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Factors Affecting Utilisation of Biosimilar Medicines in England

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Abstract

Biological medicinal products (BMPs) are medicinal products extracted from, or synthesised by, a biological system. While BMPs have been proven to be effective in treating chronic and life-threatening diseases, the utilisation of these medicines was associated with creating financial burdens for healthcare systems worldwide. Expiry of patents and marketing exclusivity rights offers an opportunity to develop similar and not identical follow-on copies called 'biosimilar medicinal products' (BSPs). The inability to produce an identical copy of the original product is related to the heterogenic molecular nature of BMPs and the complexity of the manufacturing processes involved. The United Kingdom (UK) was frequently reported to have only a limited uptake of BSPs. Factors related to prescribers' reservations and lack of encouraging national policies were reported to limit BSPs' utilisation in the UK.

In February 2015, the first high-cost monoclonal antibody (mAb), 'infliximab' (IFX-BSP), was launched; it was the first BSP to be commissioned locally compared to the previously nationally commissioned BSPs. Since its launch, there have been several encouraging national initiatives led by NHS-England and NICE. These conditions created new market daynamics that might affect uptake rates of BSPs, particularly IFX-BSP.

This thesis explores factors affecting BSPs' utilisation and integration in clinical practice in England. The aim and objectives were actualised following an explanatory sequential mixed methods design. The study's first component assessed BSPs' integration levels in local medicines formularies and investigated the prescribing practices of IFX-BSPs by English Acute Trusts. Guided by first component results, the second explanatory component investigated factors that led to the observed utilisation rates of IFX-BSPs. The explanatory study was achieved through 59 in-depth semi-structured interviews with healthcare professionals, who were involved in assessing, commissioning, introducing, managing and prescribing IFX-BSPs.

In general, formularies screening showed that the integration levels of targeted BSPs were less than expected from a generic medicines driven market. Data showed variations in the uptake levels between therapeutic and geographical areas within Great Britain; a phenomenon which needs to be further investigated and explained. In England, assessing prescribing practice showed that with time Acute Trusts were becoming more accepting of utilising IFX-BSPs and were beginning to switch their R-BMP stabilised patients over to the BSPs.

Interviews suggested that prescribers' knowledge, experience, common medical practice, professional societies and ethical obligations had influenced prescribers' acceptance and attitudes toward BSPs, in general, and to the switching of stabilised patients in particular. Data showed BSPs' utilisation was not only affected by prescribers' attitudes, but it was also influenced by pull-push dynamics between providing Acute Trusts and commissioning CCGs.

The knowledge gained from this research could be used to inform the future implementation of upcoming BSPs. Insights acquired from this research regarding interactions between providers and commissioners might be extrapolated to implementing interventions locally, especially when there is an absence of nationally specific policies or guidelines.

Publications

Alnahar S., Elliott RA., Smith MD. The uptake of Biosimilar products by British formularies.
Value in Health 2015, Vol. 18, Issue 3, A80
Abstract presentation as a poster at the 20th Annual International Meeting of the International Society For Pharmacoeconomics and Outcomes Research (ISPOR)–Philadelphia-USA, May 2015

Alnahar S, Smith MD., Elliott RA. British local formularies: are they ready for biosimilar medicines? International Journal of Pharmacy Practice. 24():29, APR 2016
Abstract presented as an oral communication at The Health Services Research and Pharmacy Practice Conference-Reading-UK, April 2016

Alnahar S, Smith MD., Elliott RA. The uptake of biosimilar infliximab by English Acute Trusts.
Value in Health 2016, Vol. 19, Issue 3, A265
Abstract presentation as a poster at the 21st Annual International Meeting of the International Society For Pharmacoeconomics and Outcomes Research (ISPOR)-Washington, DC-USA, May 2016

Alnahar S, Elliott RA., Waring J. Infliximab Biosimilar Acceptance by Local Formularies in Great Britain
Abstract presentation as a poster at United Kingdom medicines information (UKmi) Practice Development Seminar-Birmingham-UK, September 2016

Alnahar S, Elliott RA., Waring J. The utilisation of biosimilar infliximab by English Acute Trusts.
Value in Health 2017, Vol. 20, Issue 9, A663

Alnahar S, Elliott RA., Waring J. Factors Affecting the Utilisation of Infliximab Biosimilar in England (in press)

Research Paper
Alnahar S, Elliott RA, Smith MD. Biosimilar uptake by British local formularies: a cross sectional study. International Journal of Clinical Pharmacy. 2017 Sep 4:1-6. doi 10.1007/s11096-017-0523-6

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List of abbreviations

ABPI	Association Of The British Pharmaceutical Industry
ADR	Adverse Drug Reaction
API	Active Pharmaceutical Ingredient
AWMSG	All Wales Medicines Strategy Group
BGMA	British Generic Manufacturers Association
BIA	Budget Impact Analysis
BMP	Biological Medicinal Product
BNF	British National Formulary
BSP	Biosimilar Medicinal Product
BSR	British Society for Rheumatology
CCG	Clinical Commissioning Group
CMA	Cost Minimisation Analysis
CUA	Cost Utility Analysis
EEA	European Economic Area
EMA	European Medicines Agency
EPO	Recombinant human erythropoietin (epoetin)
EU	The European Union
G-CSF	Granulocyte Stimulating Factor (filgrastim)
HCP	Healthcare Professionals
HGH	Human Growth Hormone (somatropin)
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
IFX	Infliximab
INN	International Non-proprietary Name
IV	Intravenous injection or infusion
mAb	Monoclonal Antibody
MHRA	Medicines and Healthcare products Regulatory Agency
MTA	Multiple Technology Appraisal
MODB	Medicines Optimisation Dashboard
NCPE	National Centre for Pharmacoeconomics in Northern Ireland
NHS-England	National Health Service in England
NICE	National Institute for Health and Care Excellence

PD	Pharmacodynamics
PK	Pharmacokinetics
POM	Prescription-only medicines
PPRS	Pharmaceutical Price Regulation Scheme
PRCA	Pure Red Cell Aplasia
QOF	Quality and Outcomes Framework
R-BMP	Reference Biological Medicinal Product
SC	Subcutaneous injection
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
T1	First stage of translation process
T2	Second stage of translation process
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

List of main definitions

Biological Medicines

The European Union (EU) directive No. 2001/83/EC defines BMP as “a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control” (The European Parliament, 2001)

Similar Biological Medicinal Products

The European Medicines Agency (EMA) defines BSP as “a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the European Economic Area (EEA). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established” (European Medicines Agency (EMA), 2014a)

Implementation Research

Implementation research is the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services. It includes the study of influences on healthcare professional and organisational behaviour (Eccles and Mittman, 2006)

Local Medicines Formularies

The output processes to support the managed introduction, utilisation or withdrawal of healthcare treatments within a health economy, service or organisation”(The National Institute for Health and Care Excellence (NICE), 2015a)

Chapter One: Thesis Introduction Chapter

1.1. General introduction

Biological medicinal products (BMPs) have provided an innovative approach to treating chronic and life-threatening diseases (Pisani and Bonduelle, 2008). However, as the acquisition cost of these medicines is high, the utilisation of BMPs is associated with an overwhelming financial burden for health services globally (Aitken, 2016, Ventola, 2013). Patent protection and market exclusivity rights of BMPs assure a certain level of market monopoly for these medicines. Nevertheless, patent expiry allows for the development and marketing of subsequent follow-on copies of BMPs (Ventola, 2013, Kresse, 2009). As BMPs are characterised by complicated, heterogenic molecular structures that cannot be fully characterised, follow-on copies have similar rather than an identical structures to their corresponding reference BMPs (R-BMPs). Therefore, follow-on copies are called biosimilar medicinal products (BSPs) (Declerck and Simoens, 2012, Brussels, 2005). Due to the resource intensive development and manufacturing processes required for BSPs, price reductions offered by the manufacturers of these medicines are modest and significantly lower than the reductions offered by manufacturers of conventional generic medicines. However, as BSPs are intended to replace the costly R-BMPs that are consuming an ever larger proportion of drug budgets, the overall impact of utilising BSPs on the healthcare systems' financial resources is expected to be significant (Rovira et al., 2011, EGA, 2011).

Since the licensing of the first BSP in 2006, the uptake of BSPs in the United Kingdom(UK) has been varied and less, in general, than other European countries (QunitilesIMS, 2017). Lack of policies designed to incentivise BSP uptake, the lack of approval of pharmacy-level auto-substitution and prescribers' concerns regarding the safety and efficacy of BSPs, have all been flagged as factors contributing to the observed limited utilisation of these medicines in the UK (British Generic Manufacturers Association (BGMA), 2013)

Recently, the UK market has witnessed the launch of similar copies of some of the top ten medicines in terms of cost; in particular infliximab and etanercept. Moreover, both the National Health Service England (NHS-England) and the National Institute for Health and Care Excellence (NICE) have been active in promoting the utilisation of BSPs. Their activities have been both educational and informative, aimed at explaining technical aspects of BSPs and demonstrating national experiences in implementing BSPs in clinical settings (The National Institute for Health and Care Excellence (NICE), 2015d, NHS England-Medical Directorate, 2015).

The research described in this thesis was carried out to examine the integration levels of BSPs in clinical practice, and to investigate factors, which both led to, and contributed to, the observed integration levels. The research aim was achieved using a mixed methods approach; starting with a quantitative exploratory study that assessed BSPs listing status in local formularies, and their prescribing approach as demonstrated by Acute Trusts. This study was followed by a qualitative explanatory study that investigated factors that were associated with BSP uptake by interviewing professionals from different healthcare settings (providers and commissioners) in England, who were involved in assessing, commissioning and prescribing BSPs. The research focus was limited to England for feasibility and convenience reasons. Research conduct and data interpretation were broadly influenced by Rogers's theory (Rogers, 2003) on the diffusion of innovation. The findings from quantitative and qualitative parts of the thesis were synthesised to generate new insights into the variation in the extent of BSP uptake, and what factors were involved in determining that variation. A further contribution of this work is to provide recommendations around future support for the diffusion of innovation in health services.

1.2. Thesis structure

Chapter One: Introduction: This chapter provides an overall introduction and brief description of each chapter; the study's design and its main findings.

Chapter Two: Literature Review: The literature review provides a background of the research area by discussing factors reported to affect the utilisation of medicinal products in general, and BSP in particular. The chapter begins by explaining key concepts, as well as the manufacturing process of BMPs and BSPs. Second, issues relating to BSPs' licensing, pricing, reimbursement and pharmacy level policies and legislation are explained. Third, it discusses the BSPs market, considering the added value of integrating these products into medical practice and the reported uptake level in the UK in comparison to Europe's 'Big Five' countries. Fourth, the chapter critically discusses factors reported to affect the utilisation of BSPs in the UK regarding BSPs' specific demand and supply side policies, as well as prescribers' concerns about, and acceptance of, BSPs. Finally, the chapter presents the overall thesis rationale, aim, objectives and research questions.

Chapter Three: Research Methodology and Methods: This chapter discusses the overarching research methodology and method(s) used for each empirical chapter. The chapter explains how each method fits its purpose and helps in answering the overall research questions. It discusses the added value of mixed methods research and the triangulation of results in addressing research questions. Considerations related to rigour, reliability and trustworthiness are also discussed.

Chapter Four: Assessing Uptake of Biosimilar Medicinal Products by British Local Formularies and English Acute Trusts: This is the first empirical chapter, and it represents results of the exploratory quantitative study. The results are divided into two main streams: BSPs integration and listing status secondary care formularies in Great Britain, and the prescribing patterns (initiation or switching) of infliximab BSP (IFX-BSP) at English Acute Trusts. The chapter highlights variations between different countries: Scotland, England and Wales, and between regions within England.

Chapter Five: Factors Affecting Decision of Adopting Infliximab Biosimilars in England-Qualitative Study: This chapter represents results of the explanatory qualitative study. It starts by describing study participants in terms of profession and geographical location. The chapter then presents evidence grouped into four main themes: (i) participants' awareness and knowledge of BSPs' concept, regulation and licensing, (ii) the process of evaluation, assessing and accepting BSPs and switching stabilised patients, (iii) negotiations and communications between relevant professionals that have led to the decision of using or not using BSPs, mainly IFX-BSPs and (iv) BSPs integration and switch implementation in terms of the prescribing approach, patients' communications, medicines management and implementation's outcomes. Presented themes will touch upon participants' experiences, perceptions and motives in commissioning, managing, prescribing and administering biosimilar medicines. The study's results identified facilitators and barriers for integrating BSPs and switching R-BMPs stabilised patients to BSPs. The study's results might be extrapolated for future BSPs and new interventions within the NHS.

Chapter Six: Overall Discussion and Conclusion: This chapter presents an overall discussion of the research findings, and how results from each component (quantitative and qualitative) were triangulated to answer the research questions. The research findings, together with the study's overall design and conduct are critically evaluated, and areas for improvement are suggested. The chapter discusses research strengths and limitations; also key priority areas for future research projects are proposed. The chapter is concluded by highlighting the key research findings and how these might inform future policy planning.

Chapter Two: Literature Review Chapter

2.1. Introduction to the literature review

This chapter represents and discusses literature related to the utilisation of biological medicinal products (BMPs) in general, and biosimilar medicinal products (BSPs) in particular, in the UK. The chapter is structured in four main sections, as follows: (*i*) the first provides an introduction to biological and biosimilar products definitions and manufacturing; (*ii*) the second explains regulations and licensing; (*iii*) the third section discusses BSPs' market and potential impact on health systems; and (*iv*) the last section is focused on the BSPs' market in the UK regarding overall performance, related policies, and factors affecting uptake.

2.2. Biosimilar and Biological Medicinal Products

2.2.1. Concepts and Definitions

The term BMPs is used to describe a wide range of therapeutic agents synthesised by, or extracted from, biological systems. The term covers a variety of medicines such as vaccines, blood and plasma products, in addition to medicines produced by biotechnologies. In the latter group are included recombinant DNA (r-DNA) technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cell, and hybridoma and monoclonal antibody techniques. The Term (BMP) is also used to describe therapeutic agents produced using gene therapy and tissue engineering technologies. (The European Parliament, 2001, Prugnaud and Trouvin, 2012, Offeciers-Van De Wiele, 1993). Since the introduction of the first biotechnology produced medicine, insulin in 1978 (Genentech, 1978), BMPs have provided innovative treatment for some chronic and life-threatening diseases such as diabetes, cancers, rheumatoid arthritis, hepatitis C, and multiple sclerosis (Pisani and Bonduelle, 2008). With time, BMPs have become the fastest growing segment within the pharmaceutical market, with 27% of the total pharmaceutical sales in Europe between 2012 and 2013 for BMPs (Intercontinental Marketing Services Health (IMS), 2014). Eight out of the top ten selling pharmaceutical products in 2013 in Europe were BMPs (IMS Health, 2014, Mckinsey and Company, 2013). It is expected that BMPs will account for 28% of the global pharmaceutical market in 2020 (Aitken, 2016). Discovery, testing, licensing and manufacturing of innovative medicines in general, and BMPs in particular, are associated with high financial investments. For that reason, regulatory bodies and agencies grant innovators patent and market exclusivity rights to reward the innovators, sustain innovation and drug discovery, and protect manufacturers from experiencing market failure. This outcome is achieved by offering developers and marketeers exclusive marketing right for a certain period of time, to allow them to reclaim financial investment without being subjected market competition (Kesselheim et al., 2017). As a result, BMPs have been reported to be associated with financial burdens on national healthcare systems worldwide; for instance, the top eight selling BMPs (adalimumab, insulin glargine, etanercept, infliximab, rituximab, peg-filgrastim, trastuzumab and follitropin alfa) are expected to cost the big five European countries (Germany, France, the United Kingdom, Italy and Spain) around €47 billion in the period between 2016-2020, if no competition exists (Aitken, 2016). Patent and market exclusivity rights are subject to expiry, which in turns allow for the development, manufacturing and marketing of subsequent/follow-on products containing the original molecule previously covered by the patent; such products are usually called "generic" medicines. Subsequent entries change market dynamics and influence competition between manufacturers, which in many cases results in lower prices and reduced medicines costs to health care providers and/or patients (Kesselheim et al., 2017).

As BMPs' patent and market exclusivity protection rights expire, the development and marketing of off-patent copies of these medicines, known as biosimilar medicinal products (BSPs), become possible (Ventola, 2013, Kresse, 2009).The European Medicines Agency (EMA) define a biosimilar medicine as "a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the European Economic Area (EEA). The similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy, based on a comprehensive comparability exercise, needs to be established" (European Medicines Agency (EMA), 2014a). Due to the heterogenic and complex manufacturing process of biological medicines including BSPs, it is not possible to produce identical but rather similar copies of off-patent reference BMPs (R-BMPs). Therefore, unlike chemical generic medicinal products (conventional generic products) such as simvastatin or paracetamol, the term "similar" instead of "biogeneric" is considered to be more accurate and reflective. (Declerck and Simoens, 2012, Brussels, 2005). The main difference between the two types of off-patent copies are summarised in Table 1.

Table 1-Comparison between biological and chemical medicinal products

	Biosimilar medicinal product	Conventional generic product
Method of synthesis	Living systems	Chemical interaction/fermentation
Molecular size (Dalton)	Large molecule (20,000-200,000)	Small molecule (100-200)
Structural nature	Heterogenic, complex and unstable mixture of molecule that cannot be fully characterised	Simple, stable and well defines structure
Structural reproducibility	Difficult to establish	Easy to establish
Mutagenicity	As a biological medicine it is expected to trigger immunological response	As a chemical medicine it is unlikely to trigger immunological response
Route of administration	Currently parenteral route only (IV or SC)	Any route of administration (oral, parenteral)
Clinical development	Extensive clinical trial activities, including Phase *I* and *III* studies*†	Limited clinical testing, often only Phase *I* studies (bioequivalence)
Development cost ($ million)	80-120	Up to 5
Development period (years)	6-10	1-2
Regulation‡	Centrally by EMA	Single country through mutual recognition

***** BSPs development and licensing are based on at least one Phase *III* clinical trial
† Phase II are not required where the reference is available
‡ In the European Union Countries

IV: Intravenous route, **SC:** Subcutaneous route

References: (Dunn, 2012, Declerck and Simoens, 2012, Chow, 2013, European Commission, 2013 , Alten and Cronstein, 2015)

2.3. Biosimilar licensing and regulation

Policies and regulations affecting the availability and the utilisation of a medicinal product can be largely categorised into four main categories: (i) licensing regulations, (ii) pricing and market entry, (iii) pharmacy and consumer level and finally (iv) prescribing management (Ess et al., 2003). The following sections discuss these policies and their influence on the uptake of BSPs.

2.3.1. Assessment, licensing and authorisation of biosimilar medicines

In Europe, including the UK[1], BSPs are assessed and approved centrally by the European Medicines Agency (EMA). In fact, the EMA was the first regulatory agency in the world to set a pathway for authorising BSPs in 2005 (Commission Delegated Regulation (EU) 2001/83/EC of 6 November 2001, European Medicines Agency (EMA), 2014a). Along with the World Health Organisation (WHO), it is the most frequently used and referred-to pathway by other regulatory agencies worldwide (Krishnan et al., 2015). Since 2005, EMA has issued 16 guidelines related to BSPs (three overarching, eight product specific, one reflection paper and four relevant guidelines) (European Medicines Agency (EMA), 2017b).

Despite the fact that patent expiry allows for the production and marketing of follow-on copies, it does not mean that the manufacturing processes will be available in the public domain and accessible by BSPs' manufacturers. Therefore, the BSPs' manufacturers need to develop their unique process and cell lines (Declerck and Simoens, 2012, Müller et al., 2014). The unique process might be perceived to be problematic as living systems are used in producing BMPs; differences in living systems will lead to variations in molecular structure, and products' impurity profiles (Declerck and Simoens, 2012, European Medicines Agency (EMA), 2014c, European Medicines Agency (EMA), 2014b). The R-BMPs' manufacturers might hold patent rights over analytical procedures needed to assess and test the molecular quality and stability, which in turn means that manufacturers of BSPs must develop their own procedures to assess and test their molecule and product (Krishnan et al., 2015). Since the "the process defines the product" (Vulto and Jaquez, 2017), the conventional generics' licensing pathway was not considered to be scientifically appropriate for the assessing and licensing of BSPs. Therefore a more appropriate pathway that can assess quality, safety and efficacy of BSPs was needed (Commission Delegated Regulation (EU) 2001/83/EC of 6 November 2001, European Medicines Agency (EMA), 2014a).

Accordingly, the EMA's BSPs' guidelines and authorisation requirements were tailored to address the heterogeneous and special nature of biological medicines and concerns about BSPs in terms of quality, efficacy and safety (Aapro, 2011, Brussels, 2005). In authorising BSPs, the EMA follows the concept of "totality of the evidence". Accordingly, The EMA advises BSPs' manufacturers to follow a stepwise approach in developing BSPs regarding quality, safety and efficacy. Additionally, the EMA repeatedly emphasises the importance of locating the R-BMP, which is supposed to be authorised in the European Economic Area (EEA), or a country from the International Conference on Harmonisation (ICH), in the centre of a BSP's development programme (European Medicines Agency (EMA), 2014a). The process of testing and evaluating BSPs is aimed at excluding any significant differences between BSPs and the R-BMPs concerning quality, efficacy and safety. These tests should be at the level of the molecular and finished product (European Medicines Agency (EMA), 2014a, European Medicines Agency (EMA), 2014b, European Medicines Agency (EMA), 2014c).

[1] This was before the "Brexit vote" in June 2016 and the planned movement of the European Medicines Agency from London to Amsterdam. It is not clear how medicines will receive market authorisation in the UK if and when the UK leaves the EU, currently planned for March 2019.

One of the frequently reported safety concerns is the possibility that BMPs will trigger an immunogenic reaction which, although rare, might be life threatening (Kessler et al., 2006). Immunogenic reactions might be triggered by: (*i*) patient-related factors such as age, gender, comorbidities and/or other concomitant medicines, (*ii*) product-related such as route of administration, manufacturing process, impurities profile, degree of aggregation, glycosylation, amino acids sequences, storage conditions, and oxidation (Kessler et al., 2006, European Medicines Agency (EMA), 2007, Wadhwa, 2011, Dranitsaris et al., 2011).

Since the manufacturing process is product specific, it is expected that a BSP will have different process-related impurities (host cells proteins and nuclear material, reagents and downstream impurities) from its R-BMP, and hence a different immunogenic profile (Dranitsaris et al., 2011). Based on that, BSPs' immunogenicity profile is an important aspect that is assessed and tested upon licensing (Dranitsaris et al., 2011). The EMA advises BSPs' manufacturers to consider all needed measures to achieve maximum structural similarity, to keep the level of impurities as low as possible, and to assess the potential immunogenicity during clinical testing. (European Medicines Agency (EMA), 2014b, European Medicines Agency (EMA), 2014c).

The EMA assessment of BSPs does not stop at licensing, but continues after authorisation, as the EMA relies on pharmacovigilance activities to promptly capture any possible adverse drug reaction (ADR). Similar to BMPs, BSPs' applicants should submit a risk management plan (RMP) that describes procedures and steps implemented to monitor the BSPs' safety (European Medicines Agency (EMA), 2014b). Moreover, despite the fact that the EU's pathway goes beyond the conventional generic pathways and requires more data and testing, manufacturers are not required to submit a full dossier similar to that submitted by the R-BMP's applicant, but rather only an abbreviated submission. Additionally, in setting its authorisation requirements, the EMA has taken into consideration the expected variations in molecular structure, the established safety and efficacy of the R-BMPs, and the EMA's experience in assessing post-marketing changes of the R-BMPs (European Medicines Agency (EMA), 2014a). Finally, the EMA took one step further towards aiding BSPs' manufacturers by offering them help and support in structuring their product development and testing plans (European Medicines Agency (EMA), 2017d, European Medicines Agency (EMA), 2017a). Table 2 summarises the main requirements for assessing BSP quality, safety and efficacy, together with details of how the manufacturers are supposed to address these requirements.

Table 2-Summary of BSP authorisation requirements

	Required by EMA's guidelines	How to be addressed by manufacturer
Quality	•Full quality dossier (Module 3) •Head-to-head quality comparison with R-BMP •Differences should be detected, assessed and justified	•Comprehensive physiochemical and biological characterisation •Identical amino acid sequence •Similar structure •State of the art quality related testing
Non-clinical	•Sensitive, specific and discriminatory *in-vitro* methods •*In-vivo* PK and PD quantitative comparison between BSP and R-BMP	•Comparative *in-vitro* studies •*In-vivo* to test impact of structure inherited factors •Justified study duration
Clinical	•Comparative clinical studies start with PK and PD studies •Anti-drug antibodies should be measured in PK studies	•PK studies detect differences using sensitive population •PD markers relevant to clinical outcomes
Post-authorisation	•Comparative safety data to be collected pre-authorisation •Compare immune response to BSP and R-BMP	•Attention to ADRs listed in SmPC •Safety monitoring is extended to post-authorisation •Analytical assays are performed with both products in parallel

ADR: Adverse drug reaction; **BSP:** biosimilar medicinal product, **PD:** Pharmacodynamics; **PK:** Pharmacokinetics; **R-BMP:** Reference biological medicinal product, **SmPC:** Summary of Product Characteristics

In 2006, the EMA referenced Genotropin® (somatropin) in approving the first BSP (Omnitrope®), since then the EMA has approved 39[2] BSPs, refused two and withdrawn three[3] (European Medicines Agency (EMA), 2017c). **Appendix 1** and **Appendix 2** list EMA's guidelines and approved BSPs; respectively.

2.3.2. Nomenclature (INN)

Each pharmaceutical material is identified globally using the international non-proprietary name (INN), also known as generic name. The INN is considered a public priority and is assigned by the WHO (World Health Organisation (WHO), 1997). The INN has a central role in activities related to medicines regulations, pharmacovigilance activities, drug prescription including interchangeability and substitution, labelling and product information, and commercialisation such as advertisement and promotions (World Health Organisation (WHO), 1997).

As both the reference and follow-on generic, in case of chemical medicines, have an identical structure, both products hold the same INN; which is used to justify interchangeability or substitution (World Health Organisation (WHO), 2013, Lepage-Nefkens et al., 2013). However, assigning identical INNs for R-BMPs and their relevant BSPs is a controversial issue, since the two molecules are similar rather than identical (World Health Organisation (WHO), 2013). The current WHO policy distinguishes between glycosylated and non-glycosylated. As it is possible to achieve a high level of molecular similarity, the R-BMP and the BSP will share the same INN for non-glycosylated. On the other hand, because glycosylation profiles vary between molecules, a distinctive INN reflecting the differences in glycosylation, is assigned for the BSP's molecule; the BSP will hold the same INN with an added Greek

[2] As on 21 April 2018

[3] Three BSPs were withdrawn voluntary by the market authorisation holder due to commercial reasons. The two refused BSPs were rejected as a result of issues and concerns related to limited evidence, quality, stability and validation process

suffix. A different INN is perceived as a mechanism that might be able to stop unintentional switching of the R-BMP and BSP (Programme on International Nonproprietary Names (INN), 2013).

While the WHO is responsible for assigning and managing the INN programme, it cannot mandate it. The request for a unique INN is a voluntary act by the medicine's manufacturer/developer (Lepage-Nefkens et al., 2013). As a result, most of the currently available BSPs share the same INN as the R-BMPs, regardless of glycosylation status. One exception is epoetin Zeta (Retacrit®), which is a BSP of epoetin Alfa (Eprex®), for which the manufacturer applied for a distinctive INN to reflect the different glycosylation profile of the BSP, in comparison to the R-BMP.

In 2015, the WHO finalised a proposal for adopting a biological qualifier scheme for all BMPs, including BSPs. The proposal was aimed at harmonising BMPs nomenclature globally, by adding four random consonants and an optional two digits to the INN (Programme on International Nonproprietary Names (INN), 2015). However, the scheme was dropped due to lack of consensus (Brennan, 2017).

The WHO and EMA will not comment or assess interchangeability between R-BMP and their BSPs counterparts; due to the current status of assigning and sharing INN, there is a need for policies and procedures that regulate prescribing of BMPs, including BSPs, and which stop unintentional switching or substitution.

2.3.3. Pricing and market entry

In the European Union, EMA centrally approved pharmaceutical products do not need to go through a separate national licensing procedure (European Medicines Agency (EMA), 2015). However, national market entry is governed by the availability of nationally effective patent rights and market entry periods; the latter being the time needed for pricing and reimbursements decisions to be made (Carone et al., 2012). In the UK, the market entry is immediate, and the marketing authorisation holder (MAH) does not have to wait for pricing and reimbursement decisions (Carone et al., 2012, Macarthur, 2000). Therefore, in theory, the market availability of a BSP in the UK is primarily governed by EMA's licensing and expiry of patent and the market exclusivity rights of the R-BMP. In December 2017, sixteen[4] BSPs were available in the UK. **Appendix 3** lists BSPs available in the UK, with their relevant TA and commissioners.

As medicines' prices and overall expenditure are continuously growing, policymakers and regulators rely on several tools to minimise their medicine bills. Amongst the most frequently used pricing tools are reference prices (external or internal), profit control, price updates and in some cases obligatory price reduction (Kesselheim et al., 2017, Carone et al., 2012). In the UK, profit control is the principal mechanism by which medicines' prices are controlled (Carone et al., 2012, Ess et al., 2003).

In the UK, medicines are priced using one of three mechanisms: (*i*) the pharmaceutical price regulation scheme (PPRS), (*ii*) the statutory scheme and (*iii*) the national drug tariff. While the first two mechanisms are designed for branded and innovative medicines, the third is for generic non-branded medicines (The Economist Intelligence Unit, 2016, Tillet et al., 2017, Medicines and Pharmacy Directorate, 2017). The vast majority of branded medicines (90%) go for the voluntary PPRS scheme, which was designed to allow manufacturers to set their price freely upon market entry and for the NHS to assure reasonably priced medicines (Raftery, 2013). Being branded medicines, BSPs manufacturers can apply to join the PPRS (Association of the British Pharmaceutical Industry (ABPI), 2014). Free pricing means that in the UK, unlike some European countries such as France, Italy, Poland and Norway, BSPs are not subjected to obligatory price reduction upon market entry (Simon Kucher and Partners, 2016).

[4] As in December 2017 and as listed in the British National Formulary (BNF) and the electronic Medicines Compendium (eMC) website

Free pricing for BSPs might be perceived as a positive indicator for their manufacturers, as historically, obligatory price reduction created an unprofitable market for generic manufacturers. This reduction, in turn, resulted in driving these manufacturers out of the market and created another form of monopoly (Kesselheim et al., 2017).

2.3.4. Reimbursement

Reimbursement is another tool by which regulators can control medicines cost and prescribing (Carone et al., 2012). In the UK, reimbursement decisions are made with the input of health technology assessments (HTA). HTAs are carried out by four national agencies: (*i*) the National Institute for Health and Care Excellence (NICE), (*ii*) the All Wales Medicines Strategy Group (AWMSG), (*iii*) the Scottish Medicines Consortium (SMC) and (*iv*) the National Centre for Pharmacoeconomics in Northern Ireland (NCPE) (Mildred and Davies, 2014). Initially, UK TA agencies had varied and different approaches to assessing and appraising BSPs. However, it was common to follow an abbreviated submission for BSPs. Recently, TA agencies reached a consensus, where there is no need to assess BSPs upon market launch and any positive advice related to the R-BMP will be extrapolated and valid for its relevant BSPs.

Historically, both the AWMSG and the SMC were actively involved in assessing and evaluating BSPs using cost minimisation (CMA) and/or budget impact (BIA) analyses. However, NICE has adopted a different approach by which BSPs are assessed in the multiple technology appraisals (MTA), along with the R-BMPs. Following this approach, both the R-BMPs and BSPs will represent the 'same' therapeutic molecules rather than products (brand names) (The National Institute for Health and Care Excellence (NICE), 2014a, All Wales Medicines Strategy Group (AWMSG), 2015, Scottish Medicines Consortium (SMC), 2015b). To the date of writing this chapter, NICE have included five BSPs brands, representing four molecules, in five MTAs and issued one evidence summary of a new medicine (ESNM) (The National Institute for Health and Care Excellence (NICE), 2015b). Table 3 summarises previous and current positions of UK TA agencies.

Locally, NICE has advised medicine formularies committees to prioritise health tecnologies that have not been assessed nationally by NICE and that might have an impact on financial resources. As these two conditions are applicable in the case of BSPs, NICE has used BSPs as an exemplar in its updated local formularies guidelines (The National Institute for Health and Care Excellence (NICE), 2014b, The National Institute for Health and Care Excellence (NICE), 2015a). Accordingly, the decision about whether to utilise and prescribe BSPs was, to some extent, left to local arrangements.

Table 3-Position of UK technology appraisal agencies toward BSPs

Agency	Current position	Initial position
AWMSG	•If R-BMP is positively appraised by NICE/AWMSG, advice will be extrapolated to BSP •If R-BMP is negatively appraised, case-by-case assessment of BSP will be considered •If no TA relevant to R-BMP BSP will not be endorsed •*Position changed in 2015*	•CMA when R-BMP was recommended by NICE/AWMSG or is widely used •CUA when R-BMP was not recommended by NICE/AWMSG
NICE	•BSPs will not be assessed separately in an STA •BSP will be considered within MTA context •Evidence summary medicine will be issued when needed	•Not changed
NCPE	•Full pharmacoeconomic evaluation not recommended for available BSPs	•Not clear
SMC	•Full submission for BSP targeting new indication and/or population •*Position changed in May 2015*	•Full submission based on clinical and economic comparison •Abbreviated submission when the product does not contain a new API •SMC did not specify the economic model needed in appraising BSPs. However, all appraised BSPs used CMA and BIA in their submissions

API: active pharmaceutical ingredient, **AWMSG:** All Wales Medicines Strategy Group, **BIA:** budget impact analysis, **BSP**: biosimilar medicinal product, **CMA:** cost minimisation analysis, **CUA:** cost-utility analysis, **MTA:** multiple technology appraisal, **NICE:** National Institute for Health and Care Excellence, **NCPE:** National Centre for Pharmacoeconomics in Northern Ireland, **R-BMP:** reference biological medicinal product, **SMC:** Scottish Medicines Consortium, **STA:** single technology appraisal, **TA:** technology appraisal

References: The (All Wales Medicines Strategy Group (AWMSG), 2013, Mestre-Ferrandiz and Towse, 2014, National Centre for Pharmacoeconomics in Northern Ireland (NCPE), 2013, The National Institute for Health and Care Excellence (NICE), 2014a, Scottish Medicines Consortium (SMC), 2015a, Ayas M, 2015, All Wales Medicines Strategy Group (AWMSG), 2017, National Centre for Pharmacoeconomics in Northern Ireland (NCPE), 2017, The National Institute for Health and Care Excellence (NICE), 2016b)

2.3.5. Pharmacy level policies and measures

Pharmacy level policies are mainly related to the prescribing approach in terms of generic based-prescribing, also known as the international non-proprietary name (INN)-based prescribing. INN prescribing is promoted to be able to achieve more cost-effective prescribing and minimise overall cost of medicines (Ess et al., 2003). In the UK as it is considered good prescribing practice; prescribers are encouraged to prescribe generically using INN, and for pharmacists to dispense generically when INN prescribing is followed (Macarthur, 2000, Health and Social Care Information Centre (HSCIC), 2017, Generics and Biosimilars Initiative (GaBI), 2015, Simoens and De Coster, 2006). As a result, in 2016 in England, more than 77% of medicines utilised in the community were generically prescribed and dispensed (Health and Social Care Information Centre (HSCIC), 2017).

In order to assure safe and closely monitored prescribing and utilisation of BSPs, the Medicines and Healthcare Products Regulatory Agency (MHRA) has listed BMPs, including BSPs, as prescription only medicines (POM) that need to be prescribed by brand name (Medicines and Healthcare products Regulatory Agency (MHRA), 2008). Second, despite not being innovative medicine or containing new active ingredients, any newly launched BSPs will be listed under the black triangle scheme, which indicates that the medicinal product is subjected to extensive monitoring (Medicines and Healthcare products Regulatory Agency (MHRA), 2009, Drug Safety Update, 2013). Third, prescribers are advised to use product-specific identifiers (brand name, batch number and manufacturer) in reporting adverse drug reactions/events associated with the utilisation of BSPs. Prescribers are also asked to inform patients and carers about product's brand name and batch number (Medicines and Healthcare products Regulatory Agency (MHRA), 2012, Medicines and Healthcare products Regulatory Agency (MHRA), 2009). These procedures might help in addressing shortcoming of having similar INNs for the R-BMPs and BSPs, especially in the case of glycosylated molecules.

2.4. Biosimilars market

2.4.1. Added value of biosimilars

In the UK, NHS Digital, formerly known as the Health and Social Care Information Centre (HSCIC), has reported that in England, between 2013 and 2017, seven out of the top ten prescribed pharmaceuticals in terms of cost to NHS England across all sectors (primary, secondary and FP10HP)-were BMPs (Health & Social Care Information Centre (HSCIC), 2014 , Health and Social Care Information Centre (HSCIC), 2016, Prescribing & Medicines Team, 2015, Prescribing and Medicines Team, 2017). BMPs that were listed among the top twenty most costly medicines accounted for 10% of the total medicines expenditure in England. Table 4 summarises medicines expenditure and cost of top BMPs utilised by NHS England.

Table 4-Overall medicine expenditure and cost of top BMPs in England in the period of 2013-2017

Fiscal year	Total NHS medicines expenditure * (£)	BMP expenditure *† (£)	% Medicines expenditure ‡
2013-2014	14,407,600	1,427,842.3	10%
2014-2015	15,540,800	1,688,865.5	11%
2015-2016	16,795,200	1,662,220.3	10%
2016-2017	17,379,100	1,802,077.0	10%

* Thousands of pounds
† Among the top 20 medicines in terms of cost to NHS-England across all sectors (primary, secondary and FP10HP)
‡ Calculated by author based on reported figures

Resources: NHS Digital, formerly known as HSCIC, reports from 2014 to 2017
(Health & Social Care Information Centre (HSCIC), 2014 , Health and Social Care Information Centre (HSCIC), 2016, Prescribing & Medicines Team, 2015, Prescribing and Medicines Team, 2017)

The most frequently listed high-cost biological medicines (adalimumab, etanercept, infliximab, rituximab, trastuzumab, and insulin glargine) either have lost or are about to lose their patent rights; the latest by 2018 (Generics and Biosimilars Initiative (GaBI), 2012). Patent expiry allows for the development and marketing of BSPs. Additionally, all these agents, except trastuzumab, already have authorised and licensed BSPs (European Medicines Agency (EMA), 2017c). Currently, there are four EMA applications for trastuzumab BSPs (Information Management Division-EMA, 2017).

BSPs are being promoted by their developers and supporters as cost saving tools. Nevertheless, due to lengthy and resource intensive development, manufacturing, testing and authorisation processes, manufacturers of BSPs would have us believe that they are unable to offer price reductions similar to that experienced with conventional generics (Rovira et al., 2011, Declerck and Simoens, 2012, Bocquet et al., 2014, Kresse, 2009). On average, BSPs were reported to be offered at 25% price reduction compared with R-BMPs (Grabowski et al., 2014). However, as BSPs are, in theory, intended to replace expensive R-BMPs, even the 20% price reduction offered by the first approved BSPs was projected to save €1.6 billion a year for the European Union (EU) countries (Rovira et al., 2011, Declerck and Simoens, 2012, EGA, 2011).

In 2011, in London, despite the increased prescribing of granulocyte stimulating factor (G-CSF) (filgrastim), hospitals were able to save £2 million as result of procuring Zarzio® (G-CSF-BSP) instead of Neupogen® (G-CSF-R-BMP). Moreover, it was expected that £3.5 million might be saved if all G-CSF and 80% of pegfilgrastim (second generation G-CSF) prescriptions were based on a BSP brand (Thakrar, 2015). In Europe, as a result of the economic crisis and financial challenges, the Spanish government introduced further price reductions on medicines and promoted the utilisation of BSPs (Bocquet et al., 2015, Bocquet et al., 2014). Upon market entry BSPs could drive market competition, which might result in lower prices being offered by the R-BMPs. Therefore, even if a healthcare system is experiencing limited utilisation of BSPs, it could still benefit from any price reductions offered by R-BMP as a mechanism of competition (Bocquet et al., 2014, Chauhan et al., 2008).

Price reductions, despite being modest, might result in improving patients' access to biological therapy; whether to the same molecule or to a more innovative second-generation BMPs. In some cases, generated savings might be directed to other sectors within a healthcare system (Rovira et al., 2011, Dunn, 2012, IMS Health, 2014, Aitken, 2016). For example, it was reported that the introduction of BSPs, especially G-CSF and EPO, increased overall utilisation of these medicines in Eastern European countries, where national economies are going through a challenging period (Aitken, 2016). Moreover, in Sweden, availability of G-CSF-BSP resulted in relaxing prescribing restrictions by minimising number of authorisations needed to prescribe G-CSF, which was reflected in an overall increase of G-CSG prescription, as well as generating of savings (Aitken, 2016, Gascón et al., 2013).

In Rotherham Hospital, England, procuring G-CSF-BSP resulted in motivating clinicians in the haematology department to prescribe G-CSF for primary prophylaxis of chemotherapy-induced neutropenia; the same phenomenon being observed among German prescribers (Gascón et al., 2013, Verpoort and Möhler, 2012). Finally, in addition to minimising cost and facilitating patients' access, BSPs were associated with better prescriber adherence to clinical guidelines (Gascón et al., 2013, Aapro, 2011).

Real-world evidence on BSPs' added value mostly emerged from the G-CSF context, which represents a unique case of BMPs, in general, and BSPs, in particular. Firstly, unlike most of the available BMPs including BSPs, G-CSF is a small and non-glycosylated molecule that is indicated for short therapy duration, which makes its BSP relatively easier to be accepted and integrated into medical practice (Young et al., 2014, Wadhwa, 2011, Rickwood and Di Biase, 2013). Secondly, G-CSF-BSPs were offered with 30-50% price reduction, greater than with other BSPs. Lower prices enabled G-CSF-BSPs to achieve market uptake similar to that of conventional generic medicines (QunitilesIMS, 2017, Mestre-Ferrandiz et al., 2016, Farfan-Portet et al., 2014, Swartenbroekx et al., 2014). Finally, at the time G-CSF-BSP was launched, there were several reports highlighting prescribers' suboptimal adherence to the clinical guidelines in managing chemotherapy-induced neutropenia. Additionally, there was emerging evidence of neutropenia induced by chemotherapeutic agents, which had not been considered in previous guidelines or publications.

These updates led the European Organisation for Research and Treatment of Cancer (EORTC) to update its guidelines and to list additional chemotherapeutic agents as risk factors that may induce neutropenia, and hence increase the need for G-CSF therapy (Aapro et al., 2011, Aapro, 2006). Therefore, the increased utilisation of G-CSF cannot be solely attributed to the availability of BSPs; however, its use might be driven by expanding patient cohorts eligible for G-CSF therapy, as a result of the updated EORTC or national guidelines, or by national measures to assure prescribers' compliance in prescribing G-CSF for eligible patients.

Furthermore, in assessing potential financial benefits of BSPs, budget impact analysis (BIA) was the most frequently used economic assessment, which relied on offered price reduction of BSP in comparison to R-BMP. These models failed to take into consideration the dynamic nature of the market regarding new market entries, lower prices offered by R-BMP and updates in clinical practice and guidelines. Reported BIA assessments tend to follow a simplistic approach in assessing the impact of BSPs that is based on offered prices without taking into consideration costs associated with setting up practice to facilitate and accommodate BSPs (Simoens et al., 2017). In fact, in surveys assessing European healthcare professionals' attitude and acceptance of BSPs, some professionals were sceptical of BSPs' added value and their ability to generate significant cost savings (Beck et al., 2016, Dylst et al., 2014, Danese et al., 2014).

In searching for empirical evidence discussing BSPs' added value, it was noticed that published studies and research papers were, in most cases, either built on theoretical assumptions or prepared by marketing consultants, agencies or by scholars sponsored or funded by BSPs' manufacturers. Therefore, there was a possibility to overestimate BSPs' advantages. In other cases, benefits are forecast and expected, rather than actualised and achieved. However, as more BSPs are being launched and integrated into medical practice, more empirical evidence prepared by academic researchers or independent organisations is emerging; such as a recently published study that found that NHS-England was able to save £38.8 million over 2 years as a result of integrating BSP copies of infliximab and etanercept (Aladul et al., 2017a).

2.4.2. Biosimilar uptake in the UK

Before February 2015, the beginning of the research period covered by this thesis, BSPs representing four molecules were available in the UK market: (*i*) human growth hormone (somatropin) (HGH); (*ii*) epoetin alfa (EPO); (*iii*) infliximab (IFX); and (*iv*) G-CSF. Assessing market uptake of these products was based on national consumption quantities as reported by the Intercontinental Marketing Services Quintiles (IMSQuintiles), formerly known as Intercontinental Marketing Services-Health (IMSHealth). Following the market share of available BSPs showed heterogeneous and varied uptake among products and the European big five countries (EU5): France, Germany, Italy, Spain and the UK. **Table 5** represents the market shares of targeted BSPs from 2014 to the end of 2016.

Table 5-Market share of selected biosimilar in comparison to R-BMP in Europe big five countries

Country	HGH (%)			EPO (%)			G-CSF (%)			IFX (%)		
Year (20-	14	15	16	14	15	16	14	15	16	14*	15	16†
France	28	32	34	29	35	45	81	84	86	N/A	4	14
Germany	23	26	32	72	69	81	71	78	78	N/A	10	17
Italy	22	23	29	37	52	65	81	88	92	N/A	11	20
Spain	28	29	30	43	49	60	77	79	83	N/A	13	19
UK	14	17	22	7	5	6	96	98	98	N/A	9	33
Average EU‡	33	35	39	43	51	62	81	85	88	N/A	13	24

* IFX-BSP were launched in Feb 2015; therefore, 2014 market share data were not available for the UK

† Combined data of infliximab and etanercept

‡ Average market share across EU countries, which had their data available

EPO: erythropoietin, **EU:** European Union, **G-CSF:** granulocyte stimulating factor (filgrastim), **HGH:** Human growth hormone (somatropin), **IFX:** infliximab, **N/A:** not applicable, **UK:** United Kingdom

Resources: Intercontinental Marketing Services Qunitiles, formerly known as Intercontinental Marketing Services-Health (IMSHealth), reports from 2015-2017

References: (IMS Health, 2015, IMS Health, 2016, QunitilesIMS, 2017)

Reported market shares reflect a heterogeneous uptake among products and countries; as a result, it is not possible to investigate BSPs' market performance as a holistic phenomenon. Accordingly, a researcher needs to consider differences in national market in terms of structure and policies (Aitken, 2016, Mestre-Ferrandiz et al., 2016, Rovira et al., 2013). Additionally, it needs to be acknowledged that each product represents a particular case in terms of molecular structure, targeted therapeutic areas, the availability of second-generation products and targeted population (Chauhan et al., 2008, Aitken, 2016).

While in 2016 in England, generic medicines accounted for 77.7% of medicines prescribed and dispensed in the community (Health and Social Care Information Centre (HSCIC), 2017), market shares of available BSPs, except G-CSF-BSPs, did not exceed 50%. However, reported shares were comparable to the 40% market share achieved by complex generics, such as medicines with a narrow therapeutic index, hormonal products or specialised medicines, which are characterised by more than one complicated formulation and/or manufacturing aspect (Grabwski, 2009).

While BSPs are authorised based on safety and efficacy data generated from clinical trials and preauthorisation tests, the EMA relies on post-marketing and real-world evidence to confirm the safety and efficacy of these products. Therefore, for a BSP, securing market share is not only to generate profits, but is also an approach to enable regulators and prescribers to assess that BSPs' performance in real-life settings and to augment prescribers' trust in utilising BSPs (Chauhan et al., 2008).

2.5. Factors affecting biosimilar uptake in the UK

In April 2013, the British Generic Manufacturing Association (BGMA) reported that the uptake if BSPs in the UK is suboptimal and needs to be optimised (British Generic Manufacturers Association (BGMA), 2013). The BGMA had related the cause of the low uptake of BSPs in the UK, in comparison to other European countries, to the absence of national policies designed to incentivise BSP uptake, banned substitution at pharmacy level and physicians' lack of confidence in prescribing BSPs (British Generic Manufacturers Association (BGMA), 2013). However, the BGMA statement was not based on analysis of relevant national pharmaceutical policies and regulations, nor was it supported by empirical evidence from prescribers' perceptions and attitudes toward BSPs. It is possible that the BGMA's stand might represent a biased, or at least only partially informed, account of the UK BSPs market. Therefore, the BGMA statement needs to be carefully considered; especially because data presented in the previous

section showed that the uptake is not limited but varied among classes. Additionally, in the UK, there are several policies and procedures that control and direct expenditure and prescribing behaviour which, despite not being BSPs specific, might be extrapolated and waivered when dealing with the context of BMPs including BSPs. (Carone et al., 2012).

2.5.1. Biosimilars related policies

Policies affecting medicines' availability and utilisation can be classified into two categories. Supply-side policies are those "that are primarily directed towards specific stakeholders in the health care system responsible for medicine regulation/registration/quality assurance, competition among manufacturers, intellectual property rights, pricing, and reimbursement". On the other hand, demand-side policies "are directed at stakeholders such as healthcare professionals prescribing medicines (usually physicians), pharmacies and patients/consumers who prescribe, dispense and ask for medicines" (World Health Organisation (WHO), 2016). While supply-side policies are concerned with authorising, pricing and reimbursing medicines, demand-side policies take the form of incentives, prescribing targets and quotas, guidelines and educational interventions (Rémuzat et al., 2016).

As discussed in Section

2.3. Biosimilar licensing and regulation, supply-side policies regulating BSPs in the UK are either shared with the European block, in the form of licensing and authorisation pathways, or are informed by country-specific pricing and reimbursement policies. As the BSPs' authorisation pathway in the UK is shared with other EU countries, reported limited uptake of BSPs in the UK, (Table 5), cannot be attributed to the licensing pathway.

As BSPs' pricing in the UK has been left to the manufacturers and local arrangements, and their reimbursement was intrinsically affected by the R-BMP reimbursement scheme which is decided by NICE or HTA agencies, BSPs were expected to have a price-based competition to achieve market penetration. However, due to their inability to offer substantial price reductions similar to generic medicines, together with concerns regarding their safety and efficacy, BSPs cannot rely on price based-competition to achieve substantial market share (Chauhan et al., 2008, Grabwski, 2009). The market competition was also hindered by the R-BMPs manufacturers' either offering price reductions preceding BSPs launch, or by introducing more innovative, second-generation products; notably in case of EPO and G-CSF. These products are characterised by improved clinical profile and more convenient administration routes and/or schedules (Aitken, 2016, Bocquet et al., 2014, Bocquet et al., 2015, Emerton, 2013).

In their assessment of the European BSPs market it was found that even when BSPs were able to offer lower prices than R-BMP, it was not significantly associated with the uptake of the BSPs (Rémuzat et al., 2017). However, this conclusion needed to be carefully considered as the followed linear regression was not clearly described nor presented; standard deviations, confidence intervals or coefficients were not reported. Additionally, analysis was based on listed prices, rather than actual procurement prices, and it did not take into account changes in the R-BMP's prices.

The second supply-side measure that might affect the uptake of BSPs is the time for market entry, which is the time needed for a product to be actively marketed after it has been authorised (Rémuzat et al., 2016, Rovira et al., 2013). Prompt market entry of BSPs, following authorisation, might shorten the period of R-BMP monopoly, which in turn might minimise the R-BMP influence over prescribers and limit the possibility of brand loyalty being established among them (Moorkens et al., 2016). A shorter period of R-BMP monopoly was associated with higher uptake of EPO-BSPs in Germany and France, where EPO-R-BMP was introduced eleven and ten years later than in the UK; respectively (Rovira et al., 2013). Rapid entry of BSPs might allow for rising familiarity and for the generation of real-world evidence that is needed to assure regulators, prescribers and patients regarding BSPs' safety and efficacy (Rémuzat et al., 2017, Chauhan et al., 2008). However, longer market availability of BSPs has not always resulted in larger market share; as noticed with the first authorised BSP, HGH-BSP, which has not exceeded 40% after ten years of authorisation (Table 5). Limited market share of HGH-BSP might be explained by factors related to: (*i*) the nature of targeted population, that is mainly paediatrics, (*ii*) therapy duration, which is longer in comparison to other BSPs and (*iii*) the method and route of administration, that comes in the form of a self-injected device which is affected by patients' preference (London New Drugs Group, 2013, Chauhan et al., 2008, Bocquet et al., 2014). Furthermore, although time for market entry for follow-on products in the UK is among the shortest in Europe, on average four months after patent expiry (Glowicka et al., 2009), any benefit from this duration was not reflected in a more significant market share of available BSPs.

The last supply-side measure that was reported to affect BSPs' market share was the number of BSPs available within the same class (Rémuzat et al., 2017). In their analysis, Rémuzat et al. (2017) related significant market share of G-CSF-BSP to the increasing number of BSPs. However, this explanation needs to be carefully considered, as some of the available BSPs are labelled as "bioidentical-BSPs". Bioindenticals-BSPs are BSPs developed and manufactured by the same manufacturer using the same

process but marketed under two different brand names; therefore, observed market share might not be related to increased number of BSPs molecules, but rather might be due to extensive marketing campaigns led by more than one marketer.

While supply-side policies and factors in terms of offered prices, time to market entry and number of available BSPs, appear not to have had an influential impact on the BSPs' market share, demand-side policies were more influential (Rémuzat et al., 2017, Rémuzat et al., 2016, Moorkens et al., 2016, Swartenbroekx et al., 2014). Prescribing targets and quotas in Germany and Italy are considered to have accounted for the rapid uptake of BSPs in these countries (Swartenbroekx et al., 2014, Rémuzat et al., 2017). Nonetheless, reported uptake figures for IFX-BSP in Germany might indicate that prescribing targets and quotas might not always be effective and influential (Table 5). In fact, the IFX-BSPs market in countries like Germany may highlight the effect of having national manufacturers on the market performance of BSPs. It was reported that, in Germany, the rapid uptake of EPO-BSPs and G-CSF-BSPs, both of which are developed and manufactured by German companies, was in part driven by German prescribers trusting their national manufacturers (Declerck and Simoens, 2012). Therefore, the limited uptake of IFX-BSP in Germany might be attributed to the fact it is developed and made by a South Korean manufacturer (European Medicines Agency (EMA), 2013). Other factors that might have affected the uptake of IFX-BSP could be that unlike previously authorised BSPs, IFX is a monoclonal antibody (mAb) with a highly complex molecular structure of IFX. Such a structure considerably exceeds the complexity of previously approved BSPs. Also potentially negatively affecting uptake is that IFX is indicated for three main therapeutic areas (gastroenterology, rheumatology and dermatology) each with its specific guidelines and therapeutic pathways (Noaiseh and Moreland, 2013, Joint Formulary Committee, 2017).

In an assessment of the European BSPs' market in 2010, representatives from the MHRA and the Department of Health in the UK had confirmed the absence of BSP-specific national policies that might have promoted and encouraged the utilisation of BSPs (Rovira et al., 2011). The same findings were confirmed in a study conducted for the European Generic Medicines Association in 2012 (European Generic Medicines Association (EGA), 2012). In 2012, the EGA commissioned a study aimed at identifying barriers and facilitators of BSPs uptake; UK representatives acknowledged the absence of defined prescription targets, prescribing incentives, any quota system, and measures for pharmacy level automatic substitution related to BSPs. The study concluded that encouraging national policies and defined prescription targets could enhance BSPs' uptake (European Generic Medicines Association (EGA), 2012).

While BSPs' specific policies in the UK were lacking, general policies applicable for branded and/or generic medicines could be extrapolated and referred to in procuring, commissioning and prescribing BSPs (Reiland et al., 2017). Although in the UK prescribing quotas are not common, prescribing targets (budget targets), prescribing monitoring and incentives are frequently deployed to influence prescribing practice, whether in primary or secondary care. Each Clinical Commissioning Groups (CCGs) sets a prescribing budget for general practitioners, for which they are held accountable (NHS Business Services Authority (NHSBSA), 2017). In secondary care, figures of medicines purchased and utilised at Acute Trusts are annually summarised and published by NHS-Digital (Prescribing and Medicines Team, 2017). Additionally, interventions that aim to rationalise the utilisation of medicines excluded from the national tariff are being proposed and promoted; the aim of these interventions is to minimise cost and generate savings. These interventions introduce two concepts that might be applicable and relevant to the BSP context: therapeutic switching and gain share agreements (Pearson, 2010, Howard, 2012). Therapeutic switching is defined as "substitution of a lower cost treatment of equal benefit in the same 'similar' therapeutic class for an existing treatment at higher cost" (Pearson, 2010). Gain share, defined

as “an incentivisation scheme used to encourage secondary care providers to make the most efficient use of high cost drugs excluded from the then ‘Payment by Results’ tariff” (NHS-England, 2014a), is suggested as an incentivisation tool that commissioners, whether national or local, might offer to encourage the switch and to ease its implementation (Pearson, 2010, NHS-England, 2014a). As available BSPs are branded medicines excluded from the national tariff, these interventions might be waived for BSPs prescribing if these products were offered at lower prices and patients’ safety and efficacy are assured.

Following the launch of IFX-BSP, NHS England and NICE have adopted a more proactive approach to encouraging BSPs’ utilisation. This was evident by the publication of informative “educational” material explaining the concept of BSPs, licensing pathway, potential benefits and the need for brand name-based prescribing of BSPs (NHS England-Medical Directorate, 2015). NICE, on the other hand, has published an implementation guide, which explained in detail the experiences of the Southampton University Foundation Trust and University College London Hospitals Foundation Trust (UCL) in introducing IFX-BSPs into clinical practice and switching stabilised patients. Southampton went for wholesale switch of their gastroenterology patients, while UCL went for gradual implementation; initiation first then switching stabilised patients. In the implementation guide, NICE has explained the role that commissioners (CCGs) played to facilitate the implementation and the type of agreement they had with the providers (Acute Trusts) (The National Institute for Health and Care Excellence (NICE), 2015d). Educational and informative interventions which are led by regulatory authorities, similar to the above-mentioned, are presumed to act as neutral and unbiased sources of information (Rémuzat et al., 2017). These interventions might counteract the effect of R-BMPs’ marketeers on prescribers, as it is common for R-BMP to limit the market penetration of BSPs by building strong connections with the medical community through sponsoring conferences and clinical researchers. Such activities might well augment prescribers’ brand loyalty and affect their prescribing behaviour (European Generic Medicines Association (EGA), 2012, Intercontinental Marketing Services Health (IMS), 2011).

In conclusion, the UK market relies on general non-preferential (specific) policies to regulate the biological market. However, due to the nature and complexity of BMPs, including BSPs, more specific policies that are able to balance BSPs' benefits with safety concerns regarding their utilisation, are needed (Mestre-Ferrandiz et al., 2016, Chauhan et al., 2008). However, since 2014 the NHS and NICE are becoming more involved in promoting BSPs, which might be due to the fact that the recently approved MAb BSPs are classified as slightly less costly alternatives to the high-cost biological medicinal products that are currently dominating the NHS drugs budget. These less expensive medicines may have a significant impact on reducing the amount of NHS funds spent on biological medicines.

2.5.2. Biosimilars substitution, interchangeability and switching

Not allowing pharmacy-level substitution of BSPs for BMPs was the second factor, according to the BGMA, that limited BSPs utilisation in the UK (British Generic Manufacturers Association (BGMA), 2013). However, discussing substitution requires defining and differentiating three main concepts that are often used interchangeably: interchangeability, switching and substitution:

- *Interchangeability*: the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. Replacement can be done by switching or substitution (European Medicines Agency (EMA) and The European Commission (EC), 2017).

- *Switching*: the prescribing decision to exchange one medicine for another medicine with the same therapeutic intent (European Medicines Agency (EMA) and The European Commission (EC), 2017).

- *Substitution*: the practice of substituting a product, whether marketed under a trade name or generic name, with an equivalent product, usually a cheaper one, containing the same active ingredient(s) (WHO-Expert Committee on Specifications for Pharmaceutical Preparations, 2006).
    - *Substitution (automatic)*: the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level, without consulting the prescriber (European Medicines Agency (EMA) and The European Commission (EC), 2017)

The EMA has clearly stated that its authorisation recommendation will not address the issue of interchangeability, and that substitution needs to be considered and determined at the national level by relevant regulatory agencies (European Medicines Agency (EMA) and The European Commission (EC), 2017). In addressing this matter, European authorities have either issued specific mandates regarding the interchangeability; whether to allow or prohibit it, or to place an emphasis on brand name based prescribing of BMPs, including BSPs (Drozd et al., 2014).

The banned pharmacy level automatic substitution is not limited to the UK; it is a common practice in countries that have witnessed high BSP uptake such as Germany, Italy and Spain to be brand specific (Rovira et al., 2011, Agenzia Italiana del Farmaco (AIFA), 2013 , Ferré, 2014, European Generic Medicines Association (EGA), 2012). France was the only country to allow pharmacy level substitution for new (biologically naïve) patients in December 2013; however, this legislation is still not effectively implemented (Garattini et al., 2015, Rémuzat et al., 2016). Germany allowed substitution only for products labelled as bioidentical (Bocquet et al., 2014).

In the UK, banned pharmacy-level substitution is central in managing brand name, prescribed medicines, such as some of the antiepileptic and immunosuppressant drugs, as these medicines might be associated with safety, efficacy and/or the possibility of medication error (Duerden and Hughes, 2010). Therefore, banned automatic substitution of BMPs, including BSPs, might be understood as an

approach for assuring patients' safety, as well as aiding pharmacovigilance and post-marketing surveillance (Medicines and Healthcare products Regulatory Agency (MHRA), 2012, Medicines and Healthcare products Regulatory Agency (MHRA), 2009).

In addressing switching of established patients, the UK has followed a similar approach to the majority of European countries, in that it was left to the prescriber whether they decided to switch over established patients to a BSP (Rémuzat et al., 2016, The National Institute for Health and Care Excellence (NICE), 2016b).

As the UK's approach to substitution with, and switching to, BSPs has been similar to that followed in other EU countries, which have witnessed rapid uptake of BSPs, limited uptake may not be that closely related to substitution policies, or as yet they are not a driving force.

2.5.3. Prescribers' acceptance of biosimilars

While the EMA and NICE play central roles in licensing and regulating BMPs, including BSPs, both have left the decision of prescribing BSPs or R-BMPs to be determined by prescribers (Rovira et al., 2011, The National Institute for Health and Care Excellence (NICE), 2016b). The significant influence prescribers might have in driving the utilisation of BSPs is frequently reported by market experts. Some expert expected that further price reductions and bigger savings might be achieved through broader acceptance by the medical community and hence wider utilisation of BSPs (Farfan-Portet et al., 2014, Intercontinental Marketing Services Health (IMS), 2014, Rickwood and Di Biase, 2013). Therefore, BGMA listing of prescribers' reservations and reluctance to prescribe BSPs as factors that limit BSPs uptake in the UK, might be valid and justified (British Generic Manufacturers Association (BGMA), 2013). However, the BGMA did not build its conclusion upon empirical studies that had investigated prescribers' acceptance of and attitudes toward BSPs.

In the literature, the following factors were suggested as limiting and hindering the utilisation of BSPs: (*i*) unfamiliarity with and misunderstanding BSPs concept (*ii*) concerns related to BSPs' quality, safety, efficacy and immunogenicity, (*iii*) limited evidence and indication of extrapolation, (*iv*) BSPs' assessing and licensing guidelines and procedures, (*v*) initiation, substitution and switching patients and (vi) BSPs INN and nomenclature (Weise et al., 2012, European Generic Medicines Association (EGA), 2012, Intercontinental Marketing Services Health (IMS), 2011, Aapro, 2011).

In an attempt to retrieve empirical studies that had investigated prescribers' attitudes, perceptions and experiences with BSPs, Ovid-Embase, Ovid-Medline and Google Scholar were searched. The researcher used the following terms: biosimilar, biogeneric, subsequent entry biologic, physicians, prescribers, physicians' attitude, medical practice, qualitative research, health perceptions questionnaire, structured questionnaire and questionnaire. Furthermore, reference lists of identified studies were hand searched in order to identify additional information.

In total, the full texts of 27 papers and one report were retrieved as follows: 16 were from Europe (5: multiple European countries, 2: Belgium, 2: Germany, 2: Italy, 1: France, 1: Hungary, 1: Ireland, 1: the UK and 1: Ukraine); 3 from North America (2: the USA and 1: Canada); 4 from Latin America (3: multiple countries and 1 in Brazil); 4 studies included participants from a mixture of countries (developed and pharma-emerging[5]); and 1 study was carried out in New Zealand. The majority of the studies (20/27) were based on self-administered questionnaires, whether web-based (online) or paper-based. Studies

[5] Pharma-emerging countries: developing countries that are experiencing rapid growth in economy including pharmaceutical industry. Pharma-emerging countries include: Brazil, Russia, India, China, and South Africa (BRICS) and, later added, Mexico, Indonesia, South Korea, and Turkey (MIST) TANNOURY, M. & ATTIEH, Z. 2017. The influence of emerging markets on the pharmaceutical industry. *Current Therapeutic Research*.

targeted different healthcare professionals (prescribers, pharmacists and nurses) and different specialities such as rheumatology, gastroenterology, haematology, oncology and dermatology.

Studies mainly investigated and reported findings related to participants' (*i*) awareness and knowledge about BSPs, (*ii*) perceptions of, and attitudes towards BSPs' safety, quality and immunogenicity, (*iii*) willingness to prescribe, and motives for prescribing BSPs, (*iv)* acceptance of evidence extrapolation, switching stabilised patients and pharmacy level substitution and (*v*) INN of BSPs and how it was perceived. Table 6 summarises retrieved studies and their main findings.

The vast majority of retrieved studies shared similar research methods and broadly the same aims. However, integrating and presenting findings into general conclusions were precluded by the heterogeneity between studies in terms of settings (highly regulated market with well-established BSPs licensing pathways vs. pharma-emerging markets with different licensing requirements), timing (before and after market availability of relevant BSPs) and participants (different therapeutic areas, each with its own therapeutic pathways, disease severity and therapy duration (chronic vs. short term)). Heterogeneity was also observed in study quality and conduct; response rates were only reported in 11/20 of retrieved surveys, and response rates exceeded 65% limit in only two surveys (Azevedo et al., 2011, O'callaghan et al., 2017). Additionally, data collection tools (questionnaires or interview guides) were piloted and amended prior to the main study in 6/27 studies only (Hallersten et al., 2016, Beck et al., 2016, Dylst et al., 2014, Grabowski et al., 2015, O'callaghan et al., 2017, Chapman et al., 2017). Finally, retrieved studies were dominantly based on self-enrollment and self-reporting, which might be associated with bias; such methodologies may result in having a study sample that is not sufficiently representative of the whole targeted population (Althubaiti, 2016).

Three studies represented exceptional cases in terms of conduct and reporting: the first two were carried out by the same research team that assessed the acceptance of BSPs by European inflammatory bowel disease (IBD) specialists before (Danese et al., 2014) and after (Danese et al., 2016) market availability of the first BSP targeting gastroenterology therapeutic area (IFX-BSP). These two studies allowed for assessing the changes in acceptance of BSPs, with time and accumulated prescribing experience. The third study was conducted in 2016/2017 in the UK (Chapman et al., 2017), in addition to assessing prescribers' knowledge and attitudes toward BSPs, the researchers compared prescribing rates of IFX-R-BMP and IFX-BSP per speciality. This model allowed for triangulating evidence on IFX-BSP utilisation and overcoming the issue of self-reporting bias.

2.5.3.1. Prescribers' knowledge and familiarity with biosimilars

Prescribers' knowledge and familiarity with the BSPs concept was a frequently assessed attribute among retrieved studies. Healthcare professionals, who participated in retrieved studies, were reported to have inconsistent and varied levels of knowledge relative to the research topic. Market availability of BSP was not always associated with widespread understanding of the BSP concept, as unfamiliarity and lack of knowledge were reported in studies carried out both before or after market availability of BSPs (Beck et al., 2016, Grabowski et al., 2015, Zelenetz et al., 2011, Pasina et al., 2016). However, even when participants reported familiarity with BSPs, in some cases their knowledge and understanding were found to be limited and basic in nature (Dolinar and Reilly, 2014, Reilly and Gewanter, 2015, Cohen et al., 2016, Hemmington et al., 2017, Akhmetov et al., 2015). Recent studies in the UK and Ireland reported sufficient levels of awareness were identified among participating prescribers and practitioners (Chapman et al., 2017, O'callaghan et al., 2017). In addition to mixed results, clear definitions of *sufficient*, *limited* and *lack of awareness* were not always explained in these studies; it was unclear if researchers had referred to one of the BSP formal definitions that have been issued by regulatory agencies such as EMA, FDA or WHO.

2.5.3.2. Biosimilar evaluation and licensing

In their paper on the EMA BSPs' licensing pathway, Ebbers et al. (2012) have related limited utilisation of BSPs to prescribers' distrust of licensing pathways and their questioning of the scientific basis for assessing and authorising BSP (Ebbers et al., 2012). In assessing prescribers' attitudes toward BSPs' licensing procedures, three main observations were noticed. The first observation was related to whether or not participants trusted licensing agencies and BSPs' licensing guidelines (Cohen et al., 2016, Akhmetov et al., 2015, Dylst et al., 2014). The second point was related to prescribers' limited awareness and unfamiliarity of what is being assessed upon BSPs authorisation. Beck et al. (2016) reported that 45.7% of French rheumatologists, who participated in their study, assumed that licensing of BSPs followed the conventional generics pathway. A marginal majority of participants in the study by Reilly and Gewanter (2015) believed that the same regulatory requirements of R-BMP are applicable to BSPs. The third point related to what the healthcare professionals had identified as 'needed' in licensing and authorising BSPs. In a number of studies, participants identified types of studies/procedures, which they believed might better ensure the safety and efficacy of BSPs, such as more intensive pharmacovigilance and post-marketing monitoring, and indication-specific clinical trials (Danese et al., 2016, Danese et al., 2014, Chapman et al., 2017).

The first observation showed how regulatory agencies and their licensing pathways are being perceived and trusted by healthcare professionals; responses that might positively or negatively affect the utilisation of BSPs, which have been licensed by these regulatory agencies. On the other hand, the other two observations would slow down BSPs adoption, as both mirror a lack of understanding of BSPs' concepts and regulations. This lack of understanding might be attributed to an information gap that needs active involvement from regulators and manufacturers in explaining the concept and authorisation process of BSPs (Breckenridge et al., 2010, Dylst et al., 2014, Cohen et al., 2016).

2.5.3.3. Prescribers' perceptions of biosimilar safety, efficacy and immunogenicity

As discussed earlier, the totality of evidence on quality, safety and efficacy forms the base of licensing BSPs by the EMA. However, concerns related to these attributes are frequently reported barriers that stop potential prescribers from actually prescribing BSPs. Similar to prescribers' knowledge and awareness, prescribers' perceptions of safety, efficacy and immunogenicity were varied. The effect of real-world practical experience on prescribers 'attitudes was visible in Danese et al. 2016 study, which assessed gastroenterologist attitude toward IFX-BSPs after it has been marketed. Results of this study showed that a higher acceptance rate was achieved in comparison to 2014 study, which was conducted by the same team before the launch of IFX-BSPs (Danese et al., 2016, Danese et al., 2014).

2.5.3.4. Extrapolation of clinical evidence

Generally, the clinical efficacy of a BSP is tested in the one indication that is considered to be the most sensitive and representative among all of that R-BMP's indications. Once the generated evidence from quality, non-clinical and clinical studies is found to be as comprehensive and satisfactory as possible, that BSP will be licensed for all R-BMPs' indications through an evidence extrapolation exercise (European Medicines Agency (EMA), 2014b). This extrapolation exercise is considered sufficient, given that the molecule has the same mechanism of action in all licensed indications and the tested indication is sufficiently sensitive and representative (European Medicines Agency (EMA), 2014b). Extrapolation to untested indications is a repeatedly flagged barrier for the utilisation of BSPs (Growth from Knowledge (GfK), 2014). In assessing acceptance of extrapolation, general reservation and uncertainty among prescribers were reported (Beck et al., 2016, Grabowski et al., 2015). Even when prescribers' acceptance of evidence extrapolation was reported, the percentage of accepting participants did not exceed the marginal majority of 51% (Cohen et al., 2016, O'callaghan et al., 2017, Hemmington et al., 2017, Danese et al., 2016).

Similar to what was observed with safety and efficacy, prescribers' acceptance of extrapolation increased with time and practical experience; this was observed by researchers who assessed attitudes of gastroenterologists before and after market availability of IFX-BSP. It was reported that the percentage of IBD specialists who refused extrapolation dropped by half after IFX-BSP marketing (Danese et al., 2016, Danese et al., 2014).

2.5.3.5. Biosimilar substitution

As discussed earlier, pharmacy level auto-substitution is a generally banned practice in the case of BMPs, including BSPs. Prescribers were found to be against pharmacy level auto-substitution (Beck et al., 2016, Grabowski et al., 2015, Danese et al., 2016, Danese et al., 2014). Additionally, prescribers emphasised their rights to be notified about the substitution and to approve it before a BSP brand is dispensed to a patient. For some prescribers, auto-substitution was acceptable for biological-naïve patients (O'callaghan et al., 2017, Dolinar and Reilly, 2014).

2.5.3.6. Biosimilars nomenclature

As discussed earlier (2.3.2. Nomenclature (INN)) most of the currently available BSPs hold the same INN as their R-BMPs counterparts. Prescribers understood having BMPs with the same INN as having identical molecules, same indications, interchangeable and safely switchable (Reilly and Gewanter, 2015, O'callaghan et al., 2017, Dolinar and Reilly, 2014). Being familiar and experienced in prescribing IFX-BSP, IBD specialists were reported to be more accepting of an identical INN for the R-BMP and BSP (Danese et al., 2016). However, this observation might be problematic as it could reflect limited understanding of the concept of BSPs and the need to always prescribe by brand name, even if the INN is identical.

2.5.3.7. Prescribing and utilisation preference

Retrieved studies assessed prescribers' behaviour and willingness to adopt BSPs in their medical practice. Results of prescribers' acceptance of BSPs could be organised into three themes: (*i*) overall willingness to prescribe, (*ii*) motives and influences to prescribe and (*iii*) prescribing pattern (switching vs. initiation). Willingness to prescribe BSPs was not always in line with reported figures of market uptake. In spite of being presented as the highest adopters of BSPs, especially first wave, surveyed German rheumatologists and gastroenterologists preferred R-BMP over the BSP mAb (Waller et al., 2017, Sullivan et al., 2017). Conversely, despite working in a market with a varied and limited uptake of BSPs, mainly first wave, UK healthcare professionals were reported to have a generally positive attitude toward BSPs, and were willing to utilise BSPs (Chapman et al., 2017).

