University of Nottingham

The production and application of evidence: from systematic review to clinical practice guidelines in evidence-based healthcare

Submission by Jun Xia for a PhD by publication

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PAPER 2. **Xia**, J., Adams, C., Bhagat, N., Bhagat, V., Bhoopathi, P., El-Sayeh, H., Takriti, Y. (2009). Losing participants before the trial ends erodes credibility of findings. Psychiatric Bulletin, 33(7), 254-257. doi:10.1192/pb.bp.108.021949.（*JX as first author)*

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Introduction

Systematic reviews and meta-analysis are key sources of evidence in evidence-based medicine (EBM), ensuring that healthcare interventions are based on the best available empirical data(1). While these methods are mainly used to synthesize available evidence from primary studies, they can also play important role in other parts of the research process, such as identification of gaps in existing research and informing the design of new studies(2). There is an evidence ecosystem formed between primary research - conducted using epidemiological methods - and secondary analysis - using methods such as systematic reviews and meta-analysis. One type of research feeds the other, creating a synergy which has the capacity to constantly improve research, its relevance and which can bridge the gap between research and practice(3).

The following chapters present a series of epidemiological studies and evidence-based healthcare research projects that are an example of one such synergy for improved evidence-based healthcare decision making. Through a selection of her published work, the author will discuss the development of clinical epidemiology, focusing on the relationship between primary research and secondary synthesis within the evidence ecosystem, arguing for the importance of secondary syntheses and wide dissemination of findings.

Overall objectives

The primary objective of the collection of work presented is to demonstrate the methodological evolvement of EBM in the context of an evidence ecosystem, and author's contribution in generating new knowledge that accelerates these methodological advances. This is demonstrated by the:

1. Reduction in bias in systematic review through bringing Chinese biomedical databases to the attention of global healthcare research community, which encourages comprehensiveness of literature search in systematic review;
2. Provision of empirical evidence addressing the issue of missing data in clinical studies and estimation of the impact on credibility of research findings;
3. Generation of new knowledge through applying systematic reviews to critically evaluate existing evidence to answer real-world healthcare questions;
4. Utilising systematic reviews in a major clinical practice guideline, which, in turn, advances the cycle of evidence-based practice;

5. Application of good epidemiological method to the investigation of the value of techniques of dissemination.

The secondary objective is to demonstrate author's personal development as an independent researcher through resolving challenges for the EBM community at various stages of the evidence ecosystem, advancing from evidence producer to evidence user, deploying systematic review evidence to inform clinical practice guidelines, which ultimately promotes evidence-based practice and brings benefits to stakeholders.

Chapter 1. Methodological development: Surveys

Chapter highlight

This Chapter presents details of an innovative application of survey methods. The author applied traditional epidemiology survey to medical literature to highlight gaps in research. Chinese databases were used to provide empirical evidence regarding gaps in acquisition of evidence [because of language and access bias] encountered by researchers conducting systematic reviews. The findings of the paper directly led to the inclusion of four major Chinese databases in The Cochrane Central Register of Controlled Trials (CENTRAL), benefiting reviewers around the world.

Chapter background

Survey methods are used to gather information from a representative sample with the aim of understanding the population as a whole(4). In the context of the time when the work presented in this Chapter was instigated-quite early in the development of widespread adoption of systematic review methods - funding for such work was rare in the extreme. However, the survey can provide a critical source of data for assessing the status of a population [even if that 'population' is papers] – and may be inexpensive to undertake and, as such, can be a valuable, powerful and accessible tool. This Chapter reports use of basic epidemiological methods in novel ways, applied to bibliographic databases(5) as the units of investigation.

Background to paper 1

This work investigated the availability and features of mainstream Chinese biomedical databases and highlighted gaps in use of evidence not readily apparent to 'western' researchers. Systematic reviews should be based on all relevant evidence(6-8). The process of reviewing allows critical appraisal of each 'building block' of the proposed review(6, 9). The systematic review methods were instigated by the English speaking world(10, 11) and there was a concern that they carried – and perhaps perpetuated - the English language 'positive' result bias(12). Most systematic reviews relied on use of bibliographic databases such as MEDLINE and perhaps EMBASE or a specialist database such as PsycINFO. Large western databases such as PASCAL [French] and PSYNDEX [German] were largely ignored. LILACS - the large bibliographic database of Latin American and south Caribbean literature was rarely cited in systematic reviews. Using Chinese literature was rare and knowledge of

key sources and their accessibility to ‘western’ specialists very limited(5, 13). This survey attempted to help address this shortfall and remains unique and un-replicated. It has been widely cited by review methodology researchers (111 citations).

The findings of this survey led to the inclusion of four Chinese biomedical databases in the Cochrane Schizophrenia Group’s Specialised Registers(14), and collected by the Cochrane CENTRAL database(15), which is the most comprehensive source of reports of controlled trials and routinely searched by systematic reviewers around the world(16).

Coda

Comprehensive and unbiased inclusion of literature is only the first step towards answering complex health care questions. This Chapter highlighted gaps in identification of literature, particularly for systematic reviewers and argued for the judicious use of Chinese literature in all systematic reviews. Failing to do this would leave the results of systematic reviews prone to random error, or could lead to bias, or both. Findings of this survey contributed – and continue to contribute - to the accumulation of knowledge in the world of evidence synthesis, paving a way for advances in, and diverse applications of, systematic reviews to solve real-world healthcare problems.

Reference for paper 1

Citation: Xia J, Wright J, Adams CE. Five large Chinese biomedical bibliographic databases: accessibility and coverage. Health Info Libr J. 2008 Mar;25(1):55-61. doi: 10.1111/j.1471-1842.2007.00734.x. PMID: 18251914. (PAPER 1. JX as first author)

PAPER 1

Five large Chinese biomedical bibliographic databases: accessibility and coverage[1]

Abstract

Background: Much biomedical research is now undertaken in China.

Methods: Five large biomedical databases originating from China (CBM, CMCC, CNKI, VIP and WANFANG) are described and their utility and accessibility investigated.

Results: These databases index 2500 journals largely not familiar to MEDLINE users. Free access, search features, record selection, ease of downloading and cost of subscription varies considerably between databases.

Conclusion: Searches in all databases benefit from the use of simplified Chinese and all provide links to full text articles. Less than 6% of the 2500 journals in the five databases were listed as being indexed for MEDLINE.

[1] A reply to this paper has been published as:
Xia J, Wright J, Adams CE. Five large Chinese biomedical bibliographic databases: accessibility and coverage. Health Info Libr J. 2008 Mar;25(1):55-61. doi: 10.1111/j.1471-1842.2007.00734.x. PMID: 18251914.

Introduction

The people of China are about 20% of the world's population (1.3bn US). During the last 25 years, China has opened her doors to international trade and switched to a market-orientated economy. Both encouraged rapid economic growth. The resulting gains in efficiency have contributed to a more than tenfold increase in gross domestic product (GDP) since 1978 and, in 2005, China stood as the second largest economy in the world. (1)

China has modernized scientific research during the past four decades. There are 263 medical research institutions in China and an estimated 926000 researchers, only second to the USA in number. (2) China is also the second largest spender on research and development spending (US$136bn). The figure has more than tripled since 1998. The number of scientific research papers has doubled in the same period (3) and Chinese authors are increasingly prevalent in major international academic journals. (4)

Methods

By searching the Web, discussions with information specialists and contact with the Chinese Cochrane Centre (5), we found five major Chinese biomedical databases. These are Chinese Bio-medical Literature Database (CBM), Chinese Medical Current Content (CMCC), China National Knowledge Infrastructure (CNKI, formerly China Academic Journals), VIP Information, and WANFANG Data (Table 1).

One author (JX) contacted all five suppliers, requested a free trial, and recorded the response, coverage, nature of output, accessibility and searching features of each database. Either the lists of journals covered by each of these databases was downloaded, or the suppliers were contacted for these lists; these were then uploaded into MS Access and cross-checked within this database, matching on ISSN and journal title. This process was repeated for past or present holdings of MEDLINE.

Table 1 Summary of coverage and output.

Database			Coverage						Access and output		
English	**Chinese**	**URL**	**Journals**	**Articles**	**Proceedings**	**Theses**	**Start date**	**Update**	**Optional English Interface** **Access**	**Record selection**	**Download format**
Chinese Biomedical Literature database (CBM)	中国生物医学文献数据库	http:// cbmwww.imicams.ac.cn/	1600+	3 000 000			1978	Unclear	No access on website On request—free trial to full functionality + PDFs of 2002 (2 weeks) Subscription—full functionality + PDFs	All search results	Tagged text (500/file)
Chinese Medical Current Content (CMCC)	中文生物医学期刊数据库	www.cmcc.org.cn	1400+	2 700 000	300 000	N/A	1994	Fortnightly	Free—citation + abstract search Subscription—full functionality + PDFs	All search results	Tagged text (300/file)
China National Knowledge Infrastructure (CHKD-CNKI)	国家知识基础设施	www.cnki.net	1000+*	3 308 164	145 457†	47 030‡	1979	Daily—satellite; monthly—disc	✓ Free—citation + abstract search On request—access to full functionality + PDFs (1 month) Subscription—full functionality + PDFs	Search results displayed per page (maximum 10/page)	Tagged text (unlimited/file)
VIP information/ Chinese Scientific Journals database (CSJD-VIP)	维普信息/中文科技期刊数据库	www.cqvip.com	1818*	2 900 000+	N/A	N/A	1989	Unclear	✓ Free—citation + abstract search On request—access to full	Search results displayed per page (maximum 50/page)	Tagged text (50/file)

Database			Coverage						Access and output		
English	**Chinese**	**URL**	**Journals**	**Articles**	**Proceedings**	**Theses**	**Start date**	**Update**	**Optional English Interface** **Access**	**Record selection**	**Download format**
									functionality + PDFs (2 weeks) Subscription—full functionality + PDFs		
WANFANG database (Chinese Medicine Premier)	万方数据/医药卫生专辑	www.wanfangdata.com	963*	Unclear	124 646	144 318	Unclear	Unclear	✓ Free—citation + abstract search (Chinese interface only) On request—access to full functionality + PDFs (2 weeks) Subscription only— full functionality + PDFs	Search results displayed per page (maximum 20/page)	Copy and paste (unlimited/file)

*Medicine and hygiene subset; †China Proceedings of Conference database (CPCD) subset; ‡Doctorate/Masters dissertations database (CDMD) subset.

Table 2 Summary of search features

Database	Search features				
	Basic search	Advanced search	Expert search	Language sensitive	Truncation
CBM	✓	✓	✓	✓	✓
CMCC	✓	✓	✓	✓	✓
CNKI	✓	✓	✓	✓	
WANFANG		✓		✓	✓
VIP	✓	✓	✓	✓	✓

RESULTS

Four database suppliers responded to the request for a free trial (CBM - 2 weeks, CNKI - 4 weeks; WANFANG - 2 weeks; VIP - 2 weeks). CMCC supplied an installation disc containing the whole database of citations and abstracts to date.

CBM is for subscribed users only and do not provide anything for non-subscribers. CMCC, VIP, CNKI and WANFANG (Chinese interface only) do provide a free abstract search for the general user, but only subscribers can get full-text articles. All databases have links to full-text articles for those who pay, but for CMCC, VIP, CNKI and WANFANG (Chinese interface) registered users can purchase full-text articles per page or per article without full subscription to the database.

In terms of holdings, VIP is the biggest database, the main component of which is Chinese Scientific Journals Database (CSJD). It indexes over 1800 biomedical journals (from 1989 onwards), three million reports and links to full-text portable document format files (PDFs). WANFANG is the smallest database, indexing about 1000 journals.

CNKI (also known as China Academic Journal - CAJ) is another large database and additional valuable subsets can be purchased, including the China Doctor/Master Dissertations Full-text Database (CDMD, from 1999 onwards, ca. 47 000 doctorate/Master's theses), and the China Proceedings of Conference Databases (CPCD, from 2000 onwards, ca. 146 000 conference proceedings).

With free trials, JX was able to test the searching features of all five databases (Table 2).

With the exception of the WANFANG database English interface, which does not have a basic search functionality, all other data bases, including the WANFANG Chinese interface, have both basic and advanced search options. The advanced interface allows the user to combine several text words in a single search, and terms can be combined with Boolean or proximity operators with the same range of fields available as the basic search. CBM, CMCC, CNKI and VIP also have an additional 'Expert search' feature. This is a command-line-style entry box. The whole search is constructed using search terms, field names, parenthesis, Boolean operators and proximity operators. It is then entered as one search string. Truncation is available in CBM, CMCC, WANFANG and VIP offers a function similar to 'truncation' in which the user has the option of searching for a 'Precise' match or a 'Fuzzy' match of keywords.

The supplier of WANFANG informed us that the database recognizes three languages, simplified Chinese, traditional Chinese and English. JX tested this with a simple search term 'schizophrenia' in the three (simplified Chinese =精神分裂症, traditional Chinese = 精神分裂癥) in 'Abstract'. All five databases are language sensitive. When the search term is typed in simplified Chinese rather than when it is in English or traditional Chinese, they tend to produce significantly more results (Table 3). In the WANFANG database, results are displayed in either simplified or traditional Chinese depending on the language setting of the user's computer. In the other four databases, results are displayed in simplified Chinese. As the search interface is the same for different topic areas, language sensitivity is expected to be general across different topic areas. JX tested this with a search for 'electronic' (simplified Chinese =精神分裂症, traditional Chinese =精神分裂癥) in keyword in CNKI, VIP and WANFANG. Results show that English input of search terms produced significantly fewer hits compared with simplified Chinese (see Table 3). To overcome these differences, the user could try searching on an English term and identifying its Chinese counterpart through comparing 'Keywords' listed in 'Abstract' and then expanding the search to improve retrieval. Downloading from these databases is often problematic. First, selecting records can be difficult. For example, in three databases the user is only able to select references listed on the currently displayed page, and this ranges from a maximum of 10 records (CNKI) to 50 (VIP). The user must go through each page of results to select all required records before these results can be downloaded. Second, acquiring the selected records can also be

problematic. For example, the interface we investigated in WANFANG did not have a global downloading function. Each page displays a maximum of 20 results and the only way we found to acquire records was to copy and paste into, for example, MS Word. Four databases have a good output of tagged text (in simplified Chinese/English) but requiring more than the prescribed maximum number of records can involve some manipulation of selection. CBM and CMCC both have the useful combination of global selecting and large file outputting of tagged text (see Table 1). The output files of each database vary, but typically include title, author, address, source, keyword and abstract. Only a small proportion of articles in each database have an English title and abstract.

Table 3 Number of hits for the word 'schizophrenia' and 'electronic' produced with different languages/scripts

Search terms	Language					
	English		Simplified Chinese		Traditional Chinese	
	schizophrenia	electronic	精神分裂症	电子	精神分裂癥	电子
CBM	1	Not applicable	583	Not applicable	0	Not applicable
CMCC	1841	Not applicable	8082	Not applicable	0	Not applicable
CNKI	2871	3299	8820	116 188	0	0
WANFANG	1852	54 002	6006	272 892	0	11
VIP	28	710	5893	158 492	5893	158 492

Each database has an overlapping but distinct content (Table 4). CBM and CMCC are specialist bio-medical databases, both focusing on medicine, biological and natural sciences. CNKI, VIP and WANFANG, however, are more comprehensive. WANFANG has five major subject areas, Chinese studies, China business reference, China legal collections, science and technology of China and a medicine and hygiene section called 'Medicine Premier'. CNKI offers nine series on physics/astronomy/mathematics, chemistry, metallurgy, industrial technology and engineering, agriculture, medicine/health (CHKD), literature/history/philosophy, economics/politics/law, education/social sciences, and electronics/information sciences. Finally, VIP includes 21 different subject areas (philosophy/religion, social sciences, politics/law, military studies, economics, culture/

sciences/education, language studies, literature, art, history/geography, natural sciences, chemistry, astronomy/earth science, biological science, medicine/hygiene (CSJD), agriculture, transport studies, aerospace studies and environment science).

We acquired the international standard serial numbers (ISSNs) of 68% of all journals in each database (a total of 2529 journals/periodicals) as well as the 10 000 ISSNs of journals that are or have been indexed by the National Library of Medicine for MEDLINE. Over 200 journals were in all five Chinese databases (8.6%, 220) but 40% (1026) of the total were only to be found on one of the five. We cross-checked the lists of journals in each combination of Chinese databases with the ISSNs within MEDLINE. The percentage common to any combination of the Chinese databases and MEDLINE was never greater than five. We think it unlikely that many of the 32% of journals in the Chinese databases for which we were not able to acquire ISSNs are indexed in MEDLINE.

Table 4 Best coverage combinations of databases

NUMBER OF DATABASES	DATABASE OR COMBINATION OF DATABASES	NUMBER OF JOURNALS ON HOLDINGS LIST	PERCENTAGE OF ALL JOURNALS IN THE FIVE DATABASES
1	VIP	1928	**76**
	CMCC	1696	**67**
	CNKI–CAJ	1156	**46**
	CBM*	1115	**44**
	WANFANG	959	**38**
2	CMCC + VIP	2296	**91**
	VIP + WF	2080	**82**
	CBM + VIP	2053	**81**
	CNKI + VIP	2037	**81**
	CMCC + CNKI	1847	**73**
	CBM + CMCC	1844	**73**
	CMCC + WF	1815	**72**
	CBM + CNKI	1382	**55**
	CBM + WANFANG	1354	**54**
	CNKI + WF	1302	**51**
3	CBM + CMCC + VIP	2396	**95**
	CMCC + CNKI + VIP	2375	**94**
	CMCC + VIP + WF	2387	**94**
	CBM + VIP + WANFANG	2185	**86**
	CNKI + VIP + WF	2146	**85**
	CBM + CNKI + VIP	2129	**84**
	CBM + CMCC + CNKI	1943	**77**
	CBM + CMCC + WANFANG	1940	**77**
	CMCC + CNKI + WF	1921	**76**
	CBM + CNKI + WANFANG	1522	**60**
4	CBM + CMCC + WF + VIP	2481	**98**
	CBM + CMCC + CNKI + VIP	2461	**97**
	CMCC + CNKI + VIP + WF	2443	**97**

	CBM + CNKI + VIP + WANFANG	2237	**88**
	CBM + CMCC + CNKI + WF	1921	**76**
5	CBM + CMCC + CNKI + VIP + WANFANG	2529	**100**

*CBM'S MEDICINE AND HYGIENE SUBSET USED THROUGHOUT ANALYSES.

We also compared subscription cost (UK subscription for the least expensive option in 2007). For specialist biomedical databases CBM and CMCC, we requested the cost of the full database subscription, and for the other three more comprehensive databases we requested the cost for only the medicine and hygiene subsets. Subscription costs varied from £470 (CMCC) to £4000 (WANFANG) per year. Except WANFANG, all the four other databases were under £1000 per year.

Conclusions

It seems likely that in future years there will be many changes in the accessibility of this literature. Databases will merge, split, or replicate, and indexing policies will change. There will be increasing sophistication of interfaces, means by which records are downloaded, and pricing deals. However, the biomedical literature from China is already large so those wishing to undertake comprehensive literature searches do need some familiarity with existing resources.

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Chapter 2. Methodological development: missing data and credibility of study findings

Chapter highlight

This Chapter describes an empirical pilot investigation into an ignored gap in trials/systematic review methodological knowledge regarding how loss to follow up erodes credibility of data. Unique to this – now dated – study is that it did not investigate techniques of compensation for losses to follow up – it simply attempted to find when stakeholders began to feel that any results were not fully worthy of trust. The disturbing finding – which does need widely replicated but, as yet, has not been – may help explain why there can be a lag between implementation of EBM and its production. Fundamentally, clinicians and recipients of care may not feel the findings are credible.

Chapter background

This Chapter explored the problem of attrition from studies. This is not a problem specific to schizophrenia trials but one that is particularly problematic for those in mental health research. The question was when was there too much loss to follow up to 'trust' findings. A randomised trial of 100 participants loses 99 people before completion but the one person completing the study shows good improvement for the experimental compound. Claims of having discovered a breakthrough treatment are, correctly, likely to be met with scepticism. However, a randomised trial of 100 participants with 99% follow up and a clear positive result for the experimental treatment is likely to be felt to be more credible. In research we adopt a level of statistical significance of 0.05 – this is a statistical expression relating to credibility – which is a judgement or feeling (17). Judgements/feelings, albeit cloaked in statistics, are fundamental to empirical research.

Furthermore, loss to follow up introduces attrition bias into a study and potentially compromise the credibility of study findings. It is important to assess the level of risk bias that attrition causes in order to inform the level of certainty users can have towards search findings. One of the widely used tool in this area is the Cochrane Risk of Bias Table, often abbreviated as the RoB table. It guides users through a list of bias domains and invite users to decide on the likelihood of the presence of risk of bias through answering signalling questions under each risk domain. The RoB table requires a level of methodological knowledge to be applied appropriately, which not all users would have. The current survey

compliment other risk of bias assessment tools, such as the RoB table, by investigating into this single variable of attrition which undermines the credibility of outcomes in most studies.

Background to paper 2

Paper 2 describes an empirical pilot investigation into a painful and mostly ignored gap in trials/systematic review methodological knowledge regarding how loss to follow up erodes credibility of data. It is a survey into a judgement/feeling amongst clinicians, patients and consumers. Paper 2 is the first survey of opinion on the impact of missing data in clinical trials. It seems to remain unique. This is a far from perfect survey but is original, is disturbing in its finding and implications and certainly merits replication. It remains widely cited and used in systematic reviews.

