have read and agree to abide by the Research Governance Framework for Health and Social Care, and comply with all reporting requirements, systems and duties of action put in place to deliver Research Governance, including:

- All projects are liable to be monitored internally by members of the Research Governance Committee.
- That a system for recording and reviewing all adverse events in research is in place. This is in addition to the reporting of serious or unexpected adverse events and adverse drug reactions (which may affect the conduct and continuation of the study) to the approving research ethics committee. All research-related incidents must be reported on the Trust's incident system.
- Honorary Research Contracts and Letters of Access for all non Sherwood Forest Hospitals NHS Foundation Trust employees, involved in the project are obtained from Research & Innovation.
- All research staff taking consent are adequately trained to do so
- All research, which is discontinued temporarily or permanently, should be reported to R&I Department.
- All changes to the project protocol including amendments, changes in study personnel and change in duration/timescale of the project should be referred to R&I as well as the appropriate ethics committee.
- That R&I are notified when project findings are published or disseminated in any way.
- To complete biannual, annual and final reports as requested.

Copies of the Research Governance Framework for Health and Social Care and the EU directive can be found on the Department of Health's website:
http://www.dh.gov.uk/en/PolicyAndGuidance/ResearchAndDevelopment/A-Z/ResearchGovernance/index.htm

Acceptance of conditions of approval

Commencement of the research project is taken as acceptance of the conditions of Research and Innovation approval.

Any queries regarding the Research Governance Framework for Health and Social Care should be directed to the R&I office.

Yours sincerely,

Dr Samuel Kemp

Patient Advice & Liaison
01623 672222
pals.kmh@sfh-tr.nhs.uk

Chairman Sean Lyons
Chief Executive Paul O'Connor

Letter of Access from Burton Hospitals NHS Foundation Trust

Burton Hospitals NHS
NHS Foundation Trust

Date: 31 October 2014

Ms M Del Rocio Fenandez Mendez
B33 Postgraduate Office
B Floor Medical School
The University of Nottingham
Queens Medical Centre
Nottingham
NG7 2HA

Queen's Hospital
Belvedere Road
Burton Upon Trent
Staffordshire
DE13 0RB

Telephone: 01283 566333

Dear Rocio

RESEARCH STUDY: GlyCon: Glycaemic control of stress hyperglycaemia
IRAS Reference: 123960
NRES Reference: 14/EM/0177

Letter of access for research

This letter should be presented to each participating organisation] before you commence your research at that site. The participating organisation is:

Burton Hospitals NHS Foundation Trust

In accepting this letter, each participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. This right of access commences on 31 October 2014 and ends on 01 May 2015 (or on completion of the study, if this is sooner) unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from **Burton Hospitals NHS Foundation Trust**. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving confirmation from the individual organisation of their agreement to conduct the research.

The information supplied about your role in research at the organisation has been reviewed and you do not require an honorary research contract with the organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out. Evidence of checks should be available on request to the organisation.

You are considered to be a legal visitor to the organisation's premises. You are not entitled to any form of payment or access to other benefits provided by the organisation, or this organisation to employees, and this letter does not give rise to any other relationship between you and the organisation, in particular that of an employee.

While undertaking research through the organisation you will remain accountable to your substantive employer but you are required to follow the reasonable instructions of the organisation or those instructions given on their behalf in relation to the terms of this right of access, in particular of Mrs L Vaughan, Medical Records Manager.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by the organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with the organisations policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with the organisation in discharging its/their duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on the organisations premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and each organisation prior to commencing your research role at that organisation.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the organisations premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that the organisation(s) do not accept responsibility for damage to or loss of personal property.

This organisation may revoke this letter and any organisation may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of the organisation(s) or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Letter of Access from Burton Hospitals NHS Foundation Trust continued

No organisation will indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in each participating organisation] and [the R&D office] in this organisation.