Reported results suggested that willingness to prescribe might be influenced by the perceived added value of BSPs in form of facilitating patients' access to biological therapy (Baer II et al., 2014, Lammers et al., 2014, Monk et al., 2017). In other studies, participating professionals flagged the effect of financial incentives and authority mandates on encouraging/directing prescribing practice. However, professionals considered these tools to have only a limited impact (Beck et al., 2016, Grabowski et al., 2015, Baji et al., 2016). Educational interventions, which were directed to improve prescribers' understanding and familiarity with BSPs, were reported to be effective tools to increase BSP utilisation. In their interventional educational study, Perfetti et al. (2015) had reported an increase in prescribing EPO-BSP as a result of the educational intervention. Professionals were reported to consider guideline inclusion and involvement of professional bodies as a means of encouraging them to prescribe BSPs (Hallersten et al., 2016, O'callaghan et al., 2017, Danese et al., 2014, Danese et al., 2016)

In their framework on barriers affecting physicians' adherence to clinical guidelines, Cabana et al. (1999) considered knowledge and attitudes as important factors that influence prescribing behaviour. However, none of the retrieved studies discussed above assessed the impact of knowledge and/or attitudes on prescribers' willingness to utilise BSPs. The vast majority of the research relied on descriptive analysis, and only two studies investigated the effect of prescribers' characteristics (age, location, and years of experience) on their willingness to prescribe, where no significant associations were found (Beck et al., 2016, Grabowski et al., 2015). Additionally, the effect of knowledge on attitudes was not examined, and in some cases its effect was unpredictable. French participants in the study by Beck et al. (2016) were reported to have only limited knowledge about the BSPs concept; however, the majority were not concerned about the safety, efficacy or immunogenicity of BSPs, and were positive regarding implementing BSPs (Beck et al., 2016). On the other hand, German prescribers, who took part in two studies, were reported to prefer R-BMP over BSPs, despite the fact that the majority perceived BSPs to have similar efficacy to the R-BMP for safety and efficacy reasons (Waller et al., 2017, Sullivan et al., 2017). In investigating American physicians', pharmacists' and nurses' perceptions of BSPs, Zelenetz et al. (2011) found that while 55% of participants had no or very slight familiarity with BSPs, more than 60% were willing to utilise BSPs. Lastly, the percentage of Canadian rheumatologists who reported they were willing to prescribe BSPs, increased as a result of proposing further price reduction or authoritative mandates (Grabowski et al., 2015).

The available literature showed diversity in prescribers' attitudes and perceptions relating to BSPs. Furthermore, it was observed that knowledge, attitudes and preferences were not always in alignment with each other, and might be influenced and altered by external factors, such as incentives, mandates or peer effects.

Table 6-Summary of retrieved studies investigating attitude and perceptions toward BSPs (sorted by research date, if reported)

Title	Research date	Country(s)	Speciality (n)	Key Findings
1. Opinions of a sample of Brazilian rheumatologists about biosimilars (Survey)				
(Azevedo et al., 2011)	Sep 2010	Brazil	Rheumatology (189)	- **60%** reported knowing what biosimilars are - **30%** denied knowing the subject - **32%** said that BSPs already exist in the Brazilian market - **56%** said that BSPs do not exist in the Brazilian market - **67%** considered the main advantage of BSPs is offering a lower price - **23%** pointed out the problem of efficacy - **23%** had concerns regarding the possibility of therapeutic failure as a result of prescribing BSPs - **12%** had concerns of triggering immunogenicity reaction as a result of utilising BSPs - **17%** questioned the interchangeability between BSP and R-BMP - **3%** consider it problematic for BSPs to share the same INN of R-BMP
2. NCCN Biosimilars White Paper: regulatory, scientific, and patient safety perspectives (Survey)				
(Zelenetz et al., 2011)	Mar 2011	The USA	Physician, nurse, pharmacist (277)	- **36%** not at all familiar - **26%** were familiar with the recent developments regarding BSPs - **62%** had moderate to high interest in prescribing, dispensing, or administering BSP - **> 88%** required studies directly compare clinical endpoints, chemical/physical and pharmacokinetic similarities between R-BMP and BSP - **25%** indicated the need for more information to make a decision regarding the use of BSP

3. Barriers to the uptake of biosimilars and possible solutions: a Belgian case study (Semi-structured interviews)

(Dylst et al., 2014)	Oct 2012–Feb 2013	Belgium	Authority, Representative of sickness funds, Regulator, Member of Belgian Drug Reimbursement Committee, Academic, Industry originator, Physicians, Pharmacist, Patient, Industry biosimilar, Industry combined. (Total= 19)	- Lack of confidence in BSP was most pronounced by physicians, who tended to question BSP quality, safety, and interchangeability - Lack of clinical data supporting the safe and effective use of BSP was an important issue - Some physicians who tended to distrust the EMA procedures for BSP - Most interviewees agreed that initiation with BSP should be no problem - Prescribers thought that switching of established could cause some problems

4. Barriers to the use of trastuzumab for HER2+ breast cancer and the potential impact of biosimilars: A physician survey in the united states and emerging markets (Survey)

(Lammers et al., 2014)	Dec 2012-Jan 2013	USA, Mexico, Turkey, Russia, Brazil	Haematology, Oncology (351)	- **45%** would increase the use of HER2 antibody therapy if a lower cost BSP version of trastuzumab were available

5. Diffusion of biosimilar haemopoietin growth factors use in oncology practice: an Italian experience (Interventional educational study, followed by survey)

(Perfetti et al., 2015b)	Jan-Dec 2013	Italy	Oncology (11)	- **9%** thought that BSP might differ in activity compared to R-BMP - **91%** believed that BSP may represent an opportunity for relevant savings without sacrificing efficacy and safety - **55%** did not see any critical issues on the use of EMA approved BMP

6. Likelihood of use and perception towards biosimilars in rheumatoid arthritis: a global survey of rheumatologists (Survey)

(Narayanan and Nag, 2016)	May-Apr 2013	Europe big five (EU5), Brazil, China, Japan	Rheumatology (173)	- **47%** would prescribe a BSP to an eligible rheumatoid arthritis patient - **60%** reported that suspected BSP similarity to R-BMP that would stop them from prescribing BSPs - **53%** reported that inadequate safety and efficacy profile/data would stop them from prescribing BSPs - **25%** noted trust/confidence in product manufacturer as key reasons that would prevent them from prescribing a biosimilar - **51%** would gradually prescribe BSP before wider utilisation - **46%** reported that lack of long-term data would stop them from prescribing BSPs

7. Barriers to the access and use of rituximab in patients with non-Hodgkin's lymphoma and chronic lymphocytic leukaemia: A physician survey (Survey)

(Baer II et al., 2014)	Jul-Aug 2013	USA, Mexico, Turkey, Russia, Brazil	Haematology, Oncology (450)	- **> 50%** would increase their use of rituximab if a BSP with 30% price reduction was offered

8. Biosimilars naming, label transparency and authority of choice – survey findings among European physicians (Survey)

(Dolinar and Reilly, 2014)	Last quarter of 2013	France, Germany, Italy, Spain, UK	Nephrology, rheumatology, dermatology, neurology, endocrinology, oncology (470)	- **54%** reported that they were 'familiar', but with only a basic understanding, with BSP - **20%** were unable to define BSP - **22%** were 'very familiar' with a complete understanding of BSP - **59%** of the UK physicians were 'familiar with a basic understanding' with biosimilar medicines - **55%** of the UK physicians accepted extrapolating evidence to several or all of R-BMP indications - **62%** did not accepted auto-substitution - **47%** thought that switching within the same INN could be done safely with same results - **53%** of physicians held the incorrect assumption that the same INN means an identical structure - **59%** of the UK physicians linked the same INN with identical structure - **39%** believed that same INN means that the two products are interchangeable

9. Treatment issues in multiple sclerosis in Latin America (Survey)

(Vizcarra-Escobar et al., 2015)	2014	Brazil, Chile Argentina, Mexico, Peru, Colombia	KOL Neurology (77)	- **56%** knew about the availability of BSPs in the national health system - **44%** did not know about the availability of BSPs in the national health system - **33%** refused to use BSPs - **11%** used BSPs and found worst results - **24%** used BSP but can't assess differences due to short limited experience - **4%** used BSPs and did not find differences with R-BMPs - Participants showed a remarkable uncertainty about BSP safety and efficacy

10. Viewpoint: knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and Colitis Organization (Survey)

(Danese et al., 2014)	Oct-Nov 2013	Europe	IBD specialist (307)	- **70%** were aware that a BSP is a similar copy, but not equal to the originator - **61%** felt little or no confidence in using BSP in their everyday clinical practice - **41%** felt confident to use BSP - **89%** regarded cost-sparing as the main advantage of BSP - **67%** ranked different immunogenicity as the main issue of BSP - **24%** accepted extrapolation for all R-BMP indication - **39%** disagreed with the concept of extrapolation - **65%** asked for well-designed trials with validated endpoints in each medical speciality for mAb in comparison to the other BSPs - **64%** were against auto-substitution - **63%** disagreed with switching established patients - **22%** agreed with switching after informing and consenting patients - **6%** thought that R-BMP and BSP mAb were interchangeable - **67%** agreed that BSP should carry distinct INN

11. Attitudes towards subsequent entry biologics/biosimilars: A survey of Canadian rheumatologists (Survey)

(Grabowski et al., 2015)	Feb 2014	Canada	Rheumatology (81)	- **31%** indicated that they were familiar or very familiar with BSPs - **31%** would be comfortable prescribing a BSPs if they were currently available - **72%** were unlikely to offer BSP as initial therapy, where cost is not an issue - Uncertainty over the long-term safety of BSPs was often cited among those who were unlikely to offer BSP - The majority did not support practice of indication extrapolation - **88%** were concerned about auto-substitution

12. Treatment preferences of originator versus biosimilar drugs in Crohn's disease; discrete choice experiment among gastroenterologists (DCE followed by Questionnaire)

(Baji et al., 2016)	May 2014	Hungary	Gastroenterology (51)	- **12%** did not support the use of BSPs in Crohn's disease - **65%** had efficacy and/or safety concerns about using BSP in Chron's disease - **20%** had no concerns with using BSPs in Chron's disease - **60%** chose R-BMP over BSP when no benefits are offered for initiating patients - **74%** chose R-BMP over BSP when no benefits are offered for switching patients

13. Physicians prefer greater detail in the biosimilar label (SmPC) - Results of a survey across seven European countries (Survey)

(Hallersten et al., 2016)	Apr 2015	France, Germany, Italy, Poland, Spain, Sweden, UK	Nephrology, Rheumatology, Dermatology, Gastroenterology, Endocrinology, Haematology, Oncology (210)	- **59%** were already prescribing BSPs - **87%** thought it helpful to specify the origin of clinical data (BSP or R-BMP) - **70%** thought it helpful to highlight which clinical indications were extrapolated

14. A survey among hospital specialists and pharmacists about biosimilars (Educational intervention followed by survey)

(Pasina et al., 2016)	Apr-Sep 2015	Italy	Specialists (214) Hospital Pharmacists (36)	- **74%** had poor knowledge of the scientific principles for licensing BSPs - **71%** of the specialists recognized BSPs as an important opportunity for savings - Specialists doubted BSPs dues to assumed inferior efficacy especially in extrapolated indications and higher risk ADRs - **51%** would initiate naïve patients - **25%** would switch established patients

15. Prescribing practices for biosimilars: questionnaire survey findings from physicians in Argentina, Brazil, Colombia and Mexico (Survey)

(Reilly and Gewanter, 2015)	May 2015	Argentina, Brazil, Columbia, Mexico	Dermatology, Oncology, Neurology, Endocrinology, Rheumatology, Others (399)	- **53%** were familiar, with a basic understanding of BSPs - **31%** heard of them but could not define BSPs - **49%** were aware of the difference between BMP, BSP and non-comparable BMP - **70%** were aware that a BSP may be approved for all indications of R-BMP based on extrapolation - **54%** assumed that all BSP go through the same regulatory process for approval as the original biologic products - **88%** were against pharmacy level substation - **64%** were uncomfortable with switching patients on a biologic to another BMP for cost, not medical - **87%** considered it Important to receive notification of a switch - **13%** considered switching to BSP acceptable, pending agreement of the prescriber - **74%** assumed that same INN means that BSP is approved for all of R-BMP - **54%** assumed that same INN means an identical structure - **44%** assumed that same INN that the two products can be switched safely with the same results - **94%** thought biologic qualifier would be useful in ensuring patients receive the right medicine that has been prescribed for them

16. Rheumatologists' Perceptions of Biosimilar Medicines Prescription: Findings from a French Web-Based Survey (Survey)

(Beck et al., 2016)	Jun-Aug 2015	France	Rheumatologists	- Rheumatologists were rather favourable towards BSP - 58.6% had little or even no knowledge about BSP - 5.2% felt very well-informed about this issue - Almost 75% were aware of the cost-saving potential of BSP - > 80% stated that a BSP has no meaningful differences from R-BMP in terms of quality, efficacy and safety - 67.2% reported that extrapolation could form a barrier to prescribing BSP - 66.1% reported that the most common barrier to prescribing BSP was ''lack of information about tolerability'' - 57% reported that ''lack of clinical trials'' acted as a barrier for prescribing BSPs - 88.8% started a treatment with BSP for naïve patients - 25% could switch established patients to BSP - Majority expressed a negative opinion about pharmacy level auto-substitution

17. Changes in Biosimilar Knowledge among European Crohn's Colitis Organization [ECCO] Members: An Updated Survey (Survey)

(Danese et al., 2016)	Jun-Nov 2015	Europe	IBD specialist (118)	- **80.5%** felt confident in prescribing BSP - **92.4%** considered cost saving to be the main advantage of BSP - **60%** had access to BSP and were prescribing it - **27.1%** believed that BSP would have higher immunogenicity - **16.9%** estimated that BSP would have a different action than R-BMP - **32.2%** were against an extrapolation across other speciality indications - **50.8%** accepted that BSP is approved for all R-BMP indications - **42.4%** reported that the main issue remained the lack of data derived from clinical trials for all indications - **44.4%** of the responders considered BSP and R-BMP mAb were interchangeable - **27.4%** of the physicians would switch to a BSP after patient information - **89.8%** disagreed with automatic substitution - **35%** agreed that BSP should carry distinct INN

18. Awareness, Knowledge, and Perceptions of Biosimilars Among Specialty Physicians (Survey)

(Cohen et al., 2016)	Nov 2015-Jan 2016	The USA	Dermatology, Gastroenterology, Haematology, Oncology, Nephrology, Rheumatologists (1201)	- The majority had heard about BSPs - Respondents' had low knowledge of BSP fundamentals - The majority believed that BSP will enable increased access and utilisation, expand treatment options, and provide savings to the healthcare system - A large number were unsure or concerned about BSP safety - **12%** were comfortable with the concept of extrapolation - **75%** appeared to trust FDA approval decisions; however, wanted additional information when making treatment decisions - More than one-third believed that abbreviated approval translates to a greater safety risk - **91%** were open to switching patients to a BSP

19. Assessing gastroenterologist and patient acceptance of biosimilars in ulcerative colitis and Crohn's disease across Germany (Survey)

(Sullivan et al., 2017)	Dec 2015-Mar 2016	Germany	Gastroenterology (25)	- **88%** preferred R-BMP over BSP as first-line therapy for either Ulcerative Colitis or Chron's disease - **64%** would prescribe BSP due to lower cost - **60%** thought BSP is more economic prescribing - **52%** thought that BSP has similar efficacy - **36%** would prioritise prescribing BSP upon initiation - **36%** would switch to BSP in a controlled environment

20. Assessing physician and patient acceptance of infliximab biosimilars in rheumatoid arthritis, ankylosing spondyloarthritis and psoriatic arthritis across Germany (Survey)

(Waller et al., 2017)	Dec 2015-Mar 2016	Germany	Rheumatology (50)	- **95%** would prefer R-BMP over BSP as a first-line or second-line therapy - **72%** would prescribe BSPs because it is cheaper - **62%** thought that BSP has similar efficacy - **37%** on average, would prioritise BSP prescribing upon initiation and when a treatment change to a different molecule is needed

21. Assessing awareness and attitudes of healthcare professionals on the use of biosimilar medicines: A survey of physicians and pharmacists in Ireland (Survey)

(O'callaghan et al., 2017)	2015-2016	Ireland	Community pharmacists, Dermatology, Endocrinology, Gastroenterology, Haematology, Nephrology, Neurology, Oncology, Rheumatology (520)	- **85.3%** of specialists reported were familiar with the term BSP - **40.3% of** GP were familiar with the term BSP - **>60%** of medical specialists were concerned about BSPs' quality, safety, efficacy and immunogenicity profile - **84%** of medical specialists were concerned about BSPs efficacy in an extrapolated indication - **49%** believed that decisions of substitution should be taken by the prescriber on treatment initiation - **61%** believed that decisions of substitution should be taken by the prescriber during a patient's treatment course - **67%** of specialists would initiate naïve patients - **28%** of specialists would switch established patients to BSPs - **31%** of medical specialists agreed that BMPs sharing the same INN were structurally identical - **43%** of physicians agreed that two BMPs with the same INN could be safely received by patients with the same clinical outcome - **42%** of physicians were neutral over whether patients could be safely switched and still achieve the same clinical outcome between two BMP with the same INN

22. Adoption of biosimilar infliximab for rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel diseases in the EU5: A budget impact analysis using a Delphi panel (Delphi survey)

(Kanters et al., 2017)	2015	France, Italy, Germany, Spain, The UK	Rheumatology, gastroenterology (First Round: 35, Second Round 17)	- Respondents believed that IFX-BSP efficacy and safety were comparable to R-BMP - The majority of participants would not switch their patients - Increasing market shares of IFX-BSP was mainly driven by naïve patients

23. Knowledge, Attitude and practice of healthcare professionals toward infliximab and insulin glargine biosimilars: a result of a UK web-based survey (Survey)

(Chapman et al., 2017)	Aug 2016-Jan 2017	The UK	Dermatology, Diabetology, Gastroenterology, Rheumatology (234)	- **72%** thought BSP were similar copies of R-BMP - **75%** were aware BSP were available on their local formulary - Cost saving was the dominant consideration when prescribing BSP - **> 90%** of gastroenterology consultants had no or minor concerns about BSPs' safety and efficacy when initiating or switching - **> 88%** of rheumatologists had no or only minor concerns about BSPs' safety and efficacy when initiating patients - **> 53%** of rheumatologists had major concerns about BSPs' safety and efficacy when switching patients

24. A Study to Assess the Awareness of the Biosimilars among Ukrainian Physicians (Structured interviews)

(Akhmetov et al., 2015)	Not Reported	Ukraine	Endocrinology, Oncology, Nephrology, Immunology, Rheumatology (82)	- Existing low to medium levels of BSP awareness in Ukraine - **77%** expressed likelihood to prescribe BSPs - The majority were likely to gradually utilise BSP - Most respondents addressed cost-benefit of BSP - The majority trusted the safety and efficacy assessment by EMA and FDA

25. Payer and physician evidence and discount requirements for biosimilars in three Latin American countries (Structured interviews)

(Sandorff et al., 2015)	Not reported	Argentina, Brazil, Mexico	KOL (4) Payers representatives (6)	- KOLs showed a strong preference to prescribe R-BMP over BSP due to their proven track records over years of study and market experience

26. Medical specialists' attitudes to prescribing biosimilars (Survey)

(Hemmington et al., 2017)	Not Reported	New Zealand	Dermatology, Rheumatology, Oncology, Gastroenterology, Haematology (110)	- **90%** reported familiarity and understanding of BSP concept - **71%** would prescribe BSP for all or some clinical conditions meeting the relevant criteria - **> 70%** were confident of the efficacy and safety of BSP - **< 20%** reported negative views of BSP - **47%** were confident in indication extrapolation - **32%** reported that a lack of clinical data supporting the efficacy of BSP would stop them from prescribing BSPs - The majority of participants were confident to switch established patients to BSP

27. Barriers to the Access of Bevacizumab in Patients with Solid Tumours and the Potential Impact of Biosimilars: A Physician Survey (Survey)

(Monk et al., 2017)	Not Reported	USA, Europe, Brazil, Mexico, Turkey	Haematology, Oncology, Pulmonary oncology, Gynaecologic oncology (510)	- **42%–82%** would prescribe a bevacizumab BSP, if available

ADR: Adverse Drug Reaction, **BMP:** Biological Medicinal Product, **BSP:** Biosimilar medicinal products, **DCE:** Discrete Choice Experiment, **ECCO:** European Crohn´s and Colitis Organisation, **EMA:** European Medicines Agency, **FDA:** Food and Drug Administration, **HER2+:** Human Epidermal Growth Factor Receptor 2 Positive, **IBD:** Inflammatory bowel Disease, **IFX-BSP:** Infliximab biosimilar, **INN:** International Non-proprietary Names, **KOL:** Key Opinion Leader, **mAb:** monoclonal antibody, **R-BMP:** Reference Biological Medicinal Product, **SmPC:** Summary of Product Characteristics, **UK:** The United Kingdom, **USA:** The United States of America

2.6. Locally commissioned medicines in NHS England

The availability of new medicines, changes in patients' demographics and patients' high expectations have resulted in a continuously growing demand for health services. Growing demand is often associated with scarce resources, which creates a gap between what is needed and what can be offered. Hence, healthcare planning is based on decisions related to allocating resources and prioritising demands (Williams, 2011). In England, decisions, within the NHS, are being made at four hierarchal levels (Tiers 1-4), these levels being associated with the purchaser-provider split structure of the NHS (Williams and Brown, 2014).

NHS-England operates through the provider-purchaser split, where purchasers are involved in allocating resources, and providers are accountable for meeting targets and providing healthcare for the population (Smith and Curry, 2011). However, NHS purchasers have a more strategic role that is described as 'a cumulative act of assessing and identifying health needs, identifying services to address the needs, allocating resources and finally monitoring the implementation'. Therefore, the term "commissioners" is used to reflect the cumulative role of NHS purchasers (Smith and Curry, 2011). Commissioning activities occur at two levels: national (tier 1) and local (tier 2), with each being filled by a different commissioning body: NHS-England and CCG (NHS-England, 2014b). On the other hand providers, whether organisations or healthcare professionals, are involved in tier 3 and 4 decisions (Williams and Brown, 2014).

Generally, commissioning activities / decisions could fall into one of the two main approaches: transactional or transformational commissioning. The commissioning process can involve redesigning the services or adopting a new approach to healthcare delivery (transformational commissioning / technical decisions), or it can be a simple and straightforward process of contracting (transactional commissioning / allocative decisions) (NHS-England, 2014b, Smith and Curry, 2011). On the other hand, tier 3 decisions are generally technical, with some occasional allocative decisions (Williams and Brown, 2014). Despite the fact that each decision tier has its own responsibilities, these tiers are not independent of each other. In the UK, the NHS is experiencing an ongoing financial crisis, as the total deficit reached £2.45 billion in 2015/2016. As the NHS's dedicated budget is strictly constrained, it is expected that the financial pressure will escalate still further in the future (Maguire et al., 2016, Wenzel, 2017). Despite the fact that expenditure on medicines is not among the highest NHS spending sectors, its growth rate is exceeding NHS total expenditure growth (Barham, 2017, NHS England, 2017). Moreover, medicines are usually the most supported interventions based on scientific evidence (Jenkings and Barber, 2004). As a result, measures and policies aiming to rationalise and controlling spending on medicines are frequently proposed and promoted. A rational decision is defined as "a method for systematically selecting among possible choices that are based on reason and facts" (Business Dictionary, 2018). Nationally, NICE plays a central role in rationalising medicine prescribing by assessing the economic impact of health technologies and recommending the most cost-effective medicines. Accordingly, if NICE recommends a technology for reimbursement, the NHS is obliged to assure the availability of this technology for patients within three months. Therefore, the funding of recommended medicines might be perceived as an allocative decision.

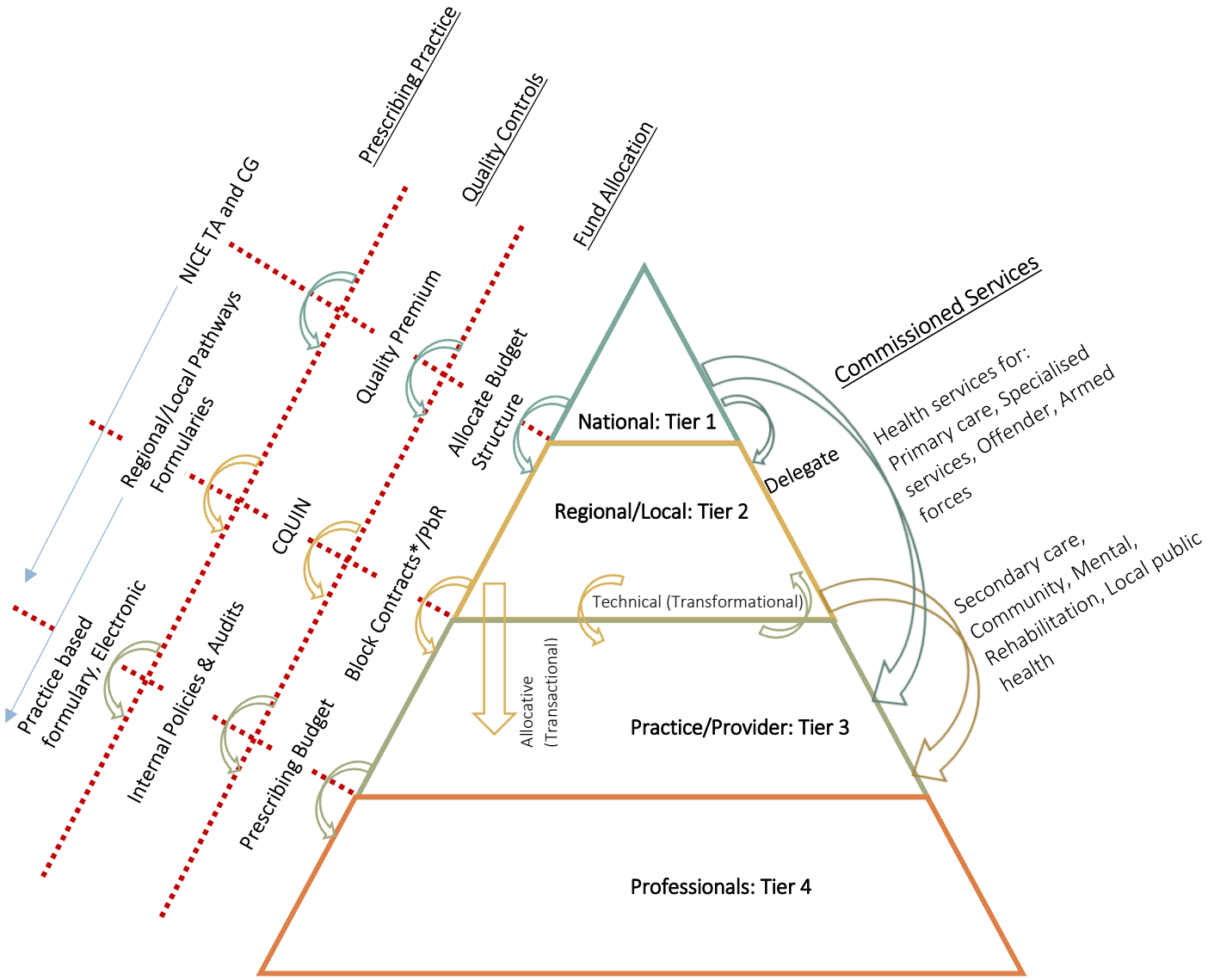
On the other hand, the absence of a NICE recommendation leaves the decision of reimbursement to relevant commissioners (The National Institute for Health and Care Excellence (NICE), 2013). Moreover, local commissioners and providers are advised to prioritise unassessed technologies in updating local medicines formularies. In England, local formularies are supposed to be the output of collaboration between different healthcare professionals locally; therefore the decision of listing, or not, of technology in local formularies is based on interactions, agreement and consensus between relevant stakeholders (The

National Institute for Health and Care Excellence (NICE), 2015a). Accordingly, the integration and hence the utilisation of BSPs might be perceived as a reflection of local dynamics and interactions.

Based on that perception, local commissioners and providers are asked to resemble NICE and to demonstrate allocative efficiencies in assessing available alternatives and directing financial resources (Palmer and Torgerson, 1999). BSPs represent a case, where NICE has recommended the molecules, but has left the decision of which brand to utilise to local arrangements and agreement.

Figure 1 explains NHS England decision tiers, fund allocation, quality control and prescribing practice related measures

Figure 1-NHS England decision tiers and accountabilities



Adapted with permission from (Williams and Brown, 2014)

* Legacy contracts

CG: Clinical guidelines, **CQUIN:** Commissioning for Quality and Innovation, **NICE:** National Institute for Health and Care Excellence, **PbR:** Payment by results, **TA:** Technology appraisal

2.7. Literature review summary

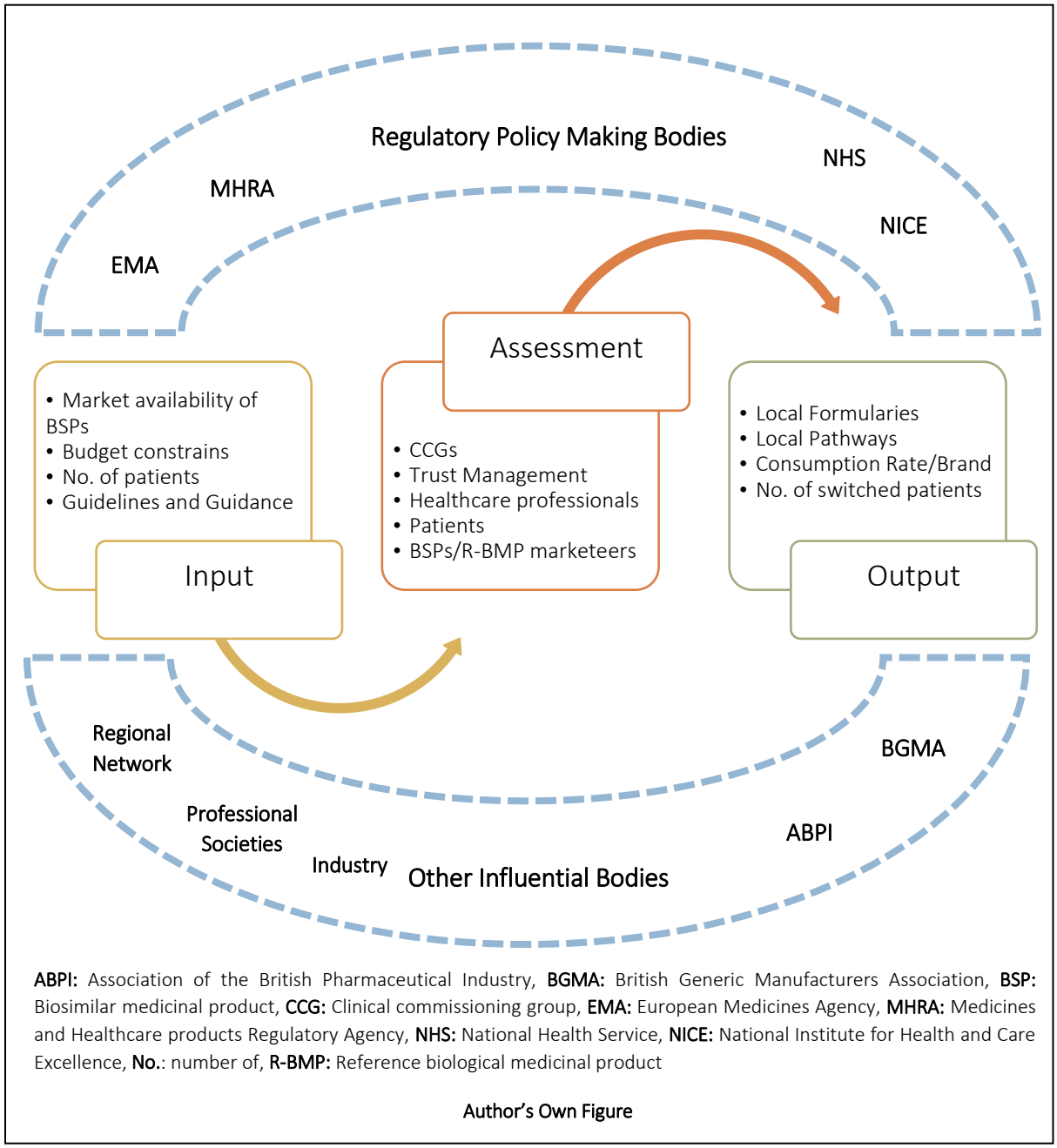
In summary, as BSPs are authorised through an abridged licensing pathway, which has triggered concerns regarding BSPs' safety and efficacy, and due to BSPs' inability to lead a price-based competition, regulators and policy makers need to intervene to assure the best possible outcomes for the BSPs and R-BMPs market. Regulators need to create market dynamics that (*i*) assure safe and controlled patients' exposure, (*ii*) limit R-BMP monopoly and (*iii*) rationalise the allocation of financial resources (Chauhan et al., 2008). In addition to market dynamics, the physicians' role is still essential and central in prescribing, switching and substituting BSPs. The reviewed literature in this chapter has shown that prescribing behaviour could be influenced by encouraging educational or restrictive interventions. The literature showed that a combined and interactive set of factors and procedures are affecting BSPs' utilisation; therefore, investigating BSPs' uptake should acknowledge the process by which these factors interact and affect BSPs' uptake.

Recently, the UK BSPs' market witnessed several updates in terms of market launches, as well as more active involvement by NHS and NICE. In Feb 2015, two brands of the first BSP mAb (IFX-BSP) (Inflectra® and Remsima®), were launched (UK Medicines Information (UKmi), 2015). IFX-BSPs represent an interesting case, as infliximab is a secondary care high-cost medicine that is commissioned locally by CCGs (Specialist Pharmacy Service (SPS), 2016). Therefore, the decision of adopting IFX-BSP might be subject to local arrangements, rather than national level arrangements. Second, concurrent to its launch on 25th Feb 2015, NICE published a technology appraisal (TA329) in which IFX-BSPs were listed as therapeutic options along with their R-BMP (Remicade®) (The National Institute for Health and Care Excellence (NICE), 2015c). Third, in July 2015, NICE issued an implementation guide that proposed a plan for Acute Trusts and CCG on how to introduce and implement IFX-BSPs (The National Institute for Health and Care Excellence (NICE), 2015d). Fourth, in Sep 2015, NHS-England issued educational material explaining BSPs concept, added value, the prescribing approach (brand name-based) and the place and role of monitoring (NHS England-Medical Directorate, 2015). Fifth, the British Society of Gastroenterology (BSG), the biggest user of IFX, had antecedently issued a statement paper in which it advised gastroenterologists against switching established patients (British Gastroenterology Society (BSG), 2014). Lastly, in its statement on BSPs, the British Society for Rheumatology (BSR) emphasised the need to prioritise patients' health and clinical needs when prescribing BMPs, including BSPS. Pointedly, the BSR refused to prioritise cost as a factor that leads to the prescribing of BMPs and their BSP counterparts (The British Society for Rheumatology (BSR), 2015).

Accordingly, investigating how IFX-BSPs are being adopted and implemented in medical practice, and the nature of interactions between relevant stakeholders, will be the first test case targeting BSP mAb in the UK.

In summary, based on what was discussed in the literature, and how medicines are assessed and commissioned locally, commissioning and utilising BSPs is influenced by several factors related to: (*i*) policies and regulations, (*ii*) market dynamics in terms of product suppliers and manufacturers, (*iii*) prescribers' attitudes and acceptance, (*iv*) financial resources and (*v*) guidelines and guidance. BSPs' adoption process might be presented in three steps: (*i*) input, (*ii*) assessment and evaluation and (*iii*) output, Figure 2 represents a summary of the context in which BSPs are commissioned

Figure 2-Summary of process that is perceived to affect the uptake of biosimilar medicines in England



ABPI: Association of the British Pharmaceutical Industry, **BGMA:** British Generic Manufacturers Association, **BSP:** Biosimilar medicinal product, **CCG:** Clinical commissioning group, **EMA:** European Medicines Agency, **MHRA:** Medicines and Healthcare products Regulatory Agency, **NHS:** National Health Service, **NICE:** National Institute for Health and Care Excellence, **No.**: number of, **R-BMP:** Reference biological medicinal product

Author's Own Figure

2.8. Research aim and objectives

The aim of this study to investigate factors and process by which BSPs were integrated in healthcare settings in England by identifying integration rate and main stakeholders' experiences with BSPs.

2.8.1. Overall Thesis Objectives

- To assess integration rates of available BSPs, at the time of this research, into medical practice in the UK through:
    - Investigating how available BSPs are listed in local medicines formularies
    - Inspecting the prescribing patterns for IFX-BSP, whether initiating or switching patients
- To understand the process by which the decision of adopting BSPs was taken by:
    - Identifying main stakeholders' experiences, perceptions and levels of involvement in assessing, managing, commissioning, prescribing and dispensing BSPs
    - Identifying and reporting types of interactions between main stakeholders that affect the decision of integrating and utilising BSPs
    - Understanding how external factors such as national policies, professional bodies and industry affect local interactions

Chapter Three: Research Methodology and Methods

"…Like an onion that wishes to be peeled so we can read what is laid bare letter by letter. It is unambiguous and often in mirror-writing or otherwise disguised. Beneath its dry and crackly outer skin we find another, more moist layer, that once detached, reveals a third, beneath which a fourth and fifth wait whispering…"
Günter Grass-Peeling the Onion

3.1. Introduction

Writing this chapter was one of the most challenging tasks I had to complete during my PhD, as I needed to discuss and talk about my experience, as a researcher, in shifting from natural to social science methods of inquiry. As a pharmacist, my training was based on, and driven by the philosophy of empiricism, by which understanding of a sensory recognised phenomenon is driven by experimental, objective and falsifiable methods and approaches (Benton and Craib, 2010). However, as I was involved in reviewing the literature and focusing the research question, it became clear to me that factors related to medicines policies and regulations, stakeholders' attitudes and acceptance, as well as contextual elements, all affected the use of BSPs. These factors are created by the human cognitive process and human interactions (Benton and Craib, 2010), which are not context-free and cannot be studied in isolation from their surrounding social structure and environment (Prosser and Walley, 2006). To be able to study these factors, I needed to wear a different hat, that of the social researcher. A social scientist tries to understand how humans make sense, interact and affect, and are affected by, the social structure surrounding them; a situation which cannot be sensed by, or measured with, empiricism's tools. Therefore, social scientists employ and rely on a different set of research methods and designs (Bryman, 2015). Social research methods are not assessed based on their correctness, but rather on their suitability and appropriateness for investigating and addressing research questions (Silverman, 2014). Therefore, a social researcher needs to justify his/her selected research design and method, to clearly address their epistemological and ontological stands, data interpretation approach and how emerging evidence will be synthesised (Silverman, 2014). In discussing an investigation that belongs to one of the social research areas, a researcher needs to discuss and base his/her argument on four basic principles: (*i*) theoretical framework, (*ii*) philosophical position, (*iii*) methodology, and (*iv*) methods (Silverman, 2014). Together, these four elements form a system that helps the researcher to conduct his/her study as well as articulating its findings and evidence. In this chapter, I have provided: (*i*) a detailed account of the overall study design, (*ii*) the philosophical position driving its conduct, (*iii*) the selected information gathering method and (*iv*) the way in which evidence is synthesised and presented. This chapter is structured into three main sections: (*i*) the first is concerned with highlighting the epistemological and ontological stands for this research, (*ii*) the second is about the overall research methodology, and (*iii*) the third talks about selected data collection and analysis methods.

3.2. Implementation science as an approach to understand BSPs uptake

Evidence available at the time of licensing was considered to be sufficient for regulatory authorities to approve and license BSPs. However, the EMA and other worldwide regulatory authorities rely on real-world post-marketing safety studies to ensure patients' safety and verify concerns regarding BSPs' quality, safety and efficacy. Therefore, limited utilisation of BSPs might hinder post-authorisation assessment, and help to maintain the uncertainty about BSPs. Additionally, that limitation might hold back potential savings the healthcare systems could achieve as a result of utilising BSPs. For a medicinal product, technology or an intervention to be adopted by, and integrated into, a healthcare system the item in question needs to go through a translational process. A translation (translating research into practice) is defined as "ensuring that new treatments and research knowledge actually reach the patients or populations for whom they are intended and are implemented correctly" (Woolf, 2008). Translation occurs through two stages: the first stage (T1) aims to create an effective intervention informed by evidence and make it available for use. The second stage (T2) actively gets a tested and effective intervention integrated (institutionalised) into specific settings or organisational structures (Woolf, 2008, Palinkas and Soydan, 2012).

Based on what has been discussed in the previous chapter, it was not the market unavailability, legal constraints such as patent and market exclusivity or absence of assessing and licensing pathways that have hindered BSPs' utilisation. The limited uptake was attributed to prescribers' acceptance of and attitudes toward BSPs, together with a lack of promotional measures and interventions that could have encouraged the commissioning, prescribing and dispensing of BSPs. Therefore, this research does not fall within the remit of T1, which is concerned with testing efficacy, biological, chemical and regulatory aspects of a medicine in a controlled environment. This study falls within T2, which is concerned with assessing factors and processes leading to the integration of an intervention in real life settings (Rabin and Brownson, 2012, Woolf, 2008, Palinkas and Soydan, 2012).

The second stage (T2) should not be perceived as one step or mono-dimensional research; in fact, some scholars went on splitting it further into T2 (synthesising evidence) and T3 (disseminating-implementing evidence) (Woolf, 2008, Westfall et al., 2007). However, whether classified as T2 or T2/T3, this research model consists of three main milestones: (*i*) deciding to adopt an intervention, (*ii*) integrating the intervention and (*iii*) finally assessing its outcomes. Getting the desired outcomes, whether these involve proven effectiveness, economic or system sustainability, is achieved through successful integration of an intervention (implementation). However, integrating an intervention follows the adoption decision, which is driven by the diffusion and dissemination of intervention related informative materials (Proctor et al., 2009, Palinkas and Soydan, 2012). Figure 3 explains the process of research translation and gives examples of research areas involved in each stage.

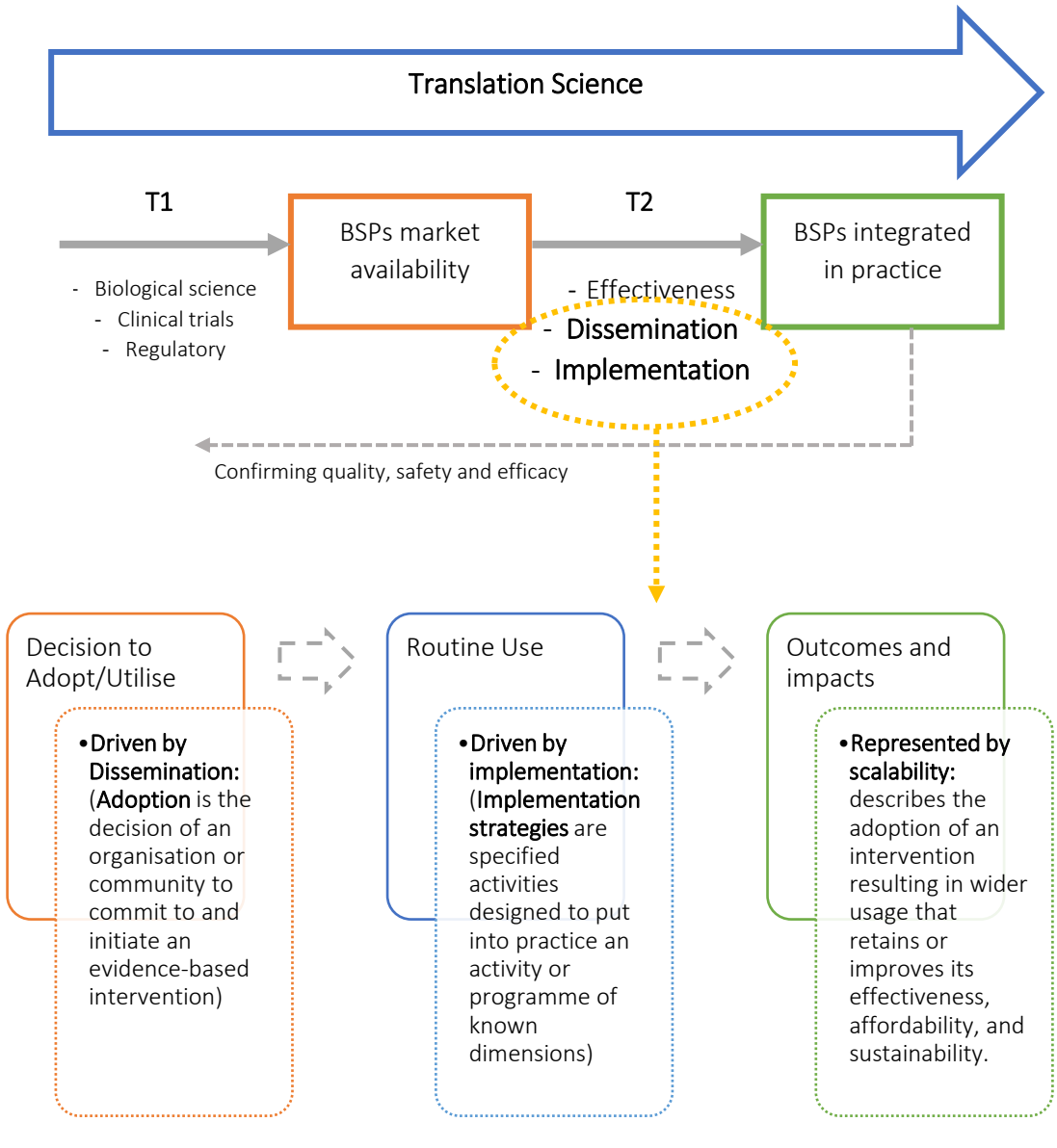
In general, projects that are concerned with understanding factors and issues driving T2 are called implementation research. However, understanding this research area and its relevant theories was challenging, due to the lack of standardised terms and definitions (Rabin and Brownson, 2012, Skolarus et al., 2017). Therefore, it is of importance to differentiate between four main definitions: diffusion, dissemination, implementation, and implementation research:

- *Diffusion:* is the passive, untargeted, unplanned, and uncontrolled spread of new interventions; it is the least focused and intense approach (Rabin and Brownson, 2012)
- *Dissemination:* is an active approach of spreading evidence-based interventions to the target audience via determined channels using planned strategies (Rabin and Brownson, 2012)
- *Implementation:* is the process of putting to use or integrating evidence-based interventions within specific settings (Rabin and Brownson, 2012)
- *Implementation research:* is the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services. It includes the study of influences on healthcare professional and organisational behaviour (Eccles and Mittman, 2006)

In some cases, the term implementation research is used with a narrower scope, which is limited to studying the integration process and comparing the actual procedures to those set out in a proposed plan (Palinkas and Soydan, 2012). However, in this chapter, the term implementation science is used to describe the theories that involve elements related to the continuum of diffusion-dissemination-implementation.

Implementation science addresses issues and factors that go beyond the end users' level of patients and prescribers, by acknowledging the role of other involved professionals, relevant organisational structure and the context in which intervention implementation takes place (Woolf, 2008, Bauer et al., 2015). As its aims to integrate an innovation into an organisation or a practice, implementation is perceived as a change process that might create a new reality or fresh practice norms. Implementation is described as "a dynamic social process that is shaped by the context or ecology in which the practice innovation takes place and the people involved in this process" (Cabassa, 2016). Accordingly, implementation is based on three main components: (*i*) content (nature of evidence), (*ii*) context (social structure and players) and (*iii*) process (procedure) (Schillinger, 2010). As implementation is affected and guided by human behaviour, knowledge and values, human interactions with each other and with the context in which the implementation takes place, the core component is the human factor (Cabassa, 2016, Damschroder et al., 2009). In conclusion, investigating the factors that affect the utilisation of BSPs could be achieved through implementation science related principles and theories.

Figure 3-Translation research stages



T1: Stage one, **T2:** Stage two

Author's Own Figure.

Informed by

Woolf, S.H., 2008. *Jama*, *299*(2), pp.211-213

Bauer, Mark S., et al., 2015. BMC psychology 3.1 (2015): 32.

Rabin, B. A. & Brownson, R. C. 2012. Dissemination and implementation research in health: translating science to practice. Oxford University Press

3.2.1. Selecting a theoretical framework

While reviewing translational research and implementation science related literature, I have noticed that there were a number of theoretical concepts and structures that I can use to develop a better understanding of my research and which can guide data analysis and synthesis of evidence. However, due to the huge number of theoretical concepts, it was not possible for me to review and assess all of them, in order to select the most suitable one for my research. Nevertheless, there were several reviews that classified these concepts according to their *complexity* into: frameworks, models and theories (Bauer et al., 2015, Carpiano and Daley, 2006); to their *focus* within T2's spectrum whether dissemination, implementation or both (Tabak et al., 2012), or according to their *scope (aim)* within the whole translational process (Nilsen, 2015).

The terms theory, framework and model are sometimes used interchangeably and confusingly by researchers. There are fundamental differences between the three in terms of complexity and ability to explain the phenomenon of interest (Bauer et al., 2015, Carpiano and Daley, 2006). A *framework* provides a structure by categorising and grouping relevant elements and drawing the borders of phenomenon of interest. In some cases the definition moves from a simplistic outline to more complex paradigm that accommodates multiple theories and models (Nilsen, 2015, Carpiano and Daley, 2006). A *model* is the most specific concept; it looks at and investigates possible sequential (causal) relationships between elements within a framework (Nilsen, 2015, Carpiano and Daley, 2006). A *theory* is composed of a set of explanatory statements and a hypothesis that explains the observed relations within a model; it is the most flexible and fluid structure amongst the three concepts (Nilsen, 2015, Carpiano and Daley, 2006, Bauer et al., 2015).

It was challenging to accept the notion that a framework has only structural capacity, because, for me, labelling the categories and defining the borders of a phenomenon is, even if implicitly, based on a certain degree of assumed relations and connections, which suggests that frameworks have an explanatory capacity. Moreover, these definitions, and the proposed relations between them, are assumed to be occurring in a mono-horizontal surface, which might fit framework's role in defining the borders of the tangible surface at which the phenomenon's outcomes become visible. However, the implementation occurs within an organisational structure (Bauer et al., 2015), which is multi-layered with vertical and horizontal structures, where models and theories operate to explain the effects of context and to identify cause-effect relationship (Bauer et al., 2015).

Among the three concepts, I concluded that a theory is the most comprehensive one, as it does not limit its explanatory capacity within defined borders; it is able to borrow from others in order to explain the phenomenon, and acknowledges the influence of surrounding context (Tabak et al., 2012). A theory might accommodate more than one model, with each represented by a hypothesis within the theory, and it might benefit from a framework to guide its focus toward the research aim and objectives.

As implementation science is concerned with T2 stage, it involves elements related to dissemination and implementation. In their narrative review, Tabak et al. (2012) classified the most frequently cited and best known frameworks and theories according to their focus (toward dissemination, implementation, or equally both), flexibility upon application and, finally, according their operational level (applicable sociological level). In the this research, the general aim was to understand factors and processes that lead to the decision to use and prescribe BSPs; it was not about how BSPs were implemented (institutionalised) or if the actual implementation went according to plan or pre-specified standards. However, it is important to understand the implementation process, which might then be extrapolated to future BSPs. Therefore, I

needed a theory that has dissemination as its main focus and is flexible enough to accommodate elements that can relate to and address the implementation process.

The last approach that might be followed when classifying and categorising frameworks, models and theories is to focus on their aim and scope (Nilsen, 2015). Nilsen has classified theoretical concepts into: (*i*) "how to" concepts that lead and guide implementation process, frequently associated with interventional studies; (*ii*) theoretical concepts that explain the observed/attained outcomes and finally (*iii*) concepts that are used for evaluating outcomes (Nilsen, 2015). However, this classification is problematic as it ignores the cyclic non-linear nature of research translation. The definition ignores that assessment can be carried out during the process and its findings might be used to correct any deviation from the original plan, or to adapt the process to unexpected contingencies (updating the 'how to' manual) (Stetler et al., 2006, Proctor et al., 2009, Palinkas and Soydan, 2012). Nevertheless, the classification helped me in understanding the direction of my research, as it was neither an interventional nor an evaluation study; but it was about understanding processes leading to BSPs' utilisation.

Based on the above discussion, I realised that I might benefit from a theory that has its main focus on the dissemination element, and is able to explain and justify the observed outcomes. Additionally, this theory should have the capacity to accommodate the particular characteristics of BSPs. One of the most commonly referenced theories is Rogers's theory on diffusion of innovation (Skolarus et al., 2017).

3.2.1.1. Innovation diffusion theory

As discussed earlier, producing, assessing and licensing a BSP is based on constant comparison to its R-BMP counterpart; a BSP needs to have a similar molecular structure, and non-significant difference levels of quality, safety and efficacy profiles when compared to the R-BMP (European Medicines Agency (EMA), 2014a). Therefore, BSPs do not represent an innovative concept, but rather they are an imitation (Niosi, 2017). Being classified as an imitation might indicate that BSPs, to a degree, resemble the already established concept and market of conventional chemical generic medicines. However, due to the complicated nature of BSPs, and the flagged concerns regarding their quality, safety and efficacy (Declerck and Simoens, 2012, Brussels, 2005, Waters Corporation, 2013), it is not possible to rely on already existing assessment and licensing pathways currently being used for conventional generic medicines. Hence there is a need to create BSP specific assessment and licensing pathways. Therefore, the introduction of BSPs into clinical practice, in comparison to generic medicines, could be considered as introducing an innovative concept. Additionally, the EMA licenses and authorises the marketing of BSPs based on quality, safety and efficacy studies; however, it does not provide advice regarding the interchangeability and substitution of BSPs. Wisely or not the EMA left this matter to national regulators; accordingly, in the absence of formal assessment, national policies and/or directives, the concept of switching might also fit the concept of innovation.

Despite having the word diffusion in its name, Rogers 2003 structured his theory to describe both diffusion (passive) and dissemination (active) communication of a new idea (innovation). The theory is based on four main concepts: (*i*) innovation (new idea/technology), (*ii*) communication,(*iii*) channels (social structure) and finally (*iv*) time. In spite of being classified as a dissemination focused theory (Tabak et al., 2012), innovation diffusion theory does include implementation as a recognised step within the five-step sequence of the innovation-decision process; immediately after the decision step. Therefore, Rogers's theory was found to be relevant and useful to accommodate this research.

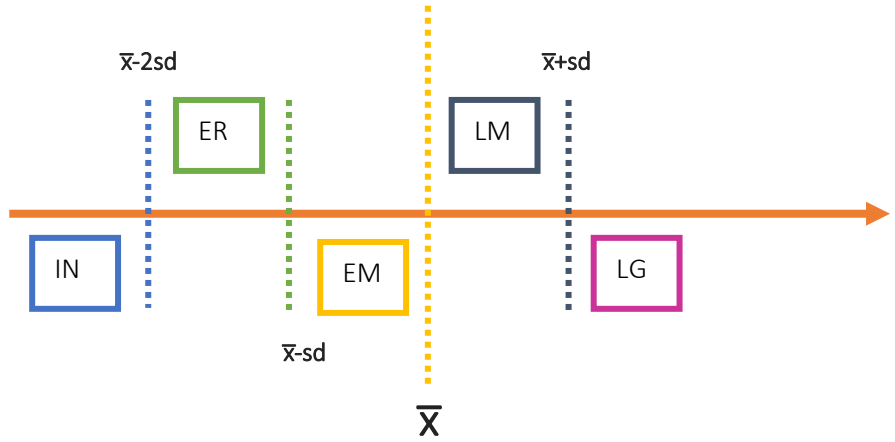
In his theory, Rogers specified three types of innovation decisions: *optional* (individual driven), *collective* (driven by consensus between members within a given system) and *authority* (driven by powerful/authoritative figures within an organisation). To address the differences between the three types, Rogers developed two main models of his theory: the first model explains diffusion decisions made by individuals (optional and collective); the second model is concerned with diffusion within an organisational structure (authoritative). For organisational innovation, in addition to describing the process of innovation diffusion, Rogers identified factors affecting organisational innovation, which is driven by independent variables related to: (*i*) the organisation leader's characteristics, (*ii*) its internal structure and (*iii*) the organisation's external characteristics.

The process of determining which model is relevant to BSPs started by identifying 'prescribing and dispensing' sites of available BSPs, at the time of the study. It was noticed that all available BSPs were either dispensed or initiated from secondary-care settings. In the UK, secondary-care providers are: (*i*) Territorial Health Boards in Scotland, (*ii*) Local Health Board in Wales, (*iii*) Acute Trusts in England, and (*iv*) Hospital Trusts in Northern Ireland. As Health Boards and Acute Trusts are (*i*) responsible for providing healthcare services to the population, (*ii*) held accountable for the local population and for governance bodies and (*iii*) employing range of professionals, whether medical or non-medical staff (NHS-Wales, 2017, Kathleen Robson, 2016, NHS UK, 2016), these bodies fit within the definition of an organisation "a stable system of individuals who work together to achieve common goals through a hierarchy of ranks and a division of labour. Organisations are created to handle large-scale routine tasks through pattern of regularised human relationships" (Rogers, 2003). Accordingly, assessing secondary-care uptake of BSPs might fall within the scope of an authoritative decision of innovation. However, due to the fact that NICE has left the decision of *prescribing* BSPs in general, and *switching* in particular, to prescribers and patients agreeing, BSPs' adoption is still governed by factors that are related to individuals, in addition to organisational factors (The National Institute for Health and Care Excellence (NICE), 2016b). Therefore, a hybrid approach between the two models might be the most appropriate to guide this research.

The hybrid approach is referred to as a "contingent innovation decision", where individuals adopt an innovation following an institutional decision to adopt the innovation and make it available for use (Rogers, 2003, Frambach and Schillewaert, 2002). Therefore, the decision to adopt BSPs could be investigated and attributed, using Rogers's two models of innovation diffusion.

In addition to following a hybrid approach incorporating Rogers's two models of innovation diffusion, Rogers's categorisation of innovation adopters was also considered. The model is based on the average and standard deviation of time needed to adopt an innovation since its first introduction. Accordingly, adopters can be categorised into five main categories: (*i*) innovators, (*ii*) early adopters, (*iii*) early majority, (*iv*) late majority and (*v*) laggards (Rogers, 2003). Figure 4 represents Rogers's adopters' categorisation.

Figure 4-Summary of Rogers's model on categorising innovation adopters



x̄-2sd: average time period needed to be considered as innovator
x̄-sd: average time period to be considered as early adopter
x̄+sd: average time period to be considered as late majority

IN: Innovator, **ER:** Early Adopter, **EM:** Early Majority, **LM:** Late Majority, **LG:** Laggards
sd: standard deviation, **x̄:** Mean time to adopt an innovation

Adapted from Rogers, E. M. 2003. Diffusion of Innovations, New York, Free Press.

3.3. Research's philosophical position

One factor that might influence the chosen research area, approaches and methods, in addition to the research question itself, is the surrounding research group. Being a student in the Pharmacy Practice and Policies (PPP) Department, University of Nottingham, where almost all the researchers are involved in research projects driven by social science methods and theories, has exposed me to social science and made me start considering its approach to understanding the factors and processes driving the implementation (uptake) of BSPs in healthcare settings in the UK.

With its aim of getting an innovation/technology which has had its efficacy tested and proven adopted by, and integrated into, an organisation or a practice, implementation is perceived as a change process that is aimed at creating a new reality or practice norms. Implementation is based on three main components: (*i*) content (nature of evidence), (*ii*) context (social structure and players) and (*iii*) process (procedure) (Schillinger, 2010). Therefore, implementation is described as "a dynamic social process that is shaped by the context or ecology in which the practice innovation takes place and the people involved in this process" (Cabassa, 2016). The core component of this social process is the human factor; in fact, implementation is affected and guided by human behaviour, informed by the person's knowledge and values (Damschroder et al., 2009), and influenced by their interactions with each other and with the context in which the implementation takes place (Cabassa, 2016, Damschroder et al., 2009). Implementation research is intertwined with other research areas and at times embraces their methods and theories (Woolf, 2008). However, three key concepts in its definition: *social*, *human action* and *context*, led me to conclude that this research can be accommodated within the scope of social science and actualised using its methods of data collection and analysis. Implementation's definition is in alignment with Weber's definition of social science as the "a science concerning itself with the interpretative understanding of social action and thereby with a causal explanation of its course and consequences" (Weber, 1978).

In conclusion, it became obvious to me, that in order to understand factors driving the utilisation of BSPs, I need to understand values and motives of prescribers and other stakeholders in introducing and prescribing BSPs; an understanding which could be achieved through social research methods.

3.3.1. Philosophical basis

In discussing their research process, social researchers need to discuss their perception and understanding of the world surrounding them (their ontology), how they know and recognise the world (epistemology "theory of knowledge"), overarching study design that leads to data collection and analysis (methodology) and finally research techniques and data collection tools (method) (Silverman, 2014, Benton and Craib, 2010). These four main concepts continuously affect and modify each other, as the epistemology inspires the selected methodology, methodology directs research conduct and methods, and the latter creates new knowledge that will be again evaluated and assessed by the followed theory of knowledge (epistemology) (Carter and Little, 2007). There are several philosophical stands a social researcher can follow to build his/her argument on; the selection of which stand to follow and to adopt depends on the research question and how the researcher perceived the surrounding world, all informed by and his or her belief system. As I read about the philosophy of social science, I evaluated philosophical stands that I came across and assessed their compatibility with the research question, implementation science and my own beliefs.

As it is described as the social science take of natural empiricism, positivism seeks to reengineer society by utilising a "positive knowledge". This position is based on its acknowledgement of the independent existence of social facts, and the emphasis on extrapolating natural science methods for use in social science (Benton and Craib, 2010, Bryman, 2015). A positivist researcher seeks to inductively produce objective unbiased knowledge (Bryman, 2015, Silverman, 2014), to establish law-like evidence that can be further tested deductively and then verified (Bryman, 2015). In doing that, a positivist mostly avoids theoretical debates and, in turn, argues for the validity and reliability of research techniques and operations (Silverman, 2014). Positivists argue for the legitimacy of their conclusions about social life by emphasising the objectivity of the methods they use, claiming that standardised value free methods allow them to generalise their conclusions and to predict future occurrences (Silverman, 2014, Bryman, 2015). As I am a trained empiricist, I believed that building my argument on a positivist's stand suits my view of life and understanding of the world surrounding me. Moreover, given that I used to work at a generic pharmaceutical company and have a personal interest in BSPs, there was a possibility that I might be perceived as a BSPs enthusiast and supporter. Therefore, a positivist account might be able to objectively and neutrally investigate prescribing practices associated with BSPs, by assessing utilisation rates and identifying factors that influence BSPs' use. Following a positivist approach might also provide me with a tool to predict and forecast utilisation rate of upcoming BSPs.

However, a philosophical stand is not only influenced by the researcher's beliefs and preferences, but it is also driven by the research question and the nature of the phenomenon under investigation. Based on what was discussed earlier in the literature review (Chapter 2), the decision of commissioning and utilising BSPs is affected by both intrinsic and extrinsic factors. Extrinsic factors might be in the form of national and local policies and guidelines, and negotiations between commissioners and providers. Intrinsic factors might be related to prescribers' and patients' acceptance and perceptions of BSPs. Whether intrinsic or extrinsic, both factors are influenced by stakeholders' values, understanding, mental processing and their interpretation of the world around them and the actions of others. Accordingly, the observed utilisation level of BSPs (social fact) is not independent from the influence of the main stakeholders and their beliefs

and attitudes. This in turn opposes the core argument of positivism relating to the independent existence of social existence, independent from the researcher and main participants, that is presented and reported using standardised measurements rather than their views and perceptions (Houghton, 2011). Another factor that hindered me from designing positivist research was the dynamic nature of the BSPs market, as policies and regulations related to BSPs and commissioning are continuously revised and updated. Therefore, positivist research with its relatively fixed and inflexible methods of data collection and analysis (Silverman, 2014, Bryman, 2015) might not be able to reflectively capture the nature of the BSP market, or how the main stakeholders adapt to and perceive new policies and regulations.

In addition to the highlighted two barriers, positivism's assumption of "exclusive rationality" of humans (Smith, 1987) was also problematic for this research. In general, prescribers are continuously requested to comply with the concept of evidenced based medicine (EBM) in their routine practice and decision making processes. As per EBM, prescribers should rationally consider the evidence and the suitability of experiments/trials used to evaluate the safety and efficacy of a medicinal product (Djulbegovic et al., 2009). Additionally, prescribers are supposed to let the evidence guide them to the truth. If a well-designed trial shows that *X* is safe and effective, *X* should be considered safe and effective till new evidence challenges this claim (Djulbegovic et al., 2009). And finally, evidence should act as the shared reference for all practitioners; the evidence should always be considered in resolving conflicts or in identifying and restoring deviations in practice (Djulbegovic et al., 2009). Based on what was discussed earlier, BSPs represent a unique and special case of medicines. While these products go through rigorous quality, safety and efficacy assessment procedures, available evidence was not derived from trials in all indications, but rather extrapolated from the reference products. Additionally, evidence available at the time of licensing, neither supports or discourages the switching of established patients to BSPs. Limited evidence caused confusion among prescribes, as it does not support the core principle of EBM; therefore to some extent the prescribing of BSPs was left to the prescribers' perceptions and beliefs, which are not always governed by rational reasoning. As a result, it was reported that the slow uptake of BSPs was due to physicians' assumptions about the inferiority of BSPs in safety, quality and efficacy attributes (Weise et al., 2012). Therefore, positivist assumptions of exclusive rationality cannot serve this research or support its conclusion.

As the positivist position was found not to be able to accommodate the research, I needed a philosophical position that fits with my understanding of the world, which exists independently, is compatible with the research question, as well as the nature and dynamics of BSPs' commissioning and utilisation. I agree with Weber's argument regarding the "dual" nature of the world: objective and subjective (mental phenomenon), and the role of subjective interpretation in capturing and reporting the social component of reality (Weber, 1978). In the case of BSPs, utilisation volumes and integration in local pathways and guidelines could be objectively assessed and reported. However, discussions and dynamics that led to the decision of commissioning and prescribing BSPs are based on mental processing and are expressed using languages in the form of speech or documents.

The philosophical stands that recognise the role of mental processing in understanding and structuring the reality we live in, are mainly those of constructivism and realism; these are two philosophical stands I could possibly follow. However, I found it challenging and uncomfortable to accept the constructivist's point of view in terms the absence of a unified external world, which we all recognise and know.

I also was not convinced with constructivism's argument that we, as knowledge creators, are able to shape the world and extend its limits according to our intentions and purpose (Schwandt, 1998). I believe that we have limited knowledge of the world, yet with time and experience we can deepen that knowledge. Therefore, it is not the world that is expanding but rather our awareness of it.

The other possible approach was critical realism, which is a philosophical stand that accommodates the ontology of a realist and the epistemology of an interpretivist (Guba, 1990). Critical realism arguments are ontological in nature, as the philosophy advocates the independent existence of an open stratified ontology that directs our knowledge (Bhaskar, Collier). Moreover, critical realism acknowledges the limitation of our knowledge and the fact that this knowledge is temporary and it subjected to be revised, updated and represented with time and experience (Collier, Bhaskar).

For a reality to be described as critical, it should be perceived as unpleasant and needs to be improved by individual living and affected by it. This is based on the notion that within a given structure/society, people's confused awareness results in stress (crisis) in that society (Fay, 1987). Critical realism, in broad terms, seeks the change and creation of a new reality; however, it does not build its argument on injustice and social conflict. Critical realism explains that the changes occur as a result of the continuously evolving (transitive) knowledge of the differentiated (stratified) nature of reality (Benton and Craib, 2010, Bryman, 2015). Critical realism bases its arguments on the multi-layered structure of reality, and that observable objects at the outermost layer are created and influenced by generative events and mechanisms at deeper, not readily observed, layers (Benton and Craib, 2010, Walsh and Evans, 2014). Scholars of critical realism argue that initially we might be misled by the facts and objects readily observable; however, as we start investigating what generated and created these facts and objects, we develop new and deeper understanding. The recognised mechanisms and our newly acquired knowledge redirect our perception of reality's surface and change our understanding of it, and how we deal and interact with it (Benton and Craib, 2010).

Critical realism might be able to develop falsifiable, testable evidence that is synthesised using textual verbatim evidence (Maxwell, 2004). Critical realists synthesise their understanding of the social world acknowledging that we, as humans, have only partial awareness and limited capacity to comprehend the external world (Smith, 1990, Benton and Craib, 2010). Additionally, adopting a critical approach in realising the social world, critical realists approach phenomenon of interest with open, flexible minds, which allows them to accept that there is nothing called the ultimate truth (Smith, 1990). Subsequently, critical realists recognise that human values, perceptions and motives form essential/original components of our knowledge (Benton and Craib, 2010). Therefore, critical realism is useful for investigating underlying mechanisms, as it acknowledges and recognises the effect of interactions between different stakeholders as well as the contextual effect of these interactions (Walsh and Evans, 2014). Additionally, critical realism is able to provide inductive knowledge based on an in-depth investigation and analysis of the human intellect, where perception may provide more reliable explanations for social phenomena (Benton and Craib, 2010).

3.4. Research methodology

3.4.1. Justification for selecting mixed methods

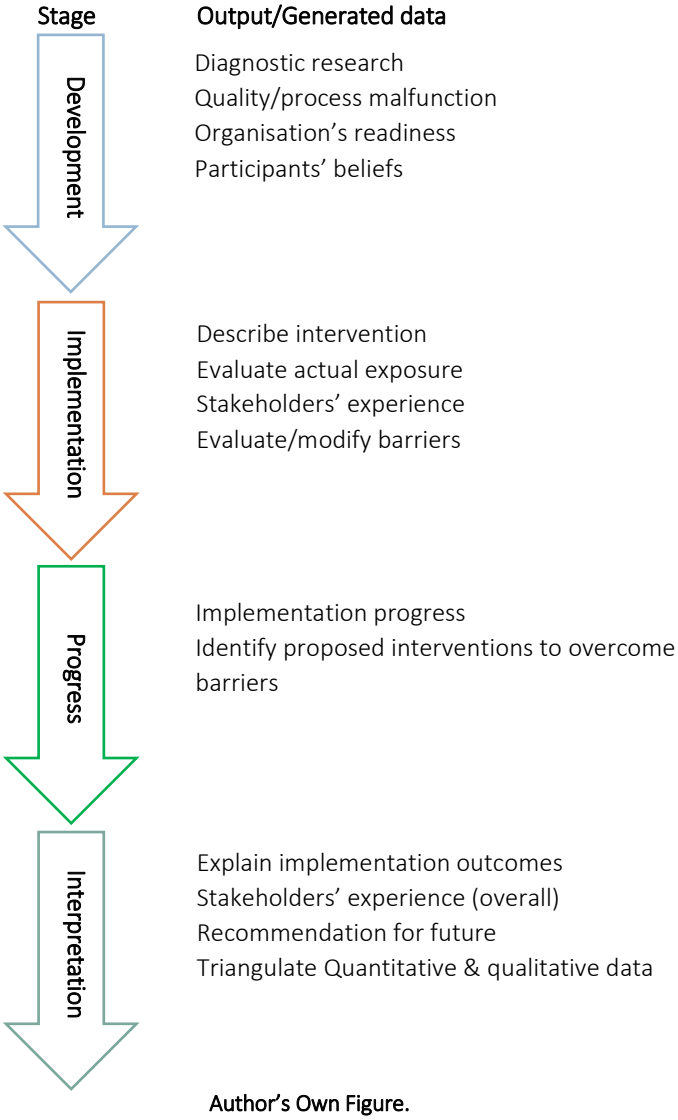
A research methodology is the overall research plan that guides research design, data collection, analysis and presentation (Silverman, 2014). Methodologies are not assessed based on their 'correctness', but rather on their suitability and usefulness in addressing the research aim and objectives (Silverman, 2014). For this research, the methodology that drove its design and conduct can be described as 'mixed methods'. Mixed methods research is defined as *"the collection or analysis of both quantitative and qualitative data in a single study in which the data are collected concurrently or sequentially, are given a priority, and involve the integration of the data at one or more stages in the process of research"* (Creswell, 2014). Advocates of mixed methods methodology stress its ability to provide a comprehensive understanding of the phenomenon of interest by tackling it from different angles and dimensions; those advocates also highlight the possibility of compensating the shortcoming and biases of one method by the strength of the other (Onwuegbuzie and Johnson, 2006, Hanson et al., 2005).

Mixed methods are perceived to be unfeasible and challenging for some scholars, who question the epistemological fidelity of mixed methods, as the approach is based on joining methods that are driven from sometimes contradictory philosophical stands (such as positivism vs. constructivism/interpretivism). On the other hand, others argue for the added value of mixed methods, as this type of research is able to achieve better and more detailed understanding of the phenomenon of interest than can mono-method research, by combining the best of two worlds. Quantitative methods generate broad and generalisable data, whereas qualitative methods secure a deep and detailed understanding of human experience and context. Additionally, some scholars perceive the fact that mixed methods mostly are not strongly theoretically driven or philosophically bounded, as an added value for this type of research, as it provides a flexible, practical and pragmatic approach in addressing research questions. These characteristics make mixed methods research a particularly useful approach for policy-oriented studies (Östlund et al., 2011, McEvoy and Richards, 2006, Bryman, 2015).

Implementing an innovation/technology is comprised of two components: its outcomes and the process (mechanism) driving it (Palinkas et al., 2011, Odom, 2009, Albright et al., 2013). During reading and reviewing literature related to implementation science and research, I noticed that a significant body of the literature was either in the form of reviews aimed at developing frameworks or models to explain implementation processes, or interventional studies in which the researchers were members of the implementation team and were involved in assessing the process and reporting its outcomes. Interventional implementation studies can be summative, process or formative evaluations. While all of these research types are interventional in nature, they differ in their scope and type of data presented (Bauer et al., 2015, Stetler et al., 2006). Summative evaluation starts with a hypothesis regarding the impact of an implemented intervention; it aims at representing a comprehensive evaluation of the implementation, mainly for aspects related to success/failure, effectiveness, impact on service quality and economic evaluation (Bauer et al., 2015, Stetler et al., 2006). Process and formative evaluation are both carried out before, during and after the implementation. However, unlike formative evaluation, process evaluation is not intended to be fed back to the implementation team or funding body, and is not expected to adjust/modify the process in light of assessment findings (Bauer et al., 2015, Stetler et al., 2006). With the general aim of optimising the implementation process to achieve the best possible outcomes, and eliminate implementation barriers, formative evaluation assesses different aspects of the process at one

stage or more of the implementation process. **Figure 5** explains the outputs of each stage of formative evaluation.

Figure 5-Output of formative evaluation at different stages



Author's Own Figure.
Informed by Stetler, Cheryl B., et al. Journal of general internal medicine 21.S2 (2006)

For this research, it was not possible to follow an interventional approach in assessing the uptake and utilisation of BSPs, due to the fact that some BSPs have already been launched and marketed in the UK. Even for the newly launched medicines, it was not within my capacity as a researcher to lead an intervention of introducing BSPs into healthcare settings. Therefore, it was not possible to follow completely one of the accepted implementation evaluation approaches. However, the last stage of formative evaluation (interpretation) is not truly a formative evaluation as it occurs at the end of the implementation stage. Therefore, it does not feed into the refinement of the current process, but rather for future implementations, which might be useful for my research. The interpretation stage is concerned in understanding implementation facilitators, barriers and outcomes, together with how these findings might feed into future and subsequent implementations, which in turn satisfies the research aim and objectives.

The introduction of a new intervention/technology into medical practice is associated with three types of outcomes: (*i*) implementation, (*ii*) service and (*iii*) client/patient level outcomes. However, service and client outcomes cannot be achieved or assessed without looking first at the implementation outcomes (Proctor et al., 2011). Implementation outcomes can take several forms such as acceptability, adoption (uptake), penetration level, cost and sustainability (Proctor et al., 2011, Odom, 2009). Implementation outcomes can be assessed at individual and at organisational level. Whether at individual or organisational levels, the assessment criteria need to have a specific and consistent definition, relevant data sources and suitable research methods, quantitative or qualitative (Proctor et al., 2011).