Coda

This Chapter provided empirical evidence regarding the credibility 'border' for researchers using clinical trials and suggested that systematic review protocols should carefully consider potential proportions of loss to follow up and how these proportions will be dealt with in final analyses. Chapter 3 builds on the work presented in this Chapter – and its predecessor - and moves towards production of systematic reviews to answer real-world clinical and research questions.

Reference for paper 2

PAPER 2. Xia, J., Adams, C., Bhagat, N., Bhagat, V., Bhoopathi, P., El-Sayeh, H., Takriti, Y. (2009). Losing participants before the trial ends erodes credibility of findings. Psychiatric Bulletin, 33(7), 254-257. doi:10.1192/pb.bp.108.021949. (PAPER 2. JX as first author)

PAPER 2

Losing participants before the trial ends erodes credibility of findings[2]

Abstract

AIMS AND METHOD

To estimate the proportion of attrition at which results of drug trials for people with schizophrenia lose enough credibility to become mistrusted by relevant groups of stakeholders. A piloted questionnaire was sent to 3.

RESULTS

We received the biggest number of responses from the service user and carer group (n=81, 76%); 43% of clinicians and 32% of researchers responded. All three groups suggested that the follow-up rate for a 12-week schizophrenia drug trial should be around 70 -75% for the trial to be credible.

CLINICAL IMPLICATIONS

This survey suggests that relevant stakeholders, including researchers, fundamentally mistrust results of the majority of drug trials in schizophrenia. Adopting a more pragmatic trial design can help address this.

[2] A reply to this paper has been published as:
Xia, J., Adams, C., Bhagat, N., Bhagat, V., Bhoopathi, P., El-Sayeh, H., Takriti, Y. (2009). Losing participants before the trial ends erodes credibility of findings. Psychiatric Bulletin, 33(7), 254-257. doi:10.1192/pb.bp.108.021949.

Randomised controlled trials relevant to people with schizophrenia are often small and of short duration (1,2). Attrition rates from these studies can be considerable (Table 1). Whatever the reason for the loss of trial sample to follow-up, whether it is because the participant requests it or because trial protocol necessitates withdrawal from the study, these people often are not able to provide, or are not available for, final outcome scores.

Although some complete information may still be obtained from routine data, this loss to follow-up does mean that many scale-derived outcomes reflect the condition of only a proportion of participants. As scale data are so commonly the primary outcomes in trials relevant to mental healthcare (2), this leaves these studies vulnerable to the many biases introduced by not undertaking an intention-to-treat analysis (3). Statistical techniques have evolved to rebuild a semblance of the complete dataset, but all such devices are imperfect and are based on assumptions that are difficult or impossible to substantiate (4,5).

We aimed to gauge the attrition level at which results of drug trials for people with schizophrenia lose enough credibility to be mistrusted by three relevant groups of stakeholders.

Method

A protocol was written, and power calculations undertaken, suggesting that for what we thought would be a meaningful difference (20%) about 100 people in each of the groups would be necessary (a=0.05, power 80%). The questionnaire was drawn up and piloted in groups of clinicians, researchers, and mental health service users (this led to refinement of the accompanying background information and of the final questionnaire question; see the online supplement to this paper). In March 2007, three groups of stakeholders were targeted. First, email contacts of all 128 general adult psychiatrists within the Yorkshire Deanery were obtained (the clinicians). Then a list of the first 100 most recently published email contacts from within the Cochrane Schizophrenia Group's Register of trials was generated (the researchers). Finally, 104 carers/service users from Rethink's regional groups across England were contacted (Rethink is a leading UK mental health membership charity, www.rethink.org). The trial gained approval from Leeds East Research Ethics Committee and one follow-up email was allowed should there be no response on first contact. On 23 March 2007, the question (see online supplement) was sent to the clinicians and researchers via email and followed up 2 months later. During this period, questionnaires were also sent out to carers and service users who attend Rethink's regional governance meetings.

Results

Response rates from clinicians and researchers were poor but all three stakeholder groups estimated the proportion of follow-up sample necessary at 12 weeks to generate a basic level of trust in the outcomes in drug trials relevant to schizophrenia to be about 70-80% (Table 2).

Table 1. Total lost to follow-up by about 10 -12 weeks in drug trials[1]

	RCTs	Lost	Total	Loss, %	95% CI
Atypicals v. typicals (mostly haloperidol)					
Clozapine	23	251	1513	17	15–19
Amisulpride	11	213	764	28	27–34
Risperidone	18	901	3066	29	28–31
Sertindole	2	164	524	31	27–35
Zotepine	7	170	477	36	31–40
Quetiapine	6	589	1624	36	34–39
Olanzapine	14	1264	3344	38	36–39
Aripiprazole	7	1138	2868	40	38–41
Ziprasidone	1	46	90	51	41–61
Typicals v. typicals (mostly haloperidol or chlorpromazine)					
Pimozide	16	36	519	7	5–9
Clotiapine	2	15	121	12	8–19
Penfluridol	3	15	118	13	8–20
Trifluoperazine	22	124	930	13	11–16
Thioridazine	19	251	1587	16	14–18
Molindone	6	51	241	21	16–27
Sulpiride	10	124	561	22	19–26
Perphenazine	19	437	1969	22	20–24
Zuclopenthixol	8	111	424	26	22–31
Perazine	5	59	193	31	25–37
Loxapine	9	157	493	32	28–36
Atypicals v. atypicals					
Risperidone v. olanzapine	7	249	1217	20	18–23
Olanzapine v. various	12	535	2304	23	22–25
Clozapine v. risperidone	5	124	467	27	23–31
Amisulpride v. risperidone	1	69	228	30	19–29
Quetiapine v. risperidone	1	235	728	32	29–36
Zotepine v. clozapine	1	17	50	34	22–48
Aripiprazole v. various	3	407	832	49	46–52

RCT, randomised controlled trial.

1. Source of data – relevant Cochrane reviews.

Table 2. Response rates and credibility rates as viewed by three groups of stakeholders

	Responses, n/N (%)	Follow-up necessary for credibility, mean (95% CI)
Clinicians	55/128 (43)	75.3 (CI 72–78)
Researchers	32/100 (32)	76.4 (CI 73–80)
Carers	81/104 (76)	70.8 (CI 67–74)

n, responded; N, total number approached.

Discussion

This is the result of a survey with variable response rate to a question that forced a binary decision in a situation that, in reality, usually involves managing degrees of discomfort with research findings. It is also feasible that a question with well-tested psychometric properties may have generated different results. Nevertheless, we know of no study in any area of healthcare that has even attempted to investigate this limit of credibility in those for whom results of trials are important. Using 70-80% follow-up at 12 weeks as a broad estimate of the limit of credibility on the data derived from trials (Table 1) shows that the evidence on many commonly used drugs falls short of this standard.

To put this finding in context, schizophrenia drug trials are often short, involve participants who are so rigorously diagnosed as to be difficult to find in everyday practice, prescribe interventions that demand rigid adherence and measure outcomes on many scales of variable quality (6) that are often reported poorly and are problematic to interpret clinically (2). These studies, nevertheless, are the well-established gold standard means by which mental health treatments are evaluated (7). This simple survey asked participants to put aside all other worries about the design, conduct and reporting of these studies and to focus on attrition. Investigation of this single variable undermines the credibility of outcomes in most studies.

Drug trials, however, often report several outcomes. Attrition from one outcome may be large, whereas other outcome data from within the same study are almost complete. Often data on outcomes such as ‘loss to follow-up’, ‘hospitalised’ or ‘in contact with services/ police/family’ are reasonably complete and it is not surprising that major trials are now beginning to use these as primary outcomes (8). This choice of simple routine outcomes, however, is still the exception rather than the rule. Most trials in this area focus on fine-grain, scale-derived outcomes. Scales, although greatly valued non-physiological measures, are mostly ordinal rather than continuous and face problems with validity, analysis and

interpretation. They are further undermined by their association with incomplete datasets. Often, however, trials generate binary outcomes such as improved to an important degree', but these are based on incomplete scale data and fail to directly ask the simple single question that would cover this outcome and for which it is likely that much more complete and credible data could be acquired.

Conclusions

Currently, clinicians, policy makers and consumers of care have to come to decisions about treatments based on information that is of questionable credibility. We believe that this allows many factors, such as fashion and advertising, to take priority over good evidence when it comes to making the difficult decisions about care. The loss of people from these studies is both an enormous opportunity and waste. One method used to give a semblance of endpoint ratings is to carry forward the last observation of the person before they left. Ratings, even from the first few weeks into the trial, are carried forward to the end of the study, perhaps months later, often with the (unlikely) assumption that the person has been stable since the point of departure. If this technique remains acceptable to users of the findings, there will be little motivation for improvement. Last-observation-carried-forward is a flawed technique that depends on considerable assumptions and can lead to erroneous results (9). The study design that wastes the resource of willing people ensures that most trials in schizophrenia remain small and difficult to apply clinically. There is now accumulating evidence that using more routine data can generate high-grade datasets even on protracted follow-up (10). Simpler pragmatic/real-world design could ensure that more studies were adequately powered for the more complete datasets of clinically meaningful outcomes.

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Chapter 3. Methodological development: systematic reviews of healthcare

Chapter highlights

This Chapter presents examples of groundwork undertaken by the author in applying the method of evidence synthesis to advance knowledge in healthcare research. This includes application of systematic review to identify gaps in research evidence and to evaluate efficacy and safety of healthcare interventions to inform stakeholders. The paper presented in Chapter 3 is a methodological extension of Chapter 1 and 2. It utilised findings from previous chapters to produce a more comprehensive literature search and to inform data synthesis plans that deals appropriately with missing data. It is innovative in its consideration and categorisation of a problematic range of interventions – and set a standard in doing this *before* any findings were created. It is illustrative of the increasingly sophisticated systematic reviewing techniques used in evidence-based health care and policy-making.

Chapter background

Evidence-based healthcare is the integration of best available research evidence, clinical experience and patients' values and preferences(18). Incorporating research into practice can be time-consuming and a challenge exacerbated by the exponential growth in medical literature(19). For example, a search on PubMed for 'stroke' retrieves over 30,000 articles in 2020 alone – five times greater a number than in the year 2000(20). Facilitating easy access to evidence becomes essential(21) and so systematic reviews and meta-analyses have become increasingly important in keeping clinicians and others up-to-date with relevant research.

Systematic reviews are a team effort and increasingly need a diverse skill set now probably never found in one individual. Working in isolation leaves any single researcher open to accusations of incorporation of bias. Work needs crosschecked and blindly assessed. This can never exclude bias but goes some way to show what efforts have been made to minimise its incorporation and to help make methods explicit. The author has been a member of many teams leading some (paper 3) or being an active co-worker in others. As much as any other form of research, systematic reviewing involves considerable academic rigour and the employment of not only logistical aptitude but also social skills.

Background to paper 3

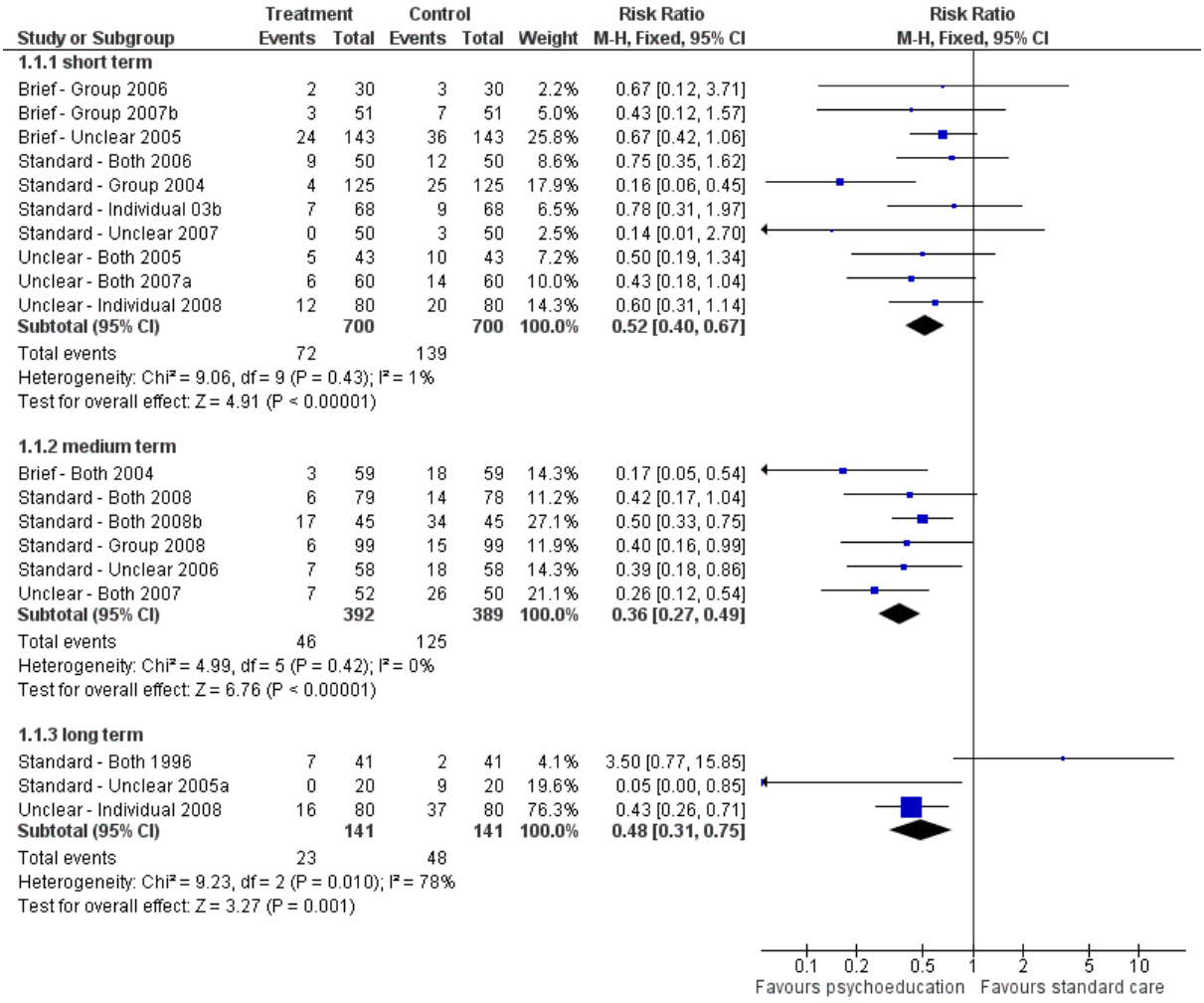
Paper 3 demonstrate the application of systematic review methods to address clinical questions in health conditions, for example, schizophrenia. Pooling clinical studies conducted in different eras, diverse cultural and clinical settings and characteristics is challenging, not least with respect to heterogeneity, but also requires careful consideration of optimal means to represent subgroup differences. Paper 3 is a typical example of such challenge the common but important problem of heterogeneity of psychological intervention. This large review includes a total of 5142 participants from 44 trials conducted between 1988 and 2009. Psychoeducation is a package of care characterised by interaction between information provider and patients. Psychoeducation varies in structure of the therapy and mode of delivery. Providing a working definition of the therapy without ambiguity for reviewers and stakeholders is a major challenge within this review - and for other similar reviews involving packages of care. Through extensive literature review, the author proposed a working definition of the therapy that highlights factors that characterise psychoeducation:

- Factor 1 - Involving interaction between information provider and the patients;
- Factor 2 - Addressing the illness from a multidimensional viewpoint, including familial, social, biological and pharmacological perspectives; and
- Factor 3 - Providing patients with support, information and management strategies - but not behavioural training, such as social skills or life skills training.

This definition paved way for accurate inclusion and exclusion of studies, which not only improved consistency between reviewers, but also led to more accurate application of the research after dissemination. PubMed records this review as having been cited 603 times (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4170907/) (22).

In the 44 trials, psychoeducation was delivered in different modalities, e.g either as individual or group therapy; and durations, e.g. some are short term (up to 12 weeks), others are medium or long term (over 52 weeks); as well as varied length of treatment, e.g. brief (<10 weeks) versus standard (>10 weeks). All of these factors could have a potential impact on the prognosis, and so need to be stratified and corresponding data analysed separately by each prognostic domain. The author also developed a creative labelling system to allow all of the above factors to be represented in a single meta-analysis (see Figure 1 below), which allows heterogeneity between studies and across subgroups to be explored in a single forest plot.

Figure 1. Creative study labelling system in a forest plot



Findings of paper 1 and paper 2 are paramount to the methodological design of paper 3. Informed by this past work, when producing paper 3, the author incorporated Chinese databases for a more comprehensive inclusion of literature, which improves precision and potentially reduces bias of the review findings. Paper 2 directly informed the missing data analysis plan and the threshold for credibility. For any particular outcome with over 50% of data unaccounted for, we did not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we marked such data with (*) to indicate that such a result may well be prone to bias.

Coda

A foundation of evidence-based medicine (EBM) is the notion of using all currently available information to guide patient care and systematic review is a vital part of EBM. Building on the work presented in Chapter 1 and 2, the paper in Chapter 3 is illustrative of increasingly

sophisticated systematic reviewing and data synthesis techniques used in evidence-based health care and policy making. In turn, the systematic review work and the commitment to clarity amidst less than clear data paved the way for the work outlined in Chapter 4.

Reference for paper 3

PAPER 3. **Xia**, J., B. Merinder Lars, and R. Belgamwar Madhvi. Psychoeducation for schizophrenia. Cochrane Database of Systematic Reviews, 2012. DOI: 10.1002/14651858.CD002831.pub2. (PAPER 3. JX as first author).

PAPER 3

Psychoeducation for schizophrenia[3]

Abstract

Background

Schizophrenia can be a severe and chronic illness characterised by lack of insight and poor compliance with treatment. Psychoeducational approaches have been developed to increase patients' knowledge of, and insight into, their illness and its treatment. It is supposed that this increased knowledge and insight will enable people with schizophrenia to cope in a more effective way with their illness, thereby improving prognosis.

Objectives

To assess the effects of psychoeducational interventions compared with standard levels of knowledge provision.

Search methods

We searched the Cochrane Schizophrenia Group Trials Register (February 2010).

We updated this search November 2012 and added 27 new trials to the awaiting assessment section.

Selection criteria

All relevant randomised controlled trials focusing on psychoeducation for schizophrenia and/or related serious mental illnesses involving individuals or groups. We excluded quasi-randomised trials.

Data collection and analysis

At least two review authors extracted data independently from included papers. We contacted authors of trials for additional and missing data. We calculated risk ratios (RR) and 95% confidence intervals (CI) of homogeneous dichotomous data. We used a fixed effect model

[3] A reply to this paper has been published as:
Xia, J., B. Merinder Lars, and R. Belgamwar Madhvi. Psychoeducation for schizophrenia. Cochrane Database of Systematic Reviews, 2012. DOI: 10.1002/14651858.CD002831.pub2.

for heterogeneous dichotomous data. Where possible we also calculated the numbers needed to treat (NNT), as well as weighted means for continuous data.

Main results

This review includes a total of 5142 participants (mostly inpatients) from 44 trials conducted between 1988 and 2009 (median study duration 12 weeks, risk of bias moderate). We found that incidences of non-compliance were lower in the psychoeducation group in the short term (n = 1400, RR 0.52 CI 0.40 to 0.67, NNT 11 CI 9 to 16). This finding holds for the medium and long term. Relapse appeared to be lower in psychoeducation group (n = 1214, RR 0.70 CI 0.61 to 0.81, NNT 9 CI 7 to 14) and this also applied to readmission (n = 206, RR 0.71 CI 0.56 to 0.89, NNT 5 CI 4 to 13). Scale derived data also suggested that psychoeducation promotes better social and global functioning. In the medium term, treating four people with schizophrenia with psychoeducation instead of standard care resulted in one additional person showing a clinical improvement. Evidence suggests that participants receiving psychoeducation are more likely to be satisfied with mental health services (n = 236, RR 0.24 CI 0.12 to 0.50, NNT 5 CI 5 to 8) and have improved quality of life.

Authors' conclusions

Psychoeducation does seem to reduce relapse, readmission and encourage medication compliance, as well as reduce the length of hospital stay in these hospital-based studies of limited quality. The true size of effect is likely to be less than demonstrated in this review, nevertheless, some sort of psychoeducation could be clinically effective and potentially cost beneficial. It is not difficult to justify better, more applicable, research in this area aimed at fully investigating the effects of this promising approach.

Note: the 27 new citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.

Psychoeducation for schizophrenia

Review information

Review number: 1055

Authors

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Citation example: Xia J, Merinder LB, Belgamwar MR. Psychoeducation for schizophrenia. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD002831. DOI: 10.1002/14651858.CD002831.pub2.

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0.61 to 0.81, NNT 9 CI 7 to 14) and this also applied to readmission (n = 206, RR 0.71 CI 0.56 to 0.89, NNT 5 CI 4 to 13). Scale derived data also suggested that psychoeducation promotes better social and global functioning. In the medium term, treating four people with schizophrenia with psychoeducation instead of standard care resulted in one additional person showing a clinical improvement. Evidence suggests that participants receiving psychoeducation are more likely to be satisfied with mental health services (n = 236, RR 0.24 CI 0.12 to 0.50, NNT 5 CI 5 to 8) and have improved quality of life.