Yours sincerely

Claire Roberts
Medical Workforce and Education Centre Manager

cc: R&D office at Burton Hospitals NHS Foundation Trust
HR department of Nottingham University

Waiver of confidentiality for ICNARC to provide with patient identifiable data:

Queen's Hospital, Burton

ICNARC
Napier House
24 High Holborn
London WC1V 6AZ
tel +44 (0)20 7269 9288
fax +44 (0)20 7831 6879
email cmp@icnarc.org

case mix programme

Waiver of Confidentiality

Case Mix Programme

This Agreement is between the Intensive Care National Audit & Research Centre (ICNARC) of Napier House, 24 High Holborn, London WC1V 6AZ and

Dr Ian Poxon, Lead Clinician (the Participant)

of **Intensive Care Unit, Queen's Hospital, Burton**

and

Rocio Fernández Méndez, PhD Student (the Recipient)

of **The University of Nottingham and Queen's Medical Centre**

THE RECIPIENT wishes to receive identified analyses based on the data supplied by the Participant and included in the ICNARC Case Mix Programme Database (the data). The data are subject to the following confidentiality clause signed by ICNARC and the Participant:

> "The identity of the source of data, whether Participant, hospital, unit, staff or patient shall remain confidential. Notwithstanding the termination of this Agreement the parties agree to keep the source of data confidential."
>
> *Clause 4 of the ICNARC Case Mix Programme Participating Unit's Agreement.*

IT IS AGREED between ICNARC, the PARTICIPANT and the RECIPIENT that

5. ICNARC shall release identified analyses based on all or part of the Participant's data to the Recipient, based on variables and derived variables from the ICNARC Case Mix Programme Dataset Specification.

   for **GlyCon Study - glycaemic control methods implemented in the NHS intensive care units of Mid Trent Critical Care Network (MTCCN)**

2. The Recipient agrees to use the Participant's identified analyses solely for these purposes..
3. The Recipient agrees to receive the Participant's identified analyses and to be subject to the confidentiality agreement set out in Clause 4 of the ICNARC Case Mix Programme Participating Unit's Agreement.
4. The Recipient agrees to acknowledge ICNARC in any publication in whatever form, based on analyses released under this agreement.

Registered as a company limited by Guarantee • Registered No. 2946727 (England) • Registered Charity No. 1039417

Signed: _____ for the Participant (Name Dr. Ian Poxon) 21/12/14
Consultant GMC: 3588318
BLOCK CAPITALS
(Position CLINICAL LEAD (Crit. Care))