Assessing outcomes is not enough to understand implementation; factors leading to the success (enablers) or failure (barriers) of implementation also need to be investigated (Albright et al., 2013, Palinkas et al., 2011). Understanding the process, the other component of implementation, involves deep investigation of stakeholders' attitudes, experiences and perceptions before, during and after the implementation. Process understanding includes investigating the effect of context and its related characteristics on driving/hindering implementation (Albright et al., 2013, Proctor et al., 2011). Moreover, investigating success/failure agents might allow for mapping out future implementations or for the optimisation of the current one (Albright et al., 2013).

Assessing implementation outcomes of a medicinal product, including BSPs, might be achieved through assessing utilisation and penetration rates into medical practice; these factors can be quantified and measured. On the other hand, human and contextual factors are reflected in and expressed by their language, whether written, spoken and/or observed; data which can be captured and qualitatively measured (Proctor et al., 2011). As a result, I came to the conclusion that the overarching methodology for this research should be mixed methods. Following such a methodology would, if it is well designed and conducted, provide the breadth (quantitative) and depth (qualitative) required to understand BSPs utilisation in the UK.

3.4.1.1. Assessing quality of mixed methods methodology

Similar to mono-method research, whether quantitative or qualitative, which seeks the generation of valid, reliable and trustworthy conclusions based on empirically obtained and observed data (Johnson and Onwuegbuzie, 2004), mixed methods research should be rigorously designed and conducted. Mixed methods research should not be perceived as merely combining two different methods and reporting their results in isolation from each other (Bryman, 2015). In addition to method specific quality assessment, a researcher should transparently and explicitly justify the need for mixed methods, the study's overall design, methods of data integration and inferences (O'Cathain et al., 2008, Creswell, 2014, Bryman, 2015).

The quality of mixed methods research is assessed through addressing six main domains: (*i*) planning (success), (*ii*) design, (*iii*) individual components (qualitative and quantitative), (*iv*) data integration, (*v*) inference and (*vi*) dissemination (Creswell, 2014, O'Cathain et al., 2008, O'Cathain, 2016, Pluye et al., 2011). Each domain has its own elements that need to be addressed in order to optimise research quality, as follows:

- Planning: start with clear research questions that determines overall design, and influences mixing rationale and purposes
- Design: openly address research design, including the following aspects:
    - *Transparency:* presenting as clearly and truly as possible the research design, openly discuss alteration between the two components, or the usage of readily available typological designs. Presenting research design using a drawing (visualisation)
    - *Suitability:* matching between research aim, objectives and overall design; appropriateness of each component with its relevant question (sub-question). Design elements in terms of sequencing, study population and sampling plan
    - *Strength:* discussing how each method augments the overall research argument, and how depth and breadth of data are achieved
    - *Rigour:* conducting research as proposed, and openly discuss when research progress results in alteration of overall research design
- Individual components: have clear purpose and role, sufficient details, method specific quality checks, analysis as sophisticated as needed, and how it affects and is affected by the other component(s)
    - *Quantitative:* observational or interventional design, validity and reliability, and possibility of generalisations
    - *Qualitative:* following one of qualitative methodologies or generic (descriptive) qualitative study, relevance of data sources, reflexive conduct, address context and role of researcher
- Data integration: describe how data emerged and discern how each component influenced the design and conduct of the other, in case of sequential design, and how data from both components are incorporated to address gaps in literature as well as answering the research question
- Data inferences: discuss the possibility of research conclusion transferability

- **Dissemination:** distribute research findings using correct and relevant language and terms whether in form of writing, oral presentation, or visualisations

The first element, the planning, was satisfied by forming a clear research question, which was addressed and clarified in the literature review chapter (**Chapter 2**). Additionally, the philosophical stand and justification for selecting mixed methods as the research methodology, have been addressed earlier in this chapter. In the following section, I discuss overall research design and how quality domains were addressed and actualised in this research.

3.4.1.2. Overall study design

Mixed methods design should be based on and driven by mixing motives (rationale) and purposes (function), which both need to be carefully selected and discussed in light of the research aim and objectives (Hanson et al., 2005, Creswell, 2014, Collins et al., 2006, Greene et al., 1989). In some cases, the two terms, rationale and purpose, are confused and used interchangeably; even being referred to using the same term (purpose). However, Collins et al. (2006) clarified the definition of, and differences between, both terms. Mixing rationale is more linked to the study's overall aim and objectives; each mixed methods research has, mainly, one mixing rationale. On the other hand, mixing purpose is more specific; the term denotes operating at individual component level (qualitative and quantitative), and it explains how mixing should be done to achieve the desired end results, an answer. Research could be driven by more than one mixing purpose (Collins et al., 2006). In addition to mixing rationale and purposes, the order of implementation (conduct of each component), whether it is simultaneous (concurrent) or sequential, needs to be clearly described and presented (Creswell, 2014, Hanson et al., 2005). Rationale, purpose and the implementation sequence are reflected in the overall study design and its visual presentation. It is expected from a researcher to be compliant to the selected design during the whole research process, starting from early stages till data analysis, presentation and dissemination. Researchers are also advised to transparently report any deviations or shortfalls of the actual implementation (O'Cathain et al., 2008). However, it is acknowledged that one component will have its research question and design developed as the research proceeds based on emerging evidence (O'Cathain et al., 2008, Albright et al., 2013, Onwuegbuzie and Leech, 2006). Moreover, researchers are expected to highlight which is the dominant method that has the most important contribution in the research (Hanson et al., 2005); **Table 7** summarises mixed methods characteristics.

Table 7-Mixed methods research rationale, purposes and most frequently reported designs

Rationale	Definition	Overarching motive that directs conduct of research, explains how its aim can be addressed, and how to analyse and interpret data. Usually, one study is designed to serve one mixing rationale.	
	Types	*Participant enrichment*	Based on achieving an inclusive sample by securing input from different participants and case studies including cases with unique or special characteristics.
		Instrument fidelity	Interventional studies aimed at modifying an intervention (instrument) at the end of one phase of the study, usually pilot phase, before moving to the subsequent phase
		Treatment integrity	Interventional and concerned in assessing the intervention's outcomes but as an end result of an implementation research
		Significance enhancement	Aimed at achieving comprehensiveness by integrating evidence emerging from different dimensions/aspects of the same phenomenon in a complementary manner. Therefore, it uses results of one study to interpret the result of the other
Purpose	Definition	A focused function of the research that influence study design and flow of data collection. Mixing purpose determines which phenomenological aspects to be targeted, dominant method, implementation sequence and dependence, number of studies and flexibility in conduct.	
	Types	*Triangulation*	Targets the same phenomenon or aspect of a phenomenon by parallel execution of two studies; mostly used in research that seek confirmation and validity testing. It can take two forms convergence or transformation
		Completion	Requires sequential interactive design to investigate either the same phenomenon, or related dimensions within the same phenomenon. It recognises the importance of context on the phenomenon under investigation, and encourages thick description of it
		Development	Assesses and creates a new tool through sequential implementation of methods, it is based on using the evidence emerged from one to design the second. This purpose might fit within the rationale of instrument fidelity
		Initiation (sampling)	Uses findings of the quantitative study to identify extreme or unique cases for the qualitative investigation, this purpose might be beneficial in actualising participants' enrichment rationale
		Expansion	Seeks the provision of a broader and deeper understanding of a phenomenon by first quantifying process's outcomes, followed by capturing involved participants' experiences and perception with the process itself through verbatim expressions. It might address the rationale of treatment integrity and significance enhancement

Design	Definition	Research element that explains actual conduct of the research, timing, whether it is simultaneous (concurrent) or sequential.	
	Types	*Convergent*	Simultaneous execution of the two methods, with both having equal priority and input. Data from each methods are merged and/or compared
		Exploratory	Qualitative component is carried out first; it aimed at generating a hypothesis
		Explanatory	Qualitative study is designed based on the quantitative component results; qualitative data explain and interpret quantitative findings
		*Intervention**	Quantitative is main component that is aimed at testing the effectiveness/impact of an intervention. The qualitative component is carried out before, during or after the intervention
		Social justice*	Design that is based on social justice theories such as feminism, racial issues or social class.
		Multistage evaluation*	Design aimed at assessing success of an interventional programme. It is consisted of multistage each can presented independently

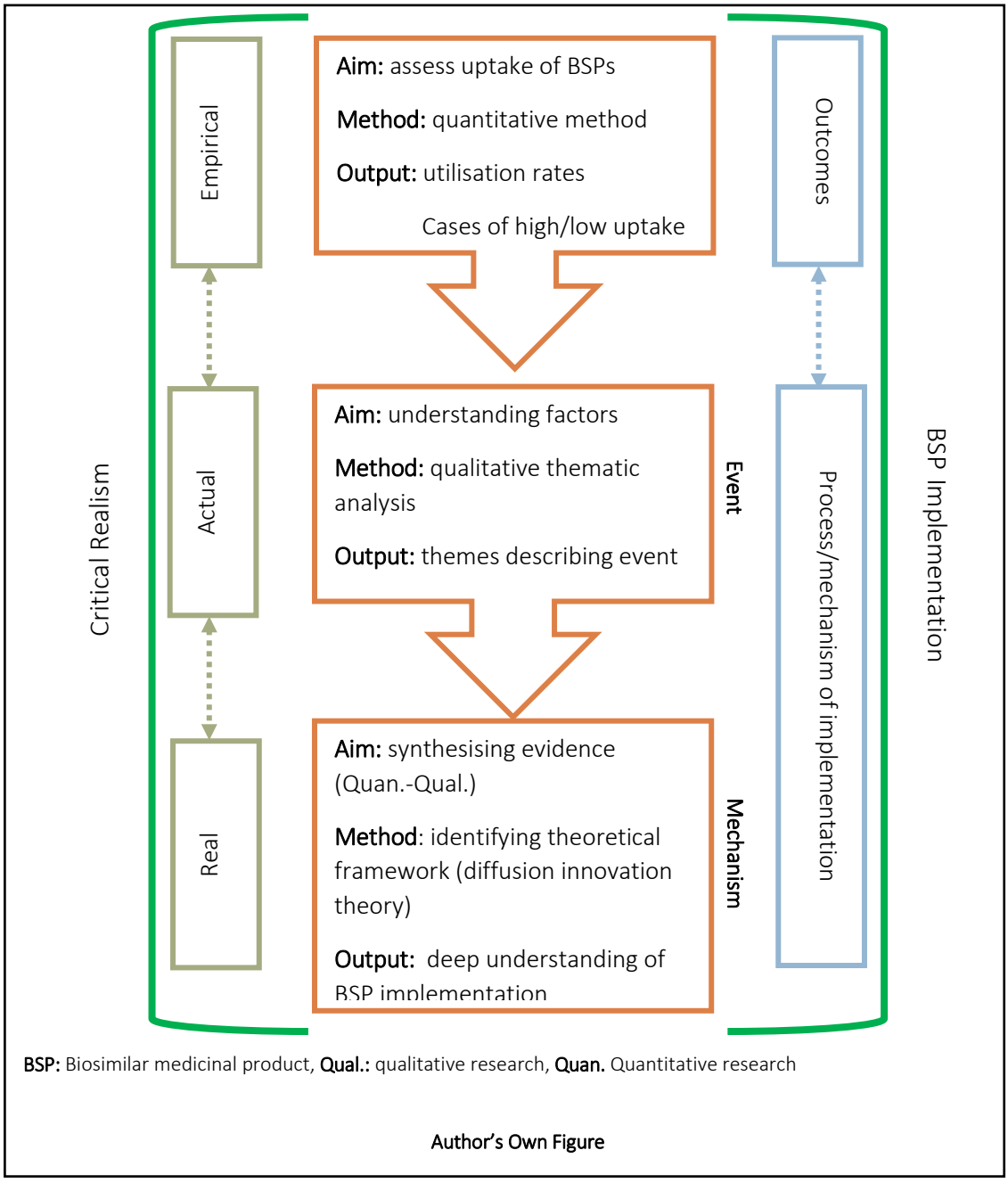
***** Advanced designs employ basic design sequences.
(Collins et al., 2006, Greene et al., 1989, Onwuegbuzie and Leech, 2006, Palinkas et al., 2011, Creswell, 2014, Hanson et al., 2005, Bryman, 2015)

As this research aimed at understanding and investigating the implementation of BSPs in the UK as comprehensively and deeply as possible, achieving significant enhancement was the mixing rationale that dominantly drove this research. Comprehensiveness can be achieved by integrating evidence emerging from different dimensions/aspects of the same phenomenon in a complementary manner (Greene et al., 1989, Onwuegbuzie and Leech, 2006). In this research, assessing utilisation of BSPs might act as an identifier of successful (high utiliser) and failed (low/limited utiliser) cases, which is then followed by a deep investigation of contextual effects and factors driving the implementation process. Overall evidence might then be used in informing future implementation of newly licensed BSPs.

Early in this research, I realised that I needed to apply mixed methods. However, as my understanding of BSPs in the UK evolved with time, and hence the research question and objectives were frequently revised and focused, it was not possible for me to specify early the mixing purpose, the overall design and implementation sequences. Additionally, as I read more mixed methods research papers, and started to get some data, I realised that it is not possible to have a clear division between mixing purposes, and that research might incorporate different elements from different purposes combined in a way that satisfies the overall research aim and direction. I came to the conclusion that it is possible not only to simply combine purposes within the same research, but also to go further and integrate these purposes in a way that one purpose will lead and facilitate the achievement of the other. Therefore, this research was broadly affected by all five purposes, with expansion and initiation (development) being its main drivers.

For this study, explanatory sequential design was the design that mapped the road for actualising the research aim and objectives; this design usually starts with a quantitative exploratory study followed by qualitative explanatory study (Creswell, 2014, Hanson et al., 2005). The term sequential might imply that there is a clear cut in time and conduct between the two arms, once one is completed the next will follow. However, the explanatory element of the methodology dictates an interconnected design between the two arms; as the findings of the first arm, usually quantitative, influence the design and progress of the second qualitative arm (Creswell, 2014). The interdependence between the two arms is not only limited to the designing of the second component; it extends to the overall data analysis and presentation, since the findings of the first act as a basis for interpreting the data of the second. The results of both approaches are pooled to present consolidated new insights of the phenomenon under-investigation (Creswell, 2014, Onwuegbuzie and Leech, 2006). Figure 6 summarises the overall study design.

Figure 6-Overall study design



BSP: Biosimilar medicinal product, **Qual.:** qualitative research, **Quan.** Quantitative research

Author's Own Figure

In terms of priority and significance, some scholars argue for the readily assigned status of one component over the other; for them, in explanatory sequential design, the quantitative component (first study) has more significant input, and therefore more importance, than the qualitative component (second component) (Creswell, 2014, Hanson et al., 2005). However, other scholars go against the readily assigned priority, and emphasise the added value of each component and its contribution to the overall research results and conclusions (Bryman, 2015). In this research, assessing utilisation rates of BSPs allowed the identification of high and low users, but it did not explain the reason for the variation and the overall dynamics governing the BSPs implementation. In fact, it is the qualitative component that provided deeper understanding of factors that affect the BSPs' rates of use. The results of the study's qualitative component might be extrapolated in implementing future BSPs or even for implementing similar interventions within the NHS.

3.4.1.3. Integrating two research components

In conducting mixed methods research, a researcher needs to address and explain how the findings of each component are going to be integrated. While all design elements discussed earlier touch, either explicitly or implicitly, upon the concept of integration, a researcher still needs to clearly explain how and when the integration will occur, and how the integration will address the overall research aim and objectives (Guetterman et al., 2015). Integration can occur at one or more stages of the research: design, methods, data interpretation and finding discussion or in the final stage of reporting (Fetters et al., 2013).

Integration at design level was already explained and justified in discussing the selected design for this research, which is a sequential explanatory model. Design integration is closely linked and influences method integration. Integration between methods can be in the form of identifying a sampling framework from one study based on the results and/or participants of the first, *connecting*. *Building* as a form of integration is common with exploratory design, where the qualitative findings direct what and how quantitative data are collected. The third type of methods integration is *merging*, which occurs when two datasets are collected in parallel and are brought together at the analysis stage; usually the two components are dealing with the same research question. The last is *embedding*, which is the most advanced form of method integration; it is usually considered for interventional studies, where collected data and results are used for refining and redirecting the overall design (Fetters et al., 2013).

Lastly, integration at the data analysis and interpretation stage, also takes several forms: narrative, conversion and joint display (Fetters et al., 2013, Guetterman et al., 2015). *Narrative* integration of data presentation might be achieved either by reporting findings of each component in separate sections and then jointly in a discussion section within the same study report; or by reporting each component in separate reports/publications. Conversion integration is when one dataset is converted to form part of the other and then jointly analysed and assessed. Lastly, data can be *jointly displayed* through the visual display of two components' results.

As this research followed an explanatory sequential design, integrating both components was achieved by connecting the two components through a sampling framework; the quantitative component identified a sampling frame of the qualitative component. In terms of analysis, narrative was considered the most suitable form of analysis integration. This was influenced first by the fact that this is a PhD level research, where it is expected that each empirical chapter will present a piece of the evidence, and then the discussion chapter will bring the results of the two components together in answering the research question.

3.5. Quantitative method

Quantitative methods are based on an objective numerical description of a readily observable phenomenon or a dimension of a phenomenon. A quantitative researcher seeks to deductively test a hypothesis or to generate generalisable knowledge regarding the reality we live in. In carrying out a quantitative investigation, researchers usually follow a fixed and replicable design to answer a specific question (Bryman, 2015, King et al., 1994, National Council of Osteopathic Research (NCOR), 2014). In addition to providing a general description of a phenomenon, some quantitative research projects are aimed to investigate the associations and causal relationships between different aspects of the same phenomenon (King et al., 1994). Conducting quantitative research is based on addressing three main components: (*i*) design, (*ii*) measurement and (*iii*) statistics. Each component has its attributes that eventually contribute to the quality of the research and the trustworthiness of its conclusion. However, before proceeding with the main component, a researcher first needs to define the variable that he or she is interested in measuring and reporting. A variable is "an attribute that varies among individuals or group" (O'Dwyer and Bernauer, 2013). For this research, assessing the utilisation of BSPs can be achieved through assessing the prescribed or dispensed volumes of BSPs in comparison to their reference counterparts. Another variable that might act as a proxy for BSPs' usage is the integration of these medicines into local clinical pathways.

3.5.1. Justification for the selected data sources

Assessing medicines utilisation depends on the availability, accessibility and suitability of data sources. In the UK, there are several databases providing data related to medical procedures and medicine utilisation; these databases are provided and supported by NHS organisations or the private sector. Selecting which database to employ in assessing BSPs use in the UK was influenced mainly by the settings: where these medicines are prescribed and the way in which prescribing data are reported.

As the available BSPs, at the time of this research, were secondary-care medicines, utilisation assessment started by looking for secondary-care related databases. One of the most commonly referred to secondary-care databases is the hospital episodes statistics (HES) (Health & Social Care Information Centre (HSCIC), 2015). HES reports bundles of procedures that were considered at each period of care per patient, without specifying which medicine(s) was/were prescribed (Health & Social Care Information Centre (HSCIC), 2015); therefore, it was not possible to use HES in assessing BSPs utilisation.

Another database used at secondary care in England, is the Define® database, offered by Rx-Info. Define® helps Trusts to monitor their prescribing by reporting cost and utilisation rates of medicines at Trusts (Rx-Info Ltd, 2017). Based on that, Define® could be considered as a suitable and useful database to assess the utilisation of BSPs, especially as it covers more than 90% of the Acute Trusts (Rx-Info Ltd, 2017). However, as Define® requires a special license in order to access it, which is not granted to the Division of Pharmacy Practice and Policy (PPP)-School of Pharmacy, University of Nottingham, it was not possible to use Define* for this research.

National Disease registries might be considered as another source of prescribing data. In the UK, there are several disease registries: (*i*) the British Society for Rheumatology Biologics Register (BSRBR) (British Society for Rheumatology (BSR), 2017b), (*ii*) the Inflammatory Bowel Disease Registry (Inflammatory Bowel Disease Registry (IBDR), 2017) and (*iii*) the British Association of Dermatologists Biologic Interventions Register (British Association of Dermatologists Biologic Interventions Register (BADBIR), 2017). As these registries collect data related to therapeutic outcomes in terms of disease progression, safety and efficacy of medicines, these registries might be useful in studies investigating therapeutic outcomes of BMPs, including BSPs (British Association of Dermatologists Biologic Interventions Register (BADBIR), 2017, British Society for Rheumatology (BSR), 2017b, Inflammatory Bowel Disease Registry (IBDR), 2017). As the collected data for these registries are mainly oriented towards clinical outcomes, registries might not be able to support research that is investigating utilisation rates and integration levels.

As assessing utilisation rates of available BSPs was not possible using available databases and registries, there was a need for me to identify alternative sources, which provide data or indicators related to the prescribing pattern of targeted BSPs and their R-BMP counterparts. Being described as having an important role in facilitating safe and cost effective access to medicines and technologies (Sir David Nicholson, 2012, Essex B, 1989), local medicines formularies might be considered as an alternative data source to assess the utilisation of targeted BSPs and R-BMPs. This outcome could be achieved by assessing the way in which targeted medicines are listed and presented in local medicines formularies. A medicines formulary is a specified list of medicines that are available for prescribing and dispensing in a healthcare settings (Duerden and Walley, 1999). In some cases, the definition of a medicines formulary goes beyond the restricted list of medicine to describe a system of procedures and protocols that is based on interactions between different stakeholders (Academy of Managed Care Pharmacy (AMCP), 2009). Along with this concept, NICE defines local formularies as "the output processes to support the managed introduction, utilisation or withdrawal of healthcare treatments within a health economy, service or organisation"(The National Institute for Health and Care Excellence (NICE), 2015a). Whether it is a list or a system, if a medicinal product is listed in a formulary, it will be available for prescription and utilisation. Accordingly, listing status of targeted BSPs might act as an indirect indicator "proxy" of their utilisation, as the listing status could indicate which products, in this case brands of R-BMP or BSPs, are available for prescribing.

In 2014, in England, a publicly available national drug utilisation platform, the medicines optimisation dashboard (MODB), was launched. As an approach to monitor Acute Trusts medicines use, MODB reports uptake and utilisation data of medicines positively appraised by NICE at Acute Trust level (NHS England, 2014, NHS Business Service Authority (NHSBSA), 2016); therefore, those reports could be used in assessing the utilisation of BSPs. Since November 2015, the MODB has been reporting purchasing data related to IFX-BSPs and their R-BMP counterparts, starting from the third quarter (July-September) of 2015. At the beginning of this research, MODB was only reporting purchasing data of IFX in England; therefore, its research deployment was limited to IFX-BSP in England; therefore other available BSPs and countries within the UK were excluded.

In conclusion, assessing utilisation patterns of BSPs available at the time of this study was based on two data sources: (*i*) local medicines formularies for all targeted BSPs and in all countries within the UK, and (*ii*) MODB for IFX-BSP in England.

3.5.2. Quantitative study aim and objectives

With a general aim of assessing the national utilisation and prescribing patterns of BSP HGH, EPO, G-CSF and IFX, the quantitative component of this study was carried out in two phases reflecting time of market entry of targeted BSPs and the availability of data sources. Each study phase was conducted at different time periods and has different specific objectives.

3.5.2.1. Quantitative-Phase I objectives

This phase aimed to assess the utilisation of first wave BSPs, which have been launched in the UK prior to the starting date of this study; specifically: HGH-BSP, EPO-BSP and G-CSF-BSP. Utilisation assessment was based on screening local medicines formularies in the UK. This phase had the following specific objectives:

- Assess formulary listing of first wave BSPs licensed and marketed in the UK (HGH-BSP, EPO-BSP and G-CSF-BSP)
- Compare the listing frequencies and status of targeted BSPs with their R-BMP counterparts
- Report incidents where the BSPs were listed in preference to the R-BMP or vice versa

3.5.2.2. Quantitative-Phase II objectives

This phase targeted IFX-BSP, which was newly launched at the time of the study. Assessing the utilisation of IFX-BSP was achieved through the deployment of two data sources: local medicines formularies in all Great Britain countries, and the MODB for England. The following specific objectives directed the conduct of Phase II*:*

- Assess formulary listing of IFX-BSP brands marketed in the UK in February 2015 (Remsima® and Inflectra®)
- Compare listing frequencies and listing status of targeted IFX-BSPs brands with their R-BMP counterpart
- Compare uptake and listing status of IFX-BSPs in the therapeutic areas for which IFX is indicated: dermatology, gastroenterology and rheumatology
- Investigate if formularies have distinguished between IFX established or naïve patients in terms of which brand (R-BMP or BSP) to be prescribed for each group
- Classify English Acute Trusts into IFX-BSP non-users, initiators (which prescribe IFX-BSP to IFX naïve patients), or switchers (which switch R-BMP-IFX established patients to IFX-BSP); using MODB reported purchasing percentages and IFX quarterly purchasing data
- Classify Acute Trusts according to Rogers's classification of innovation adopters, as discussed earlier in this chapter (3.2.1.1. Innovation diffusion theory)
- Investigate the effect of an Acute Trust's characteristics, which might address Rogers's model of organisation innovation decision-making; such as governance, complexity, organisation culture and strategic orientation, system openness and location on its status of being switcher or initiator.

3.5.2. Quantitative research design

Quantitative studies can follow two main designs: experimental (interventional) or non-experimental (observational). While experimental designs help in establishing causality, observational studies can be descriptive, predictive or exploratory in nature (Levin, 2005, O'Dwyer and Bernauer, 2013). As the aim of this component of the research was to value the outcomes of implementing BSPs in the UK, a non-experimental descriptive design was considered the most suitable for this study. Non-experimental (observational) studies are classified, according to the time horizon for data collection, into three main categories: (*i*) cross-sectional (current time point), (*ii*) prospective (follow up over a period in the future) and (*iii*) retrospective (over a period of time in the past) (O'Dwyer and Bernauer, 2013). Although observational studies fall short in establishing causality and time-event sequences, they allow reporting of associations between main outcomes of interest and other related features tested (Levin, 2005, Levin, 2006). For this research a cross-sectional design was used to assess the current status of BSPs utilisation, as it provides a descriptive "snapshot" of the present situation (Levin, 2005, Levin, 2006). Each phase has its own specific design, reflecting its specific objectives and utilised data sources.

In conducting quantitative research, there are three quality related attributes that need to be addressed: (*i*) the measurement tool's validity, (*ii*) the measurement tool's reliability and (*iii*) data analysis approach. The measurement tool is described as valid (appropriate) "when it measures what it is intended to measure" (O'Dwyer and Bernauer, 2013, King et al., 1994). The second quality is the reliability, which means "applying the same procedure, in the same way, will always produce the same measure", in other words, the assurance of consistency of results over replications. Based on that definition, reliability is connected with another concept which is replicability. In some cases, replicability is not possible, especially if data are related to temporary or time bound observations. Therefore, it is advisable to specify the time frame over which the research took place (King et al., 1994, O'Dwyer and Bernauer, 2013). As highlighted earlier in the literature review chapter, the market of BSPs is very dynamic and is witnessing frequent updates regarding market entries and policy revisions. Therefore, it is possible that the BSP utilisation rates might change over time. Accordingly, it is important to specify the time frame over which utilisation assessment took place, which is in turn is consistent with the definition of cross-sectional studies (occurring at a specific time point).

The last attribute is data analysis (O'Dwyer and Bernauer, 2013). Data analysis can be either a descriptive analysis counting frequencies and percentages or an inferential design for investigating associations between variables (dependent and independent variables). For this research, descriptive analysis was the optimal analytical approach.

3.5.2.1. Justification for developing research specific assessment criteria and screening form

Local formularies assessment criteria were assembled based on the study objectives, NICE guidelines on developing and managing local formularies (The National Institute for Health and Care Excellence (NICE), 2014b) and the literature (Fijn et al., 2000, Fijn et al., 1999). These criteria were revised as the study progressed and moved from phase (I) to phase (II).

Assessing Acute Trusts prescribing practice, whether initiation or switching, was based on monitoring changes in purchased quantities of IFX-R-BMP and IFX-BSP. The assessment was based on the assumption that the purchased amount in one quarter will be used in the same quarter.

3.5.3. Quantitative study's ethical considerations

Data sources, whether local formularies or MODB, are readily available in the public domain. In fact, formularies are considered public documents falling within the remit of the freedom of information (FOI) scheme (Her Majesty's Passport Office, 2010). Therefore, there was no need for ethical approval from a research ethics committee.

3.5.4. Quantitative study-Phase I

3.5.4.1. Sample

During November-December 2014, a list of 157 English Trusts (organisations within NHS England that manage and control the performance, services quality and financial efficiency of clusters of hospitals in England), 21 (14 in Scotland and 7 in Wales) Health Boards (organisations within NHS Scotland and NHS Wales that are responsible for the delivery of healthcare services to the local population), and 5 Hospital Trusts in Northern Ireland –was acquired from their relevant authority websites: NHS-England, NHS-Scotland, Welsh NHS and Northern Ireland Health and Social Care; respectively.

Official websites of targeted healthcare organisations were searched for the most recent medicines formularies, either by downloading the list directly from the pharmacy department/service child-page, or typing in the word/phrase '*formulary*' or '*medicines list*' in the search box. When direct access to the medicines formulary was not possible, a FOI request asking for a softcopy or a link to the most recent medicines formulary was sent to the relevant Trust or Health Board.

In total, access was obtained for: (*i*) 155 English Acute Trusts, two were excluded as one was dissolved and the other one was still in the process of developing a formulary list, and (*ii*) 21 Health Boards in Scotland and Wales. Northern Ireland was excluded as there was an initiative underway to develop a joint formulary for the whole country, and some of its chapters were still under development.

3.5.4.2. Formularies assessment Criteria

Formularies were screened for five main aspects:

- Formulary status of targeted medicines
- Listing approach using brand or generic names
- Preferred product for prescription
- Prescribing restrictions
- Special consideration of patients' related factors and/or intended indications

Research data were grouped and clustered in categories that address the assessment criteria, reflect research findings, and help in actualising Phase I objectives. Data were clustered in the following categories:

- *Formulary country* : Scotland, England or Wales
- *Formulary type*: (*i*) joint, which is shared and/or developed by more than one healthcare providing organisation, or (*ii*) non-joint formularies. This latter category was not predicted before the conduct of this research, it was noted as the formulary screening process proceeded
- *Formulary listing approach*: brand name listers; molecular name listers; or cross-over (brand-molecular) name listers
- *Listed brand*: R-BMP, BSPs, or both
- *Preferred type*: R-BMP, BSPs, not specified
- *Clear prescribing restrictions*: as per assessment criterion #7, Table 8

Table 8-Phase I formulary assessment criteria

No.	Assessment Criterion	Definition	
1.	Is this formulary a joint formulary? (Yes/No)	Formulary list that is developed and/or used by more than one healthcare setting (primary and/or secondary care).	
2.	Is the targeted molecule listed? (Yes/No)	BNF chapter* 6.5.1: somatropin (HGH) BNF chapter 9.1.3: epoetin alfa/zeta† (EPO) BNF chapter 9.1.6: filgrastim (G-CSF)	
3.	How is it listed? (Formulary/non-formulary)	Formulary	Medicinal product that is routinely available for prescription.
		Non-formulary	Medicinal product that is not routinely available for prescription. However, if it is deemed needed, it will be made available for the patient.
4.	What is the listing approach? (Brand name/INN/Both)	As per brands listed in BNF chapters 6.5.1, 9.1.3 and 9.1.6.	
5.	What are the listed brands? (R-BMP/BSP/Both)	BNF chapter 6.5.1: 1 R-BMP and 1 BSP BNF chapter 9.1.3: 1 R-BMP and 2 BSPs BNF chapter 9.1.6: 1 R-BMP and 3 BSPs	
6.	What is the preferred type? (R-BMP/BSP/Not specified)	Being the only listed brand/type; Clearly stated that this brand/type is the preferred for prescription; or Brand/type listed as formulary while other brands/type listed as non-formulary.	
7.	Are there clear restrictions in prescribing? (Yes/No)	Whether or not there are specified restrictions in terms of who can prescribe these products and/or prescribing settings i.e. primary or secondary care.	
8.	Is there specified brand of choice? (Yes/No)	If it is clearly stated that a specific brand is considered as the brand of choice.	
9.	Are there special population considerations? (Yes/No)	If there are considerations related to patients' age, medical history and/or life style factors that might affect type/brand of preference (R-BMP or BSP).	
10.	Are there special indications' considerations? (Yes/No)	If there are considerations related to indications that might affect type/brand of preference (R-BMP or BSP).	

***** The BNF chapter numbering structure was changed in BNF70, published in Sep 2015. Therefore, the chapters' numbers presented in this study reflects previous structure

† R-BMP-EPO has two BSPs, one shares the same INN of the R-BMP and the other got different INN, epoetin zeta

BNF: British National Formulary; **BMP:** Biological medicinal product; **BSP:** Biosimilar medicinal product; **EPO:** Recombinant human erythropoietin (epoetin alfa/zeta), **G-CSF:** Granulocyte colony-stimulating factor (filgrastim), **HGH:** human growth hormone (somatropin), **INN:** International non-proprietary name (molecular name); **R-BMP:** Reference biological medicinal product

Data entry and categorisation were accomplished using Excel® 2013 workbook (Microsoft Office MS, 2013). To assure accuracy of data, the researcher screened formularies twice; in the second screening episode, formularies were checked against data entered from the first episode. Additionally, in a case of confusion, a freedom of information (FOI) request was sent to the relevant Trust or Health Board. Research data were discussed with the researcher's supervisors and submitted and presented in a number of research conferences. Additionally, findings were compared with uptake rates of targeted BSPs published by marketing and business intelligence agencies.

3.5.4.3. Data analysis

As collected data were categorical in nature, descriptive analysis was considered to be the most suitable analytical approach; data were analysed using Excel® 2013 workbook (Microsoft Office MS, 2013). Research findings were reported in the form of frequencies and percentages of formularies assessment criteria per country.

3.5.5. Quantitative study-Phase II-local medicines formularies

3.5.5.1. Sample

The starting point of Phase II was to assess the uptake and listing status of IFX-BSPs in British local formularies. It was assumed that the researcher could rely on the database assembled in Phase I; however, it was noticed that a number of included organisation, Acute Trusts and Health Boards, had gone through changes in terms of merging with other organisations, had been dissolved, or had changed their referenced medicines formularies. Accordingly, it proved necessary to assemble an up-to-date database, which reflected these updates and changes.

During April-September 2016, new lists of English Acute Trusts and Health Boards in Scotland and Wales were acquired following the same approach as Phase I. While the number of Health Boards in Scotland and Wales remained the same, it was noticed that three Acute Trusts[6] were either dissolved or had merged with other Trusts. Furthermore, Acute Trusts were now clustered, being based on their geographical locations into four main regions within the NHS: (*i*) North, (*ii*) Midlands and East, (*iii*) London and (*iv*) South. In total, medicines formularies of 154 English Acute Trusts, and 21 Health Boards in Scotland and Wales, were obtained and retrieved.

3.5.5.2. Formularies assessment

In addition to Phase I assessment criteria, additional criteria were considered which were based on, and derived from, Phase I findings and observations and Phase II objectives:

- Listing status of IFX-BSP in indicated therapeutic areas
- Listing of educational materials related to BSPs
- Listing NICE technology appraisals, which included IFX-BSPs, TA 329, 375 and 383 (The National Institute for Health and Care Excellence (NICE), 2015c, The National Institute for Health and Care Excellence (NICE), 2016a, The National Institute for Health and Care Excellence (NICE), 2016c)
- Specifying brand of choice for prescribing
- Formulary structure

[6] Torbay and Southern Devon Health and Care NHS Trust merged with South Devon Healthcare NHS Foundation Trust to form a new integrated care organisation, Torbay and South Devon NHS Foundation Trust, on 1st October 2015. West Middlesex University Hospital NHS Trust acquired by Chelsea and Westminster Hospital NHS Foundation Trust in Feb 2015. And Ealing Hospital NHS Trust, and The North West London Hospitals NHS merged into London North West Healthcare NHS Trust

Phase II design and conduct were influenced by Phase I findings and observations. In Phase I, it was noticed that local formularies varied in structure and content. In terms of structure, some formularies had grouped medicinal products according to the therapeutic areas for which they are indicated; some had chosen chapters resembling the previous structure of the British National Formulary (BNF) with the same numbering system, while other formularies had followed an un-structured layout, where medicines are listed alphabetically. In terms of content, some formularies limited their content to available medicines for prescription; others went one step further by adding instructions related to prescription by specifying: (*i*) prescriber speciality and/or site of prescribing, (*ii*) primary or secondary care, (*iii*) listing relevant NICE TAs and/or clinical guidelines (CGs), (*iv*) identifying commissioner, and (*v*) clarifying if a certain medicine is listed as 'out of tariff'. Being indicated in three different therapeutic areas, in addition to having different commissioners, as well as considering formularies content and structural related features, might help in addressing Phase II objectives when comparing between therapeutic areas and different commissioners. A detailed list of assessment criteria is presented in Appendix 4. Additionally, in order to have a more systematic and organised approach to formularies screening, a formularies screening form (Appendix 5) was developed to facilitate the formularies screening process. The form allowed for assessing formularies as per assessment criteria, distinguish between structured and unstructured formularies, therapeutic areas and the commissioner.

Following the same approach as in Phase I, data were clustered in categories as follows:

- Formulary layout as structured or non-structured
- Formulary content in terms of educational materials and NICE TA, which included IFX-BSP
- Listing the preferred product for prescribing, whether the BSP or the R-BMP
- Listing of prescribing guidance instructions for IFX established patients and IFX naïve patients
- Allow/prevent switching IFX-R-BMP established patients to IFX-BSP

Similar to Phase I, data entry and categorisation were completed using Excel® 2013 workbook (Microsoft Office MS, 2013). This researcher checked screened formularies at least twice, and FOI requests were sent when needed.

3.5.5.3. Data analysis

Descriptive analysis aided by Excel 2013 (Microsoft Office MS, 2013) was used to analyse assembled categories per country and per therapeutic area.

3.5.6. Quantitative study-Phase II-Medicines Optimisation Dashboard (MODB)

3.5.6.1. Sample

Data collection was completed for 143 Acute Trusts. Eleven Acute Trusts were excluded due to the predominantly specialist nature of their medical service such as women's health, cancer centres, or eye and ophthalmology diseases. IFX is not a routinely prescribed medicine at these Acute Trusts. **Table 9** lists all excluded Acute Trusts, and reasons for exclusion.

Table 9-Excluded Acute Trusts from Phase II analysis

No.	Acute Trust Name	Reason for Exclusion
1	Birmingham Women's NHS Foundation Trust	Women's Health Services
2	Liverpool Heart And Chest NHS Foundation Trust	Cardiothoracic Services
3	Liverpool Women's NHS Foundation Trust	Women's Health Services
4	Moorfields Eye Hospital NHS Foundation Trust	Ophthalmic Services
5	Papworth Hospital NHS Foundation Trust	Cardiothoracic Services
6	Queen Victoria Hospital NHS Foundation Trust	Reconstructive Surgery, Burns Care and Rehabilitation Services
7	Royal National Orthopaedic Hospital NHS Trust	Orthopaedic Services
8	The Christie NHS Foundation Trust	Cancer Services
9	The Clatterbridge Cancer Centre NHS Foundation Trust	Cancer Services
10	The Royal Orthopaedic Hospital NHS Foundation Trust	Orthopaedic Services
11	The Walton Centre NHS Foundation Trust	Neurology, neurosurgery, spinal and pain management services.

For each Acute Trust, quarterly published prescription percentages of IFX-BSPs and R-BMP, and IFX purchasing data were collected from MODB and NHS Digital websites (NHS-England, 2016, Prescribing and Medicines Team-NHS Digital, 2017). Collected data were only limited to English Acute Trusts, as the MODB is an initiative led by NHS England. Starting from Q4-2016, the MODB changed the base of its definition of reported percentages from purchased volume of IFX to defined daily dose of IFX (NHS Business Service Authority (NHSBSA), 2016, NHS Business Service Authority (NHSBSA), 2017). Therefore, proceeding with data collection beyond Q3-2016 was not possible as the new definition of reported percentages became incompatible with data reported by NHS Digital. Data collection continued for 5 quarters only, starting from Q3-2015 till Q3-2016.

3.5.6.2. Classification of Acute Trusts according to prescribing practice and Rogers's classification of adopters

In addressing Phase II objective in classifying Acute Trusts according to their prescribing practices, Acute Trusts were categorised into (*i*) IFX-BSP non-users, (*ii*) initiators and (*iii*) switchers. This classification was based on monitoring changes in the total purchased amounts of IFX, IFX-R-BMP and IFX-BSP, per quarter, per Acute Trust. As MODB data were presented in the form of purchased percentages, it was necessary for me to convert percentages into quantities. This was achieved by combining MODB data with quarterly purchased volume per medicine, without brand specification, for each Acute Trust as reported by NHS-Digital (previously known as HSCIC).

The Acute Trust categorisation process was carried out in four steps:

First: *Calculating the purchased amount of IFX-R-BMP and IFX-BSP by each Acute Trust per quarter*

This was achieved by multiplying percentages purchased (reported by MODB) by the total purchased quantity of IFX as reported by NHS Digital.

Second: *Defining Acute Trusts as IFX-BSP users or non-users*

This was based on the purchased amounts of IFX-BSPs, when the total purchased amount of IFX-BSPs of an Acute Trust was higher than zero in a one quarter, then it was considered as a BSP user for that quarter and afterwards.

Third: *Categorising Acute Trusts as initiators or switchers*

This was based on the differences between total IFX purchased and IFX-R-BMP purchased between two consecutive quarters. When the total IFX purchased increased and IFX-R-BMP purchased decreased, or when the decrease in the IFX-R-BMP purchased was greater than the decrease in the total IFX purchase, the Trust was considered to be a switcher for that quarter; and afterwards if the differences in quantities were reflected in the quantities of IFX-BSP purchased. For Q3-2015, purchased quantities were compared with Q2-2015 and it was assumed that all the purchased quantities in Q2-2015 were R-BMP only, as the MODB started reporting from Q3-2015.

Fourth: *Categorising IFX-BSP using Acute Trust according to Rogers's model of innovation adopters*

This was needed to classify Acute Trusts according to Rogers's adopters' categories: (*i*) innovators, (*ii*) early adopters, (*iii*) early majority, (*iv*) late majority and (*v*) laggards. The classification was achieved by calculating time needed to implement the switch. However, as it was not possible to get the exact date on which an Acute Trust started switching patients, if indeed they had, it was assumed that the switching started at the middle of every quarter (approximately 90 days). Table 10 summarises the assumed time periods needed to reach the decision of switching to IFX-BSP, starting from first day of Q3-2015, expressed in days.

Table 10-Assumed number of days to start switching

No.	Quarter	Assumed number of days to start switching*
1.	Q3-2015	45 days
2.	Q4-2015	135 days
3.	Q1-2016	225 days
4.	Q2-2016	315 days
5.	Q3-2016	405 days

* Assumed number of days to start switching since first day of Q3-2015

3.5.6.3. Building a regression model

An Acute Trust status, as being an early or late switcher to IFX-BSPs, was the dependent variable for this model. Independent variables were related to Acute Trusts characteristics namely: (*i*) governance, (*ii*) complexity, (*iii*) location, (*iv*) system openness and (*v*) organisational culture and strategic orientation. Identified variables were selected based on those identified in Rogers's theory on innovation in organisations (Rogers, 2003), when applicable, and the literature (Williams and Brown, 2014). Table 11 summarises independent (explanatory) variables

Table 11-Summary of identified independent variables

No.	Independent Variable	Relevant Organisation Characteristics
1.	Foundation Trust	Governance
2.	Educational Trust	Complexity
3.	BSPs listed/mentioned in the formulary	Organisation's strategic orientation
4.	Formulary distinguishes between IFX naïve and established patients	Organisation's strategic orientation
5.	Formulary encourages switching	Organisation culture and strategic orientation
6.	Involved in joint formularies	System openness
7.	Region	Location

The regression model was built to test the hypotheses that if an Acute Trust switched its patients to IFX-BSPs (early adopter) it would be: (*i*) foundation trust, (*ii*) educational trust, (*iii*) having IFX-BSP listed in the formulary, (*iv)* referring to a formulary that distinguishes between new and established patients, (*v*) referring to a formulary that encourages switching, (*vi*) involved in a joint formulary and (*vii*) belonging to a specific region within NHS England.

3.5.6.4. Data analysis

Data preparation

Data were logged in an Excel® workbook (Microsoft Office MS, 2013). Data were descriptively analysed using Excel® 2013 (Microsoft Office MS, 2013).

Missing data

Missing data were observed quarterly in both datasets; therefore, in order to compensate for the missing purchased quantities and/or percentages, the following qualifying assumptions were made:

- If an Acute Trust had its MODB data available for a particular quarter and the totally purchased IFX was missing, the most recent available total purchased data were used under the assumption that the Acute Trust had maintained the same utilisation rate. This assumption was considered for six Acute Trusts [7]
- In a given quarter, if an Acute Trust had both datasets missing, but the datasets were available in the prior and following quarter, then the assumption was made that the prescribing practice for the missing quarter would remain the same as the prior quarter. The prescribing practice was reassessed in the following quarter only if the Acute Trust was initially labelled as an initiator

Descriptive analysis

Descriptive frequencies and percentages were utilised to describe Acute Trusts characteristics in terms of: (*i*) region, (*ii*) status as a foundation Trust, (*iii*) status as an educational Trust, (*iv*) IFX-BSPs user, (*v*) switcher or initiator, and (*vi*) involved in joint formulary.

[7] Data of IFX total purchased of Q3-2015 were extrapolated to Q4-2015 for University Hospitals of Morecambe Bay NHS Foundation Trust and Wrightington, Wigan and Leigh NHS Foundation Trust. Data of Q4-2015 were extrapolated to Q1-2016 for South Tyneside NHS Foundation Trust and Colchester Hospital University NHS Foundation Trust. Data of Q1-2016 were extrapolated to Q2-2016 for Homerton University Hospital NHS Foundation Trust and Mid Cheshire Hospitals NHS Foundation Trust

Inferential analysis

Inferential analysis (logistic regression) was used to assess the association between an Acute Trust's characteristics (independent variables) and the probability of it being an early switcher to IFX-BSP. For this model, the dependent variable of an Acute Trust's status as being an early switcher to IFX-BSP, is labelled (Yes). 'Yes' equals 1 whenever an Acute Trust was classified as an early switcher, and 0 otherwise. All independent variables, except region, were binary coded with one of two values: 0 for 'No' or 1 for 'Yes'. The 'region' was coded as a categorical variable; based on the fact that the first Acute Trust to switch its patients to the IFX-BSP was a southern Trust (The National Institute for Health and Care Excellence (NICE), 2015d); the South region was therefore considered as reference category. Statistical modelling was carried out using STATA® data analysis and statistical software (StataCorp, 2016). Table 12 summarises binary coding of dependent and independent variables.

Table 12-Summary of variables coding

No.	Variable	Variable Description
Dependent variable		
1.	**Early Switcher**	Classification of an Acute Trust as an early adopter (early switcher to IFX-BSP). Falls within the area to the left of the mean time needed to adopt an innovation minus one standard deviation. *Yes=1, No=0*
Independent Variables		
1.	**Foundation Trust**	Refers to a Trust that possesses a greater degree of freedom and control over its resources than other types of Trust (GOV.UK, 2017 , NHS UK, 2016). This variable might reflect the degree of an organisation's governance. *Yes= 1, No=0*
2.	**Educational Trust**	Refers to an Acute Trust that is being described as an educational/teaching facility; either as it is reported by third party bodies/report or stated in its mission/vision statement (The Association of UK University Hospitals (AUKUH), Mathieson, 2011). This variable might reflect the degree of an organisation's complexity. *Yes=1, No=0*
an3.	**IFX listed/mentioned in the formulary**	Refers to an Acute Trust refers to a formulary that lists IFX-BSP, as per Phase II formulary screening study. This variable might be used to reflect the degree of an organisation's strategic orientation. *Yes=1, No=0*
4.	**Formulary distinguishes between patients**	Refers to the Acute Trust refers to a formulary that distinguishes between established and new patients, as per Phase II formulary screening study. This variable might be used to reflect the degree of an organisation's strategic orientation. *Yes=1, No=0*
5.	**Formulary allows switching**	Refers to the Acute Trust refers to a medicines formulary that allows/encourages patients switching, as per the Phase II formulary screening study. This variable might be used to reflect degree of an organisation's strategic orientation. *Yes=1, No=0*
6.	**Involved in joint formulary**	Refers to the Acute Trust being involved in a joint formulary, as per Phase II of the formulary screening study. This variable might be used to reflect the degree of an organisation's openness and connectedness with its external environment. *Yes=1, No=0*
7.	**Region**	Refers to the region, from NHS main regions(NHS-England, 2015), an Acute Trust is located in. This variable might be used to reflect an organisation's location. This is a categorical variable with the South region being the reference category. *Category 1: London Region; Category 2: Midlands and East Region; Category 3: North Region; and Category 4: South West and South East Region*

3.6. Qualitative method

Similar to quantitative methods, qualitative methods can follow one of the commonly used designs (methodologies) such as narrative research, phenomenology, grounded theory, case study, ethnography and generic qualitative research (Patton, 2014, Cooper and Endacott, 2007).

While critical realism is the broad philosophical stand driving this research, I selected a generic design for the qualitative component of this research. Generic qualitative research, similar to other qualitative approaches, is based on naturalism; a perspective which is concerned in studying a phenomenon in its natural settings and keeping a faithful account of the involved individuals, as the basic theoretical foundation (Silverman, 2014). However, unlike the vast majority of qualitative methodologies which are heavily theoretically and philosophically laden, generic qualitative studies, also known as qualitative descriptive research, adopt a more flexible approach to reporting and understanding people's perceptions. Additionally, generic research can operate within a broader philosophical or theoretical position, but can still deviate from the theoretical. A researcher following a generic approach is still committed to qualitative research standards and has to give a detailed and honest account of the research design and conduct (Cooper and Endacott, 2007, Sandelowski, 2010).

In general, any research starts with a defined research question and study design. However, in an explanatory sequential mixed methods design, objectives of the explanatory component (qualitative study) develop in light of the output of the explanatory (quantitative) component (Albright et al., 2013). Therefore, the aim and objectives of the qualitative component, and its design, were not finalised until the quantitative data had been at least partially analysed.

Findings of the exploratory study (quantitative component), represented in Chapter 4, show the varied uptakes of BSPs in the UK, in general, and England in particular. In this thesis, exploring and providing snapshot of BSPs' current situation is followed by an explanation phase, which provides some explanations of the quantitative findings (King et al., 1994).

In planning the qualitative inquiry, I needed to develop a better understanding of the assessing, commissioning and managing of medicinal products in general, and biologics in particular, in the UK. This goal was achieved through two main routes: the first is based on reviewing and reading the literature and NHS published documents related to medicines commissioning and reimbursement. The second was through preliminary fieldwork in the form of interviews with four NHS pharmacists who were approached by my supervisor: (*i*) a high cost medicines pharmacist; (*ii*) a commissioner pharmacist; (*iii*) a regional formulary pharmacist and (*iv*) a hospital pharmacist. These meetings clarified certain aspects related to medicines commissioning and reimbursement, tendering activities and negotiations with the industry. The four interviewees also provided information about the process of managing medicines at local and practice level through creating and updating local therapeutic pathways and medicines formularies.

While the exploratory component targeted all marketed BSPs, at the time of the study and all countries in Great Britain (GB), the explanatory component was more specific and focused on IFX-BSP in England. This focus was influenced by five main factors:

- *First* : the varied uptake was more evident in the case of IFX-BSP
- *Second*: IFX-BSP was the most recently launched BSP, therefore processes and discussions related to its commissioning, assessment and prescribing were still occurring
- *Third:* unlike other available BSPs, IFX is indicated in three different therapeutic areas: dermatology, gastroenterology and rheumatology, which, theoretically, might help in comparing perceptions and experiences between three different therapeutic areas
- *Fourth:* IFX main commissioning route, which is locally driven by the CCG. This created an opportunity to examine different localities and how differences in structure and context were reflected in the observed uptake levels
- *Fifth:* logistic considerations, which made it more feasible and possible to locate the study in England than other countries within GB.

3.6.1. Qualitative study aim and objectives

This study aimed to understand the process of local decision making within NHS-England, through exploring and understanding the factors that facilitate or raise barriers affecting the uptake of BSPs in clinical practice in England. The study's aim was achieved through the following objectives:

- *Identify* main stakeholders involved in assessing, commissioning, managing and prescribing IFX-BSPs, locally
- *Explore* stakeholders' experiences, perceptions, motives and beliefs toward BSPs
- *Assess* if prescribers' characteristics in terms of experience, background, location of qualifications influenced their acceptance of BSPs
- *Investigate* how the interactions between named stakeholders resulted in the decision to utilise/not to utilise of IFX-BSPs
- *Identify* main component of the process that led to the observed utilisation levels of IFX-BSPs

3.6.2. Qualitative study: overall study design and conduct

In broad terms, qualitative data can be collected by using one or more of the main three data collection tools (methods): observations, interviews and document analysis (Patton, 2014). In selecting the most appropriate and useful method there are several factors that researchers need to consider, such as the kind of information they are looking for; type of, and access to, participants; and available resources in terms of time and expertise (Silverman, 2013).

The general aim of this research was to understand local decision-making processes by reporting and capturing the experience of, and the interactions between, relevant stakeholders. Therefore, observations seemed to be the most appropriate data collection method; as observational studies can provide hands on, real time, rich and detailed descriptions of behaviours, activities and interactions between targeted participants. 'Observation' can also define the system in which the participants operate and interact (Patton, 2014, Mays and Pope, 1996). However, it was not possible to use this method because it would not be feasible or *practical* to go to all of the selected identification study sites across NHS-England. Even if fewer sites were considered, it still would not have been possible since some sites, at the time of study, had already finalised and completed the process of introducing and implementing IFX-BSPs, and would not be involved in further discussions and interactions related to it; therefore *timing* was a critical factor.

Researcher related, observational studies rely heavily on the researcher to capture, interpret and report what he/she observed while being in the field. This paradigm was problematic for me as I am an international student with limited familiarity regarding the NHS procedures and structure. Another consideration was that I might still be subjected to the effects of the language barrier, which could hinder my understanding of some common English phrases. Therefore, my interpretations would have been an inaccurate presentation, potentially hindered by limited explanations and insights of what was going on at different sites.

Analysing documents, such as meeting records, internal policies and memorandum might help in identifying involved personnel in terms of profession, discussion points, and elements of commissioning agreements and contracts. However, these documents are normally written in an abstracted template-like style. Therefore, document analysis would have fallen short in reporting the personal experiences and impression of relevant stakeholders. Nevertheless, during the process of assessing local medicines formularies, I came across some of these documents, whenever the formulary document was referred to by me for more details and clarifications.

Eventually, qualitative interviewing stood out as the most appropriate data collection method to meet the study's aim and objectives. Qualitative interviews enable researchers to capture participants' (interviewees) perceptions, beliefs and experiences with the phenomenon of interest; they also allow participants to report their personal accounts of the process, dynamics and interactions with other stakeholders within a given context (Bryman, 2004, Kvale and Brinkman, 2009a). Furthermore, being a pharmacist, I was trained and involved in patients' counselling, during which I was asking patients to provide me with details related to their lived experiences and feelings. Therefore, I felt that with some additional training, offered through my university's training courses and modules, I could carry out an interview-based study.

In considering interviews for data collection, a researcher must explore the most appropriate interviewing technique; whether it is a group interview (focus group) or one-to-one interview (Creswell, 2012). Focus group design allows researchers to capture interactions and dynamics between participants and might, in some cases, highlight the differences, tensions and conflicts among them. However, focus groups would not be useful in capturing personal accounts with the phenomenon of interest, and might, in some cases, inhibit participants from expressing and discussing their opinions and impressions freely, especially in sensitive or controversial topics (Creswell, 2012, Crabtree and Miller, 1999). Accordingly, focus groups were ruled out as an option for collecting data.

There are three broad types of qualitative interviews: structured, semi-structured and unstructured (deep) (Britten, 2006); the selection of which type to be used depends on the overall research design, scope and aims (Bryman, 2004). A semi-structured interview follows a balanced approach between structured and unstructured interviewing styles; as it has a defined scope of the interviews, and certain degree of flexibility, which allows exploration of new aspects related to the interviews' focus (Bryman, 2004, Kvale and Brinkman, 2009a, Britten, 2006). Additionally, semi-structured interviews allow comparisons between different professionals and different regions/teams (Bryman, 2004); a facility which fits conveniently within this research aim to understand the reasons for varied uptake rates of IFX-BSPs within NHS-England regions.

In addition to specifying interview types, the choice of interview mode, whether face-to-face interviews or over-the telephone, needs to be considered and determined (Sturges and Hanrahan, 2004). The selection of the optimal interview mode is critical as it can affect the interview's flow, interaction between interviewer and interviewee, depth of conversations and overall quality of collected data (Creswell, 2012,

Novick, 2008, Irvine, 2010). Selecting an interview mode depends on several factors such as access, time, cost, safety and mostly, type of topic being investigated and discussed (Novick, 2008, Sturges and Hanrahan, 2004). Face-to-face interviewing is being promoted as the "gold standard" for qualitative interviews, as when properly conducted that mode allows researchers to collect high quality data in terms of depth and rapport with participants. However, over-the-telephone interviews are being increasingly considered as they are easier to be carry out, they facilitate access, reduce time and cost and are safer for interviewers and interviewees, without significantly affecting interview flow and quality of data (Sturges and Hanrahan, 2004, Irvine, 2010, Novick, 2008). In order to maximise the chance of getting access to participants who are located in different regions within England, I decided to adopt three interviewing modes: face-to-face; over-the-telephone; and through Skype®.

Semi-structured interviews are based on developing and utilising an interview guide (topic guide), which is commonly used to facilitate the interviewing process. (Bryman, 2004, Kvale and Brinkman, 2009a, Britten, 2006). As the study participants were representing different professional roles with different expertise, different agendas, different demands and accountabilities and key performance indicators, it was necessary to create role-specific interview guides. In framing and constructing interview guides, researchers are advised to consider issues related to perceptions, attitudes, emotions, relationships, interactions and process, in addition to the research aim and objectives (Bryman, 2004). Structuring the interview guides was influenced and guided by the literature, NICE guidelines on updating and managing local formularies, and the NICE guide on how to introduce IFX-BSPs into practice (The National Institute for Health and Care Excellence (NICE), 2015a, The National Institute for Health and Care Excellence (NICE), 2015d). This study interview guides touched upon common issues related to background, knowledge and relations and communications between different stakeholders. However, profession-specific questions were also included, for example:

- Background and experience: *What do you think about biosimilar medicines? How do you perceive the availability of BSPs? Can you please tell me about your organisation experience with BSPs?*
- Knowledge and training: *Have you been at seminars/workshops/webinars related to BSPs? In your opinion, who should be responsible for training and educational materials related to biological products in general and biosimilars in particular?*
- Interactions with other stakeholders: *In your opinion, how do professionals namely (physicians, pharmacists and drugs and therapeutics committee members) influence uptake of BSPs? Who tend to be more involved in the decisions whether BSPs are put in the formulary?*
- Policies and guidelines: *In your opinion, is there a need to optimise the utilisation of biosimilars? In your opinion, to which degree it is easy/possible to implement/apply NICE recommendations?*
- Technical and practical experience with BSPs in general and IFX-BSPs in particular: *What do you consider in planning for future tendering? (For commissioners), How do you describe biosimilars to your patients? (For physicians and nurses), What do you consider in getting a product listed in the formulary? (For formulary pharmacist)*

Interviewing is based on human interaction, although staged and not truly spontaneous, but it still includes exchanges of ideas, knowledge, perceptions and feelings. Spoken (verbal) clues can be captured using audio or video recorders or in writing; however, non-spoken clues such as facial expressions, body language, voice tone and overall attitude can be observed and felt. In addition to personality and discussion topic, physical settings and surrounding can influence the interactions between interviewer and interviewees (Muswazi and Nhamo, 2013). Therefore, field-note taking during and after encounters with participants, is frequently promoted as a tool that acts as a reminder of the interview flow, overall impression, behaviours, and main discussion points (Gill et al., 2008, Muswazi and Nhamo, 2013). Before entering the field and started my interviews, I was advised to consider note taking and to keep research journals; therefore, I created an 'interview notes' form (Appendix 6) and 'post interview reflection' form (Appendix 7). These two forms were designed to capture discussion points that I might need to get back to during the course of the interview, or to highlight new or interesting discussion avenues that I did not think of when preparing the interview guide. Field notes can also enable the interviewer (me) to reflect upon the overall impression, the interviewee and how I felt after each interview.

3.6.2.1. Qualitative study settings and targeted participants

In the guidelines on developing and managing local medicines formularies, and in its advice on how to introduce IFX-BSPs into practice, NICE has named several stakeholders who are either working at Acute Trusts or CCGs, as being central in the process of assessing, commissioning, managing, prescribing and utilising BSPs including IFX-BSPs (The National Institute for Health and Care Excellence (NICE), 2015a, The National Institute for Health and Care Excellence (NICE), 2015d). Table 13 summarises preferred categories of eligible participants.

Table 13-Preferred criteria of eligible study participants

No.	Eligible participant categories	Justification for inclusion
1.	Professionals (physicians) involved in prescribing biological medicines in general and BSPs in particular in the targeted therapeutic areas: dermatology, gastroenterology and rheumatology	Targeting these professionals might aid in investigating physicians' perceptions, experiences and attitudes toward BSPs, and in predicting medical community's acceptance of BSPs
2.	Professionals, who are involved in medicines management and assessment in general, and BSPs in particular; either members of the pharmacy departments at targeted Acute Trusts, formulary pharmacists or medicines management pharmacists at CCGs	Including these pharmacists might give an insight of the way in which BSPs are being assessed and incorporated in local formulary lists, clinical guidelines and disease pathways.
3.	Professionals who are involved in negotiating commissioning agreements with Acute Trusts, or procuring medicinal products, such as Commissioner pharmacists at CCGs, high cost medicines* pharmacists at Acute Trusts and/or procurement pharmacists at regional level	Including these professionals might help in understanding types of negotiations that take place at Acute Trusts level, CCGs level and regional level with regard the commissioning and the introduction of IFX-BSPs
4.	Patients or patients' representatives who have been offered to be initiated on or switched to IFX-BSPs	Involving these participants might highlight the way in which patients perceived IFX-BSPs, report their experience and their beliefs
5.	Any other healthcare professionals, who might be involved or contributed in introducing and implementing IFX-BSPs at Acute Trusts and/or at CCGs	Keeping a generic (fluid) description of additionally eligible participants might help in maintaining reflective and flexible approaches in targeting new professional categories without the need for updating or amending the ethical approval application

***** A pharmacist who is responsible for managing the utilisation of high cost medicines with healthcare settings, the pharmacist is also responsible for liaising between providers and commissioners, whether national or local.
CCG: Clinical commissioning group, **IFX-BSP:** Infliximab biosimilar

Although patients were considered to be eligible to participate in this study and to have valuable input in explaining the process of implementing IFX-BSPs, the category was excluded from this study based on two factors. *First*, it was highlighted in the literature that most of the resistance to implementing BSPs came from healthcare professionals, who are involved in patients' management and prescribing BSPs. *Second*, the decision to exclude was based on the location of patients within the process of implementing IFX-BSP as end-users. As such, they will be subjected to and affected by the decision of utilising IFX-BSPs, which is more related to the implementation element than the dissemination element; the latter being the main focus of this research.

One of the major differences between quantitative and qualitative studies is the sampling approach (securing data sources). Quantitative researchers follow probabilistic or random sampling to enable them to generalise their findings; qualitative studies on the other hand are based on convenience, purposeful[8] (purposive) and/or theoretical sampling approaches (Marshall, 1996, Patton, 2014). In order to get the most relevant and informative data sources (participants) (Marshall, 1996), I followed purposeful sampling as the general approach for identifying eligible participants from the most relevant study sites. The sampling framework was informed by: (*i*) IFX-BSP high and low utilisers as it was reported by preliminary data of Phase II-MODB, (*ii*) locally established communication channels, (*iii*) IFX utilisation volume/Acute Trust, (*iv*) rheumatoid arthritis prevalence rates per CCG and (*v*) geographical diversity. Selection criteria were considered for each of NHS-England's four main regions (NHS-England, 2015). Table 14 represents selection criteria and purpose they served. The full list of the 41 targeted sites is available in Appendix 8.

Table 14-Selection criteria for study sites

No.	Selection Criterion/Source	Purpose
1.	Acute Trusts that are either IFX-BSPs high or low utilisers per region *Quantitative component preliminary results of MODB*	Investigating factors and mechanisms generated observed utilisation levels
2.	Acute Trusts and CCGs involved in joint formularies *Quantitative component*	Exploring the effect of the local established communication channels on the process of implementing IFX-BSPs
3.	Acute Trusts with high utilisation volume of infliximab *NHS Digital (formerly HSCIC)-secondary care innovation scorecard*	Investigating how a Trust's utilisation burden affected its willingness to utilise/switch to IFX-BSPs. Addressing the effect of infliximab main utilisers, gastroenterology
4.	CCGs with high prevalence rates of rheumatoid arthritis *NHS Digital QOF*	Exploring the effect of disease burden on CCG motivation to utilise BSPs, knowing that future BSPs launches, such as etanercept, are targeting rheumatology
5.	Acute Trusts or CCGs that will guarantee geographical variation *NHS-England four main regions*	Maintaining and allowing regional diversity

BSP: Biosimilar medicinal products, **CCG:** Clinical Commissioning Group, **HSCIC:** Health and Social Care Information Centre, **IFX-BSP:** Infliximab biosimilars **MODB:** Medicines Optimisation Dashboard, **NHS:** National Health Service, **QOF:** The Quality and Outcomes Framework

[8] In his book (Qualitative Research and Evaluation Methods), Michael Patton highlighted that purposive and purposeful can be used interchangeably. However, while the first is frequently used by methodologists and academics, the second is preferred by non-researchers. Although mine is an academic research initiative, I chose to use the term "purposeful" to emphasise the significant role of the targeted sample in addressing the study's main aim, which is explaining the reason for variation. In other words, the selected sample is fulfilling its purpose.

3.6.2.2. Qualitative study ethical considerations

As this study was aimed at investigating perceptions, experiences and beliefs of different participants representing different professional roles, there was a possibility of revealing sensitive issues related to inter- and intra-professional politics, interactions and/or potential conflicts and frictions. Therefore, careful ethical considerations were needed to gain participants consent and to assure their anonymity, and confidentiality. It is important to avoid confusion between anonymity and confidentiality (Pope and Mays, 2006). Confidentiality is about data and opinions provided by participants, who usually assume that these data are not being shared with someone else (Lichtman, 2010). As such, researchers are obliged to inform participants that confidentiality is limited, since it is likely to report direct quotes and comments in the study report (Pope and Mays, 2006). On the other hand, anonymity involves details related to participants' personal identity, professional role, and research settings. Researchers should also think about the amount of details needed to back up and substantiate their claims (Pope and Mays, 2006). In some cases it is unavoidable to have identifying details such as; professional role and settings. Therefore, the personal identity can be recognised easily, especially if the research has targeted only a small number of participants who share the same settings or who hold recognisable or special positions. Participants should be informed of this possibility. Anonymity is not only limited to the publication phase of the research, but it should also be considered during transcription and other data management phases of the data (Pope and Mays, 2006).

Informed consent is used as a tool to communicate details related to the research aim; sponsoring organisation; who is conducting the research (researcher(s) and organisation); participation is voluntary and participant's right to withdraw; data collection method(s); research scope; expected duration of interactions; measures to maintain participants' anonymity and data confidentiality; and access to data and participants identity (Ritchie et al., 2014)

This study was granted ethical approval from Research Ethics Committee-School of Medicine and Health Sciences, University of Nottingham, on Monday the 18th of January 2016; Reference number: B18012016 SoP 15116. Amendment No. (2:20.03.2016) was approved in April 2016[9]. Approval letters are presented in Appendix 9 and Appendix 10.

3.6.2.3. Qualitative study conduct

As soon as the study protocol had been approved, I started securing access to selected sites by obtaining contact details of the Research and Development (R&D) Department/Unit at each site from the National Directory of NHS Research Offices website (http://www.rdforum.nhs.uk/content/contact-details/). For sites that were not listed, I acquired relevant contact details through their general enquiries' portal. Using available and acquired contact details, I started notifying selected sites about my intention to recruit some of their staff to participate in my study. In addition, I sent them study documents and forms for their review, comments and approval. As expected, access was not possible to all selected sites, as some sites did not respond despite repeated reminders, some did not agree to host the study, and some stated that there was no one whose role was relevant to the study. Although access was not granted at some sites, a varied sample of sites in terms of IFX-BSPs' prescribing practice and geographical location, was achieved. In summary, access was secured at 28 sites (16 Acute Trusts and 12 CCGs) out of the 41 initially targeted sites. Appendix 11 lists identified sites' feedback on whether or not to host my study.

[9] An amendment was issued to approve major changes in the study protocol, relating to supervision affiliations and the research team.

Once a site had agreed to host the study, communications with relevant departments (pharmacy, rheumatology, gastroenterology and dermatology) at Acute Trusts, and nominated commissioners at the CCGs were begun by sending an introductory email briefly explaining the study, type of participants eligible for the study, and providing them with a copy of the participants' invitation letter (Appendix 12). Additionally, email recipients were asked to communicate participation requests to relevant professionals who might be interested in taking part in the study. As soon as a participant was identified either by R&D personnel, service/unit head or administrative staff and/or their colleagues, he/she was sent a participant's invitation letter and information sheet (Appendix 13) via email and, in some cases, via mail.

Although gaining access to research participants is a time consuming and challenging step in conducting an in-depth study, its details are rarely reported by researchers. Sometimes it is considered as a purely technical issue (Okumus et al., 2007). Purposeful sampling was established as the main sampling approach for this study; however, other techniques were considered such as convenience sampling whenever and wherever access to participants was not granted or was delayed. Convenience sampling was used in identifying and recruiting dermatologists, who were the least responding participants. Recruiting dermatologists was accomplished by circulating study details in the UK Dermatology Clinical Trials Network Newsletter to its members. Convenience sampling facilitated my access to healthcare professionals who attended the NHS-England-Academic Health Science Networks (AHSNs)-Biosimilar Medicines Workshop (Leeds, March 2016), and the Health Services Research and Pharmacy Practice (HSRPP) Conference (Reading, April 2016). I also considered convenience sampling in approaching participants, who were identified by other participants for their involvement in introducing IFX-BSPs at local settings. Combining different recruitment routes improved access to a varied sample of professionals across the four NHS-England regions.

Eligible participants were given sufficient time, at least five working days or as per participant's preference, to consider their participation and to ask for clarifications, if needed. Participants were assured about their anonymity and the interview's confidentiality. Once a participant agreed to take part in the study, the interview date, time and mode were discussed and agreed on; an outlook meeting request was sent to the participant to have it fixed in his/her calendar. Interested participants were asked to sign and date the consent form (Appendix 14) before the interview took place.

In total, 59 professionals were recruited for the study. All of the NHS-England regions were represented in the sample, with the maximum number of participants achieved in the North of England region. Over-the-telephone was the dominant interview approach, as 54 interviews were over-the-telephone, 5 interviews were face-to-face and none through Skype®. Table 15 summarises the sample's characteristics.

Table 15-Number of participating professionals per role and region

	Number of Participants
Region	
North of England	19
Midlands and East of England	18
London	6
South of England	16
Gender	
Female	32 (54%)
Professional Role	
Commissioner	14
High Cost Medicines Pharmacist	4
Formulary Pharmacist	16
Prescribers*	24
Speciality Nurse	3

* 18 physicians (six per speciality (therapeutic area)), 3 nurse prescribers (2 gastroenterology and 1 dermatology) and 1 prescribing pharmacist

The majority of participants (54/59) opted for over-the-telephone interviews; this resulted in creating comfortable arrangements for interviews to take place. Over-the-telephone interviewing allowed participants to schedule the interviews at times that did not interrupt their daily schedules, as most of the interviews occurred at lunch time, early morning, or after working hours; a few even took place on the participants days off. Another telephone-interview advantage was that participants did not have to go through the hassle of finding rooms for the interview; the only arrangement needed was to have access to landline or mobile phone. The over-the-telephone interviewing mode was also convenient for me, as it allowed easy access to participants from all the different regions in England, for the cost of a phone call.

On the day of the interview, I checked with the participant to establish if he/she could still participate in the study, if the interview timing was still suitable, if there is any concern regarding the interview topic or conduct, and if it was acceptable to audio record the interview. For face-to-face interviews, I used two recorders (one as a backup); in the case of over-the-telephone interviews, I used an adaptor that connected the telephone with one recorder, it was not technically possible to have a backup recorder for this mode. At the beginning of an interview, a participant was briefed about the general aim of the study and the reason why he/she had been targeted and recruited.

Using interview guides created a balance between discovering new aspects and issues related to the study. The guide helped in steering the interview to what needed to be addressed and within the allowable limited time. As the interview guide's content was influenced by the NICE guidelines and what was reported in the literature; there was still a possibility that I might have missed some important aspects related to the introduction and utilisation of BSPs. This concern was especially valid bearing in mind that there were different arrangements in place between different localities. Therefore, a reflective approach was maintained in the conduct of the interview by asking participants if there was any question or issue that they wanted to discuss that had been missed (Sobh and Perry, 2006). Additionally, I followed the advice offered by Kvale and Brinkmann (2009a) on asking participants at the end of the interviews about their feelings, impression and experience of being interviewed; asking such a question might end up opening

new venues for discussions, thereby adding to the richness of the collected data (Kvale and Brinkman, 2009a).

The differences between the two interviewing modes became visible and tangible during the process of note taking. During face-to-face interviews, I was unable to take notes as I had hoped to; actually I was worried that I might lose momentum with the interviewee or even to offend the interviewee by interrupting eye contact and being busy writing notes. On the other hand, the flexibility of over-the-telephone mode eased and facilitated note taking, so this mode resulted in deeper and richer interviews. In fact, I felt that I was more involved and focused in the over-the-telephone interviews, than during the face-to-face situations. This outcome is contrary to what Irvine (2010) mentioned in her reflections on her experience with over-the-telephone interviewing. She suggested that getting distracted and losing the flow of the discussion was more common in over-the-telephone interviews, in comparison to face-to-face interviews; such difficulties might in some cases affect the quality of data (Irvine, 2010). The other occasion when I noticed the differences between the two modes was when I was filling the post reflection form; I found that I mentioned issues related to the interviews' locations and how the interviewees acted in general during face-to-face mode. However, in case of over-the-telephone interviews, note taking was more thorough and included some extra details related to the tone of the interviewees and how they talked and expressed their opinions in general.

As interviewing, note taking and reflecting proceeded, it became necessary to update and revise interview guides as the interviewees highlighted issues not in the guide. Examples of issues omitted included; i) the effect of service design and capacity on implementing the switch to BSPs, ii) third party service providers' involvement such as homecare companies, and iii) the possibility of changing local guidelines and disease pathways. This observation is where the flexibility aspect of semi-structured interviews and the benefit of note taking and post interview reflection become visible. In addition to adding new questions to the interview guides, some questions were rephrased and redirected, especially those related to the structure of local formularies and NICE statements, guidelines and guidance. Amended interview guides were shared with the research team to get their feedback and approval. In total, commissioners' and formulary pharmacists' interview guides were amended three times, and the physicians' interview guide was amended twice. All interview guides were date and version controlled. Final versions of interview guides are listed in Appendix 15,Appendix 16, and Appendix 17respectively.