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Note: the 27 new citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.

Plain language summary

Psychoeducation added to standard treatment for schizophrenia reduces relapse.

The purpose of patient education/teaching (or psychoeducation) is to increase patients' knowledge and understanding of their illness and treatment. It is supposed that increased knowledge enables people with schizophrenia to cope more effectively with their illness. Psychoeducational interventions involve interaction between the information provider and the mentally ill person. This review compares the efficacy of psychoeducation added to standard care as a means of helping severely mentally ill people with that of standard care alone. The evidence shows a significant reduction of relapse or readmission rates. There seems to be some suggestion that psychoeducation may improve compliance with medication, but the extent of improvement remains unclear. The findings show a possibility that psychoeducation has a positive effect on a person's wellbeing and promotes better social function. In the medium term, treating four people with schizophrenia with psychoeducation instead of standard care resulted in one additional person showing a clinical improvement. The scarcity of studies made the comparison between the efficacy of different formats (programmes of 10 sessions or less or 11 or more, individual or group sessions) weak.

Background

Description of the condition

Schizophrenia is a chronic, severe and disabling illness which affects approximately 1% of the population. It is a worldwide illness that crosses all cultures and socioeconomic groups (1). The severe and long-lasting symptoms of schizophrenia cause considerable disability.

Description of the intervention

Psychoeducation may be defined as the education of a person with psychiatric disorder in subject areas that serve the goals of treatment and rehabilitation. The terms 'patient education', 'patient teaching', and 'patient instruction' have also been used for this process. All imply that there is a focus on knowledge. The purpose of patient education is to enable the patient to engage in behaviour change. Compliance with treatment for seriously or persistently mentally ill people is of great concern and is often a focus of patient education. Many people with severe mental illness are frequently and repeatedly hospitalised due to poor compliance with treatment. Many patients feel stigmatised by their illness and may deny its existence, which ultimately increases non-compliance. This issue is even more of a problem when people are living in the community, and is often related to adverse effects of medication as well as a lack of adequate knowledge about medication (2). Therefore, the goal of patient education may be to try to prevent hospitalisation or to manage the illness or condition to help the patient attain her/his maximum degree of health. The psychiatric and mental health nursing practice standards include patient teaching and, according to these standards, client adherence to treatment regimens increases when health education is an integral part of the client's care (3).

How the intervention might work

Education is a gradual process by which a person gains knowledge and understanding through learning. Learning, however, involves more than knowledge and, according to (4), it can involve cognitive, affective and psychomotor processes. Learning implies changes in behaviour, skill or attitude (5). Patient education can take a variety of forms depending upon the abilities and interest of the patient and family. For example, the education may take place in small groups or on a one-to-one basis; it may involve the use of videotapes or pamphlets or a combination of these.

Why it is important to do this review

Relapse is a major challenge in the rehabilitation of people with schizophrenia (6), and high relapse rates are often related to non-compliance with treatment (7). Therefore, teaching patients and families with a view to improving treatment compliance is a major goal in psychiatric nursing (2). Illness management programmes such as psychoeducation have traditionally provided information for adhering to treatment and minimizing relapse. Extensive research has been conducted around the effectiveness of such interventions. While many prior studies indicated positive effects of psychoeducation on reducing symptoms and minimising relapse (8, 9), others showed that the intervention increased patients' knowledge about mental illness but didn't affect other outcomes or their behaviour (10, 11). The previous version of this review was also inconclusive, as most of the included studies produced equivocal effects or skewed data. Many new studies have been conducted since the previous review, and therefore it is important that we re-evaluate the effectiveness of psychoeducation with the presence of new evidence. This review represents an important and considerable update of the previous version of this work.

Objectives

The primary objective was to assess the efficacy of psychoeducational interventions as means of helping severely mentally ill people when added to 'standard' care, compared to the efficacy of standard care alone.

The secondary objective was to investigate whether there is evidence that a particular kind (individual/ family/group) or duration (brief/other) of psychoeducational intervention is superior to others.

Methods

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials (RCTs). We excluded quasi-randomised trials, using, for example, alternation as the method of randomisation.

Types of participants

People suffering from severe non-affective mental disorders such as schizophrenia and schizophreniform, schizoaffective or schizotypal disorders, and including those with multiple diagnoses.

Types of interventions

1. We included all didactic interventions of psychoeducation or patient teaching involving individuals or groups. We have defined psychoeducational interventions as any group or individual programme involving interaction between information provider and patient. These programmes address the illness from a multidimensional viewpoint, including familial, social, biological and pharmacological perspectives. Patients are provided with support, information and management strategies. We considered programmes of 10 sessions or less as 'brief', and of 11 or more as 'standard' for the purposes of this review. We excluded interventions including elements of behavioural training, such as social skills or life skills training, as well as education performed by patient peers, from this review. We also excluded staff education studies.

2. Standard care was defined as the normal level of psychiatric care provided in the area where the trial was carried out.

Types of outcome measures

For the first version of the review (12) we did not pre-specify specific time periods into which to cluster outcomes. For this update we asked an editor of the Cochrane Schizophrenia Group, who was not familiar with the data to help us divide the data by time. For this update we grouped outcomes into the short term (up to 12 weeks), medium term (13-52 weeks) and long term (over 52 weeks).

Primary outcomes

1. Compliance
1.1 Compliance with medication
1.2 Compliance with follow-up

2. Relapse

Secondary outcomes

1. Knowledge
1.1 Improvement of understanding of his/her illness and need for treatment recipient/family member
1.2 Level of knowledge about expected and undesired effects of medication recipient/family member

2. Behaviour

2.1 Level of psychiatric symptoms

2.2 Symptom control skills

2.3 Problem-solving skills

2.4 Social skills

3. Social functioning*

3.1 No clinically important change in social functioning

3.2 No change in social functioning

3.3 Average endpoint in social functioning

3.4 Average change in social functioning

4. Global functioning*

4.1 No clinically important change in general functioning

4.2 No change in general functioning

4.3 Average endpoint in general functioning

4.4 Average change in general functioning

5. Service utilisation

5.1 Use of outpatient treatment

5.2 Length of hospitalisation

6. Global state*

6.1 No overall improvement

6.2 Use of additional medication

6.3 Average endpoint score

6.4 Average change score

6.5 Average dose of drug

7. Mental state*

7.1 No clinically important change in general mental state

7.2 No change in general mental state

7.3 Average endpoint general mental state score

7.4 Average change in general mental state scores

8. Expressed emotion*

8.1 No clinically important change in expressed emotion

8.2 No change in expressed emotion

8.3 Average endpoint general expressed emotion

8.4 Average change in general expressed emotion

9. Quality of life*

9.1 No clinically important change in quality of life

9.2 Not any change in quality of life

9.3 Average endpoint quality of life score

9.4 Average change in quality of life score

9.5 No clinically important change in specific aspects of quality of life

9.6 No change in specific aspects of quality of life

9.7 Average endpoint specific aspects of quality of life

9.8 Average change in specific aspects of quality of life

10. Satisfaction with care*

10.1 No clinically important change in satisfaction

10.2 No change in satisfaction

10.3 Average endpoint in satisfaction

10.4 Average change in satisfaction

11. Adverse effects/event*

11.1 Clinically important general adverse effects

11.2 Any general adverse effects

11.3 Any serious, specific adverse effects

11.4 Average endpoint general adverse effect score

11.5 Average change in general adverse effect scores

11.6 No clinically important change in specific adverse effects

11.7 No change in specific adverse effects

11.8 Average endpoint specific adverse effects

11.9 Average change in specific adverse effects

12. Health economic outcomes

12.1 Treatment costs

* Additional outcomes added for 2010 update (please see Differences between protocol and review and Appendix 1).

Search methods for identification of studies

We performed both the electronic search and the hand search. We inspected the references of all identified studies to identify additional studies.

Electronic searches

1. Update 2011 - Cochrane Schizophrenia Group Trials Register (May 2011)
We searched the register using the phrase:

[*Psychoeducat* in interventions of STUDY]

This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module).

2. Previous searches
Please refer to Appendix 2; Appendix 3; Appendix 4 for detail of previous searches.

3. The Trials Search Co-ordinator, Samantha Roberts, searched the Cochrane Schizophrenia Group Trials Register register (November 2012) using the phrase:

[*Psychoeducat* in interventions of STUDY or title of REFERENCE]

The Cochrane Schizophrenia Group's Trials Register is compiled by systematic searches of major databases, hand searches of relevant journals and conference proceedings (see Group Module). Incoming trials are assigned to relevant existing or new review titles.

Searching other resources

1. Reference searching
We inspected reference lists of identified studies for more trials.

2. Personal contact
We contacted authors of relevant studies to enquire about other sources of relevant information.

Data collection and analysis

Selection of studies

Reviewer JX inspected all abstracts of studies identified as above and identified potentially relevant reports. In addition, to ensure reliability, LBM and MRB inspected a random sample of these abstracts, comprising 10% of the total. Where disagreement occurred we resolved

this by discussion, or where there was still doubt, acquired the full article for further inspection. We also acquired the full articles of relevant reports for reassessment and carefully inspected for a final decision on inclusion (see Criteria for considering studies for this review). Once we obtained the full articles, JX and LBM in turn inspected all full reports and independently decided whether they met inclusion criteria. JX and LBM were not blinded to the names of the authors, institutions, or journal of publication. Where difficulties or disputes arose, we asked author MRB for help and if it was impossible to decide, added these studies to those awaiting assessment and contacted the authors of the papers for clarification.

Data extraction and management

1. Extraction

JX extracted data from all included studies. In addition, to ensure reliability, LBM and MRB independently extracted data from a random sample of these studies, comprising 10% of the total. Again, we discussed any disagreement, documented decisions and, if necessary, contacted authors of studies for clarification. With remaining problems, LBM helped clarify issues, and we documented those final decisions. We extracted data presented only in graphs and figures whenever possible, but included these only if two authors independently had the same result. We attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. Where possible, we extracted data relevant to each component centre of multi-centre studies separately.

2. Management

2.1 Forms

We extracted data onto standard, simple forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:

a. the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (13); and
b. the measuring instrument was not written or modified by one of the trialists for that particular trial; and
c. the measuring instrument is either i. a self-report or ii. completed by an independent rater or relative (not the therapist).

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint) which can be difficult in unstable and difficult to measure conditions such as schizophrenia. We decided to primarily use endpoint data and only use change data if the former were not available. We combined endpoint and change data in the analysis as we used mean differences rather than standardised mean differences throughout (14) (chapter 9.4.5.2).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aim to apply the following standards to all data before inclusion: a) standard deviations and means are reported in the paper or obtainable from the authors; b) when a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (15); c) if a scale started from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above was modified to take the scale starting point into account. In these cases skew is present if 2SD > (S-S min), where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied. When continuous data are presented on a scale which includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We entered skewed data from studies of fewer than 200 participants in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at means if the sample size is large and were entered into syntheses.

2.5 Common measure

To facilitate comparison between trials, we intended to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we made efforts to convert outcome measures to dichotomous data. This could be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. We generally assumed that if there had been a 50% reduction in a scale-derived score such as the Brief Psychiatric

Rating Scale (16) or the Positive and Negative Syndrome Scale (PANSS, (17)), we could consider this as a clinically significant response (18, 19). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for psychoeducation.

2.8 Summary of findings table

We anticipated including the following short- or medium-term outcomes in a summary of findings table. (JX was not biased by being familiar with the data.)

1. Compliance with medication
2. Loss to follow-up
3. Relapse
4. Satisfaction with care
4.1 Not improved to an important extent
5. Adverse effects
5.1 Specific adverse event
6. Quality of life
6.1 Not improved to an important extent
7. Economic data

Assessment of risk of bias in included studies

JX and LMB worked independently to assess risk of bias by using criteria described in the Cochrane Collaboration Handbook (14) to assess trial quality. This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagree, the final rating was made by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials were provided, authors of the studies were contacted in order to obtain further information. Non-concurrence in quality assessment was reported, but if disputes arose as to which category a trial was to be allocated, again, resolution were made by discussion.

The level of risk of bias will be noted in both the text of the review and in the Summary of findings table 1.

Measures of treatment effect

1. Binary data

For binary outcomes we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (20) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (21). For statistically significant results we had planned to calculate the number needed to treat to provide benefit/to induce harm statistic (NNTB/H), and its 95% confidence interval (CI) using Visual Rx (http://www.nntonline.net/) taking account of the event rate in the control group. This, however, was superseded by Summary of findings table 1 and the calculations therein.

2. Continuous data

For continuous outcomes we estimated mean difference (MD) between groups. We preferred not to calculate effect size measures (standardised mean difference (SMD)). However, had scales of very considerable similarity been used, we would have presumed there was a small difference in measurement, and we would have calculated effect size and transformed the effect back to the units of one or more of the specific instruments. We made a post-hoc decision to pool the GAF scale (22) and its virtually similar earlier version, the GAS scale (23), using WMD statistics.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (24) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (25, 26).

Where clustering is not accounted for in primary studies, we presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation coefficients for their clustered data and to adjust for this by using accepted methods (26). Where clustering had been incorporated into the analysis of primary studies,

we present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC) (Design effect = 1+(m-1) * ICC) (27). If the ICC was not reported we assumed it to be 0.1 (28).

If cluster studies had been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (29). As both effects are very likely in severe mental illness, we only used data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, we presented the additional treatment arms in comparisons. Where the additional treatment arms were not relevant, we did not reproduced these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up data must lose credibility (30). For any particular outcome should more than 50% of data be unaccounted for, we did not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we marked such data with (*) to indicate that such a result may well be prone to bias.

2. Binary

In the case where attrition for a binary outcome is between 0 and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis

(an intention to treat analysis). We assumed those leaving the study early to have the same rates of negative outcome as those who completed, with the exception of the outcome of death. We undertook a sensitivity analysis testing how prone the primary outcomes were to change when 'completed' data only were compared to the intention to treat analysis using the above assumption.

3. Continuous

3.1 Attrition

In the case where attrition for a continuous outcome is between 0 and 50% and completer-only data were reported, we have reproduced these.

3.2 Standard deviations

We have first tried to obtain the missing values from the authors. If not, where there are missing measures of variance for continuous data but an exact standard error and confidence interval are available for group means, either P value or T value are available for differences in mean, we will, for the update of this review, calculate them according to the rules described in the Cochrane *Handbook* (14) but for later versions of this review: When only the standard error (SE) is reported, standard deviations (SDs) are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the Cochrane *Handbook* (14) present detailed formula for estimating SDs from P values, T or F values, confidence intervals, ranges or other statistics. If these formulas do not apply, we will calculate the SDs according to a validated imputation method which is based on the SDs of the other included studies (31) in later versions of this review. Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We plan, nevertheless, to examine the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Last observation carried forward

We anticipated that in some studies the method of last observation carried forward (LOCF) would be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results. Therefore, where LOCF data has been used in the trial, if less than 50% of the data had been assumed, we reproduced these data and indicated that they are the product of LOCF assumptions.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying situations or people which we had not predicted would arise. When such situations or participant groups arose, we have fully discussed these.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods which we had not predicted would arise. Should such methodological outliers arise we will fully discuss these.

3. Statistical heterogeneity

3.1 Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2statistic

We investigated heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (32). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). We interpreted I^2 estimate greater than or equal to 50% accompanied by a statistically significant Chi^2 statistic as evidence of substantial levels of heterogeneity (Section 9.5.2 - (14)). When we found substantial levels of heterogeneity in the primary outcome, we explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (33). These are described in Section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (14). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small study effects. We did not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies

were of similar sizes. In other cases, where funnel plots were possible, we sought statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. Therefore, we chose the fixed-effect model for all analyses. The reader is, however, able to choose to inspect the data using the random-effects model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We are interested in whether a brief form of psychoeducation may have as many effects as the standard and more protracted form. For the purposes of this review we define 'brief' as up to 10 sessions and 'standard' as 11 sessions or more. In addition, we are interested whether a group approach would have similar effects to individual psychoeducation. We proposed to undertake comparisons only for primary outcomes to minimise the risk of multiple comparisons.

2. Investigation of heterogeneity

If inconsistency was high, we have reported this. First we investigated whether data had been entered correctly. Second, if data had been correct, we visually inspected the graph and successively removed studies outside of the company of the rest to see if heterogeneity was restored. Should this occur with no more than 10% of the data being excluded, we have presented data. If not, we have not pooled data and discussed issues.

Should unanticipated clinical or methodological heterogeneity be obvious we simply stated hypotheses regarding these for future reviews or versions of this review. We pre-specify no characteristics of studies that may be associated with heterogeneity except quality of trial method. If no clear association could be shown by sorting studies by quality of methods, we have performed a random-effects meta-analysis. Should another characteristic of the studies

be highlighted by the investigation of heterogeneity, perhaps some clinical heterogeneity not hitherto predicted but plausible causes of heterogeneity, we have discussed these post hoc reasons, and analyse and present the data. However, should the heterogeneity be substantially unaffected by use of random-effects meta-analysis and no other reasons for the heterogeneity be clear, we have presented the final data without a meta-analysis.

Sensitivity analysis

1. Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation. For the primary outcomes we included these studies and if there was no substantive difference when we added the implied randomised studies to those with better description of randomisation, then we employed all data from these studies.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see Dealing with missing data), we compared the findings of the primary outcomes when we used our assumption compared with completer data only. If there was a substantial difference, we reported results and discuss them but continue to employ our assumption.

Where assumptions had to be made regarding missing SDs data (see Dealing with missing data), we compared the findings on primary outcomes when we used our assumption compared with complete data only. We undertook a sensitivity analysis testing how prone results were to change when 'complete' data only were compared to the imputed data using the above assumption. If there was a substantial difference, we have reported results and discussed them but continue to employ our assumption.

3. Chinese studies

Concerns were raised about the quality of some of the Chinese trials (34, 35). For this reason, we performed sensitivity analysis for all primary outcomes where Chinese trials were included.

Summary of findings and assessment of the certainty of the evidence

Results

Description of studies

For more detailed description of each studies, please refer to the Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

1. 2010 update

For the 2010 update we found 210 citations of which we ordered 99 for close inspection. Of these we have included 23, for a total of 44 studies now included in this review.

For results of any previous search, please refer to Appendix 2 and Appendix 3.

Included studies

See Characteristics of included studies for descriptions of each study. We have chosen to use a rather unconventional means of tagging studies. This is usually done by using the key author's name accompanied by the date of the main publication, for example 'Smith 2005'. For this review we thought that using a different and more informative convention would be valuable. We have decided to include some details of the experiential intervention in the study tag trying to succinctly describe length of intervention where reported and whether the education was given one-to-one or by group, and finally the date of study. We are aware that this lengthens the tags - but we think it makes them informative and clusters them in the graphs for easier understanding.

1. Methods

All included studies were randomised controlled trials. Only 11 of the included studies described randomisation method. Two studies were randomised by independent institutions (36-45); five studies used random number table (46-49); one study drew lots (50); one study used toss a coin to randomise (51); one study used block randomisation (8, 52-57) and one study used computer generated cards (58, 59) this is also the only study that described allocation concealment (concealed with sealed envelope). Blinding was generally not described. One study (48) was double blind. Four studies were single (assessor) blind (52-62). One trial did not use blinding (46). Four other studies had some of their outcomes assessed single blind, but not for all outcomes (11, 36-45, 63-70). Blinding method was not stated in the other 35 included studies.

2. Study duration

Study duration varied from one session (71, 72) to five years (73) (but intervention frequency

was not stated in this particular study). (74-78) and (58, 59) are both of 18 months' duration but the median study duration of all other studies is around 12 weeks.

3. Settings

Most studies were conducted with inpatients, except four (60) (8, 52-57, 73, 79). Most of the included trials were carried out in China, while one trial was conducted in France, three in the USA, one in Canada, two in Germany, three in the UK, one in Demark and one in Malaysia.

4. Participants

A total of 5142 participants are included from 44 trials conducted from 1988 and 2009. Participants are patients with schizophrenia or schizoaffective disorder diagnosed using operationalised criteria (DSM, ICD, CCMD). The majority of the studies included patients between the ages of 18 and 60 years, except four that did not describe the age range (80-83). Four studies included only men (49, 84-86) and one study included female participants only (61). Four other studies did not describe gender and all other remaining studies involved both male and female participants. Size of the included studies range from 20 (70) participants to 286 (87). The three other studies with over 200 participants are (52-57, 62, 88-90).

5. Interventions

Thirteen trials used brief psychoeducation, 22 standard psychoeducation and nine did not state whether brief or standard intervention was used (tagged in this review as 'unclear'). Of the 44 included studies, 17 used group therapy, six individual therapy, 13 employed a mixture of both group and individual therapy and eight other studies did not state the type of therapy used.

6. Outcomes

A variety of scales were used to assess clinical response and adverse events. We were, however, unable to use some of the scale derived data due to poor reporting. Details of scales that provided usable data are shown below.

6.1 Compliance

6.1.1 Schedule for Assessment of Insight - SAI (91)

The SAI rates three dimensions of insight: treatment adherence, recognition of illness and symptom re-labelling. These three sub-scales provide a summed total of insight score. High score indicates better insight. One study reported data from this scale.

6.2 Knowledge

6.2.1 Insight Treatment Attitude Questionnaire - ITAQ (92)

The ITAQ is a 11-item semi-structured interview that measures awareness of illness and attitude to medication and services, as well as follow-up evaluation. Its scores range from 0 to 22, with high score indicating better insight. Four studies reported data from this scale.