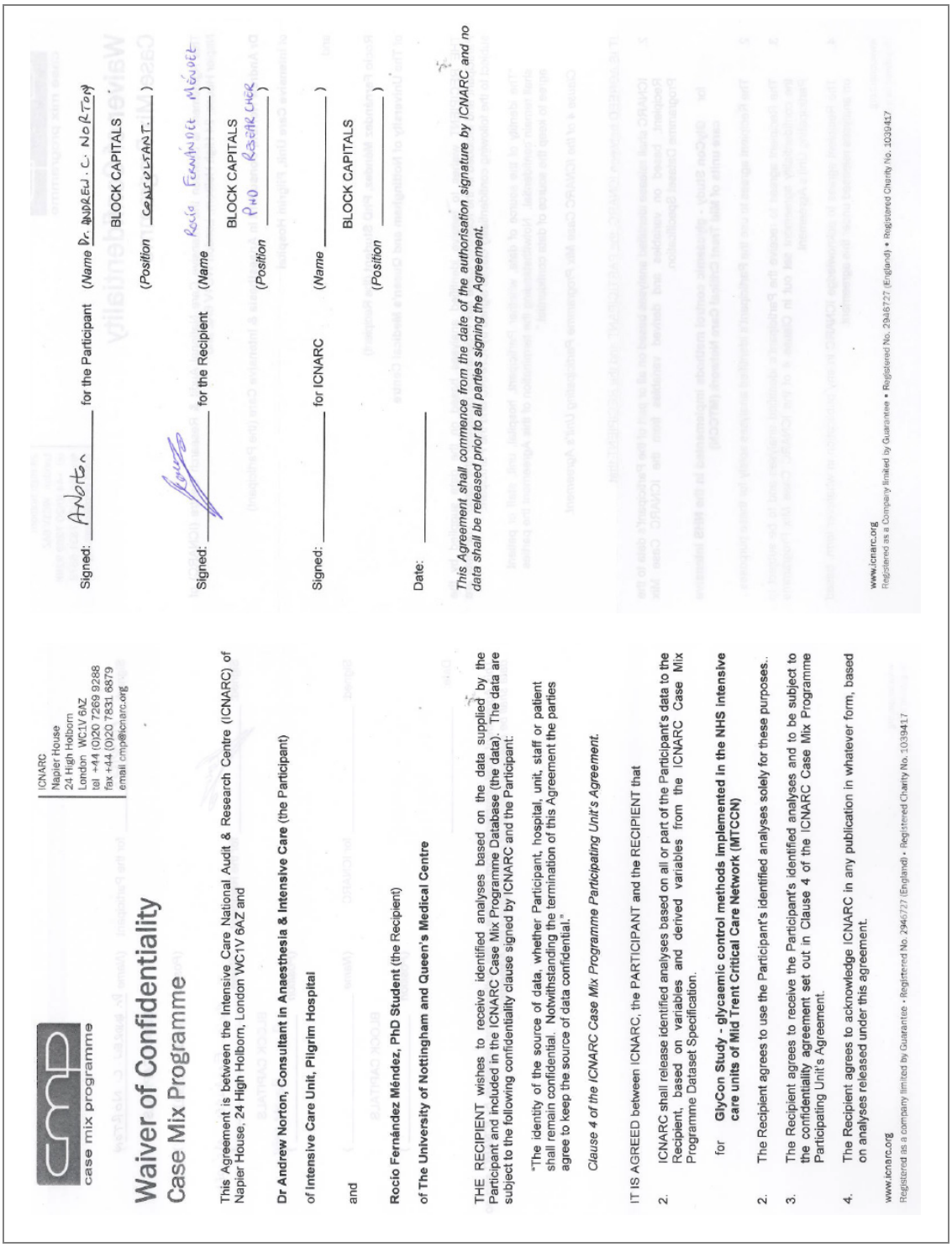
Signed: _____ for the Recipient (Name Rocio FERNÁNDEZ MÉNDEZ)
BLOCK CAPITALS
(Position PhD RESEARCHER)

Signed: _____ for ICNARC (Name _____)
BLOCK CAPITALS
(Position _____)

Date: _____

This Agreement shall commence from the date of the authorisation signature by ICNARC and no data shall be released prior to all parties signing the Agreement.

Waiver of confidentiality for ICNARC to provide with patient identifiable data: Pilgrim Hospital



cmp
case mix programme

ICNARC
Napier House
24 High Holborn
London WC1V 6AZ
tel +44 (0)20 7269 9288
fax +44 (0)20 7831 6879
email cmp@icnarc.org

Waiver of Confidentiality
Case Mix Programme

This Agreement is between the Intensive Care National Audit & Research Centre (ICNARC) of Napier House, 24 High Holborn, London WC1V 6AZ and

Dr Andrew Norton, Consultant in Anaesthesia & Intensive Care (the Participant)

of **Intensive Care Unit, Pilgrim Hospital**

and

Rocio Fernández Méndez, PhD Student (the Recipient)

of **The University of Nottingham and Queen's Medical Centre**

THE RECIPIENT wishes to receive identified analyses based on the data supplied by the Participant and included in the ICNARC Case Mix Programme Database (the data). The data are subject to the following confidentiality clause signed by ICNARC and the Participant:

> "The identity of the source of data, whether Participant, hospital, unit, staff or patient shall remain confidential. Notwithstanding the termination of this Agreement the parties agree to keep the source of data confidential."
>
> *Clause 4 of the ICNARC Case Mix Programme Participating Unit's Agreement.*