Early stages of interviewing highlighted the influential role specialist nurses have in managing the introduction and utilisation of BSPs. Accordingly, I started communicating with nurses as potential interviewees, who were nominated by either other interviewees or Acute Trusts R&D staff. At this stage, it was not needed to amend the study protocol or to seek approvals from ethics committee at the University of Nottingham, as there was a fluid definition of healthcare professionals that I included in the first protocol. Nurses were interviewed using an interview guide developed specifically for them (Appendix 18*)*. The interviews were focused on issues relating to nurses' perceptions of BSPs, their experience in utilising BSPs and the process of switching stabilised patients.

As the study proceeded, I noticed that some participants had a dual role, as some described themselves as embedded pharmacists or who had the title of high cost medicines pharmacists, who were involved in commissioning as well as formulary management activities. The same thing was applied in the cases of nurse and pharmacist prescribers who, in addition to the common definition of their role, were involved in prescribing biologics to patients. Accordingly, in these cases, I decided to use more than one interview guide in a complementary manner, to extract the maximum possible information and knowledge from these participants' experiences.

Data collection continued until no more new discussion points, new ideas or concepts were highlighted or emerged. However, as I had noticed variations between sites, I decided to continue until all sites were exhausted, in order not to miss the opportunity of new data, concepts or observations emerging. Subsequently, the end of the study reporting form was signed and sent to participating sites, sponsor's office, University of Nottingham and the Research Ethics Committee-School of Medicine and Health Sciences, University of Nottingham on Wednesday 26 October 2016 (Appendix 19).

3.6.2.4. Data management

Data management, analysis and processing occurred at my office in the Division of Pharmacy Practice and Policy (PPP), School of Pharmacy, University of Nottingham. Access to research and personal data was restricted to the research team. Electronic data were stored on the University of Nottingham computers with restricted, password protected access. Interview records were transferred to the University's computers immediately after each interview. Hard copy data in the form of consent forms, field notes, post interviews reflection forms, transcripts, filled out questionnaires and any other related documentation were stored in secured cabinets and/or drawers with restricted access. A cover page for each participant's documents was also created (Appendix 20) and the storage of hard data was at my office.

Participant anonymity was ensured through assigning identification code numbers to correspond to research data in any research paperwork and computer files. Each identification code consisted of four letter and two digit number; the first two letters represented the participant's initials, and the third and fourth letter represent his/her role, the two digits number represented the sequence of the interview per role. For example ATCP-09 (AT: participant's initials, CP: commissioner pharmacists and 09 mean that this is the ninth interview with a commissioner pharmacist).

Identity codes of participants were not disseminated outside of the research team. Personal data were only stored as per the permission of the consent forms and for the minimum time period required for its purpose in this study. Where there was an overlap between personal data and research data, such as names on the consent forms, names and positions in the filled demographic questionnaire, names and other personal data captured and taped during the interviews, this information was stored as research data but the linkage was kept confidential outside the research team.

3.6.2.5. Interview transcribing

Transcribing is the first step in qualitative data analysis. The selected tactic of transcribing is driven by the data analysis approach, whether it is meaning or language focused (Kvale and Brinkman, 2009b). In meaning focused analysis, the transcript should be presented in a readable and naturalised way (Bucholtz, 2000). On the other hand, language driven analysis mandates linguistics representation of the transcripts. This approach preserves as much as possible of the spoken language and pays attention to the way in which people talk and express their thoughts and feelings (Bucholtz, 2000, Kvale and Brinkman, 2009b). While meaning focused analysis requires producing literature similar transcripts, attention to some contextual elements such silences, laughter, sarcasm, etc. should be considered; a balanced approach between naturalised and denaturalised transcription might be followed (McLellan et al., 2003, Bucholtz, 2000). A midway approach might be considered as, in addition to verbal (spoken) expressions, the approach is able to capture unspoken clues such as a sigh, laughter, sarcastic tone and so on, especially when it is possible to have a meaning changed or disturbed. Moreover, following this approach might help in compensating for lack of non-verbal and contextual data that the over-the-phone interviewing mode is stigmatised by.

To ensure a systematic approach in transcribing, a guideline and instructions are needed to maintain consistency in preparing interview transcripts (McLellan et al., 2003, Kvale and Brinkman, 2009b). While interviews are different in content and flow, their transcripts should look identical in terms of layout and formatting (McLellan et al., 2003). Identical formatting eases the processes of analysis and transferring to qualitative analysis software (McLellan et al., 2003). Accordingly, I created a transcribing guideline (Appendix 21) and transcript cover page to ensure consistency among all transcripts (Appendix 22).

Transcripts were checked for accuracy. Three independent reviewers were asked to check transcripts against original records. Reviewers were native English speakers who had experience in working in organisations within the NHS; two reviewers were hospital pharmacists, and one worked as a pharmacist technician and as a commissioner. Their professional expertise helped them in understanding technical terms and common phrases used by me (the interviewer) and the interviewees, and hence provided a more accurate account of the transcripts. Each reviewer was asked to sign a confidentiality acceptance form before the reviewing process (Appendix 23). In order to guarantee consistency in transcript reviewing, the reviewers were advised to follow their role specific guidelines (Appendix 24), and to fill in a post review reflection form (Appendix 25). It should be noted that the reviewers only received anonymised copies of transcripts.

3.6.2.6. Data analysis

While quantitative studies are carried out through sequential steps of data collection, checking, analysis, interpretation and presentation, qualitative studies are in general based on overlapping and iterative steps. In fact, this overlapping and going back and forth between different stages is both a desirable feature and a strength of qualitative research (Caudle, 2004). Although intensive and focused analysis occurs after the data collection phase, a researcher cannot isolate himself or herself from their data, or stop thinking and reflecting on the meaning of their data. In other words one "*cannot stop data from whispering*". This might become visible in reviewing and updating interview guides as the data collection proceeds.

Analysing qualitative data can follow three main strategies: induction, deduction and abduction (Reichertz, 2004). *Induction* seeks the discovery of new concepts and observations; it is free and unbounded by theoretical concepts or prior assumptions. *Deduction* is based on testing an already established theory, a more confirmatory approach (Reichertz, 2004). *Abduction*, in its simplest definition, is a combination of both; it starts with prior (flexible/soft) concepts and allows for the emergence of new insights from the data. Abduction in its most sophisticated form (logical inference) ends up adding to and upgrading an established theory through discovering unanticipated connections and association (Reichertz, 2004, Patton, 2014). As this study is the explanatory component of a sequential design, its conduct and data analysis needed to be influenced by the results and observation of the explanatory component, and the literature review process that was related to it. Therefore, for this research abduction, which is based on lose/soft prior-concepts, was considered the most suitable analytical strategy.

Another aspect related to analysing qualitative data, is the analysis mode; methodologically driven studies follow an analysis mode bounded by its relevant methodologies such as grounded theory analysis, phenomenological analysis and case study analysis. However, generic qualitative studies similar to this current research, follow a more flexible and relaxed analysis mode such as thematic analysis (Braun and Clarke, 2006). Thematic analysis is based on grouping and clustering codes, which are labels tagged to describe segments of data based on similarities of definition and scope, into bigger categories which are then grouped within a theme. A theme provides pieces/segments of evidence towards answering the research question (Braun and Clarke, 2006).

In order to improve and establish rigour of qualitative analysis, researchers are advised to adopt a systematic and clear approach in analysing data. For this research, this rigour was achieved through using a variation of thematic analysis called 'template analysis' (Brooks and King, 2012). Template analysis is characterised by (*i*) its flexibility in terms of philosophical stance, (*ii*) its ability to accommodate large data sets, (*iii*) the possibility it can accommodate abduction as an analytical strategy, and d) its systematised step-wise tactic of analysing data (King and Brooks, 2016, Brooks and King, 2012, King, 2012). It also allows a researcher to tailor his/her approach of tackling data according to the nature of the research, data set and experience (Waring and Wainwright, 2008).

The process of template analysis goes through six steps: (*i*) familiarisation, (*ii*) preliminary coding, (*iii*) clustering, (*iv*) developing the first template, (*v*) applying the template and finally (*vi*) interpreting and reporting what the template has yielded. Researchers are advised to develop their first template based on a representative sample, not in terms of numbers, but in terms of diversity of roles and content (King and Brooks, 2016, Brooks and King, 2012).

Finally, interpreting and presenting qualitative data might be facilitated and augmented, if it is matched with an already established theory. A theory helps in arranging scattered data and themes in a more representative and understandable way, by directing the researcher towards their main (focal) findings. While a matching theory "solves the puzzle" by providing a directive structure to organise and discuss data, that should not hinder the researcher from exploring new venues and addressing new findings (Dubois and Gadde, 2002, Boudon, 1991). As already discussed in the literature review chapter (Chapter 2), diffusion of innovation theory was considered as a hosting theory for this research.

Data analysis went through ten main stages:

- First: creating a list of sensitising concepts, which acted as signposts to guide the analysis process. This list was assembled based on six main sources: (Appendix 26)
    - NICE recommendations on implementing IFX-BSP
    - NICE guideline on developing and updating local formularies
    - Reported experiences of some Acute Trusts in introducing IFX-BSPs
    - Notes taken during participants interviewing, familiarisation steps and during the transcribing process
    - Study aim and objectives
    - Literature review

- Second: producing the first analysis template: template analysis was the selected thematic analysis approach, which is based on the following six sequential and interrelated steps of analysis (King and Brooks, 2016, King, 2004). As per King and Brooks advice for researchers to develop their first template based on a representative sample, not in terms of number, but rather in terms of diversity of roles and content (King and Brooks, 2016, Brooks and King, 2012). Therefore, the first template was based on 10 transcripts representing all targeted professionals and all regions within NHS-England. This step was achieved through the following:
    - *Familiarisation:* this step represents an early stage engagement with research data; it started with the transcribing process, during which the researcher noted down frequently reported issues and ideas. Following the transcribing process, the researcher read and reread each transcript and also took notes

    - *Preliminary codes:* at this step I started assigning labels (codes) to describe extracts of the transcripts. This action was driven by sensitising concepts; however, the researcher kept an open mind to allow new codes (tags) to emerge inductively

    - *Clustering:* resulting codes from previous stages were condensed into richer, more descriptive codes. This process resulted in codes being organised into hierarchical structures of different levels of codes, sub categories and categories; each level had a broader scope than the previous one, and acted as a heading for it

    - *Creating first template:* a first analysis template was produced. This was achieved through looking at connections created at the clustering stage between codes, sub-categories and categories. This stage created connections between different codes/categories and produced an overarching theme that represented the main idea of the clustered group of codes. Resulted themes and clusters were then organised into a template (Appendix 27). The first template was structured into eight domains (themes) scattered through five main spheres, with each representing specific stakeholders.

- Third: applying, updating and refining template. The coding book of the first template guided the coding process of the second subset of transcripts. The template went through several cycles of iterations, refinements and updating. Each time the template witnessed a major change in terms of creating new themes, merging themes and/or relocating themes, the template was allocated a new version number. After coding 32 transcripts, the template reached a degree of stability with no major changes or refinements. In total four versions of the template (date and version controlled) were created. At this stage, the fourth template was structured into six main themes (norms, negotiations, influencers, decision, implementation and outcomes)

- Fourth: meeting for a brain storming session: in this session, the fourth template was presented and discussed with the transcripts reviewers, an experienced qualitative researcher and a former NHS chief pharmacist. During the session, the participants were asked about their impression of the template and emerging themes; in particular if they thought that the template was relevant to what they heard in the transcripts. The researcher and the NHS chief pharmacists were asked for their advice, based on their experience, regarding the template, especially if it reflected actual practice. Session participants generally agreed with the template presentation and structure; however, they also made some suggestions and comments regarding the definition, phrasing and scope of some codes and categories. Appendix 28 lists these comments

- Fifth: creating fifth analysis template: which was created based on the output of the brain storming session

- Sixth: matching with an implementation science established theory. This goal was achieved by mapping out the fifth template themes' codes and scope with an established implementation theoretical explanation. Matching did not limit the scope of the themes, but rather helped in the reorganisation of some, as well as expanding the scope of others.

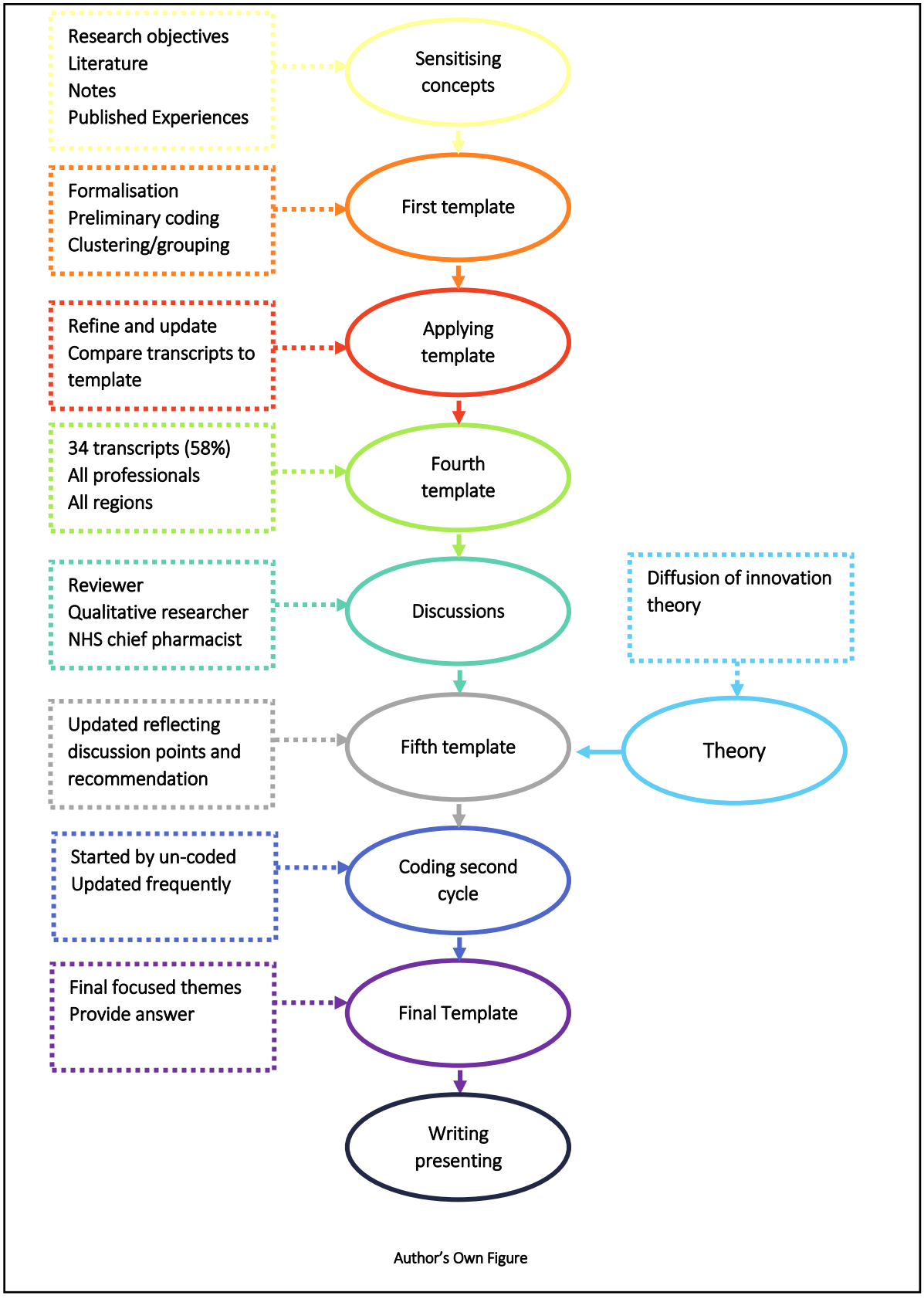
- Seventh: coding second cycle. This coding cycle included the whole dataset and was guided by the sixth template layout and codes. When needed, modifications on the template were reflected in an updated version of the template. This coding cycle is a more focused and guided process. Coding was facilitates using Nvivo® software (NVivo, 2015). Final template themes are represented in Chapter 5.

- Eighth: creating the final template with all if relevant codes, sub-categories and categories

- Ninth: interpretation by linking the final template with theory. While previous steps provided a systematic approach for organising data and creating connections, this stage provides a means of explaining data and connections. It tells the story of the data; it links research questions with emerging themes. This step is aimed at using a theory to facilitate data interpretation and presentation; data were not coded as per the theory, but were interpreted according to it.

- Tenth: writing up and presenting data. Writing itself is an analytical process as it provides direction for the way in which data are presented. The process of analysis is summarised in Figure 7.

Figure 7-Steps followed in analysing and presenting qualitative data



3.6.3.7. Quality attributes and checks

In qualitative research, rigour can be established through assessing research integrity (trustworthiness) in terms of credibility, transferability, dependability and confirmation. Some scholars even go one step further and use the term 'goodness' instead of 'rigour' to discuss quality attributes of qualitative studies (Tobin and Begley, 2004). In establishing the 'goodness' of a qualitative study, researchers must take into consideration the cyclic and iterative nature of the qualitative model. Therefore, it is not advisable to check the quality of a study only at its final stages, as such quality checks should be built into the research throughout the whole process (Tobin and Begley, 2004). In this study, trustworthiness was established through assessing credibility, transferability, dependability and confirmation. Table 16 provides a summary of measures and steps followed to address and ensure study quality (goodness). This summary is based on Shenton's discussion of qualitative research quality (Shenton, 2004).

Table 16-Summary of study quality checks

Concept	How to be checked	How it was checked in this research
Credibility *(internal validity)*	**Definition and concept:** Credibility is the qualitative definition of internal validity, it assures that what the researcher is presenting is what was actually reported and experienced by study participants (Tobin and Begley, 2004, Shenton, 2004, Bryman, 2015). Several measures need to be clearly and transparently discussed in order to assure research credibility; for example: selected design, sampling approach, triangulation methods, sources or analysts triangulation and member checks (Bryman, 2015, Shenton, 2004). Credibility is not limited to research conduct and findings, but it is extended to the researcher him/herself. Therefore, a researcher needs to demonstrate sufficient experience and training in conducting qualitative research, highlight any potential conflict of interest in terms of funds and employment and any possible 'pre-assumptions' which might affect data interpretations (Patton, 1999).	
	- Rely on well-established methods	- The semi-structured interview method is a commonly and frequently employed qualitative research tool
	- Development of an early familiarity	- This was achieved through the preliminary interviews with four NHS pharmacists and reviewing the literature
	- Random sampling	- Not possible, this study represented an explanatory component of the research and was guided, mainly, by the results of the explanatory component. Therefore, purposeful sampling was more relevant and suitable. Additionally, random sampling is not possible with this research, as I was targeting NHS professionals, which is not an open access environment
	- Triangulation	- Triangulation was in the form of multiple resources; different professionals representing different organisation and different regions in NHS-England
	- Ensure honesty	- Participants were free to take part in or withdraw from the study. The researcher checked and reviewed all interviewees' transcripts, and 52 out of the 59 were reviewed by independent reviewers

- Iterative questioning	- Whenever a participant did not understand a question, questions were rephrased and redirected. Moreover, in case there was something unclear or an unfamiliar term was used, the researcher asked the interviewee to clarify
- Negative case analysis	- This can be achieved by addressing the outlier cases. However, study sample, in terms of organisations, represented two opposite situations: high and low users of IFX-BSP
- Frequent debriefing	- Frequent meetings with supervisors, where the analysis process was discussed and challenged
- Peer scrutiny	- Brain storming session allowed for peer review and evaluation
- Reflective commentary	- Provided throughout the chapter, how new participants were targeted (nurses) and how the interview guides were updated
- Researcher's qualification	- Training courses and modules provided by the University of Nottingham or other institutions helped in becoming familiar with qualitative methods and analysis
- Member checks	- Referring to research participants was not possible
- Thick description	- Literature review chapter
- Examination of previous findings	- Integrating findings of both component

Transferability *(external validity/ generalisability)*	**Definition and concept:** Transferability is the qualitative alternative of generalisability. However, due to the fact that the qualitative data were context and time bound, and based on small numbers of participants/sites, the concept detours to transfer evidence from one context to another based on similarities between the contexts (Shenton, 2004, Bryman, 2015). Transferability is facilitated by thick description of the phenomenon in terms of background, context and research participants (Shenton, 2004).	
	- Thick description of the context	- Literature review explained the context
	- No. of participating organisations and their geographical location	- 28 sites, locations were provided
	- Selection criteria of research participants	- Eligibility criteria were explained
	- No. of research participants	- 59 participants, their roles and locations were provided
	- Data collection tool	- Semi-structured interviews based on interview guide
	- Timeframe for data collection	- Data collection started on 1st Feb 2016 and ended on the 30th of Sep 2016
	- No. and duration of interviews	- 59 interviews in total

Dependability *(reliability)*	**Definition and concept:** While quantitative methods need to prove reliability in generating consistent results, qualitative scholars acknowledge that it is not possible to have the same findings and conclusions utilising the same methods and targeting the same participants. However, a qualitative method should be shown to be repeatable. Therefore, a researcher needs to provide a detailed and reflective account of the research proceedings, so making it possible for others to repeat the process, although they may not necessarily end up with the same conclusions (Shenton, 2004, Bryman, 2015) Dependability as a concept is tightly linked to credibility, as ensuring credibility will lead to dependability (Shenton, 2004).	
	- Describe research design and execution	- Detailed description in section 3.5.2.2. of this chapter
	- Detail description of fieldwork	- Detailed description in section 3.5.2.3. of this chapter
	- Evaluating and reflecting on research conduct	- Reflection accounts were presented throughout the chapter

Confirmability *(objectivity)*	**Definition and concept:** The last quality attribute is confirmation (objectivity) which, as a concept, is challenging when employing qualitative methods, as there will always be the human element (the human biased account) in selecting what to study, why and how to proceed and interpret (Shenton, 2004). Confirmation can be assured through providing a full and detailed description of the research conduct, acknowledging any previous assumptions and explaining reflectively how analytical decisions were made (Shenton, 2004, Bryman, 2015).	
	- Detailed description of methodology and methods	- Detailed description of the methodology (generic qualitative research) and methods were provided in section 3.4.2.4. and 3.5.2.2.on this chapter; respectively
	- Audit trail (data oriented)	- Analysis templates were date and version controlled. Analysis journal were always used.

3.7. Discussion and synthesis of evidence

As each component, quantitative and qualitative, provides some insights into the process of implementing BSPs in the UK, it is the integration step that provides a better and more comprehensive understanding of BSPs implementation. As discussed earlier, this research followed a sequential explanatory design. The first instance of integration between the two components occurred during the design and conduct of the qualitative component, as the quantitative component helped in developing the qualitative study's aims and objectives, as well as directing its design and conduct. The qualitative component aimed to provide an explanation of the observed variations in utilisation and uptake of BSPs, which was not possible through quantitative study.

The second point of integration occurred in the data analysis phase, as the influence of the exploratory component was observed in the qualitative data analysis, when I referred to quantitative results in order to make sense of what I was reading and coding in the transcripts. This option was especially valuable when I was comparing two types of users (low and high), and when I wanted to understand the process of developing, structuring and presenting local medicines formularies.

Although the results of each study (quantitative and qualitative) are presented in separate chapters, the discussion chapter (**Chapter 6**) merged total evidence and presented it collectively in a way that addresses the overall research aim and objectives.

Chapter Four: Assessing Uptake of Biosimilar Medicinal Products by British Local Formularies and English Acute Trusts

4.1. Introduction

This chapter reports the findings of two cross-sectional studies. With the general aim of assessing the utilisation of BSPs in the UK, this research was carried out in two separate phases, each targeting different products and at different time points. Based on factors related to updates in the local market, national policies and availability and accessibility of data sources, each phase had its own specific objectives and method. Phase I assessed the listing status of first wave BSPs which were available in the market prior to October 2014: HGH-BSP, EPO-BSP and G-CSF-BSP, in British local formularies. Phase II assessed GB local formularies' uptake of IFX-BSP, and investigated English Acute Trusts' prescribing practice, whether switching or initiating patients.

4.1.1. Justification for assessing the utilisation of biosimilar medicines

As discussed earlier in the literature review chapter (**Chapter 2**), the UK has been characterised by limited uptake of BSPs (Intercontinental Marketing Services Health (IMS), 2011, British Generic Manufacturers Association (BGMA), 2013). However, as available reports and studies were based on sales figures and/or non-publically or academically accessible databases, it was not possible to verify the reported utilisation independently. Moreover, limited utilisation was reported without providing details related to specific indications or patient groups; therefore, it was not possible to confirm the notion that extrapolation of safety and efficacy evidence has hindered BSPs prescribing for untested indications or for specific patient groups (Aapro, 2011). As a result, it was necessary to assess the utilisation of available BSPs using independently available data sources, and to investigate the differences between tested and untested indications.

Implementation science and related theories accommodated this research. The scope of implementation research is not limited to identifying factors and processes which led to the institutionalisation of an intervention; indeed, it also involves assessing implementation outcomes. Implementation outcomes might be presented in the form of utilisation rates, implementation's impact (negative or positive), quality of implementation, implementers' acceptance of the intervention and identification of successful or failed cases (Bauer et al., 2015, Odom, 2009, Palinkas et al., 2011, Albright et al., 2013). Measuring uptake and utilisation levels might serve as an indicator for the acceptance of an innovation within an organisation (Odom, 2009, Bauer et al., 2015). As physicians' acceptance of BSPs was highlighted as a main barrier to hinder BSPs' utilisation, assessing utilisation rate might reflect their acceptance of BSPs.

The quantitative study's aim, objectives, design and methods were discussed in detail in the Research Methodology and Methods Chapter (**3.5. Quantitative method**).

4.2. Quantitative study results

4.2.1. Phase I

One hundred and forty-six formularies were identified: 129 in England, 10 in Scotland and 7 in Wales. These formularies were developed and put to use by 155 Acute Trusts in England, 14 Regional Health Boards in Scotland and 7 Local Health Boards in Wales. Sixty-three formularies were found to be jointly developed and/or used by more than one healthcare providing organisation: 60 in England and three in Scotland.

Formulary uptake of targeted BSPs was variable across the three countries. Twenty seven percent of English formularies had listed G-CSF-BSP in preference to the R-BMP, versus 12.5% and 14.3% amongst Scottish and Welsh formularies, respectively. In the cases of HGH-BSP and EPO-BSPs, 7% and 4% of English formularies respectively preferred BSP over R-BMP, but no Scottish or Welsh formularies did so. Table 17 summarises formulary uptake and status by country.

Table 17-Phase I formulary status and listing by country

	Scotland	England	Wales	Total
Targeted Organisations	14	157*	7	178
No. of Formularies	10	129	7	146
No. of Joint Formularies	3	60	0	63
List HGH	8	111	7	126
Prefer HGH-R-BMP	4 (50%)	19 (18%)	6 (85.5%)	29
Prefer HGH-BSP	0 (0%)	7 (7%)	0 (0%)	7
List EPO	6	102	7	115
Prefer EPO-R-BMP	1 (17%)	51 (50%)	0 (0%)	52
Prefer EPO-BSP	0 (0%)	4 (4%)	0 (0%)	4
List G-CSF	8	104	7	119
Prefer G-CSF-R-BMP	0	10 (10%)	0	10
Prefer G-CSF-BSP	1 (12.5%)	28 (27%)	1 (14.3%)	30

* As of November 2014, the total number of Acute Trusts in England was 157. It was not possible to obtain the formulary list of two Acute[10] Trusts since one had been recently dissolved and one was developing a formulary list.

BSP: Biosimilar medicinal product, EPO: Recombinant human erythropoietin (epoetin), G-CSF: Granulocyte-colony stimulating factor (filgrastim), HGH: Human growth hormone (somatropin), R-BMP: Reference biological medicinal product

In addition to observed variations between countries, variations were observed in formulary uptake and listing approaches across the three targeted groups. Being listed in 86% (126/146) of retrieved formularies, HGH-BSP achieved the highest frequency of medicine listing; on the other hand, a brand name-based listing approach was the highest in the case of EPO-BSPs. Although it was the latest to be introduced to the market, G-CSF-BSP was observed to be most frequently listed in preference to the R-BMP amongst the targeted groups. Table 18 provides more details. Only six formularies listed at least one BSP from all three targeted groups. There were no instances of BSPs being preferred to R-BMPs across all three targeted groups but, at the opposite extreme, there were only two formularies in which R-BMPs were always preferred over BSPs.

[10] Tees and North East Yorkshire NHS Trust was superseded by North Tees and Hartlepool NHS Foundation Trust and Gloucestershire Hospitals NHS Foundation Trust was in the process of developing their formulary.

Table 18-Phase I results summary by group

Investigated Attributes		Medicine Group		
		Filgrastim (G-CSF)	Epoetin alfa (EPO)	Somatropin (HGH)
Molecule being listed				
	Not listed	27 (18%)	31 (21%)	20 (14%)
	Listed as Formulary	115 (79%)	107 (73%)	120 (82%)
	Listed as Non-formulary	4 (3%)	8 (6%)	6 (4%)
	Total	**146**	**146**	**146**
Clear Prescription Restrictions				
	Yes	78 (66%)	77 (67%)	84 (67%)
	No	41 (34%)	38 (33%)	42 (33%)
	Total	**119**	**115**	**126**
Listing approach				
	INN name	58 (49%)	44 (38%)	64 (51%)
	Brand names	49 (41%)	60 (52%)	59 (47%)
	Mixed Listing	12 (10%)	11 (10%)	3 (2%)
	Total	**119**	**115**	**126**
Listed Brands				
	Both	36 (59%)	21 (30%)	25 (40%)
	R-BMP Only	11 (18%)	48 (68%)	4 (7%)
	BSPs Only	14 (23%)	2 (3%)	33 (53%)
	Total	**61**	**71**	**62**
Preferred Type				
	R-BMP	10 (16%)	52 (73%)	29 (47%)
	BSPs	30 (49%)	4 (6%)	7 (11%)
	Unclear	21 (34%)	15 (21%)	26 (42%)
	Total	**61**	**71**	**62**
Specified Brand of Choice				
	Yes	13 (21%)	4 (6%)	9 (15%)
	No	48 (79%)	67 (94%)	53 (85%)
	Total	**61**	**71**	**62**
Special Population Considerations				
	Yes	3 (5%)	8 (11%)	10 (16%)
	No	58 (95%)	63 (89%)	52 (84%)
	Total	**61**	**71**	**62**
Special Indication Considerations				
	Yes	9 (15%)	7 (10%)	0 (0%)
	No	52 (85%)	64 (90%)	62 (100%)
	Total	**61**	**71**	**62**

***** Factors related to patient population or indication that might affect prescriber brand/product of choice.
BSP: Biosimilar medicinal product; **EPO:** Recombinant human erythropoietin (epoetin), **G-CSF:** Granulocyte-colony stimulating factor (filgrastim), **HGH:** Human growth hormone (somatropin), **INN:** International non-proprietary name (molecular name); **R-BMP:** Reference biological medicinal product

4.2.2. Phase II

4.2.2.1. Formulary screening results

In Phase II, it was possible to retrieve all medicines' formularies referred to by all Acute Trust and Health Boards in GB. In total, there were 149 medicines' formularies: 10 in Scotland, 132 in England and 7 in Wales. Out of the 149 obtained formularies, 143 (96%) listed IFX, out of which 54 (38%) did not specify or mention a brand name, 9 (6%) formularies listed IFX-BSP only, 34 (24%) formularies listed R-BMP only and 46 (32%) listed both. In addressing prescribing practice, switching or initiating, it was found that 23 formularies differentiate between IFX-established patients and IFX-naïve patients; these formularies had recommended R-BMP for the former and the BSP for the latter group of patients. Out of the 23 differentiating formularies, three recommended the switch from the R-BMP to the BSPs. In listing NICE technology appraisals (TAs), for which IFX-BSPs were considered and assessed, TA 329, 375 and 383, it was noticed that gastroenterology related TA, TA 329, was the most frequently listed among the three appraisals.

During the process of assessing the listing status of IFX, it was found that formularies varied in structure and layout; while 129 (87%) were structured in a way that resembled the BNF structure, therapeutic area specific chapters, 20 (13%) followed a simpler and unstructured layout. Table 19 summarises the main findings of Phase II formulary screening.

Table 19-Phase II formularies screening comparison between the countries in Great Britain

	Scotland	England	Wales	Total
Targeted Organisations	14	157*	7	**178**
No. of Formularies	10	132	7	**149**
No. of Joint Formularies	3	68	0	**71**
No. of Structured Formularies	10	113	6	**129**
No. of Non-structured Formularies	0	19	1	**20**
Listing Infliximab	8	128	7	**143 (100%)**
Not Listing Infliximab	2	4	0	**6 (4.2%)**
List/Mention IFX-BSPs †	6	44	5	**55 (38.5%)**
List IFX-BSP Brand(s)	6†	42	5	**53 (37.1%)**
List IFX-R-BMP Brand	4	69	7	**80 (55.9%)**
List IFX-BSPs inclusive NICE TAs (Gastroenterology) ‡	3	77	6	**86 (60.1%)**
List IFX-BSPs inclusive NICE TAs (Rheumatology) §‖	0	31	6	**37 (25.9%)**
BSPs relevant educational/informative materials	2	23	6	**31 (21.7%)**
Distinguish Between Established and New Patients	4	17	2	**23 (16.1%)**
Allow Switching of Established Patients	0	3	0	**3 (2.1%)**

***** Including dissolved and merged Acute Trusts

†Some formularies listed/mentioned IFX-BSP without brand specification, or listed without specifying chapter, indication or disease area. IFX-BSP was mentioned as a bullet point within the formulary update

‡ NICE TA 329: Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262) (The National Institute for Health and Care Excellence (NICE), 2015c)

§ NICE TA 375: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (The National Institute for Health and Care Excellence (NICE), 2016a)

‖ NICE TA 383: TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (The National Institute for Health and Care Excellence (NICE), 2016c)

Given that Phase II aimed to assess uptake of IFX (R-BMP and BSP), which is indicated in three different therapeutic areas, dermatology, gastroenterology and rheumatology, having 87% of formularies following therapeutic areas based structure and layout structured based allowed for the comparison of IFX-BSP uptake between these therapeutic areas. While IFX is indicated in all targeted therapeutic areas, it varied in listing frequencies with the dermatology listing IFX least frequently and rheumatology most frequently listed.

Categorising formularies according to the preferred product/brand for prescribing and utilisation was not a straightforward process; this was especially difficult in cases of formularies that distinguished between two groups of patients, with the recommendation of IFX-BSP for IFX-naïve and IFX-R-BMP for established patients. Therefore, classification of medicines' formularies was based on one or more of the following criteria: (*i*) listing one brand/product only, (*ii*) listing one product/brand as formulary while the other is listed as non-formulary, (*iii*) stating clearly that a given product/brand is the first/preferred choice, (*iv*) encouraging switchover from one brand/product to another and (*v*) recommending one product/brand for new patients or new incidents of care. Based on that classification, it was noticed that, despite the fact that IFX-BSP was not tested in gastroenterology indication (European Medicines Agency (EMA), 2013), gastroenterology achieved the highest preference percentage (37.5%) of IFX-BSPs in comparison to the other two therapeutic areas.

Table 20 represents the comparison between the targeted therapeutic areas for structured formularies, and Table 21 represents data related to unstructured formularies.

Table 20-Phase II structured formularies results-comparison between targeted therapeutic areas

Investigated Attributes		BNF Chapter		
		Gastro-intestinal system (1.5.3)	Musculoskeletal and joint diseases (10.1.3)	Skin (13.5.3)
Molecule being listed				
	Not listed	15 (11.6%)	8 (6.2%)	30 (23.3%)
	Listed as Formulary	111 (86.0%)	119 (92.2%)	94 (72.9%)
	Listed as Non-formulary	3 (2.3%)	2 (1.6%)	4 (3.1%)
	Total	**129**	**129**	**129**
Clear Prescription Restrictions				
	Yes	83 (72.8%)	88 (72.7%)	71 (71.7%)
	No	31 (27.2%)	33 (27.3%)	28 (28.3%)
	Total	**114**	**121**	**99**
Listing approach				
	INN name	58 (50.9%)	55 (45.5%)	51 (51.5%)
	Brand names	48 (42.1%)	53 (43.8%)	44 (44.4%)
	Mixed Listing	8 (7.0%)	13 (10.7%)	4 (4.0%)
	Total	**114**	**121**	**99**
Listed Brands				
	Both	30 (53.6%)	27 (40.9%)	21 (43.8%)
	R-BMP Only	20 (35.7%)	29 (43.9%)	24 (50.0%)
	BSPs Only	6 (10.7%)	10 (15.2%)	3 (6.30%)
	Total	**56**	**66**	**48**
Distinguish between established and new patients				
	Yes	17	16	11
Preferred Type				
	R-BMP	19 (33.9%)	28 (42.4%)	24 (50.0%)
	BSPs	21 (37.5%)	22* (33.3%)	13 (27.1%)
	Unclear	16 (28.6%)	17 (25.8%)	11 (22.9%)
	Total	**56**	**66**	**48**
Allow Switching of Established Patients				
	Yes	1	2*	1

***** One formulary listed IFX-BSP without brand specification and recommended switching from R-BMP to BSP

BSP: Biosimilar medicinal product; **INN:** International non-proprietary name (molecular name); **R-BMP:** Reference biological medicinal product

Table 21-Phase II results of screening unstructured local medicines formularies

Assessment Criteria	No.	Assessment Criteria	No.
Molecule being listed		**Listing approach**	
Not listed	1	*INN name*	10
Listed as Formulary	19	*Brand names*	3
Listed as Non-formulary	0	*Mixed Listing*	6
Total	**20**	**Total**	**19**
Listed Brands		**Preferred Type**	
Both	4	*R-BMP*	5
R-BMP Only	5	*BSPs*	2
BSPs Only	0	*Unclear*	2
Total	**9**	**Total**	**9**
Clear Prescription Restrictions		**Distinguish between established and new patients**	
Yes	7	*Yes*	**2**
No	12	**Allow Switching of Established Patients**	
Total	**19**	*Yes*	**1**

4.2.2.2. Medicine Optimisation Dashboard (MODB) results

Descriptive analysis data

In assessing Acute Trusts' prescribing practice of IFX-BSPs, 44 (31%) of included Acute Trusts switched their IFX-stabilised patients to the BSP in Q3-2015, the very next quarter of IFX-BSPs market launch. It was noticed that while 84 (59%) of Acute Trusts went for switching directly, 39 (27%) of Acute Trusts followed a gradual approach in introducing IFX-BSPs; data suggest that these Trusts started prescribing IFX-BSPs for IFX-naïve patients in one quarter, then changed their practice to switching in the following quarters. Results showed that, with time, Acute Trusts became more accepting of IFX-BSPs, whether in initiating new patients or switching established ones. **Figure 8** represents uptake of IFX-BSPs by Acute Trusts in the period between Q3-2015 to Q3-2016. In comparing Phase II formularies screening data with MODB data, it was noticed that 77 (54%) of included Acute Trusts that were found to be utilising IFX-BSPs, whether for initiating or switching patients, were referring to medicines' formularies in which IFX-BSPs were not listed.

Based on the assumed time period needed to implement the switch, as explained in the Methodology and Methods chapter (**3.2.1.1. Innovation diffusion theory**), the average time needed for an Acute Trust to start switching established patients to IFX-BSP-was (163.5 days) with standard deviation equals to (118.3). In categorising Acute Trusts according to Rogers's classification of innovation adopters, none of the Trusts was categorised as an innovator, while 44 Acute Trusts (31%) were categorised as early adopters of innovation; these Acute Trusts were therefore labelled as early switchers to IFX-BSP, **Figure 9**. The London region had the highest percentage of early switchers, while the Northern region had the lowest. **Table 22** summarises Acute Trusts' categorisations and main characteristics by region in England.

Figure 8-Progress of IFX-BSP uptake by English Acute Trusts

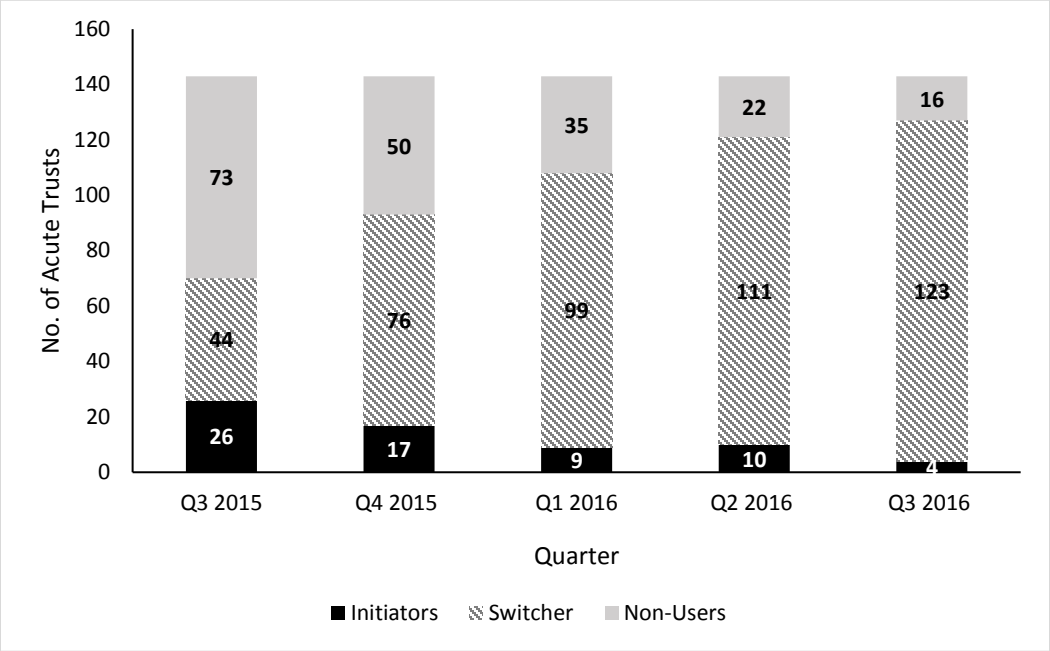
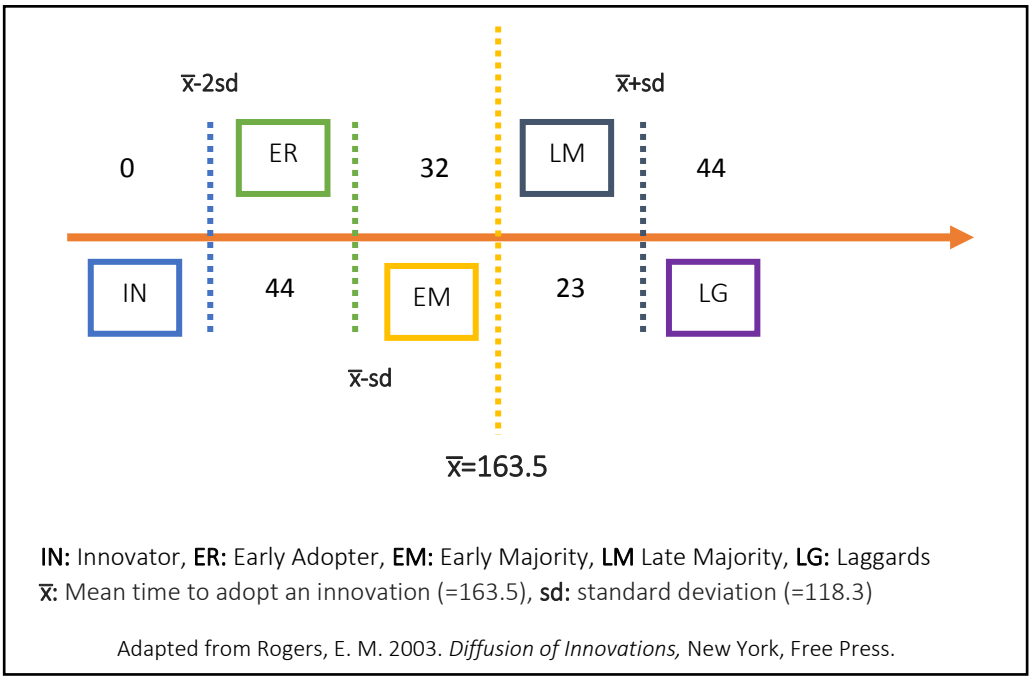


Figure 9-Number of Acute Trusts categorised by Rogers's classification of innovation adopters



IN: Innovator, **ER:** Early Adopter, **EM:** Early Majority, **LM** Late Majority, **LG:** Laggards
x̄: Mean time to adopt an innovation (=163.5), **sd:** standard deviation (=118.3)

Adapted from Rogers, E. M. 2003. *Diffusion of Innovations,* New York, Free Press.

Table 22-Summary of Acute Trust characteristics, prescribing practice and adopter class/by region

	North	Midlands & East	London	South	Total
Acute Trusts (total)	50	45	24	38	**157**
Acute Trusts (Excluded)*	5	3	3	3	**14**
Acute Trusts (included)	45	42	21	35	**143**
Formularies	39†	41	19	29	**128**
Joint Formularies	25 (64.1%)	17 (41.5%)	7 (36.8%)	20 (69%)	**69 (54%)**
Formularies Structured	37 (94.9%)	35 (85.4%)	11 (57.9%)	27 (93.1%)	**110 (85.9%)**
Formularies Listing IFX-BSP	11 (28.2%)	13 (31.7%)	4 (21.1%)	16 (55.2%)	**44 (34.4%)**
Differentiating Formularies ‡	3 (7.7%)	6 (14.6%)	1 (5.3%)	8 (27.6%)	**18 (14.1%)**
Formularies allowing switching	1 (2.6%)	1 (2.4%)	0 (0%)	1 (3.4%)	**3 (2.3%)**
Trusts involved in a joint formulary committee §	17 (37.8%)	7 (16.7%)	8 (38.1%)	11 (31.4%)	**43 (30.1%)**
Trusts Refer to IFX-BSP listing formulary ¶	15 (33.3%)	14 (33.3%)	4 (19.0%)	22 (62.3%)	**55 (38.5%)**
Trusts refer to Distinguishing formulary	3 (6.7%)	6 (14.3%)	1 (4.8%)	10 (28.6%)	**20 (14%)**
Trusts to formulary allows switching**	1 (2.2%)	1 (2.4%)	0 (0.0%)	1 (2.9%)	**3 (2.1%)**
Innovators	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
Early adopters (Early switchers)	6 (13.3%)	12 (28.6%)	11 (52.4%)	15 (42.9%)	**44 (30.8%)**
Early majority	7 (15.6%)	9 (21.4%)	5 (23.8%)	11 (31.4%)	**32 (22.4%)**
Late majority	11 (24.4%)	6 (14.3%)	0 (0.0%)	6 (17.1%)	**23 (16.1%)**
Laggard	21 (46.7%)	15 (35.7%)	5 (23.8%)	3 (8.6%)	**44 (30.8%)**

* Number of Acute Trusts that were excluded from analysis due to the specialisation of their services, as explained earlier in the methodology chapter, Chapter 3

†A Northern Acute Trust refers to a Scottish medicines formularies

‡ Formularies that differentiate between IFX-naïve patients (new starters) and IFX-established patients (stabilised)

§ Acute Trusts that were involved in regional/joint formulary committee whether or not having their own specific formulary

¶ Acute Trusts that referred to medicines formularies in which IFX-BSP(s) was/were listed in

** Acute Trusts that referred to medicines formularies that recommend and encourage switching stabilised patients to IFX-BSP

Inferential analysis results

The inferential analysis model revealed that there were two factors significantly associated with a Trust status of being an early switcher to the IFX-BSP: referring to formulary that listed/mentioned IFX-BSP (Odd Ratio (OR) =2.8, 95% Confidence Interval (CI): 1.08-7.26), and being located in the Northern region of England (OR=0.24, 95% CI: 0.08-0.77). While referring to IFX-BSP listing formularies increased the likelihood of a Trust to switch to IFX-BSPs in Q3-2015 ((probability value) *p*=0.03), being in the Northern region meant that Acute Trusts were 76% less likely to switch to IFX-BSPs in comparison to their southern counterpart (*p*=0.02). Other variables were found not to have significant association with the Acute Trust's willingness to switch to switch IFX-BSP. Table 23shows regression model output.

Table 23-Logistic regression outputs

Early Adopter (n=143)	OR (SE)	(95% CI)
Educational Trust	1.35 (0.58)	(0.58-3.15)
Foundation Trust	1.18 (0.51)	(0.51-2.75)
Involved in joint formulary	0.64 (0.28)	(0.27-1.51)
IFX-BSP listed in the formulary	2.80 (1.36)*	(1.08-7.26)
Formulary allows switching	1 (omitted†)	
Formulary distinguish between patients	1.63 (0.83)	(0.60-4.44)
London	2.14 (1.42)	(0.58-7.86)
Midlands	0.66 (0.34)	(0.24-1.82)
North	0.24 (0.14)*	(0.08-0.77)
South	Reference category	
_cons	0.31 (0.23)	(0.07-1.32)

* *P value < 0.05*

† Omitted due to collinearity with other variables, its omission would not affect model

CI: Confidence Interval, **N:** number, **OR:** Odd ration, ***p*:** probability value, **SE:** Standard Error

4.3. Discussion

In this study, the formulary uptake of four BSPs groups, EPO-BSP, G-CSF-BSP, HGH-BSP and IFX-BSP, was used as an indicator of BSPs integration in GB medicines formularies, which is, as discussed earlier, an outcome of implementing an intervention. In general, the uptake of BSPs by British local formularies was less than could be predicted from a classical generically driven market for medicines. The two phases of this study showed a varied formulary uptake of targeted BSPs between different therapeutic areas. Variations were not limited to therapeutic areas, but were also observed between countries within GB. Although both the Scottish Medicines Consortium and the All Wales Medicines Strategy Group have been actively involved in evaluating BSPs (Scottish Medicines Consortium (SMC), 2015a, All Wales Medicines Strategy Group (AWMSG), 2013), Scottish and Welsh formularies were less likely to list BSPs in preference to the R-BMP compared with their English counterparts.

While the most frequently listed BSP, was the first licensed and authorised BSP, HGH-BSP (Committee for Proprietary Medicinal Products (CPMP), 2003), the maximum preference for BSPs over R-BMP was achieved by G-CSF-BSPs. On the other hand, brand name-based listing was more frequent in the case of EPO-BSP. The duration of market availability was not translated into higher formulary uptake; this was evident in the case of G-CSF-BSP, which achieved higher preference and listing frequencies in comparison to the earlier authorised BSPs, HGH and EPO-BSP (European Medicines Agency (EMA), 2017c). The same observation was

noticed in the case of IFX-BSP which, despite being authorised six years after EPO-BSP, achieved a comparable listing rate to EPO-BSP, which was authorised six years earlier (European Medicines Agency (EMA), 2017c). In comparing listing status, frequencies and preference between targeted BSPs and their R-BMP counterparts, it was not possible to gain a complete understanding of the variations between targeted groups from the available data. However, it might be broadly explained by factors related to the molecular nature, therapy duration, patients' demographics, preferences and life style and/or available guidelines and guidance.

Having several other BMPs within the same group, where each has different dosing frequencies, administration devices and storage conditions, might affect acceptance of BSPs. For example, one HGH product is a needleless device, making it more attractive to paediatric and needle-phobic patients. Another HGH product can be stored out of the refrigerator which often made it the brand of choice for frequent travellers (London New Drugs Group, 2013).

Despite the fact that G-CSF-BSP was the most recently authorised and launched amongst Phase I assessed BSPs, it achieved the highest preference rate. A possible explanation, though, was not evident in the available data. It might be similar to the proposal of Müller et al. and Rickwood and Di Biase regarding G-CSF molecular structure and therapeutic indication. G-CSG is a relatively small, easily characterised and non-glycosylated molecule, which does not trigger immunogenic reaction. Additionally, being indicated for short therapeutic duration might suggest that the possibility of unintended switching is unlikely (Müller et al., 2014, Rickwood and Di Biase, 2013).

Among Phase I and II assessed BSPs, EPO-BSPs were the least preferred. The limited preference of EPO-BSPs could be explained by reported cases of pure red cell aplasia (PRCA) in the preauthorisation clinical trials in chronic kidney disease (CKD) patients, who received the product subcutaneously. This resulted in the authorising of EPO-BSP (Binocrit®) for intravenous administration only, while the R-BMP is authorised for subcutaneous and intravenous administrations (Casadevall et al., 2017, Jelkmann, 2010). The same reason might explain why EPO, as a molecule, achieved the highest brand-name listing, among Phase I targeted BSPs. Following brand name-based listing might be an approach to avoid unintended, or unmanaged switching between different products with different administration route and glycosylation profile. The authorisation status of Binocrit® (EPO-BSP) was changed in April 2016, as the EMA authorised Binocrit® for subcutaneous administration through Type II variation (Althoff and Mohan, 2016). The new authorisation could result in changing the uptake level of EPO-BSPs in the near future.

In the case of IFX-BSP, while the evidence on its safety and efficacy in gastroenterology was extrapolated from rheumatology clinical trials (European Medicines Agency (EMA), 2013), formulary uptake of IFX-BSP in gastroenterology was comparable to that in rheumatology, that is, 36% and 37%; respectively. This observation contradicts what was reported in the literature regarding the effect that the limited evidence and data extrapolation had in terms of creating anxiety and concerns among prescribers and hindering BSPs' utilisation. A possible explanation for the comparable listing frequencies is the position statement of the British Society of Gastroenterologists (BSG) that encouraged the prescription of IFX-BSP for inflammatory bowel disease patients (The British Society of Gastroenterology (BSG), 2016). An additional factor that might positively affect the acceptance of IFX-BSP in gastroenterology is NICE TA 329, which was issued before the rheumatology related TAs, 375 and 383. In TA 329, NICE has positively recommended IFX, including BSPs brands, for ulcerative colitis, which could serve as an assuring sign to the utilisation of IFX-BSPs (The National Institute for Health and Care Excellence (NICE), 2015c). Lastly, NICE has issued a BSP

implementation guide in which it has presented the experience of two Acute Trusts in introducing and switching stabilised gastroenterology patients to IFX-BSPs (The National Institute for Health and Care Excellence (NICE), 2015d). Despite the limited evidence about licensing, sharing positive experience of other centres and prescribers might reassure gastroenterologists regarding the safety and efficacy of IFX-BSPs and encourage them to prescribe it for their patients.

The effect of patient related considerations in terms of indication, age group and established therapy was observed in the case of G-CSF-BSP and IFX-BSP. In the case of G-CSF-BSP, the R-BMP was listed as the preferred product for two main indications, where the BSP was not tested and the evidence was extrapolated to: (*i*) paediatric patients and (*ii*) stem cell mobilisation. In the case of IFX-BSP, the effect of established therapy was observed, as, in some cases, IFX-BSPs was specified for IFX naïve patients in 23% of screened formularies. In these cases, restricting BSPs' prescribing might reflect the effect of limited evidence and clinical data.

Interestingly, results of this study reflected a varied acceptance of BSPs especially in terms of G-CSF. The brand that was approved, based on results of a pharmacokinetics/pharmacodynamics trial in healthy volunteers instead of patients, and in a non-comparative safety-focussed study in patients (Jimenez and Brake, 2011), was recommended for use ahead of G-CSF-R-BMP in more local formularies than was any other BSP/R-BMP pairing. Therefore, this might suggest that decisions about utilising BSPs were not always dependent on available evidence and results of clinical trials

Recommending brand name prescribing might be perceived as introducing new prescribing norms. Formularies are generally considered an influential tool in standardising, promoting and guiding prescribing practice (Gunnarsdottir and Kinnear, 2005, Tan et al., 2004, Petrie and Scott, 1987, Ess et al., 2003); therefore, formularies might have an effect in directing, or reminding, prescribers to prescribe by brand. However, more than one third of local formularies did not specify brand names when listing BMPs in the groups examined in this study. Unintentional switching between brands might affect patients' safety, if not carefully monitored and managed. Such harm might be avoided in the cases of G-CSF and EPO because of their short duration of prescription, but possibly not otherwise for HGH and IFX which are typically used for prolonged periods.

An innovator is described as venturesome when they have a strong drive and the ability to seek innovation, even from resources external to the innovator own cycle (Rogers, 2003). In classifying Acute Trusts according to Rogers's innovation adoption categories, it was not possible to locate any of the Trusts in the innovator category as it is not possible for a Trust to start using a BSP without it is being assessed, approved, licensed and launched, and being available in the Trust's own external environment.

In assessing a Trust's willingness to switch, it was noticed that referring to a formulary that listed IFX-BSP positively drove the Trust to switch established patients. This finding draws attention to the important role formularies can have in guiding the prescribing practice. The same effect of formularies was noticed in controlling and restricting antibiotic utilisation, and in the implementation of an antibiotic stewardship programme (Bassetti et al., 2000, Reynolds et al., 2012). However, this finding needs to be carefully considered and interpreted as there was a time gap of ten months between the starting point of reporting MODB data and the formulary screening process.

Being located in the Northern region was associated with the lower tendency to switch to IFX-BSP in the first quarter after the market launch, compared to the Southern region. It was not possible to explain such an association, but it might be due to the fact that the Northern region has more CCGs and Trusts than the South, which could result in the need for more effort and resources in order to reach an agreement on the switch programme between all involved parties.

Interestingly, indicators related to the governance of Acute Trusts (Foundation Trusts) and complexity (Educational Trusts) did not affect the Trust's willingness to early adopt IFX-BSP into practice, despite the fact that these factors were reported in the literature to act as drivers for innovation adoption (Williams and Brown, 2014).

4.4. Study strengths and limitations

This study relied on publically available and relevant sources of data that are developed, published and referred to by healthcare professionals, who are actively involved in assessing, managing and prescribing these medicines. Moreover, it was possible to classify Trusts according to their prescribing practice to investigate the possibility of an NHS target to switch patients to BSPs within the first year of a market launch, and to identify factors that are associated with the Trust's willingness to switch.

Assessing formulary uptake of BSPs might reflect the degree to which these medicines are integrated and institutionalised in British healthcare settings. Relying on the formularies to estimate utilisation of BSPs might not necessarily provide a highly accurate reflection of BSP prescribing, as it is not known to what degree these lists are adhered to. This was evident in the case of IFX, R-BMP and BSP, as only 50% of Acute Trusts that were classified as early switchers referred to IFX-BSP listing formularies. Additionally, Inflectra ® was listed as the All Wales Contract choice (Abertawe Bro Morgannwg University Health Board Formulary (ABMUHB), 2015), and more than 50% of prescribed IFX were IFX-BSP (The Welsh Analytical Prescribing Support Unit (WAPSU), 2017), although only two health boards preferred BSP over the R-BMP.

Data and figures reported by MODB and NHS-Digital are generally considered to be collected by robust research and data collection methods. Nevertheless, relying on these sources might be problematic and misleading, due to the fact that these data represent purchasing data. Accordingly, there is a possibility that the actual utilisation did not occur in the same quarter as purchasing.

Furthermore, categorising Acute Trusts according to Rogers's model of innovation was based on the time needed to start switching; however, it did not address the efforts and resources needed to plan and agree on the switching programme between different stakeholders, whether internally within the Trust or externally between the Trusts and their local commissioners (CCGs).

4.5. Conclusion

Research data and analysis indicate that some formularies encourage BSP prescribing. However, variations and lack of specificity in some formularies may suggest a vague understanding of the concept and nature of BMPs in general, and BSPs in particular, by the professionals involved in developing local formularies.

If equally safe and effective as the originator BMP, lower prices for BSPs could potentially increase access to treatment for more patients, or reduce drug spending in an increasingly constrained financial environment. However, as highlighted by NICE (The National Institute for Health and Care Excellence (NICE), 2015d), the introduction of these medicines requires a collaborative effort between involved organisations (Trusts and commissioners) and active interactions between different stakeholders.

This study has provided a proxy of the utilisation of BSPs in GB; however, it has also highlighted that there are regional variations in the utilisation of these medicines that need to be investigated and addressed. Notwithstanding this situation, it was not possible to explain observed variations and predict factors that led to achieved uptake levels. Therefore, an explanatory study is needed.

Chapter Five: Factors Affecting Decision of Adopting Infliximab Biosimilars in England-Qualitative Study

"Truth is individualistic…" ***Friedrich Nietzsche***

5.1. Introduction

In the previous chapter, the quantitative study was able to report current listing status and frequencies of available BSPs in Great Britain's local medicines formularies. The study also assessed and categorised English Acute Trusts according to their utilisation pattern of IFX-BSPs using data and purchase figures reported by the MODB and NHS-Digital. However, the study's findings did not provide an explanation for the observed variations in utilising BSPs, especially in the case of IFX-BSPs.

In its guidelines on the management of local medicines formularies, NICE has described the process of developing and managing local medicines formularies as the output of collaboration, interactions and agreements between relevant stakeholders locally. Additionally, NICE has explained how the implementation of IFX-BSP was driven by the input of relevant stakeholders at Acute Trusts and Clinical Commissioning Groups (CCGs) (The National Institute for Health and Care Excellence (NICE), 2015a, The National Institute for Health and Care Excellence (NICE), 2015d). Therefore, it is safe to assume that the observed variations between local economies might reflect different local interactions and dynamics between relevant stakeholders

This chapter represents results and findings of the explanatory component, the qualitative study. The study is based on 59 semi-structured interviews (54 were over-the-telephone and 5 interviews were face-to-face). Interviews targeted professionals who were involved in commissioning, assessing, managing and prescribing BSPs. The rationale for selecting targeted sites and participants was based on the quantitative study's results, NICE guidelines on local formularies, and the NICE IFX-BSPs implementation guide (The National Institute for Health and Care Excellence (NICE), 2015a, The National Institute for Health and Care Excellence (NICE), 2015d). Details of participants' selection criteria and recruitment, study conduct and analysis were provided in the Methodology and Methods Chapter (3.6. Qualitative method).

5.2. Study results

Broadly, the process that led to the adoption and the implementation of BSPs at English clinical settings as reported by research percipients, together with the factors that affected those processes, are grouped into four substantive themes: (*i*) knowledge, (*ii*) persuasion, (*iii)* decision and (*iv*) implementation process and outcomes. Two integrative (overlapped) themes were also included: (*i*) structure and (*ii*) communication.

In addition to its role in guiding data analysis and clustering codes into themes, Rogers's theory aided in classifying involved professionals into three main categories: (*i*) change agents (mainly commissioners and high cost medicines pharmacists), (*ii*) mediators (hospital based and formulary pharmacists) and (*iii*) adopters (prescribers, specialist nurses and patients). However, it was noticed that adopters, mainly prescribers, experienced a shift in their roles and became change agents during their communications with patients. Although almost all participants, whether change agents, mediators or adopters, discussed aspects related to all themes, it was noticed that different roles had different focuses and degrees of involvement. While the majority of commissioners and high cost medicines pharmacists focused their discussions on decision steps, prescribers discussed evidence, compatibility and patients' management in greater details. On the other hand, pharmacists were interested in all aspects, especially negotiations with commissioners, implementation management and communications with clinical teams; they focused less than prescribers on patients' communication. These observations might be related to differences in professional roles and expected deliverables. However, the study design in terms of interview guide might have also played a part; as each role had

its role-specific interview guide, which might result in directing discussions during interviews toward different dimensions, thereby hindering the exploration of other relevant aspects.

The following sections explain and present the process through which BSPs were assessed, introduced and managed in healthcare settings.

5.3. Themes one: Knowledge and awareness

Knowledge is the first step in the process of adopting an innovation or a new technology. Knowledge ensures that potential adopters are aware of the innovation's existence, understand its technical aspects and know to implement it In his theory, Rogers has classified knowledge into three main types: (*i*) awareness, (*ii*) principle knowledge and (*iii*) knowhow knowledge (Rogers, 2003). During interviews, participants had discussed aspects related to the three types of knowledge.

5.3.1. Awareness and market updates

Awareness is essential to initiate the adoption process, and it mediates and triggers the other two types of knowledge. Awareness knowledge could be acquired through active or passive approaches, or a combination of both. Individual's characteristics and role requirements might prompt their involvement in seeking knowledge and updates related to potential innovations (Rogers, 2003).

In the case of BSPs, awareness was in the form of keeping up with market updates in terms of new market entries and new NICE technology appraisals and clinical guidelines. Commissioners and high cost medicines pharmacists (change agents) had discussed how routine horizon scanning activities, which are the expected deliverables of their roles, had helped them in keeping a vigilant eye on market dynamics. Several resources were referred to for horizon scanning; the most frequently reported was the United Kingdom medicines information network (UKmi) prescribing outlook. Other resources were regional network/groups, which are actively involved in disseminating updates related to market entries and medical practice. Participants had explained how awareness of market dynamics had triggered planning for future contracts, negotiations, utilisation and, in some cases, formularies applications.

> *"We tend to look at the EMA, and new drugs online and things like that, and just keep an eye on who is coming to market when and we also get sort of that regional information is to, you know, things like biosimilars etc. as well so that we're not just looking at it at an individual level, we're looking at what NICE is coming up with, or what NICE might be looking at in the next year, what is going to be newly licensed, so we do that as a routine, but for any drug" (**MRCP-05**) (**Commissioner Pharmacist**)*

> *"Generally we do an annual budget which starts in about January, and as part of that we use the UKmi, or what's called prescribing outlook. Their horizon scanning document which go through and normally that would give you the information certainly about biosimilars coming through, and the other thing we do is we do is have a bit of an awareness of what drugs we think will be coming to market when, so obviously we know that rituximab is on its way or we know that adalimumab will be tumbling in. Everybody is looking to see when that will be coming along. So there is a general awareness of it…Well we do research organised TAs and clinical guidelines. We have a NICE planning and assurance group it is called for the whole of Devon, in which we look at NICE guidelines and make sure we are not missing any as they come through…So we kind of do the horizon scanning work and then we*

> *would bring the proposal usually to the formulary group" (**LSCP-15**) (**Interface Pharmacist**)*

Awareness of market updates was not limited to knowing which BSPs are available, but, in some occasions, participants were aware of licensing conditions and actual manufacturers. Research participants were aware of the fact that the available IFX-BSPs, at the time of this research, were two brands of the same molecule, manufactured by the same manufacturer and marketed by two different marketeers. On the other hand, some participants knew that due to marketing exclusivity rights, etanercept-BSP was not licensed for paediatric indications.

> *"Yeah, they (IFX-BSPs) are made at the same factory, yeah. We did hear that at the regional procurement group. Because there is the only ... there is one manufacturer, is not it? In South Korea, there are just literally brands, products with different names. So, yeah, we did know.*
> *But it is quite funny, because we switched from ... So, first time we switch to Inflectra and then we switched to Remsima® and the Inflectra ® rep came around and said: You know, oh, you do not want to do another switch do you? But we are going to switch anyway, because we know it is the same product from the same factory, But you know. Sometime they like to keep things to themselves. But, you know, it is quite an interesting thing to know, but yes we did know that" **(PDFP-03) (E-Prescribing Pharmacist)***

The role of awareness knowledge in changing prescribing practice and reviewing and updating local medicines formularies in the UK was also reported and confirmed in the literature (Reynolds et al., 2012). Awareness knowledge is not enough for getting an innovation adopted, other types of knowledge that explain "what it is" (principle knowledge) and "how to use it" (knowhow knowledge) are still needed to influence the accepting or rejecting of an innovation (Rogers, 2003).

5.3.2. Principle knowledge

Principle knowledge is concerned with understanding the fundamentals of an innovation and the science behind its creation and functions (Rogers, 2003). In the literature, prescribers' limited or basic understanding of the BSPs' concept, manufacturing and licensing was a frequently reported observation. Therefore, one the first questions participants, including prescribers, were asked was regarding their understanding of BSPs. The way in which participants expressed their understanding of BSPs was checked against aspects derived from the EMA BSPs' definition and what was reported in previous studies that assessed prescribers' understanding of BSPs. Aspects of the BSP definition were: (*i*) similarity concept, (*ii*) licensing process, (*iii*) biological variations and (*iv*) manufacturing process.

Participating prescribers showed understanding and knowledge of the similarity concept, evidence extrapolation and manufacturing process. Prescribers linked their understanding of BSPs with their awareness of biological variations and their experience with the R-BMP. Moreover, they acknowledged the uncertainty associated with BSPs and available evidence. Similar to prescribers (adopters), commissioner and Trusts-based pharmacists (change agents) showed understanding of BSPs, the concept of similarity, manufacturing and licensing processes.

> *"I understand that they are similar, not identical. But having said that, the way batches of current biological drugs are being made, there is always going to be a potential…you potentially get some genetic variation between the different batches anyway. So, I kind of understand that they are not identical but that is to in terms of purposes, and certainly the ones that we are potentially get into use it seems to behave in a very similar way, and I'm happy with the knowledge that they are similar enough that we wouldn't anticipate any particular differences in terms of efficacy or in terms of side effects…I am also aware that we can't absolutely predict, we cannot be absolutely certain there may be some longer terms problems that we are not yet aware of which can happen with any drug, any biologic. So, I understand all of that…that is kind of some factual basics about what I know about them. In terms of what I think about them, that is an interesting one"* ***(SORP-02) (Rheumatology Consultant)***

> *"Well I know quite a lot about them.., I yeah, essentially I know them, I understand them very well in terms of, you know, what they are, what they are not, how they are made, the issues around extrapolation, similarity, how much it is... how close they have to be etc., etc."* ***(JKFP-11) (Clinical Lead pharmacist)***

In addition to their own understanding of BSP concepts, discussions involved participants' perceptions toward other stakeholders' understanding of BSPs. In this case, participants had reported mixed accounts about the degree of other professionals' understanding of the similarity concept and their ability to handle available evidence on BSPs' quality, safety and efficacy.

In discussing adopters' knowledge, there was a consensus regarding adopters' understanding of BSPs. In some cases, participants believed that prescribers were qualified enough and had sufficient levels of awareness to facilitate their engagement and enable them to assess available evidence; some even believed that adopters did not need any specific training about BSPs. However, variations were observed among participants, whether prescribers or non-prescribers, perceptions regarding change agents, mainly commissioners, understanding of BSPs and ability to handle available evidence. While, some participants had positive perceptions toward knowledge of involved commissioners, especially that most of them are pharmacists, others had questioned commissioners' ability to assess available evidence on BSPs' safety and efficacy.

> *"No, no, there's no need for any training. You mainly need to persuade them (nurses) that these are the same. They often act as the patient's advocate and have the most to do with the patients…So there is no need for any training other than the training you get to do this in the first place as a nurse"* ***(PDFP-17) (Head of Pharmacy & Quality Control Laboratory Services)***

> *"No, I don't, commissioners…Well it depends what sort of commissioner it is. If they are from a pharmacy background they probably would do (have sufficient knowledge) but they are advised by the clinical staff so we, the pharmacists would advise them"* ***(SMFP-06) (Chief Pharmacist & Clinical Director for Medicines Management)***

> *"Commissioners? No. I find commissioners rely heavily on clinicians, and in this instance, I would be pleased to tell them... at the ones in Nottingham, the ones that I have worked with, they tend to rely often on you…They would not know much about how many RCTs are there in BSPs in IBD, who is leading this nationally. They rely on you, to actually tell them why you are switching, is the drug actually effective, what is the background data, and in this case it is OK, financially why you are doing it"* ***(GMGP-03) (Academic Gastroenterology Consultant)***

While there was a general trust in the knowledge and competence of involved stakeholders with clinical backgrounds, knowledge of involved non-clinical professionals, such as financial managers and non-clinical commissioners, was questioned by some participants. Nevertheless, the impact of limited knowledge, or lack of knowledge, of these professionals was perceived to be minimal as they are not actively involved in assessing or prescribing BSPs

> *"No, I don't think they (financial managers) do, they do not understand what they (BSPs) are at all, but they do understand when clinicians are happy to use such products. If it comes along with significant cost-savings then they're happy to support negotiations but I don't think they really understand what a biosimilar is"* ***(MSFP-04) (Senior Pharmacist-Medicines Information, Formulary & Clinical Economy)***

> *No, I don't think our finance department really have any influence over whether we do switch or not. Mainly, it's clinician and pharmacy led"* ***(MSFP-05) (Head of Medicines Management)***

While awareness knowledge triggers the dissemination-diffusion process, principle knowledge enables adopters to assess the innovation, understand it and then utilise it. The influential role of principle knowledge was noticed among prescribers in the United States, where BSPs' market is relatively new, as more knowledgeable prescribers were more accepting and willing to prescribe BSPs (Cohen et al., 2016). Interventions aimed at improving the principle knowledge of prescribers had positively contributed to increasing the utilisation rate of EPO-BSPs at an Italian oncology unit (Perfetti et al., 2015a). Similar to this study's findings, variations in knowledge between different professional roles were also observed in a recent Irish study, where pharmacists and specialists were reported to have deeper and better understanding of BSPs than general prescribers(O'callaghan et al., 2017). Perceived knowledge of others was important in understanding what affected the communications between CCGs and Trusts. What was considered necessary in order to improve some professionals' understanding of BSPs; was any training needed and who was involved in providing and leading educational interventions?

5.3.3. Knowhow knowledge (how-to-knowledge)

The last type of knowledge is the knowhow knowledge. This kind of knowledge is directive in nature rather than informative; it explains what is needed to implement the innovation. Knowhow knowledge allows adopters to assess early on the complexity of the innovation and to decide if they are willing to adopt the innovation and how to proceed with the implementation process. In the case of adopting BSPs and switching stabilised patients, the knowhow was in the form of the NICE IFX-BSPs implementation guide (The National Institute for Health and Care Excellence (NICE), 2015d). In discussing the NICE implementation guide, based mainly on Southampton's experience, it was noticed that almost half of the participants who were asked about the guide were not aware of it and were not familiar with the reported experiences. Among participants who reported they were familiar with the guide, commissioner and Trusts based pharmacists were more familiar with the experience than the

adopters (prescribers and specialist nurses); moreover, it was noticed that the most familiar adopters were gastroenterologists.

In discussing NICE implementation guide, participants had varying accounts regarding the importance and relevance of the reported experiences. For some sites, the guide helped in identifying factors for successful implementation of the switch in terms of interactions with main stakeholders and resources needed to be secured. On the other hand, other participants thought that it was not possible to follow that guide due to issues related to negotiations and discussions between Trusts and CCGs, service size and prescribers' resistance.