6.2.2 Knowledge About Schizophrenia Questionnaire - KASQ (93)

This is a 23-item multiple-choice questionnaire, which covers the illness-related topics. The maximum score is 23, indicating a high level of knowledge about the illness. One study reported data from this scale.

6.2.3 Krankheitskonzeptskala - KK (94)

KK is a self-rating instrument which consists of 29 Likert-scale items. People are asked to express their agreement or disagreement with each item on a five-point scale. The scale describes seven dimensions of illness-related attitudes: confidence in medication, confidence in physician, negative expectations towards medication, attribution of illness to chance, susceptibility to illness and to relapse, attribution of guilt and fear to side effects of medication. The higher the score, the higher the expression of the respective item. One study reported data from this scale.

6.2.4 Knowledge Questionnaire - KQ (95)

The maximum score of this questionnaire is 70. High score indicates better outcome. One study reported data from this scale.

6.2.5 Recovery Attitudes Questionnaire - RAQ (96)

This is a seven-item self-report scale that assesses attitudes about recovery. Score ranges from 7 to 35, with lower scores indicating more appropriate attitudes. One study reported data from this scale.

6.2.6 Schizophrenia Knowledge Questionnaire - SKQ (97)

High score indicates a better outcome. One study reported data from this scale.

6.2.7 The Scale to Assess Unawareness of Mental Disorder - SAUMD (98)

There is a total of 20 questions in SAUMD. Score range 1 to 5 points, high score prompted a poor understanding and attribution. Two studies reported data from this scale.

6.2.8 Understanding of medication questionnaire - UMQ (46)

UMQ measures knowledge of antipsychotic treatment. Fourteen stem questions generate

eight sub-scale knowledge scores, relating to factual information, treatment practice, treatment rationale, effects of stopping treatment, side effects, precautions, tardive dyskinesia and risk/benefit evaluation. The UMQ is an extended version of scales measuring knowledge of illness and treatment and knowledge of tardive dyskinesia. Total knowledge score is 35. Knowledge scoring 0 = no understanding and 35 = full understanding. One study reported data from this scale.

6.3 Behaviour

6.3.1 Nurse Observation Scale for Inpatient Evaluation-30 - NOSIE-30 (99)
An 80-item scale with items rated on a five-point scale from zero (not present) to four (always present). Ratings are based on behaviour over the previous three days. The seven headings are social competence, social interest, personal neatness, cooperation, irritability, manifest psychosis and psychotic depression. The total score ranges from 0 to 320 with high scores indicating a poor outcome. Three studies reported data from this scale.

6.4 Social functioning*

6.4.1 Inpatient Psychiatric Rehabilitation Outcome Scale - IPROS (100)
High score indicates poor outcome. One study reported data from this scale.

6.4.2 Morningside Rehabilitation Status Scale - MRSS (101)
High score indicates worse outcome. One study reported data from this scale.

6.4.3 Zung Self-Rating Anxiety Scale - SAS (102)
This scale is self-administered and has 20 questions. Each question is scored on a scale of 1-4. High score indicates poor outcome. Three studies reported data from this scale.

6.4.4 Social Adjustment Scale II - SAS II (103)
SAS is an interview-based operationalised instrument with two versions; patient version and family version. SAS has 89 items covering widely social, interpersonal, and household aspects. High score indicates poor outcome. One study reported data from this scale.

6.4.5 Zung Self-Rating Depression Scale - SDS (104)
High score indicates poor outcome. Three studies reported data from this scale.

6.4.6 Social Disability Screening Schedule - SDSS (105)
High score indicates poor outcome. Two studies reported data from this scale.

6.4.7 Social functioning schedule - SFS (106)
Lower scores indicate improved behaviour/function. One study reported data from this scale.

6.4.8 Social Networks Schedule - SNS (107)

Social Networks Schedule modified consists of mean number of total social contacts: daily, weekly and monthly, mean number of different type of contacts with relatives, confidants, and friends. Low score indicates better outcome. One study reported data from this scale.

6.5 Global functioning*

6.5.1 Global Assessment of Functioning - GAF (22)

The scale is a 90-point rating scale that assesses psychological, social and occupational functioning. GAF is included in DSMIII-R as axis V, but in spite of this there is little research on the reliability and validity of the instrument. A few reliability and validity assessments have been made, indicating that an acceptable interrater reliability can be attained and that modest validity in relation to a disability measure has been demonstrated. High score indicates better outcome.

6.5.2 Global Assessment Scale - GAS (23)

GAS is a 0-100 point rating scale, a global measure of overall functioning and symptomatology. High scores indicate better functioning.

6.5.3 Specific Level of Functioning Scale - SLOF (108)

A Likert-like scale with high score indicating better outcome. One study reported data from this scale.

6.6 Global state*

6.6.1 Clinical Global Impression - CGI (109)

The CGI is a three-item scale commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement. It employs a seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery. One study reported data from this scale.

6.7 Mental state*

6.7.1 Brief Psychiatric Rating Scale - BPRS (16)

The BPRS is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms. The original scale has 16 items, but a revised 18-item scale is commonly used. Scores can range from 0 to 126. Each item is rated on a seven-point scale varying from 'not present' to 'extremely severe', with high scores indicating more severe symptoms. Seventeen studies reported data from this scale.

6.7.2 General Well-being Schedule - GWB (110)

This is an 18-item, reliable measurement scale for psychological well-being. High scores indicate better outcome. One study reported data from this scale.

6.7.3 Positive and Negative Syndrome Scale - PANSS (17)

This is a 30-item scale, each of which can be defined on a seven-point scoring system from absent to extreme. It has three sub-scales for measuring the severity of general psychopathology, positive symptoms (PANSS-P), and negative symptoms (PANSS-N). A low score indicates lesser severity. Two studies reported data from this scale.

6.7.4 Rosenberg Self-esteem Scale - SES (111)

The scale is a 10-item Likert scale with items answered on a four-point scale from strongly agree to strongly disagree. High scores indicate better outcome. One study reported data from this scale.

6.8 Expressed emotion*

6.8.1 Family Questionnaire - FQ (112)

The FQ is based on the Camberwell Family Interview and is a 20-item questionnaire developed to enable a less time consuming evaluation of expressed emotion in relatives. It covers the two dimensions of criticism and emotional over involvement and the items are scored on a four-point scale. The questionnaire is reliability tested and validated in the German language (Feinstein1994 personal communication).

6.9 Quality of life*

6.9.1 Family Assessment Device - FAD (113)

High scores indicate unhealthy family functioning. Two studies reported data from this scale.

6.9.2 Family Burden Interview Schedule - FBIS (114)

High scores indicate worse outcome. Two studies reported data from this scale.

6.9.3 Quality of Life - QOL (115)

The scale consists of four factors: interpersonal relations and social network, instrumental role functioning, intrapsychic foundations and common objects and activities. The scale consists of 21 items. Each item is rated on a seven-point scale 0-6. Range is 0-126. The scale is rated from a semi-structured interview providing information on symptoms and functioning during the preceding four weeks. High score reflects normal or unimpaired functioning.

6.9.4 General Quality of Life Inventory -74 - GQOLI-74 (116)

A 74-item quality of life assessment scale. It contains four sub-scales that assess physical functioning, psychological functioning, social functioning, and standard of living. High scores indicate better quality of life. One study reported data from this scale.

6.9.5 Psychological General Well-being Scale - PGWB (117)

High scores indicate better well-being. One study reported data from this scale.

6.10 Satisfaction with care*

6.10.1 Verona Service Satisfaction Scale - VSSS (118)

The scale consists of 54 items in versions for patients and relatives. It is a questionnaire that covers seven dimensions of satisfaction with service: overall satisfaction, professionals' skills and behaviour, information, access, efficacy, types of intervention and relatives involvement. (119) The VSSS satisfaction ratings
are given on a five-point Likert scale. The instrument has been validated in community psychiatric samples (119, 120). One study reported data from this scale.

Outcomes with '*' are extra outcomes added in this 2010 update review.

6.11 Missing outcomes

Most trials reported on primary outcomes that we were interested in, i.e. compliance and relapse. However, there were few data on health economic outcomes; only one study (58, 59) reported some skewed data on hospital charges.

Excluded studies

We excluded 68 studies from the review. Many had to be excluded because they were not randomised controlled trials. We excluded 12 studies because there were no usable data reported, usually due to the lack of mean or standard deviation. (121) had to be excluded because the outcome data in this study are identical (to the decimal points) to another included trial (122). We suspect these two trials are the same study but are not sure and therefore treated (121) as separate but we felt we could not prove the veracity of the data.

Studies awaiting assessment

Two studies await assessment (123, 124). In both cases we have not been able to locate the full text of the studies and were unable to make a decision regarding inclusion without the full report.

From the 2012 update search 27 studies were added to this section and 29 studies are now awaiting assessment.

Ongoing studies

(125) is an ongoing study, which is expected to complete in August 2010.

Risk of bias in included studies

Our overall impression of risk of bias in the included studies is represented in Figure 1. The suggestion is that there is, at the very least, a moderate risk of bias and therefore a risk of overestimating any positive effects of psychoeducation.

Allocation (selection bias)

All 44 included studies were stated to be randomised, but only seven provided descriptions of the methods used to generate the sequence (47-50, 52-59, 62, 126). Only (58, 59) described method of concealment. Most studies, therefore, are classified as of 'unclear' quality with a moderate risk of selection bias and of overestimate of positive effect.

Blinding (performance bias and detection bias)

Seven studies were stated to have used single (assessor) blinding (47, 52-59, 62-67, 70, 127). One trial was double blind (48) and one open label (46). Of those studies that were blinded in some way, most did not describe the blinding methods used, and none tested the success of blinding for participants or assessors. The remaining studies did not report whether blinding had been used. We therefore had to rate the risk of observer bias as (at best) 'unclear'. This gathers further potential for overestimate of positive effects and underestimate of negative ones.

Incomplete outcome data (attrition bias)

Most studies used Intention-to-treat (ITT) method of analysis, except for eight which did not include any data from those who left early (47-50, 87, 126, 128, 129).

Selective reporting (reporting bias)

We did not have any protocols for the included studies. Most studies included in this version of the review seemed to report all outcomes measured, except for four. (83) measured PANSS and ITAQ scores, but did not report numerical data. (130) measured SSQ-6 and SES score and, again, did not report. (73) and (49) collected data on BRRS, SOSS and MRSS, but failed to report these data in the report.

Other potential sources of bias

There were no other obvious potential sources of bias. We are aware that research in China has shown that trials many from China may not be of high quality (34). This is a significant issue for this review, in which 31 out of 44 trials are certainly from China. It was problematic to illustrate this in Figure 1 but, until quality control improves in Chinese trials, many of the results from these studies have to be treated with caution.

Effects of interventions

1. Comparison 1. Any form of psychoeducation vs standard care

1.1 Compliance (primary outcomes)

1.1.1 Compliance: 1a. With medication - non-compliance

(Analysis 1.1)

We included 10 short-term studies and found incidences of non-compliance were lower in the psychoeducation group (n = 1400, RR 0.52 CI 0.40 to 0.67, NNT 11 CI 9 to 16) compared with standard care. Medium-term (6 RCTs, n = 781, RR 0.36 CI 0.27 to 0.49, NNT 5 CI 5 to 7) and long-term data (3 RCTs, n = 282) also favoured the psychoeducation group, but long-term data were heterogeneous (RR 0.48 CI 0.31 to 0.75, NNT 6 CI 5 to 12, I^2 = 78%). Also see Figure 2.

1.1.2 Compliance: 1b. With medication-partial compliance

(Analysis 1.2)

Overall, partial compliance data favours the psychoeducation group (n = 590, RR 0.53 CI 0.37 to 0.76, NNT 6 CI 5 to 12). However, medium-term data were not statistically significant (RR 0.57 CI 0.26 to 1.26).

1.1.3 Compliance: 1c. With medication - continuous outcomes - skewed data

(Analysis 1.3)

(46) did not demonstrate a significant advantage in compliance for the intervention groups with one or three sessions of education, and presented skewed data at one month on the compliance sub-scale of SAI.

1.1.4 Compliance: 2a. With follow up - loss to follow-up for any reason

(Analysis 1.4)

We found no significant difference between psychoeducation and standard care groups in

terms of loss to follow-up in general. Medium-term (RR 1.0 CI 0.79 to 1.26) and long-term results are equivocal (two years RR 0.83 CI 0.62 to 1.10; five years RR 0.77 CI 0.48 to 1.23).

1.1.5 Compliance: 2b. With follow up - received intervention but left the study early

(Analysis 1.5)

Outcome data show an equivocal effect between two groups. No significant difference was found between group in the short term (RR 3.04 CI 0.36 to 25.67), medium term (RR 0.56 CI 0.29 to 1.10) or long term (RR 0.63 CI 0.38 to 1.04).

1.1.6 Compliance: 2c. With follow up - allocated but never accepted treatment

(Analysis 1.6)

Compared with standard care, more people in the psychoeducation group allocated to the treatment but never accepted it (n = 213, RR 12.27 CI 2.58 to 58.33, NNT 9 CI 64 to 2).

1.2 Relapse (primary outcomes)

1.2.1 Relapse: 1. Relapse for any reason

(Analysis 1.7)

Medium-term relapse outcome included data from 11 RCTs and results favour the psychoeducation group (n = 1214, RR 0.70 CI 0.61 to 0.81, NNT 9 CI 7 to 14). Long-term data up to five years (RR 0.73 CI 0.62 to 0.85, NNT 8 CI 6 to 14, exclusive of five years) and at seven years (RR 0.62 CI 0.42 0.92, NNT 3 CI 2 to 15) also favour the psychoeducation group. The five year follow-up result appears to favour the psychoeducation group too, but wasn't statistically significant (RR 0.89 CI 0.73 to 1.08).

1.2.2 Relapse: 2. Relapse with readmission

(Analysis 1.8)

Psychoeducation group had better long-term outcome data on relapse with readmission (n = 206, RR 0.71 CI 0.56 to 0.89, NNT 5 CI 4 to 13). Medium-term data appear to favour the psychoeducation group, but was not statistically significant (n = 206, RR 0.77 CI 0.56 to 1.07).

1.3 Knowledge

1.3.1 Knowledge: 1a. Average endpoint scale scores on various knowledge scales

KQ data favour standard care group in both the short (WMD -12.00 CI -17.67 to -6.33) and long term (WMD -8.00 CI -14.64 to -1.36). Both short-term (WMD 0.20 CI -2.12 to 2.52)

and medium-term (WMD 1.60 CI -0.84 to 4.04) KASQ scores showed an equivocal effect between two groups. ITAQ scores favour the psychoeducation group in both the short (WMD 5.53 CI 4.56 to 6.49) and medium term (WMD 4.83 CI 1.51 to 8.15). Short-term SKQ score favours standard care group (WMD -16.26 CI -22.72 to -9.80).

1.3.2 Knowledge: 1b. Average change (UMQ, high = favourable, data skewed)

Brief intervention: in the brief individual intervention group, (46) showed knowledge change at one month follow-up in favour of the single session intervention as well as the three sessions' intervention, but data were skewed.

1.3.3 Knowledge: 2. Average endpoint scores on various insight scales

Neither short-term SAUMD data (WMD -0.63 CI -1.86 to 0.61) nor medium-term RAQ data (WMD 1.80 CI -0.85 to 4.45) showed any significant differences between groups. These outcome data are also highly heterogeneous (I^2 = 91% and 86% respectively).

1.3.4 Knowledge: 3. Average endpoint score on illness related attitudes 4 months (KK, high = high expressed)

Results favoured the psychoeducation group in terms of 'confidence in physician' (MD -1.40 CI -2.73 to -0.07). No significant results were found between groups with any other sub-scales.

1.3.5 Knowledge: 4. Level of knowledge did not improve

More people in the standard care did not have improved knowledge level compared with psychoeducation group (RR 0.13 CI 0.06 to 0.28, NNT 3 CI 3 to 4).

1.4 Behaviour

1.4.1 Behaviour: Average score (NOSIE-30, endpoint, high = poor)

Results were from three RCTs, all favoured standard care group (short-term MD 16.85 CI 11.90 to 21.80; medium-term MD 14.00 CI 3.03 to 24.97; long-term MD 41.33 CI 31.02 to 51.64).

1.5 Social functioning

1.5.1 Social functioning: 1a. Average change scores on various scales - medium term (high = poor)

Medium term MRSS (MD 13.68 CI 12.51 to 14.85) and SDSS (MD 1.96 CI 1.83 to 2.09) data from one small study (131) both favour standard care group.

1.5.2 Social functioning: 1b. Average endpoint scores on various scales (high = poor)

Short term IPROS score from one small study (132), n = 116, MD -6.64 CI -11.02 to -2.26), SAS score (n = 378, MD -8.53 CI -10.50 to -6.55), SDS score (n = 378, MD -5.60 CI -7.55 to -3.65) and medium-term SDSS score (n = 85, MD -3.74 CI -6.05 to -1.43) all favoured the psychoeducation group, although SAS outcome data are heterogeneous (I^2 = 99%).

1.5.3 Social functioning: 1c. Average SAS, SFS, SNS scale scores-skewed data (low = favourable)

There did not appear to be any significant differences between groups.

1.6 Global functioning

1.6.1 Global functioning: 1. No clinically significant improvement

Medium-term outcome included two RCTs and result favours psychoeducation group (n = 178, RR 0.59 CI 0.43 to 0.82, NNT 4 CI 3 to 10), but the data were heterogenous (I^2 = 69%). Short-term (n = 208, RR 0.61 CI 0.32 to 1.13) and long-term (n = 132, RR 0.70 CI 0.48 to 1.04) outcomes also appear to favour the psychoeducation group, but results are not statistically significant.

1.6.2 Global functioning: 2. Average endpoint scale score

Medium term GAF/GAS data included four RCTs and results favoured standard care group (n = 321, MD -5.44 CI -8.51 to -2.38), as does the long-term GAS outcome at two years' follow-up (MD -6.70 CI -13.38 to -0.02). Short-term outcome data of the same scales were from one small trial (63-66) and were not significant (MD -2.64 CI -12.74 to 7.46). SLOF data came from one small trial (60), and both short-term (MD 23.60 CI 11.88 to 35.32) and medium-term (MD 46.40 CI 34.45 to 58.35) outcomes favour the psychoeducation group.

1.7 Service utilisation

1.7.1 Service utilisation: days in hospital

Outcome data were from two small trials (60, 133) and results favoured the psychoeducation group in both the short (MD -3.23 CI -5.44 to -1.01) and medium term (MD -8.40 CI -10.44 to -6.36).

1.7.2 Service utilisation: Days in hospital using 'acute services' - during 18 months (data skewed)

These particular outcome data were from one small study (58, 59) and were markedly skewed. It did not appear to favour any one particular group.

1.8 Global state

1.8.1 Global state: 1. Medium term average endpoint score (CGI, high = poor)

Medium term CGI severity score favours standard care group (n = 61, MD 0.50 CI 0.08 to 0.92). But medium-term CGI change score favours psychoeducation group (n = 61, MD -0.80 CI -1.45 to -0.15).

1.8.2 Global state: 2. Increased medication dose by 25%

More people in the standard care group required increased medication dose (n = 20, RR 0.43 CI 0.15 to 1.20) compared with the psychoeducation group, but this result was not statistically significant.

1.8.3 Global state: 3. Disability

Long-term disability data from one small trial (129) clearly favoured the psychoeducation group (RR 0.29 CI 0.13 to 0.64, NNT 3 CI 3 to 6).

1.9 Mental state

1.9.1 Mental state: 1a. Global - continuous - average total endpoint scale score (high = poor)

BPRS scores generally favoured the psychoeducation group in the short term (10 RCTs, n = 1107, MD -1.00 CI -1.38 to -0.63), medium term (seven RCTs, n = 760, MD -4.73 CI -5.55 to -3.91) and long term up to two years (n = 370, MD -6.89 CI -8.55 to -5.23). However, short-term and medium-term data are heterogeneous (I^2 = 88% and 79% respectively). Longer term BPRS follow-up data (from one small trial up to seven years) did not show any difference between groups (n = 48, MD -0.20 CI -6.55 to 6.15). Medium PANSS outcome also favoured the psychoeducation group (n = 163, MD -2.52 CI -5.01 to -0.04).

1.9.2 Mental state: 1b. Global continuous average change scale scores medium term (high = good)

Data were from one small RCT (131). Compared with the standard care group, psychoeducation achieved better outcome with both GWB (n = 118, MD 10.89 CI 9.82 to 11.96) and SES assessments (n = 118, MD 8.00 CI 7.77 to 8.23).

1.9.3 Mental state: 1c. Global continuous average total endpoint scale scores (BPRS, high = poor, data skewed)

The skewed data did not show any significant difference between groups in either the short or long term.

1.9.4 Mental state: 2a. Specific-binary specific-symptoms short term

Data from a small RCT (134) showed that in the short term, the standard care group had worse outcomes with both anxiety (n=146, RR 0.49 CI 0.25 to 0.93, NNT 7 CI 5 to 47) and depression (n=146, RR 0.47 CI 0.25 to 0.88, NNT 5 CI 4 to 20) compared with psychoeducation.

1.9.5 Mental state: 2b. Specific-continuous-average endpoint PANSS scores (high = poor)

Only one small RCT (47) reported specific PANSS scores and data did not show any significant differences between groups, except for medium term negative symptoms (n = 61, WMD 3.10 CI 0.16 to 6.04), which favoured the standard care group.