IT IS AGREED between ICNARC, the PARTICIPANT and the RECIPIENT that

2. ICNARC shall release identified analyses based on all or part of the Participant's data to the Recipient, based on variables and derived variables from the ICNARC Case Mix Programme Dataset Specification.

   for **GlyCon Study - glycaemic control methods implemented in the NHS intensive care units of Mid Trent Critical Care Network (MTCCN)**

2. The Recipient agrees to use the Participant's identified analyses solely for these purposes..
3. The Recipient agrees to receive the Participant's identified analyses and to be subject to the confidentiality agreement set out in Clause 4 of the ICNARC Case Mix Programme Participating Unit's Agreement.
4. The Recipient agrees to acknowledge ICNARC in any publication in whatever form, based on analyses released under this agreement.

Signed: Anorton for the Participant (Name Dr. ANDREW C. NORTON)
BLOCK CAPITALS
(Position CONSULTANT)

Signed: _____ for the Recipient (Name Rocio Fernández Méndez)
BLOCK CAPITALS
(Position PhD Research Chem)

Signed: _____ for ICNARC (Name _____)
BLOCK CAPITALS
(Position _____)

Date: _____

This Agreement shall commence from the date of the authorisation signature by ICNARC and no data shall be released prior to all parties signing the Agreement.

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Waiver of confidentiality for ICNARC to provide with patient identifiable data:

Royal Derby Hospital

ICNARC
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fax +44 (0)20 7831 8879
email cmp@icnarc.org

case mix programme

Waiver of Confidentiality
Case Mix Programme

This Agreement is between the Intensive Care National Audit & Research Centre (ICNARC) of Napier House, 24 High Holborn, London WC1V 6AZ and

Dr James Low, Clinical Lead for Intensive Care (the Participant)

of **Adult Intensive Care Unit, Royal Derby Hospital**

and

Rocío Fernández Méndez, PhD Student (the Recipient)

of **The University of Nottingham and Queen's Medical Centre**

THE RECIPIENT wishes to receive identified analyses based on the data supplied by the Participant and included in the ICNARC Case Mix Programme Database (the data). The data are subject to the following confidentiality clause signed by ICNARC and the Participant:

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>
> *Clause 4 of the ICNARC Case Mix Programme Participating Unit's Agreement.*

IT IS AGREED between ICNARC, the PARTICIPANT and the RECIPIENT that

7. ICNARC shall release identified analyses based on all or part of the Participant's data to the Recipient, based on variables and derived variables from the ICNARC Case Mix Programme Dataset Specification.

   for **GlyCon Study - glycaemic control methods implemented in the NHS intensive care units of Mid Trent Critical Care Network (MTCCN)**

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Signed: _____ for the Participant (Name James Low)
BLOCK CAPITALS
(Position Lead Consultant)

Signed: _____ for the Recipient (Name Rocío Fernández Méndez)
BLOCK CAPITALS
(Position PhD Researcher)

Signed: _____ for ICNARC (Name _____)
BLOCK CAPITALS
(Position _____)