> *"Because of the Southampton project, as I said, it was like a pilot site to sort of lead the way to see what it is needed to be done. But it has uncovered, you know, quite...there is quite a lot of things, steps, that need to be put into place to do this safely, be it that, certainly our gastroenterologists want to... It is where to start with this, because it is a number of steps with the switching…. For me, it is not actually the clinicians are a problem with all of this, with the using BSPs, it is the CCG and it is the Trust's management of it, because the Southampton pilot showed that there was quite a lot of implementation for the Trust to do, you know, to get it all working and happening and that required some sort of reimbursement and that is where the term, when you then see this benefit share coming in"* ***(NBCP-02) (Senior Prescribing Advisor)***

> *"But they (at Southampton) have less numbers than we do. Our service is about twice the size of Southampton and they only did it on gastroenterology; their rheumatology department hasn't actually done anything. So, they have actually implemented it in one area, whereas we are trying to do it across all areas at the same time, which is a lot harder"* ***(VRFP-15) (Specialist Clinical Pharmacist-Specialist Medicine)***

> *"My understanding, they just did a wholesale switch straightaway, didn't they? It seemed to be a very rapid uptake, I am not sure that the clinicians will be happy to do that, I think it would be more of a gradual uptake so that they can monitor the first couple of patients, make sure that they are happy with how the drugs are working. I would think, they would do slower uptake more gradual, but it depends on how the contract teams and finance teams are pushing them to make the savings I suppose"* ***(ERCP-08) (Senior Medicines Optimisation Pharmacist)***

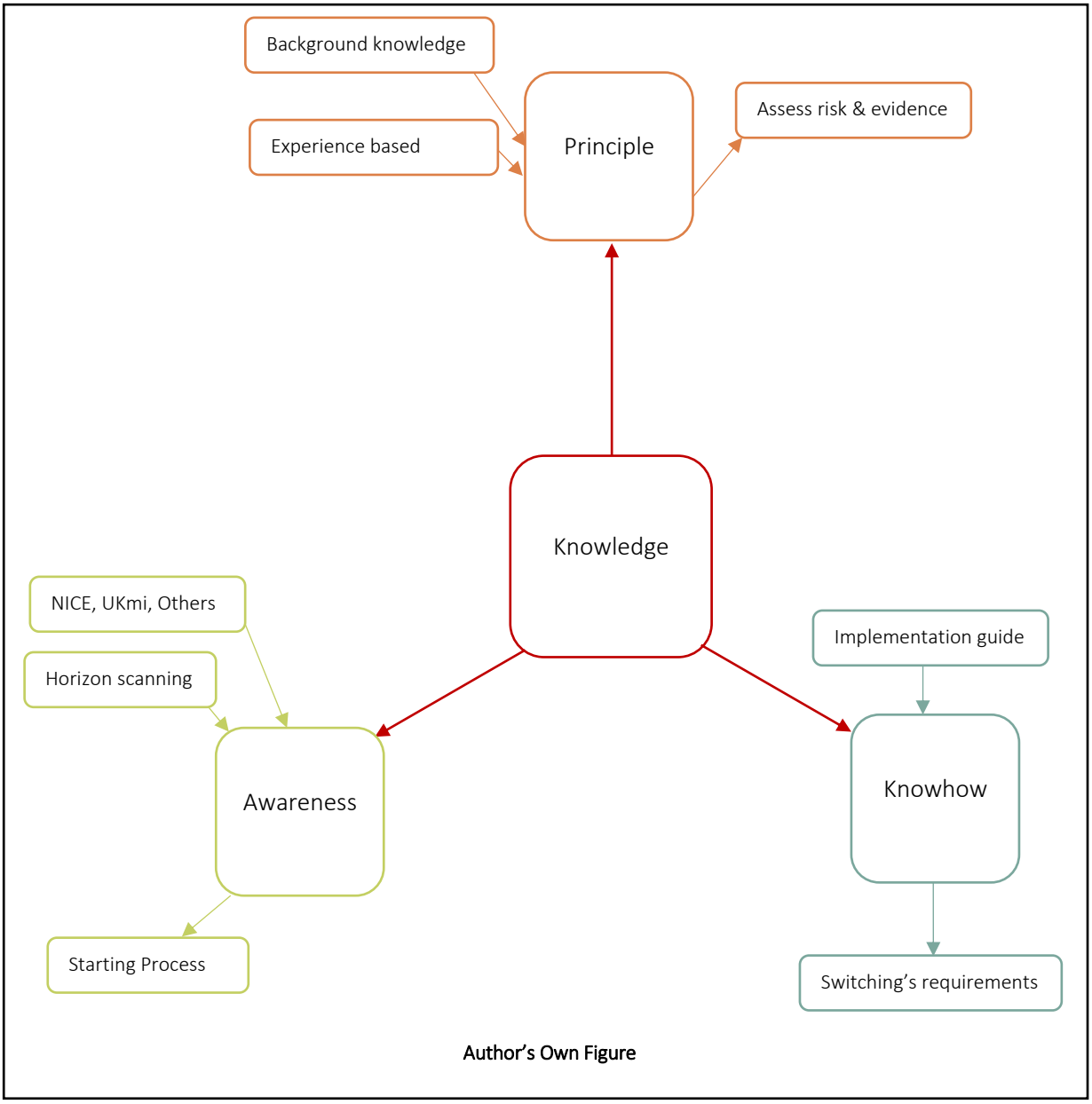
As change agents are expected to promote the innovation and facilitate its adoption (Rogers, 2003), it is reasonable to have pharmacists (commissioners and Trusts based pharmacists) to be more aware and familiar with the implementation guide than the prescribers (adopters). On the other hand, the fact that the two featured experiences were gastroenterology related might explain the reason why gastroenterology prescribers were more familiar than other targeted specialities. For the implementation guide not to be known by almost 50% of the participants might reflect that the guide was not sufficiently or widely promoted by NICE. Lastly, the effect of site specific arrangements and service layouts on hindering sites' ability to follow the implementation guide, echoed what Kneale et al. (2017) reported in their recent systematic review. They found that decision makers in local public health authorities in England perceived national guidelines and advice to have limited influence as these guidelines failed to address the special nature of their localities (Kneale et al., 2017).

5.3.4. Knowledge themes summary

In summary, the three types of knowledge feed into the subsequent step of persuasion, in terms of assessing BSPs and switching's attributes. Awareness of new market entries of BSPs and offered prices by their suppliers makes stakeholders, whether change agents or adopters, consider the possibility of sourcing and utilising cheaper products. Principle knowledge enables stakeholders to assess evidence and potential risks that might be associated with switching stabilised patients. Lastly, knowhow acts as a guiding tool on how to implement and what to consider in negotiations between adopters and change agents. **Figure 10** summarised the knowledge themes and shows how each type in reflected in the subsequent step.

Although knowledge triggers the innovation diffusion process, its effect is not limited to the early stages of the process, but it continuously evolves and takes different manifestations in the subsequent steps; mainly in the form of growing familiarity, together with a growing body of evidence and published literature.

Figure 10-Knowledge theme summary



Author's Own Figure

5.4. Theme two: Persuasion

Following the primary awareness and knowledge stage, comes the second and most important step in adopting an innovation: the persuasion stage. At the persuasion stage it became clear that the central phenomenon of interest was not the BSP itself, but it was the concept of switching stabilised patients. Persuasion ends up with the potential adopters forming either positive or negative attitudes toward the innovation under consideration (Rogers, 2003). Attitude is defined as "expressing the degree of like or dislike of something, which might affect the tendency or behaviour" (Murshid and Mohaidin, 2017). Liking (accepting), disliking (rejecting) and an innovation's adoption rate are based on how potential adopters understand, assess and evaluate the innovation's main characteristics (attributes) (Rogers, 2003).

Assessing switching and BSPs' attributes had served two main aims: (*i*) motivating relevant stakeholders and organisations to adopt and integrate BSPs and (*ii*) planning the switch process. Attributes assessment was later reflected during negotiations between the service providers (Acute Trusts) and commissioners (CCGs) and was actualised in introducing BSPs and implementing the switch; in other words, related attributes were, whenever possible, practically actualised.

5.4.1. Biosimilars and switching attributes

An innovation's attributes are the core elements of the diffusion process, as their assessment is influenced by the knowledge stage, subjected to contextual factors and dynamics and is reflected during the implementation stage (Rogers, 2003, Frambach and Schillewaert, 2002). In his theory, Rogers identified five main attributes (*i*) relative advantages, (*ii*) complexity, (*iii*) compatibility, (*iv*) observability and (*v*) trialability (Rogers, 2003). Nevertheless, other attributes have been proposed to affect diffusion of an innovation within healthcare settings; these attributes include: (*i*) associated risk, (*ii*) fuzzy boundaries, (*iii*) task's issues, (*iv*) evidence strength and quality, (*v*) uncertainties, (*vi*) cost and g) innovation's design quality and packaging (Greenhalgh et al., 2004, Frambach and Schillewaert, 2002, Damschroder et al., 2009). In this research, as it is advisable to maintain reasonable (manageable) numbers of criteria (attributes), in order to avoid redundancy (Baltussen and Niessen, 2006), BSPs and switching attributes were grouped into: (*i*) relative advantages, (*ii*) risk complexity, (*iii*) practical complexity, (*iv*) compatibility and (*v*) observability. However, in order to address the special nature of healthcare settings, other proposed attributes by other scholars were considered as dimensions of Rogers's main innovation's characteristics.

5.4.1.1. Relative advantages (What can we get out of it?)

Frequently, BSPs' marketeers have emphasised BSPs' ability to reduce costs and improve patients' access to biological therapy. In discussing BSPs' potential advantages, almost all participants acknowledged BSPs' added value as a cost saving tool. For some, utilising BSPs addresses an ethical obligation toward the NHS to save and maintain its scarce financial resources; for such respondents utilising BSPs fits within the concept of rational drug use.

> *"I mean, certainly at the moment we are doing a lot of work around trying to introduce biosimilars, I think from a cost point of view it is obviously really crucial because there's such, you know, huge savings to be made; and my work with the commissioners they are very keen for us to start using the biosimilar products"* ***(KCFP-13) (Prescribing Advisor)***

> *"Well, I mean...they (BSPs) are cheaper. And, you know, So, in terms of my motivation, I mean it is basically a motivation for helping the health service as a whole, that.... You know, doctors not only have a duty to patients, but they have a duty to try and manage resources for everyone's benefit. Especially if these drugs are exactly the same as the previous drug, but significantly cheaper. Then we are obliged that opportunity"* ***(PRPR-04) (Rheumatology consultant)***

On the other hand, improving patients' access to biological therapy was questionable. While some participants highlighted the possibility of treating more patients with biological therapy, especially in poor countries, others were sceptical. They questioned the BSPs' ability to improve patients' access to biological therapy especially with NICE TAs acting as safeguards, which have already defined patients and disease criteria to received biological therapy. Interestingly, some participants, mainly prescribers, addressed how availability of BSPs changed patients' access, rather than improving patients' access, in terms of which product would be prescribed for them first, was mainly reported in case of IFX-BSPs. Changing patients' access (treatment sequences) might result in changing medical practice and create new practice norms for subsequent BSPs and switching campaigns, which reflect the dynamic and continuously evolving nature of biological market in general and BSPs, in particular.

> *"So in such a way as I have described, it won't really change that much because it doesn't mean that we can treat any more patients than we could before. I mean it might mean you have got more incentive to treat a patient with infliximab rather than one of the others, because you can use this cheaper biosimilar"* ***(NBRP-05) (Rheumatology Consultant)***

> *"Yeah, when the biosimilar comes out, that will be, you know, huge, it will big change in practice, I think. So I think sometimes... I think that will probably.... You know the actual order of the given therapies, would probably change. Because they tend to give the most cost effective therapy first, and if adalimumab comes the most cost effective therapy, that probably would move up the treatment ladder. And I think everyone will switch to biosimilar and probably use more of it, yes. It probably move up the treatment pathway to be used like first liner"* ***(PDFP-03) (E-Prescribing Pharmacist)***

> *"I think what we're seeing right now is a bit of a switch in our preference towards infliximab vs adalimumab because we know it's cheaper to give them infliximab biosimilar. That's different because previously the economics were such that for Health-care at home, adalimumab, was a bit cheaper and we were quite happy for patients to accept that option, whereas now we would tend to direct them a little bit more towards the infliximab. That will change end of next year when there is cheaper adalimumab which is coming anyway biosimilar adalimumab. I think it will be back on an even playing field and we'll make the choice or the patient will make the choice on lifestyle again. So I think there's been a drift towards intravenous but I think it will swing back again next year"* ***(CPGP-06) (Honorary Consultant Gastroenterologist)***

In discussing innovation's relative advantages, Rogers suggested innovations might be adopted to secure or reflect social status of the adopters as being pioneers and better equipped (Rogers, 2003). In this research, relative social advantages were manifested in adopters' (prescribers and Trusts) desire to be incentivised and to avoid being forced into implementing and switching to BSPs, so reclaiming their medical autonomy.

> *"So, when we initiated it, we have avoided the pressure from the CCG and I have to say, it may have been let's get in now, get some funding, because it is going to happen anyway, you know? That's how we saw it, let's get in there; get the best we can for our patients-now, before...Because, now a lot of people is being enforced on them, because the saving's too great, you know, if the saving is quarter million pound for our small Trust, some of the bigger Trusts where they have got hundreds of patients on infliximab, it is outstanding amounts of money, isn't it? So, I imagine, you know, some people are kicking themselves they wishing they'd been a bit braver"* ***(PANS-03) (Lead Inflammatory Bowel Disease Nurse Specialist Gastroenterology)***

> *"So, it was the right thing to do, to save money for the NHS. An opportunity to make savings for us and for the CCG. An opportunity to get a pharmacist in, which would help with the quality of prescribing and sort of medicines management within the sort of affected areas. Yeah"* ***(JKFP-11) (Clinical Lead pharmacist)***

> *"Because they (Trusts) can see a benefit to doing it. If they can save money, and that money can be reinvested in the service they are providing, then they will be able to do more things to their patients, depends on what they need. They might want extra nurse support, they might want IT, databases support for that. You know, all sort of things that can be invested on just that to be able more patients"* ***(JPCP-16) (BCAP Interface Pharmacist)***

In two exceptional cases, IFX-BSPs were perceived as rescue treatment for patients who were irresponsive to the R-BMPs or other BMPs within the disease pathway. However, these were very rare occurrences and were not reported by the prescribers themselves; therefore, it was not possible to verify these cases and to investigate the prescribers' reasoning. Using IFX-BSPs for R-BMP irresponsive patients might either indicate limited understanding of the similarity concept, as it is expected for licensed BSPs to be recognised and attacked by R-BMP's antibodies, or that BSPs are not BSPs for the R-BMP, and are in fact substantially different.

> *"You see, she (a patient) is a very complicated patient so she had originally been on Remicade® (IFX-R-BMP) and done very well on that, and then switched to etanercept. She had Remicade® (IFX-R-BMP), etanercept and adalimumab and ustekinumab and secukinumab and she was failing secukinumab, so we know the best treatment she had had was Remicade® (IFX-R-BMP) so we decided to try her again on Remicade® (IFX-R-BMP) or on IFX, but now it was biosimilar, so we just explained that this was very, very similar, and we could not foresee any difficulty with her going onto that, but it wasn't exactly the same. She was comfortable with that"* ***(CGDP-04) (Foundation Professor of Dermatology)***

> *"One of our clinicians who is actually using the differences between them from the originator to try and re-stimulate a response from a lady whose response to one of the of the originator products was worn off a little bit, So, he is trying to actually use the difference… he is almost using the biosimilar infliximab as an alternative biologic to some extent. So, because the person has a really good response to infliximab, to Remicade® (IFX-R-BMP), in the first place, had a good response for a quite some time, but it is beginning to beat her out. And, they are not currently responding as well. So, actually, he is using the biosimilar, one of the BSP IFX products, to try... to sort of see if he can increase the response, says if you, you know, changing to a slightly different molecule, will it give greater efficacy again, in the same way it would, if you switched one of the alternative biologics"* ***(SCFP-14) (Formulary Pharmacist)***

Participants', including prescribers', acknowledgement and recognition of the BSPs' added values were confirmation of what was reported in the literature. In this research, BSPs' added values acted as motivation to integrate BSPs and switch stabilised patients.

5.4.1.2. Compatibility (Does it fit?)

Compatibility is defined as the degree to which an innovation fits within an adopter's day-to-day routine practice, cultural values and social norms (Rogers, 2003). In case of adopting BSPs, compatibility was manifested in elements related to common medical and professional practice, practice based experience, ethical obligations, and, to a lesser degree, prescribers' characteristics.

Common medical practice in terms of disease management pathways, sequence and frequencies of prescribing medicines, has resulted in gastroenterology being the most frequently or firstly targeted area for switching IFX-stabilised patients, and for rheumatologists and, to some degree, dermatologists to switch their etanercept cohort.

> *"Now, rheumatology have started using it (IFX-BSP) but we had a very small number of rheumatology patients on IFX, so they didn't want to do it straight away because most of their patients are on adalimumab. So a lot of the gastroenterology patients are on the IFX, so they did it first, and then rheumatology only started switching a few months ago, whenever they saw that the gastro people had switched back in July and there was no problems with gastroenterology"* ***(DMFP-08) (Medicines Management Pharmacist)***

> *"The discussions that we had been around the switch…the negotiations have been specific to infliximab and specific to different clinical areas...I mean, the vast majority of our use of infliximab within gastroenterology, so the switch has been driven by gastroenterology and it has been driven specifically; they hadn't had a strong preference between the two biosimilar available, so that choice was based on cost, and cost consistently across the three organisations"* ***(PWCP-13) (Lead Pharmacist: High Cost Medicines Management)***

Understanding the effect of common medical practice and disease pathways might help in identifying therapeutic area(s) with the largest eligible patients' cohort size to be targeted and prioritised for switching. Additionally, identifying the largest eligible cohort also addresses BSPs' added value in saving costs. As the bigger the cohort size the bigger the rescued financial resources.

> *"I think so, yes. Yes I mean most of it is just persuading people to do it, isn't it? And I would say that it is part of my job to communicate with the MDT and influence change and maximise cost savings when it comes to drugs if savings are to be made. So I would just say it is part of my job description"* ***(SCFP-16) (Consultant Pharmacist – Gastroenterology/Hepatology)***

Compatibility, as a concept, addresses the degree to which an innovation fits and resemble common practices (Greenhalgh, 2017). Therefore, some participants relied on their previous experiences with specialised generic medicines, which share BSPs' argument regarding dosing and switching stabilised patients, such as immunosuppressant, in introducing BSPs. In some cases, participants, including prescribers, considered BSPs introduction as "business as usual" that does not require special training and should be done smoothly without creating anxiety among prescribers and patients. Lastly, the effect of common practice was not limited clinical and disease management, but it acted, to a certain extent, as a drivers for involved professionals, mainly pharmacists, to be actively involved in planning, communicating and implementing the switch, for pharmacists this was their job and their role's expected deliverables.

> *"It's fine, yeah. No problem at all. As I've probably reflected, I think that people are over-playing some of the complexity of this and when you look at….I know money isn't everything, but when you look at the amount of money involved and the potential savings and so on and so forth, I just think people need to get on board with it. You know, as I said earlier, I know this is different to the branded to generic prescribing issue but if you use the licensing system as it should work then there's no reason why you can't treat these in a sort of generic way. I think you people…you know, you can understand people's sort of reservations; nobody wants to get wrong, but equally, I'm sure you know, you can look at the data looking at uptake of these things across the country and it's hugely variable. There are some places that have done what we've done and pretty much just you know, with infliximab just switch; whereas others haven't done anything with it and I don't understand that at all, it just seems wrong to me, but anyway..."* ***(MSFP-05) (Head of Medicines Management)***

> *"We have agreed in the first instance that it was a bit like how we adopted generic small molecules so for example cyclosporine that we would only use it for new patient initially and then consider whether we were going to switch patients who were well established and doing well on biosimilar infliximab or etanercept. About whether they want to switch for infliximab, because in my particular area and because of our practice being tertiary and because infliximab, you know, there is some drugs specific considerations that went into the decision about how you introduced the biosimilar"* ***(CSDP-06) (Professor of Dermatology & Therapeutics)***

> *"So, the one that is bringing us to mind there, is Tacrolimus for immune suppression. And there is two products, they are not BSPs, but there is a different products, it is a generic, I have to check. But basically, there is two type of Tacrolimus available now, and ... but again, as you can appreciate, critically sensitive, that we make sure that the patient is fine with those, because, obviously, it could potentially lose kidney, or, you know, some of... because how far the drug has been used. But, that is, that has been shown to be a quite straight forward switch, it has been easy to do. The Trusts have not come back and said that they needed X, Y and Z in terms of staff, or, you know, resources, and so, agreeing that and actually mobilising it has been very straight forward. But whereas, I think with CCG ones, with the IFX and the etanercept, because they are much more other factors we need to take into account, it has not been straight, it is not a straight forward matter"* ***(NBCP-02) (Senior Prescribing Advisor)***

> *"You know, it is part of the pharmacist job to put the work in to be more cost effective. So, it is always part of your job to initiate generics switches and to save money as much as we can. So, it is, kind of, just being part of our normal jobs, really. And it is, you know, because we got results, we have saved a lot of money, so, it good for the Trust, because this will make them invest in more pharmacists, hopefully"* ***(PDFP-03) (E-Prescribing Pharmacist)***

The effect of previous experiences was also evident in participants' willingness to extrapolate their experiences in managing IFX-BSPs switch to future BSP launch such as etanercept and adalimumab; in these cases, experiences with IFX-BSPs acted as a new practice norm that stakeholders were able to rely on, and refer to, in managing new switches.

> *"…But certainly looking forward to, you know, in the next few years there are a number of, obviously as you are aware, a number of biosimilar products that are coming into the market and you know, we now need to start to make sure that we've got the right processes involved so people are comfortable to start moving towards those. I think the last year or two, people have been a little, you know, have some concerns obviously because it's something new and we don't want to rush into anything and I would totally support that. I think now we're starting to get experience, I think we have got to start making sure we start using these things routinely because there are such massive savings to the, you know, the whole health community, and to the NHS. And, that we need to explore"* ***(KCFP-13) (Prescribing Adviser)***

> *"We have got an action plan of how we do biosimilars switches, which I can send you, it is not like confidential or anything. It is because we have done so many biosimilar switches, we, kind of, put together a kind of checklist of what we look for when we are switching, and it is quite a big list, but basically look at safety and efficacy and make sure it has been approved by MMC (Medicines Management Committee), we look at the products themselves to see are they different, is it going to affect anything to do with homecare, Is the dose the same, is the formulation the same, etc.? So, we have got quite a big list, and we kind of have to make changes to our order systems, to the pharmacy computer. We also, outsource dispensing to community pharmacy; informing them is necessary as well. Because every time we have done biosimilar switch, sometimes we forgotten bits and bobs, we have put together this check list, so, every time we do biosimilar switch now, we go through this list, we do it all. And we have kind of action plan. Yeah I will send that, I have sent it to another Trust as well, to kind of, you know, help them as well"* ***(PDFP-03) (E-Prescribing Pharmacist)***

Extrapolating the experience in switching to one BSP to future BSPs switches could indicate the building of organisational memory that may eventually lead to institutionalising and routinising certain practices, in this case switching stabilised patients (Williams and Brown, 2014).

Another dimension associated with innovation compatibility is the adopters' characteristics in terms of gender, age and socio-economical background. Similar to what was reported in the literature, in general prescribers' characteristics were not reported to have a profound effect on prescribers' acceptance and willingness to switch their stabilised patients. For prescribers' characteristics and demographics to have only a limited effect on prescribers' acceptance of BSPs might mean that there is no need to have gender/age specific promoting interventions; any resistance might, to some extent, be based on objective rather than subjective reasoning.

> *"Interviewee: I think the younger they are, the more accepting they are. Since more recently you know, it's like most things in life you know, if it's IT or anything else. You know, my experience is that usually the younger trained doctors are the ones who are more flexible, more accepting of the will embrace this, and that's the general rule.*
> *Interviewer: What about the gender, do you think that might affect the acceptance? progress, more accepting of change?*
> *Interviewee: No I don't think so. I mean, bear in mind dermatology now is predominantly female. So of course women are far more tolerant than men so probably they will do, yeah! Much smarter in general. They would see it sooner the pros and the cons and probably the pros you know. But no, we have biologics committees, sub-committees in dermatology and we have most of the work comes through from Manchester. So we, you know, it's a very, I haven't seen any gender differences actually, as to acceptance or not acceptance of change, or both of biosimilar actually to be fair"* ***(CGDP-04) (Foundation Professor of Dermatology)***

> *"I do not think you can. I do not think there is any specific, as far as I know, as to, you know, whether, your gender, or years of experience actually influences that. It could be, but I am not aware of that being the main issue, I do not know the answer"* ***(HSRP-06) (Rheumatology Consultant)***

Identifying therapeutic areas with the highest compatibility, relying on previous experiences, institutionalising BSPs switch and, finally, considering BSPs "business as usual" are all factors that increase BSPs' compatibility with clinical practice.

5.4.1.3. Complexity-Risk (Is switching risky?)

Complexity, is the second most important attribute that affects the decision about, and adopting rate of, an innovation; basically, the more complicated an innovation is, the less likely it will be adopted and implemented. (Rogers, 2003). In general, innovation's added value is reported to be the most influential attribute to promote its acceptance and drive its adoption (Rogers, 2003). However, in medical practice the combined effect of an intervention's safety, efficacy and cost promotes its integration and utilisation (Weekes and Brooks, 1996). This conclusion was evident in case of BSPs, as BSPs' ability to minimise cost and improve patients' access was not enough to drive BSPs' utilisation. As previously discussed in the literature, the main arguments and debates were related to BSPs' quality, safety and efficacy, as well as their ability to trigger immunogenic reactions.

In this research two main types of complexity, (*i*) risk and (*ii*) practical complexity, were identified. Risk, as an attribute, is related to the uncertainty of an intervention's outcomes and consequences (Greenhalgh et al., 2004). In licensing BSPs, the EMA does not assess the interchangeability between R-BMP and BSPs; nor is any data required to demonstrate switching's safety or outcomes. Finally, the EMA has left the decision of switching to individual countries, to either approve or reject it. Therefore, switching patients, in theory, is associated with a certain degree of uncertainty and limited evidence. Risk was considered as a complexity demission, as it was not limited to the assessment of available evidence and how it was perceived by research participants; risk also had practical manifestations that had been reflected at the implementation stage.

Similar to what was reported in the literature, switching stabilised patients was considered to be more challenging than initiating biological naïve patients in terms of patients' wellbeing and disease control. While there was a cross board acceptance of prescribing BSPs for biological naïve patients, some participants, mainly prescribers, were reluctant to accept, being concerned about triggering flare ups in stabilised patients. For such participants there was a need for more evidence and practical experience in prescribing BSPs.

> *"No, prescribe biosimilars for existing patients. Everyone's been okay with biosimilars in a first presenting patient. It's the switch for a patient who's already established on a biosimilar where there is a natural reluctance. Not unsurprisingly to take a patient who's clinically stable and then switch them to a biosimilar. It's just that feeling, is it equivalent enough that I can switch my patient to the same therapeutic effect?"* ***(KGFP-10) (Pharmacy Manager)***

> *"Well again we are just expecting that biosimilars are going to become business as usual for new patients. That is our expectations, that once a biosimilar is on the market, new patients should be using that. Existing patients as I said, there is need to be some discussions with clinicians support given to patients to explain that, you know. That your product is changing and it is exactly the same efficacy, safety. But, as from next month it will be a different pen device, let me give you some training on it. They should become main stream practice. And as I say, if we can have some kind of national tariff price that says this is all that you can pass through, then that would incentivise the Trust to uptake more rapidly"* ***(STCP-10) (Medicines Optimisation Pharmacist)***

In discussing switching stabilised patients, the effect of principle knowledge in terms of BSPs' concept and licensing procedures and requirements was evident. Participants, including accepting prescribers, referred to available licensing evidence and the literature in assessing switching safety. Some prescribers relied on their understanding of biological variation (batch-to-batch variations) to consider switching to BSPs as a common practice; for them, biological variation meant that an R-BMP is BSP to itself and that they have been switching frequently without addressing it.

> *"Well, I think, what was really interesting about infliximab, was how much it is changed since it was launched 10 or whatever years ago. I do not think, I have really quite appreciated how much it changed anyway, And what we were actually prescribing as Remicade® was very different than Remicade® that we had been prescribing eight years before. And, I think, once we have realised it is almost in evolution that is changing overtime a little bit anyway, it tend to become more relaxed and we are happy with it. And, that was in a way assuring. Also, we have, you know, we even have got 10, 11 years of experience of using it, we have become more confident with them as a group of drugs anyway"* ***(ABGP-04) (Gastroenterology Consultant)***

> *"The originator compound by the pure nature of being a biologic has undergone several transformations anyway so you could argue it is a biosimilar in its own right to some extent...And like I said, the originator products probably changed about thirty odd times anyway"* ***(SCFP-16) (Consultant Pharmacist–Gastroenterology/Hepatology)***

In addition to available evidence and experiences in prescribing R-BMPs, the influence of national and international professional societies such as British Association of Dermatologists (BAD), British Society of Gastroenterology (BSG) and British Society for Rheumatology (BSR), was strongly evident. For these societies to adopt a supportive or opposing position toward the switch, provided a point of reference for prescribers to reassure them regarding the safety of switching or legitimated their reservations toward the switch. In some cases, changes in the position adopted by these societies were reflected in the changing of prescribers' stands toward switching patients.

> *"I think particularly with the BSG, they have changed the position statement during the last year, so initially they were sort of negative and now it endorses and even talks about switching. I think that is very helpful from the perspective of organisations that are trying to make switches both from commissioners and trust because it's sports what they do. I think certainly there is an individual clinicians in Nottingham, who were…that helps in that position from being slightly against the concept of being, feeling like it's now accepted practice nationally and that is what we should be doing"* ***(PWCP-13) (Lead Pharmacist: High Cost Medicines Management)***

> *"The biggest negatives were obviously, there were concerns from ECCO, the European body and from the BSG from 2014 advising that the lack of study evidence of benefit for our group of patients was concerning. Our understanding of everything was that the original biologics which we are still prescribing at the time were biosimilar of themselves. They were basically re-inventing themselves and they were common with the infliximab, I think it was a 19th or whatever the original biological model"* ***(SBGP-02) (Gastroenterology Consultant)***

Similar to what was reported by the research participants, key opinion leaders and professional affiliates are reported to significantly influence prescribing behaviour and the driving of change (Hunter et al., 2016, Fixsen et al., 2005, Grol and Wensing, 2004). Moreover, professional bodies represent interpersonal cosmopolitan communication channels that facilitate communication between individuals sharing the same profession, but which are not located within the same organisational structure (Rogers, 2003).

Whether there was acceptance or reluctance to switch stabilised patients, a common feature among participants was the emphasis on having a "controlled, managed and proper" switching process. The proposed elements of a controlled switch can be grouped into six main categories: (*i*) gradual introduction of the switch, where BSPs are prescribed for biological naïve patients first for a while, then proceed with the switch, (*ii*) after the switch disease management in terms of providing more frequent disease progression monitoring, overall health checks or managing patients, who might experience therapy failure or flare ups as a result of the switch (*iii*) patients' rights to be properly informed and consented before the switch, (*iv*) managing patients with special considerations in terms of disease control and overall health status, (*v*) proper documentation, labelling, reporting and pharmacovigilance activities and (*vi*) inclusion in disease and medicines national registries. While patients' acceptance and consent were considered as a 'must' by almost all participants, including prescribers, other elements did not witnesses the same consensus; a lack of conformity which resulted in variations at the implementation stage, as will be explained in the implementation theme.

> *"Yes, I would say so, the rheumatologists and the…but I mean in general I think the view of everybody has been more or less the same, you know, that we need to follow the EMEA guidance, you know, that the biologic needs to be clearly labelled, but they need to be robust safety monitoring so that the patients should be put on to pharmacovigilance registries and that they need to be involved in any decision to switch"* ***(CSDP-06) (Professor of Dermatology & Therapeutics)***
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> *"I think generally speaking, all clinicians that I have been liaising with... have been pretty keen to use biosimilars. Certainly, for the three organisations that we work with; for the local three Trust that we work with directly. They are OK to use, they are happy to use it, but they want to use it in a controlled manner"* ***(KLCP-04) (Head of Medicines Management)***
>
> *"We thought it is, you know, short term studies done by the drug companies to prove that the drugs are equivalent, are not going to flag up problems with immunogenicity that might only come out with long term use after the patients have been on it for a few years. So, for that reason, I think it could only be captured as part of a registry. So, I think that was proposed. I am not sure how far they have got with it, but I think it is in the pipeline if is not being done already"* ***(NBRP-05) (Rheumatology Consultant)***

For prescribers to rely on their knowledge about BSPs and experiences with the R-BMPs in assessing BSPs, reflects the role of indigenous knowledge and experience in driving innovation adoption. The effect of knowledge in assessing switching's observability confirmed the ongoing effect of knowledge and the overlap between different stages of the innovation adoption process (Rogers, 2003).

5.4.1.4. Observability (Was it tried before?)

Observability is the degree to which the results of implementing an innovation are visible to other potential adopters (Rogers, 2003). In this research, healthcare professionals relied on international and national experiences and a growing body of evidence on implementing the switch. While the international experiences provided data on patients and disease outcomes, it is mainly national experiences that provide guidance on how to plan the switch, what to consider and what to ask for. In terms of international experiences, the NOR-Switch is a 52 week phase IV trial publically funded by the Norwegian Ministry of Health and Care Services that aimed to assess the safety and efficacy of switching IFX-R-BMP stabilised patients to IFX-BSP in all licensed indications; the trial is by far the most commonly mentioned experiment in the field (Jørgensen et al., 2017). On the other hand, nationally, experiences of other Trusts within the same region, or within the country, served as guides on how to implement and provided assurance regarding switching outputs. These experiences, whether international or national, were perceived as compensation for the limited evidence on the switch's safety.

> *"And I think in terms of adverse effects, I think we are now getting, as I said earlier, we are getting experience from other areas who've done switches and found that, because I think the original trials they're quite small when you look at the trials for comparison to show they are all similar, they're not huge numbers of patients. But I think now real life data is emerging and we can see there aren't that many problems. And the problems that are arising are probably problems that would have arisen anyway even if the patient hadn't switched. I think that's the sort of the safety bit is really important"* ***(KCFP-13) (Prescribing Adviser)***

> *"We had conversations with different Trusts in our region like, Huddersfield and Calderdale. And we have spoken to York and Leeds and Bradford and Pinderfields. But I think, we ... because we are considered like one of the first ones to switch. Yeah, people have been asking us kind of questions and I just sent out the information with the action plan on"* ***(PDFP-03) (E-Prescribing Pharmacist)***

> *"Before we did the Infliximab switch I also telephoned a lot of hospitals in our region I heard were thinking of doing some switches to ask whether they have done them or not, there was one Trust in the South West that had already switched with all of their patients, so I had a telephone consultation with their clinical pharmacy manager about how they had gone about that and how they had informed their patients, and sort of form what he said we decided that it was good for the pharmacist to have face-to-face interview with the patients to really explain it to them"* ***(DMFP-08) (Medicines Management Pharmacist)***

> *"The inflammatory bowel disease one will have the statement about biosimilars in it. And, it is just looking at the real world data, so like Norway, Ireland, Poland and seeing how the introduction has gone there. So, we are looking at the real world data, not the trail data"* ***(VRFP-15) (Specialist Clinical Pharmacist-Specialist Medicine (Gastroenterology/Hepatology and Rheumatology)***

Practical experience was not limited to others' experiences, whether national or international; but, it was also self-generated. Self-generated experiences fed positively into discussions between involved professionals, including prescribers, and formed the base for future switches. It is here where the link between observability (evidence) of the switch and its compatibility (experience) becomes visible. In discussing growing familiarity with BSPs and switching process, participants had also highlighted how accumulated evidence, based on practical experiences and studies, acted as a source of assurance and increased their acceptance of BSPs, as well as the notion of switching stabilised patients.

> *"Well, I think there was limited understanding at the beginning. 18 months or two years ago about the data and the strength of the data and what biosimilars meant and over the last year we've had a lot of understanding a lot more education and chance to read and accepted ourselves that the biosimilars were what they said they were, and then as opinion leaders we've told the rest of the BSG what are biosimilars and how we should be using it"* ***(CPGP-06) (Honorary Consultant Gastroenterologist)***

> *"I think, I suppose initially, particularly with IFX, it was for us to go and find a lot of information, but I think eventually that is forthcoming. And I think now there is a lot more of information. There has been... national, UK medicines information (UKmi) briefings on BSPs which are very useful. And. So there has been more trials now being done; so importing of those has supported us"* ***(DACP-17) (Regional Medicines Assurance and Lead Procurement Pharmacist)***

> *"I think they (prescribers) have an increasing understanding. I think, if you had asked two year ago, I would have said no. I think, some of them having to get up to speed fairly quickly. If you'd have asked me probably six months ago, I would have just said it was not this good as it is now, especially for.... But, I think for different groups of clinicians, they are more familiar, So, obviously, because the IFX has been such a big deal, I suspect that the BSP producers of, have helped in educating consultants and I first started looking at BSPs about five years ago, and at that point very few people were using them, and it was, sort of, a novel concept. But, I think now with more and more information out there and more people using them and I think, certainly, gastroenterologists completely have favoured BSPs, I would say. The rheumatologists are, too; because they are using them, or beginning to use them, but I suspect if you are to ask clinicians who do not prescribe biologics, if you are to ask a whole load of cardiologists what do you think about a BSP, they would not have a clue, probably. Because they do not have any drugs, although they will do by the time we have the low molecular heparins, I think there is going to be BSP of those out"* ***(JCFP-01) (BCAP Interface Pharmacist)***

> *"There was originally, when we first used biosimilar G-CSF, the clinicians didn't want to use the biosimilar for bone marrow transplant patients, they didn't feel there was adequate data, and also the haematology society had actually specifically said not to use biological for biosimilar G-CSF in bone marrow transplants. But as time has gone on and clinicians have had more experience with G-CFS, they are now happy to use for a BMT patient, so we've actually moved over. The only people we don't use it for now are the healthy donors"* ***(NSFP-12) (Cancer Consultant Pharmacist)***

The output of observability provides evidence which might feed into assessing the switch risk and guide its planning and implementation. While risk assessment identified the elements of a controlled switch, observability explained how to implement that switch.

5.4.1.5. Complexity practical (Is switching doable? Switching is demanding)

As discussed earlier, complexity adversely affects the adoption rate of an innovation (Rogers, 2003). In planning the switch, participants had often described switching as a "resource and manpower demanding process". Despite the fact that utilising BSPs is considered as a cost saving tool for the NHS, implementing a managed switch is expensive in terms of resources and manpower. In addition to considerations and procedures needed to ensure a safe and controlled switch, considerations related to service design, logistics and industry contracting also needed to be factored into the practical complexity of the switch. Identified "needed resources" form the base for negotiations between providers (Acute Trusts) and commissioners (CCGs). Practical complexity, together with added value, forms a platform for industry competition and contracting.

> *"I think, it is going to be, as I said, there is going to be a lot of pressure on services to actually switch patients. And switching it itself, does take a little bit of manpower, extra manpower, I think it depends on how many more become available, I think it is, you know, if there few more become available, I think there is going to be one: obviously an issue about, you know, how often do you switch patients and how much, you know, how often we are going to be switching patients. I think it is going to have an effect on the way we deliver services"* ***(HSRP-06) (Rheumatology Consultant)***

> *"If you are making the effort to make the switch and there is an effort because it requires staff time to discuss it with the patients and requires nurse time because some of the devices are slightly different, it requires pharmacy time to arrange the different, so you have to make sure it's absolutely worth the switch, so you have to do it on an organisational across speciality scale for it to be cost effective, made cost saving but then those cost savings there has been a strong push that any money's that's saved should be reinvested in the service that delivered those savings and that possibly where there is a bit of discussion and debate and lack of clarity"* ***(CSDP-06) (Professor of Dermatology & Therapeutics)***

As discussed earlier, during the data collection phase of this study, a new BSP (etanercept-BSP) became available. Etanercept is a self-administered medicine that is delivered through the homecare service. Therefore, it requires different practical considerations from the clinic-based IV-administered IFX. While the main issues with IFX were related to compounding and clinic capacity, the homecare route required procuring a patient-friendly self-administered device, training switched patients on how to use the new device and contracting a homecare company that will ensure a continuous, unconfused medicines supply to patients.

> *"So, obviously, there is a large saving to be made from switching to the BSP; particularly for some of the ones that are coming up with etanercept and adalimumab. The particular issue around IFX was, obviously, it is a compounded bags; So, it needs to…in some situations our cytotoxic aseptic unit manufacture bags, there was a lot of work to do around stability, making sure that the new product was stable and the solutions getting the testing done. But, also general issues around making sure we have got the patients' information in place, we have got patient advocates who are familiar with it. Check with the homecare company so they can deliver these new products. So, there was a lot of implementation work that had to be done by secondary care"* ***(PMFP-07) (Medicines Management Pharmacist)***

> *"When we go out for tender, we are looking at the way the product is presented. What, does it come in pre-filled syringe, or is it a vial. How it is labelled? Is all of this is appropriate. As long as it does not look as it is going to present any risk, because if they are used in hospitals, it is bit different to drugs are used for patients at home. If you are in a hospital situation on a ward, and a nurse is going to choose from a range of the products in a cupboard, if things look very similar, that can be a risk to safety; if the wrong product was selected. So, we look at labelling quite carefully, to make sure that it is unlikely to be an errors and things like that. But as long as product meets the necessary quality criteria, then it will be awarded into a framework contracts"* ***(JPCP-16) (Regional Procurement Pharmacist)***

Another factor to add to switching practical complexity was industry competition and its implications on procurement processes. The continuously changing market has resulted in creating complicated contexts and uncertainties. Market competition, in some cases, has made it difficult to determine which product/brand should be stocked and how the medicines should be managed.

> *"It was delayed to an extent, hardly because if an awareness from us that there was... the biosimilars market was changing, and so we were aware that is going to be new contracts for biosimilars coming out at a certain time, and what we did not want to do ... to switch people from one biosimilar to then actually find that it would far better to switch them to another biosimilar. And, so we waited for those contracts... that contract information to become available to us, because the last thing we wanted was, for example, for infliximab, to have three different infliximab products within the Trust. So, we delayed from that perspective… But, Also it is very changing market within the NHS, So, the companies are all trying to, you know, to challenge each, will not to challenge each other, but you know, the driver very much for the NHS. It is obviously saving this ... but, when you are aware that savings, the prices are changing all the time and new stuff coming out and different products are going to be available, what you do not want to do is just jumping and do one thing and then find a couple of months down the track actually, the situation has changed so much, that you would have been choosing an alternative product, and then you are switching patients from one biosimilar to another, which could be crazy. So, I guess it is... the challenges of the market do not help, necessarily"* ***(SCFP-14) (formulary pharmacist)***

> *"Well, I do not think it is a conflict. It is slightly different thing than you have mentioned. You said it is clinicians' preference and not the patients' preference. So clinicians' preference is the result, when you are dealing with pathways and some clinical guidance. Yeah, if you as a region have agreed that, I do not know, infliximab is your fist line product and biosimilar infliximab is your first line product of choice in X, Y, Z conditions, then there should be no concern, there should be no confusion in that. Because, you start using... the region will procure the cheapest product, if that was decided. And your pathways state the way that you should be treating the patients. So, you standardise the way it would be working. It should never be the case where, I do not know, your pathways states infliximab biosimilars, and then clinicians go, I do not know, I do not want to do that., I do not want to follow that, I would do something else. Is should never be the case. It needs to be standardise way of operating within health economy. Otherwise, it will be a chaos"(****KLCP-04) (Head of Medicines Management)***

Discerned evidence addressed four out of Rogers's five attributes; the exception was 'trialability'. Trialability was not visible at the persuasion stage, but rather at implementation in the form of a gradual switch; a factor which is also a component of a controlled switch. Research findings have shown that while each attribute addresses a specific angle related to switching benefit, risk, fitness and ease of implementation, these attributes were interconnected and fed to and from each other. In planning the switch, identified attributes were concerned with (*i*) securing information and evidence, (*ii*) assuring technical competencies, (*iii*) checking service design and fitness and (*iv*) overall internal structure. The same factors were reported in a 2004 study that investigated managing medical error(s) in healthcare setting in England (Waring, 2004). In summary, the switch was perceived to be financially beneficial, as well as more challenging in terms of available evidence and the implementation's requirements.

In healthcare settings, decisions are made based on to what degree the innovation answers four main questions: (*i*) does it work? (*ii*) does it solve a problem?, (*iii*) could it be done? and (*iv*) is it feasible to implement and does it save money? (Bowen and Zwi, 2005, Guindo et al., 2012). Results showed that in planning the switch, these four questions were addressed as it is presented in Table 24.

Table 24-Switching attributes addressing decision making criteria

Assessment question	Switching attributes (as discerned from data)
Does it work?	Evidence upon licensing (Risk) Others' experiences (Observability)
Does it solve a problem?	Save costs and improves patients' access (Relative advantages)
Could it be done?	Implementation plan (Practical complexity) Common medical practice and norms (Compatibility)
Is it feasible to implement and does it save money?	Implementation plan (Practical complexity) Cheaper alternative (Relative advantages)

5.4.2. Healthcare professionals' attitudes

The persuasion stage results in forming a positive (accepting) or negative (reservation or rejection) attitude toward the innovation (Rogers, 2003); switching attributes which influenced the attitudes of participants, including prescribers, had towards the switch. While there was general acceptance of prescribing BSPs for biological naïve patients, the act of switching stabilised patients witnessed response variations among prescribers and within therapeutic areas.

Based on the assessment of switching attributes, a positive attitude "a willingness to switch" was commonly achieved as a result of: (*i*) accepting available evidence, either at licensing or from real-world experiences, (*ii*) endorsement from professional bodies, (*iii*) medical practice in terms of commonly prescribed medicines and the patients' cohort size, (*iv*) ethical obligations to save financial resources and (*v*) a desire to reclaim autonomy and to be incentivised. In addition to factors related to BSPs and switching attributes, accepting the switch was influenced by acknowledging the authority of budget holders, mainly commissioners. An interesting case was of a prescriber who had strong feelings against prescribing BSPs, whether for biological naïve or stabilised patients; he questioned the adequacy of available evidence and licensing requirement, but was willing to accept budget holders' mandates and ended up prescribing BSPs to his patients.

> *"I think that they (BSPs) are tricky because they are not exactly equivalent; they are cheaper than the original biologics, but they may not be biologically equivocal unless they had to have a comparison of clinical trials and this is because of the structure of biologics, if you change a little it can change the quality of, the biological function quite a lot. So it's like adding sugar or changing the amino acids, it could actually have a dramatic impact on biological activity, so it's not my favourite choice if I have original molecule…If commissioners tell us to use it we will use it, we don't have much choice, so it depends on the CCGs and commissioners who will try to make us to use it or not to use it. Given a choice, I would not use them but I may not have a choice.*
> ***Interviewer:*** *And when you said that commissioners are asking you to use it, is it only for the new patients or established patients?*
> ***Interviewee:*** *I would speculate that the commissioners would probably ask us to use it for any patients, for all patients"* ***(AADP-05) (Dermatology Consultant)***

Nevertheless, some BSPs-accepting participants stressed the priority of patients' safety and rigours of evidence over possible cost savings in prescribing BSPs.

> ***"Interviewer:*** *And, How do you think that biosimilars might fit there or change the pathway?*
> ***Interviewee:*** *I think, we would be very worry if they (BSPs) were, because then we will feel the other factors rather than just the drug efficacy that making us change, for example because it is cheaper. It is interesting thought. I am not sure"* ***(ABGP-04) (Gastroenterology Consultant)***

> *"Well, they.... first of all, it's having the time to meet with them; so, you know, they (prescribers) don't really prioritise it (the switch), because they are not thinking of the cost. But I think they are quite open to looking at the evidence, and are likely to support of switching if they agree that the evidence is strong enough. So, I don't think it is a big, a large barrier; sort of, clinician perception, but it will depend on the evidence"* ***(LMCP-14) (Lead Pharmacist for Operational Services)***

> *"I am happy to save money, but actually not happy to save money if I'm putting my patients at risk, kind of my patients being, not put at risk but I don't want to save money at the expense of my patients getting the right treatment"* ***(SORP-02) (Rheumatology Consultant)***

Reservations toward the switch were triggered by (*i*) concerns about losing disease control and special patient's considerations, (*ii*) limited evidence and (*iii*) disapproval of professional bodies. Attitudes toward the switch were not always unified within the same Trust, as some Trusts had witnessed variations in acceptance between prescribers within the same area and, more frequently, between different therapeutic areas.

> *"…So, we got some (prescribers) really switched on clinicians and pharmacists and nurses who are, actually I cannot speak of experience on nurses, but clinicians and pharmacists are really switched on, I think there are, you know, were a great way to help the NHS and have no impact on patients. And there are people who are, I think down to lack of understanding or a lack of confidence, who are quite worried about using them. And again it depends on whether we are starting patients on them or swapping patients around them; and there is a definite difference between those two groups in perception. Starting them, I think, most people do not have huge issues of initiating patients, but when it comes to swapping from a legacy biologic to a BSP, there is a bit more concern and hesitancy"* ***(BFCP-01) (Interface Pharmacist Lead-Clinical Effectiveness and Medicines Optimisation Team)***

> *"I have not really had that level of discussion, to be honest. So, I am not clear where they sit the main discussion has been gastro and rheumatology, and gastro are more reluctant than rheumatology"* ***(STCP-10) (Medicines Optimisation Pharmacist)***

> *"The gastroenterologists seem to be the most keen to start using the medicines. The rheumatologists tend to be a little bit more reluctant, actually in my experience. So far, we haven't really pushed the rheumatologists. Dermatologists, you'd be surprised to see we're using an awful lot of infliximab anyway and so yeah, that's the only biosimilar I've got available at the moment. Diabetologists tend to be…they're reasonably ok with biosimilar glargine, so yeah"* ***(MDCP-07) (Head of Medicines Management)***

> *"It depends on the hospital. In the IFX case, there was a little bit more reluctance from rheumatologists. But, in our main hospital, the switch happened across all disciplines. In the second hospital that we have, the switch happened without question with gastroenterologists, and the rheumatologists did not want to switch"* ***(MWCP-09) (Specialised Commissioning & Interface Prescribing Advisor-Prescribing and Medicines Management Team)***

Lastly, while prescribers reported, and were reported, to have mixed attitudes toward BSPs and the switching process, a consensus was observed regarding commissioners' as being keen and enthusiastic toward integrating BSPs and switching patients. Commissioners' attitudes toward the switch could be explained by the norms and expectations of their professional role, which in turns fits with the concept of compatibility.

> *"Well I work to support CCGs, and as CCGs' commissioners who pay for the path through cost for tariff excluded drugs. We are keen that the rate of adoption of biosimilars is rapid. We therefore do not have a great uptake in this area, and therefore we have moved toward some gain share arrangements with Acute Trusts in some areas. But we have not yet got in place across all our CCGs, but we keen for adoption to be faster than it is"* ***(STCP-10) (Medicines Optimisation Pharmacist)***
>
> *"And also I know about it from CCG perspective, not as a trust pharmacist might be involved. So what we are really interested in is insuring that biosimilars are used by the Trust and that means that CCG is benefiting from the prescription of the more cost effective medicine, because ultimately we are paying for it"* ***(STCP-03) (Medicines Optimisation Pharmacist)***
>
> *"The CCG have been aware that these are coming from early planning stages, and they (CCGs) have been very keen to push for them to be introduced as soon as possible. But they acknowledge that clinicians need to be on board and to be comfortable with the process"* ***(SACP-18) (Principal Pharmacist, Clinical Effectiveness & EPMA)***

In summary, to a certain extent reported attitudes reflected professional norms and ethical obligations, which are based on assuring and ensuring patients' safety and wellbeing, accepting evidence and rational drug use. Innovation's perceived advantages, followed by their complexity to implement, are considered to be the most influential of innovation's attributes (Rogers, 2003). However, reported attitudes showed that while professionals acknowledged the relative advantages of BSPs in freeing up NHS financial resources, their attitudes were significantly influenced by the risk, complexity and compatibility of the switch. In other word, relative advantage was not the most influential factor regarding stakeholders' attitudes. In fact, as presented in the following theme, the risks, complexity and compatibility associated with switching made up the core of discussions and interventions considered during negotiations between providers (Acute Trusts) and payers (commissioners), even if these attributes resulted in minimising, though not massively, the switch's added value. For compatibility and complexity to have significantly visible roles comes in alignment with the principles of evidence based medicines and rational drug use, which prescribers in highly regulated healthcare systems are expected to follow.

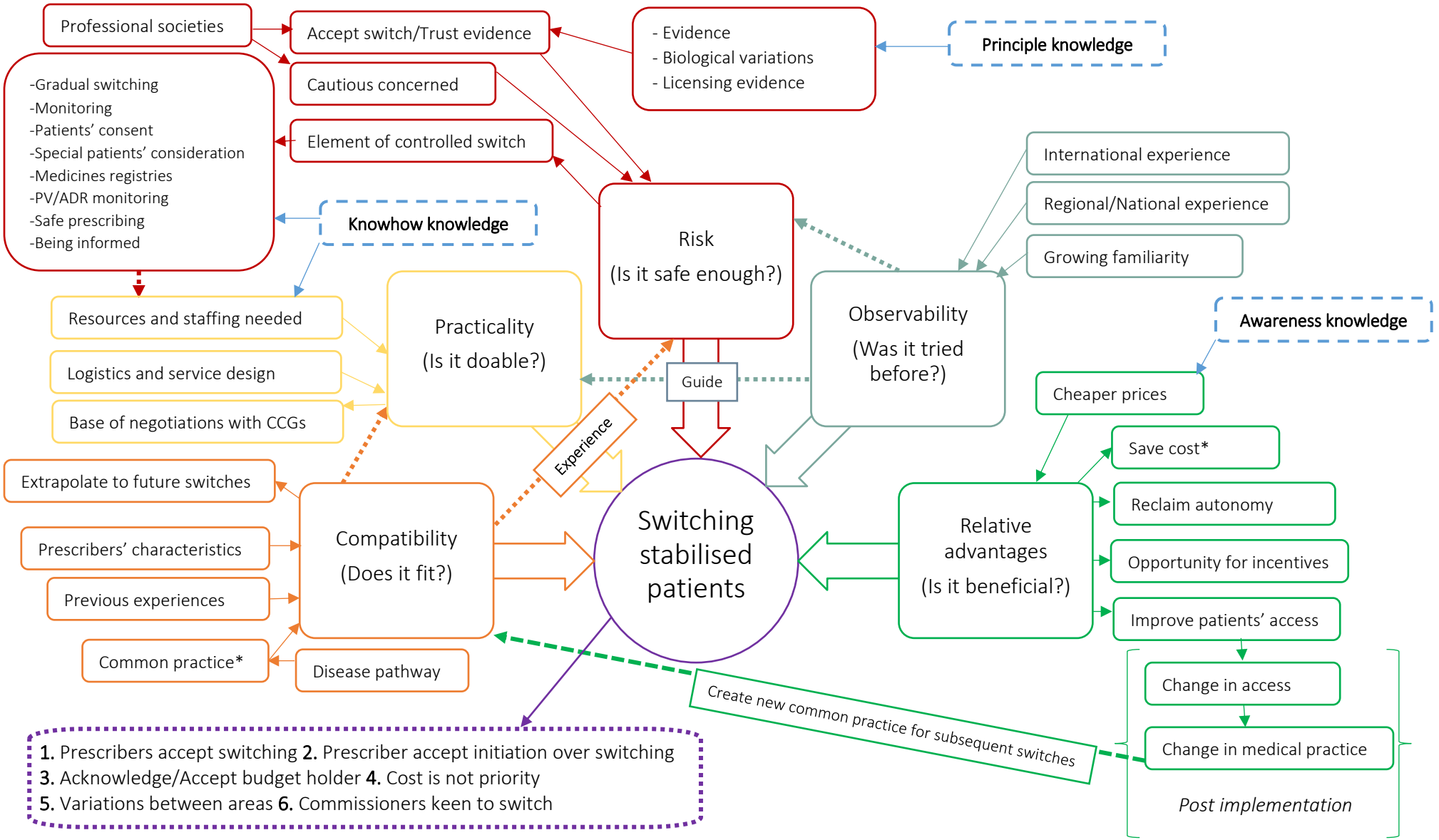
5.4.3. Persuasion theme summary

Recognising innovation's attributes might be either self-generated or highlighted (shown) by others, mainly change agents (Rogers, 2003). In this research, it was not always possible to distinguish whether the perception toward BSPs was self-generated or imposed by change agents. The adoption rate is influenced by how innovation's attributes are being recognised and assessed (Rogers, 2003). In other words, the adoption rate is affected by human cognition which is, mostly, subjective rather than objective factor. Subjective reasoning is more influential in individual/elective decision-making than authoritative/organisational innovation decision-making, which is based on assessing the fitness of an innovation within the organisation's needs and structure (matching) (Rogers, 2003). Therefore, while innovation's attributes are subjectively assessed in individual decisions, these attributes are objectively and formally addressed in organisational innovation decisions.

As research participants were professionals working within established organisational structures, whether Acute Trusts or CCGs, it is expected that participants would follow policies and authoritative mandates as per employee-employer contractual agreement, whether explicitly or implicitly expressed (Simon, 1979). Participants had discussed switching attributes without differentiating between compatibility, risk or practicality. It appeared that for them, as participants, it was an ongoing cognitive and, to some extent, emotional process that influenced their attitudes toward the switch. Therefore, it was evident that assessing BSPs and switching was influenced by both individual reasoning, hereinafter (individual), and organisational/structural considerations. Therefore, assessing switching attributes was influenced by organisational and individual (professional) perspectives.

Subjective (individual subjectivity) reasoning is based on the adopters' own experiences, perceptions and point of view (Rogers, 2003). In this research, participants were targeted based on their professional identity (professional roles), and were asked about their professional involvement and experiences in introducing BSPs and switching established patients. Therefore, their assessment of BSPs and switching's attributes was not mainly influenced by their own personality traits and characters; rather they were influenced by their professional identities and professional norms, deliverables and practices (professional subjectivity). However, individual subjectivity might still be influential, as it is still possible to have different interpretations of professional norms and deliverables amongst professionals. As a result, it might be reasonable to assume that reported perceptions toward BSPs and switching reflect both professional and individual subjectivities, in addition to factors related to organisational structure and policies

The persuasion stage resulted in identifying prescribers' acceptance or reservation/rejection of the switch, implementation requirements, targeted therapeutic area and prescribing practice (initiation or switching). Early identification of an implementation's requirements speeds up intervention's implementation and makes it easier for relevant stakeholders to identify and solve potential barriers (Fixsen et al., 2005). 'Attitude' is a cognitive and perceptual concept that might or might not be translated into actual adoption of the innovation. Therefore, the next step (the decision) should, in theory, augment the positive attitude and solve or minimise the effect of a rejecting / reserving attitude. During the decision stage, other tools such as incentives, contractual powers, mandates and guidelines might be used to drive the adoption. Figure 11 summarised the persuasion theme.



ADR: Adverse drug reaction, **CCG:** Clinical commissioning group, **PV:** Pharmacovigilance activities

* These two dimension should be linked as common medical practice helps in identifying BSPs heaviest prescribers and hence capitalise the potential of cost saving

– – – Links with knowledge theme

Figure 11-Persuasion theme summary

Authors Own Figure

5.5. Theme three: Decisions

Attitudes and attributes assessment is an intellectual process which needs to be translated into actual adoption or rejection. Relevant stakeholders need to be involved in an interactive process that might or might not end up in a decision that is in alignment with their attitudes (Rogers, 2003). In this research, the decision stage involved making two main decisions: (*i*) whether or not to switch stabilised patients and (*ii*) which supplier to contract and which brand to procure. At the decision stage, the identities of involved organisations: Acute Trusts, CCGs and product suppliers, became clear. While Acute Trusts were considered as adopting organisations, CCGs and product suppliers acted as promoting bodies.

Discussions in the following section are focused on negotiations between Trusts and CCGs, as these negotiations served as prerequisites to industry contracting and product procurement.

5.5.1. Interactions and negotiations between Acute Trusts and CCGs

Negotiations between Acute Trusts and CCGs aimed to: (*i*) define BSPs' utilisation approach, whether initiating or switching patients, (*ii*) specify needed resources required to facilitate the switch and communicate with the patients and (*iii*) agree on an incentive scheme, mainly in form of gain share.

> *"**Interviewer:** Can you please tell about your experience in commissioning and handling BSPs in your area. What was considered as helpful?*
> ***Interviewee:** To be honest, we had agreement from the beginning, that they would use the BSP on new patients. But, we had to put that into contract for that to happen. They (the Trust) did not just do it freely, they had to actually be contracted to do it. So, having the contract contractual lever were was very helpful as well…we do give incentives. We offered for the first BSP switch. We offered a 50% gain share on savings to be used for patient outcomes, you know, good outcome; for example, setting up a database or something that would benefit patients. And we offered that for six months period"* **(MWCP-09) (Specialised Commissioning & Interface Prescribing Advisor-Prescribing and Medicines Management Team)**

> *"Essentially, you have to put forward a business proposal to them (commissioners) that says: we will at this point consider switching all of our existing patients on infliximab for example over to one of the biosimilars; based upon additional nurses being available or admin person or whatever. We predict that we could approach. Say 50 patients a month of 100 patients a month or whatever. Then they have to go in and say: Well, that the savings that they would make from switching to the biosimilar is X thousands pounds, they would have to pay out X thousands pounds to pay for the staff and what is left would be their savings"* **(SACP-18) (Principal Pharmacist, Clinical Effectiveness & EPMA)**

> *"We need to do an additional number of blood tests that cost a certain amount of money; so we have been, all three provider Trusts in the area, Sherwood Forest, treatment centre and NUH have approach the CCGs and their unit and we said we would like to ask for share that savings to be transferred back to the provider Trusts, to pay for that, and to incentivise changing the treatment for the cheaper biosimilar"* **(PWCP-13) (Lead Pharmacist-High Cost Medicines Management)**

In discussing negotiations between Trusts and CCGs, the power dynamics between the two parties became visible. While the CCGs, the funder holders could, in theory, mandate the switch, Trusts could facilitate or hinder it based on the fact that NICE has left the decision of prescribing BSPs and switching stabilised patients to prescribers' clinical judgement and patients' acceptance and agreement (The National Institute for Health and Care Excellence (NICE), 2016b). Switching was actualised when collaboration was achieved, which depended on the CCGs being supportive and offering incentives and the Trusts securing prescribers' acceptance, welcoming offered support and incentives and, in some cases, taking the initiative and proposing the switch. In some cases, switching was actualised when the CCGs used their contractual powers to mandate the switch.

> *"Well, at the end of the day, the CCG is the only one that can agree any gain share. If they do not agree the gain share, then the Trust is not very likely to do any switching. So, the CCG has the upper hand from that point of view; they can incentivise. But the Trust can also refuse to do anything. It is a bit difficult. The better thing is when you got a Trust with somebody in it who can negotiate well with the CCG to get an arrangement in place that suits both parties. So, you get a win-win on both sides. But, it is not always possible. I am not sure that there is an answer, the upper hand, it depends on personalities. And both got the ability to the work"* ***(JPCP-16) (Regional Procurement Pharmacist)***

> *"Yes, what we have decided is as soon as we went to our regional society prescribing forum and it was discussed there with the other local hospitals and the commissioning CCG. We decided earlier on as the only hospital in this region, that we would not just start new patients on but we'd switch existing patients to the biosimilar. We debated which biosimilar to go for, we went for Inflectra® (IFX-BSP) but that was a different issue. There were two, three advantages, there is definitely cost issues, but also by switching to Inflectra® (IFX-BSP) we would be offered drug anti body and trough level for the first time which we thought that would improve care. Thirdly we were offered a further IBD specialist support in order to implement the switch which we thought would improve data collection and also improve overall care for IBD populations. It was very attractive, the switch option"* ***(SBGP-02) (Gastroenterology Consultant)***

> *"I think yes when the contracts are signed off as to who gets the money and when, they (commissioners) are often looking at trends of a number of patients that are on treatment. So we have to predict the number of patients they are going to treat each year. You know, there are penalties if you go way over. They come and audit to make sure they are using it appropriately. And I don't work specifically in commissioning so it is quite a complex area I am afraid"* ***(SCFP-16) (Consultant Pharmacist–Gastroenterology/Hepatology)***

> *"I think, they (commissioners) were led by us, I think we told them what we wanted, and they agreed, they, you know, we said we will do it. They actually asked for us to communicate with them about efficacy and how well it would have gone, so we have been sending them any data we have gathered, we sent that information to the CCG to say Look, it is fine, everyone is OK. So no, I think, they were very, actually for once, you know, it is happening, they are listening to clinicians and they listened to us. So no, it was fine"* ***(PANS-03) (Lead Inflammatory Bowel Disease Nurse Specialist Gastroenterology)***

On the other hand, hindering and delaying the switch were the results of conflicts and disagreement between the two parties. Unsupportive CCGs, resisting Trusts that asked for more than was offered, and prescribers' reservations were reported to hinder the switch. In some cases, lengthy negotiations and hesitation among negotiating parties delayed the switch.

> *"I am keen to use biosimilars as soon as I can, because as commissioners obviously we pay the drug bill for a lot of these products. So, we keep trying to bring down drug bill as much as we can….So, the uptake, the uptake is very important to me. But the clinicians are unwilling to implement biosimilars, because they are not, because they do not believe, that it is the same. That makes a problem to us. If a clinician wants to try it at first, utilising it to gain a bit of experience first, then that it is OK with me. Because it means that it is a more controlled way of introducing the products into the market, and if they just need the experience and they need the confidence in the use of the sort of products. That is fine. It is clinical judgement after all…But, ultimately, like I have said, my main aim is to make sure that biosimilars are out there, that they are being used"* ***(KLCP-04) (Head of Medicines Management)***

> *"**Interviewer:** When you mentioned that you have lengthy discussions with one of your Trusts that you have, what was considered as a barrier? So why did it take a long time?*
> ***Interviewee:** Well, the clinical argument is over the direction they wanted to go, and there is a discussion on how big the gain share would be and how long it would last. Then they had their own internal discussions about if the hospital is making a million pounds out of the gain share, how much actually heads to the department?*
> ***Interviewer:** So when you mentioned directions, can you please just elaborate a little bit more?*
> ***Interviewee:** If they are going to do it or not, because ultimately the consultants said "clinically, we do not feel that this is appropriate." No matter how many directors from the department of Health"* ***(PJCP-12) (Primary Care Development Manager)***

> *"I think we would need more support from our CCG because they don't actually seem to support any....they haven't so far supported any gain share proposals, which would help us to focus resources on introducing biosimilars"* ***(LMCP-14) (Lead Pharmacist for Operational Services)***

> *"Well, we are in the early stages of that, the.... there really has not been much interest actually. Sort of surprisingly, we made some initial sort of approaches about whether we would have a gain share agreement, so that if we have switched patients, whether some of, you know, money saved for the CCG would actually come back to us. But after these very short initial discussions, they really did not seem interested in pursuing that at all. So that, that has rather killed that, really"* ***(PRPR-04) (Rheumatology Consultant)***

Factors related to: (*i*) regional level negotiations, (*ii*) engagement of prescribers in discussions, (*iii*) established good communication channels and (*iv*) proactive involvement of lead clinicians, were all identified to have had positively driven the negotiations between Trusts and CCGs. Interestingly, while engaging different professionals was perceived to positively influence the negotiations, patients, who are the end users and ultimate adopters of BSPs, were either not represented or had only very limited involvement in these discussions.

> *"We are part of, like, Yorkshire regional procurement contracts, so whenever there is a new biosimilar, there is like a regional team that assess it and make, kind of, a recommendation about it. So, when we are deciding if we are going over or not, we get a lot of the clinical trial data and consider it and discuss it with the clinicians and the nurses and within pharmacy. And, obviously, the product, you know, the licensed as well, we look at the data we get, which usually come from the Yorkshire regional procurement team, and we make decision on that really, that usually goes to our... we got something called medicines management committee which is a bit like Drugs and Therapeutics Committee, So, they will have a look at the evidence as well. So It is basically comes from recommendations from like a regional group, but also the Trust has a governance body that looks at the data as well…Our regional procurement group, because they are encouraging people to change. Yeah, there is a big driver to use biosimilars, and it has been very easy to get the information that we need. Yeah, we have not found it a problem"* ***(PDFP-03) (E-Prescribing Pharmacist)***

> *"**Interviewer:** Who was involved in these discussions? Is it only physicians, pharmacists or other stakeholders?*
> ***Interviewee:** It's a combination, its clinicians, infliximab we spoke about with the rheumatology and the gastroenterology teams, so not just consultants but specialist nurses etc. as well. Certainly, some of them were pharmacy led as well so pharmacists were always involved. And the models in different hospitals as to who has been managing the switches etc. It was a mix of clinical people but also then looking at the impact on sort of commissioners not just within pharmacy but outside and also contracting of finance staff as well. It has been a bit of a mixture really.*
> ***Interviewer:** What was discussed in these meetings?*
> ***Interviewee:** Obviously the clinical teams were looking at the clinical aspects and the practicalities of exactly how a biosimilar could be introduced. So looking at really, down to the individual patient's level, what was going to be monitored, how the messages were going to be delivered to the patients, how to get consent and then how to do the actual switches. And the financial contract inside was actually about, you know, the contractual issues around say for example a gain share or something like that. So it depends who you are speaking to as to what element you are picking up"* ***(MRCP-05) (Senior Commissioner Pharmacist)***

> *"It is probably me, sorry! I have driven the process for the last twelve months, and I might be the lead, the lead inflammatory disease lead clinician. So, it is probably me who pushed most of this in unit with on my colleagues, after discussions with colleagues, and commissioners and Trust management staff. That is the best thing for everyone. So, yeah, I have led most of the discussions"* ***(GMGP-03) (Academic Gastroenterology Consultant)***

> *"Interviewer: And, were there any discussions with patients or patient representatives in these meetings before the introduction of biosimilars?*
> *Interviewee: No, not to my knowledge. We do not have a very active patient group, here in Nottingham. There is a group. But, do I think it is needed? Not necessarily provided that we are informing every patient, which we are. That's my opinion. I think it creates complications because it's very easy to get somebody who decides that patients are being, somehow, disadvantaged by it, which I don't think is the case. So, we do... we have a duty to inform every patient, which we will. But each patient is informed individually rather than having a patient group, you know. The discussions are being long enough and complicated enough, without any additional"*
> ***(AJGP-05) (Gastroenterology Consultant)***

In summary, while assessing BSPs and switching attributes had identified factors that influenced stakeholders' attitudes toward utilising BSPs, interactions between stakeholders had identified factors that influenced the decision toward or away from a switch. For incentives to directly influence prescribers' attitudes toward guidelines and practice procedures is a frequently reported phenomenon in the literature (Cabana et al., 1999). The well-established communication channels resulted in developing a joint agreement towards the switch; these channels helped different stakeholders to communicate and to understand each other's perceptions.

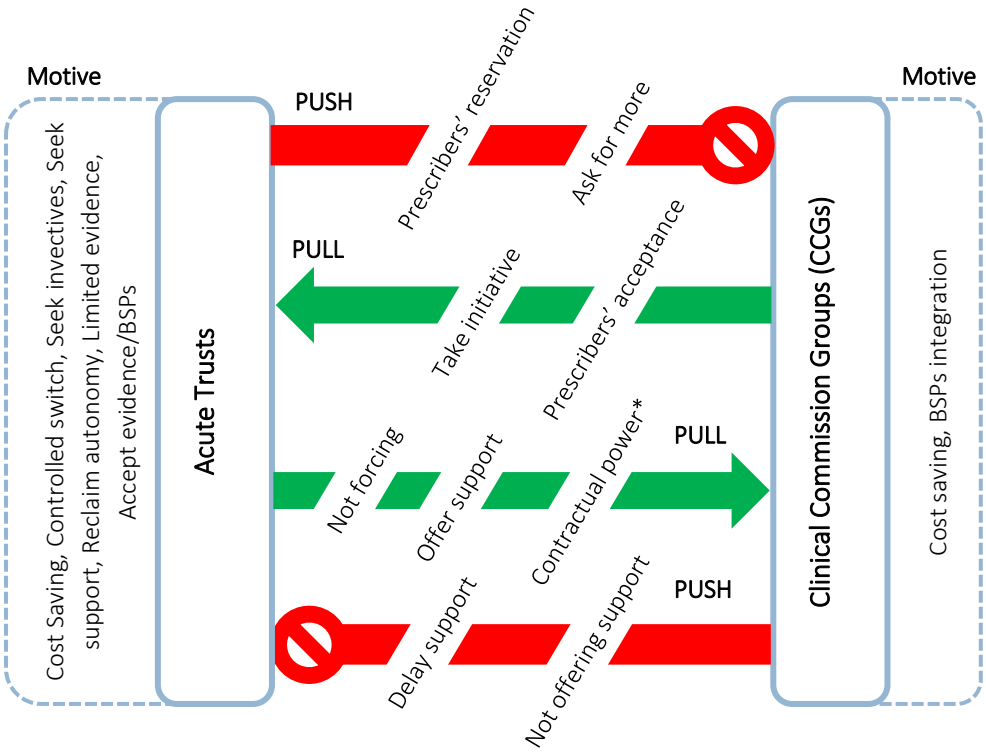
5.5.2. Decision theme summary

Negotiations between Trusts and CCGs aimed to capitalise switching's positive attributes and to minimise and facilitate its negative (challenging) attributes. During negotiations, each party relied on their tools to influence the negotiations in a way that satisfies their motives and agendas. The observed dynamics could be explained as a *Pull-Push* model (Figure 12).

Discussions were based on identified switching's requirements and, in some cases, what was reported in the NICE implementation guide. However, as some sites followed a multi-disciplinary approach in negotiating BSPs' integration, an overlap between the persuasion and decision stages was observed; the stages were closely linked and it was not possible to determine which occurred first. The spontaneous occurrence of more than one stage or of different sequences was also proposed by Rogers (2003) and confirmed by real-world and practical evidence.

The decision theme helped in clarifying the roles of involved professionals as per the following: (*i*) prescribers and nurses as adopters, (*ii*) high cost medicines and formulary pharmacists as mediating agents and (*iii*) commissioners as change agents. The role identity will become more visible at the implementation stage. Figure 13 provides a summary of the decision theme.

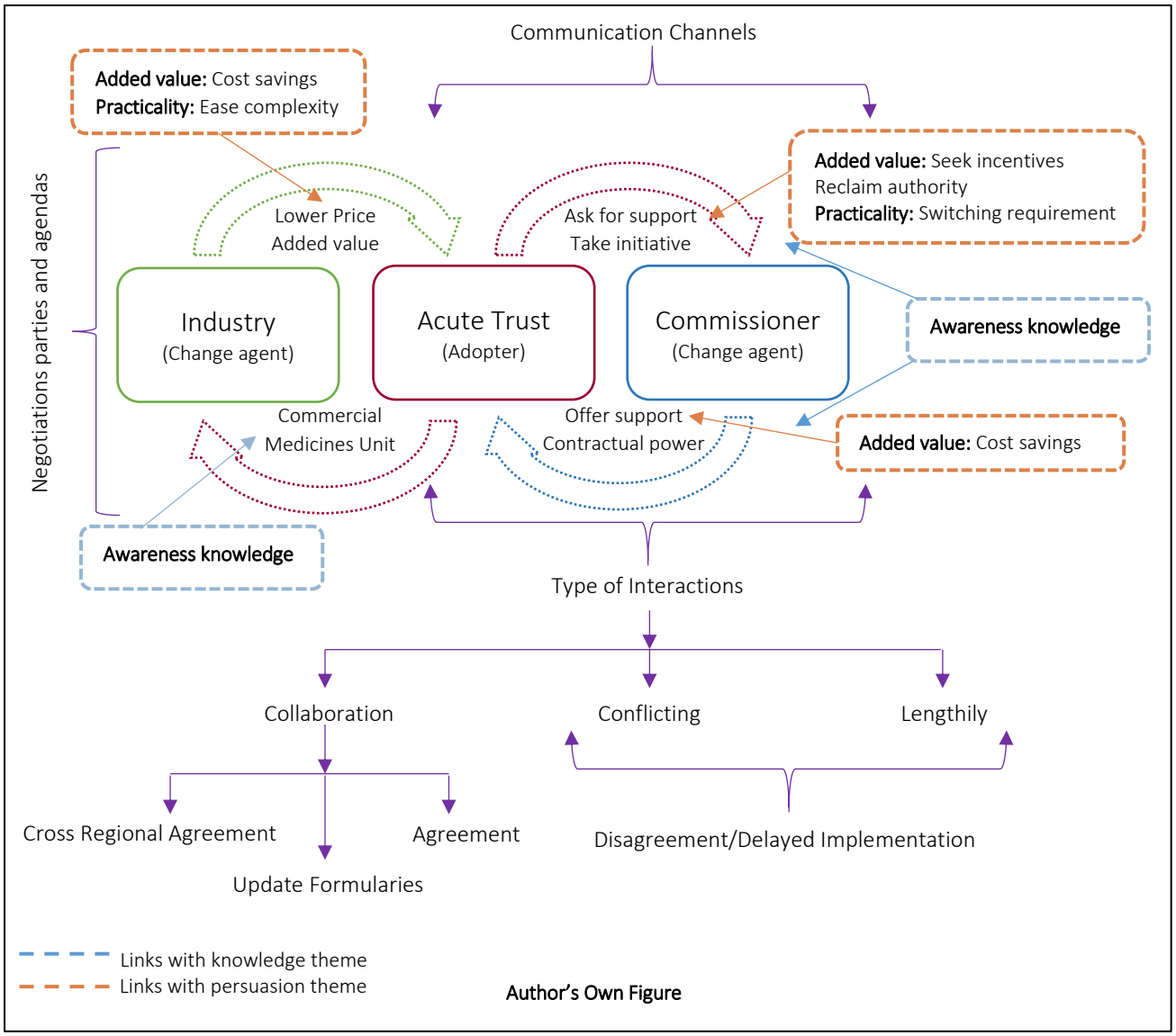
Figure 12-Pull-Push dynamics between Acute Trusts and CCGs



Pull: collaborating, encouraging, supporting and mandating
Push: Conflicting and delay
***** Contractual power is not a supportive mechanism, but it actualises the switch

Authors' Own Figure

Figure 13-Decision theme summary



5.6. Theme four: Implementation process and outcomes

Implementation is the stage at which the adopters actualise their adoption decision; it is the stage at which "the innovation is put into practice" (Rogers, 2003). In theory, implementation is perceived to directly follow the decision stage; however, in some cases it could take a loop-like approach, where the implementation occurs before the adoption decision is finalised; especially if there are logistics related issues (Greenhalgh et al., 2004). As noted earlier, main discussions were related to introducing the switch; therefore, findings presented in the following sections refer to 'switch implementation' rather than BSPs' prescribing in general.