1.10 Expressed emotions

1.10.1 Expressed emotions: Participants with high EE relatives (FQ)

Short-term outcome favoured the psychoeducation group (n = 282, RR 0.84 CI 0.76 to 0.94, NNT 8 CI 5 to 20), whereas outcome at nine to twelve months was not significant (RR 1.07 CI 0.64 to 1.78).

1.11 Quality of life

1.11.1 Quality of life: Average endpoint scores on various scales

Medium term FAD score favoured the psychoeducation group (n = 146, MD -6.79 CI -11.67 to -1.91), although short-term data were equivocal. Short-term GQOLI-74 score was not significant (n = 62, MD 0.63 CI -0.79 to 2.05), but medium-term data favoured the psychoeducation group (n = 62, MD 2.13 CI 1.03 to 3.23). One small trial reported PGWB data (47), which did not show any significant differences between groups. QOL data from a small trial (80) favoured standard care group (n = 108, MD -9.70 CI -17.22 to -2.18).

1.11.2 Quality of life: Average endpoint scores FBIS (high = poor)

Psychoeducation group had better outcome on the FBIS scale compared with standard care group in both the short (n = 84, MD -4.70 CI -7.19 to -2.21) and medium term (n = 84, MD -6.24 CI -7.80 to -4.68).

1.12 Satisfaction

1.12.1 Satisfaction with mental health services: 1. Short term - average change score (VSS, high = good)

No significant differences were found between groups either in term of patients' satisfaction (n = 32, MD -2.15 CI -13.96 to 9.66), or relatives' satisfaction (n = 17, MD -8.31 CI -29.72 to13.10).

1.12.2 Satisfaction with mental health services: 2. Average change - at 1 year (VSS scale, high = poor)

Standard care group had better patient satisfaction with relatives' involvement compared with the psychoeducation group (n = 30, MD -4.35 CI -7.09 to -1.61). No other significant differences were found between groups.

1.12.3 Satisfaction with mental health services: 3. Binary outcome

More people in standard care group were unsatisfied with mental health services compared with the psycheducation group (n = 236, RR 0.24 CI 0.12 to 0.50, NNT 5 CI 5 to 8).

1.13 Adverse event: Death

No significant differences were found between groups in terms of death.

1.14 Economic outcome

1.14.1 Economic outcomes: Costs (US$ per person, data skewed)

Economic data were skewed and did not show any significant differences between groups.

2. Subgroup analyses 1. Brief psychoeducation/standard psychoeducation versus standard care

2.1 Compliance (primary outcomes)

2.1.1 Compliance: 1a. With medication - binary outcomes

(Analysis 2.1)

Short-term non-compliance data showed an equivocal effect between brief psychoeducation

group (n = 448, RR 0.63 CI 0.41 to 0.96) and standard psychoeducation group (n = 286, RR 0.41 CI 0.25 to 0.67). Equivocal effect was also found for medium-term outcome.

2.1.2 Compliance: 2 With follow up - loss to follow up for any reason

(Analysis 2.2)

While medium-term data favoured brief psychoeducation group (n = 170, RR 0.59 CI 0.37 to 0.94), long-term data showed an equivocal effect between the two types of interventions.

2.1.3 Compliance: 2a with follow up - received intervention but left the study early

(Analysis 2.3)

No significant differences were found between groups.

2.1.4 Relapse: Relapse for any reason

(Primary outcomes, Analysis 2.4)

Medium-term relapse data were equivocal between brief psychoeducation group (n = 292, RR 0.61 CI 0.43 to 0.89) and standard psychoeducation group (n = 438, RR 0.87 CI 0.77 to 0.99), but standard group's data were heterogeneous (I^2 = 63%). Long-term relapse data favoured standard psychoeducation group (n = 666, RR 0.70 CI 0.59 to 0.84). Medium-term relapse with readmission data were equivocal, but the long-term data favoured standard psychoeducation group (n = 82, RR 0.53 CI 0.35 to 0.82).

3. Subgroup analyses 2. Group psychoeducation/individual psychoeducation versus standard care

3.1 Compliance (primary outcomes)

3.1.1 Compliance: 1a. With medication - binary outcomes

(Analysis 3.1)

Short-term non-compliance data favoured group psychoeducation (n = 412, RR 0.26 CI 0.13 to 0.52), while short-term partial compliance data favoured individual psychoeducation (n = 136, RR 0.61 CI 0.41 to 0.92).

3.1.2 Compliance: 2. With follow up - leaving the study early/loss to follow-up

(Analysis 3.2)

Equivocal effect was found between group (n = 213, RR 0.52 CI 0.25 to 1.0) and individual psychoeducation (n = 20, RR 3.00 CI 0.14 to 65.90) in terms of receiving intervention but left the study early. No significant differences were found between groups with medium-term

loss to follow-up for any reason data. There was a trend that individual psychoeducation group had a better outcome (n = 124, RR 0.70 CI 0.43 to 1.15), but it was not statistically significant. Again, no significant difference was found between groups for long-term loss to follow-up for any reason data.

3.1.3 Relapse: relapse for any reason

(Primary outcomes, Analysis 3.3)
Compared with the individual psychoeducation group, medium-term relapse for any reason data slightly favoured group psychoeducation (n = 410, RR 0.74 CI 0.57 to 0.96). But the long-term data were equivocal.

4. Sensitivity analysis

4.1 Chinese studies versus non-Chinese studies

In the 2010 update we included 31 trials that were conducted in China. We performed sensitivity analyses for all primary outcomes and results demonstrated that the outcomes of Chinese trials followed the same general affect as trials conducted in western countries. For instance, the medium-term relapse rate in non-Chinese studies were (n = 514, RR 0.85 CI 0.73 to 0.99). Whilst, in medium-term Chinese studies were (n = 700, RR 0.48 CI 0.35 to 0.66). Similarly, the risk ratio for lost to follow-up in medium term non-Chinese studies were (n = 603, RR 1.04 CI 0.8 to 1.34) compared with three medium-term Chinese studies (n = 346, RR 0.85 CI 0.48 to 1.51).

The only exception was the long-term non-compliance outcome, where the result of two Chinese studies (n = 200, RR 0.35 CI 0.22 TO 0.58) showed significant difference from the only non-Chinese study (58, 59) (n = 81, RR 3.5 CI 0.77 to 15.85). However, the difference is unlikely to be due to the settings of the studies, as the compliance outcome of this particular non-Chinese study was significantly different from all other studies under the same outcome, including both Chinese and non-Chinese studies.

4.2 Chinese studies versus full analysis

We also compared primary outcomes of Chinese studies with primary outcomes of the full analysis (full analysis = Chinese studies + non-Chinese studies) and found no clear differences. For example, non-compliance rate of Chinese studies was 0.85 CI 0.48 to 1.51 (n = 346) and that of all studies 1.00 CI 0.79 to 1.26 (n = 949). The same applies to the outcome

of relapse (Chinese studies n = 700, RR 0.48 CI 0.35 to 0.66; all studies n = 1214 RR 0.7 CI 0.61 to 0.81). Please see Table 1 for details.

4.3 English studies versus full analysis

We performed similar sensitivity analysis for non-Chinese trials (i.e. trials of any other language) and found no significant difference. Please refer to Table 2 for details.

Discussion

Summary of main results

Comparison 1. Any form of psychoeducation versus standard care

(Summary of findings table 1)

1.1 Compliance

This was a primary outcome of this review. Overall, psychoeducation promoted considerably better compliance with medication compared with standard care. This was recorded over different time periods and by different means, but the finding seems to be a consistently favouring the psychoeducation group. Even with the risk of overestimation of effect (135) there may be some residual evidence that a psychoeducation approach does help people towards taking medication on a more regular basis. Numbers needed to treat are relatively small, and, although they may inflate in everyday care, where the skill of the psychoeducation therapist may not be as great as was seen in these trials, the effort expended to gain increased medication compliance may be seen as acceptable.

Where it comes to loss to follow-up or leaving the study early, there is no evidence that either treatment is less acceptable than the other. About 25% of people left early in both groups. For the outcome of 'allocated but never accepted treatment' (Analysis 1.6) more people in the psychoeducation group were not compliant (2 RCTs, n = 213, RR 12.27 CI 2.58 to 58.33, NNT 9 CI 64 to 2) but we are unsure if this outcome was available to the standard care group.

1.2 Relapse

Psychoeducation group had less relapse in the medium term and long term, compared with standard care group (short term data are heterogeneous, $I^2 = 59\%$). Overall, these data are taken from quite a few trials with large total numbers of participants. Again, biases may have inflated the estimate of effect, but there is more than a suggestion that a psychoeducation approach may have beneficial effects in the short, medium and even long term. Of course,

this may be mediated by compliance with medication but may also have other positive effects. In terms of relapse with readmission, psychoeducation also had a better outcome than standard care group although readmission data were only from two small trials (n = 206).

1.3 Knowledge-KQ, KASQ, ITAQ, SKQ and SAUMD data

KQ data found standard care group to have had more improvement on the knowledge of the illness compared with psychoeducation group. Short term SKQ data also favoured the standard care group. KASQ and SAUMD scores showed an equivocal effect between two groups but ITAQ score and the binary outcome on 'level of knowledge' both favoured the psychoeducation group. (52-57, 62) reported how psychoeducation group promotes confidence in physician, compared with standard group. As can be seen, conflicting conclusions were offered by different measures. Most data are from 1-3 small RCTs. Without better data it is difficult to make any conclusions as to whether psychoeducation improves knowledge of schizophrenia any more than a good standard approach to care.

1.4 Behaviour

All results from three trials using the NOSIE-30 favoured standard care. We are not clear on the clinical meaning of differences of 14-40 points but feel it likely that these may be of clinical importance. It is hard to see how the improvements reported overall for the psychoeducation group fit with a deterioration in behaviour.

1.5 Social functioning

It is also difficult to be clear about the various measures of social functioning. Change scores seem to favour the standard care, whereas psychoeducation promotes better social functioning compared with standard care group according to endpoint scores (although some of these data are unacceptably heterogeneous). It may well have been better to record binary, clinically relevant, outcomes consistently across all studies (e.g. 'considerably less socially isolated').

1.6 Global functioning

For the gross outcome overall 'no clinically significant improvement', in the medium term, treating four people with psychoeducation instead of standard care resulted in one additional person showing improvement. Short-term and long-term data also favoured the psychoeducation group, but they were not statistically significant. Data from various scales, again, were confusing and conflicting. A consistent approach to recording data would greatly

help understand findings. Overall, there is a suggestion that global functioning is helped by the psychoeducation approach.

1.7 Service utilisation

On average people treated with psychoeducation had fewer number of days in hospital. These data were from very small studies (total n = 200), and findings could be even more prone to bias than larger trials. If, however, psychoeducation reduces inpatient care by about three days over only 12 weeks, or by eight days across a full year, as these data suggest, this is a finding of considerable clinical and economic importance.

1.8 Global state

Only one small trial (n = 61) reported conflicting data on CGI scale over short and medium terms. More people in the standard care group needed increased medication and longer-term disability seemed also to favour the psychoeducation group. All these findings are based on too few numbers and are prone to bias. Nevertheless, psychoeducation does seem to positively affect several important and clinically meaningful outcomes.

1.9 Mental state

We found studies indicated a greater improvement for participants in the psychoeducation group compared with those allocated to standard care, but the data were heterogeneous, the differences in overall reduction were small, and the clinical significance of a difference of this magnitude may be questioned. PANSS scores based on two small trials (n = 163) were also found to favour the psychoeducation group. Also, data from one small RCT ((131), total n = 118) indicated that participants in the psychoeducation group achieved better self-esteem and general well-being compared with standard care. Only one study reported outcome on specific mental state symptoms. Results suggested that less participants in the psychoeducation group suffered from anxiety or depression. As with all findings from few small studies, these findings should be replicated before being considered reliable and conclusive.

1.10 Expressed emotions

Short-term outcome based on two trials (n = 282) demonstrated statistically significant reduction on expressed emotion status of relatives in the psychoeducation group as compared to control group. This improvement was not sustained in the medium term. Without more data, it is difficult to conclude if psychoeducation is indeed better than standard care on

reducing expressed emotion in relatives, but these and other findings are consistent with the picture of psychoeducation helping the person as well as the family dealing with the illness.

1.11 Quality of life

Again the various measures serve to confuse rather than clarify. Data tended to be equivocal or favour the psychoeducation group. Consistency of measure as well as more data are needed before anyone can be confident of the effects of psychoeducation on quality of life.

1.12 Satisfaction

Only (63-66) reported on patients and relatives' satisfaction using the VSS scale. Most data indicated an equivocal effect between groups. This is an important outcome. It is to the credit of those designing (63-66) that they have considered the satisfaction of patients and relatives but much more data are needed to understand how psychoeducation really effects this outcome.

1.13 Adverse event: Death

Across the time periods of the few studies that reported on this outcome (about two years) about 1% of people died. There was no suggestion that psychoeducation had any effect on this outcome.

1.14 Economic outcome

As is frequent, economic data being few and skewed. It would seem likely that, if psychoeducation does really have an effect on relapse and service use that, if recorded properly and reported clearly, there should be an economic effect to find.

2. Subgroup analyses 1. Brief psychoeducation/standard psychoeducation versus standard care

For subgroup analyses we found no direct comparisons. We therefore compared each approach (brief/standard and group/individual) with the standard (non-psychoeducational) care. We are aware that techniques are available to undertake indirect comparisons of interventions (section 16.6.2 of *Cochrane Handbook*, (14)) but have not employed these at this juncture on such weak data.

2.1 Compliance

For the various measures of compliance, we found no clear difference in measures of effect size between brief versus standard care and standard duration psychoeducation versus

standard care. This could be a function of power but there are several hundred participants per sub-group.

2.2 Relapse: Relapse for any reason

The same applies to the outcome of relapse and, certainly, this generates the hypothesis that a brief form of psychoeducation may be cost efficient and effective. Direct comparisons are justified.

3. Subgroup analyses 2. Group psychoeducation/individual psychoeducation versus standard care

There were fewer numbers in each of these subgroup analyses compared with the findings reported in the brief/standard duration set of calculations.

3.1 Compliance

We found no convincing evidence that those given psychoeducation in a group differed in terms of compliance with those where the intervention was delivered individually.

3.1.3 Relapse: Relapse for any reason

There was no suggestion that relapse rates really did differ between those who had the intervention delivered by group compared with people given individual psychoeducation.

These findings were, however, not direct comparisons, were not well powered and serve only to generate theories for future studies.

Overall completeness and applicability of evidence

1. Completeness

We were pleased that most included studies did report the outcomes of compliance and relapse - the outcomes we had chosen as being of primary interest.

A general problem in assessing the efficacy of psychoeducational interventions for people with schizophrenia is, however, the scarcity of data. Poor reporting of data compounds the problem. We excluded 11 studies primarily due to lack of extractable data. This is potentially a truly valuable intervention and policymakers are still left having to make sweeping decisions for services based on outcomes with only a few hundred participants involved in less than ideal studies. This point is especially obvious where it comes to scale-derived continuous measures. It is possible to add data from different but similar scales and perform meta-analysis, but we feel that this gives spurious authority to weak data. There are too many

assumptions. Scale-derived data are proxy measures, often not truly continuous and are frequently incomplete. Then to calculate an effect size estimate and then estimate how that would relate to one favoured scale is, we suggest, more of an academic contrivance than of direct clinical value.

Outcomes were mainly physician-oriented. Participant-oriented outcomes, such as quality of life, satisfaction or days out of hospital were seldom reported. Participant satisfaction was only reported in three studies and no studies reported family burden. We would suggest that future research should focus more on participant-oriented aspects, such as general and social functioning, family burden and participants acceptability. Policymakers will certainly want more and better reported economic data.

2. Applicability

Most trials were undertaken in hospital, whereas the majority of people with schizophrenia are treated in the community. We are unsure that, in the context of well-functioning community services, psychoeducation, as a separate package, has a place. This is the sort of information that would not be difficult to generate.

As many of the included trials are conducted in China, the findings of this review are applicable to the Chinese population. Nevertheless, most of the included Chinese trials are also conducted in hospitals, thus raising the same concern that it may be inappropriate to apply the results to community-based patients.

Quality of the evidence

Overall, the quality of reporting was poor. Most included studies did not describe how the randomisation was conducted. Blinding was only used in eight studies and blinding concealment was not tested. Therefore, there is a moderate risk of overestimating the estimate of effect. Please refer to Figure 1 for a graphic representation of the methodological quality of included studies.

Potential biases in the review process

The process of searching for studies was thorough. We strictly followed the review protocol in the process of study selection, data extraction and analysis. However, we only worked with published reports in this review and may be perpetuating a publishing bias. Many trials included in this update version were from the People's republic of China. The quality of some of the Chinese trials has been called into question (34), as many that are stated to be

randomised are not. In this update version, we found two Chinese trials (121, 136) conducted at different places and time periods to have reported exactly the same numerical outcomes. We excluded the one found at a later date (121). However, we did not find any other overt bias in the results and therefore, have left these Chinese trials in.

Agreements and disagreements with other studies or reviews

This review substantially updates and improves past work (12). It largely concurs with findings from the previous version but puts less emphasis on the positive findings, perhaps because of the new Risk of Bias table function of this version of RevMan.

Authors' conclusions

Implications for practice

1. For people with schizophrenia

Psychoeducational interventions may initially seem 'off putting' for the person with schizophrenia, but it can reduce the relapse, readmission and encourage medication compliance, as well as reduce the length of hospital stay. It may well have other outcomes that are, at this point, under-researched.

2. For clinicians

The reduction in relapse and length of hospital stay with psychoeducational interventions and the increase of medication compliance rate should make it useful for clinicians as a part of their treatment programme. More should be known on other important outcomes and efficient ways of implementation.

3. For managers and policy makers

Not much data exists concerning the economic consequences of implementing psychoeducation as a routine service. A single study indicates that the combined costs for hospital and ambulatory services are comparable for the intervention group and standard treatment group. Much better work should be undertaken in this area to explore the true costs of the intervention and variations of approach, such as use of a brief form of psychoeducation or group delivery rather than individual to individual.

4. Note: the new 27 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.

Implications for research

1. General

We had to exclude 11 trials (please refer to Characteristics of excluded studies for detail), due to the poor quality of data reporting, diminishing the already limited evidence-base. Following CONSORT for good reporting of clinical trials more closely would have helped to considerably increase the amount of data available in this review.

2. Specific

More well-designed, conducted and reported randomised studies investigating the efficacy of psychoeducation are needed. This is an intervention that looks as if it works in terms of compliance and relapse, but we still know relatively little about many important effects. Certainly, any future trials should employ well standardised psychoeducational programmes with clear definitions of the content of interventions to help professionals planning evidence-based psychoeducational interventions, people with schizophrenia and family members participating in psychoeducation programmes. Not only should compliance, relapse and readmission be recorded as outcomes, but also psychosocial function, quality of life and insight. Health economic outcomes should also be measured, as the efficiency of psychoeducation is crucial in making it an attractive option for managers and policy makers. Continuous data should be reported with mean, standard deviations and number of participants. Endpoint scores should always be used when reporting data derived from scales. We have not the experience nor have we invested the effort of thought or commitment of those who have undertaken trials in this difficult area. There are, however, some gains from producing an overview in this way and we suggest an outline design for future trials (Table 3). Further research is also needed for assessment of the efficacy of different formats of psychoeducational interventions as brief or group approaches may well be cost efficient.

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The Methods section of this review uses text from the Cochrane Schizophrenia Group's generic text for methods sections. This has been written over a period of years to ensure consistency and clarity. We fully acknowledge use of this text which we have adapted for relevance to this particular review.

Contributions of authors

1. Original review

Eila Pekkala initiation of the review, protocol production, searching, data extraction, analysis, data interpretation and writing the final report.

Lars Bertil Merinder protocol production, analysis, data interpretation and writing the final report of the original review.

2. 2010 update

Jun Xia selected studies, extracted data and wrote up report during the 2010 update.

Madhvi R Belgamwa extracted and input English trial data during 2010 update.

Lars Bertil Merinder extracted data of English trials and handled all queries relating to trials from the original review.

Declarations of interest

None.

Differences between protocol and review

1. Wording of protocol

We have substantively reworded the protocol of this review. We think that this rewording represents an improvement in clarity but, also, that it did not substantively change the procedures by which we undertook the review. For the record the methods section of the previous version of this review is reproduced in Appendix 1.

2. Additional outcomes

Many studies found in the 2010 update search reported data on outcomes such as social function, mental state, adverse event etc, which were not listed in the original protocol. But

we feel that these outcome data are of significant clinical value and important to this review. Therefore, we amended the original protocol and added/supplemented the following secondary outcomes: social function, global function, global state, mental state, expressed emotion, quality of life, satisfaction with care and adverse events.

Author note

Due to the size of this systematic review, all Tables and Figures, as well as references are moved to the end of the thesis under '**Appendix 1. Supplement material for paper 3**'.

Chapter 4. Methodological development: application of systematic reviews in clinical practice guideline

Chapter highlights

This Chapter illustrates the role of systematic reviews in supporting production of clinical practice guidelines (CPG) and, in this case, CPGs developed using the GRADE Evidence to Decision (EtD) framework (see **Appendix 2**). Paper 4 presents details of the first Chinese national CPG in the subject of bacterial infection and antimicrobial resistance to follow the WHO CPG development process whilst also adopting GRADE methodology. This marks a milestone in CPG quality improvement. The recommendations are supported by sixteen systematic reviews. The methodological design of these systematic reviews is informed by the work produced in Chapter 1, 2 and 3.