Date: _____

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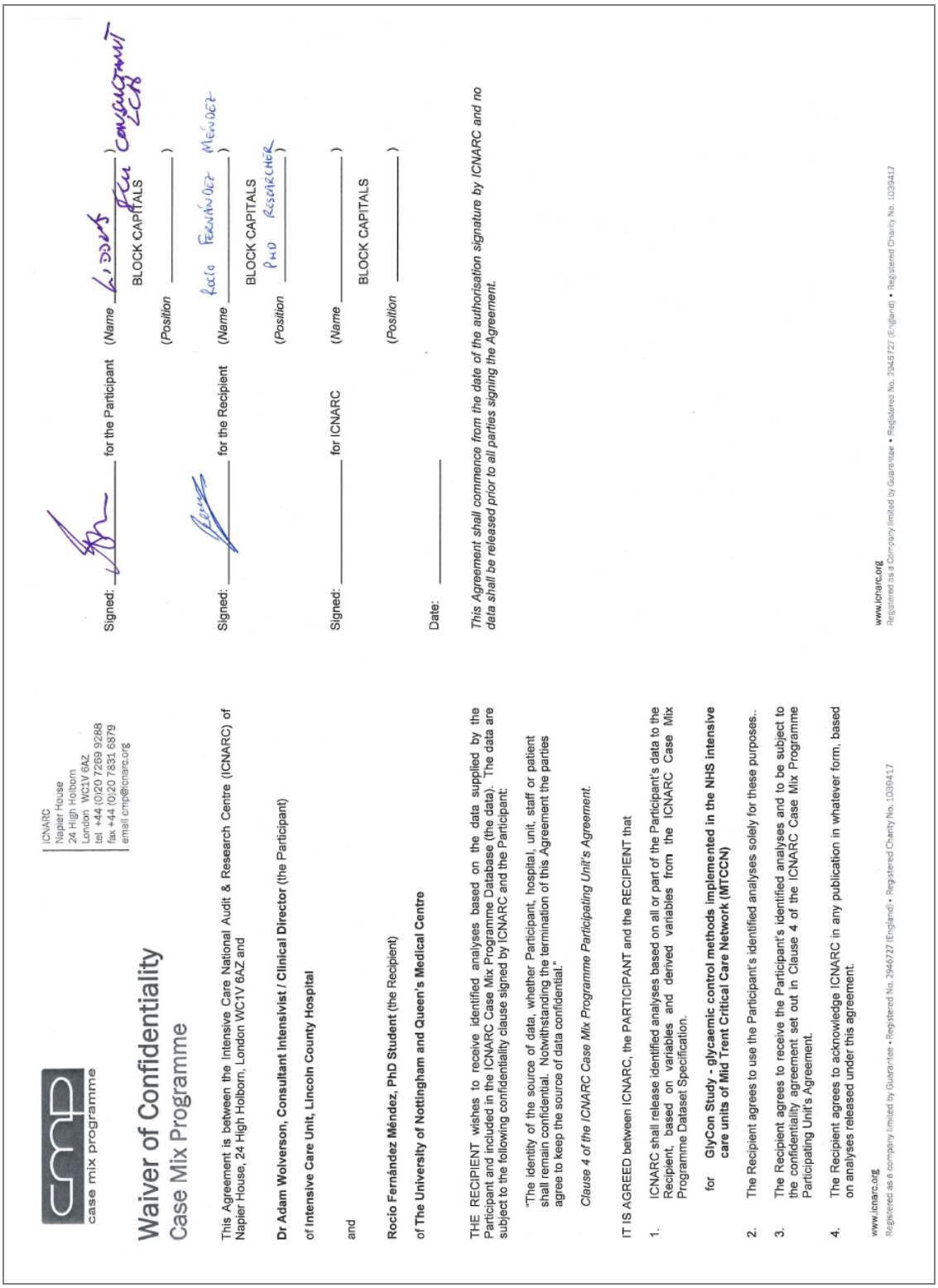
Lincoln County Hospital



case mix programme

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Waiver of Confidentiality

Case Mix Programme

This Agreement is between the Intensive Care National Audit & Research Centre (ICNARC) of Napier House, 24 High Holborn, London WC1V 6AZ and

Dr Adam Wolverson, Consultant Intensivist / Clinical Director (the Participant)

of **Intensive Care Unit, Lincoln County Hospital**

and

Rocío Fernández Méndez, PhD Student (the Recipient)

of **The University of Nottingham and Queen's Medical Centre**

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4. The Recipient agrees to acknowledge ICNARC in any publication in whatever form, based on analyses released under this agreement.