Commonly, professionals who are involved in implementing an intervention are not the ones who took the adoption decision. Therefore, despite the fact that implementation might be perceived as the practical stage, it will still involve knowledge and information-seeking and disseminating activities (Greenhalgh et al., 2004, Rogers, 2003). In this research, in addition to the effect of communication and information sharing activities in facilitating the switch implementation, the implementation stage had witnessed the emergence of new adopter categories and changes in role identities. At this implementation stage the role of patients as adopters became clearer; also a switch in prescribers' identities from the perspective of their patients, from adopters to change agents, was observed.

At the implementation stage, technical personnel's role became visible (Rogers, 2003). In this research, in discussing implementing the switch, the voice of Trust-based participants became more dominant; as it is expected the majority of commissioners did not have first-hand experience in implementing the switch. The implementation stage was based on five main dimensions: (*i*) internal communication and dissemination, (*ii*) informing and consenting patients, (*iii*) prescribing practice and management, (*iv*) service design and (*v*) professionals' involvement. Implementation practicalities varied between sites, which reflected the variations in agreement each site had and confirmed the variations observed in Chapter 4.

5.6.1. Internal communications and the dissemination process

Communications within the Trust or service took place at different stages of the adoption process; whether before, during or after CCG-Trust negotiations. In most cases, internal discussions aimed to assure prescribers' agreements, identify the switch requirements and ensure relevant professionals' awareness of the switching decision and the agreement with the CCGs. Communicating the switch was either achieved through the already established communication channels within the same therapeutic area, or with the pharmacy department, or, in the form of Trust-wide policies, mandate and newsletter.

> *"Well I mean, you know, we have got a very good, we're very multidisciplinary, we've got a pharmacist sitting and we have got a specialist pharmacist who works with us in our multi-disciplinary team, (XXX), so she, you know we were talking about it, we knew that it was coming and the specialty dermatology, rheumatology and inflammatory bowel disease, we have had ongoing discussions in person and on email as to the clinical leads as to whether or not we want to do it, whether we got any concerns about doing it, the introduction of infliximab was a graded approach, so that was a first biosimilar that we used and the inflammatory bowel disease team used it first in their patients and we been sharing experience and on how that went"*
> ***(CSDP-06) (Professor of Dermatology & Therapeutics)***

> *"Okay, basically, we kind of have a team management meeting; I have already taken this through to them. I took it through to my colleagues and said look what do you think and they all kind of, you know do you have any major problems with it. So basically when I say I, I kind of mean 'we' but I just happen to be leading on it. It is all being discussed with my colleagues, in terms of the potential, you know… whether we think it's a good idea or bad idea, and if we do go down that route, how we might use it, how we look at the gain share aspect of it. What we think what would be, what the logistics of switching would be and, you know, how we would like to plough back a little bit of that money into patient care you know opening up on our pathway, a bit"* ***(SORP-02) (Consultant Rheumatologist)***

> *"Actually it was announced at our department meeting after the deal had been done, and the people who had done the deal were saying it was a great victory for our Trust, because they are going save a whole heap of money and then the finance guy at meeting then suddenly announced that NHS England had said that these savings can only be for one year, then you get nothing. So it sounded like that these people had done this thing that they thought was a great deal that is going to save us heaps of money, and then the finance guy told them that "Actually no, NHS England has said that you can only get that saving for one year"""* ***(NBRP-05) (Rheumatology Consultant)***

Involving relevant professionals, mainly prescribers and nurses, in discussing the switch might be an approach to confirm prescribers' status and ensure their autonomy, as if the decision is theirs. Being involved ensured prescribers' acceptance and collaboration. The emphasis of being involved, or at least being notified, in deciding the utilisation of BSPs, was also reported in studies assessing prescribers' attitudes toward BSPs (Reilly and Gewanter, 2015, Dolinar and Reilly, 2014, O'callaghan et al., 2017).

> *"So, they (pharmacists) very much liaise, as I said, with us, provide us with all the information, seek our advice early on, and keep us informed. So, when we are going through service level agreement with Benepali® (etanercept-BSP brand), sort of homecare provision. We just kept informed and we are asked for our opinion, so what we thought, you know, would be a concern through the process"* ***(HSRP-06) (Rheumatologists)***

Despite the fact that IFX and etanercept-BSP are indicated in different therapeutic areas, limited interactions and communications between the targeted areas were reported. In some cases, professionals in one area did not know what the other areas were prescribing (BSPs or R-BMP), or how (switching or initiating). When interactions between areas were reported, these were mainly between dermatology and rheumatology; a relationship which might explain why the management of some indications, such as psoriatic arthritis, needs the involvement of both therapeutic areas.

> *"Well yeah it is interesting, and I know other units is doing it in a different ways, and to be honest half of the problem we all work in isolation these days, so we never quite know how other people are doing it. None of that has sort of come out yet"* ***(SORP-02) (Consultant Rheumatologist)***

> *"I am not sure... I know what the rheumatologists are doing, because we had some discussion with them. I am not sure what the gastroenterologists are doing…Yeah, I mean, I think the rheumatologists in our Trust are taking the same stand as our Department; to not to switch people who are already established on drug to biosimilar"* ***(DSDP-03) (Consultant Dermatologist)***

> *"Well we have a combined clinic with the patients with psoriatic arthritis and psoriasis. We have some interactions with rheumatologist as far as that group of patients is concerned, but I'm not aware yet of those being switched to either. Because, again, we do not use much etanercept or IFX in those patients"* ***(CGDP-04) (Foundation Professor of Dermatology)***

The reported limited communications between therapeutic areas might explain the observed differences in IFX-BSPs formulary listing between those targeted areas. Active communication could serve as a medium through which knowledge and experiences are shared and transferred. Communications help in creating organisational memory, which facilitates the adoption of new technologies based on previous knowledge and experiences (Rogers, 2003, Williams and Brown, 2014). In other words, having proper communications, especially between areas that have an experience in implementing BSPs, avoids the possibility of "reinventing the wheel", thereby preventing the waste of time and resources.

5.6.2. Patients' communications and positions

Patients are the end-users of any healthcare intervention, including medicines. Therefore, it is their right to be informed and to provide or withhold consent before a prescriber proceeds with prescribing and administering a medicine, whether biological or chemical. Measures and procedures followed to notify and obtain consent from patients were mainly targeting stabilised patients, who were eligible to be switched. Notifying new starters (biological naïve patients) was considered as part of everyday practice that does not require special measures. The emphasis on notifying and obtaining consent from stabilised patients comes in alignment with NICE recommendations that patients have the right to receive transparent and honest information and to be involved in the decision of prescribing BSPs (The National Institute for Health and Care Excellence (NICE), 2016b).

> *"For new patients in particular there should be no problem with the some being used as first line agents. I think that changing of a stabilised patient, I can understand that there might be slightly more concern about that"* ***(STCP-10) (Medicines Optimisation Pharmacist)***

> *"There will be when it comes to switching, but not as regarding implementing in new patients. But all the new the patients have been counselled that they are on a biosimilar drug"* ***(VRFP-15) (Specialist Clinical Pharmacist-Specialist Medicine)***

In patients' communications, while few sites relied on group communication to pave the way for introducing the switch to patients in early stages of switch planning, almost all sites followed individual communication during the switching process. Group communication tended to be educational; the switching plan was shared with patients, who were given the opportunity to ask for more clarification regarding the procedure. On the other hand, individual communications ensured patients' approval and consent that were needed in order to proceed with the switch.

> *"We had a meeting with Crohn's and Colitis UK...We had a meeting that was organised by Crohn's and Colitis UK in the local area, which was an educational evening and the question was asked at the meeting and the other... this city has got two Trusts, two big Trusts, and the other side of the city, the North side of the city had already switched, and somebody asked about that, and we said yes, we would be doing the same thing and we explained to them that there was a there was not an inferior product, and in fact it was a lot cheaper, so made a lot of sense…..We formulated a letter, which we sent out to patients, explain to them what BSP was, why we wanted to change, and the cost saving that would mean for the CCG, probably the cost saving is not for us, so we have a bit of a gain share from it, and the fact that it allows us to have another nurse, which obviously important. And then I contacted each patient with that letter, when we switched them, So as I prescribed it, because I am the one who prescribe it and then switch them and send the switching letter… And then I spoke to any patient who had any concerns, which was about 6 phone calls, and one patient I saw in clinic, who did not want to switch, and so she did not switch in the first round, but she switched when she came in for her next one, because in actual fact, she could not find a reason not one"* ***(AFSN-01) (Lead Inflammatory Bowel Disease Nurse)***

In discussing individual communication, participants highlighted the effect of service design on the selected communication approach; while clinic-based IFX patients were contacted directly: face-to-face or over-the-telephone. Homecare etanercept patients were indirectly approached using a patients' information letter. Some sites had adopted both approaches by sending an information letter following or before face-to-face or over-the-telephone discussions between patient and clinicians, mainly nurses. Direct communication might be perceived to be a more personalised way of communication than indirect, notification letter based communication. However, evidence from literature showed that patients positively perceived an information letter, as it acts as a point of reference for them whenever they need to check their information (Boons et al., 2016). However, in this research, it was not clear if one approach was preferred over the other; whether by participants or by patients. The selected communication approach was mainly influenced by practicalities related to service design, capacity and availability of staff.

In communicating the switch plan with patients, the main discussion points were related to: (*i*) specifying switching time and the product to be prescribed, (*ii*) assuring patients by explaining BSPs' concept, available evidence, prescribers' acceptance of the switch and continuous disease management and monitoring, (*iii*) explaining the reason for the switch and how it would benefit the NHS and lastly, (*iv*) offering time to consider the switch and the chance to ask for more information. Participants stressed the importance of following a transparent, clear and informative communication approach with patients. Interestingly, some prescribers used the phrase "exactly the same" when they described how they explained BSPs' concept to their patients. Describing BSPs as being "exactly the same" might be problematic and misleading. However, this observation was based on what the prescribers had said and recalled from memory, it was not verified by obtaining a copy of the patients'

information letter or by attending any patients' counselling sessions. As a result, this observation needs to be cautiously considered and reported.

> *"Very similar to how I have just described them to you, that they are basically the same drug, with the same action. But they are going, you know, the same result will be, hopefully, clinical remission of your symptoms. And as far as we have concerned here, that is how we presented it. That they were the same, but we have to call them biosimilars, for legal reasons… What we promised them was closer monitoring during the switch…. if they ask the question 'why you are doing it?', be honest and say because it is a lot cheaper, and it is going to do the same thing. So, that is an easy conversation to have, I think…"* ***(PANS-03) (Lead Inflammatory Bowel Disease Nurse Specialist Gastroenterology"***

> *"If a patient refuses to switch, there will be nothing further. They will continue in the one that they are on"* ***(SACP-18) (Principal Pharmacist, Clinical Effectiveness & EPMA)***

> *"How do we describe them... we say that they are exactly the same, it has come off patent, and that the evidence says that they are extremely safe, and we wrote to them informing them that we are going to change and sent it, and that worked very well"* ***(ABGP-04) (Gastroenterology Consultant)***

> *"So, we have produced a standard leaflet in convention with our pharmacist. And, essentially in that leaflet, we have sort of laid down saying that it has exactly similar to the originator products. The originator products, anyway, have undergone many changes over the years, and therefore, we think that these drugs are, you know, pretty comparable to what we have been using until now. So, that is basically a summary of what we have described"* ***(SSGP-01) (Consultant Gastroenterologist)***

Adopting a transparent approach in communicating with patients echoed participants' ethical obligations toward the patient's 'right to know' and to provide or withhold consent to the switch. It is also in alignment with national patients' support groups, such as Crohn's and Colitis UK, and the National Rheumatoid Arthritis Society (NRAS), in describing the similarity concept and the unfeasibility of producing identical molecules (National Rheumatoid Arthritis Society (NRAS), 2017, Crohn's and Colitis UK, 2015).

The desire to follow a detailed approach in describing BSPs to patients was also reported in at least two studies, which examined prescribers' attitudes toward BSPs' prescribing and switching (Hemmington et al., 2017, Danese et al., 2014). Moreover, in recent studies that targeted rheumatology and gastroenterology, those patients demanded to be notified about which brand they were being prescribed and the potential ADRs and associated risks with the prescribed BSP (Peyrin-Biroulet et al., 2016, Aladul et al., 2017b). Therefore, providing informative messages to patients might satisfy patients' demands, ensure patients' acceptance of the change and facilitate switch implementation.

5.6.2.1. Patients' positions

In general, patients were reported to have positive attitudes toward BSPs and had consented to the switch. As reported by participants, patients' positivity was triggered by trusting prescribers' medical judgments and assurances they received regarding their health and disease management. Patients' understanding of the switch's potential financial impact on the NHS budget was also reported to have positively influence patients' positions.

> *"And as I said, the patients have great faith in the consultant and they seem to have faith in us as well, yeah we have not had any resistance from the patients. Well, whether the consultants have in the clinic, I do not know, but I have not heard anything"* ***(RDSN-05) (Dermatology Nurse)***

> *"I think a lot of the patients understand the benefits of the BSPs in terms of releasing money that can be utilised to treat greater number of patients I suppose with those medicines to benefit from them. I think the majority, when they have been given information and evidence to explain why we want to switch them, have had accepted that"* ***(DACP-17) (Regional Medicines Assurance and Lead Procurement Pharmacist)***

For some participants, patients were not truly free to refuse or to challenge the switching decision; the decision had already been made *for* them, not *by* them. This might be true, especially for those patients who had only limited involvement in pre-switch discussions; and bearing in mind that the gain share agreements had already set a target of percentage of patients to switch over a specified time period.

> *"I suppose when it comes to the point of switching all the existing patients there would have to be some form of discussion with the patients. But it's not really a discussion in the sense of 'do you want to switch or not?', because CCG are saying they will only pay for the biosimilar, then the patients choices are going to be either switched to the biosimilar or you have to stop your treatment, so there won't be an option to continue on the drug that they are on. So it's not really a discussion, I suppose it is just informing the patient what is going to happen"* ***(NBRP-05) (Rheumatology Consultant)***

> *"Bear in mind that patients do not have much of choice, because our CCG will not fund non-biosimilars when biosimilars are available, so that decision had been made at regional level. So really, unless for clinical reason, which there are not really any, then they all get switched"* ***(BWDP-01) (Dermatology Consultant)***

Cases of patients' refusal to switch were also addressed; however, almost all participants stated that disagreement was not a frequent phenomenon. Patients refused out of fear of deterioration in their health status or increased anxiety. Some patients perceived BSPs as cheaper products of inferior quality. Factors related to patients' demographics, in terms of age, gender or life factors, were not reported to have an influence on patients' attitudes toward the switch. Patients who declined were dealt with on a one-to-one basis; prescribers, mainly nurses, investigated the reasoning behind a patients' disagreement and tried to reassure them regarding the efficacy and safety of BSPs.

> *"So, we have patients who straight, who have immediately said no we do not want to switch. Very few who have actually expressed the concerns, we have not explored their concerns yet. But, we have one or two who have very much, are reluctant to change... We have a patient cohort who are reluctant to change treatment anyway. So, we have a particular group of patients, who do not want to change whatever treatment they are on…Well, honestly, it is their nature. So, anytime, we come across some patients, who anytime you want to change the treatment, are reluctant to change, and we have that. Obviously, we are dealing with a lot of patients with chronic disease, and they feel they are doing quite well on the treatment, you know, do not want to rock the boat, they do not want to change, do not want to have something new, something different that could probably give them side effects or not work. So, we do have that a general feature in patients with chronic conditions… I would say the patients, the patient that has refused, and the one who has said no. Is actually slightly older... No, it not, it is actually across ages and across gender, this feature. It is not, you know, it is not specific"* ***(HSRP-06) (Consultant Rheumatologist)***

> *"One patient was reluctant to switch and after a further discussion switched. All the others had no problem…the only one patient thought he was been giving something cheap because he works in a non-medical part of the NHS. He thought he understood that the NHS was full of rip-offs, cheap drugs and he was not going to have one, but he was corrected on that"* ***(CPGP-06) (Honorary Consultant Gastroenterologist)***

Another factor that might affect patients' attitudes toward the switch is the peer-effect; in this case the potential for patients to influence each other. Participants have reported a mixed picture; while some considered that patients are able to influence each other either directly, through face-to-face interactions, or indirectly through social media, others failed to notice any effect of patients' opinions influencing each other's attitudes. National patients' support groups presented another form of peer-effect, as they provide informative and educational materials for patients, which were referred to, at some sites, in discussing the switch with patients.

> *"We find the patients sitting next to each other will say, "Oh, I'm on the new one." Rather than someone saying, "I'm on the old one", "and it's half the price". So you get a kind of interaction between patients. So we've had no problems with the patients we have initiated it on. We don't anticipate there will be problems when switching"* ***(PDFP-17) (Head of Pharmacy & Quality Control Laboratory Services)***

> *"I don't know the answer to that question because our patients never get together. They receive their Infliximab at one of our medical day-case centres. They don't get to socialise with each other. I don't think they really meet"* ***(MSFP-04) (Senior Pharmacist-Medicines Information, Formulary & Clinical Economy***

> *"I think, the advent of forums. So, you know, the IBD forums that you can go into online and things like that. I think that affects people's perceptions and decisions, yeah. So, yes, I think* they *are affected by others. Interestingly, I would say, they haven't been, I've have nobody saying to me "Well my friend is having the drug somewhere else, and they are not switching." I haven't had that conversation with anybody in this. But, normally, I would say, IBD patients are very affected by others, by each other, yeah"* ***(PANS-03) (Lead Inflammatory Bowel Disease Nurse Specialist Gastroenterology)***

> *"Not so far, the ones I have seen, I've met with a few people who represent these big societies and by and large, they're supportive of the introduction of biosimilars so long as care is taken to make sure that the patients are fully informed about the processes and that they're involved in the decision making process, rather than being told what they have to do…So, yeah, and that was the key message that came across from, I can't remember which patient society, which patient group it was but yeah, the minute you start doing them to the patients, they get very twitchy about it. But if you have a good process for informing and gaining consent, they were okay with that. And you know, that's a sensible position to take, because actually there is no reason for, or there's no clinical reasons for objecting to the use of biosimilars, so"* ***(MDCP-07) (Head of Medicines Management)***

Emerging evidence showed that good patient-prescriber relationships, patients' trust in their prescribers and understanding the potential impact (benefit) of utilising BSPs on the NHS, had positively affected patients' attitudes toward a switch. These factors were reported in a recent survey of rheumatoid arthritis patients, who were prescribed BSPs, in the UK and in a 2016 survey which targeted European inflammatory bowel disease patients (Peyrin-Biroulet et al., 2016, Aladul et al., 2017b). In addition to the main factors, actively involving individual patients through providing sufficient explanation, assurances, and enough time to consider the switch, might encourage patients to accept the change. The same was reported to positively affect patients' acceptance of conventional generic medicines (Dunne and Dunne, 2015).

Similar to generic anti-epileptic medicines, factors related to disease severity, risk of losing control and perceived inferior quality of the generic products, negatively affected patients' acceptance of BSPs and the switch (Crawford et al., 2006, Krämer et al., 2007). These factors might explain the reason why some prescribers asked for extra monitoring for switched patients, as well as discussing aspects related to after-switch and therapeutic failure management in planning for the switch.

As factors reported to be affecting patients' attitudes toward the switch, including a possible peer-effect, were not directly reported by patients but mainly by prescribers and nurses, informed by their interactions with patients, these findings need to be carefully considered and interpreted.

5.6.3. Service design

Data showed that similar factors influenced the adoption of IFX-BSPs and etanercept-BSP. However, differences were observed during the implementation stage, as the two products are delivered through different service routes: clinic based for IFX-BSPs and homecare for etanercept-BSP.

During the persuasion stage, the available BSPs were found to be fit and compatible with the already established service designs. Therefore, the introduction of these BSPs did not represent radical changes in service delivery.

> *"How do I think they have affected the current service design? To be honest with you, I don't think it has changed very much yet. We are providing the service in exactly the same way as we were doing. It's just patients are having biosimilars instead. Like I say I think as more products come to market, I think we are going to start having some different discussions about patient pathways and how we use the new drugs. But we are certainly not there yet"* ***(LSCP-15) (Interface Pharmacist)***

While factors related to clinic capacity and infusion rate affected the implementation of the IFX-BSPs switch, practicalities related to contracting a reliable homecare company, proper and continuous supply and device design were influential in the case of etanercept-BSP. In switching etanercept-stabilised patients, it was important to minimise the possibility of medication error by avoiding any confusion between the two products. It was also necessary and to ensure that patients are adequately trained to use the new device, which was reported to be slightly different from the R-BMP one.

> *"So, I think it is probably different for those two products. Because, particularly around how they are administered to patients. So, for IFX being infusion as patient attendance at the hospital, on a six or eight weekly basis depends on the frequency of their infusions. So, considerations are really around capacity in the infusion clinics"* ***(DACP-17) (Regional Medicines Assurance and Lead Procurement Pharmacist)***

> *"So, again, it is…So, let's talk about etanercept that is the most common one at the moment. For me, it is how this switch can be managed, i.e. the price; number two is, are we going to have a smooth transition, because what I do not want o is wasted drugs or patients not having supply. So, making sure, the patient is informed of it. So, they know that they are going to have potentially two different products in their fridge for a little time to use one up and switch over, or to make sure that they have got their supply. And, if it is a change in any way it is given, sufficient education available and information given to make sure that patient knows what they are doing. Because at the end of the day, what we do not want, is a cheaper drug not to be used or used incorrectly because they may not want to use it in the first place"* ***(BFCP-01) (Interface Pharmacist Lead-Clinical Effectiveness and Medicines Optimisation Team)***

> *"We have got a contract with a homecare company, they are supportive of switching from one product to another and the company that we are switching to, the BSP company, actually offer at home nursing visit, so everybody who is now in the process of switching etanercept brand gets a nursing at home visit to explain the change and deal with any issues. Because it is a slightly different product, the device used for the injection is slightly different from the original brand. So, the homecare company has been fine, has been quite helpful in terms of paperwork and change and ... Yeah, they have been absolutely fine, yeah. No problem so far"* ***(PDFP-03) (E-Prescribing Pharmacist)***

In addition to difference in practicality, the service design affected the form of the extra services (added value) offered by the industry and the main approach of patients' communication, direct for IFX-BSPs and indirect for etanercept-BSPs. Table 25 summarises the differences between the two service delivery routes.

Table 25-Summary of differences between the two service delivery routes as emerged from data

Criteria	Clinic base (intravenous route)	Homecare (subcutaneous route)
Product	Infliximab	Etanercept
Logistics	Clinic capacity	Homecare company
Administration related	Infusion rate	Device design/ease of use
Added value	Compounding (pre-prepared infusion bags)	Patients training (nurses and/or information/educational material)
Product's visibility	Unclear	Clear
Communication approach	Direct (one-to-one meeting/phone calls)	Indirect (patients' letter)

In addition to practicalities and contracting, participants discussed how the differences between the two routes of service delivery affected the products' visibility and its recognition by the patients. Being an intravenously administered solution, patients were not able to tell the difference between the IFX-R-BMP and IFX-BSPs, especially if the compounding did not take place in front of the patients. Therefore, patients were not able to tell if they were receiving the R-BMP or the BSPs. On the other hand, with differences in product presentation and the self-administration devices, etanercept patients easily noticed that they were receiving different products after they were switched.

> *"I think with IFX the patient does not necessarily see the box so much, they just see the bag getting hung next to them, and they about sure it is IFX. I think the bigger issue may come when the patient see a different product so with the etanercept and adalimumab those being injections the patients can give themselves at home. When they are seeing something different come in, then it may be, a sort of, a more complicated switch to make sure that their confidence is at the side of the product that they're getting is appropriate for them"* ***(PMFP-07) (Medicines Management Pharmacist)***

Logistics related to service design presented a practical application of compatibility considerations, which were discussed in planning the switch. The link between the two stages, persuasion and implementation, was also confirmed by Rogers (Rogers, 2003).

5.6.4. Prescribing practice, monitoring and management

The fourth demission of the implementation stage was about how the prescribing process was managed and control. Three main elements relevant to prescribing and switching to BSPs emerged from the data: (*i*) the prescribing approach and practice, (*ii*) after switch patients' management and (*iii*) prescribing management and control. These three elements reflected, to an extent, factors that were discussed during BSPs assessment.

5.6.4.1. Prescribing practice

Although the implementation stage is characterised by the active involvement of Trust-based professionals with minor input from CCG commissioners, when discussing prescribing approaches most commissioners were aware of the Trusts prescribing approach (initiation or switching). This observation might be explained by considering it is in the commissioners' best interests to promote BSP utilisation, as they are responsible for commissioning BMPs in the targeted disease areas. Therefore, some data related to prescribing approaches emerged from commissioners' interviews.

Chapter 4 showed that English Acute Trusts had followed varied prescribing practices of IFX-BSPs; with some classified as 'switchers' (concurrently initiating biological naïve patients and switching stabilised patients); while others were labelled as initiators (initiating biological naïve patients and maintaining stabilised patients on R-BMPs). Qualitative data confirmed the observed variations between Trusts and therapeutic areas. Discussions showed how prescribing norms, variations in attitudes and agreements which were observed and discussed at the persuasion and decision themes, were actualised and reflected in practice.

Similar to what was discussed in the persuasion theme, prescribing guidelines and common practices influenced which therapeutic area to be prioritised for implementing the switch. Gastroenterology services were reported, in most cases, to be more involved than the other two areas, dermatology and rheumatology, in switching their patients to IFX-BSPs. On the other hand, rheumatology services were more willing and engaged in switching their etanercept-cohort than their IFX-cohort. However, some Trusts had witnessed wholesale switching for all their patients in all targeted areas.

While there were Trusts that went for a wholesale switch of all their stabilised patients in all targeted areas, other Trusts limited their BSPs utilisation to the initiation of biological naïve patients; a decision informed by (*i*) prescribers' reservations, (*ii*) issues related to logistics and practicalities or (*iii*) lack of incentives and support. Some Trusts had followed a gradual approach in introducing BSPs by prescribing BSP for biological naïve patients first, then after a while switching their stabilised patients. Gradual introduction of BSPs represented a case of 'trialability'; gradual switching was an approach by which BSPs' safety and efficacy were confirmed by first-hand experience, which then made prescribers more confident and accepting of switching their stabilised patients.

In managing chronic disease, the aim of initiating medicines is control of symptoms; however, the aim of switching is to maintain an already established control (Krämer et al., 2007, Crawford et al., 2006). Therefore, some Trusts had excluded patients with complicated or challenging disease histories from the switching process, due to the sensitivity of the patients' disease condition.

Patients' demographics in terms of age or gender were not perceived to be influencing the switching decision. However, this finding needs to be carefully considered as most of interviewed professionals were involved in providing and commissioning services for adult patients and not paediatric patients.

> *"As I said, stable patients, so patients that we thought were losing response whose doses have been increased or had anti-bodies, they were not being switched, I can't give you details of how many that applies to"* ***(CPGP-06) (Honorary Consultant Gastroenterologist)***

> *"Dermatology are going to do a three-phase switch. They are going to take their stable patients first then they are going to move onto the stable psoriasis patient's first, and then they are going to move on to their psoriatic arthritic patients, and finally any patients who has got an unstable disease, they will look at those last to make a decision on what they are going to do with those…Whereas rheumatology are more keen to keep all their patients on IFX because they tend to be, the rheumatology patients with eye involvements who've got quite unstable disease so they do not want to do anything that might lose control of those patients. We've got a spectrum of how it is being implemented"* ***(PMFP-07) (Medicines Management Pharmacist)***

Some Trusts experienced varied prescribing practices, associated with utilising different brands, as a result of area specific considerations, patient-related considerations and, to some degree, area/prescribers' attitudes. Varied prescribing practices might be a source of some confusion and administration errors, especially if these two brands (R-BMP and BSPs) are, presumably, stocked in the same Pharmacy Department/Store. Product presentation might be an additional source of administrative error, especially in the case of IFX-BSPs, as patients will not be able to tell the difference between the R-BMP and BSPs upon administration. Furthermore, the outer packaging of available brands is quite similar, and the trade name of the R-BMP (Remicade®) and one of the BSPs (Remsima®) are very close to each other. Figure 14 shows IFX-R-BMP and BSPs outer packs and vial presentation. Therefore, it is reasonable to conclude that introducing BSPs needs careful prescribing measures and procedures, which are discussed in the following section.

In summary, implementing the switch was governed by several factors related to: (*i*) prescribers' attitude, (*ii*) practical/logistical considerations, (*iii*) therapeutic area's guidelines and common prescribing norms and (iv) special patients' considerations. Table 26 provides exemplar quotes.

Figure 14-Outer pack and vial presentation of IFX R-BMP and BSPs

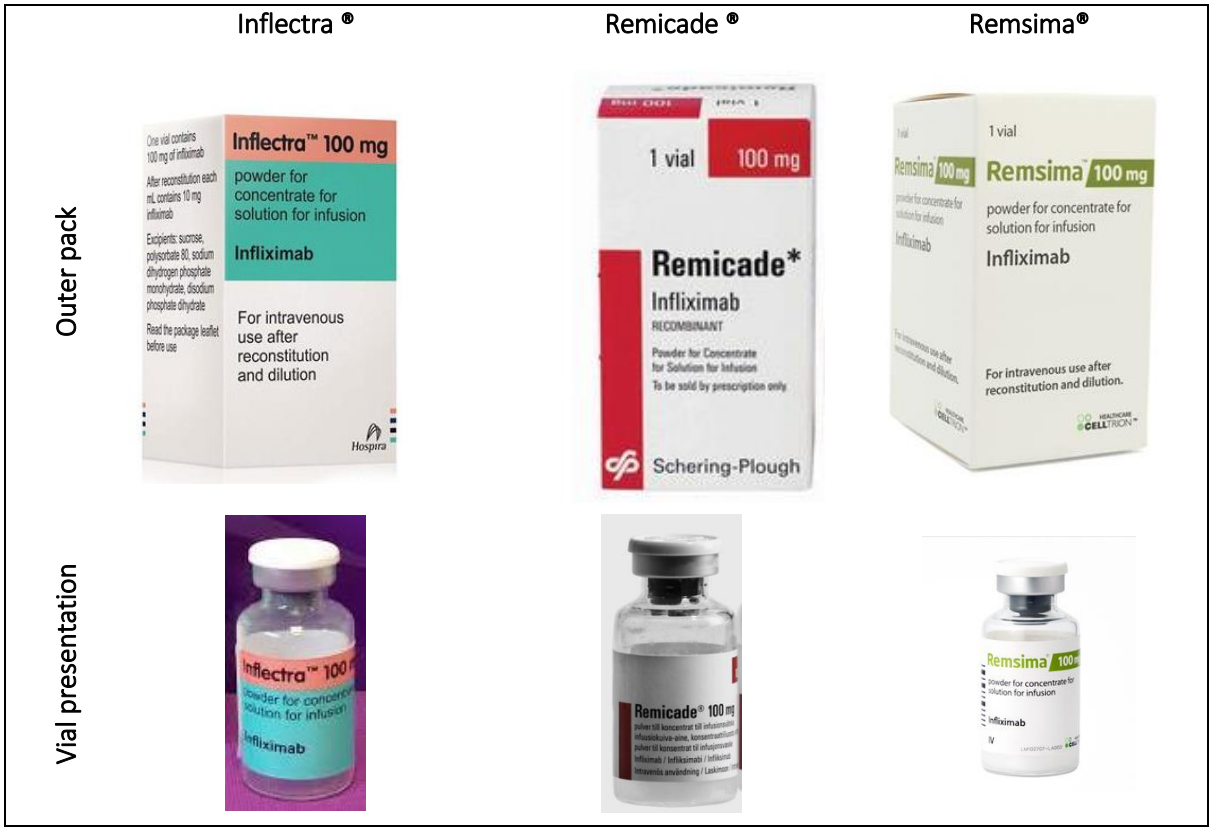


Table 26-Prescribing practices of available BSPs

Prescribing practice	Exemplar Quotes
Prescribing Practice *Initiating patients-General*	*"Well from the Trust point of view at the moment, both gastroenterology and rheumatology for new starters. We haven't switched everyone. And, the patients that we have on that started Remsima® (IFX-BSP) have no problems. Have started biosimilars, absolutely no problem, yeah. Just been exactly the same, you know, as if they have started Remicade® (IFX-R-BMP)"* ***(VRFP-15) (Specialist Clinical Pharmacist-Specialist Medicine)*** *"We are not, not switching our patients. We are using biosimilars for those who are starting, you know, they are starting, start fresh with those…we have not got a huge amount of, amount of experience. I suppose we are using IFX, I suppose we are using the... Or we are being encouraged to use the biosimilar of infliximab for patients who have either had an interruption in treatment or are starting fresh. And, I suppose the biosimilar for etanercept, they just, just been made available, and to be honest we have not got a huge amount of patients, we do not tend to use a lot of etanercept in our practice. So, Not sure where that to fit, really"* ***(DSDP-03) (Consultant Dermatologist)***

Prescribing practice	Exemplar Quotes
Prescribing Practice-Initiation *Lack of incentives*	*"Yes, we have been planning for a while. Obviously IFX was the first. We have been engaging with our commissioners for well over a year and have still to agree a benefit share…So we have not introduced IFX as a switch product although we have started to start new patients in adult rheumatology and inflammatory bowel disease areas. We haven't yet touched children. So we are using Infliximab, but we are not using it as much as we would want to mainly because of the lack of the gain share"* ***(PDFP-17) (Head of Pharmacy & Quality Control Laboratory Services)*** *"No we are in discussion about it, we haven't started it. So, we are still using the originator product. We are in discussions with pharmacist in CCG, I am kind of in the middle of that at the moment. To basically look at whether we will go down that road or whether we will stick to the originator drug, because that is now significantly cheaper"* ***(SORP-02) (Rheumatology Consultant)***

Prescribing Practice-Switching Variations between therapeutic areas	*"Right, for the IFX and the etanercept we are switching patients, it's not just for new patients. There's a biosimilar insulin glargine. We are not switching patients that are stable, so it's just the new patients. So it depends on the product and the disease really"* ***(SMFP-06) (Chief Pharmacist & Clinical Director for Medicines Management)*** *"As I say Gastroenterology, it varies to the specialty…So at the moment rheumatology are just initiating. Gastroenterology are generally trying to switch their patients"* ***(KGFP-10) (Pharmacy Manager)***	**Switching**	*"We're doing both. We switched all, I mean I'm talking really about the mAb medicines rather than glargine and things like that, which are prescribed in primary care, but in secondary care we switched all our IFX to a biosimilar now, and any new initiations are a biosimilar, and we're in the process of doing the same and switching from Enbrel to Benepali however you say it, although there are very few new patients, to be honest with you, being initiated on that drug at the moment…Well it's really difficult because we saw that one of the risks was that if you have 2 different products in your pharmacy. Then that's a risk in itself, isn't it? If the patient doesn't get the correct product, and it's much easier to do a wholesale switch and have everybody on the same thing. So I think we were quite lucky that people agreed to it, and I don't know to be honest with you what we would have done or what the team in the hospital would have done if anybody had said adamantly absolutely not, I'm not switching"* ***(LSCP-15) (Interface Pharmacist)*** *"Ok, for new patients, we are starting the patients on Remsima® (IFX-BSP), which is the BSP for Remicade® (IFX-R-BMP). And they are now saying, the consultants are saying that, if the patient has been stable and the blood has been fine and the patient in agreement, we can start swapping them over the cheaper products"* ***(RDSN-05) (Dermatology Nurse)***

5.6.4.2. Prescribing management

In discussing the management of prescribing medication, there was cross board consensus on having special measures that ensure careful prescribing of BMPs, including BSPs. These measures are needed to avoid any confusion that could lead to harming patients and/or endangering their health and safety. Evidence showed that prescribing management aimed to achieve two main functions: (*i*) ensure patients' safety and prescribing consistency, and (*ii*) guide and ensure prescribers' compliance with the switch decision. Each function was achieved using a number of tools, which varied in their effect and frequency of deployment among sites and professions. In discussing prescribing management, pharmacists, and in some cases nurses, were the most frequently named professionals to have significant and influential roles in the management of prescribing.

Although UK prescribers were reported to be the less likely to prescribe and report BSPs by brand name (Dolinar and Reilly, 2014), almost all participants in this research, both prescribers and non-prescribers, stated brand-name-based prescribing was a commonly followed practice. Knowing that the medical practice in the UK is generically driven, participants' acknowledgement of the importance of prescribing BSPs by brand name-might reflect their understanding of BMPs' special nature. This practice also suggests awareness of MHRA's requirement for brand name-based prescribing and reporting of BMPs, including BSPs. In addition to brand name prescribing, clear prescribing procedures and proper documentation were commonly used to ensure that patients are receiving what they have been prescribed and there is a consistency in supply over the treatment course.

Switching patients and demanding brand name prescribing in a generic prescribing culture might represent a case of changing prescribing behaviour. Prescribing guidelines, protocols and restrictions are commonly used tools to influence and guide medical practice. The influence of guidelines and prescribing restrictions on prescribing behaviour is reported to be prompt and powerful in comparison to other tools, such as educational interventions (Schumock et al., 2004, Raisch, 1990b). In BSPs' context, guiding prescribing practice was achieved through: a) electronic prescribing, b) pre-printed prescribing protocols, c) prioritising BSPs' prescribing, d) monitoring BSPs utilisation and e) ensuring prescribers' compliance with the switching decision and, to a lesser extent f) medicines formularies. These measures, in addition to their role in guiding prescribing practice, had also contributed to maintaining prescribing consistency. Guiding prescribing practice also benefited, although not always considered needed or necessary, from the provision of information and data related to BSPs' safety and efficacy, such as a summary of product characteristics (SmPC) and leaflets. Table 27 summarises prescribing management functions and tools.

Table 27-Summary of measures and procedures followed to manage BSPs' prescribing

Function	Exemplar Quotes
Patients' safety and prescribing consistency *Brand name prescribing*	*"I can only tell you what I have been told regarding the prescribing, which is that if you are prescribing the infliximab as the originator molecule you have to write Remicade® (IFX-R-BMP) because if you write it by the brand name the pharmacy will not be able to substitute the biosimilar. But if you are prescribing the biosimilar, it is being prescribed as Remsima®/Inflectra® (IFX-BSP), because they are both the same drug although they are marketed by two different companies. So you will prescribe it as Remsima®/Inflectra® (IFX-BSP)and then the pharmacy can use either one of those because it is the same thing"* ***(NBRP-05) (Rheumatology Consultant)*** *"Well I said we should be prescribing by, now for biologics, as we changed our registry as I told you BADBR registration information. They should be prescribed by brand so we know exactly what's happening, so the patient knows they are on brand X or brand Y or whatever okay"* ***(CGDP-04) (Foundation Professor of Dermatology)***
Patients' safety and prescribing consistency *Clear prescribing procedures and documentation*	*"There is a whole process about making sure that you have documented all properly, and through the pharmacy system, and through the prescribing system that it is clear which, said it has been described by brand, you know exactly which BSP product the patient has had. So then switching requires more effort, in terms on the ongoing governance around it, but it is not impossible and it needs to build up a framework around it, so you can be clear who had what, when; and they have consented, they knew what they are going to get"* ***(JCFP-01) (BCAP Interface Pharmacist)*** *"OK, so we (nurses) do all our ordering on a Friday for not the next week, but for the week after, and.... So, on the Thursday night the night staff have a look and see which patients are coming in, in the next few week, and pull out all the charts, we hold all the charts on the ward. And then it is written on the chart, when it is written IFX, underneath the doctor has got to state the brand that they want, and all the Remicade® (IFX-R-BMP) go on one sheet to be ordered from pharmacy and all the Remsima® (IFX-BSP) go on a different sheet. So, we have two different sheets for each drug to make sure that there is no mix up. There has been, the old one, that was sent up incorrectly, but the nurses picked on that and returned it to pharmacy and got the right one sent up"* ***(RDSN-05) (Dermatology Nurse)***

Guiding and restricting prescribing *Electronic-prescribing/Pre-printed protocol*	*"Well we get them pre-printed. So, all biologic prescriptions all are pre-printed. We have a system, where the biologic nurse will be informed of those who are requiring prescription; they will print it off for relevant consultant to sign it and then it goes to pharmacy. So, that is the system we have, here"* ***(HSRP-06) (Rheumatology Consultant)***
Guiding and restricting prescribing *prioritising BSPs' prescribing*	*"But for our rheumatology if everything else was equal then BSP etanercept will be the first choice, at the moment. If someone could have etanercept, IFX, tocilizumab, you know, if you could, it doesn't matter which one. They have, then they would be encouraged to go for the etanercept because it is the cheapest. But only if all the others circumstances agree with the patient, so they have to, they do look at the clinical condition of the patient, first"* ***(DMFP-08) (Medicines Management Pharmacist)*** *"So like infliximab is formulary. But then we have the information about, kind of, which brand that we are using at the moment. So for, like, for us, kind of, Remicade is non-formulary, but the other kind of cheaper brand is formulary. So I guess it have to kind of refer to brand name, just to be really clear on which one is formulary and which is not formulary"* ***(PDFP-03) (E-Prescribing Pharmacist)***

Guiding and restricting prescribing *Prescribing monitoring*	*"But, every time we get a prescription for Remicade® (IFX-R-BMP), we will then question it to say well, why is it the branded product, the originator product, being prescribed? But because we have only got a handful of patients, we would know the names, that again this patient has authorisation. But, we have a spread sheet of the names of the patients that has gone through BSP sub-group meeting, so they are the ones who have been authorised to continue on the originator, so they can check that"* ***(PBFP-02) (Principal Pharmacist–Formulary, Medicines Management & Clinical Trials/Lead Pharmacist)***
	"We have got all our prescriptions going via the pharmacist involved, we are ordering the products on a patient's specific bases, so we are ordering those branded products from an external company, pre-made, took to the dose bands for IFX, so again, we have got the ordering side of things controlled. So, basically, the clinicians cannot access infliximab anymore without pharmacy being involved, So we have managed to control the dynamic of prescribing, and we know who is on what, and we know why they are on what" ***(JKFP-11) (Clinical Lead Pharmacist)***
Guiding and restricting prescribing *Formulary listing*	*"With the BSP it's slightly different, isn't it? Because you have to prescribe by brands and it is important that we do. So we are putting information into the formulary… Certainly at the minute, the IFX is listed as Remicade® (IFX-R-BMP) for existing patients and now Remsima® (IFX-BSP) for new patients, we just have Inflectra® (IFX-BSP), and now it changed…So I think having it in the formulary, you know, like with any other formulary section, any other formulary choice you want to try and rationalise as much as you can. So I think, we've now got two IFX products we've got Remicade® (IFX-R-BMP), we've got Remsima® (IFX-BSP). I would say, once …we haven't started using the BSP etanercept yet, but the Benepali® (etanercept-BSP), when we do we will list it as Benepali® (etanercept-BSP) and Enbrel® (etanercept-R-BMP) and make sure we've got both of those listed."* ***(KCFP-13) (Prescribing Adviser)***
	"We got in our formulary we actually have Remicade® (IFX-R-BMP) and Remsima® (IFX-BSP) and Inflectra® (IFX-BSP) all in the formulary, and I know that's because we have 1 Trust using Remsima® (IFX-BSP) and 1 Trust using Inflectra® (IFX-BSP), so it is a mixture" ***(LSCP-15) (Interface Pharmacist)***

Guiding and restricting prescribing *Providing product information materials*	*"So, it should be listed IFX Remicade® (IFX-R-BMP) or BSP IFX Remsima®, we are not using Inflectra® (IFX-BSP). Would be there any information more?! I think that is all what you need, really. Would you need any more information in regards? No I think that is all you need, those two; generic name and brand name"* ***(GMGP-03) (Academic Gastroenterology Consultant)***
	"Well, we do make it available. So the SmPC (summary of product characteristics), and the BNF, they are distributed throughout the hospital electronically so people have access to them but clearly it's incumbent on all clinical professionals to keep up to date and use products accordingly…We would expect people to refer to the SmPC (summary of product characteristics) in the first instance. I think they're (the SmPCs) pretty good these days, I mean you have to make sure that you're looking at the most recent web based version, but I think they're pretty good at updating them nowadays" ***(MSFP-05) (Head of Medicines Management)***

Guiding and restricting prescribing *Providing product information materials*	*"**Interviewer:** do you think that there is a need for guidance; how to prescribe them? What is the difference….?* *Interviewee: So, I have for all of the intravenous, for the intravenous biologics, there are administration guidelines for each one, are available on the internet. Yeah"* ***(VRFP-15) (Specialist Clinical Pharmacist-Specialist Medicine)***
	"We just list the drugs and then, give some detail about the drugs and links to useful information. In terms of, we would list that as the first line as it's the BSP…With links to NICE guidance and guidelines and the like, really cost comparison graphs. Safety information, yeah…Yeah. Yeah, yeah. All those sort of things would be from the formulary, when I put in, if you put in IFX, into out formulary you get about 20 different documents that you can link to" ***(SMFP-06) (Chief Pharmacist & Clinical Director for Medicines Management)***

In addition to explaining formularies' role in managing BSPs prescribing, further discussions helped in understanding the main issues that were detected during Phase *I* and *II* formularies screening: (*i*) INN/generic listing or listing of all available brands of a single molecule without specifying the preferred brand for prescribing, (*ii*) having simple, list like formularies, that do not have clear prescribing guidelines, restrictions, links to relevant guidance or product information materials and (*iii*) having outdated formularies, which had not been updated for more than two years.

In discussing formularies' structure and content, the following factors might explain the above mentioned observations:

- Minimising formularies updating burden every time a new brand is procured
- Considering formulary as a tool to demonstrate compliance to NICE by confirming that positively appraised medicines, which are usually generically listed in TAs and CGs, are included in the formularies and are available for prescribing without the need for brand specification
- Developing an inclusive joint formularies that is referred to by neighbouring Acute Trusts, which had procured different brands, by following INN based listing or listing all available brands
- Overlooking formularies by prescribers, who felt that they were qualified enough not to consult the formulary in prescribing; for them formularies are for primary and non-specialised services, this might explain the observed lack of restrictions, prescribing guidelines and product's information in some formularies and to less extent
- Avoiding intervening in the market dynamics and acting as promotional tool for a specific brand or a specific manufacturer

Highlighted factors contradict NICE recommendation and advice in the role of medicines formularies in standardising, homogenising and rationalising prescribing practice within health localities (The National Institute for Health and Care Excellence (NICE), 2015a)

As more BSPs, which might be sharing the same INN with the R-BMPs, are becoming available, prescribers might not be able to rely on memory and experience in prescribing BMPs, including BSPs. Therefore, there might be a growing dependence on guidance tools for prescribing and, to some extent, reliance on other professionals, such as pharmacists and nurses, in monitoring and assuring prescribing consistency. However, since formularies are supposed to guide prescribing practice, developing extra tools might represent a case of confusion, waste of resources and duplication of efforts. Table 28 represents some exemplar quotes of the perceived role of medicines formularies.

Table 28-Perceived role of medicines formularies as reported by study participants

Formulary Role	Exemplar Quote(s)
Burden of formularies updating	*"The problem is, if you start listing brand names you've got to keep your eye on it. So we've got one as an example currently, of biosimilar insulin, but we'll have three or four before the end of the year, and I don't particularly want to be making up notes on the Formulary all the time. So, it's far easier to say, "Guys if you're going to be using insulin glargine, prescribe by the brand you intend"* ***(MDCP-07) (Head of Medicines Management)***
NICE compliance	*"So, I do not.... So, the formulary will have listed in there, but not specifically other than, only for NICE reasons and sort of things. Discussions would be, tend to be not formulary within that hospital, it will be via the DTC committee and the relevant pharmacist there with the relevant clinicians input to it... But not... formulary would just be a stamp putting it actually in a list"* ***(BFCP-01) (Interface Pharmacist Lead-Clinical Effectiveness and Medicines Optimisation Team)***
Limited influence on prescribing practice	*"To be honest, I think from a clinician's point of view they generally don't use the formulary in that way so I don't think they would actually look at it to see what it was listed as. But I suspect we probably ought to brand list the biosimilars in there as well as the parent compound but on the other hand it is just as easy to say"* ***(KGFP-10) (Pharmacy Manager)*** *"I tend not to look for formulary. I, within dermatology, you know, I tend to know what is on the formulary, but I would not go and look on the formulary to get advice about prescribing. I do not think I have looked at our formulary. I certainly wouldn't know where to look for our formulary as I'd have to go and search for it on the internet. I have been working here for twenty years, 21 years...so, I have a good idea about which drugs are on our formulary. And as clinical director, I am responsible for signing off any drug which go on out formulary, or goes off our formulary. Personally, I do not actually have to look it up, I know what is on the formulary in my head, really"* ***(NLDP-02) (Director of Dermatology)*** *"Well, it depends on how you manage your formulary. Our formulary is pretty much just a product list. So it just, if you look under rheumatoid arthritis, it'll list the product that are available there; it's not there to replicate prescribing and safety information that's available through other sources. We would expect people to look elsewhere for that"* ***(MSFP-05) (Head of Medicines Management)***
Avoid intervening in market dynamics	*"I think what we would do is, and I think there is a lot of pressure from the industry to say, "well our product's been NICE approved so therefore it must be on the formulary" which is why we would say any of these is on the formulary. For formulary purposes I think we would list it as IFX as being the chemical entry. In terms of our computer systems and how we use it, how we label it, we would have "IFX Inflectra®" as the name. To differentiate which one is being used"* ***(PDFP-17) (Head of Pharmacy & Quality Control Laboratory Services)***

Effect of joint formularies	*"Yes I'm just bringing it up here now. OK yeah we got in our formulary we actually have Remicade® (IFX-R-BMP) and Remsima® (IFX-BSP) and Inflectra® (IFX-BSP) all in the formulary, and I know that's because we have 1 Trust using Remsima® (IFX-BSP) and 1 Trust using Inflectra® (IFX-BSP), so it is a mixture"* ***(LSCP-15) (Interface Pharmacist)***
	*"**Interviewee:** Well, our formulary covers four providers and one CCG so it covers the whole of Dorset. It's called the Pan Dorset formulary you can look at it online if you like, and it lists medicines generally generically, so my view would be that the Formulary should list the names of the drugs generically so in this case Infliximab should specify you should provide the drug with the lowest acquisition cost much like NICE does and they make various treatment recommendations.* ***Interviewer:** how do you think that formulary list can help in optimising biosimilar and utilisation?* ***Interviewee:** By giving provider Trusts the freedom to utilise biosimilars, and the biosimilar that is the cheapest to procure.* ***Interviewer:** So without brand specification?* ***Interviewee:** That's correct"* ***(MSFP-04) (Senior Pharmacist-Medicines Information, Formulary & Clinical Economy)***
	"Our formulary, though, is across more than one Trust. So, you could not... in effect, they are all available, so we would not want to specify which one, because they could the wrong one in our Trust, it is more important that our prescriptions are quite clear to them as to how they should make that decisions, not the formulary for us…So, in our formulary, it has infliximab that is included in the formulary, it says 100 mg vial for intravenous infusion, and then it says Remicade®(IFX-BSP), Inflectra®(IFX-BSP) and Remsima® (IFX-BSP). So, it got all three listed" ***(SCFP-14) (Formulary Pharmacist)***

Although some Trusts had been switching for a while, with some even having switched all their patients' cohort, only one participant (a dermatologist) talked about a case of dispensing errors, in which a patient had been switched to a BSP without him, or his prescriber, knowing about it. Limited reporting of prescribing or dispensing errors might be for several reasons: (*i*) proper prescribing management, (*ii*) prompt capture of these incidents before a BSP/R-BMP was administered to a patient, (*iii*) missed cases that went under the radar or (*iv*) it was still early days, for some sites, to identify such cases. Additionally, the interview dynamics and interview guide, which might not allow for a thorough investigation of these incidents, could have limited the reporting of prescribing/dispensing errors.

5.6.4.3. Patients' management after switching

The switching process involved aspects related to switched cohort management and disease monitoring. Based on the fact that the safety and efficacy of IFX-BSPs were tested and confirmed through clinical trials in biological naïve patients, it was expected that the switched cohort would have been subjected to more frequent monitoring and disease progression checks than initiated cohort. However, extra monitoring for switched patients was not a common practice; however, variations were a frequent feature of the research findings, particularly in the way

Managing a switched cohort of patients was either preventive/confirmatory (extra monitoring) or corrective (restoring disease control). Preventive measures targeted the whole switched cohort; these measures aimed to ensure disease control and to detect early signs of treatment failure and adverse drug reactions. The patients involved received more frequent blood tests to check drug levels and disease markers, and more frequent clinical visits, than did the non-switched patients. On the other hand, corrective measures were directed to patients, who experienced treatment failure, adverse drug reactions or flare-ups. Disease control was restored either by switching patients back to the R-BMPs, starting patients on another BMP or running extra blood tests and clinical examinations to rule out the effect of switching. According to the research participants, cases of treatment failure were very limited and were triggered by psychological factors rather than physiological/pharmacodynamics factors.

While there was consensus in offering corrective measures, variations were observed in preventive measures. Whether preventive (extra monitoring) procedures were offered or not, both cases draw back to dimensions related to professional experience and ethical obligations, as discussed earlier in the persuasion theme. Offering extra monitoring might be a practical presentation of prescribers' ethical obligations to assure patients' safety and wellbeing. On the other hand, considering corrective measures only might reflect a prescriber's confidence in the available evidence and in their own practical experience and perception of BSPs prescribing as normal practice. Additionally, both cases might reflect principle knowledge: (*i*) offering extra monitoring might indicate professionals' awareness of BSPs' licensing and authorisation requirements, whereas (*ii*) not offering extra monitoring might reflect professionals' understanding of biological variations and that the molecular structure of BMPs is subjected to batch-to-batch variations, rendering extra monitoring superfluous. Another factor that might influence whether preventive or corrective measures were offered is the commissioning and contracting agreements with the CCGs and products suppliers. At some sites these agreements involved offering financial resources and sources to support extra-monitoring (preventive measures).

Finally, offering extra monitoring was in alignment with prescribers' promises to patients to maintain both their safety and disease control, which were discussed during consenting stage; however, not offering extra monitoring might be perceived as a denial or repudiation of that promised post-switch safety and wellbeing. However, due to the research design and data collection method, it was not possible to check what the patients were promised, or if any promised measures to assure safety and disease control were specifically or generically described. Table 29 provides a summary of procedures considered to manage a switched cohort.

Table 29-Summary of after switch management measures with exemplar quotes

Measure	Meaning and Exemplar Quote(s)
Not offering preventive extra monitoring	*"We used the same, we did the same blood testing, we did the same checks we have always done. Because... regardless of whether it is the originator brand or a BSP, you still need to do the same checks, the same safety needs to be maintained. And I have ... I would not be using a product that I thought, as I said, was inferior. So, we do not…we did not do anything different"* ***(AFSN-01) (Lead Inflammatory Bowel Disease Nurse)*** *"No I mean they; obviously they are in a follow-up routine and annual reviews, specific things that we are checking. Obviously with infliximab, they are coming back every eight weeks so we are liaising with them and checking clinical signs and symptoms. They know if they feel their symptoms are deteriorating they phone in and we will repeat blood tests, CRP and that sort of thing. So I mean I suppose the only additional monitoring we were doing was taking baseline blood tests, blood levels and obviously CRP and that sort of thing so we can calculate things like Harvey-Brandshaw score, but as I say we didn't have any problems that we could specifically attribute to a change in drugs"* ***(SCFP-16) (Consultant Pharmacist – Gastroenterology/Hepatology)***
Offering preventive extra monitoring	*"So, we will be collecting in Crohn's and UC (Ulcerative Colitis), we will be collecting Harvey-Bradshaw Indexes and Mayo score which is a UC score. We will be collecting CRP, scull protectin and trough level, IFX trough levels every three months. Prospectively for twelve months"* ***(GMGP-03) (Academic gastroenterologist)*** *"We have asked, they will be assessed at three months, just to be sure that. Because, normally, we assess them every six months, if somebody on biologic. So, if we are going to switch, we have said that they will need a review at three months, just to ensure that they are doing well, the disease under control and there is nothing significantly different, yeah. So, there is one extra visit to the biologic nurse, yeah"* ***(HSRP-06) (Rheumatology Consultant)***

Corrective and disease control restoring measures	*"Oh, well, okay. Well if patients have a reaction to the biosimilar for a particular reason then obviously we would, that would be a clear cut reason to go back to using the original product"* ***(SMFP-06) (Chief Pharmacist & Clinical Director for Medicines Management)***
	"She (a patient) developed joint pain, and she, sort of, put it down to the fact that this has happened around the same time as she had the switch, and that she was seen in clinical by the consultant and all blood markers and her general health were assessed there. And, she was in remission and her blood had improved, since the switch. So, and we have checked her anti-body levels and thing, and they were all negative. So, she was, sort of, reassured by what he has said to her. We arranged that meeting on the basis that they were unhappy about the switch" ***(JCSN-04) (IBD Nurse Specialist)***

Offering or not offering post-switch monitoring might represent a challenging and complicated situation which is based on: (*i*) both positions could be explained and justified by professional norms and ethical obligations and (*ii*) professional bodies such as British Rheumatology Society (BSR) have asked for patients to be closely monitored to ensure their safety and efficacy (British Society for Rheumatology (BSR), 2017a). However, NICE has not specified any particular type of monitoring in its implementation guide (The National Institute for Health and Care Excellence (NICE), 2015d). Therefore, there is a need to have a clear position on whether or not to offer extra monitoring, as well as who should fund these extra tests: the commissioners, funds to be deducted from a Trust's part of the gain share or to be paid for by the BSP's manufacturer?

5.6.5. Implementation theme summary

Measures/issues that were considered to facilitate implementing and managing the switch included: (*i*) internal communications, (*ii*) patients communication, (*iii*) clear prescribing procedures, (*iv*) proper documentation, (*v*) formulary listing and (*vi*) post switching management, together with (*vii*) Trust wide policy or mandates, could represent a form of routinising. Routinising is the final step of adopting an innovation; it is the stage at which the innovation becomes fully integrated into an organisational structure (Rogers, 2003).

This theme provided a description of how the switch was implemented in practice. Evidence showed that variations in attitude and agreements were reflected in whether or not the switch was implemented and how. Evidence confirmed what Rogers had described regarding the ongoing effect of each stage on the subsequent one. In summary, implementing the switch was governed by several factors related to: (*i*) prescribers' attitude, (*ii*) practical/logistical considerations, (*iii*) therapeutic area's guidelines and common prescribing norms and (*iv*) special patients' considerations.

The fifth step of Rogers's theory, the confirmation, was not found to be applicable or relevant, as it was concerned with the continuity of adoption and re-innovation; information which was not possible to be captured within the study timeframe.

5.7. Qualitative study discussion

This study investigated factors that led to the adoption, or not, of BSPs by English Acute Trusts. The study was based on information gained from semi-structured qualitative interviews with professionals, who are involved in commissioning, introducing, managing and prescribing BMPs, including BSPs. This study aimed to identify factors that facilitated or hindered IFX-BSPs uptake by targeting Trusts according to their prescribing practice of IFX-BSPs: users and/or non-users. However, as the research progressed, it was noticed that targeted sites were at different stages of adopting-implementing IFX-BSPs. While some Acute Trusts were still negotiating the switch with their relevant CCGs, others were implementing the switch or had completed their IFX-BSPs switch and moved on to a new switching campaign targeting BSP-etanercept (note: the latter became available during the course of this study). Therefore, it was noticed that some Acute Trusts had experienced changes in prescribing practice and jumped from being non-users to switchers. Furthermore, the BMPs' market had witnessed rapid and continuous changes, in the form of new market entries, guidelines and statement papers issued by professional bodies; changes which had created environmental (contextual) differences between early and late adopters. Therefore, a comparison between early and late adopters was challenging, as each category operated in a different environment with different push-pull forces in action. Nevertheless, the study was able to highlight multiple factors informing the adoption of BSPs, as well as those issues involved in implementing the switch.

Although identified factors could be classified into barriers and facilitators, their effect varied between cases. In some instances the absence of a facilitator (pulling) factor, such as incentives or extra support, did not hinder or delay the switch. Moreover, influencing factors took different manifestations in different contexts; for example, common medical practice mostly promoted IFX-BSP switching in gastroenterology; however, in some cases reluctance and lack of interest was evident among low, infrequent IFX prescribers in rheumatology and dermatology.

Broadly, BSPs uptake facilitators took the form of: (*i*) positive previous practical and clinical experiences, (*ii*) the peer effect at national, regional and local level, (*iii*) support of professional bodies, (*iv*) professional norms, (*v*) ethical obligations and (*vi*) financial incentives and support. The absence of these factors, in some cases, or considering different dimensions related to these factors, had acted as hindering elements (barriers).

In his theory, Rogers (2003) listed knowledge as the prerequisite for adopting an innovation. The effect of knowledge in directing and changing prescribing practice is frequently acknowledged in the literature (Ashford et al., 1999, Hulscher et al., 2010, Moe-Byrne et al., 2014). Understanding an intervention's attributes and scientific base helps prescribers to form a positive attitude toward the intervention, which in turn makes them more capable and confident in explaining the intervention to the patients (Dunne and Dunne, 2015, Rodrigues et al., 2013). Reviewing the literature has shown a mixed and heterogenic picture of prescribers' understanding of BSPs and 'similar' concepts (Beck et al., 2016, Grabowski et al., 2015, Zelenetz et al., 2011, Pasina et al., 2016, Dolinar and Reilly, 2014, Reilly and Gewanter, 2015, Cohen et al., 2016, Hemmington et al., 2017, Akhmetov et al., 2015). Similar to the study by Chapman et al. (2017) which targeted prescribers in the UK, research participants, especially prescribers, showed adequate understanding of the concept of BSPs and biological variation.

Asking prescribers to switch their stabilised patients might be considered as proposing a change in prescribing behaviour. Changing prescribing behaviour is defined as "educational programmes or administrative policies designed to alter drug use pattern, excluding marketing programme provided by drug manufacturers" (Raisch, 1990a). Interventions and continuous educational activities are critical in improving practitioners' knowledge and awareness of a health intervention (Schumock et al., 2004, Hulscher et al., 2010). Given that BSPs are not real innovative products, asking prescribers to utilise BSPs could not be considered as an actual change in prescribing behaviour. Such a conclusion might explain why participants, in general, did not feel the need for educational interventions. Awareness of an intervention, and understanding its scientific base, make a professional able to assess its attributes and characteristics (Ashford et al., 1999, Baltussen and Niessen, 2006). Therefore, principle knowledge facilitated the progress of the adoption process but did not push it. Prescribers' knowledge, understanding of biological variations, and their experiences in prescribing IFX-R-BMP, made them confident and comfortable enough when switching their stabilised patients to IFX-BSPs. These factors led to the observed "self-efficacy" among prescribers, especially gastroenterologists, which compensated for the limited clinical evidence of switching safety and efficacy (Cabana et al., 1999).

While participants felt that they are knowledgeable and qualified enough to assess and utilise BSPs, knowhow knowledge presented a mixed picture. Knowhow knowledge could have an authoritative voice in demanding certain actions in a certain manner at a certain time; it could be also in the form of a directive, practical manual telling its readers "what to do and how to do it", or it could be midway between the two approaches (Rogers, 2003, Fixsen et al., 2005). The NICE implementation guide helped, to a degree, in explaining to professionals what is needed to be considered in implementing a BSPs switch. However, the guide's effect was limited as some stakeholders had not come across it, or in some cases the switch had started before the guide was published. On the other hand, similar to what was highlighted earlier in the literature review chapter, the lack of BSPs' specific policies was confirmed by participants, especially change agents (commissioners and high cost medicines pharmacists); these respondents highlighted the need for guiding (directive) interventions. The need for directive intervention emphasises the fact that principle knowledge is not enough; more enforcing tools such as guidelines are needed (Cabana et al., 1999, Raisch, 1990b, Sbarbaro, 2001).

Several implementation science scholars had explained the central role of innovation's attributes in driving the decision of adoption. An innovation adoption rate is affected by its attributes and how these attributes interact with, and are affected by, factors related to the context in which the adoption is taking place (Rogers, 2003, Frambach and Schillewaert, 2002, Damschroder et al., 2009, Greenhalgh et al., 2004). Assessing an intervention's attributes should be based on defined assessment criteria "measure of performance by which the option will be judged" (Baltussen and Niessen, 2006). For clinical interventions, assessment criteria are usually focused on (*i*) clinical effectiveness and safety, (*ii*) evidence and quality, (*iii*) patients and disease outcomes and(*iv*) impact on practice interms of cost and process (Wilson et al., 2006, Tanios et al., 2013); taking these assessment criteria into account had allowed for expanding Rogers's attribute to involve aspects related to patients and disease status and progress.

BSPs, if compared with BMPs, are promoted as cheaper medicines with comparable quality, safety and efficacy profiles. However, while available evidence at the time of licensing BSPs supports the initiation, it does not address the switching practice. Furthermore, the EMA has clearly stated that it will not assess switching and has left the decision of switching to national agencies. Similar to what has been reported (Chapman et al., 2017), participants, in general, had a positive attitude toward IFX-BSPs and the switching process; however, there were certain reservations expressed by some rheumatologist and dermatologists.

Observability as a concept addresses other adopters' experiences in implementing an innovation and the resulting outcomes (Rogers, 2003, Aarons et al., 2011). In this research, data have shown that limited evidence on switching safety and efficacy, in particular, was compensated for by real-world experiences. Involved professionals were encouraged to switch their patients' cohort through observing the experiences of other Trusts within the same region or country. Further, some cases were informed by the emerging international evidence. Other sites' experiences acted as a guide on how to implement, and what to ask for to support the switch. To some extent, others' experiences compensated for the lack of knowhow, especially for early adopters (early switchers). The effect of neighbouring organisations was evident in research that had focused on the management of antibiotic prescribing (Hulscher et al., 2010, Ashford et al., 1999).

In addition to the commonly reported attributes, research data showed the effects of disease and area-specific considerations on adopting BSPs. Having IFX as the first choice for prescribing, gastroenterologists were more accepting and encouraged to switch their cohort than were those working in the fields of rheumatology and dermatology. The effect of a disease's complicated nature and a patient's often complex history was seen to hinder the utilisation of BSPs; the same being reported in countries with issues of patients' access to biological therapy (Sandorff et al., 2015, Hemmington et al., 2017).

Similar to the findings from systematic review by Kneale et al. (2017), professional bodies which acted as key opinion leaders (KOLs), were highly influential in directing the decision making process by driving prescribers' attitudes toward BSPs. In some cases changes in a professional body's position toward BSPs use, together with the associated act of switching stabilised patients, was translate into changing prescribers' attitudes toward BSPs. The reasons for English prescribers to trust their professional bodies were found to be similar to those of their European and Irish counterparts (Danese et al., 2016, Danese et al., 2014, O'callaghan et al., 2017). It is common for professional bodies to assure prescribers, especially in cases of limited evidence and practical experience (Raisch, 1990b, Sbarbaro, 2001). The effect of local KOLs was not strongly evident; however, it was possible to recruit senior level prescribers who were actively involved in the switching process, especially through leading educational sessions, communication, or both.

Although it was not clearly stated by participants, their professional bodies seemed to be more influential than NICE. This observation is based on the fact that in the time period between issuing the professional bodies' first position statement and the amended one, NICE had published its implementation guide. However, change in prescribers' attitudes was attributed to changes in their professional bodies' position, not the NICE implementation guide. Another possible explanation for the limited influence of NICE might be lack of an active dissemination mechanism, which would have ensured widespread dissemination of the implementation guide.

Although prescribers appeared, in general, to be accepting BSPs, where evidence upon licensing was limited, as was the case with anti-epileptic drug prescribers, they were concerned about losing disease control (Crawford et al., 2006, Sharott, 2013). Therefore, some prescribers asked for extra monitoring and baseline blood tests; a request that could well reduce achievable cost savings.

Generally, the perceived added value of an innovation is considered the primary adopting driver (Rogers, 2003, Greenhalgh, 2017). As BSPs are promoted as 'cheaper' medicines with compatible safety and efficacy profiles, BSPs in theory, represent a case of an option with dominance. Dominance is defined as "a situation where one option performs at least as well as another in all criteria and strictly better than one of the other one in at least one criterion" (Baltussen and Niessen, 2006). Dominance in the case of BSPs is routed in their ability to save cost and improve patients' access. Therefore, it might be expected that the integration of these medicines should be a smooth and effortless process. However, in healthcare an innovation/intervention is assessed for its added value and impact on patients' health, safety, wellbeing and overall outcomes (Guindo et al., 2012, Dunne and Dunne, 2015, Hoffmann et al., 2002). Due to limited evidence regarding BSPs' safety and efficacy in extrapolated indications, and in switching stabilised patients, utilising BSPs should be based on balancing patients' outcomes and overall cost and financial impact, as is the current situation with the use of anti-epileptic drugs (Krämer et al., 2007, Crawford et al., 2006). Therefore, dominance could be established in initiating biological naïve patients, but still questioned in case of switching stabilised patients, which has the most significant financial impact.

The study's results showed that while all participants, whether prescribers or non-prescribers, acknowledged patients' rights to safe and effective therapy, and their obligation to rationally use the finite financial resources of the NHS, their direct exposure and handling of these values were different. Commissioners and high cost-medicine pharmacists are accountable for avoiding budget overspend; by role definition they do not have direct, face-to-face, interactions with patients and they do not review the patients' disease progression. On the other hand, prescribers, whether physicians or nurses, have to deal directly with patients and manage their diseases. Therefore, the implementation of BSPs was perceived and assessed from different angles, using different lenses based on role-specific deliverables and key performance indicators at the same time. Different angles might create tension between change agents and adopters; a possibility which could be eased by commissioners offering support and incentives and prescribers' willingness and acceptance to switch stabilised patients. Incentives are commonly used as a tool to influence prescribing practice and drive the change of medical practice (Raisch, 1990b, Moe-Byrne et al., 2014). Additionally, results showed that human factors played a significant role in accepting BSPs, especially in the absence of guiding/directive policy. Therefore, collaboration and on ongoing communication played a role in having a mid-way approach to implementing the switch, which ensured savings and patients' safety and allowed extra staffing hours for managing and running the switch. It is common for change agents to rely on incentives and collaboration to promote their agendas and influence adopters (Rogers, 2003, Narine and Persaud, 2003, Shepherd and Rudd, 2014, Brown et al., 2011, Akyürek et al., 2015).

The way in which healthcare professional perceive the medicinal product manufacturer affects their acceptance and confidence in prescribing these medicines (Toverud et al., 2015, Dunne and Dunne, 2015). In the case of BSPs, it was reported that confidence and trust in national BSPs manufacturers resulted in increasing German prescribers' willingness to prescribe BSPs (Declerck and Simoens, 2012). However, in this current research, participants did not report any concerns regarding manufacturers or product quality. Moreover, manufacturers' related factors, such as reputation and supply-chain, did not appear to have any impact on participants' acceptance of BSPs.

The direct effect of BSPs and R-BMP manufacturers was seen in the way in which these producers competed. Factors identified include: (*i*) offering lower acquisition prices, (*ii*) having extra service added to the contracts such as compounding services or pre-prepared bags for IV administered BMPs, (*iii*) patients' training for the SQ administration route and (*iv*) providing materials/reference for patients' communication. These activities did not affect the decision to switch, but it affected which brand to procure, especially in the case of IFX-BSPs. However, BSPs entry has changed the medicine market's dynamics and driven prices down. This outcome, in some cases, was reported to affect the switching decision as the R-BMP's manufacturers lowered their prices to a level at which the cost-effectiveness of switching to BSPs was questionable. This was reported by a limited number of participants and expected by some. Therefore, there is a need to reassess market performance and the desire to switch, especially with more BSPs being launched and made available.

The other effect of the industry was in the form of educational sessions and seminars targeting healthcare professionals. Nevertheless, participants did not perceive these interventions to be highly influential and did not allocate to these interventions any great importance when considering the switch. However, the industry might be affecting professionals' knowledge indirectly, through the literature. Research participants, mainly prescribers, mentioned published literature as a source of knowledge, which they prefer to consult when trying to understand BSPs and obtain data on BSPs' safety and efficacy. Nonetheless, the pharmaceutical industry was found to influence sections of the available literature by sponsoring and promoting papers that almost always show favourable results from the use of their products (Lexchin et al., 2003, Lundh et al., 2017). The effect of the industry's influence on research and promotion of product was also observed during this study's literature review.

Based on the notion that all Acute Trusts and CCGs are within the same country, England, and are governed by the same general policies and regulations; this qualitative study aimed to identify factors that can influence the uptake and utilisation of innovation/intervention. However, results showed that factors affecting the adoption and the implementation of BSPs were generally context-specific. Also these factors were also affected, to some extent, by local economy-related dynamics. Specificity was not limited to the local context, but was also observed at therapeutic/disease area. Each therapeutic area has (*i*) its disease management guidelines, (*ii*) patients' cohort characteristics, (*iii*) experiences and (*iv*) relevant evidence. Therefore, extrapolating qualitative evidence to another context or implementation intervention should be considered with caution and based on careful mapping of the extrapolated context.