Chapter background

CPGs are '*statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefit and harms of alternative care options*'(23). A CPG supports informed, collaborative decision-making between clinicians and patients and assists healthcare professionals to navigate the intricacies of patient care. Generally, the development of CPGs follow a series of steps (24) Evidence synthesis is an integral part of guideline development, and systematic reviews of efficacy and safety form the basis for the formation of recommendations. Users can judge the reliability of guideline recommendations by evaluating the method employed to synthesise the data supporting the guidelines (25).

Background to paper 4

The wide spread of carbapenem-resistant Gram-negative bacilli (CRGNB) has become a global public health issue. CRGNB isolates are usually extensively drug-resistant (XDR) or pandrug-resistant (PDR), for which antimicrobial treatment options are limited. Such difficult-to-treat CRGBN infections result in great healthcare burden and high mortality.(26)

A multidisciplinary guideline development group covering clinical infectious diseases, clinical microbiology, clinical pharmacology, infection control, and guideline methodology experts jointly developed the present clinical practice guidelines based on best available scientific evidence. The guidance focused on addressing clinical issues regarding laboratory testing, antimicrobial therapy and prevention of CRGNB infections.

Sixteen clinical questions were proposed from the perspective of current clinical practice and translated into research questions using PICO (population, intervention, comparator, and outcomes) format to collect and synthesize relevant evidence to inform corresponding recommendations. The grading of recommendations, assessment, development and evaluation (GRADE) approach was used to evaluate the quality of evidence, benefit and risk profile of corresponding interventions and formulate recommendations or suggestions. This is the first Chinese national CPG in bacterial infection and antimicrobial resistance subject area to follow the WHO recommended CPG development process, and adopting GRADE methodology. This is a milestone in CPG quality improvement.

Coda

The systematic review provides a reliable evidence basis to inform recommendations in this CPG. The validity and reliability of the data that underpin the recommendations in guidelines are jeopardized by the use of non-systematic approaches, which might provide results that are false and unreliable. This Chapter is methodologically an extension of the work presented in Chapter 1, 2 and 3. Paper 4 performed sixteen systematic reviews incorporating the findings of paper 1 and 2 and applying the systematic review method to critically appraise current evidence to generate new knowledge to inform clinical practice. This also represents the evolvement of EBM in the context of evidence ecosystem, going from primary studies to secondary evidence synthesis, and eventually making clinical practice recommendations on that basis. However, for this to sit in a small silo of researchers would limit its impact. Wide dissemination of findings may enhance impact and Chapter 5 considers empirical evaluation of dissemination techniques.

Reference for paper 4

PAPER 4. Zeng M, **Xia** J, Zong Z, Shi Y, Ni Y, Hu F, Chen Y, Zhuo C, Hu B, Lv X, Li J, Liu Z, Zhang J, Yang W, Yang F, Yang Q, Zhou H, Li X, Wang J, Li Y, Ren J, Chen B, Chen D, Wu A, Guan X, Qu J, Wu D, Huang X, Qiu H, Xu Y, Yu Y, Wang M; Society of Bacterial Infection and Resistance of Chinese Medical Association; Expert Committee on Clinical Use of Antimicrobial Agents and Evaluation of Antimicrobial Resistance of the National Health Commission; Infectious Diseases Society of Chinese Medical Education Association. Guidelines for the diagnosis, treatment, prevention and control of infections caused by carbapenem-resistant gram-negative bacilli. J Microbiol Immunol Infect. 2023 Feb 18:S1684-1182(23)00036-1. doi: 10.1016/j.jmii.2023.01.017. Epub ahead of print. PMID: 36868960. (PAPER 4. JX as joint first author, contributed equally with Mei Zeng).

PAPER 4

Guidelines for the diagnosis, treatment, prevention and control of infections caused by carbapenem-resistant gram-negative bacilli[4]

Abstract

The dissemination of carbapenem-resistant Gram-negative bacilli (CRGNB) is a global public health issue. CRGNB isolates are usually extensively drug-resistant or pandrug-resistant, resulting in limited antimicrobial treatment options and high mortality. A multidisciplinary guideline development group covering clinical infectious diseases, clinical microbiology, clinical pharmacology, infection control, and guideline methodology experts jointly developed the present clinical practice guidelines based on best available scientific evidence to address the clinical issues regarding laboratory testing, antimicrobial therapy, and prevention of CRGNB infections. This guideline focuses on carbapenem-resistant Enterobacteriales (CRE), carbapenem-resistant Acinetobacter baumannii (CRAB), and carbapenem-resistant Pseudomonas aeruginosa (CRPA). Sixteen clinical questions were proposed from the perspective of current clinical practice and translated into research questions using PICO (population, intervention, comparator, and outcomes) format to collect and synthesize relevant evidence to inform corresponding recommendations. The grading of recommendations, assessment, development and evaluation (GRADE) approach was used to evaluate the quality of evidence, benefit and risk profile of corresponding interventions and formulate recommendations or suggestions. Evidence extracted from systematic reviews and randomized controlled trials (RCTs) was considered preferentially for treatment-related clinical questions. Observational studies, non-controlled studies, and expert opinions were considered as supplementary evidence in the absence of RCTs. The strength of recommendations was classified as strong or conditional (weak). The evidence informing recommendations derives from studies worldwide, while the implementation suggestions combined the Chinese experience. The target audience of this guideline is clinician and related professionals involved in management of infectious diseases.

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[4] A reply to this paper has been published as:
Zeng M, Xia J, Zong Z, Shi Y, Ni Y, Hu F, Chen Y, Zhuo C, Hu B, Lv X, Li J, Liu Z, Zhang J, Yang W, Yang F, Yang Q, Zhou H, Li X, Wang J, Li Y, Ren J, Chen B, Chen D, Wu A, Guan X, Qu J, Wu D, Huang X, Qiu H, Xu Y, Yu Y, Wang M; Society of Bacterial Infection and Resistance of Chinese Medical Association; Expert Committee on Clinical Use of Antimicrobial Agents and Evaluation of Antimicrobial Resistance of the National Health Commission; Infectious Diseases Society of Chinese Medical Education Association. Guidelines for the diagnosis, treatment, prevention and control of infections caused by carbapenem-resistant gram-negative bacilli. J Microbiol Immunol Infect. 2023 Feb 18: S1684-1182(23)00036-1. doi: 10.1016/j.jmii.2023.01.017. Epub ahead of print. PMID: 36868960.

Introduction

The extensive spread of carbapenem-resistant Gram- negative bacilli (CRGNB) has become a global public health issue. The World Health Organization (WHO) identified carbapenem-resistant Enterobacteriales (CRE), carbapenem-resistant Acinetobacter baumannii (CRAB), and carbapenem-resistant Pseudomonas aeruginosa (CRPA) as the pathogens of critical threat in the global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics in 2017 (1). Escherichia coli, Klebsiella pneumoniae, A. baumannii and P. aeruginosa are listed among the six leading pathogens for resistance associated death, and CRAB and carbapenem resistant K. pneumoniae (CRKP) are among the top seven multidrug resistant (MDR) pathogens each causing more than 50000 deaths attributed to antimicrobial resistance (2). The China Antimicrobial Surveillance Network (CHINET) monitoring data shows, E. coli, K. pneumoniae, A. baumannii and P. aeruginosa are among the top five bacterial species in clinical isolates from hospitals across China, demonstrating a growing CRGNB prevalence over time (3,4) from 3% in 2005 to 23.1% in 2021 for CRKP, and from 31.0% to 71.5% for CRAB. Although the prevalence of CRPA decreased from 36.8% to 23.0%, it remained at high level in general (4).

CRGNB isolates are usually extensively drug-resistant (XDR) or pandrug-resistant (PDR), for which antimicrobial treatment options are limited. Such difficult-to-treat CRGNB infections result in heavy healthcare burden and high mortality (5). Some novel antimicrobial agents have been approved for clinical use in the treatment of CRGNB infections in recent years, but there is a delay for their launch in some countries such as in China, further limiting choices of antimicrobial agents in these countries and increasing the challenge of providing effective treatment. In 2016, experts specialized in clinical infectious diseases, clinical microbiology, clinical pharmacology, and infection control, jointly developed the Chinese expert consensus statement on laboratory diagnosis, clinical management and infection control of infections caused by XDR-GNB to address the intractable clinical problems of XDR-GNB. The consensus statement published in Clinical Microbiology & Infection provided a practical guidance primarily to clinicians for the management and control of XDR-GNB infections (6).

The current clinical practice guideline (CPG) is an update of the 2016 consensus with a more focused scope on CRGNB. While retaining the same structure as the 2016 consensus

statement, the current CPG improves on methodological reliability and transparency. It is prepared in accordance with the standards and processes recommended by WHO, and adopting the internationally recognized grading of recommendations assessment, development and evaluation grade (GRADE) system. It integrates available evidence and new advances to formulate recommendations or suggestions for clinical practice to address a series of clinical priority questions concerning diagnosis, treatment and control of CRGNB infections. The Society of Bacterial Infection and Resistance of Chinese Medical Association, the Expert Committee on Clinical Use of Antimicrobial Agents and Evaluation of Antimicrobial Resistance of the National Health Commission, the Infectious Diseases Society of Chinese Medical Education Association, and the China Clinical Practice Guideline Alliance jointly developed this guideline.

In 2022, several international guidelines or guidance were published on the treatment of MDR GNB including CRGNB by the Infectious Diseases Society of America (7,8), the European Society of Clinical Microbiology and Infectious Diseases (9), and the Infectious Diseases Society of Taiwan (10). While the current CPG focuses on CRGNB (CRE, CRAB and CRPA), it complements the aforementioned CPGs by including broader scope related to the management of CRGNB infections: in addition to antimicrobial therapy, recommendations relating to diagnosis (antimicrobial susceptibility testing and synergy testing, carbapenemase detection), therapeutic drug monitoring of common anti-microbials for CRGNB and infection control are also included in this CPG. Where possible, meta-analysis were carried out for comparison on efficacy and safety of various therapy regimens. This CPG aims to provide guidance on management of CRGNB infections mainly for clinicians, and related professionals involved in management of infectious diseases.

Methodology

Guideline development group (GDG) composition

GDG members are elected by the chair of guideline panel. They composed of 31 multidisciplinary clinical experts related to the diagnosis and treatment of CRGNB, such as infectious diseases, intensive care, respiratory, hematology, pediatrics, surgery, clinical microbiology, clinical pharmacology and infection control. Their conflict of interest (CoI) was collected and assessed using a standard form constructed under the guidance of principles listed on Guideline International Network (GIN). All GDG members were free of financial and intellectual CoI and were permitted full participation. China Clinical Practice

Guideline Alliance (GUIDANCE) provided methodological expertise and systematic review support. This CPG is registered on GIN website (https://guidelines.ebmportal.com/node/69996).

Guideline development

This CPG is developed following the WHO recommended process (11), which adopts GRADE in assessing evidence quality, and utilizing Evidence to Decision (EtD) framework to formulate clinical recommendations. GRADE categorizes the quality of evidence into high, moderate, low and very low, through assessing risk of bias, inconsistency, indirectness, imprecision and publication bias of the body of evidence. Quality of evidence is taken into account informing the final recommendation, together with the balance of benefit and harm, stakeholders' values and preferences, cost effectiveness, acceptability and feasibility (12). This CPG categorized strength of recommendation into strong, weak and conditional. Factors promote strong recommendation including high certainty of evidence, similarity in stakeholders' values and preferences, cost effectiveness, and sharp contrast between benefit and harm (12).

The GDG identified 16 important clinical questions through discussion and converted these into research questions using PICO format to pave way for systematic reviews. The GDG held 5 online meetings between September and October 2021 to review evidence under each PICO question and reaching consensus on corresponding recommendations through open discussion and voting. Eighty percent votes are adopted as a threshold to pass a recommendation.

Upon completion, the full CPG report was sent to external guideline methodologists and clinicians without direct involvement to the current CPG for review. Their feedbacks were collected and incorporated as appropriate. We referenced AGREE II before and during the conduct of CPG to ensure conduct quality and scientific rigor of reporting.

Evidence synthesis

The systematic review team searched PubMed, Embase, Web of Science, Cochrane Library in March 2021 without date limit (Supplementary material S1). Additionally, reviewers hand searched references of all included articles for further relevant studies, and contacted clinicians for potentially relevant studies. The final update of hand search was conducted in December 2022. Two separate sets of searches were carried out to identify studies on efficacy

and safety, and studies on other factors including cost effectiveness, values and preferences, acceptability and feasibility.

Reviewers worked in pairs to independently carry out reference screening, data extraction, and resolved any disagreements through discussion or consulting a third reviewer (Supplementary material S2). A data extraction form with standardized variable headings was used in this process. We employed Cochrane risk of bias table (RoB, version 1.0) to assess the risk of bias for RCTs, Newcastlee Ottawa Scale (NOS) for observational studies. We used RevMan 5.3 to analyze data from controlled clinical studies or RCT and R 4.0.2 for single arm studies. For binary outcome, we calculated Risk Ratio (RR) and its 95% confidence interval (CI); for continuous outcome, where possible, we calculated Mean Difference (MD) with its 95% CI. We employed $I^2 > 50\%$ as a general guide to identify heterogeneity in pooled analysis, and explored heterogeneity through subgroup analysis on clinical, methodological and statistical variations between studies. As stated in previous section, quality of evidence is appraised using GRADE and presented as Summary of Findings tables (SoF) (Online supplement tables).

Evidence extracted from systematic reviews and randomized controlled trials (RCTs) was considered preferentially for treatment related clinical questions. Observational studies, non-controlled studies, and expert opinion were considered as supplementary evidence in absence of RCT, or if RCT evidence is indirect evidence, or if quality of evidence was very low. Evidence extracted from systematic reviews or cross-sectional studies was adopted preferentially for the clinical questions related to clinical microbiological diagnosis.

Recommendations

Sixteen key clinical questions were deemed to be of high priority in the management of CRGNB infections by the guideline development group (GDG), including three PICO questions for laboratory testing of CRGNB, ten for antimicrobial therapy and three for infection prevention and control.

Laboratory testing of CRGNB

CRGNB isolates are usually presented as XDR phenotypes, for which only limited number of antimicrobial agents remain effective. Some newly approved antimicrobial agents have not yet been included in routine antimicrobial susceptibility testing, which limits the choice of effective antimicrobials for the treatment of CRGNB infections. The precision treatment for

CRGNB relies on clinical microbiology for determination of minimum inhibitory concentration (MIC) and rapid identification of the carbapenemase genotype of CRGNB isolates, as well as antimicrobial synergy testing to screen appropriate treatment options.

PICO question 1. Should MIC testing be performed for determining antimicrobial susceptibility of CRGNB?

Recommendation: MICs should be determined where possible for commonly used antimicrobial agents which are available at local hospitals for treating CRGNB infections such as carbapenems, ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-cilastatin-relebactam, meropenem-vaborbactam, cefiderocol, tigecycline, eravacycline, polymyxin and fosfomycin (weak recommendation, low-quality evidence). Most automated antimicrobial susceptibility testing systems can measure MIC value, but their clinical value is limited by the narrow concentration range of individual antibacterial agent. Broth microdilution (BMD), agar dilution method or E-test method are recommended as preferential methods in accordance with the requirements of the Clinical Laboratory Standards Institute (CLSI) or the European Committee for Antimicrobial Susceptibility Testing (EUCAST) documents regarding methodology.

Implementation suggestion: 1) Other methods can be used to determine MIC values of antimicrobial agents in the health care facilities where the above recommended method is unavailable; 2) It is suggested to initiate empirical antimicrobial therapy in parallel to MIC testing in the interest of providing earlier treatment. 3) For fosfomycin MIC testing, agar dilution method supplemented with glucose-6-phosphate is recommended by CLSI and EUCAST, but not broth dilution method.

Evidence summary: Five studies comparing the accuracy of other methods versus BMD in identifying CRE and testing the susceptibility of CRGNB to some key antimicrobial agents were included. A multi-center study (13) in Europe showed that EUCAST disc diffusion method has a good accuracy comparing with BMD to identify CRE, but it would likely miss the detection of CRE strains with meropenem MIC <1 mg/L. The semi-automated instruments VITEK 2 and Phoenix reported higher MIC values of meropenem compared to BMD MIC, resulting in higher proportion of major errors (MEs) (false resistant, 26% and 14%, respectively). The gradient MIC method such as E-test showed higher categorical agreement (73%) and lower ME rate (7%) in identifying CRE compared with BMD (13). A study (14) conducted in the US indicated that for the 74 CRE isolates identified by

carbapenemase genotype, E-test and disc diffusion method showed categorical agreement of 96% and 72% with BMD for ceftazidime-avibactam susceptibility, suggesting E-test was superior to disc diffusion method. Another US study showed that disc diffusion method had higher categorical agreement with VITEK 2 in testing the susceptibility of P. aeruginosa to meropenem (15). A study in China demonstrated that agar dilution method, E-test, and Phoenix assay yielded higher categorical agreement (96%, 88%, and 93%, respectively) with BMD in determining the susceptibility of CRE strains to tigecycline (16). Another study (17) in China reported that E-test and modified disc diffusion method (adding a re-sensitization buffer containing 175 mg EDTA to the disc) had high categorical agreement (96.7% and 96.5%) with BMD in determining susceptibility of CRKP isolates to tigecycline, while modified disc diffusion method yielded high categorical agreement (91.0%) with BMD in determining susceptibility of CRAB isolates to tigecycline.

Rationale for recommendation: 1) MIC values provide more accurate susceptibility information of CRGNB to antimicrobial agents, and thus directly influence clinicians' choice of antimicrobial therapy. 2) Although there is a lack of direct evidence demonstrating the impact of MIC results on clinical endpoints (e.g., mortality), the GDG believes MIC results can lead to improved clinical outcomes through improved precision on guiding antimicrobial choice. 3) BMD is the most widely recognized method for determining MIC, but has varied feasibility across different healthcare facilities due to its complexity in laboratory operation. In settings where BMD is unavailable, agar dilution and E-test method are suitable alternatives with relatively high accuracy. Automated antimicrobial susceptibility testing systems can also be used as alternative because they are convenient for use despite the relatively low accuracy.

PICO question 2. Should carbapenemases detection (including phenotypic and genotypic tests) be recommended for CRE isolates?

Recommendation: It is suggested to detect carbapenemases of CRE isolates. This can be achieved by phenotypic or genotypic test in healthcare facilities, particularly in settings where the susceptibility results of novel β-lactamase inhibitor combinations such as ceftazidime-avibactam are unavailable (weak recommendation, low-quality evidence).

Implementation consideration: Genotypic test is preferred where possible, and phenotypic test could be used in settings where genotypic test is unavailable. Hospital laboratory could

take into consideration of its own specific circumstances to select genotypic and/or phenotypic assay.

Evidence Summary: We included four studies reporting sensitivity and specificity of various phenotypic and genotypic tests in detecting carbapenemases of CRE isolates. For the CRE isolates confirmed by whole genome sequencing (WGS), both reverse transcription-polymerase chain reaction (RT-PCR) and Carba NP tests were highly sensitive (98.0% and 95.9%, respectively) and specific (both 100%) in detecting CRE with less than 3 h turnaround time (18). Of the 60 carbapenem-resistant Gram-negative bacteria (CRGNB) isolates, 48 were identified to produce carbapenemase. Modified Hodge test and combined disc test (CDT) identified 47 and 48 isolates producing carbapenemases (NDM-1 and KPC), respectively. The loop- mediated isothermal amplification (LAMP) assay of carbapenemase genes showed consistent sensitivity and specificity to CDT in phenotypic test of carbapenemases, with a higher positive detection rate than PCR (44 isolates positive). LAMP assay had a turnaround time of 2-3 h (19). CDT (meropenem disc plus 3-aminophenylboronic acid or meropenem disc plus EDTA) has a sensitivity of 100% in detecting the isolates producing KPC or metallo-beta-lactamases alone, 96.8% in detecting the isolates producing both KPC and metallo-beta-lactamases, and a specificity of 98.8% in detecting KPC producers (20). In a recent study including the 247 CRE isolates, the compliance of phenotype results with genetic detection (by PCR amplification method) was 94%, 95%, 98%, and 99%, respectively for CDT, modified carbapenem inactivation method (mCIM)/EDTA-modified carbapenem inactivation method (eCIM), NG-Test CARBA 5 (CARBA), and color developing immunoassay (CDI) (21). However, CDT did not accurately detect IMP and showed a low specificity for carbapenemase detection, low negative predictive value (NPV), and low sensitivity for metallo-b-lactamase (79%, 55%, and 88%, respectively). The sensitivity and specificity of CARBA and CDI were higher than CDT and mCIM/eCIM, but CDI was unable to detect IMP-8 (21). These studies suggest that phenotypic tests are highly sensitive and specific in detecting carbapenemases and are highly consistent with genotypic tests. Therefore, it is recommended to use CDT and mCIM to detect the phenotype of carbapenemase-producing CRE in the resource-constrained laboratories.