Signed: _____ for the Participant (Name _____) Consultant ICCU
BLOCK CAPITALS
(Position _____)

Signed: _____ for the Recipient (Name _____) Rocío Fernández Méndez
BLOCK CAPITALS
(Position PhD Researcher)

Signed: _____ for ICNARC (Name _____)
BLOCK CAPITALS
(Position _____)

Date: _____

This Agreement shall commence from the date of the authorisation signature by ICNARC and no data shall be released prior to all parties signing the Agreement.

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Waiver of confidentiality for ICNARC to provide with patient identifiable data:

King's Mill Hospital

cmp
case mix programme

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London WC1V 6AZ
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fax +44 (0)20 7831 6879
email cmp@icnarc.org

Waiver of Confidentiality

Case Mix Programme

This Agreement is between the Intensive Care National Audit & Research Centre (ICNARC) of Napier House, 24 High Holborn, London WC1V 6AZ and

Dr Lisa Milligan, Lead Clinician for Critical Care (the Participant)

of Integrated Critical Care Unit, King's Mill Hospital

and

Rocio Fernández Méndez, PhD Student (the Recipient)

of The University of Nottingham and Queen's Medical Centre

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4. The Recipient agrees to acknowledge ICNARC in any publication in whatever form, based on analyses released under this agreement.

Signed: _____ for the Participant (Name LISA MILLIGAN)
BLOCK CAPITALS
(Position _____)

Signed: _____ for the Recipient (Name Rocio Fernández Méndez)
BLOCK CAPITALS
(Position PhD RESEARCHER)

Signed: _____ for ICNARC (Name _____)
BLOCK CAPITALS
(Position _____)

Date: _____

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Waiver of confidentiality for ICNARC to provide with patient identifiable data:

Nottingham City Hospital

case mix programme

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Waiver of Confidentiality
Case Mix Programme

This Agreement is between the Intensive Care National Audit & Research Centre (ICNARC) of Napier House, 24 High Holborn, London WC1V 6AZ and

David Sperry, Clinical Director (the Participant)

of Adult Intensive Care Unit, Nottingham City Hospital

and

Rocio Fernández Méndez, PhD Student (the Recipient)

of The University of Nottingham and Queen's Medical Centre

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Signed: _____ for the Participant (Name DA SPERRY)

BLOCK CAPITALS

(Position Consultant Intensivist)

Signed: _____ for the Recipient (Name Rocio Fernández Méndez)

BLOCK CAPITALS

(Position PhD Student)

Signed: _____ for ICNARC (Name _____)

BLOCK CAPITALS

(Position _____)

Date: _____

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Waiver of confidentiality for ICNARC to provide with patient identifiable data: Queen's Medical Centre

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case mix programme

Waiver of Confidentiality
Case Mix Programme

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David Sperry, Clinical Director (the Participant)

of **Adult Intensive Care Unit, Queen's Medical Centre**

and

Rocio Fernández Méndez, PhD Student (the Recipient)

of **The University of Nottingham and Queen's Medical Centre**

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Signed: _____ for the Participant (Name DA SPERRY)
BLOCK CAPITALS
(Position Consultant Intensivist)

Signed: _____ for the Recipient (Name Rocio Fernández Méndez)
BLOCK CAPITALS
(Position PhD Student)

Signed: _____ for ICNARC (Name _____)
BLOCK CAPITALS
(Position _____)

Date: _____

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Appendix F

Relevant training courses in data protection and confidentiality

Short course: Introduction to Good Clinical Practice

NHS
National Institute for Health Research
Clinical Research Network

Certificate of Attendance

Maria del Rocio Fernandez Mendez

attended

Introduction to Good Clinical Practice (GCP):
A practical guide to ethical and scientific
quality standards in clinical research

on 10/04/2013

Sessions include:
1. The Value of Clinical Research and the role of the NIHR CRN
2. GCP: the standards and why we have them
3. Study set up: responsibilities, approvals and essential documents
4. The process of informed consent
5. Case report form, source data and data entry completion
6. Safety reporting in clinical trials

Emma Lowe
NIHR CRN Learning and Development Lead

Short course: Access to information and information sharing in the NHS

Short course: Introduction to Information Governance