5.8. Study conclusion

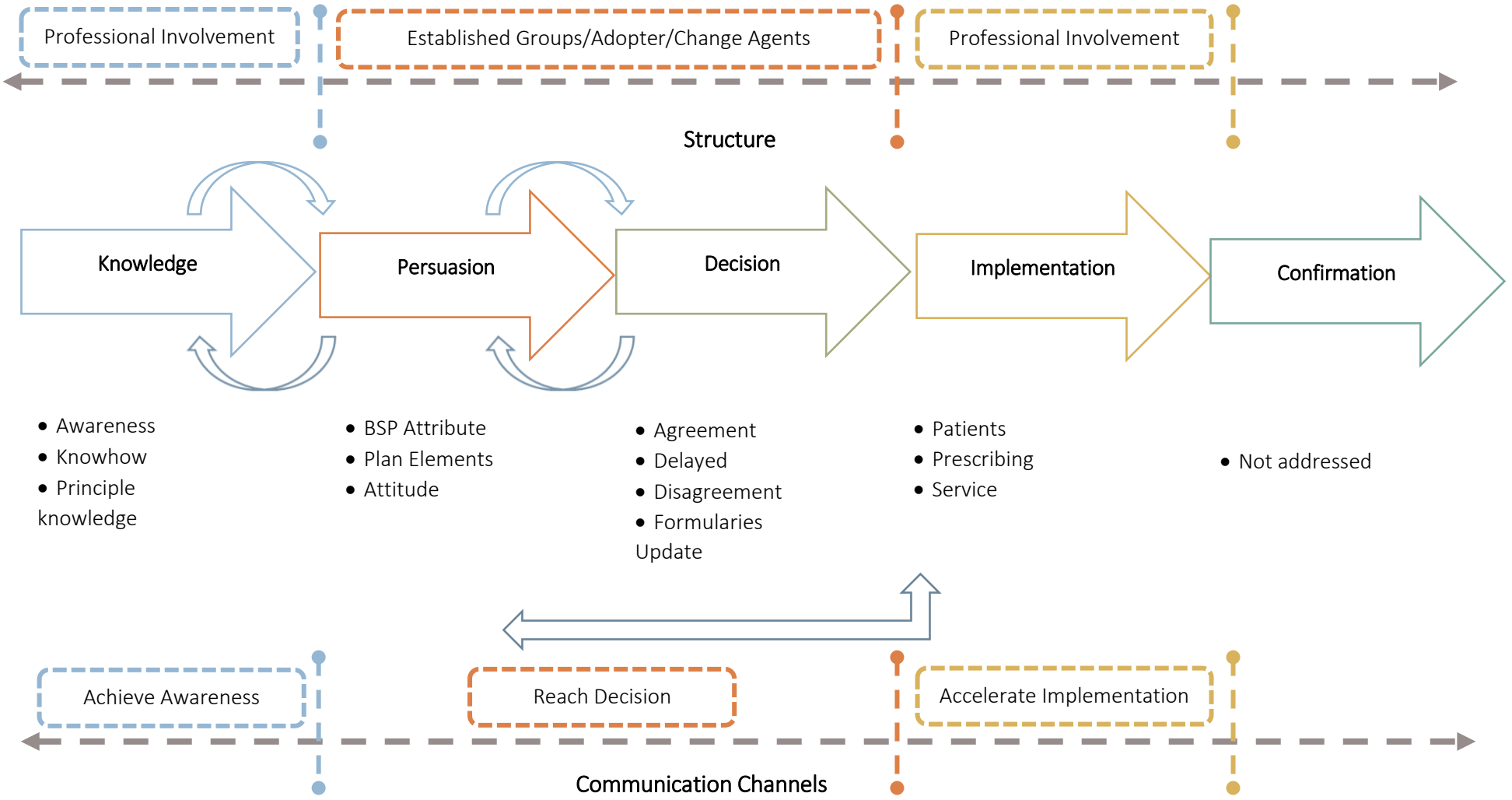
In conclusion, identified factors which affected the decision of adopting BSPs, were not BSP specific, but in fact were in alignment with what is reported in the literature as 'factors affecting prescribing behaviour and driving change in healthcare practice'. However, this study's findings showed how professionals responded to, and interacted with each other, relying on their cognitive reasoning, experiences and professional ethics to understand, assess and introduce an innovation/intervention into practice.

To successfully implement a BSP, a supportive context is needed in order to facilitate and encourage bi-directional communications and mutual understanding. A supportive context is based on having established and proper communication channels, supportive commissioners, accepting prescribers and active mediating agents. Table 30 and Figure 15 summarise study main themes

Table 30-Themes summaries and main related subthemes and categories

No.	Theme Title (Type)	Theme Description	Summary of subthemes/categories
1.	Knowledge (Substantive)	Knowledge at first stage of the process, it ensures participants' awareness of BSPs availability, participants' understanding of BSPs concepts, how to implement and what to consider upon implementation	Knowledge included awareness of market updates (new entries), new guidelines, availability of guidance and recommendations on how to implement, technical knowledge of BMPs, manufacturing processes and licensing requirements
2.	Persuasion (Substantive)	Persuasion is the essential stage in the process of diffusion. It is based on interactions and negotiations between change agents and adopters that end up either with positive (acceptance) or negative (refusal) attitudes	The persuasion stage included evaluating BSPs and switching attributes regarding added value, switching complexity, switching compatibility with service design, common medical practice and professional norms. Attitudes and any observed variations between professionals
3.	Decision (Substantive)	Decision is the third stage; it is the output of the persuasion stage. It is where stakeholders, mainly adopters, decided to proceed, or not to proceed, with the switching process	Types of interactions between adopters and change agents. The decision could be in the form of agreeing to switch, delaying the switch, or in some cases as a cross-regional (joint) agreement. The decision stage also addresses industry contracting and competition between suppliers
4.	Implementation (Substantive)	Implementation is the stage where the switching plan is executed. The plan is based on what had been discussed, offered and agreed on during persuasion stage	Implementation involves procedures and activities related to updating therapeutic guidelines/formularies, patients' communication, prescribing management and service related logistics
5.	Communication (Integrative)	Communication is an integrative theme; it discusses communication channels, purpose of communication and type of communication	The communication theme starts at the knowledge stage by reporting parties involved in educational and awareness intervention; at the persuasion stage by identifying involved parties, type of communication (collaborative/conflicting); at the implementation stage by disseminating the implementation decision and by describing communication approaches used with patients.
6.	Structure (Integrative)	Structure is the second integrative theme; it describes involved professionals and established working groups	Structure discusses types of commissioners, professionals involved, champions and liaisons, and the effect(s) of established working groups on the process

Figure 15-Biosimilar diffusion process



Chapter Six: Overall Discussion

"…Complete "realism" is clearly unattainable, and the question whether a theory is realistic "enough" can be settled only by seeing whether it yields predictions that are good enough for the purpose in hand or that are better than predictions from alternative theories…" Milton Friedman-Positive Economics

6.1. Thesis discussion

Healthcare systems could benefit from utilising BSPs by saving costs, improving patients' access or both. However, due to highly complex manufacturing and licensing processes, BSPs are not offered with a significant price reduction, compared to the R-BMPs. Therefore, BSPs cannot rely solely on price-based competition to achieve significant market-shares. Reported sales figures show a varied uptake of BSPs among countries and therapeutic areas. Evidence from the literature has shown the impact of encouraging national policies, which were based on: (*i*) incentivisation, (*ii*) prescribing targets or (*iii*) prescribers' attitudes; the latter being reported as varied and heterogeneous. Prescribers questioned evidence extrapolation, auto-substitution and switching stabilised patients.

At the beginning of this study in the UK, the limited uptake of BSPs in comparison to other European countries was attributed to prescribers' negative attitudes and a lack of encouraging policies. However, the recently considered BSPs' promotional activities, as well as new market entries, might change market dynamics and trigger different attitudes and prescribing norms. While most of the available literature was focused on assessing prescribers' attitudes toward BSPs, through the dominant use of quantitative surveys, to the researcher's knowledge there was no study that had investigated: (*i*) integration levels of BSPs into medical practice in the UK and (*ii*) the process by which the decision of utilising BSPs was made.

This study's conduct and data interpretation were led by implementation research theories. Implementation research, in general, and diffusion of innovation theory, in particular, are frequently referred to in research projects investigating the uptake of new technologies/innovation in healthcare settings.

This thesis represents research that investigated factors and processes by which BSPs were integrated into healthcare settings in England. The research was achieved through mixed methods methodology with component-specific objectives.The first component, the quantitative study, aimed to assess the current adoption rates of available BSPs into medical practice in England and compare it with other countries within GB (Chapter 4). The second component, the qualitative study, explored relevant stakeholders' experiences in assessing, commissioning, managing and prescribing BSPs in English secondary care settings (Chapter 5).

6.2. Factors affecting biosimilars' uptake

Assessing formulary listing status of targeted BSPs, EPO-BSP, G-CSG-BSP, HGH-BSP and IFX-BSP, confirmed the reported variable utilisation rates of BSPs between different therapeutic areas. The assessment also showed variations between different countries within GB and local geographies within England. Formularies listing rates and preferences were not associated with, and nor did they reflect, the duration of market availability of targeted BSPs. While assessing formularies listing acted as an indicator of BSPs integration, available data did not provide an explanation of the varied formulary listings. Assessing English Acute Trusts prescribing practices showed that, with time, Trusts became more accepting of IFX-BSPs, as more Acute Trusts began switching their patients. While the issue of "geographical location" had been shown to influence prescribing practice, other Trust characteristics did not seem to be influential. The evidence on the formularies' effect on prescribing practice was contradictory; being an early switcher was positively associated with IFX-BSP being listed in the formulary, but only half of the early switchers got IFX-BSPs listed in their medicine formularies. Formularies and MODB assessment provided a snapshot of BSPs' integration and utilisation rates; however, the assessment had fallen short in providing an explanation of the varied uptakes.

Interviewing relevant professionals showed that a mixture of prescribers' attitudes, switching-related attributes, commissioners' strategies and service designs had influenced BSPs' utilisation and switch implementation. Discerning evidence had shown how knowledge, practical experience, ethical obligation, practice norms and professional bodies influenced prescribers' attitudes. Funders and commissioners were able to influence the prescribing practice by juggling between carrot (incentives) and stick (contractual power). Evidence showed that following a collaborative approach between providers and commissioners promoted mutual understanding and satisfaction. Participants had discussed the central role of pharmacy departments in liaising and mediating interactions between providers and commissioners, as well as doing the same within their Trusts. Lastly, while perceptions, attitudes and interactions drove the decision of adoption, service design influenced the implementation. Different service designs and delivery routes had resulted in different logistical considerations, including patients' communication approach.

As discussed earlier in (Chapter 3-Methodology and Methods), the two components of a mixed methods study might be of equal or dissimilar importance. In this research, while quantitative results addressed technical issues such as: (*i*) formulary listing of R-BMP and BSP, followed listing aproach (brand vs generic name); (*ii*) specification of the preferred product/brand for prescribing; (*iii*) inclusion of supportive and educational materials, and (*iv*) specification prescribing practice (switching vs initiating), those results did not explain the observed variability of BSPs uptake. Moreover, the possibility of extrapolating a followed method and findings might be limited to the context of brand- only prescribed medicines, which require special formulary listings and prescribing considerations, such as: BMPs, anti-epileptic, immunosuppressant and narrow therapeutic index medicines.

Results obtained from the qualitative study were able to explain and describe factors and dynamics that influenced adoption of the BSPs. These findings could be extrapolated to future BSPs or healthcare interventions that are subjected to local negotiations between providers (Acute Trusts) and commissioners (CCGs). Therefore, for this research, the qualitative study was of the highest importance and significance. Accordingly, most of the following discussion will be built on its findings.

6.2.1. Factors driving biosimilars adoption in England based on combined evidence from the mixed methods research

Adopting a new medicine is a decision making process based on four main factors: (*i*) decision characteristics, (*ii*) decision makers, (*iii*) available information and (*iv*) external environment (Williams and Brown, 2014). As NICE has left the decision of utilising BSPs to prescribers' medical judgement, prescriber related factors needed to be addressed. However, given that prescribers work within their Acute Trusts' formal and hierarchical structures, their decisions could be influenced and driven by factors and attributes related to that variable. Lastly, as IFX is locally commissioned, factors related to CCGs and their interactions with providers might be influencing BSPs' utilisation. Accordingly, three governance and decision making tiers were involved in driving BSPs adoption: tier 2, tier 3 and tier 4 (2.6. Locally commissioned medicines in NHS England). Therefore, a fifth factor needed to be addressed, that of organisation characteristics (Shepherd and Rudd, 2014, Williams and Brown, 2014). In the following sections, dimensions related to each factor are discussed according to their emergence from the empirical chapters (Chapters 4 and 5).

6.2.1.1. Decision makers' characteristics

In the decision-making literature, scholars categorise involved professionals into two main categories: (*i*) managerial level professionals, who make the decision, and (*ii*) employees, who are responsible for achieving managerial targets and plans. For this research, professionals were divided into: (*i*) change agents, who played a similar role to managers and (*ii*) mediators / adopters, who acted as employees. However, Chapter 5 results showed that decisions relating to adopting IFX-BSPs and switching stabilised patients were driven by both managers and employees; no party was able to function without the agreement and the collaboration of the other. Therefore, any decision would be influenced by individual factors related to change agents, mediators and adopters. In making a decision and evaluating an intervention, individuals are shown to rely on their education/knowledge, values, personality, affiliation and the group they work within (Williams and Brown, 2014, Shepherd and Rudd, 2014, Wainwright and Waring, 2007).

The availability of an innovation, and awareness of its technical functions, encourage stakeholders' engagement with, and positive drive for, the adoption process (Akyürek et al., 2015, Rogers, 2003). Prescribers' knowledge and educational interventions have been frequently reported to positively affect prescribers' willingness and confidence to prescribe, or their unwillingness to prescribe, conventional generic medicines (Dunne and Dunne, 2015, Hulscher et al., 2010, Moe-Byrne et al., 2014). In the case of BSPs, the act of reviewing the literature revealed mixed accounts of prescribers' awareness and understanding of BSPs; where mostly limited levels of knowledge/understanding were observed. However, the research participants showed an understanding of the BSP concept, BSPs' biological variations and, in some cases, the licensing process and clinical evidence extrapolation. Moreover, Trust-based professionals, mainly prescribers, did not feel the need for extra training and educational interventions related to BSPs.

The effect of knowledge is not limited to prescribers, but it is extended to help commissioners negotiate better deals and contracts with Trusts. In addition, most Trust-based prescribers and pharmacists were confident about the commissioners' knowledge and understanding of BSPs. This confidence was based on the fact that most involved commissioners were pharmacists, who through their training and education had gained a sufficient understanding of BMPs, including BSPs. Commissioners' knowledge helped to shift the power toward them, thereby augmenting their position in the contracting process (Smith and Curry, 2011).

Professional experience is another concept that intertwines with knowledge. Previous experiences with similar situations improve innovation's compatibility with practice norms and procedures (Rogers, 2003). In assessing new medicines or interventions, prescribers rely on their own previous experiences to form a positive or a negative attitude (Talukder et al., 2008, Dunne et al., 2014, Schumock et al., 2004). In discussing previous practical experiences, including experience with R-BMP, it appeared that prescribers perceived experience and knowledge as inseparable and that the concept of 'self-learning by doing' applies to them (Wainwright and Waring, 2007). Furthermore, previous experiences were, to some extent, affected by common medical practice and therapeutic guidelines and pathways; guidelines which usually dictate first choice medicines for prescribing. Therefore, gastroenterologists were the most willing group to prescribe IFX-BSPs, while rheumatologists were more engaged with etanercept-BSP. The same observation was confirmed by a 2017 study, which targeted gastroenterologists, rheumatologists and dermatologists in the UK (Chapman et al., 2017). Similar to prescribers, the commissioners and Trust-based pharmacists also relied on their experiences with conventional generic medicines that were challenging to be introduced into medical practice, such as immunosuppressant medicines.

The cumulative effect of previous experience, knowledge or familiarity led to improving professionals' self-efficacy, being confident enough to commission, introduce and prescribe BSPs, as well as switching stabilised patients (Cabana et al., 1999).

As research participants were healthcare professionals working for a publically funded healthcare system that does not aim to maximise revenues or generate profits, their values were concerned with patients' health and wellbeing, rational drug use and reducing expense for the NHS. Therefore, all participants shared the same values and common norms, despite being from different regions, working at different organisation (CCGs and Trusts) and having different professional roles. Participants' values and ethical obligations influenced their assessing and planning of a potential switch, as well as their negotiations between CCGs and Trusts. For instance, a switch's financial added value addressed the desire to reduce costs for the NHS and the need for rationalising medicines' use. On the other hand, patients' health and safety form the base for a managed and controlled switch. Issues loaded with, and linked to, ethical values while also addressing organisational norms, usually achieve high uptake and broad acceptance (Akyürek et al., 2015). Nevertheless, as some Trusts had limited utilisation of IFX-BSPs, values and ethical obligations were not enough to drive the uptake of IFX-BSP or accelerate its implementation. Moreover, in this research observed ethical values were, to some extent, in conflict; the need for a carefully managed switch was a resource demanding process, which in turn could minimise financial savings, or actually increase costs.

Prescribing BSPs in general, and switching stabilised patients in particular, might represent an ethical dilemma for prescribers. Prescribing licensed, authorised and cheaper medicines (in this case BSPs) aligns with the definition of rational drug use: "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" (World Health Organization (WHO), 2002). However, prescribing BSPs for untested indications, for which clinical evidence was extrapolated, as well as for switching stabilised patients, could challenge the principle of evidence-based medicines; a principle based on evaluating evidence and relying on available data to ensure safety and efficacy of the prescribed medicine (Djulbegovic et al., 2009). This situation was particularly true in the case of gastroenterology, for which the evidence regarding the safety and efficacy of IFX-BSPs was extrapolated from rheumatology indications. This extrapolation is challenging because the mechanism of action for IFX in gastroenterology is slightly different from rheumatology. Additionally, unlike gastroenterology, in rheumatology IFX is prescribed with immunosuppressant agents as a multiple-therapy regimen, which might camouflage its immunogenic effect (Weise et al., 2014, Gecse et al., 2013). Such a situation creates a certain level of uncertainty that needs to be addressed and eased; therefore, frequent observations were the key to having a controlled and well managed switch which would safeguard patients' health and wellbeing.

Studies investigating the effect of prescribers' demographics on their prescribing reported contradictory results. While some studies and reviews found an association between professionals' demographics including gender, age, educational background and attitudes, others found no such association (Talukder et al., 2008, Williams and Brown, 2014). In the case of BSPs, only a few studies assessed the association between prescribers' knowledge, their attitudes and their demographics. Hospital-based and more experienced prescribers were found to be more familiar and aware of BSPs; on the other hand, female prescribers were found to be more reserved and less accepting of BSPs compared to their males colleagues (Baji et al., 2016, Beck et al., 2016, Grabowski et al., 2015). In this research, any effect of an individual's demographics was not visible; however, due to the research design's limitations, this finding needs to be

carefully reported and interpreted. First, as this study did not involve access to prescribing databases or medical records, it was not possible to assess the effect of demographics on the actual prescribing practices. Second, the research was not based on a survey which spontaneously collected data related to prescribers' demographics and their knowledge and attitude toward BSPs; therefore, it was not possible to examine any potential associations between prescribers' demographics and their attitudes/knowledge. Third, the limited effect of demographics on prescribers' attitude was reported by participants, who had discussed prescribers' attitudes toward BSPs. Therefore, it is possible that participants tried to be diplomatic and so avoided reporting gender, age and/or experience related effects.

Communications and connections: affiliations and group norms are the last two factors to affect decision makers' attitudes (Williams and Brown, 2014). Both factors represent the effect of peers (fellow professionals) at the practice, regional or national levels. To some extent affiliations and loyalties act as a directive tool towards a particular stand or position (Williams and Brown, 2014). In the case of BSPs, affiliations were in the form of professional bodies and societies, which played key roles in promoting the acceptance of BSPs and the practice of switching. Professional bodies acted as interpersonal cosmopolite channels, where prescribers within the same therapeutic area or speciality are connected nationally over a wider range than at the practice or local levels (Rogers, 2003). Professional bodies convey the stand and experience of key opinion leaders within the speciality. These experts could affect prescribers' attitudes and practice if they recommend or do not recommend a medicine or practice, even when the evidence is limited or questionable (Cabana et al., 1999, Damschroder et al., 2009, Ashford et al., 1999). Professional bodies' roles in promoting, recommending and providing educational or informative materials related to BSPs were also evident in the literature (Danese et al., 2014, Danese et al., 2016, O'callaghan et al., 2017). Group norms exert social pressure on prescribers to follow the group's decision and agree on practice. Therefore, prescribers would accept certain practices in order not be labelled as 'an outlier, a rebel' (Raisch, 1990b). In assessing group attitudes, joint agreement was frequently reported; only limited variations within the same team were reported.

6.2.1.2. Organisational factors

Secondary care settings, whether an Acute Trust or a Health Board, fit the definition of an organisation (NHS UK, 2016, Rogers, 2003). Due to the complexity of the NHS, introducing new practices or interventions is driven by both individual and organisational level factors (Ashford et al., 1999). Elements related to organisation size and services, resources, location, governance, policies, internal connectedness, internal culture and capacity, were reported to influence the decision-making process (Shepherd and Rudd, 2014, Williams and Brown, 2014).

Scholars frequently refer to organisational culture as a set of norms and values shared amongst professionals working within the organisation (Akyürek et al., 2015). However, in this research, organisation-related factors were captured based on what was reported by the participants. The study's design did not allow for verifying the actual effect of organisational values on discussions, prior to and during the implementation phase. Research participants were professionals who were working within formal healthcare settings; it is therefore expected that they would adopt the organisation's values and norms (Simon, 1979). In fact, in discussing internal culture and norms, it was not possible to discern if what the participants reported was related to their own values and norms or to their particular organisation's values and norms. Therefore, it might be assumed that values observed at the individual level are the same as the organisation they work at; ultimately the NHS.

An organisation's size might be an indicator of its complexity, formalisation and professionalism. Size is also an indicator of hospital capacity and the number of patients who could be treated and served (Starkweather, 1970). For this research, the effect of Acute Trusts' and Health Boards' overall size was not investigated or discussed. However, service size took on a different manifestation; evidence presented in Chapter 5 showed that patients' cohort size played a role in determining which service would be prioritised for switching. Patients' cohort size was not a stand-alone factor, but it was driven and determined by two other factors: common medical practice and therapeutic guidelines. The effect of the contemporary available therapeutic guidelines was also evident in formularies assessment; for example whether the R-BMP or BSP version of IFX was listed in dermatology, the least frequent prescribers of IFX. Gastroenterology on the other hand was frequently the first service to start switching. It should be noted that in addition to which area to be targeted first for the switch, cohort size affected clinical capacity during the implementation stage.

In their review, Williams and Brown (2014) considered the involvement of an organisation in educational (teaching) activities as an indicator of sophisticated and specialised services. A health organisation's status as an educational (teaching) facility reflects the degree of professionalism encompassed within that organisation. Both specialisation and professionalism positively drive the adoption decision (Williams and Brown, 2014, Starkweather, 1970). Another factor that might drive the adoption decision is the organisation's governance (Williams and Brown, 2014). However, chapter four's results showed no associations between a Trust being an early switcher and its status as an educational or foundation Trust. Furthermore, referring to the qualifying status of 'foundation' as an indicator of a Trust's governance could be a challenging, as such a 'label' reflects the Trust's control over its financial resources and autonomy from the central control of the NHS; however, such status does not reflect the centralisation of decision-making within the Trust.

An organisation's geographical location could affect its exposure to, and acceptance of, innovation as well as facilitating the adoption of that which is 'new' (Rogers, 2003). Despite having several well-developed medicines management groups and formularies committees, such as the Greater Manchester Medicines Management Group (GMMMG), the Pan Mersey Prescribing Area and the Northern Treatment Advisory Group (NTAG), Northern Acute Trusts were found to have lower tendencies to switch to IFX-BSPs than Southern Trusts. Despite the fact that discussions with participants had identified issues related to conflicting or lengthy negotiations between providers and commissioners, prescribers' reservations and uncertainty regarding market dynamics; these factors were not specific to the Northern sites, being also reported in other regions.

As discussed in Chapter 3 the impact of adopting an innovation such as new technology, could be assessed by evaluating its penetration level within a given structure. Penetration levels might be assessed by referring to innovation utilisation rates or through assessing related policies and guidelines. Therefore, this research started by evaluating the most visible attribute of the BSP phenomenon; the integration levels of BSPs in medical practice, and specifically secondary care settings. Medicines' listing and inclusion in formularies is supposed to reflect allocative decisions in terms of what medicines are readily available for prescribing (Williams and Brown, 2014). Moreover, formularies are considered to act as a platform through which pharmacy teams could convey educational and informative materials and decisions (Haslé-Pham et al., 2005). However, the results presented in Chapter 4 showed that brand name-based listing was not a widespread practice in listing BMPs, including the BSPs. It is therefore possible that formularies might not be accurately reflecting actual prescribing rates. Moreover, listing frequencies of first wave BSPs (HGH-BSP,

G-CSF-BSP and EPO-BSPs) were less than the reported market share. In the case of IFX-BSPs, listing frequencies were inconsistent with IFX-BSP MODB data; additionally, the formularies were not reflecting the actual prescribing practice of IFX-BSPs, whether in initiation or switching.

Inconsistency between actual prescribing practice and formularies' listings was a result of limiting the formularies' role to demonstrating compliance with NICE, rather than guiding prescribing behaviour; a phenomenon explained by the research participants. Furthermore, other tools might act as alternatives to formularies in influencing prescribing behaviour, such as electronic prescribing and pre-printed protocols (Fischer et al., 2008). Finally, prescribers' confidence in their knowledge and experience in prescribing BMPs, including BSPs, had limited their reliance on formularies to receiving advice about their prescribing practices. Therefore, updating formularies to reflect available brand(s) for prescribing might not be considered as an urgent task that needed to be completed. These factors resulted, in some cases, in creating static formularies with no influence or impact on the process of prescribing (Reynolds et al., 2012).

Organisational memory is another dimension of an organisation's policies (Williams and Brown, 2014). In adopting an innovation, organisations rely on their previous experiences with similar technologies, information now collecting in the organisational memory, to assess the innovation's fitness within the organisation's structure and norms (Rogers, 2003, Williams and Brown, 2014). In this research, the matter of an organisation's memory was evident in the participants' willingness to extrapolate their experiences gained when introducing and switching IFX-patients to future BSPs. In this case, it was a cyclic process that starts by building familiarity and knowledge of BSPs, together with switching processes, and ends up by creating new practice norms and a new memory.

Healthcare services are based on the knowledge and the performance of individuals who, in most cases, work within teams and groups (Aarons et al., 2011). Therefore, organisational connectedness is significant in influencing the uptake decision of an innovation/intervention (Williams and Brown, 2014). Professionals rely on internal channels to understand and share experiences in implementing an innovation (Wainwright and Waring, 2007, Akyürek et al., 2015). In general, communications between targeted areas and other areas that had experienced BSPs earlier, such as oncology and haematology, were reported to be limited. However, connectedness was observed between therapeutic areas and pharmacy departments; this liaising emphasises the central role of pharmacists in introducing and managing BSPs. The involvement of pharmacists in medicines' management is frequently acknowledged in the literature (Perfetti et al., 2015a, Tan et al., 2004, The National Institute for Health and Care Excellence (NICE), 2015d).

The final element to affect organisational adoption and acceptance of an innovation is the availability of excess or slack resources, which can sometimes provide an organisation with a certain level of freedom to adopt innovative ideas, even if financially demanding (Rogers, 2003, Williams and Brown, 2014, Aarons et al., 2011). Availability of financial resources helped private hospitals in the USA to integrate innovations more rapidly than publically funded healthcare settings (Aarons et al., 2011). Healthcare services in the UK are mostly publically funded and usually do not enjoy the luxury of such extra financial resources. Therefore, in the case of BSPs, the priority issue is not the availability of resources, but the scarcity of resources, and the ever-present pressure to save costs. Therefore, funders and providers should strive to demonstrate allocative, technical and productive efficiencies (Palmer and Torgerson, 1999). This situation is where the effect of the fourth factor influencing decision-making processes becomes visible: the external environment.

6.2.1.3. External environment and available information

An environment is "a system that is outside the organisation, but which influences the behaviour and properties of the organisation" (Damanpour and Gopalakrishnan, 1998). Similar to other factors affecting decision making, the environment has several dimensions related to it, such as: (*i*) fundholder, (*ii*) guidelines and national policies, (*iii*) external connections, (*iv*) dynamics and (*v*) time (Gravel et al., 2006, Berg et al., 2001, Aarons et al., 2011, Wainwright and Waring, 2007).

In allocating funds and consuming financial resources, stakeholders and involved organisations are obliged to demonstrate efficiency; colloquially "getting the best value for your money". There are three main types of efficiencies: allocative, technical and productive (Palmer and Torgerson, 1999). Allocative efficiency takes a strategic scope and is concerned in achieving the best interests of the whole population, similar to what NICE attempts to achieve through its TAs (Palmer and Torgerson, 1999). Technical efficiency is concerned with the actual implementation and practicality, made concrete in through the mix of resources and health outcomes (Palmer and Torgerson, 1999). Productive efficiency acts as a link between both types of efficiencies; it operates either by improving outcomes or minimising costs (Palmer and Torgerson, 1999). Commissioners and service providers are understood to be involved with technical and productive efficiencies.

In case of IFX-BSPs, NICE has attempted to achieve allocative efficiency by setting patients and disease criteria for IFX treatment in its technology appraisals (TAs). However, NICE has assessed and recommended IFX as a molecule and left the choice of brand to local arrangements. Chapter 2 showed that in the UK at the time of introducing IFX-BSPs, there was no BSP-specific policy or mandate. As a result, these two factors had created a situation where the decision was left to self-regulation, rather than external (authoritative) regulation (Brown et al., 2011). Accordingly, local agreements between relevant stakeholders needed to ensure technical and productive efficiencies in deciding which brand (BSP or R-BMP) to commission and how to use it once chosen: via switching or initiating?

In adopting an innovation, decision makers could follow one of two innovation selection theories: search or satisficing[11] theories (Simon, 1979). In search theory, decision makers are actively involved in searching for an innovation that could be the most appropriate regarding acquisition cost and return on investment. On the other hand, satisficing theory occurs when a decision maker (potential adopter) has a set of criteria that is used to assess available innovations in order to select the most suitable one (Simon, 1979). As local commissioners, CCGs, are accountable for delivering safe, effective and good quality health services to their populations, and at the same time are required to avoid budget overspend (NHS Commissioning Board (NHS CB), 2012), their decisions could follow two innovation selection theories. In the case of IFX-BSPs, the CCGs as the primary commissioners of IFX followed search theory rather than satisficing theory. This choice is based on the fact that the quality, safety and efficacy of IFX-BSPs were assessed by the EMA and that BSPs were actively monitoring by the MHRA. Second, patients' and disease eligibility criteria for IFX therapy were already set by NICE. Third, as presented in Chapter 5, role requirements and job descriptions meant that commissioners and high-cost medicine pharmacists were involved in horizon scanning; which in turn meant that they were actively involved in monitoring updates regarding new market launches and product availability. Lastly, deciding on which brand to commission and on the most appropriate prescribing approach was informed by financial impact and patients' health status, as was discussed in the NICE BSP implementation guide (The National Institute for Health and Care Excellence (NICE), 2015d). The same

[11] Satisficing: is a concept invented by Herbert Simon; and it is a combination of two words ("satisfy" and "suffice")

concept was confirmed in Chapter 5, which showed that BSPs formulary application was mostly an abbreviated one; driven by commissioners rather than prescribers.

As explained earlier, commissioner (change agents) played the role of managers in negotiating and introducing BSPs. Similar to managers in healthcare settings, commissioners are subjected to an ongoing monitoring by NHS-England to assure their compliance to adopt and offer high quality, safe and cost effective healthcare services and interventions (Brown et al., 2011, Health Policy and Economic Research Unit, 2013). Adopting an innovation could be driven by the urgency for satisfying an ongoing demand or need, or as a response to new updates in the field that are introduced by the innovation's producers (Castro et al., 2014). For that reason, an adoption was based on both need and response to market updates. The market availability of BSPs created changes in the market that allowed for the availability of a similar but cheaper alternative to R-BMPs, which in turn acted as a cost containment tool.

In healthcare settings, managers rely on clinicians to actualise their plans and put their decisions into action (Brown et al., 2011). Relying on clinicians means relying on human behaviour and norms (Simon, 1979). As discussed earlier, IFX-BSPs were associated with a certain level of uncertainty and challenges for medical norms; especially for gastroenterologists who are the IFX's heaviest prescribers of IFX. Uncertainties generally encourage bargaining and deploy incentives to facilitate adoption and limit resistance (Shepherd and Rudd, 2014, Eccles et al., 2005). The decision theme in Chapter 5 showed how commissioners and providers relied on negotiations to promote the uptake of IFX-BSPs. During negotiations, incentives and additional support were offered to encourage prescribers and ease the switch implementation. Incentives and support are commonly used tools to influence prescribing behaviour, to limit resistance and to promote the uptake of a new or novel intervention (Rodrigues et al., 2013, Raisch, 1990b, Schumock et al., 2004).

In addition to incentives, in some cases commissioners relied on their contractual powers to overcome resistance or delays, especially when incentives were not offered, or when Trusts asked for more than what was offered. In these cases, contractual power counteracted prescribers' or a Trust's negative attitudes and so compensated for the absence of BSPs' specific policies and defined prescribing targets. Expressing capability in issuing executive orders and setting restrictions are reported to influence prescribing behaviour (Schumock et al., 2004, Raisch, 1990b, Simon, 1979). However, unlike educational interventions, restrictions usually have a temporary effect and do not lead to changes in beliefs and attitudes (Cabana et al., 1999).

While commissioners offered incentives, mainly in the form of gain share agreements to encourage BSP prescribing, BSPs' manufacturers offered incentives for contracts, to get their brand procured. Examples of industry-offered incentives that helped with switch implementation include pre-prepared IV bags, funding extra nursing time and patients' information letter. The effect of the industrial intervention was also observed in promoting the prescribing of conventional generic medicines (Dunne and Dunne, 2015, Toverud et al., 2015, Jenkings and Barber, 2004).

The dynamic nature of the environment and time both play a role in directing relevant stakeholders and influencing their acceptance and willingness to adopt an innovation (Damanpour and Gopalakrishnan, 1998, Shepherd and Rudd, 2014, Simon, 1979). In understanding the effect of an environment's dynamics, two elements need to be addressed: predictability and stability (Damanpour and Gopalakrishnan, 1998). In the case of BSPs, dynamic nature was evident in form of changes in market structure in terms of new launches and NICE TAs. While horizon scanning activities helped relevant stakeholders in predicting new launches of BSPs, or new/innovative BMPs, competition between the manufacturers of both BSPs and R-

BMPs in some cases resulted in creating instability and uncertainty of what brand to procure and when. Therefore, the dynamics could be described as creating an unstable situation. In such an environment, time is a crucial factor; one which is more significant for managers and other change agents, than practitioners. In some cases the time factor influenced the potential savings; market competition pushed R-BMP's manufacturers to lower their prices, which in turn minimised cost differences between BSPs and R-BMP. Time and highly dynamic environments encourage managers to push for innovation adoption. In the case of IFX-BSPs, commissioners, as both managers and fund holders, were frequently described by respondents as keen and "pushy" to get IFX-BSPs integrated into practice. Organisations in dynamic environments, rely on their memory to accelerate the adoption (Damanpour and Gopalakrishnan, 1998, Simon, 1979). In this case, organisational memory was manifested as pharmacy departmental memory. Pharmacists relied on their previous experiences for driving and facilitating the switch. However, this explanation should not neglect the effect of a person's professional role, job description and the expected deliverables.

External connections and networks also affect an organisation's decision making process (Aarons et al., 2011, Wainwright and Waring, 2007). In its guideline, NICE has considered a joint formulary as a tool to reflect and create consensus and unified practice within a given health economy (The National Institute for Health and Care Excellence (NICE), 2015a). However, Phase II formularies assessment showed that referring to a joint formulary was not associated with a Trust's status as an early switcher to IFX-BSPs. However, the external connections' effect was evident in observing the experiences of what other Trusts within the region or the country, when implementing IFX-BSPs. Observing other organisations' practice and implementing their approaches echoed findings of a 2004 study, which showed that members of drug and therapeutic committee referred to other committees' decisions to compensate for the limited evidence available to them at that particular time (Jenkings and Barber, 2004).

In this research, patients' involvement is another aspect of external connectedness. NICE has frequently emphasised the need to involve patients in decision-making processes, whether in formulary decisions or in planning IFX-BSPs' integrating (The National Institute for Health and Care Excellence (NICE), 2015a). Patients' inclusion in a decision-making process is an indicator of good governance, which is based on transparency, by giving a voice to all relevant and affected stakeholders (Williams, 2011, Daniels, 2015). However, it was noticed that patient involvement in decision-making processes was mostly limited or completely absent. Upon further investigation, respondents explained that patients' exclusion was, in some cases, either an attempt to avoid provoking anxiety among them, or an effort to avoid losing time in negotiation with an additional group of stakeholders, or both. Another possible explanation for the lack of involvement might be traced back to the time factor; in situations where time is significant, managers tend to adopt more centralised procedures and minimise non-centralised (lateral) communications (Shepherd and Rudd, 2014).

Information is reported to be a stand-alone factor that affects the decision process (Williams and Brown, 2014). However, in this research, it was found that this factor is linked to, and influenced by, the environment. Therefore, the effect of information on decision-making is discussed within the environment effect. The definition of information and its sources depends on both professional roles and affiliation (Williams and Brown, 2014). In their review of decision making in healthcare settings, the authors referred to information as "available evidence on an intervention's safety and efficacy that influences allocative decisions". For them, the role of information in technical decisions was not strongly evident (Williams and Brown, 2014). Interestingly, limited evidence on IFX-BSPs safety and efficacy was not a key element in facilitating its acceptance and utilisation. Participants, including prescribers, showed confidence in their

knowledge and showed general acceptance of available evidence. As the decision to use IFX-BSP was technical rather than allocative in nature, it might be linked to knowhow, in this case the NICE implementation guide. Guidelines could influence prescribing behaviour and positively affect the adoption of an innovation (Akyürek et al., 2015, Berg et al., 2001, Raisch, 1990b, Schumock et al., 2004, Rodrigues et al., 2013). However, the introductory nature of the NICE guidelines acted as a barrier for some participants, which echoed what was reported in the literature regarding the impact of the scarcity of BSPs-specific guidelines (technical knowledge) on limiting BSP utilisation. In summary, stakeholders relied on observing others' experiences (peer effect), previous experiences (individual and organisational memory), incentives and authoritative mandates (contractual power) to facilitate IFX-BSP utilisation.

The effect of the environment (external factors) cannot be studied in isolation from internal and individual factors; organisations and professionals do not operate in a vacuum and are always affected by what happens externally; even if that relationship is not always entirely recognised and acknowledged. External factors affect the humans who drive the adopting and implement the changes (Talukder et al., 2008, Brown et al., 2011).

6.2.1.4. Decision characteristics

The last factor to affect the decision-making process is 'decision characteristics'. Elements related to potential added value, complexity, compatibility and controversy jointly build up the effect of decision characteristics (Williams and Brown, 2014). Adopting and implementing innovation is a multiple-stage process; each stage is built on and influenced by the output of the previous one. However, all these stages feed in and out the innovation's characteristics. All the previously discussed factors would not be effective if they were not directly linked with at least one of the innovation's characteristics (Frambach and Schillewaert, 2002).

Added value or perceived benefits are reportedly the most significant attributes of innovation (Rogers, 2003, Greenhalgh, 2017). Marketing efforts related to BSPs are based on promoting BSPs' ability to reduce costs and improve patients' access to biological therapy (Intercontinental Marketing Services Health (IMS), 2011, IMS Health, 2016). Participants, including prescribers, recognised the benefit of utilising BSPs for NHS cost saving. Improving patients' access, however, was questionable; particularly as limited access to medicines is not a common issue in highly regulated healthcare systems like the UK's NHS. In studies of prescribers in developing (pharma-emerging) and developed (highly regulated) countries, prescribers from the latter were less concerned about patients' access; their main motive for prescribing BSPs was cost savings (Baer II et al., 2014, Lammers et al., 2014, Monk et al., 2017). Changes in patients' access to BMPs were proposed by changing patients eligiblility criteria for biological therapy. This suggestion is similar to what was proposed by the National Rheumatoid Arthritis Society (NRAS), a national patients' support group, in their 2015 appeal to NICE (National Rheumatoid Arthritis Society (NRAS), 2015). The other approach to changing access to medication is by changing the sequence of a therapy's application by deciding which agent to start with as a result of lower prices being offered. The latter approach might be possible; however, it did not acknowledge the impact of industry competition on market dynamics and how the competition might complicate the situation further.

Switching, as a prescribing approach, was perceived to have more significant financial impact than initiating biological naïve patients. However, the majority of participants, especially prescribers, considered switching to be a more challenging and demanding process than initiation. Differentiating between the two prescribing approaches (initiation and switching) was also observed with generic anti-epileptic drugs, which to a certain degree mimic BSPs (Krämer et al., 2007, Sharott, 2013). Therefore, negotiations between Trusts and commissioners were not influenced by BSPs' characteristics, but these discussions were based on the requirements associated with switching. Switching characteristics reflect aspects related to the BSP itself: (*i*) patients, (*ii*) disease factors, (*iii*) system and (*iv*) service logistics. The results showed that unlike what is reported in implementation science narratives, added value was not the leading influencer in discussing switching patients; that category was allocated to issues associated with the risk and practical complexity of the switch.

Despite the fact that licensing of IFX-BSPs was based on clinical evidence in rheumatology patients, some rheumatologists were reluctant to switch their stabilised patients; a state of mind that was shared with the dermatologists. In addition to the perceived minimal financial advantage, due to the small numbers of patients in the cohorts, rheumatologists and dermatologists related their attitudes to disease complexity and concerns of flare ups upon switching stabilised patients. These were patients who had been challenging to be stabilised using other biologics; IFX, for some, was their last resort. Concerns over safety and efficacy for life-threatening or complex diseases are a commonly reported barrier to hinder changes in prescribing practice (Sandorff et al., 2015, Hemmington et al., 2017). The effects of disease complexity were not limited to rheumatology and dermatology, but were also evident with gastroenterologists. However, while gastroenterologists were reluctant to switch unstable patients they did agree to switch the whole cohort. Prioritising disease complexity over perceived added value echoes the position of two professional bodies which firmly rejected switching based on economic reasons only (The British Society for Rheumatology (BSR), 2015, The British Society of Gastroenterology (BSG), 2016). The effect of disease complexity was also indirectly observed in the results presented Chapter 4. While G-CSF-BSPs achieved the highest formularies listing among all targeted BSPs, G-CSF-R-BMP was preferred over the BSPs for the sensitive patient group, paediatric, and complex indication, stem cell mobilisation.

While the difference in financial impact between switching and initiating was explicitly addressed by research participants, the difference in the aim of therapy between the two prescribing approaches was only implicitly addressed. Initiating biological naïve patients aims to treat patients and relieve their symptoms; on the other hand, switching is concerned with maintaining disease control (Krämer et al., 2007). Moreover, similar to what was discussed when considering decision makers' characteristics, utilising BSPs, especially in gastroenterology, presented somewhat of an ethical dilemma. In similar situations, prescribers try to balance potential hazards affecting patients' health and their overall wellbeing against cost implications (Krämer et al., 2007). In doing that, involved professionals assess the cost of therapy failure or losing control over the patient's illness, against the cost of switch implementing (Crawford et al., 2006). These considerations resulted in perceiving switching as a challenging process, which in turn had led prescribers to ask for a managed and controlled switching of their patients. Managed switching is crucial to secure prescribers' acceptance and collaboration (Sullivan et al., 2017, Danese et al., 2016, Crawford et al., 2006). A managed switch was based on one or more of three basic components: (*i*) patients' communication, monitoring and support, (*ii*) positioning of BSPs within current service designs and practice norms and (*iii*) having a gradual approach in switching. Desire for a managed (controlled) switch, despite the possibility it might result in minimising savings, might reflect participants' ethical obligations. However,

in some cases prescribers did not see the need for extra monitoring; they justified their position by scientific reasoning, knowledge and experience with R-BMPs and associated batch-to-catch biological variations.

In conclusion, medical decision-making is a complicated process; it is not only affected by the innovation's characteristics, but the decision is also influenced by perceived potential risks, patients' factors (medical history and psychology) and available clinical evidence and information related to and affecting the innovation's characteristics (Berg et al., 2001). Moreover, human factors regarding norms and ethics, knowledge and experiences, cognitive processing and professional roles, are vital factors in driving adoption decisions in healthcare settings (Berg et al., 2001, Brown et al., 2011, Simon, 1979). Elements and factors discussed in this section and the previous ones, emphasised the effects of power shifting from external formal regulation to self-regulation (Brown et al., 2011). Therefore, as evidence discerned, there is a need to have a BSPs specific national policy that is able to create a balanced approach to adopting and implementing BSPs. This outcome can be achieved by considerating different aspects related to patients' health and wellbeing, prescribers' comfort and acceptance, service designs and delivery logistics and finally, the dynamic nature of the market.

This research aimed to identify facilitators and barriers that affect BSPs utilisation in England. However, as this research progressed it became clear that there was not a standard mix of factors that affected the uptake. Each site had its own unique basket of factors and set of dynamics that affected its adoption levels. Offering incentives and support facilitated the implementation at some sites; however, the absence of these incentives did not always hinder or delay the adoption. Moreover, commissioners did not always take the initiative and propose the switch; in some cases the switch was proposed by service providers who were motivated by the need for reducing financial deficits or avoiding being pushed or enforced to switch by commissioners. In conclusion, if the motives of each party were pointed in the same direction, addressed collaboratively in a timely manner, then the agreement was achieved, and benefits were gained. However, the study revealed evidence that challenging and contradictory agendas led to conflicts and delayed adoptions.

6.3. Research strength and weakness

This research has investigated factors and processes by which BSPs were integrated into healthcare settings in England. The research was accomplished through two main studies; the first assessed BSPs' integration levels in healthcare settings, and the second investigated the processes by which the decisions to adopt BSPs were taken.

Integration levels were assessed through evaluating BSPs uptake by local medicines formularies and classifying Acute Trusts, according to their prescribing practices. In addition to confirming reported variations between therapeutic areas, results showed geographical variations within England, and between countries when compared with other GB countries. The MODB study revealed the effect of regional locations on the prescribing practices that were followed. Despite being the first study to assess BSPs' integration levels in England, as far as this researcher is aware, its results might not accurately present actual prescribing practices. Moreover, tested characteristics which were considered to affect Trusts' prescribing practice, might not be the most relevant and influential ones. Factors related to patients' cohort size and the Trusts' financial performance were not considered, due to limitations in study design and available data. Recently, there has been a growing body of research, assessing utilisation rates of new BSPs, IFX-BSP, etanercept-BSP and insulin glargine-BSP, based on prescribing databases. These studies might

provide more accurate and unbiased assessments of BSPs utilisation in the UK, including England (Chapman et al., 2017, Aladul et al., 2017a).

The second part of my study, the qualitative component, investigated the process by which the observed integration levels were achieved. This study was based on exploring relevant stakeholders' experiences in assessing, managing, commissioning, introducing and prescribing BSPs. The study gave voice to 59 healthcare professionals to discuss their own professional and personal experiences in utilising BSPs. Relaying of multiple recruitment strategies was proven to be fruitful in securing input from healthcare professionals representing different professionals' roles and regions. In addition to investigating the process of BSPs adoption, the study attempted to understand the involvement and inputs of different professional roles. It was possible to identify and understand high cost-medicines' pharmacists and nurses' roles as mediating agents and adopters.

Following the semi-structured interviewing approach meant that it was possible to explore new ideas, which were not considered in planning phases. In fact, some participants, who were still at the switch planning stage, suggested the interviews made them think about additional issues to consider, such as patients' involvement, patients' monitoring and the need for educational interventions targeting professionals.

Selection bias is a major threat for this study; it was noticed that most participants who agreed to take part in this study had, in general, positive attitudes toward BSPs. However, a recent study by Chapman et al. (2017) showed comparable results regarding prescribers and other professionals' positive attitude and acceptance of switching stabilised patients, which goes some way to reducing this researcher's concern.

The regulatory environment in which the research was conducted is different from the current environment. Therefore, the findings of this research might be transient and time limited. However, research participants discussed how their previous experiences influenced their actions and their willingness to extrapolate their experiences with IFX-BSPs to their future dealings with BSPs. Therefore, results might still be relevant and eligible to be transferred to other situations that involve local level dynamics and power bases.

Finally, despite this research having captured the experiences of multiple professional roles, it missed hearing the voices of patients, carers and those in the pharmaceutical industry. It is desirable that this limitation is addressed in future research projects.

6.4. Implications and recommendations for policy, practice and research

6.4.1. Implication for policy

As highlighted in the literature review chapter, in the UK there was not a BSPs specific policy that regulates BSPs adoption and implementation. As a result, one this study's objectives was to propose elements of a national policy that aims to optimise BSPs' utilisation. However, since the beginning of this research, UK BSPs' market has witnessed several strategic and national interventions and initiatives.

In September 2015, NHS-England published an informative guide, which explained BSP concepts, licensing processes and considerations related to safe prescribing and monitoring (NHS England-Medical Directorate, 2015). In addition to educational materials, NHS-England organised workshops for professionals involved in introducing, managing and prescribing BMPs and BSPs. During these workshops, the experiences of Trusts involved with switching stabilised patients were shared and discussed (NHS-England and Academic Health Science Network (AHSN), 2016). NICE has also been active in encouraging BSP use. Following the IFX-BSP launch, NICE published an implementation guide, which detailed the experiences of two Trusts in implementing IFX-BSPs (The National Institute for Health and Care Excellence (NICE), 2015d). In addition to the implementation guide, in Feb 2016 NICE published the key therapeutic topic guide related to BSPs, which explained NICE's position, BSPs licensing, safety monitoring and prescribing, introduction of BSPs into practice and, finally the monitoring of prescribing and the MODB's role (The National Institute for Health and Care Excellence (NICE), 2016b). However, for some participants, educational interventions were considered to be basic, introductory and lacking technical details. In some cases, participants had not even come across or known about publications, guides and workshops, suggesting those respondents were ahead of NICE at that point, regarding knowledge of BSPs.

This research confirmed the role of professional bodies in setting and directing practice norms (Ess et al., 2003). Following the IFX-BSPs launch, professional bodies of targeted therapeutic areas updated their positions by adopting positive positions toward BSPs, in general, and switching in particular (British Society for Rheumatology (BSR), 2017a, The British Society of Gastroenterology (BSG), 2016). Recently, professional bodies of newly targeted areas, such as oncology, have preceded the introduction of BSPs by issuing positive statements and implementation guides (British Oncology Pharmacy Association (BOPA), 2017b, British Oncology Pharmacy Association (BOPA), 2017a).

Prescribing audits and monitoring are among the measures that fundholders might use to direct prescribing behaviour and ensure clinical compliance to guidelines (Hulscher et al., 2010, Sbarbaro, 2001). Starting from November 2015, the MODB began reporting purchasing data of high-cost BSPs and their R-BMP counterparts, namely IFX-BSPs and etanercept (NHS England, 2014, NHS Business Service Authority (NHSBSA), 2016). However, reported data are neither speciality nor demographic specific; they do not specify prescribing practice, initiation or switching.

Lastly, on the 12th of Sep 2017, after data collection was finalised, NHS-England published a commissioning framework for BMPs, including BSPs. The framework set percentages of patients to be initiated or switched to "best value biologic" within a specific period of time (Diagnostic and Personalised Medicine Policy Team, 2017). Best value biologic is "the biological product that can achieve both best outcomes for patients and best cost for the taxpayer" (Thomas, 2017). Avoiding specifying which product to prescribe, R-BMP or BSPs, might reflect policymakers' awareness of the fact that BSPs are not always the cheaper products/molecules available. In addition to prescribing targets, commissioners including CCGs were held accountable for achieving prescribing targets (Diagnostic and Personalised Medicine Policy Team, 2017). Setting a timeframe over which the prescribing targets should be achieved, whether for switching or initiating, might help in limiting the impact of uncertainty created by competition between manufacturers.

In addition to setting prescribing targets, the framework identified four main stages for implementing best value biologics: (*i*) opportunity assessment, (*ii*) engagement, (*iii*) implementation and (*iv*) monitoring and data collection. While the proposed stages showed an abstract presentation of the adoption process, these stages did not contradict research participants' accounts of their experiences in introducing BSPs, which were more detailed and specific than the framework. However, this situation does not suggest contradiction, but instead represents a case of differences between practical rationality and formal (scientific) rationality (Berg et al., 2001). Practical rationality addresses how guidelines, recommendations and policies are put into practice depending on what is actual available, but which is still within the framework proposed by the policymakers' rationality (formal rationality) (Berg et al., 2001). Comparing main considerations proposed in the framework with the research findings, the following strengths and limitations were identified (Table 31).

Table 31-Strengths and limitations of NHS commissioning framework when compared to findings presented in this study

	Proposed/Missing Element	Comment/Recommendation
Strengths	Emphasising involving all relevant stakeholders whether professionals (pharmacists, commissioners, prescribers, nurses and finance) or patients (individual and representatives) in different stages of the adoption process; assessment, planning and implementing	Collaborating and involving different professionals had positively influenced the adoption process and acted as a pull force that encouraged the switch and ensured prescribers' agreement. Patients' involvement in the planning stage was limited; however, this framework might encourage their involvement and active participation
	Setting prescribing targets and addressing consideration of special patients	Setting a 20% margin of patients, to be excluded from the switch, satisfies the need for special patient consideration based on their health status as reported by participants
	Offering incentives and support	Incentivising and willingness to support switch implementation encouraged Trusts to adopt BSPs
	Encouraging transparent communication between commissioners and Trusts in terms of offered prices by suppliers, contacts added value, patients' outcomes and utilisation rate	Being transparent hold Trusts accountable to achieve switching targets, assure prescribers' compliance, help in costing of commissioning contracts and ensure reporting of patients' outcomes and wellbeing
Limitation	Proposing appropriate monitoring of patients	Not specifying the kind of monitoring (extra or regular), eligible patients, frequencies, funders (Trusts, commissioners or industry) creates confusion and variation within regions/country
	Addressing financial impact mainly in terms of offered prices	Limiting financial impact to prices is not sufficient. Switching is a resource demanding process. Therefore, it might be more accurate to factor in switching's associated costs, added value offered by the suppliers and third party contracts.
	Addressing market dynamics	The framework did not set a specific time line for inclusion in tendering contacts and allowed for follow-on additions. However, this model maintains uncertainty and complexity of adoption
	Discussing pharmacovigilance and safety monitoring	The framework did not address the need for having all switched patients included in biologic registries in a way that allows for assessing their health status before and after the switch
	Presenting process as sequence of steps	This presentation ignored the cyclical/overlapping nature of the adoption and implementation processes
	Switching within the same INN	Ignoring the implication of market competition might be extended to affect the whole class and result in another product, with another INN, being labelled as best value biologics

Finally, over the course of this research, one major issue that might significantly affect pharmaceutical regulation in the UK has emerged; the withdrawal of the UK from the European Union EU ("*Brexit*"). Medicines regulation after Brexit still needs to be clarified and agreed on; whether the UK will maintain access to the centralised procedures, or have mutual recognition of the EMA licensed medicines (Barber, 2017).

6.4.1.1. Policy recommendations

In summary, based on these research findings the following recommendations might be considered:

- Develop educational and implementation guides that have deeper content, reflective of actual practice and which contain more technical considerations and advice
- Follow better dissemination channels of educational material and guides, to assure wide dissemination and awareness of relevant stakeholders
- Assure acceptance of relevant professional bodies before actual launch on BSPs or other healthcare interventions
- Support the development of a database that captures patients' medicines prescribing and utilisation levels at secondary care

6.4.2. Implications for practice

As there is an ongoing demand to rationally utilise and dispense medicines, the launch of new BSPs with the same INN indicates that there might be a possibility of switching between BSPs. However, the framework has left the decision of cross BSPs switching to clinical judgement and emerging evidence, the latter being shown to be limited. The lack of guidance in these cases might result in creating similar situations to the ones that existed before the framework issuance. There is a need to set a limit of how many times a patient can be switched from one brand to another. All these issues need to be clearly addressed; elements of proper management of BMPs, including BSPs, need to be identified and communicated with relevant organisations and stakeholders.

Different Trusts have followed different prescribing management procedures to assure compliance and to avoid unintended switches. It is not expected, or even feasible, to ask Trusts to follow unified procedures and to change the ones they have as a result of introducing BSPs. Nevertheless, since all Trusts have an in-house formulary, whether regional or Trust level, it might be beneficial to have a nationwide standardised approach for listing brand-name prescribed medicines, such as BMPs, anti-epileptics, immunosuppressant agents and narrow therapeutic index medicines. The standardised way should specify: (*i*) how these medicines should be listed, prescribed and reported, (*ii*) types of auxiliary information and data to be listed and (*iii*) issues related to the consideration of special patients. This proposal might be feasible, to a degree, especially as a few Trusts and health boards referred to formularies management software, such as Net-Formulary® and Inform Online Formularies ®.

6.4.3. Implications for research

The market, together with the regulatory and political environment, has changed considerably since the beginning of this research. As the UK is due to leave the European market as a result of Brexit, it is necessary to know if the possibility of having standalone separate licensing pathways, and the small size of UK BMPs market when compared to other European markets such as Germany, might significantly reduce its attractiveness for new BSPs entries.

A number of research participants discussed the possibility of extrapolating switching experiences to future BSPs, investigating how this might be achieved in the new regulatory context. This new regulatory environment which has witnessed the issuance of the commissioning framework and the establishment of regional medicines optimisation committees (RMOCs), might show different forms of dynamics and interactions.

The research findings confirmed the known local variations within NHS-England; also showing that in some cases there were duplications of effort within the same region, covered by the same tender contracts. As the new RMOCs will not replace local medicines management groups, and their role will be more of advisory rather than directive, mapping differences between medicines management groups within the same region might identify the mechanism by which a unified practice could be created.

6.4.4. Implementation research for pharmacy practice

Pharmacists are increasingly involved in the implementation or de-implementation of healthcare interventions, guidelines and medicines. However, the quality of reported experiences is questionable and, in some cases, lacks sufficient rigour (Seaton, 2017). Conducting this research has enabled me, as a pharmacist, to develop a better understanding of factors affecting intervention's implementation in healthcare settings. Currently, there are a number of health service related initiatives that need pharmacists' active involvement, such as antimicrobial stewardship, pregnancy counselling, disease screening and smoking cessation (Matowe et al., 2012).

For a pharmacist to drive and report an implementation project, he or she needs to: (*i*) locate the project, whether if it is dissemination or implementation focused, (*ii*) be aware of the intervention's context and environment, (*iii*) know the type of decision; organisational, individual or hybrid between both, (*iv*) know who are the main involved stakeholders, (*v*) be aware of the available funding and (*vi*) know the type of outcome evaluation; summative, process or formative evaluation.

Once the design and type of decision are determined, a pharmacist needs to start assessing main drivers, barriers and facilitators. The process could start by assessing the intervention's attributes regarding relative advantages, associated risk, compatibility and implementation complexity. The attribute assessment process identifies the expertise, knowledge and finance that will be needed, which in turn should be communicated to the key stakeholders: mainly funders.

Following the attribute assessment, established communication channels between implementers and funders should be identified. These channels facilitate the negotiations between providers and funders. As a mediating agent, pharmacists should capitalise on the pull factors (incentives, acceptance and collaboration) and ease the push factors (conflicts and lack of support).

Driving an implementation project requires considering the surrounding environment; specifically: (*i*) policies, (*ii*) guidelines (*iii*) position of professional bodies and other key opinion leaders. Whether acting as an implementation leader or mediator, pharmacists have a good opportunity in implementation science to make their presence felt as they can speak the language of clinicians, commissioners and patients.

6.5. Proposed future work

The study's findings were able to answer the research question and address the objectives. It helped me, the researcher, to develop a better understanding of BSPs in the UK and the dynamics affecting their integration. However, as the research proceeded several questions were raised which need to be investigated. These newly developed questions create opportunities for future research projects that could be achieved using both quantitative and qualitative methods. Moreover, new market updates in the form of new entries and commissioning policies might trigger changes in the dynamics, which also need to be investigated and compared with the research findings. The following are potential research opportunities that can be achieved through secondary or primary research:

- As there is a growing body of literature investigating prescribers, other healthcare professionals and patients' attitudes and perceptions toward BSPs, a systematic review bringing these studies together might be beneficial. The proposed systematic review could be based on this research literature review chapter (2.5.3. Prescribers' acceptance of biosimilars) to identify MeSH terms and keywords. As most of the available studies are surveys, data synthesis cannot be done by combining and aggregating percentages and numbers, due to expected heterogeneity. Therefore, a narrative synthesis driven by grouping findings into themes could be used
- The recent market launch of expensive innovative biological medicines, some of which have been rejected by NICE, flagged the question regarding the potential of BSP copies of these medicines. This question would address how a BSP copy of a rejected R-BMP will be assessed by NICE, and how it should be priced to be considered cost-effective. This research could be achieved by a Delphi exercise targeting members of NICE HTA committees, experts in health economics and the industry
- As newly launched BSPs, such as insulin glargine, are targeting new disease areas and are prescribed in new settings (primary care), a research opportunity to investigate general practitioners (GPs) understanding and acceptance of BSPs opens up. Moreover, prescribing rates and patients' outcomes could be captured and assessed using Clinical Practice Research Datalink (CPRD). Finally, integration of new BSPs into local medicines formularies and therapeutic pathways could be assessed using methods similar to those that were deployed in this research
- Formulary inclusion was reported by NICE as an approach to integrate and institutionalise health technologies. Nevertheless, in this current research, formularies were found to have limited impact on prescribing behaviour and did not reflect actual prescribing behaviour. Therefore, a research project that targets prescribers (physicians, including GPs and specialists, nurses and pharmacists) to assess professionals' reliance on formularies in prescribing, their overall impression, and what is needed to be considered to make these formularies more relevant and effective. This project could be accomplished by first sending questionnaires to individuals in identified professional roles asking for their understanding of formularies role. Items to be included might cover: (*i*) their routine practice in referring to formularies (how frequent, when and for what type of prescribing), (*ii*) what kind of information prescribers want to be displayed, and (*iii*) overall experience (satisfactory, neutral, unsatisfactory). Questionnaire results could be used in designing qualitative research that

aims at identifying what is needed to augment the role of formularies and make that role more reflective of actual practice

These opportunities need to be further investigated, clarified and assessed for feasibility before applying for research funds.

6.6. Reflections

Critical reflexivity of qualitative researchers addresses and challenges factors related to the researcher's background and experiences that might affect his/her method(s) of approaching the research problem, analysis, presentation and findings reporting (Hsiung, 2008). Critical reflexivity is also related to the way by which the researcher considers and assesses the effect of personal interactions and relations with the participants (Tong et al., 2007).

6.6.1. Methodological reflection

In discussing reflexivity, researchers are advised to show and demonstrate sufficient sensitivity to the context in which the research took place. Context sensitivity could be demonstrated through: (*i*) purpose context, (*ii*) inquiry focus context, (*iii*) location context, (*iv*) broader context and (*v*) relationship context (Patton, 2014).

Purpose context relates to addressing why the research is needed, the standards followed and the audience targeted (Patton, 2014). The aim and objectives of this research were addressed and discussed. Furthermore, component-specific objectives were also listed. In the methodology chapter, the research design was detailed, along with quality checks for each component. As this research was carried out for the fulfilment of a PhD degree, the expected audience is academics. Therefore, this thesis was revised by the student's supervisors to make sure that it fits at least minimal requirements for academic research regarding design, conduct and presentation.

Inquiry context refers to research tradition, applied methodology and theoretical stand (Patton, 2014). Research methodology and the philosophical stand were discussed in the methodology chapter. In the same chapter, the explanation for accommodating the research within implementation research was provided. Additionally, the selection of Rogers's theory on the diffusion of innovation was justified and explained.

Location context refers to the place and type of the organisation in which research was carried out (Patton, 2014). Phase I of the quantitative arm targeted medicines formularies used in secondary care settings in Great Britain. Phase II and the qualitative component were mainly in England due to issues of data availability and feasibility. For the qualitative study, site selection criteria were explained and driven by results from the quantitative component. Furthermore, targeting healthcare professionals at CCGs and Acute Trusts was informed by the way in which targeted BSPs and IFX-BSPs are commissioned and prescribed, both locally and at secondary care.

The broader context is addressed through having a sensitive account of the broader culture of the organisation, and society (Patton, 2014). During the research process, the researcher kept an up-to-date account with policies and commissioning statements released by NHS, position papers issued by professional bodies, and new market entries. The effect of these updates varied according to the stage of the research; it was mainly considered during data analysis and discussion.

Relationship context is related to reflecting on the nature of interaction the researcher (interviewer) had with interviewees (Patton, 2014). The point was discussed earlier that having an academic identity facilitated my discussions with the study's participants.

Although this research is a mixed methods design, I realised in the end that while qualitative data were physically undemanding, analysing and interpreting such data was intellectually challenging. I believe that analysis could be an ongoing process and every day new insights may be discerned. However, as there is a limited time for submitting, I needed to keep the analysis lens focused, as well as limiting my thought to issues that will help to answer my question: "how the decision of adoption was made and what had facilitated it?"

6.6.2. Theoretical reflections

In the methodology chapter, I discussed how Rogers's theory on diffusion of innovation was used to guide this research and interpret its findings. As the research proceeded and I was more involved in data analysis, I realised that the theory was not only suitable to host my research, but it was flexible enough to be expanded to accommodate medical and healthcare specific concepts. The expansion was possible by borrowing from other frameworks and models, which referred to Rogers's theory in their development.

Rogers discussed the possibility of having a mid-way model between individual and organisational adoption models. However, he did not discuss in detail how it might be possible to integrate the two models. Therefore, I relied on other frameworks and models to understand how the same innovation (intervention) is assessed, based on individual and organisational factors simultaneously (Greenhalgh et al., 2004, Damschroder et al., 2009, Frambach and Schillewaert, 2002).

Rogers, as a researcher, was based in agricultural and industry areas, he did not have a deep understanding of healthcare organisations and medical decision making processes. This was particularly evident in classifying innovation adopters; prescribers cannot prescribe a medicine before it is assessed, licensed and launched. Therefore, it is not a frequent phenomenon to have innovators involved in the adoption of medicinal products.

Lastly, the beauty of this theory is that it works and fits easily with concepts and theories related to governance, decision making processes and driving change. This compatibility might be explained by the fact it is a theory based on four main concepts: (*i*) innovation, (*ii*) communication, (*iii*) time and (*iv*) social structure; all of which are main pillars of governance and decision making processes.

As a researcher, I learnt that it is not possible to apply a theory without making some alterations to it; modifications that help the theory evolve and survive. Alterations allow for the sharing of expertise across professions and research areas.

6.6.3. Personal reflections

The first time I heard the term "biosimilar" was during a business meeting at my workplace in a generic pharmaceutical company based in Jordan. From a discussion during that meeting I realised the BSPs represent a particular case of off-patent follow-on products, which cannot be licensed through generic licensing pathways and cannot be marketed using a similar approach. As a result, I started looking in more detail at these products in terms of concept and licensing. I had noticed that in Jordan and the Middle East in general, licensing pathways were still in development, and there were ongoing debates concerning authorisation requirements. Therefore, at the beginning of my PhD studies, I was aiming to understand the BSPs market and related policies in the UK and how this experience can be extrapolated to my own country, Jordan. However, after revising market-related reports prepared by marketing consultation and business intelligence agencies, I realised that BSPs uptake in the UK was not similar to that of conventional generics. Consequently, my research took on a different direction and scope.

Similar to the majority of foreigners, I was under the assumption that the health system in the UK is a unified and centrally controlled system. However, to my surprise it appeared to be managed and operated locally. Doing this research allowed me to develop my skills as a researcher, and to gain knowledge and understanding of pharmaceutical policies and regulations in particular, as well as the NHS system in general.

Acquired knowledge was not limited to the pharmaceutical sector; as a result of the research methods employed, my understanding of human interactions and the meaning the respondents put in their words and acts developed significantly.

6.7. Thesis conclusion

At the beginning of this research the UK market was characterised by having a limited uptake of BSPs as a result of the absence of national encouraging policies and prescribers' reservations. However, evidence from this research showed that BSPs' uptake varies across localities and practices. Research findings showed that in the absence of a BSP-specific national policy, which guides the adoption and implementation of an innovations, healthcare professionals mapped their own way depending on their common medical practice, ethical and professional norms and obligations. Communications channels between organisations (providers and commissioners) and directive tools in form of incentives, support and authoritative mandates-helped in facilitating BSPs uptake and utilisation.

Evidence showed that lack of NICE specific guidelines and recommendation had created a situation similar to that before NICE establishment, where decision of commissioning and utilising an intervention was left to local push-pull powers; a situation that resulted in variations between localities which is a common feature of the NHS. Absence of NICE guidance pushed healthcare professionals to look for support and back up from other authoritative figures such as professional bodies. The professionals relied on their own reasoning and medical judgment, while depending on others' experiences, whether nationally or internationally, to compensate for the lack of national guidance and limited evidence.

In its five-year efficiency plan, the NHS listed the controlling cost of medicines (using the best value of medicines) as an approach through which savings might be generated. Accordingly, the NHS might benefit from integrating BSPs into medical practice. The results of this research showed a varied uptake of BSPs in the UK. Factors related to the switching process involving professional, organisational and service designs and influence of external environmental, were found to affect the adoption of BSPs. Elements related to provider-commissioner agreement, encouraging policies, support of professional bodies, availability of real-life evidence and financial incentives positively affected BSPs utilisation. On the other hand, the conflict between commissioners and providing Trusts and, to some extent, market uncertainty hinders BSPs integration. However, identifying a generalisable set of facilitators and barriers that affect the uptake of BSPs locally was not possible due to heterogeneity in settings, dynamics and, in some cases, motives and expertise. As new national policies and interventions were introduced, new market dynamics were created, which might be reflected in the market performance of the upcoming BSPs.

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Appendix 1-European Medicines Agency (EMA) BSPs' guidelines

OVERARCHING BIOSIMILAR GUIDELINES

No.	Guideline Title	Reference number	Publication date	Effective date	Scope
1.	Similar biological medicinal products-Revision 1	CHMP/437/04 Rev. 1	29 Oct 2014	30 Apr 2015	Application of BSP, the choice of R-BMP and the principles for establishing biosimilarity
2.	Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues-Revision 1	EMEA/CHMP/BMWP/42832/2005 Rev. 1	09 Jan 2015	01 July 2015	Guidance on the pharmaco-toxicological assessment, requirements for PK, PD, and efficacy studies, clinical safety studies, including immunogenicity, and risk management plan
3.	Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues-Revision 1	CHMP/BWP/247713/2012	3 Jun 2014	01 Dec 2014	Manufacturing processes, comparability exercise for quality, considering the choice of R-BMP, analytical methods, physicochemical characterisation, biological activity, purity and specifications of BSP

PRODUCT-SPECIFIC BIOSIMILAR GUIDELINES

No.	Guideline Title	Reference number	Publication date	Effective date	Scope
1.	Biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues)-Currently under revision*	EMEA/CHMP/BMWP/31329/2005	22 Feb 2006	01 Jun 2006	Guidance for demonstration of comparability of two recombinant granulocyte colonystimulating factor-containing medicinal products
2.	Non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins-Revision 1	EMEA/CHMP/BMWP/118264/2007 Rev. 1	24 Nov 2016	01 Jun 2017	Non-clinical and clinical requirements for low molecular weight heparins (LMWHs, low molecular mass heparins, LMMH) containing medicinal products claiming to be similar to another one already marketed
3.	Non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues-Revision 1	EMEA/CHMP/BMWP/32775/2005 Rev. 1	11 Mar 2015	01 Sep 2015	Non-clinical and clinical requirements for recombinant insulin-containing products, including human insulin and insulin

					analogues, claiming to be similar to another one already authorised R-BMP
4.	Similar biological medicinal products containing interferon beta	EMA/CHMP/BMWP/652000/2010	06 Mar 2013	01 Sep 2013	Non-clinical and clinical requirements for interferon beta (IFN-β) containing medicinal products claiming to be similar to another interferon beta already marketed
5.	Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues	EMA/CHMP/BMWP/403543/2010	15 Jun 2012	01 Dec 2012	Non-clinical and clinical requirements for monoclonal antibody (mAb) containing medicinal products claiming to be similar to another one already authorised
6.	Similar biological medicinal products containing recombinant erythropoietins	EMEA/CHMP/BMWP/301636/08	14 Apr 2010	01 Dec 2012	Non-clinical and clinical requirements for recombinant human erythropoietin (epoetin)-containing medicinal products claiming to be similar to another one already marketed
7.	Similar biological medicinal products containing recombinant follicle-stimulating hormone	CHMP/BMWP/671292/2010	06 Mar 2013	01 Sep 2013	Non-clinical and clinical requirements for recombinant human follicle stimulating hormone (r-hFSH)-containing medicinal products claiming to be similar to another one already marketed
8.	Similar medicinal products containing somatropin (Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues)	EMEA/CHMP/BMWP/94528/2005	22 Feb 2006	01 Jun 2006	non-clinical and clinical requirements for somatropin-containing medicinal products claiming to be similar to another one already marketed.