Rationale for recommendation: 1) Vast majority of CREs are carbapenemase-producing isolates. The detection of carbapenemase phenotype or genotype is of great value in predicting the susceptibility of bacteria to carbapenems. Such test results enable clinicians to

optimize treatment plan by adjusting antibiotics accordingly. Therefore, the GDG is highly confident that phenotypic/genotypic tests will improve clinical outcomes, despite the lack of direct evidence linking the tests to improvement in clinical outcomes (e.g., mortality). 2) The genotypic and some phenotypic tests are rapid and accurate in detecting carbapenemases, which can inform the clinicians in selection of antimicrobial agents at early stage.

PICO question 3. should antimicrobial synergy testing be performed to support treatment of CRGNB infections?

Recommendation: Antimicrobial synergy testing may be useful for prescribing precise anti-infective drugs for managing CRGNB infections, especially in situations where drug choices are limited (e.g., poor response to monotherapy, conventional susceptibility testing prompts no effective treatment option, or limited treatment option). In such cases, it is suggested to perform antimicrobial synergy test to screen for appropriate combination treatment regimens if possible (conditional recommendation, low-quality evidence).

Implementation consideration: Antimicrobial synergy testing is not routinely performed in clinical microbiology laboratory; therefore, clinicians should ensure adequate communication with laboratory when requesting the test. Appropriate testing method should take into account of local laboratory conditions. If possible, the checkerboard method is preferred, followed by disc elution method, MIC strip crossing or stacking method.

Evidence summary: A systematic review with 136 included studies (using time-kill and pharmacokinetic/ pharmacodynamic (PK/PD) methods for testing antimicrobial synergic activities) found significantly enhanced bactericidal activity and lowered emergence of resistant strains with polymyxin and/or carbapenem-based combinations (with tigecycline, fosfomycin, amikacin), indicating considerable synergistic effect on CRAB, CRKP, and CRPA. This evidence suggests that antimicrobial synergy testing can inform clinicians to prescribe antimicrobial agents for the treatment of CRGNB infections (22). One study compared methods in testing the activity of ceftazidime-avibactam combined with aztreonam against CRE and CRPA. Taking modified broth microdilution (mBMD) method as reference, the most accurate and reproducible methods were broth disc elution and strip stacking or crossing methods using MIC test strips (MTS), all with 100% sensitivity and specificity, followed by E-test strip crossing (95.8% sensitivity, 100% specificity) or stacking (87.5% sensitivity, 100% specificity). Despite of an 100% specificity value, the sensitivity value of the conventional disc stacking method is only 42.7%. MTS methods yielded higher

categorical agreements and lower MEs relative to E-test. This study indicates that broth disc elution method is particularly valuable in resource-constrained laboratories (23). In the other four studies, different methods of antimicrobial synergy testing (e.g., checkerboard microdilution method, time- killing curve, disc approximation assay) were used to determine the in vitro antimicrobial activity of antimicrobial combinations against CRE, CRPA and CRAB. Results showed that some antimicrobial agents were inactive against CRGNB when used alone, but demonstrated good in vitro synergistic effect on CRGNB when combined with other antimicrobial Agents (24-27). A study, however, showed that in vitro synergism between colistin and meropenem did not translate into clinical benefit in the treatment of severe CRGNB infections (28).

Rationale for recommendation: 1) Antimicrobial synergy testing can be used to determine in vitro activity and synergistic effect of antimicrobial combinations on CRGNB, thus may be informative to clinicians on selection of appropriate antimicrobial combination therapy. 2) Categorical agreement varies across the methods used in anti- microbial synergy testing. Checkerboard assay uses fractional inhibitory concentration (FIC), a quantitative index, to evaluate the level of synergy. It is the most frequently applied standard method but the procedure is complex and inconvenient. Time-killing curve assay is highly accurate but also complex and time-consuming, which hinders its clinical application. Broth disc elution and MTS crossing or stacking methods provide high sensitivity and specificity, and low complexity of operation. Disc stacking method performs poorly in sensitivity. The GDG has moderate level of confidence in the accuracy of anti-microbial synergy test. 3) The GDG believes that test result may be informative to clinicians on optimizing antimicrobial regimen.

Antimicrobial therapy of CRGNB infections

It is highly challenging to treat CRGNB infections. Accurate selection of effective antimicrobial agents and prescription of appropriate dosing regimen play a key role in improving clinical efficacy and reducing adverse reactions. This section focuses on the antimicrobial agents used to treat CRGNB infections, including polymyxins (intravenous and aerosolized preparations), ceftazidime-avibactam, tigecycline and other new tetracycline derivatives, sulbactam and sulbactam-containing combinations, aminoglycosides, and fosfomycin, especially those combination therapies containing these antimicrobial agents.

Research evidence on efficacy and safety was collected and analyzed to inform recommendations on treatment.

PICO question 4. should polymyxin combination therapy be preferred over polymyxin monotherapy for treatment of CRGNB infections?

Recommendation: Polymyxin combination therapy is recommended as a preferential choice over monotherapy for treating CRGNB infections in patients who requires polymyxin treatment (strong recommendation, moderate quality evidence).

Implementation consideration: 1) Patients' renal function should be monitored during polymyxin treatment. The GDG encourages therapeutic drug monitoring (TDM) to be performed for polymyxin where possible. 2) The ototoxic and nephrotoxic drugs (including antimicrobial agents) should be avoided in combination with polymyxin. 3) Polymyxin carbapenem combination may be suggested for treatment of CRGNB infections if meropenem MIC is $\leqslant$ 8 mg/L for CRE or $\leqslant$ 32 mg/L for CRAB, and with an extended-infusion of meropenem for 3h (9,10). 4) The dose unit of polymyxin is expressed in different ways, so attention should be paid to the correct conversion of dosage. There are two ways to express the dosage of colistin methanesulfonate (CMS): international unit (U) and colistin base activity (CBA) in mg (an active unit, not a mass unit). Dose conversion: 1 million U $\approx$ 80 mg mass CMS $\approx$ 33 mg CBA; polymyxin B sulfate: 1 mg $\approx$10000 U; colistin sulfate: 1 mg$\approx$ 22700 U.

Evidence summary: Six RCTs (N = 876) compared CMS combination therapy versus CMS monotherapy in the treatment of CRGNB infections, two of which investigated ventilator-associated pneumonia (VAP) caused by CRAB (CMS combined with rifampicin, ampicillin-sulbactam) (29,30), one on hospital-acquired pneumonia (HAP)/VAP caused by CRKP (combined with meropenem) (31), one on CRAB infections (78.7% pneumonia, followed by primary bacteremia, urinary tract infection, combined with fosfomycin) (32), one on XDR A. baumannii infections (77.5% HAP/VAP, 20.1% bloodstream infection, combined with rifampicin) (33), and one trial on CRAB, CRPA or CRE infections (51.0% HAP/VAP, 42.6% bloodstream infection, combined with meropenem) (34).

Compared to CMS monotherapy, in every 1000 patients receiving CMS combination therapy there might be on average 14 fewer deaths (N= 779, RR = 0.97, 95% CI 0.84-1.13, moderate-quality evidence) (Online supplement Fig. S4.1), probably on average 119 fewer treatment

failure (N = 578, RR = 0.82, 95% CI 0.72-0.93, moderate-quality evidence) (Online supplement Fig. S4.2) (29,32,34), might be on average 74 fewer cases of pathogen eradication failure (N = 779, RR = 0.81, 95% CI 0.67-0.98, low-quality evidence) (Online supplement Fig. S4.3) (29,30,32,34), and probably shorter time to microbiological clearance (29). There were no apparent differences in renal toxicity and hepatotoxicity between groups (29, 31- 33). The AIDA study reported CMS-meropenem combination reduced incidence of mild renal failure (30% vs 20%), but increased incidence of diarrhea (27% vs 16%) (34). One RCT on XDR A. baumannii infections reported no difference in length of hospital stay between polymyxin monotherapy and combination therapy (33). SoF available in Online Supplement Table.

A network meta-analysis showed that there was no difference in clinical cure, microbiological cure, and mortality between colistin monotherapy and other combination therapy (including colistin-based combination therapy) for treatment of CRAB pneumonia. Nonetheless, colistin-carbapenem combinations ranked first in improving clinical cure (SUCRA, 91.7%) and second in microbiological cure (SUCRA, 68.7%) among various treatment regimens (10).

The application of polymyxin and carbapenem combination therapy in the treatment of CRGNB is somewhat controversial. Two recent guidelines (9,10) and a guidance (8) attached specific conditions to the recommendation of this combination. Both guidelines recommend polymyxin- carbapenem combinations for CRE infections when meropenem MIC is $\leqslant 8$ mg/L, and high-dose extended-infusion meropenem is used. Polymyxin-meropenem combination is recommended for the treatment of CRAB infections (8), for CRAB pneumonia and bloodstream infections if carbapenem has in vitro synergistic benefit even if carbapenem MIC $\leqslant$ 32 mg/L, and for the treatment of moderate to severe CRAB infections with the combination of CMS and high-dose, extended-infusion meropenem with a third agent (8).

Rationale for recommendation: 1) The benefit of polymyxin combination therapy may outweigh any potential harm, compared to polymyxin monotherapy in the treatment of CRGNB infections, evidenced by lower rates of mortality, treatment failure, and eradication failure. 2) In vitro antimicrobial synergy tests demonstrated synergistic effect of polymyxin combinations on CRGNB (22). 3) Several colistin-based combinations have been shown in

vitro to prevent the emergence of the resistant sub-populations, but its clinical impact needs further investigation (35).

PICO question 5. should aerosolized polymyxin be used for treatment of CRGNB respiratory tract infections?

Recommendation: It is suggested using aerosolized polymyxin in addition to intravenous polymyxin in patients with CRGNB respiratory tract infections (weak recommendation, low quality evidence).

Implementation consideration: 1) Aerosolized polymyxin can be considered in addition to intravenous polymyxin when the clinical efficacy is less than desirable. In general, aerosolized polymyxin is not used alone. 2) Currently, no polymyxin preparation is available specifically for inhalation in some countries. CMS is preferred for inhalation therapy, even though all of the three intravenous polymyxin preparations are appropriate (in addition to CMS and polymyxin B sulfate, polymyxin E sulfate is also available in China). Relevant adverse events (especially bronchospasm) caused by inhalation should be monitored closely.

Evidence summary: Seven observational studies (N = 1177) (36-42) compared the efficacy of aerosolized CMS plus intravenous CMS versus intravenous CMS alone (or combined with other intravenous antimicrobial agents) in the treatment of VAP/HAP caused by resistant pathogens such as CRAB/MDR A. baumannii, CRPA/MDR P. aeruginosa, and CRE (mainly CRKP)/MDR K. pneumoniae (36-40). Six observational studies described the administration of inhaled colistin (36-40,42) For spontaneously breathing patients or extubated patients, inhaled colistin was delivered by a jet nebulizer (36,37,39), vibrating-mesh nebulizer (40), ultrasonic nebulizer (39), or with oxygen flow (38). For patients receiving ventilator support, inhaled colistin was delivered by ventilator (38,40), vibrating plate nebulizer (42), or ultrasonic nebulizer (39). Compared to intravenous CMS alone, intravenous CMS plus aerosolized CMS therapy may be associated with an average of 50 fewer deaths (RR = 0.86, 95% CI 0.72-1.03) (Online supplement Fig. S5.1), 77 fewer clinical treatment failure (RR = 0.82, 95% CI 0.70-0.96) (Online supplement Fig. S5.2) (36-42) and an average of 62 fewer pathogen eradication failure (N = 607, RR = 0.84; 95% CI 0.69-1.03) (Online supplement Fig. S5.3)(37, 39-42) in every 1000 patients treated, but the certainty of these evidence are either low or very low, which indicates these effect might be altered by future study. SoF available in Online Supplement Table.

One study showed that aerosolized plus intravenous CMS therapy was associated with significantly fewer days of mechanical ventilation than intravenous CMS alone (8 vs 12 days, P Z 0.001). Aerosolized plus intravenous CMS therapy was an independent predictor of clinical cure (39). There appears no obvious difference in 28-day ventilator weaning rate between aerosolized plus intravenous CMS therapy and intravenous CMS alone in HAP patients (50.6% vs 44.0%) (36).

Rationale for recommendation: 1) Intravenous polymyxin combined with aerosolized polymyxin may reduce mortality rate, clinical treatment failure, and increase clearance of pathogens. 2) Polymyxin inhalation is relatively simple to operate in clinical practice.

PICO question 6. should ceftazidime-avibactam be preferred over other antibacterial therapies for the treatment of serine carbapenemase-producing CRE infections?

Recommendation: Ceftazidime-avibactam is suggested to treat infections caused by CRE producing serine carbapenemase, including KPC and OXA-48, which may be more effective than other antibacterial therapies (weak recommendation, very low-quality evidence).

Implementation consideration: It is suggested to determine the carbapenemase type and/or ceftazidime-avibactam susceptibility of CRE isolate before initiation of treatment. The application should be a joint decision by doctor and patient in healthcare settings where ceftazidime-avibactam is outside of medical insurance coverage.

Evidence summary: Five observational studies (N = 592) compared the efficacy of ceftazidime-avibactam versus other antimicrobial agents in the treatment of infections caused by CRE (43-45), CRKP (97% KPC-producing strains) (46), and KPC-producing CRKP (47). One study characterized the genotypes of CRE isolates (OXA-48 positive in 62%, KPC-positive in 12%, and NDM-positive in 26% of the 61 strains) (45). Infections included bloodstream infection (45,46) and multiple site infections (bloodstream, pulmonary, urinary tract, and intraabdominal infections) (43,44,47). Compared to other antimicrobial therapies, ceftazidime- avibactam may be associated with, on average, 182 fewer deaths (N = 592, RR = 0.55, 95% CI 0.42-0.72) (Online supplement Fig. S6.1) (43-47), 307 fewer treatment failures (N= 247, RR = 0.49, 95% CI 0.34-0.70) (Online supplement Fig. S6.2) (43,45,46 52), fewer relapse (N = 455, RR = 0.67, 95% CI 0.39-1.14) (Online supplement Fig.S6.3), (43,45-47) 179 fewer pathogen eradication failure (N = 127, RR = 0.37, 95% CI 0.16-0.83) (Online supplement Fig. S6.4) (43,45), and 95 fewer acute renal injury (N= 242, RR = 0.55, 95% CI

0.23-1.33) (Online supplement Fig. S6.4) (44-46) per 1000 patients treated, but due to the low certainty of evidence, these observed effect may change by future studies. Ceftazidime-avibactam had a shorter mean length of ICU stay compared to the control group (44.9 ± 7.6 and 55.9 ± 7.8 days, respectively), but the difference was not significant (43). Clinical harm associated with ceftazidime-avibactam treatment was not observed in these studies. Quality of the body of evidence derived from observational studies is very low. SoF available in Online Supplement Table.

Rationale for recommendation: 1) In China, the majority of CRE strains, especially CRKP, produce KPC enzymes. Nearly 100% of KPC-producing and OXA48-producing CRE strains are susceptible to ceftazidime-avibactam (48). 2) Our meta-analysis shows that in patients with CRE infection, ceftazidime-avibactam treatment may reduce the risk of mortality and treatment failure. Incidence of adverse events is low during ceftazidime-avibactam treatment. 3) Although the cost of ceftazidime-avibactam is relatively high, a study demonstrated ceftazidime-avibactam is a cost-effective treatment for CRE bacteremia and pneumonia (49).

PICO question 7. should ceftazidime-avibactam combined with aztreonam be preferred over other antimicrobial therapies for the treatment of infections caused by metallo-β-lactamases-producing CRE?

Recommendation: Ceftazidime-avibactam combined with aztreonam is suggested as a preferential choice over other antimicrobial therapies for the treatment of infections caused by metallo-β-lactamases-producing CRE (weak recommendation, very low-quality evidence).

Implementation consideration: In practice, the carba-penemase type produced by CRE strain should be ascertained before initiation of ceftazidime-avibactam treatment, whenever possible.

Evidence summary: Aztreonam shows good in-vitro synergy activities with ceftazidime-avibactam against NDM- producing and KPC-producing CRKP isolates, as, aztreonam is not hydrolyzed by metallo-β-lactamases (50,51). One prospective study evaluated treatment outcome of patients with bloodstream infection caused by metallo-β-lacta- mases-producing CRE (52). The 30-day mortality rate was 19.2% in 52 patients received ceftazidime-avibactam plus aztreonam and 44% in 50 patients treated with other active antimicrobial agents (P = 0.007). Ceftazidime-avibactam combined with aztreonam was associated with lower 30-day mortality rate (HR: 0.37, 95% CI 0.13-0.74), lower clinical treatment failure

rate (HR: 0.30, 95% CI 0.14-0.65), and shorter length of hospital stay (HR: 0.49, 95% CI 0.30-0.82) (52). In another study including 57 cases of CRE infection (71.9% critical cases, 57.9% intraabdominal infection and HAP), the curative rate was 77.5% in 40 patients who received ceftazidime-avibactam combined with aztreonam (plus polymyxin or fosfomycin if indicated) for treatment of NDM- or NDM ＋ OXA-48-positive CRE infection, and 82.3% in 17 patients who received ceftazidime-avibactam alone (plus polymyxin or fosfomycin if indicated) for treatment of OXA-48-positive CRE infection, The overall mortality rate was 21% (53). Quality of evidence on critical outcomes from these two studies is very low.

Rationale for recommendation: 1) Studies indicate that ceftazidime-avibactam combined with aztreonam is associated with lower mortality rate and clinical treatment failure rate compared to other antimicrobial therapies in treatment of CRE infections. However, the GDG has low confidence in the observed efficacy due to very low certainty of evidence. 2) Aztreonam combines with ceftazidime-avibactam shows good invitro synergy activities against CRE produces metallo-β-lactamases. 3) Overall, the GDG believes the benefit of ceftazidime-avibactam combined with aztreonam probably outweighs potential harm (very low quality evidence).

PICO question 8. should tigecycline-based combination therapy or polymyxin-based combination therapy be preferred in treatment of CRAB pulmonary infections?

Recommendation: Both tigecycline-based combination therapy and polymyxin-based combination therapy are equally preferable in the treatment of pulmonary infection caused by CRAB. Choice of therapy regimen should be made according to patient's condition (weak recommendation, very low-quality evidence).

Implementation consideration: 1) In practice, the GDG suggests choice of antimicrobial regimen should balance strength and weaknesses of tigecycline-based and polymyxin-based combination therapy based on the clinical conditions. 2) It is suggested to determine the MIC value of tigecycline against CRAB before treatment initiation. Studies indicated that tigecycline treatment achieved higher success rate when MIC is ⩽2 mg/L (54). 3) Polymyxin should be used judiciously in patients with renal insufficiency and tigecycline should be used cautiously in patients with liver insufficiency.

Evidence summary: Seven retrospective observational studies (N = 745) evaluated the efficacy of tigecycline-based versus CMS-based antimicrobial therapies in treatment of

infections caused by CRAB, MDR, or XDR A. baumannii, five of which were pulmonary infection (54-58), and two studies on multiple site infections with pulmonary infection accounting for 74.5% (59) and 50.5% (60) of patients. The antimicrobial regimens were primarily antimicrobial combinations (e.g., in combination with carbapenems, sulbactam, aminoglycosides, rifampicin, minocycline, doxycycline, or fosfomycin).

Compared to CMS-based combination therapies, tigecycline-based therapy was associated with an average of 58 more deaths (N = 658, RR = 1.12, 95% CI 0.95-1.33) (Online supplement Fig. S8.1), an average of 90 more clinical treatment failure (N = 190, RR = 1.17, 95% CI 0.91-1.51) (Online supplement Fig. S8.2) (57-59) and an average of 225 fewer nephrotoxicity (N = 383, RR = 0.23, 95% CI 0.11-0.46) (Online supplement Fig. S8.3) (54, 55, 58, 59) in every 1000 patients treated, but due to the low and very low certainty of evidence, the observed differences between groups may be changed by future studies. A retrospective observational study showed that pathogen eradication rate did not show significant difference between tigecycline-based and CMS-based treatment groups (23% vs 30%, P = 0.54) (58). Another study reported that the clinical efficacy of tigecycline was associated with its MIC value against MDR A. baumannii. Its efficacy was comparable to polymyxin when tigecycline MIC $\leqslant$ 2 mg/L, and inferior to polymyxin when tigecycline MIC >2 mg/L (54). One study reported that tigecycline-based therapy was associated with significantly lower incidence of nausea and vomiting (6.3% vs. 35.9%, P = 0.025; N = 55), but significantly higher incidence of abdominal pain (18.8% vs. 2.6%, P = 0.036; N = 55), and possibly higher but statistically insignificant incidence of other adverse events, such as thrombocytopenia and aspartate aminotransferase elevated (59). These retrospective studies were of very low-quality evidence. SoF available in Online Supplement Table.

Tigecycline is a broad-spectrum antibiotic which can potentially reach high tissue concentration, for example, the concentration of tigecycline in lung was 2 times higher than the simultaneously concentration in serum (61). Tigecycline is recommended for treatment of pulmonary and intra-abdominal infections caused by CRAB and CRE (7,8,9,10). The in vitro antibacterial activity of eravacycline was 2-8 times higher than that of tigecycline against CRAB and CRE. Eravacycline showed higher concentration in lung tissue and lower incidence of adverse events than tigecycline. Therefore, eravacycline appears to have advantages over tigecycline (62,63), the clinical efficacy of which requires further studies to confirm.