REFLECTION PAPERS

No.	Guideline Title	Reference number	Publication date	Effective date	Scope
1.	Non-clinical and clinical development of similar biological medicinal products containing recombinant interferon alpha or pegylated recombinant interferon alpha	EMEA/CHMP/BMWP/102046/2006	23 Apr 2009	N/A	Non-clinical and clinical development of recombinant interferon alfa-containing medicinal products claiming to be similar to another such product already authorised

OTHER GUIDELINES RELEVANT FOR BIOSIMILARS

No.	Guideline Title	Reference number	Publication date	Effective date	Scope
1.	Comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues	EMEA/CHMP/BMWP/101695/2006	19 Jul 2007	01 Nov 2007	Requirements for non-clinical and/or clinical bridging studies to demonstrate that the manufacturing change has no impact on safety and efficacy
2.	ICH Q5E Biotechnological/biological products subject to changes in their manufacturing process: comparability of biotechnological/biological products	CPMP/ICH/5721/03	01 Jun 2005	01 Jun 2005	Collection of relevant technical information which serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety and efficacy of the drug product
3.	Immunogenicity assessment of biotechnology-derived therapeutic proteins-Revision 1	EMEA/CHMP/BMWP/14327/2006 Rev.1	01 Jun 2017	01 Dec 2017	Guidance for assays for immunogenicity, and integrated analysis of the clinical significance of immunogenicity
4.	Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use	EMA/CHMP/BMWP/86289/2010	15 Jun 2012	01 Dec 2012	Issues relating to the unwanted immunogenicity of monoclonal antibodies intended for clinical use

EMA: European Medicines Agency, **BMWP:** Biological Monitoring Working Party, **CHMP:** Committee for Medicinal Products for Human Use, **CPMP:** Committee for Proprietary Medicinal Products,
ICH: International Conference on Harmonisation
***** As in December 2017

Appendix 2-BSPs authorised, refused or withdrawn by the EMA since 2006

No.	Medicine Name	Product Number	Active Substance (INN)	Marketing Authorisation Holder	Status	Authorisation date
1	Omnitrope	EMEA/H/C/000607	somatropin	Sandoz GmbH	Authorised	12 Apr 2006
2	Abseamed	EMEA/H/C/000727	epoetin alfa	Medice Arzneimittel Pütter GmbH & Co. KG	Authorised	28 Aug 2007
3	Binocrit	EMEA/H/C/000725	epoetin alfa	Sandoz GmbH	Authorised	28 Aug 2007
4	Epoetin Alfa Hexal	EMEA/H/C/000726	epoetin alfa	Hexal AG	Authorised	28 Aug 2007
5	Retacrit	EMEA/H/C/000872	epoetin zeta	Hospira UK Limited	Authorised	18 Dec 2007
6	Silapo	EMEA/H/C/000760	epoetin zeta	Stada Arzneimittel AG	Authorised	18 Dec 2007
7	Ratiograstim	EMEA/H/C/000825	filgrastim	Ratiopharm GmbH	Authorised	15 Sep 2008
8	Tevagrastim	EMEA/H/C/000827	filgrastim	Teva GmbH	Authorised	15 Sep 2008
9	Filgrastim Hexal	EMEA/H/C/000918	filgrastim	Hexal AG	Authorised	06 Feb 2009
10	Zarzio	EMEA/H/C/000917	filgrastim	Sandoz GmbH	Authorised	06 Feb 2009
11	Nivestim	EMEA/H/C/001142	filgrastim	Hospira UK Ltd	Authorised	08 Jun 2010
12	Inflectra	EMEA/H/C/002778	infliximab	Hospira UK Limited	Authorised	10 Sep 2013
13	Remsima	EMEA/H/C/002576	infliximab	Celltrion Healthcare Hungary Kft.	Authorised	10 Sep 2013
14	Ovaleap	EMEA/H/C/002608	follitropin alfa	Teva Pharma B.V.	Authorised	27 Sep 2013
15	Grastofil	EMEA/H/C/002150	filgrastim	Apotex Europe BV	Authorised	18 Oct 2013
16	Bemfola	EMEA/H/C/002615	follitropin alfa	Gedeon Richter Plc.	Authorised	27 Mar 2014
17	Abasaglar (previously Abasria)	EMEA/H/C/002835	insulin glargine	Eli Lilly Regional Operations GmbH	Authorised	09 Sep 2014
18	Accofil	EMEA/H/C/003956	filgrastim	Accord Healthcare Ltd	Authorised	18 Sep 2014
19	Benepali	EMEA/H/C/004007	etanercept	Samsung Bioepis UK Limited	Authorised	14 Jan 2016
20	Flixabi	EMEA/H/C/004020	infliximab	Samsung Bioepis UK Limited (SBUK)	Authorised	26 May 2016
21	Inhixa	EMEA/H/C/004264	enoxaparin sodium	Techdow Europe AB	Authorised	15 Sep 2016
22	Thorinane	EMEA/H/C/003795	enoxaparin sodium	Pharmathen S.A.	Authorised	15 Sep 2016
23	Lusduna	EMEA/H/C/004101	insulin glargine	Merck Sharp & Dohme Limited	Authorised	04 Jan 2017
24	Terrosa	EMEA/H/C/003916	teriparatide	Gedeon Richter Plc.	Authorised	04 Jan 2017
25	Movymia	EMEA/H/C/004368	teriparatide	STADA Arzneimittel AG	Authorised	11 Jan 2017
26	Truxima	EMEA/H/C/004112	rituximab	Celltrion Healthcare Hungary Kft.	Authorised	17 Feb 2017
27	Amgevita	EMEA/H/C/004212	adalimumab	Amgen Europe B.V.	Authorised	22 Mar 2017
28	Solymbic	EMEA/H/C/004373	adalimumab	Amgen Europe B.V.	Authorised	22 Mar 2017
29	Rixathon	EMEA/H/C/003903	rituximab	Sandoz GmbH	Authorised	15 Jun 2017
30	Riximyo	EMEA/H/C/004729	rituximab	Sandoz GmbH	Authorised	15 Jun 2017
31	Erelzi	EMEA/H/C/004192	etanercept	Sandoz GmbH	Authorised	23 Jun 2017

32	Blitzima	EMEA/H/C/004723	rituximab	Celltrion Healthcare Hungary Kft.	Authorised	13 Jul 2017
33	Ritemvia	EMEA/H/C/004725	rituximab	Celltrion Healthcare Hungary Kft.	Authorised	13 Jul 2017
34	Rituzena (previously Tuxella)	EMEA/H/C/004724	rituximab	Celltrion Healthcare Hungary Kft.	Authorised	13 Jul 2017
35	Insulin lispro Sanofi	EMEA/H/C/004303	insulin lispro	Sanofi-aventis groupe	Authorised	19 Jul 2017
36	Imraldi	EMEA/H/C/004279	adalimumab	Samsung Bioepis UK Limited (SBUK)	Authorised	24 Aug 2017
37	Cyltezo	EMEA/H/C/004319	adalimumab	Boehringer Ingelheim International GmbH	Authorised	10 Nov 2017
38	Ontruzant	EMEA/H/C/004323	trastuzumab	Samsung Bioepis UK Limited (SBUK)	Authorised	15 Nov 2017
39	Mvasi	EMEA/H/C/004728	bevacizumab	Amgen Europe B.V.	Authorised	15 Jan 2018
40	Valtropin*	EMEA/H/C/000602	somatropin	BioPartners GmbH	Withdrawn	24 Apr 2006
41	Biograstim†	EMEA/H/C/000826	filgrastim	AbZ-Pharma GmbH	Withdrawn	15 Sep 2008
42	Filgrastim ratiopharm‡	EMEA/H/C/000824	filgrastim	Ratiopharm GmbH	Withdrawn	15 Sep 2008
43	Alpheon§	EMEA/H/C/000585	recombinant human interferon alfa-2a	BioPartners GmbH	Refused	N/A
44	Solumarv||	EMEA/H/C/003858	insulin human	Marvel Lifesciences Ltd	Refused	N/A

N/A: Not Applicable

* On the 10th of May 2012, the European Commission issued a decision to withdraw the marketing authorisation as per a request submitted by the marketing authorisation holder for Valtropin®, BioPartners GmbH, for commercial reasons.

† On the 23rd of September 2015, the European Commission issued a decision to withdraw the marketing authorisation as per a request submitted by the marketing authorisation for Biograstim® (filgrastim), AbZ Pharma GmbH, for commercial reasons.

‡ On the 20th of April 2011, the European Commission issued a decision to withdraw the marketing authorisation as per a request submitted by the marketing authorisation holder for Filgrastim ratiopharm®, ratiopharm GmbH, for commercial reasons.

§ The product was refused due to concerns related to differences identified between the BSP and R-BMP in quality aspects such as impurities, product stability, validation and product efficacy

|| The product was refused due to concerns related to undefined manufacturing process for Solumarv® in sufficient detail. As such, it was not possible to show that Solumarv used in clinical studies was representative of batches intended for the market and that its quality was comparable to Humulin S® (R-BMP)

Appendix 3-BSPs available in the UK

No.	Medicine Name (*INN name*)	Black Triangle	R-BMP	NICE TA*	Including BSP(s)	Commissioner
1	Omnitrope *somatropin*	No	Genotropin	NICE TA188:, NICE TA64	NICE TA188	CCG: In all indications NHS-England: in specialist centres for indications falling outside NICE guidance
2	Binocrit *epoetin alfa*	No	Eprex	NICE TA323	NICE TA323	NHS-England
3	Retacrit *epoetin zeta*	No	Eprex	NICE TA323	NICE TA323	NHS-England
4	Zarzio *filgrastim*	No	Neupogen	Not available	N/A	NHS-England
5	Nivestim *filgrastim*	No	Neupogen	Not available	N/A	NHS-England
6	Inflectra *infliximab*	Yes	Remicade	NICE TA134, NICE TA163, NICE TA187, NICE TA195, NICE TA199, NICE TA329, NICE TA375, NICE TA383	NICE TA329 NICE TA375 NICE TA383	CCG: Adult patients NHS-England: Paediatric patients
7	Remsima *infliximab*	Yes	Remicade	NICE TA134, NICE TA163, NICE TA187, NICE TA195, NICE TA199, NICE TA329, NICE TA375, NICE TA383	NICE TA329 NICE TA375 NICE TA383	CCG: Adult patients NHS-England: Paediatric patients
8	Ovaleap *follitropin alfa*	Yes	Gonal-f	Not available	N/A	CCG §
9	Bemfola *follitropin alfa*	Yes	Gonal-f	Not available	N/A	CCG §
10	Abasaglar *insulin glargine*	Yes	Lantus	Not available	N/A ESNM64 ‡	CCG §
11	Accofil *filgrastim*	Yes	Neupogen	Not available	N/A	NHS-England
12	Benepali *etanercept*	Yes	Enbrel	NICE TA103, NICE TA195, NICE TA199, NICE TA375, NICE TA383	No	CCG: Adult patients NHS-England: Paediatric patients

13	Flixabi *infliximab*	Yes	Remicade	NICE TA134, NICE TA163, NICE TA187, NICE TA195, NICE TA199, NICE TA329, NICE TA375, NICE TA383	No	CCG: Adult patients NHS-England: Paediatric patients
14	Inhixa || *enoxaparin sodium*	Yes ¶	Clexane	Not available	N/A	CCG §
15	Truxima *rituximab*	Yes ¶	Mabthera	NICE TA308, NICE TA195, NICE TA243, NICE TA137, NICE TA193, NICE TA226, NICE TA174, NICE TA359, NICE TA65	No	CCGs: In non-cancerous haematological conditions (e.g. ITP) and non-specialist auto-inflammatory conditions (e.g. RA)
16	Rixathon *rituximab*	Yes ¶	Mabthera	NICE TA308, NICE TA195, NICE TA243, NICE TA137, NICE TA193, NICE TA226, NICE TA174, NICE TA359, NICE TA65	No	CCGs: In non-cancerous haematological conditions (e.g. ITP) and non-specialist auto-inflammatory conditions (e.g. RA)

* Relevant NICE technology appraisals, whether or not BSP(s) was/were included
† Commissioners for the main indication
‡ Evidence summary new medicine (ESNM) for Diabetes mellitus type 1 and type 2: insulin glargine biosimilar (Abasaglar)
§ Based on personal communication with a CCG pharmacist
|| Launched in Sep 2017, was not listed in the BNF nor emc, but was confirmed through personal contact
¶ Since newly launched, by definition these medicines will be listed under black triangle scheme

Appendix 4-Phase *II* detailed list of assessment criteria

1. Administrative Features
    a. Formulary name
    b. Country
    c. Formulary type (joint, non-joint)
    d. Number of involved of organisations, both primary and secondary-care
    e. Formulary layout (structured, unstructured)
2. IFX listing status per therapeutic area (if applicable)
    a. If IFX molecule is listed
    b. Therapeutic areas where it is listed
    c. Listing status(formulary, non-formulary) of IFX molecule per therapeutic area
    d. Listing approach of IFX (brand name, generic name, or crossover between both) per therapeutic area
    e. Brand(s) listed per therapeutic area
    f. Listing status (formulary, non-formulary) per brand per therapeutic area
    g. Listing relevant NICE TAs and CGs per therapeutic area
    h. Having clear prescribing instructions per therapeutic area (Yes, No)
        i. Specifying prescriber (Yes, No) per therapeutic area
            - Specifying type of prescriber (Specialist, Consultant, or other)
        ii. Specifying prescribing settings (Yes, No) per therapeutic area
            - Specifying type of prescribing settings (primary, secondary, or shared)
3. IFX commissioners per therapeutic area (if applicable)
    a. Specifying if IFX subjected to Payment by Result per therapeutic area (PbR)[12] scheme (Yes, No)
    b. Specifying commissioner per therapeutic area (CCG, NHS-England)
4. Special prescribing consideration, affecting which product/brand to prescribe, per therapeutic area (if applicable)
    a. Listing special considerations related to patients per therapeutic area (Yes, No)
    b. Listing special consideration related to the indication per therapeutic area (Yes, No)
5. Switching and initiating related consideration per therapeutic area (if applicable)
    a. Distinguish between initiating and switching patients per therapeutic area
    b. Allow switching per therapeutic area
    c. Specify brand of choice per therapeutic area
6. Educational and Informative Materials
    a. NHS-England document on “What is a biosimilar medicines” (NHS England-Medical Directorate, 2015)
    b. NICE statement paper on biosimilars (The National Institute for Health and Care Excellence (NICE), 2016b)
    c. MHRA safety update regarding brand name prescribing of biological products (Medicines and Healthcare products Regulatory Agency (MHRA), 2012)
    d. UK medicines information (UKmi) document on biosimilar
    e. Other materials and documents

[12] High cost medicines out of tariff medicines formerly known as Payment by Results (PbR) excluded drugs

Appendix 5-Phase II formulary screening form

1. Formulary Name:		
2. Country	☐England ☐Wales	☐Scotland ☐Northern Ireland
3. Joint formulary	☐Yes	☐No
4. No. of involved organisation List involved organisation in the last page.	Acute Trusts: Health Boards:	CCGs: Total:
5. Soft copy available URL of the formulary: URL of the local drive:	☐Yes	☐No
6. Hard copy available:	☐Yes	☐No
7. Formulary structured into chapters	☐Yes	☐No

If the answer to question #7 was yes, then continue to questions 8-29 if No then continue questions 30-50

8.Infliximab listed in all areas	☐Yes	☐No
9. Which therapeutic area?	☐Gastroenterology (1.5.3) ☐Rheumatology (10.1.3) ☐Dermatology (13.5.3)	Date: Date: Date:

10. How it is listed			
Gastroenterology	☐Formulary	☐Non-formulary	☐N/A
Rheumatology	☐Formulary	☐Non-formulary	☐N/A
Dermatology	☐Formulary	☐Non-formulary	☐N/A

11. What is listed				
Gastroenterology	☐INN	☐Brands	☐Mix	☐N/A
Rheumatology	☐INN	☐Brands	☐Mix	☐N/A
Dermatology	☐INN	☐Brands	☐Mix	☐N/A

12. Which brand(s) is/are listed?				
Gastroenterology	☐Remicade®	☐Inflectra®	☐Remsima®	☐N/A
Rheumatology	☐Remicade®	☐Inflectra®	☐Remsima®	☐N/A
Dermatology	☐Remicade®	☐Inflectra®	☐Remsima®	☐N/A

13. How each brand is listed?				
Gastroenterology	☐Remicade®	☐Formulary	☐Non-formulary	☐N/A
	☐Inflectra®	☐Formulary	☐Non-formulary	☐N/A
	☐Remsima®	☐Formulary	☐Non-formulary	☐N/A
Rheumatology	☐Remicade®	☐Formulary	☐Non-formulary	☐N/A
	☐Inflectra®	☐Formulary	☐Non-formulary	☐N/A
	☐Remsima®	☐Formulary	☐Non-formulary	☐N/A
Dermatology	☐Remicade®	☐Formulary	☐Non-formulary	☐N/A
	☐Inflectra®	☐Formulary	☐Non-formulary	☐N/A
	☐Remsima®	☐Formulary	☐Non-formulary	☐N/A

14. NICE technology appraisal guidance (TAs) and Clinical Guidance (CGs)

Gastroenterology	☐TA 40 ☐CG 166	☐TA 140 ☐CG 152	☐TA 163 ☐None	☐TA 187 ☐N/A	☐TA 329
Rheumatology	☐TA 36 ☐TA 375	☐TA 104 ☐TA 383	☐TA 130 ☐CG 79	☐TA 143 ☐None	☐TA 195 ☐N/A
Dermatology	☐TA 134	☐TA 199	☐CG 153	☐None	☐N/A

15. Clear prescription restrictions

Gastroenterology	☐Yes	☐No	☐N/A
Rheumatology	☐Yes	☐No	☐N/A
Dermatology	☐Yes	☐No	☐N/A

16. Prescriber specified

Gastroenterology	☐Yes	☐No	☐N/A
Rheumatology	☐Yes	☐No	☐N/A
Dermatology	☐Yes	☐No	☐N/A

17. Prescribing settings specified

Gastroenterology	☐Yes	☐No	☐N/A
Rheumatology	☐Yes	☐No	☐N/A
Dermatology	☐Yes	☐No	☐N/A

18. Describe the prescriber

Gastroenterology	☐Specialist	☐Consultant	☐Others	☐N/A
Rheumatology	☐Specialist	☐Consultant	☐Others	☐N/A
Dermatology	☐Specialist	☐Consultant	☐Others	☐N/A

19. Describe the settings

Gastroenterology	☐Primary	☐Secondary	☐Shared	☐N/A
Rheumatology	☐Primary	☐Secondary	☐Shared	☐N/A
Dermatology	☐Primary	☐Secondary	☐Shared	☐N/A

20. Subjected to Payment by Result (PbR) Scheme

Gastroenterology	☐Yes	☐No	☐Not Reported	☐N/A
Rheumatology	☐Yes	☐No	☐Not Reported	☐N/A
Dermatology	☐Yes	☐No	☐Not Reported	☐N/A

21. Commissioner

Gastroenterology	☐NHSE	☐CCG	☐Not Reported	☐N/A
Rheumatology	☐NHSE	☐CCG	☐Not Reported	☐N/A
Dermatology	☐NHSE	☐CCG	☐Not Reported	☐N/A

22. Special patients consideration

Gastroenterology	☐Yes	☐No	☐N/A
Rheumatology	☐Yes	☐No	☐N/A
Dermatology	☐Yes	☐No	☐N/A

23. If Yes, specify
Gastroenterology
Rheumatology
Dermatology

24. Special indication consideration

Gastroenterology	☐Yes	☐No	☐N/A
Rheumatology	☐Yes	☐No	☐N/A
Dermatology	☐Yes	☐No	☐N/A

25. If Yes, specify

Gastroenterology
Rheumatology
Dermatology

26. Distinguish between initiating and switching patients

Gastroenterology	☐Yes	☐No	☐N/A
Rheumatology	☐Yes	☐No	☐N/A
Dermatology	☐Yes	☐No	☐N/A

27. Allow switching

Gastroenterology	☐Yes	☐Not Reported	☐N/A
Rheumatology	☐Yes	☐Not Reported	☐N/A
Dermatology	☐Yes	☐Not Reported	☐N/A

28. If applicable, describe how the formulary distinguishes and/or allows the switching process
Gastroenterology
Rheumatology
Dermatology

29. What is the brand of choice?

Gastroenterology	☐Remicade®	☐Inflectra®	☐Remsima®	☐N/A
Rheumatology	☐Remicade®	☐Inflectra®	☐Remsima®	☐N/A
Dermatology	☐Remicade®	☐Inflectra®	☐Remsima®	☐N/A

If the answer to question #7 was yes, then continue questions 8-29if No then continue questions 30-50

30.Infliximab listed ☐Yes ☐No

31. How it is listed
☐Formulary ☐Non-formulary ☐N/A

32. What is listed
☐INN ☐Brands ☐Mix

33. Which brand(s) is/are listed?
☐Remicade® ☐Inflectra® ☐Remsima® ☐N/A

34. How each brand is listed?

☐Remicade®	☐Formulary	☐Non-formulary	☐N/A
☐Inflectra®	☐Formulary	☐Non-formulary	☐N/A
☐Remsima®	☐Formulary	☐Non-formulary	☐N/A

35. NICE technology appraisal guidance (TAs) and Clinical Guidance (CGs)

☐TA 40	☐TA 140	☐TA 163	☐TA 187	☐TA 329
☐CG 166	☐CG 152	☐TA 36	☐TA 104	☐TA 130
☐TA 143	☐TA 195	☐TA 375	☐TA 383	☐CG 79
☐TA 134	☐TA 199	☐CG 153	☐None	☐N/A

36. Clear prescription restrictions
☐Yes ☐No ☐N/A

37. Prescriber specified
☐Yes ☐No ☐N/A

38. Prescribing settings specified
☐Yes ☐No ☐N/A

39. Describe the prescriber
☐Specialist ☐Consultant ☐Others ☐N/A

40. Describe the settings

☐Primary ☐Secondary ☐Shared ☐N/A

41. Subjected to PbR
☐Yes ☐No ☐Not Reported ☐N/A

42. Commissioner
☐NHSE ☐CCG ☐Not Reported ☐N/A

43. Special patients consideration
☐Yes ☐No ☐N/A

44. If Yes, specify

45. Special indication consideration
☐Yes ☐No ☐N/A

46. If Yes, specify

47. Distinguish between initiating and switching patients
☐Yes ☐No ☐N/A

48. Allow switching
☐Yes ☐Not Reported ☐N/A

49. If applicable, describe how the formulary distinguishes and/or allows the switching process

50. What is the brand of choice?
☐Remicade® ☐Inflectra® ☐Remsima® ☐N/A

48. List of informative/educative materials/documents
☐NHS Biosimilars ☐NICE Statement ☐UKmi ☐MHRA
☐Others Specify:
☐Not Listed ☐N/A

Date of last update (formulary) ☐Not available

Screened Date:

Logged Date:

Checked Dated:

No.	Acute Trust	Health Boards	CCG
1.			
2.			

Notes/Comments:

Appendix 6-Interview notes form

University of Nottingham
School of Pharmacy
Division of Social Research in Medicines and Health
Factors Affecting BSPs Uptake in the UK
Interview Notes



Interview Day and Date:	**Friday, 12 August 2016**
Interviewee Name:	
Interviewee research ID number:	
General Notes Related to the Interview	

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Appendix 7-Post interview reflection form

University of Nottingham
School of Pharmacy
Division of Social Research in Medicines and Health
Factors Affecting BSPs Uptake in the UK
Semi-structured Interviews Study
Post Interview Reflection Form

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Interview Day and Date:	Friday, 12 August 2016		
Interview Method:			
☐Face-to-Face	☐Over the Phone	☐Skype®	
Interview guide used:			
Version Number and Date:			
Interview recorded:	☐Yes	☐No	
Interviewee Name:			
Interviewee research ID number:			
How was the interview?			
☐Informative	☐Did not add much	☐Balanced	
How was the interviewee?			
☐Talkative	☐Passive	☐Negative	☐Cooperative
Comments Related on the Interview (overall impression).			
New information/themes added by this interview.			
In case face-to-face interviews, Describe the surroundings and settings.			

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Appendix 8-Selected participants' identification sites

No.	Organisation Name	Region	Organisation Type	Reason for Selection
1.	University Hospital of South Manchester NHS Foundation Trust	North of England	Acute Trust	Formulary representative
2.	Royal Liverpool And Broadgreen University Hospital	North of England	Acute Trust	Infliximab Top Prescriber
3.	Newcastle Upon Tyne Hospitals NHS Foundation Trust	North of England	Acute Trust	R-BMP Top Prescriber
4.	North Tees and Hartlepool NHS Foundation Trust	North of England	Acute Trust	Balance in prescribing of BSP and R-BMP
5.	Calderdale And Huddersfield NHS Trust	North of England	Acute Trust	BSP Top Prescriber
6.	NHS Central Manchester CCG	North of England	CCG	Geographical variation
7.	NHS Northumberland CCG	North of England	CCG	Prevalence Rate
8.	NHS Newcastle Gateshead CCG	North of England	CCG	Prevalence Rate
9.	NHS Halton CCG	North of England	CCG	Prevalence Rate
10.	South Warwickshire NHS Foundation Trust	Midlands and East	Acute Trust	Formulary representative
11.	University Hospital Birmingham NHS Foundation Trust	Midlands and East	Acute Trust	BSP Top Prescriber
12.	Derby Hospitals NHS Foundation Trust	Midlands and East	Acute Trust	R-BMP Top Prescriber
13.	University Hospitals Leicester NHS Trust	Midlands and East	Acute Trust	Geographical variation
14.	Nottingham University Hospitals NHS Trust	Midlands and East	Acute Trust	Formulary representative
15.	University Hospitals Of North Midlands NHS Trust	Midlands and East	Acute Trust	Infliximab Top Prescriber
16.	The Royal Wolverhampton NHS Trust	Midlands and East	Acute Trust	Infliximab Top Prescriber
17.	The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust	Midlands and East	Acute Trust	R-BMP Top prescriber
18.	Birmingham Cross City CCG	Midlands and East	CCG	Geographical variation
19.	Nottingham City CCG	Midlands and East	CCG	Geographical variation
20.	Warwickshire North CCG	Midlands and East	CCG	Geographical variation
21.	NHS North Norfolk CCG	Midlands and East	CCG	Prevalence Rate
22.	NHS West Norfolk CCG	Midlands and East	CCG	Prevalence Rate
23.	Royal Free London NHS Foundation Trust	London	Acute Trust	Infliximab Top Prescriber
24.	University College London Hospitals NHS Foundation	London	Acute Trust	R-BMP Top Prescriber
25.	Guy's and St Thomas' NHS Foundation Trust	London	Acute Trust	R-BMP Top Prescriber
26.	Homerton University Hospital NHS Foundation Trust	London	Acute Trust	BSP Top Prescriber
27.	Croydon University Hospital	London	Acute Trust	BSP Top Prescriber
28.	Havering CCG	London	CCG	Prevalence Rate
29.	NHS Bexley CCG	London	CCG	Geographical variation
30.	Kingston CCG	London	CCG	Prevalence Rate
31.	South Devon Healthcare NHS Foundation Trust	South of England	Acute Trust	R-BMP Top Prescriber
32.	University Hospitals Bristol NHS Foundation Trust	South of England	Acute Trust	Infliximab Top Prescriber

33.	Royal United Hospital Bath NHS Trust	South of England	Acute Trust	R-BMP Top Prescriber
34.	Dorset County Hospital NHS Foundation Trust	South of England	Acute Trust	BSP Top Prescriber
35.	Royal Devon And Exeter NHS Foundation Trust	South of England	Acute Trust	BSP Top Prescriber
36.	Bath and North East Somerset CCG	South of England	CCG	Prevalence Rate
37.	Dorset CCG	South of England	CCG	Prevalence Rate
38.	NHS Thanet CCG	South of England	CCG	Prevalence Rate
39.	North Somerset CCG	South of England	CCG	Prevalence Rate
40.	NHS Northern, Eastern and Western Devon CCG	South of England	CCG	Geographical variation
41.	South Devon and Torbay CCG	South of England	CCG	Prevalence Rate

Appendix 9-Ethical Approval Letter

The University of Nottingham

Faculty of Medicine and Health Sciences

Research Ethics Committee
School of Medicine Education Centre
B Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham
NG7 2UH

Direct line/e-mail
+44 (0) 115 8232561
Louise.Sabir@nottingham.ac.uk

18th January 2015

Ms Saja Alnahar
PhD Research Student
c/o Dr Murray D Smith
Associate Professor
Division of Social Research in Medicines & Health
School of Pharmacy
University of Nottingham
University Park
East Drive
Nottingham
NG7 2RD

Dear Ms Alnahar

Ethics Reference No: B18012016 SoP 15116 – **please always quote**
Study Title: Exploring Specialists, pharmacists, commissioners and other relevant stakeholders' perceptions on prescribing, assessing and commissioning biosimilar medicinal products in secondary care settings in the UK.
Short Title: Exploring Factors Affecting Biosimilar Medicines Utilisation in UK
Chief Researcher/Academic Supervisors: Dr Murray Smith, Associate Professor, Professor Rachel Elliott, Lord Trent Professor of Medicines and Health, School of Pharmacy.
Other Key researchers/Student: Ms Saja Alnahar, PhD Student, School of Pharmacy.
Duration of Study: 01/02/16-31/10/16, 8 mths **No of Subjects:** 60 (18+ years)

Thank you for submitting the above application which has been considered by the Committee at its meeting on 18th January 2016 and the following documents were received:

Exploring Factors Affecting Biosimilar Medicines Utilisation in UK:

- Full set of Project Data IRAS Version 5.2.0
- NHS R&D Form IRAS version 5.2.0
- Evidence of Insurance- The University of Nottingham, Henderson Insurance Brokers dated 21 July 2015.
- University of Nottingham Sponsor Approval Letter, RGS ref: 15116 IRAS Project ID 189995 dated 16th December 2015.
- Protocol Final Version 1.0 13 Dec 2015
- INVITE LETTER V1.0 date 13.12.2015
- INFO SHEET Final V1.0 date 13.12.2015
- Consent Form Final Version 1.0 – 13 Dec 2015
- QUESTIONNAIRE V1.0 -13.12.2015
- CV for Research Applicants: Dr Murray D Smith date 20 November 2015
- CV for Research Applicants: Professor Rachel A Elliott 19 November 2015
- CV for Research Applicants: Ms Saja Alnahar, 05 November 2015

These have been reviewed and are satisfactory and the study has been given a favourable opinion.

Appendix 10-Study amendment approval

The University of Nottingham

Faculty of Medicine and Health Sciences

Research Ethics Committee
School of Medicine Education Centre
B Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham
NG7 2UH

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11th April 2016

Ms Saja Alnahar
PhD Research Student
c/o Professor Rachel Elliott
Lord Trent Professor of Medicine and Health
Division of Social Research in Medicines & Health
School of Pharmacy
University of Nottingham
University Park
Nottingham
NG7 2RD

Dear Ms Alnahar

Ethics Reference No: B18012016 SoP 15116 – **please always quote**
Study Title: Exploring Specialists, pharmacists, commissioners and other relevant stakeholders' perceptions on prescribing, assessing and commissioning biosimilar medicinal products in secondary care settings in the UK.
Short Title: Exploring Factors Affecting Biosimilar Medicines Utilisation in UK
Chief Researcher/Academic Supervisors: Professor Rachel Elliott, Lord Trent Professor of Medicines and Health, School of Pharmacy.
Other Key researchers/Student: Dr Murray Smith, Research Fellow, Community Health Research Unit, University of Lincoln, Professor Justin Waring, Professor of Organisational Sociology, Division of Management School of Business, Ms Saja Alnahar, PhD Student, School of Pharmacy, University of Nottingham.
Duration of Study: 01/02/16-31/10/16, 8 mths **No of Subjects:** 60 (18+ years)

Thank you for notifying the Committee of amendment no 2: 20.03.2016 as follows:

- Change of Chief Investigator to Professor Rachel Elliott
- Addition of Dr Murray Smith and Professor Justin Waring as Co-investigators.
- Recruitment Strategy: addition of Professional networking during conferences, workshops, seminars etc and/or team's professional connections,

And the following revised documents were received:

Exploring Factors Affecting Biosimilar Medicines Utilisation in UK:
- Study Protocol Final Version 2.0:31 March 2016
- Participants invitation Letter, Final Version 1.5 date 13 March 2016
- Participants Information Sheet, Final Version 2.0: 13 March 2016
- Participants Information Sheet, Final Version 2.1: 11 April 2016
- Participants Consent Form, Final Version 1.5: 13 March 2016
- Participants Demographic Questionnaire, Final Version 1.5: 13 March 2016

These have been reviewed and are satisfactory and the study amendment no 2: 20 March 2016 has been given a favourable opinion.

The University of Nottingham

A favourable opinion is given on the understanding that the Conditions set out below are followed.

These have been reviewed and are satisfactory and the study is approved.

Approval is given on the understanding that the conditions set out below are followed:

1. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).

2. You must notify the Chair of any serious or unexpected event.

3. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.

4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely



Professor Ravi Mahajan
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Appendix 11-Response of participants' identification sites

No.	Organisation Name	Region	Organisation Type	Access Granted
1.	University Hospital of South Manchester NHS Foundation Trust	North of England	Acute Trust	Yes
2.	Royal Liverpool And Broadgreen University Hospital	North of England	Acute Trust	Yes
3.	Newcastle Upon Tyne Hospitals NHS Foundation Trust	North of England	Acute Trust	No
4.	North Tees and Hartlepool NHS Foundation Trust	North of England	Acute Trust	Yes
5.	Calderdale And Huddersfield NHS Trust	North of England	Acute Trust	Yes
6.	NHS Central Manchester CCG	North of England	CCG	Yes
7.	NHS Northumberland CCG	North of England	CCG	Yes
8.	NHS Newcastle Gateshead CCG	North of England	CCG	Yes
9.	NHS Halton CCG	North of England	CCG	Yes
10.	South Warwickshire NHS Foundation Trust	Midlands and East	Acute Trust	No
11.	University Hospital Birmingham NHS Foundation Trust	Midlands and East	Acute Trust	Yes
12.	Derby Hospitals NHS Foundation Trust	Midlands and East	Acute Trust	Yes
13.	University Hospitals Leicester NHS Trust	Midlands and East	Acute Trust	Yes
14.	Nottingham University Hospitals NHS Trust	Midlands and East	Acute Trust	Yes
15.	University Hospitals Of North Midlands NHS Trust	Midlands and East	Acute Trust	Yes
16.	The Royal Wolverhampton NHS Trust	Midlands and East	Acute Trust	No
17.	The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust	Midlands and East	Acute Trust	No
18.	Birmingham Cross City CCG	Midlands and East	CCG	Yes
19.	Nottingham City CCG	Midlands and East	CCG	Yes
20.	Warwickshire North CCG	Midlands and East	CCG	No
21.	NHS North Norfolk CCG	Midlands and East	CCG	Yes
22.	NHS West Norfolk CCG	Midlands and East	CCG	Yes
23.	Royal Free London NHS Foundation Trust	London	Acute Trust	No
24.	University College London Hospitals NHS Foundation	London	Acute Trust	Yes
25.	Guy's and St Thomas' NHS Foundation Trust	London	Acute Trust	No
26.	Homerton University Hospital NHS Foundation Trust	London	Acute Trust	Yes
27.	Croydon University Hospital	London	Acute Trust	Yes
28.	Havering CCG	London	CCG	No
29.	NHS Bexley CCG	London	CCG	No
30.	Kingston CCG	London	CCG	No
31.	South Devon Healthcare NHS Foundation Trust	South of England	Acute Trust	Yes
32.	University Hospitals Bristol NHS Foundation Trust	South of England	Acute Trust	Yes

33.	Royal United Hospital Bath NHS Trust	South of England	Acute Trust	Yes
34.	Dorset County Hospital NHS Foundation Trust	South of England	Acute Trust	Yes
35.	Royal Devon And Exeter NHS Foundation Trust	South of England	Acute Trust	No
36.	Bath and North East Somerset CCG	South of England	CCG	Yes
37.	Dorset CCG	South of England	CCG	Yes
38.	NHS Thanet CCG	South of England	CCG	No
39.	North Somerset CCG	South of England	CCG	Yes
40.	NHS Northern, Eastern and Western Devon CCG	South of England	CCG	Yes
41.	South Devon and Torbay CCG	South of England	CCG	No

Appendix 12-Participants' invitation letter

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Participant Invitation Letter
(Final Version 1.5: 13 Mar 2016)

Title of Study: Factors Affecting Biosimilar Medicines Utilisation in UK

Name of Researcher(s): Prof Rachel Elliott - The Chief Investigator

Dear Sir/Madam (Titles (Role) will be specified in every letter)

We are writing to you to invite you to participate in qualitative research study that we are carrying out to explore factors affecting the utilisation of biosimilar medicinal products in United Kingdom.

The research team are inviting professionals and experts like your kind self who are involved in prescribing, assessing and procuring biosimilar products. We would like to invite you to tell us about your experience and perception toward biosimilar products. The data that will be obtained during the interviews may help us to achieve a more comprehensive understanding of biosimilar product in the context of UK's health system. Furthermore, knowledge gained through these interviews may help the research team to identify key elements of a national policy that will optimise biosimilar utilisation. The interview will be based on open-ended questions and there are no right or wrong answers. We are trying to achieve the maximum variety possible in participants to gain wide variety of opinion and point of views.

Before you decide whether or not you would like to tell us your views, please take time to read the enclosed information sheet carefully and take time to think about whether or not you would like to take part.

If you have any questions about the study then please do contact Saja Alnahar (the researcher) on Tel: 0115 82 15353; email: saja.alnahar@nottingham.ac.uk, and she will do her best to discuss with you any questions you may have. Alternatively you can email us.

Please fill in the enclosed consent form if you are interested in taking part in this study and send it back to us via email.

Thank you very much for reading this letter,

Yours sincerely,

Prof Rachel Elliot,

Chief Investigator

Lord Trent Professor of Medicines and Health

Division for Social Research in Medicines and Health

School of Pharmacy

University of Nottingham

Phone: +44(0) 115 84 68596

Email: rachel.elliott@nottingham.ac.uk

Appendix 13-Participants' information sheet

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Participant Information Sheet
(Final Version 2.1: 11 April 2016)

Title of Study: Factors Affecting Biosimilar Medicines Utilisation in UK

Name of Researcher(s): Prof Rachel Elliott - The Chief Investigator

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?
According to the Health and Social Care Information Centre (HSCIC) biological medicinal products (BMPs) represent seven out of the top ten prescribed products in terms of cost, the HSCIC claimed that these products cost NHS-England £1.4 billion in 2013 and 2014. The patent expiry of some BMPs creates an opportunity for developing similar but not identical copies, called biosimilar products (BSPs). While the price reduction offered by BSPs is lower than that offered by conventional generic products (CGMPs), the European generic medicines association (EGA) estimated that European Union (EU) countries could in combination save € 1.6 billion/year as a result of the 20% price reduction offered by the first approved BSPs.
The aim of this study is investigate factors that affect BSP medicines utilisation in UK. We are interviewing physicians (rheumatologists, gastroenterologists and dermatologists), formulary pharmacists, drug and therapeutic committees' member, commissioners and other healthcare professional in order to explorer their perception and experience in prescribing, assessing and procuring BSPs.

Why have I been invited?
You are being invited to take part because you are involved in prescribing, assessing or procuring BMPs and BSPs in particular infliximab, etanercept and/or rituximab. We are inviting at least 10 participants like you to take part.

Do I have to take part?
It is up to you to decide whether or not to take part; participation is entirely voluntary. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?
This study will be based on semi-structured interviews. If you agree to participate in this study you will receive a consent form to be signed before the interview.
The interview will last for about 30 minutes and you are free to choose a face-to-face or over the phone interview. The interview's location, date and timing will be as per your preference. The interview will be audio-recorded and hand-written notes will be taken. If you prefer the researcher not to audio-record the interview, detailed hand written notes will be taken, with your permission. At the end of the interview you will be asked to fill in a demographic questionnaire.

Expenses and payments

Participants will not be paid to participate in the study. Travel expenses will be offered for any visits incurred as a result of participation.

What are the possible disadvantages and risks of taking part?
Like many research studies involving healthcare professionals, there is a time commitment to taking part. For this study the time commitment will the interview and this may take up about 30 minutes of your time.

What are the possible benefits of taking part?
We cannot promise the study will help you but the information we get from this study may help in understanding BSPs in context of UK health system. The knowledge gained and emerged themes could be of value in identifying key elements of national policies that will optimise BSPs' utilisation in UK.

What happens when the research study stops?
The end of the research will be the last interview of the last participants. Interview analysis will be done by the researcher under direct supervision of her supervisors: Dr Murray Smith (Chief Investigator) and Professor Rachel Elliott. The interview's transcript will be sent to you upon your request. Research's findings and conclusion will be shared with you upon your request.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to Saja Alnahar (the researcher) who will try her best to answer your questions, the researcher's contact details are given at the end on this information sheet. If you are still unsatisfied, please feel free to speak to Dr Murray Smith (Chief Investigator) whose contact details are given at the end of this information sheet or the Administrator, Faculty of Medicine and Health Sciences Research Ethics Committee c/o School of Medicine Education Centre, B Floor, The Medical School, QMC Campus, Nottingham University Hospitals NG7 2UH (FMHS REC ref no: B18022016 15116).

Will my taking part in the study be kept confidential?
We will follow ethical and legal practice and all information about you will be handled in confidence.
If you join the study, some parts of the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.
All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the organisation will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.
Your personal data (address, telephone number) will be kept for twelve months after the end of the study so that we are able to contact you about the findings of the study *and possible follow-up studies* (unless you advise us that you do not wish to be contacted). All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.
Although what you say in the interview is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What will happen if I don't want to carry on with the study?
Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

What will happen to the results of the research study?
The findings from this research will be disseminated and published in peer-reviewed journals and communicated at seminars and conferences and as part of PhD thesis. The study sponsor and funder will be acknowledged in all publications. Your identity will be completely anonymised by removing any personal information. Copy of published papers and/or conference abstracts will be shared with you upon your request and of it is applicable.

Who is organising and funding the research?
This research is being organised by the University of Nottingham and is being funded by Yarmouk University in Jordan as doctoral studentship awarded to the researcher, Saja Alnahar.

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee (ref B18012016 15116).

Further information and contact details

Chief investigator:
Professor Rachel Elliott
Lord Trent Professor of Medicines and Health
Division for Social Research in Medicines and Health
School of Pharmacy
University of Nottingham
University Park
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NG7 2RD
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Appendix 14-Participants' consent form

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

CONSENT FORM
(Final Version 1.5- 13 Mar 2016)

Title of Study: Exploring Factors affecting Biosimilar Medicines Utilisation in UK

REC ref: ***(to be added after approval given)***

Name of Researcher: **Prof Rachel Elliott - The Chief Investigator**

Name of Participant:	**Please initial box**
1. I confirm that I have read and understand the information sheet version number XXX dated XXX for the above study and have had the opportunity to ask questions.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my employment or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.	☐
3. I understand that relevant sections of data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.	☐
4. I understand that hand-written notes will be taken, and that anonymous direct quotes from the interview/focus group may be used in the study reports.	☐
5. (Optional) I understand that the interview/focus group will be audio recorded	☐
6. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.	☐
7. I agree to take part in the above study.	☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

2 copies: 1 for participant and 1 for the project notes

Appendix 15-Commissioners' interview guide

Commissioner Interview Guide- v2.5-030516

- **Before the Interview Starts**
  - **Thank** the interviewee for his/her acceptance to take part in this study;
  - **Make** sure that he/she has read and understood the participant information sheet;
  - **Make** sure that he/she has signed the consent form;
  - **Obtain** permission to audio record the interview;
  - **Assure** confidentiality;
  - **Give** a brief introduction about the research: (*Thank you for being willing to participate in my research. In this study I am investigating factors that might affect the uptake of biosimilar medicinal products in the United Kingdom. In order to achieve this I am interviewing professionals, like your kind self, who are involved in procuring, assessing, evaluating, managing and prescribing biological products in general and biosimilars in particular*);
  - **Ask** if he/she has any questions;
  - **TURN** on the RECORDER.

- **During the interview**
  - Ask about their **background/experience**:
    - How do you perceive the availability of BSPs?
    - What do you think about BSPs?
      - How do you think that the availability of BSPs might be/is affecting medical practice?
      - What about the market?
      - What about your organisation?
    - Tell me please about your experience in commissioning and handling BSPs in your area/institute.
      - What was/is considered helpful in introducing BSPs;
      - What do/did you use/consider?
      - What was/is considered as a barrier in introducing BSPs?
    - In your opinion, do you think that commissioners are sufficiently equipped to manage the introduction of BSPs?
      - What kind of support do/did you receive? Offered by whom?
      - Any training, references?
      - What do you think about it? Was it sufficient?
      - What is missing/what might be helpful?

- Ask about the **effect on BSPs uptake of other stakeholders**:
  - How do you think physicians, pharmacists and speciality nurses perceive/understand BSPs?
    - Was it discussed in meetings?
    - How does HCPs' understanding affect your role as a commissioner?
    - What might be considered to affect them?
    - In your opinion, how the utilisation of BSPs might affect patients/patient support group?
    - In case of objection from patients regarding the prescription of BSPs, how these cases were dealt with?

  - Please tell me more about physicians at your organisation?
    - Have you noticed differences between therapeutic areas (specialities)?
    - Are there different procedures for new and established patients?
    - In your opinion are they (physicians) getting sufficient support to deal with BSPs? Training, Source of information?

  - How do you interact with the formulary management team?
    - Type of discussions?
    - Evidence?
    - Who tend to be more involved in the decisions whether BSPs are put in the formulary? (commissioners (including primary care commissioners), financial managers, patients, pharmacists and drugs and therapeutics committee members (dedicated committee for formulary));

- Ask about national **policies/guidelines and regulations**:
  - In your opinion, to which degree it is easy/possible to implement/apply NICE recommendations?
    - How to create balance between NICE BSP statement and TA? Provide brief description of NICE statement and TAs recommendation
    - Can you foresee physicians and patients views regarding NICE publications/documents?
  - How do you think professional societies' views or actions might affect the acceptance of BSPs?
    - Any examples?
  - In your opinion, what is needed to increase or optimise utilisation of BSPs?
    - In your opinion, what is needed from the demand side (other stakeholders (HCPs)/policy makers/managers etc. to optimise BSPs utilisation?
    - Do you think that the clinical community is ready?

- Ask about considerations related to **service design:**
  - Do you think the BSPs fit in the current service design, for example homecare patients ;
  - How is that;
  - In your opinion, what is needed;
  - From whom;
    - What did/will you consider for upcoming BSPs (etanercept)?
    - What if a BSP adalimumab is launched in the UK, how do you think its uptake might progress?

- Ask **about horizon scanning/future** scenarios:
  - What do you consider in planning for future tendering?
    - EMA;
    - NICE TA, CG.

- Ask about **Southampton University** Experience:
  - Have you heard about their experience? If the answer is (NO), (provide a brief description (*this is of the first Acute Trusts to switch patients to BSPs infliximab. The initiative was led by the gastroenterology team; they proposed a managed switch of all of their patients and asked for administrative personnel, IBD nurses specialist and sessions of pharmacy support. The switch programme was discussed with IBD patient panel. The switch was within a gain share agreement*)
  - Do you think it is applicable to your context?
  - How?
  - What you will/not consider in your context?

- **At the end of the interview**
  - **Thank** the interviewee for his/her time and participation;
  - **Ask** how he/she felt about interviewed and asked about their experience with BSPs;
  - **Ask** if he/she wants to add or discuss any further issues;
  - **Thank** him/her again;
  - **Assure** confidentiality;
  - **State** clearly that the interviewer has no further questions;
  - **State** clearly that interview will be transcribed and analysed and reviewed by the research TEAM.

Appendix 16-Formulary pharmacists interview guide

Formulary Pharmacist Interview Guide-v1.0-030516

- **Before the Interview Starts**
  - **Thank** the interviewee for his/her acceptance to take part in this study;
  - **Make** sure that he/she has read and understood the participant information sheet;
  - **Make** sure that he/she has signed the consent form;
  - **Obtain** permission to audio record the interview;
  - **Assure** confidentiality;
  - **Give** a brief introduction about the research: (*Thank you for being willing to participate in my research. In this study I am investigating factors that might affect the uptake of biosimilar medicinal products in the United Kingdom. In order to achieve this I am interviewing professionals, like your kind self, who are involved in procuring, assessing, evaluating, managing and prescribing biological products in general and biosimilars in particular*);
  - **Ask** if he/she has any questions;
  - **TURN** on the RECORDER.

- **During the interview**
  - Ask about their **Background/Experience**:
    - What is your understanding of BSPs?

  - Ask about their experience in **Assessing/Evaluating** biosimilars:
    - What do you consider in getting a product listed in the formulary?
      - Evidence (Clinical vs. Economic) (difference between therapeutic areas);
      - NICE recommendations (how easy to put into practice; when these are not available, what do you consider);
      - MHRA safety alert;
      - EMA and other regulatory bodies;
      - Literature;
      - Neighbouring organisations' decisions;
      - Horizon scanning (Clarify what do you mean: upcoming BSPs, UKmi publications, NICE TAs, etc.);
      - Professionals' inputs/experiences/recommendations.

    - Who is involved in assessing/deciding medicinal products to be listed in the formulary list?
      - What is this committee/body called?
      - Who is the chair (in terms of profession)?
      - Frequency of meetings?
      - Who tends to be more involved in the decisions about whether a medicinal product/brand is listed as a formulary medicine/brand?

1

- Can you please tell me about your organisation experience with BSPs?
  - Are BSPs listed in the formulary?
  - If Yes, What has been helpful/effective in listing BSPs as formulary medicines?
  - If No, What has been a barrier against listing BSPs as formulary medicines?

- Ask about the **effect on BSPs uptake of other stakeholders** (commissioners, financial managers, patients, physicians, pharmacists and drugs and therapeutics committee members (dedicated committee for formulary):
  - In your opinion, how do professionals namely (physicians, pharmacists and drugs and therapeutics committee members) influence uptake of BSPs?
    - Tell me please about your (your organisation experience);
    - Have you experienced an objection or appeal against listing BSPs;
    - If Yes, from whom; their rational, evidence;
    - Who tend to be more involved in the decisions whether BSPs are put in the formulary? (commissioners (including primary care commissioners), financial managers, patients, physicians, pharmacists and drugs and therapeutics committee members (dedicated committee for formulary));

- Ask about **knowledge/training** related to BSPs:
  - How do you think that commissioners/financial managers, patients, physicians, pharmacists and drugs and therapeutics committee members perceive BSPs?
    - What do you think is missing and might increase acceptance of BSPs;
    - Who is responsible (in delivering training and education sessions related to BSPs);
  - Have you been at seminars/workshops/webinars related to BSPs?
    - How was it;
    - Who delivered it;
    - Was it sufficient?

- Ask about **Initiating** new patients or **Switching** established patients
  - Tell me please about your organisation utilisation of BSPs; is it for new patients, established patients or both?
  - Were there any discussions with patients/patients representatives before starting BSPs utilisation?
  - What was considered? Do you think it was enough?
  - How it is possible to manage and control initiating new patients and maintaining or switching established patients (make sure that terms are clear to the interviewee);
  - Effect of professional societies and disease supporting societies;
  - Difference between therapeutic areas.

- Ask about the **Development and the Structure** of the formulary list:
  - In your opinion what should be considered in listing biological products in general and biosimilars in particular;
  - How do think formulary lists can help in promoting biosimilar prescription;
  - How formularies should be structured;
  - What should be included with regard to biological products including biosimilars;
  - What is missing;
  - Could you please tell about your organisation experience;
  - In your opinion, what is feasible to consider for each and every BSP?
    - Updating frequencies?
    - Meetings?
    - Listing approach?
    - Horizon scanning?

- Ask about **upcoming BSPs** (etanercept, adalimumab and pegfilgrastim):
  - Extrapolating the experience;
  - New disease areas;
  - Different patients' demographics;
  - Different service delivery model.

- **At the end of the interview**
  - **Thank** the interviewee for his/her time and participation;
  - **Ask** how he/she felt about being interviewed and asked about their experience with BSPs;
  - **Ask** if he/she wants to add or discuss any further issues;
  - **Thank** him/her again;
  - **Assure** confidentiality;
  - **State** clearly that the interviewer has no further questions;
  - **State** clearly that interview will be transcribed and analysed and reviewed by the research TEAM.

Appendix 17-Physicians interview guide

Physicians Interview Guide-v1.0-030516

- **Before the Interview Starts**
  - **Thank** the interviewee for his/her acceptance to take part in this study;
  - **Make** sure that he/she has read and understood the participant information sheet;
  - **Make** sure that he/she has signed the consent form;
  - **Obtain** permission to audio record the interview;
  - **Assure** confidentiality;
  - **Give** a brief introduction about the research: (*Thank you for being willing to participate in my research. In this study I am investigating factors that might affect the uptake of biosimilar medicinal products in the United Kingdom. In order to achieve this I am interviewing professionals, like your kind self, who are involved in procuring, assessing, evaluating, managing and prescribing biological products in general and biosimilars in particular*);
  - **Ask** if he/she has any questions;
  - **TURN** on the RECORDER.

- **During the interview**
  - Ask about their **Background/Experience** in prescribing biosimilars:
    - What do you think about biosimilar medicines?
      - In general terms, how do you think that BSPs are affecting medical practice? Tell me please about your own experience
      - Reasoning and motives to prescribe/not prescribe biosimilars?
      - What factors do you consider when prescribing BSPs?
        - Initiating/switching patients;
        - Trust internal procedures;
        - Formulary List;
        - National disease specific societies;
        - NICE Guidelines and disease pathway.

  - Ask about **Interactions with patients**:
    - How do you describe biosimilars to your patients?
      - How do you reassure them in regards to efficacy, safety and quality;
      - What reference sources do you rely on (evidence, patient information leaflet, internally produced educational materials, etc.);
      - Have you received any complaints from patients you have prescribed (initiated or switched) to a BSP;
      - How do patients' age, medical history, etc. affect your decision to prescribe/not prescribe biosimilars;
    - Could you please tell me about your own experience in prescribing BSPs

- In your opinion, what are/were patients' motives to accept/refuse biosimilars?
  - Effect of patients' support groups;
  - Other patients;
  - Family members;
  - Service design;
  - Information sources (web, social media, newspapers, etc.).

- Ask about **Initiating** new patients or **Switching** established patients:
  - Tell me please about your organisation utilisation of BSPs; is it for new patients, established patients or both?
  - Were there any discussions with patients/patients representatives before prescribing BSPs?
  - How it is possible to manage and control initiating new patients and maintaining or switching established patients (make sure that terms are clear to the interviewee);
  - Effect of professional societies;
  - Difference between therapeutic areas.

- Ask about **Interactions with other healthcare professionals and stakeholders (financial managers, commissioners)**:
  - In your opinion, how do professionals namely (physicians, pharmacists and drugs and therapeutics committee members) influence uptake of BSPs?
    - Who led the introduction of biosimilars in your organisation?
      - How did they approach other professionals?
      - How did you feel about their approach?
      - What were their reasoning/motives?
      - In your opinion, what is/was missing in managing the introduction of BSPs?
  - Tell me please about discussions that you have with your team (internally);
    - Have you noticed any differences in accepting biosimilars among your colleagues? Could you please tell more about it?
      - Was this related to experience;
      - Work load;
      - Gender.
  - Who tend to be more involved in the decisions whether BSPs are put in the formulary? (commissioners (including primary care commissioners), financial managers, patients, pharmacists and drugs and therapeutics committee members (dedicated committee for formulary));

- Ask about **knowledge/training** related to BSPs:
  - In your opinion, who should be responsible for training and educational materials related to biological products in general and biosimilars in particular?
    - Tell me about your organisation.
  - Have you been at seminars/workshops/webinars related to BSPs?
    - How was it;
    - Who delivered it;
    - Was it sufficient?

- Ask about **Policy Makers** (national policies):
  - In your opinion, is there a need to optimise the utilisation of biosimilars?
  - If Yes, How?
  - If No, Why?
  - Who should be responsible?

- Ask about the **Development and the Structure** of the formulary list:
  - In your opinion what should be considered in listing biological products in general and biosimilars in particular;
  - How do think formulary lists can help in promoting biosimilar prescription;
  - How formularies should be structured;
  - What should be included with regard to biological products including biosimilars;
  - What is missing;
  - Could you please tell about your organisation experience;
  - In your opinion, what is feasible to consider for each and every BSP?
    - Updating frequencies?
    - Meetings?
    - Listing approach?

- Ask about **Southampton University** Experience:
  - Have you heard about their experience? If the answer is (NO), provide a brief description (*this is of the first Acute Trusts to switch patients to BSPs infliximab. The initiative was led by the gastroenterology team; they proposed a managed switch of all of their patients and asked for administrative personnel, IBD nurses specialist and sessions of pharmacy support. The switch programme was discussed with IBD patient panel. The switch was within a gain share agreement*)
  - Do you think it is applicable to your context?
  - How?
  - What you will/not consider in your organisation context?

- **At the end of the interview**
  - **Thank** the interviewee for his/her time and participation;
  - **Ask** how he/she felt about being interviewed and asked about their experience with BSPs;
  - **Ask** if he/she wants to add or discuss any further issues;
  - **Thank** him/her again;
  - **Assure** confidentiality;
  - **State** clearly that the interviewer has no further questions;
  - **State** clearly that interview will be transcribed and analysed and reviewed by the research TEAM.

Appendix 18-Specialist nurses interview guide

Speciality Nurses Interview Guide-v0.0-070616

- **Before the Interview Starts**
  - **Thank** the interviewee for his/her acceptance to take part in this study;
  - **Make** sure that he/she has read and understood the participant information sheet;
  - **Make** sure that he/she has signed the consent form;
  - **Obtain** permission to audio record the interview;
  - **Assure** confidentiality;
  - **Give** a brief introduction about the research: (*Thank you for being willing to participate in my research. In this study I am investigating factors that might affect the uptake of biosimilar medicinal products in the United Kingdom. In order to achieve this I am interviewing professionals, like your kind self, who are involved in procuring, assessing, evaluating, managing and prescribing biological products in general and biosimilars in particular*);
  - **Ask** if he/she has any questions;
  - **TURN** on the RECORDER.

- **During the interview**
  - Ask about their **Background/Experience** in prescribing biosimilars:
    - What is your understanding of biosimilar medicines?
    - Tell me please about your role in utilising biosimilar medicines in your organisation.
  - Ask about **Initiating** new patients or **Switching** established patients:
    - Tell me please about your organisation utilisation of BSPs; is it for new patients, established patients or both?
    - Were there any discussions with patients/patients representatives before prescribing BSPs?
    - How it is possible to manage and control initiating new patients and maintaining or switching established patients (make sure that terms are clear to the interviewee);
    - Effect of professional societies;
    - Difference between therapeutic areas.
  - Ask about **Interactions with patients**:
    - How do you describe biosimilars to your patients?
      - How do you reassure them in regards to efficacy, safety and quality;
      - What reference sources do you rely on (evidence, patient information leaflet, internally produced educational materials, etc.);
      - Have you received any complaints from patients you have prescribed (initiated or switched) to a BSP;
      - How do patients' age, medical history, etc. affect your decision and their acceptance of biosimilars;

- Could you please tell me about your own experience in prescribing/administering BSPs

- In your opinion, what are/were patients' motives to accept/refuse biosimilars?
  - Effect of patients' support groups;
  - Other patients;
  - Family members;
  - Service design;
  - Information sources (web, social media, newspapers, etc.).

- Ask about considerations related to **service design:**
  - Do you think the BSPs fit in the current service design, for example homecare patients ;
  - How is that;
  - In your opinion, what is needed;
  - From whom;
    - What did/will you consider for upcoming BSPs (etanercept)?
    - What if a BSP adalimumab is launched in the UK, how do you think its uptake might progress?

- Ask about **Interactions with other healthcare professionals and stakeholders (financial managers, commissioners)**:
  - In your opinion, how do professionals namely (physicians, pharmacists, commissioners) influence uptake of BSPs?
    - Who led the introduction of biosimilars in your organisation?
      - How did they approach other professionals?
      - How did you feel about their approach?
      - What were their reasoning/motives?
      - Have you been offered (as a profession any sort of support/incentives)? How?
      - In your opinion, what is/was missing in managing the introduction of BSPs?
  - Tell me please about discussions that you have with your team (internally);
    - Have you noticed any differences in accepting biosimilars among your colleagues? Could you please tell more about it?
      - Was this related to experience;
      - Work load;
      - Gender.
  - Who tend to be more involved in the decisions whether BSPs are used within your organisation? (commissioners (including primary care commissioners), financial managers, patients, pharmacists and drugs and therapeutics committee members (dedicated committee for formulary));

- Ask about **knowledge/training** related to BSPs:
  - In your opinion, who should be responsible for training and educational materials related to biological products in general and biosimilars in particular?
    - Tell me about your organisation.
  - Have you been at seminars/workshops/webinars related to BSPs?
    - How was it;
    - Who delivered it;
    - Was it sufficient?

- **At the end of the interview**
  - **Thank** the interviewee for his/her time and participation;
  - **Ask** how he/she felt about being interviewed and asked about their experience with BSPs;
  - **Ask** if he/she wants to add or discuss any further issues;
  - **Thank** him/her again;
  - **Assure** confidentiality;
  - **State** clearly that the interviewer has no further questions;
  - **State** clearly that interview will be transcribed and analysed and reviewed by the research TEAM.

Appendix 19-End of study notification form

The University of Nottingham

Faculty of Medicine & Health Sciences Research Ethics Committee

End of Study Reporting Form

Please complete this form electronically and submit to louise.sabir@nottingham.ac.uk .

1. Details of Research Project

Full Title *(short title in brackets)*:	Exploring Factors Affecting Biosimilar Medicines Utilisation in UK
Ethics Reference Number *(e.g. A10112011) as detailed on Approval email)*:	B18012016 SoP 15116
What is the status of this study? *(please delete as appropriate)*	☐ Ongoing ☐ Stopped Prematurely ☒ Completed ☐ Not Yet Started
Start Date:	1 February 2016
End Date: *(If not completed, please put estimate)*	30 September 2016
If the study stopped prematurely please provide details why:	Not Applicable

2. Details of Principal Investigator / Supervisor

Name:	Professor Rachel Elliott
School / Department:	Division of Pharmacy Practice and Policy School of Pharmacy

3. Details of Student Investigator (if applicable)

Name:	Saja Alnahar
School / Department:	Division of Pharmacy Practice and Policy School of Pharmacy

4. Other members of the Research Team

Please include and identify co-investigators/ Research assistants/ students **if different to those listed in initial application:**	**Name**	**Department**	**Role**
	Professor Justin Waring	Division of Management School of Business	Co-investigator

The University of Nottingham

5. Research Site Information

Please list any research sites which have been added since the initial ethics approval was obtained.	NHS Newcastle Gateshead CCG (was listed as a participant identification centre, and as per the CCG representatives request, it was listed as a research site).
Are any more sites going to be added? If yes, how many?	☐ **Yes** ☒ **No**

6. Participants / Data / Tissues

	Participants / Data	**Tissue samples**
Annual number recruited (from date of approval)	59 participants	Not Applicable
Target (for study as a whole) *IF APPLICABLE*	60 participants	Not Applicable
If the project has ended, are you intending to destroy any human tissue obtained as a result of the project?	☐ **Yes** ☒ **No**	Not Applicable
If no, **please note you will be required by law to inform the person designate in your department to ensure that you comply with standard operating procedures in your department relating to the Human Tissue Act.**		

7. Adverse events

Have there been any adverse events during the last year? If so, please provide a brief summary:	☐ **Yes** ☒ **No**
Have you notified the Chair of REC & Research Governance Officer of these AEs ?	Not Applicable

8. Declaration (for signatures, please type names)

• **The information I have provided in this form is accurate to the best of my knowledge.**	
Signature of Principal Investigator / Supervisor: *(please delete as appropriate)*	**Professor Rachel Elliott** 
Signature of Student Investigator: *(if applicable)*	**Saja Alnahar** 
Date: 30/09/2016	**30 Sep 2016**

Appendix 20-Interview cover page

University of Nottingham
School of Pharmacy
Division of Social Research in Medicines and Health
Factors Affecting BSPs Uptake in the UK
Semi-structured Interviews Study
Interview Cover Page

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Interview Day and Date:	**Friday, 12 August 2016**	
Interview Duration:		
Interview Timing:		
Interview Method:		
☐**Face-to-Face**	☐**Over the Phone**	☒**Skype®**

Interview guide used:		
Version Number and Date:		
Interview recorded:	☐**Yes**	☐**No**
Consent form signed:	☐**Yes**	☐**No**

Interviewee Name:	
Interviewee research ID number:	
Interviewee Professional Role:	
Interviewee Organisation:	
Email:	
Mobile Phone Number:	
Land Line Phone Number:	

Interviewer Signature	

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Appendix 21-Transcribing guideline

University of Nottingham
School of Pharmacy
Division of Social Research in Medicines and Health
Factors Affecting BSPs Uptake in the UK
Semi-structured Interviews Study
Transcription Guideline

The University of Nottingham
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Transcribing is the first step in qualitative data analysis. The selected tactic of transcribing is driven by the data analysis approach, whether it is meaning or language focused (Kvale and Brinkman, 2009). In meaning focused analysis, the transcript should be presented in a readable and naturalised way (Bucholtz, 2000). On the other hand, language driven analysis mandates linguistics representation of the transcripts; preserves as much possible the spoken language and pays attention to the way in which people talk and express their thoughts and feelings (Bucholtz, 2000, Kvale and Brinkman, 2009). While meaning focused analysis requires producing literature similar transcripts, attention to some contextual elements such silences, laughter, sarcasm, etc. should be considered; a balanced approach between naturalised and denaturalised transcription might be followed (McLellan et al., 2003, Bucholtz, 2000).

To assure a systematic approach in transcribing, a guideline and instructions are needed to maintain consistence in preparing interviews' transcripts (McLellan et al., 2003, Kvale and Brinkman, 2009). While interviews are different in content and flow, their transcripts should look identical in terms of layout and formatting (McLellan et al., 2003). Identical formatting will ease the processes of analysis and transferring to qualitative analysis software (McLellan et al., 2003).

Data analysis of this research will be meaning focused; interviews will be transcribed verbatim. The following instructions should be followed in transcribing interviews:

1. Fill the transcript cover page;
2. Transcribe only interview relevant text i.e. discussions not related to the interview topic do not need to be transcribed;
3. Use Calibri font theme size 12;
4. Use justified alignment double spaced paragraphs;
5. Use 2.54 cm top, bottom, left and right margins;
6. Use time stamp at the beginning of new question and/or idea;
7. Use page numbering and continuous line numbering;
8. Use the following to label the source:
    a. Initial (SAN) and bold and green colour font for the interviewer, for example: **SAN: Tell me what you think about ….?**;
    b. ID code-number and normal and black colour font for the interviewee, for example: ZZ CP-01: No one has told about the change.
9. Use the following abbreviations:
    a. **CCG**: clinical commissioning group;
    b. **BMP**: biological product;
    c. **BSP**: Biosimilar medicine;
    d. **ETA**: etanercept;
    e. **INF**: infliximab;
    f. **R-BMP**: reference biological product/Innovator product
10. Use the following symbols:
    a. **(??)** for questionable text, for example: heterogenic characteristics(??), or for inaudible segment
    b. Use "CT" to indicate overlapping conversation;

Transcription Guideline-SAN-v0.5-130117

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Semi-structured Interviews Study
Transcription Guideline

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c. Use Italic text to indicate reporting of other people sayings;
d. Add! Mark in case of sarcasm.

References:

BUCHOLTZ, M. 2000. The politics of transcription. *Journal of pragmatics,* 32, 1439-1465.

KVALE, S. & BRINKMAN, S. 2009. Transcribing Intrviews *Interviews Learning the Craft of Qualitative Research Interviewing*. Sage

MCLELLAN, E., MACQUEEN, K. M. & NEIDIG, J. L. 2003. Beyond the qualitative interview: Data preparation and transcription. *Field methods,* 15, 63-84.

Appendix 22-Transcripts cover page

University of Nottingham
School of Pharmacy
Division of Social Research in Medicines and Health
Factors Affecting BSPs Uptake in the UK
Semi-structured Interviews Study
Transcript Cover Page



Interview Day and Date:	Click here to enter a date.
Interview Method:	Choose an item.
Interview Duration:	
Interviewee Name:	
Interviewee research ID number:	
Interviewee Role:	Choose an item.
Interviewer Region:	Choose an item.
Interview Guide/Version #	

Ideas for Analysis	
Transcriber Name:	
Total No. of pages of transcript	
Soft copy retrieval path:	
Transcribing Date:	Click here to enter a date.
Review Date:	Click here to enter a date.

Transcript Cover Page-SAN-v0.0-180616

Appendix 23-Transcript reviewer's confidentiality agreement

University of Nottingham
School of Pharmacy
Division Division of Pharmacy Practice and Policy
Factors Affecting BSPs Uptake in the UK

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CONFIDENTIALITY ACCEPTANCE
FOR TRANSCRIPTS REVIEWERS

- I understand that the material I am reviewing is confidential.
- I undertake to store the data securely on a password protected computer/flash drive and to delete the file of each interview transcript once I have received confirmation from a member of the research team that they have received and stored the transcript.
- I will store discs and other media containing interviews and other data in a locked cabinet pending return to the research team.
- I undertake to maintain the confidentiality of persons and information revealed in the interview recordings and transcripts and will not divulge any details of these to anyone other than members of the research team.

Transcript Reviewer Name: …… **Date**:……

Transcript Reviewer Signature: ……

Research Team Member Name: …… **Date:**……

Research Team Member Signature: ……

Confidentiality Acceptance for Transcripts Reviewer Form version 1.0-110117

Appendix 24-Transcript reviewer guidelines

University of Nottingham
School of Pharmacy
Division Division of Pharmacy Practice and Policy
Factors Affecting BSPs Uptake in the UK
Semi-structured Interviews Study
Transcript Review Guidelines

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Thank you for being willing to review interviews' transcripts.

- Please make sure that you have considered the following before starting the review process:
  1. Signed the confidentiality acceptance form
  2. Familiarised yourself with the transcribing guidelines
  3. Stored the audio records and transcripts in password protected laptop and/or desk top.

- During the reviewing process, please consider the following:
  1. Activate track changing button to edit, delete, and/or add any text;
  2. Add comment whenever and wherever you think the transcribing guidelines were not followed, or when a sentence does not make sense;
  3. Take notes of things you think/find interesting.

- After the review process, please consider the following:
  1. Make sure that you have saved the reviewed transcript with your initials and dates added to the to the transcript document title;
  2. Summarise your comments, finding, etc. on the reflection form (attached);
  3. Share edited transcripts and reflection form with research team;
  4. Discarded all related documents and audio records after receiving a request from research team to do so
  5. Attend the brain storming session (date to be confirmed).

Transcripts Review Guideline-SAN-v0.5-110117

Appendix 25-Transcript reviewer reflection form

University of Nottingham
School of Pharmacy
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Factors Affecting BSPs Uptake in the UK
Semi-structured Interviews Study
Transcript Reviewer Post Reflection Form

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Review Period	**Start Date:**	Click here to enter a date.
	End Date:	Click here to enter a date.
Reviewer Name and Initials		
Number of transcripts reviewed		
Comments on the interviews (overall impression).		
Comments on the interviewer interviewing techniques and approach		

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Factors Affecting BSPs Uptake in the UK
Semi-structured Interviews Study
Transcript Reviewer Post Reflection Form



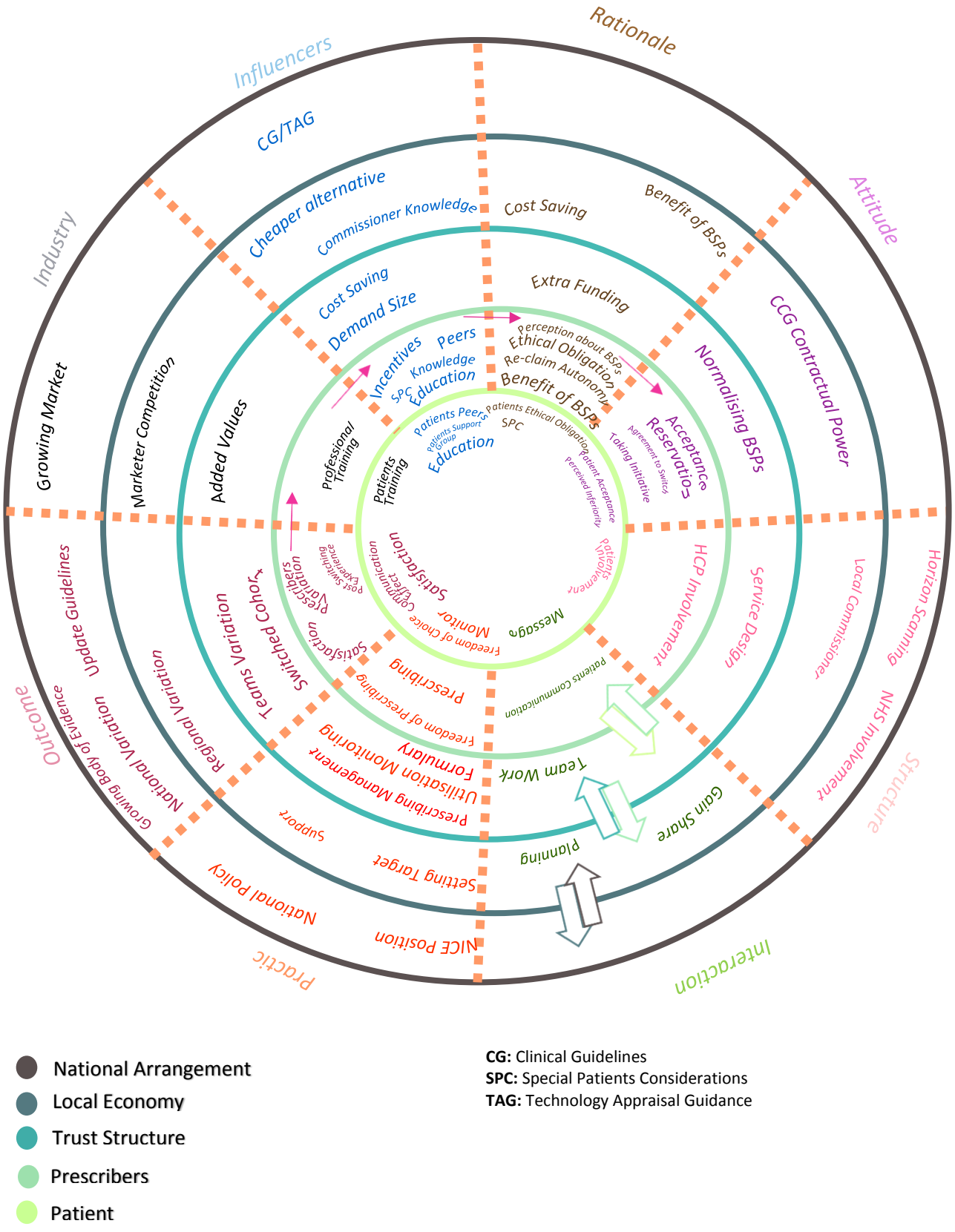
Comments/ideas or discussion points that should be considered in the analysis

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Appendix 26-List of sensitising concepts and their definitions

Category	Subcategory	Code	Sub-code
Factors affecting process	Dynamics	Inter (local) CCG & Trusts	Power conflict Collaboration
		Intra (Trust) Trusts & Prescribers	Time Communication MDT* Champion Reclaim autonomy
	Factors	CCG agenda Trust Agenda Duration of negotiations	
Implementation	Type	Switching Initiating	
	Players	Prescribers Patients	
		Industry	R-BMP manufacturers BSP manufacturers Offered support
	Practice	Staff	Nursing Pharmacy Admin
		Guidance/pathway Procedures Cost of implementation	
	Delivery Route	Service design	Home-care delivery Clinic
		Capacity	
Results/Output	Gain	Financial	Percentage Duration
		Extra Staff	
	Change in market	Market share	
		Prices	
	Changes in Practice	Pathways	
		Preference	
		Formularies	

Appendix 27-First template chart



- National Arrangement
- Local Economy
- Trust Structure
- Prescribers
- Patient

CG: Clinical Guidelines
SPC: Special Patients Considerations
TAG: Technology Appraisal Guidance

Appendix 28-Brain storming session comments and feedback

The session's participants recommended the following modifications:

- Consider redrawing the template chart, emphasis on the fact that the process is not linear and straightforward, but rather a cyclic and iterative process
- Rename the following codes:
    - Disagreement/hindered implementation of switching (4.2): to (no decision, or delay in implementation)
    - Lost opportunity (6.1): to delayed opportunity
    - Saving money to the NHS (5.5.3.4.1.) sub-tree, especially the code (avoid cheaper concept (5.5.3.4.1.1.1.); this code need to be reassessed, and the analyst needs to look carefully at it, as it is not said by participants, but instead it is her interpretation (bracketing)
- Keep clear account of codes related to patients, these codes do not represent patients' position and experience but rather how the prescribers perceived patients' experiences and perceptions (5.5)
- Consider comparing the way in which participants described BSPs to patient to the actual/formal definition of BSPs (EMA, NHS, and patients' support group), check if there are simplification of the term and (watered down) risks and safety concerns (5.5.3.)
- Investigate the involvement in knowledge sharing and knowledge seeking behaviour (1.2.4.2.1.1. and 1.2.4.2.1.2.) if these codes are associated with leadership role
- Investigate how/what the R-BMP manufacturers contribute with regard BSP (evidence, education, etc.) (3.2.3.1)
- Clarify who was approached by the industry at the Trust and local level (2.4.1.4.3.)
- Add code describing commissioners' motive to (seek saving to the NHS) (1.4.2)
- Expand role of professional bodies in terms of already established disease management and prescribing guidelines, not to limit their role to their statements on BSPs
- Expand and consider other dimensions related prescribers' motives to reclaim autonomy (1.4.4.)
    - Professional boundaries
    - Statuary vs actual professional roles
    - Linked with ethical obligations (emphasis on evidence viability)