Rationale for recommendation: 1) Both tigecycline-based and polymyxin-based combination therapies have their unique strengths and weaknesses. Tigecycline-based combination therapy may reduce the incidence of adverse events such as nephrotoxicity, but its efficacy is numerically lower than polymyxin-based combination therapy. 2) Current evidence is derived from observational studies and deemed to be very low quality, therefore the GDG is uncertain about the observed magnitude of effect. 3) Combination therapy including two in vitro active antibiotics such as polymyxin, tigecycline, eravacycline is recommended for the treatment of CRAB infection in the ESCIMD and IDSA guidelines (8,9,10). Overall, the GDG believes either tigecycline-based or polymyxin-based combination therapy can be used for treatment of CRAB pulmonary infections as clinically indicated.

PICO question 9. should sulbactam-containing combination or non-sulbactam-containing combination be recommended for the treatment of CRAB infections?

Recommendation: Sulbactam or sulbactam-containing β- lactamase inhibitor combination therapy regimens are suggested for the treatment of CRAB infections (weak recommendation, low-quality evidence).

Implementation consideration: 1) In clinical practice, sulbactam or sulbactam-containing b-lactamase inhibitor combination is usually augmented with tigecycline, polymyxin, doxycycline, or minocycline according to the results of antimicrobial susceptibility testing. 2) The sulbactam- containing combination therapy is not indicated for patients who are hypersensitive to penicillin. 3) The dose of sulbactam can be increased to 6.0-9.0 g/d for severe CRAB infections.

Evidence summary: Of the four RCTs investigating VAP caused by CRAB or MDR A. baumannii (N = 142) (30,64-66), three used ampicillin-sulbactam-based combination therapy (combined with intravenous or aerosolized polymyxin, meropenem), and one used ampicillin-sulbactam alone. Intravenous polymyxin alone or in combination with aerosolized polymyxin or meropenem was used as control groups.

Compared to the control groups, ampicillin-sulbactam-based therapies had an average of 103 fewer 28-day mortality (RR = 0.77, 95% CI 0.51-1.15) (Online supplement Fig. S9.1), 140 fewer treatment failure (RR = 0.72, 95% CI 0.49-1.04) (Online supplement Fig. S9.2), 255 fewer pathogen eradication failure (RR = 0.49, 95% CI 0.31-0.77) (Online supplement Fig.

S9.3), and 134 fewer acute renal injury (N = 103, RR = 0.54, 95% CI 0.25-1.14) (Online supplement Fig. S9.4) (64-66) per 1000 patients. All of the above were of low quality of evidence, indicating the observed effect could be altered by future studies. SoF available in Online Supplement Table.

One retrospective study in China included 210 cases of CRAB bloodstream infection showed that cefoperazone-sulbactam group had significantly lower 28-day mortality rate (29.3%, 22/75) than tigecycline group (51.9%, 70/135) (P = 0.001), and cefoperazone-sulbactam combined with imipenem-cilastatin had significantly lower mortality than cefoperazone-sulbactam alone (P = 0.048) (67). One systematic review with 29 included studies (N = 2529 patients) reported no clear difference among various antimicrobial regimens in the treatment of infections caused by MDR/XDR.

A. baumannii. However, polymyxin plus sulbactam-containing combination resulted in higher pathogen eradication rate than polymyxin combined with tigecycline, and safety was comparable to polymyxin monotherapy (68). Another systematic review with 18 included studies demonstrated that high-dose sulbactam (⩾6 g/d) in combination with tigecycline or levofloxacin achieved higher clinical cure rate and efficacy rate than other antimicrobial regimens, while polymyxin-based combination therapy group had higher risk of nephrotoxicity than other antimicrobial treatments (69).

Rationale for recommendation:1) Sulbactam-containing combination therapies demonstrated clinical benefits. 2) Ampicillin-sulbactam and cefoperazone-sulbactam are the two sulbactam combination available, while the former is used worldwide, the latter is mainly used in some Asian countries. The most frequently pre-scribed β-lactamase inhibitor in China is cefoperazone-sulbactam, because the in vitro antimicrobial susceptibility testing demonstrated that A. baumannii isolates in China were more susceptible to cefoperazone-sulbactam than to ampicillin-sulbactam (resistance rates 48.8% vs 59.1% in 2021) (3,4). 3) With consideration to the above, the GDG believes the aforementioned interventions is likely to produce clinical benefit despite of the low quality of evidence.

PICO question 10. Should aminoglycosides-containing combination therapy be recommended for improving clinical efficacy of CRE infections?

Recommendation: Combination therapies containing amikacin or other aminoglycosides are suggested for treatment of CRE infection in patients without contraindication for aminoglycoside use. (Conditional recommendation, very low quality evidence).

Implementation consideration: The use of amino-glycoside can lead to ototoxicity and nephrotoxicity, so patient should be monitored closely for any potential adverse effects during treatment. Other nephrotoxic drugs should be avoided in the combination regimen. It is suggested that TDM should be performed during aminoglycoside treatment if available, especially when high dose is administered. CRE strains may show highly variable susceptibility to different aminoglycoside drugs. For example, CRE isolates in China showed significantly higher susceptibility to amikacin than to gentamicin (4). Aminoglycosides should be prescribed appropriately according to the results of local antimicrobial susceptibility testing.

Evidence summary: We included nine observational studies on CRE infection (N = 608 patients) with aminoglycoside-containing regimens for the treatment of bloodstream infection (70-74), urinary tract infection (75), multiple infections (bloodstream, pulmonary, urinary tract, surgical site, intraabdominal, and skin and soft tissue infection) (76-78). The therapy regimens include gentamicin (N = 174) (70,77), amikacin (N = 160) (71,72,76,78), both gentamicin and amikacin (N = 274) (73-75), as well as combination therapies (e.g., in combination with tigecycline, polymyxin, carbapenem, or fosfomycin). The antimicrobial regimens used in control groups include tigecycline-, polymyxin-, or fosfomycin-containing combination therapies.

Compared with combination therapies without amino-glycosides, aminoglycoside-containing combination therapy had an average 59 fewer deaths (N = 525, RR = 0.86, 95% CI 0.69-1.07) (Online supplement Fig. S10.1) (70-74,76-78) and had 417 fewer clinical treatment failure (N = 84, RR = 0.41, 95% CI 0.25-0.69) (Online supplement Fig. S10.2) (75, 76) per 1000 patients in the treatment of CRE infection, but the certainty of evidence are very low indicating future studies may well change the current observed effect. There were no adverse events reported in these studies relating to aminoglycoside-containing combination therapy. However, the quality of evidence derived from these studies is very low, which limits our confidence in the estimates of effects. SoF available in Online Supplement Table.

Rationale for recommendation: 1) Aminoglycoside-containing combination therapy may improve curative rate and reduce mortality rate in the treatment of CRE infections. 2)

Aminoglycosides are easily accessible and inexpensive. 3) With consideration to the above, the GDG concludes that the clinical benefits probably outweigh any potential harms in patients without contraindications to aminoglycoside use, despite of low quality of evidence.

PICO question 11. Should intravenous fosfomycin- containing combination therapy be recommended for patients with CRE infections?

Recommendation: It is suggested to use intravenous fosfomycin-containing combination therapies for patients with CRE infection when CRE isolate is susceptible to fosfomycin or fosfomycin combination has synergistic effect on the CRE isolate (conditional recommendation, very low-quality evidence).

Implementation consideration: 1) Before treatment initiation, pathogens should be confirmed to be susceptible to fosfomycin through antimicrobial susceptibility testing or fosfomycin-containing combination has synergistic effect confirmed by antimicrobial synergy testing. 2) Patients with hypernatremia, cardiac or renal insufficiency should avoid use of fosfomycin.

Evidence summary: Fosfomycin susceptibility rates in CRKP are variable, from 39% to 99% (79) fosA-like genes may be prevalent in CRKP causing fosfomycin resistance (50,80). Fosfomycin presents synergistic in-vitro activity against CRKP even if against CRKP strains carrying fosA-like genes (50). Four observational comparative studies (N = 213, including one study of neonatal infection) (70,81- 83). compared the efficacy of fosfomycin-containing combination therapies versus other antimicrobial combinations in the treatment of CRKP infection, including sepsis, bacteremia, urinary tract infection, or multiple infections. The antimicrobial agents used to combine with fosfomycin included tigecycline, polymyxin, and carbapenems. Compared to the control groups, fosfomycin-containing combination therapy had an average of 114 fewer deaths (RR = 0.55, 95% CI 0.28-1.10) (Online supplement Fig. S11.1) per 1000 patients in the treatment of CRKP infections (very low-quality evidence) (70,81-83). Due to the very low certainty in evidence, the current observed effect may be changed by future studies. SoF available in Online Supplement Table.

One Italian study compared the outcomes of ceftazidime-avibactam plus fosfomycin combination with ceftazidime-avibactam plus other antimicrobials in the treatment of bloodstream infections caused by KPC- producing K. pneumoniae (KPC-Kp). It found no difference in overall mortality between these two groups, while the control group had more new non-bloodstream KPC-Kp infections and a higher number of deaths attributable to

secondary infections (84). One single-arm observational study in Greece reported 48 ICU patients with CRKP and CRPA infection (including bloodstream infection and VAP) who received fosfomycin-containing combination therapy, primarily in combination with polymyxin or tigecycline (85). In this study, all the bacterial isolates were susceptible to fosfomycin, the treatment efficacy was 54.2%, the bacterial eradication rate was 56.3%, the 28-day mortality rate was 37.5%, and the main adverse reaction was reversible severe hypokalemia (15.2%). Antimicrobial resistance emerged during treatment in 3 patients (85). A systematic review suggests that intravenous fosfomycin is generally safe and the adverse reactions are mild in general (86).

Rationale for recommendation: 1) Fosfomycin has synergistic in vitro activity against CRKP. 2) Evidence derived from observational studies suggests that fosfomycin-containing combination therapy may reduce mortality rate in treatment of CRE infections. However, the quality of evidence is very low indicating low certainty in the treatment efficacy and clinical benefit. 3) The adverse reactions of fosfomycin are mostly reversible. Fosfomycin treatment is generally safe. After comprehensive assessment of the balance between benefit and harm, the GDG believes that fosfomycin-containing combination therapy probably yields more benefits than harm.

PICO question 12. Should antimicrobial TDM be performed during the treatment of CRGNB infections?

Recommendation: It is suggested to perform TDM where possible in patients receiving polymyxins, aminoglycosides, or carbapenems for treatment of CRGNB infections (weak recommendation, very low quality evidence).

Implementation consideration: Antimicrobial TDM has important clinical value in treatment of CRGNB infections, especially in critical cases of CRGNB infections. Antimicrobial TDM should be carried out whenever possible in the following cases: 1) Narrow therapeutic index drugs including polymyxins and aminoglycosides, for which, small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity (87). 2) Antimicrobial agents, the dosage of which is difficult to adjust in case of organ dysfunction or hyperfunction, such as renal insufficiency or hyperfunction; 3) The sites of infection that are difficult to reach effective therapeutic concentration, such as central nervous system, and severe infections, such as bloodstream infection and sepsis.

Evidence summary: One systematic review with two RCTs and three retrospective comparative cohort studies evaluated the effect of carbapenems TDM on the treatment outcome in adults with severe infection, sepsis, or septic shock. The results indicated that TDM may be associated with therapeutic target attainment and clinical cure rate (clinical cure was defined as 80% of reduction in procalcitonin level or favorable outcome and resolution of infection), but may not be associated with reduction of mortality rate (low quality evidence) (88). In a report involving 30 cases of infection caused by KPC-producing CRKP, meropenem MIC was ⩾16 mg/L for the CRKP strains isolated from 16 (53.3%) patients who received continuous intravenous infusion of high dose meropenem combined with polymyxin or tigecycline. The dosage was adjusted according to real-time TDM, leading to treatment success rate of 73.3% after a median treatment of 14 days. The clinical efficacy was significantly correlated to Css/MIC ratio ⩾1. This study suggests that real-time TDM can improve the outcome of patients who receive continuous IV infusion of high dose meropenem combination therapy for treatment of CRKP infection (89).

In 2020, several international societies jointly issued a position paper on the antimicrobial TDM for critically ill patients, recommending TDM for aminoglycosides and b-lactams including carbapenems, and neither supporting nor opposing polymyxin TDM. Aminoglycoside TDM can optimize dosing regimen, improve treatment efficacy, and reduce incidence of nephrotoxicity during the treatment of gram-negative bacterial infections in critically ill patients (90). One study reported that TDM-guided gentamicin treatment (n = 105) was associated with shorter hospital stay (20.0 ±13.7 vs 26.3 ± 31.5 days), lower mortality rate (8.6% vs 14.2%), and lower incidence of nephrotoxicity (2.8% vs 13.4%) compared with non-TDM-guided gentamicin (n = 127) in the treatment of Gram-negative bacterial infections (91).

In 2019, the international consensus on optimal application of polymyxins recommended that TDM should be carried out for clinical use of polymyxins, which can optimize dosage, improve clinical efficacy, and reduce adverse reactions (92). An international multicenter study showed that 162 critically ill patients with various levels of renal function received polymyxin E treatment at the dose recommended by the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA), resulting in highly variable rates of reaching average plasma steady-state concentration ($C_{ss,\ avg}$). The dose recommended by the EMA achieved higher rate of attaining therapeutic target than the dose recommended by the FDA.

For patients with creatinine clearance rate ≤80 ml/min, both recommended doses yielded $C_{ss,avg} \geqslant 1$ mg/L in only 65%-75% of the patients (93). This study suggests that TDM is necessary in critically ill patients to adjust the individualized doses of polymyxins to reach effective target therapeutic concentration.

Rationale for recommendation: As demonstrated by the above evidence, TDM can inform clinicians to prescribe timely and precise dosing regimen, the GDG concludes that TDM probably results in more benefits than harms. TDM should be performed as far as possible for the main categories of antibiotics used to treat CRGNB infections.

Prevention and control of nosocomial infections caused by CRGNB

CRGNB infections are mostly hospital-acquired. Effective implementation of infection control measures is paramount in the prevention and control of CRGNB infections. This section investigates the effect of measures such as active CRE screening and contact isolation, decolonizing intestinal CRE, and sink design and placement in hospital units on the prevention and control of CRGNB.

PICO question 13. Should active CRE screening be performed in hospital settings, particularly for patients with hematologic malignancy, be recommended to receive CRE screening before chemotherapy or transplantation?

Recommendation: It is recommended to actively screen for CRE carriage in the following populations in hospital setting (conditional recommendation, very low quality evidence):

1) patients with a history of CRE colonization/infection; 2) patients sharing hospital wards with other patients who have CRE colonization/infection; 3) patients who are expected for ICU admission (including neonatal ICU) for greater than 2 days; 4) patients with hematologic malignancy before chemotherapy, solid organ, bone marrow or hematopoietic stem cell transplantation, and febrile neutropenic patients.

Implementation consideration: The decision to perform active CRE screening and in which populations to perform screening is determined by individual healthcare facilities, with reference to the actual local situations, specific needs and feasibility in the individual facilities (e.g., prevalence of CRE in specific population, distribution pattern in each ward/department, screening tests and methods available locally). It is suggested to collect feces for CRE screening from patients with low platelet count or rectal/perianal lesions (such

as abscess or ulcer). Selective culture media can be used for bacterial culture. Genetic testing for carbapenem resistance can also be used in health care facilities if possible.

Evidence summary: A systematic review reanalyzed 17 studies meeting the effective practice and organization of care (EPOC) criteria and interrupted time series (ITS) design. The results of which indicates that bundle interventions including active screening for infection prevention and control could reduce incidence of CRE, CRAB and CRPA infection or colonization (94). Nine CRE-related studies demonstrated that series of interventions including active screening significantly reduced the incidence of CRE infection or colonization (slope change: -0.01 to-3.55, level change or immediate change: -1.19 to -31.80). Four studies showed that the incidence of CRE infection per 10000 patient-days reduced significantly after interventions (slope change: -0.32 to -3.55, level change: -1.19 to -31.80). A study in Israel demonstrated that weekly active screening of intestinal CRKP in addition to contact precautions for hospitalized patients in ICU and in step-down units during an outbreak of CRKP infection decreased the rate of CRKP infection in high-risk units by 4.7-fold at 17 months after implementation of active screening intervention (95). The evidence currently available is derived from observational studies with relatively high risk of bias. Moreover, it is difficult to accurately judge what proportion of the observed clinical benefits is directly related to screening. Due to the lack of direct evidence, the body of evidence for critical outcomes is of very low quality.

Three before-and-after intervention studies (N = 2971) in China (96-98) evaluated the effect of CRE screening (continuous or one-off) versus no screening in patients undergoing hematopoietic stem cell transplantation, receiving chemotherapy or immunotherapy. Active CRE screening on average reduced 13 cases of CRE infection (RR = 0.47, 95% CI 0.29-0.77) (Online supplement Fig. S13.1) and 12 deaths (RR = 0.32, 95% CI 0.16-0.64) (Online supplement Fig. S13.2) in every 1000 patients compared to no active screening. The quality of the body of evidence is very low. SoF available in Online Supplement Table.

Rationale for recommendation: 1) Studies on active CRE screening consistently show that the incidence of CRE infection decreases significantly with implementation of screening, suggesting such an intervention may bring some clinical benefits. 2) Active CRE screening using conventional methods (such as collecting feces or rectal swabs) is feasible and acceptable in most healthcare facilities. 3) Active screening may incur additional health resource consumption and potential harms (such as mucosal damage caused by rectal swab

sampling). The space for isolation of CRE carriers is very limited in many medical institutions. Overall, the GDG agrees that active screening is favorable because its benefits outweigh costs and harms.

PICO question 14. Should bundle interventions including contact isolation of CRGNB infected patients/carriers be implemented to prevent CRGNB infections?

Recommendation: It is recommended to adopt bundle intervention scheme including single room or cohorting isolation for patients with CRGNB infections or colonization in hospital settings (strong recommendation, low quality evidence).

Implementation consideration: 1) Single room isolation is preferred, and separate toilet should be provided for those infected/colonized with CRGNB. 2) When resource is limited (e.g. too many patients requiring isolation while too few rooms available), priority of single room isolation should be given to those with fecal or urinary incontinence, using invasive device/equipment, or having continuous wound secretion; cohorting isolation for those infected or colonized with the same CRGNB species. 3) Nursing staffs designated to care for patients with CRGNB infections or colonization should not participate in caring for other patients (Nursing staff cohorting). 4) It is recommended that no caregivers be permitted to stay in the ward to care for the isolated patients.

Evidence summary: Bundle management measures such as contact isolation and active screening are closely linked to the prevention and control of nosocomial infection. Usually, the first step is screening, followed by isolation. Therefore, the evidence and conclusions of several studies are the same as those in PICO 13 (94). Three CRAB-related studies showed that multiple interventions including isolation of infected/colonized individuals reduced the rate of CRAB infection/colonization significantly (slope change from -0.01 to -4.81) (94). Multiple interventions including isolation reduced the rate of CRPA infection/colonization significantly (slope change: -1.36) (94). A study in a Korean hospital demonstrated that active contact precautions and isolation combined with intensive hand hygiene education and active monitoring significantly decreased the rate of CRE infection or colonization (99). A Chinese study reported that active screening of CRE colonization was implemented for the hospitalized children across CRE high-risk departments (pediatric ICU, neonatal ICU, and hematology), and more than 80% of the CRE-positive neonates were isolated in single room or cohorting isolation. These interventions reduced the incidence of nosocomial CRE infection from 1.96% to 0.63% in neonatal ICU, from 0.57% to 0.30% in general neonatal

wards ($P < 0.05$). However, in the same period, the rate of nosocomial CRE infection showed no significant change in other non-neonatal wards where isolation was not implemented (100). The evidence currently available is derived from observational studies. The evidence is somewhat indirect, and the quality of the evidence for critical outcomes is low or very low.

Rationale for recommendation: 1) Although no high-quality RCT has been conducted to explore this clinical question, observational studies consistently show that bundle management scheme including contact isolation may reduce the rate of CRGNB infection or colonization in hospitalized patients. 2) Expert experience derived from clinical practice shows that bundle management including isolation is generally well accepted during clinical management, and it is feasible in most medical institutions. However, the feasibility of single room isolation is poor in some countries, and no sufficient single rooms are available for CRGNB-infected/colonized patients in most medical institutions. 3) Isolation may cause psychological discomfort in some patients and increase consumption of health resources, particularly single room isolation. The GDG agrees that clinical adoption of bundle management scheme including isolation results in more benefits than harm.

PICO question 15. Should patients with CRE colonization, particularly those with hematologic malignancy be recommended for intestinal CRE decolonization?

Recommendation: The GDG does not support or refute intestinal CRE decolonization in clinical practice (no recommendation, low quality evidence).

Implementation consideration: The evidence currently available is insufficient to either support or refute intestinal CRE decolonization. Intestinal decolonization should be considered on individual case basis, and fully evaluate its potential benefit (the possibility of progression to infection, e.g., whether the patient is in a state of serious immunodeficiency or poor immunity) and harm (impairing the intestinal flora and causing collateral damage). At present, no definitely effective protocol is available for decolonization.

Evidence summary: Two RCTs (N = 192) (101,102) and one observational before-and-after controlled study (N = 221) (103) from Israel evaluated the effect of intestinal CRE decolonization. The regimen for decolonization included oral gentamicin or polymyxin E alone or in combination for 7 or 60 days (101,102), oral gentamicin or amikacin combined with neomycin for 10 days or until discharge (103). These RCTs demonstrated that intestinal CRE decolonization is effective and on average reduced 238 all-cause deaths (RR = 0.50,

95% CI 0.31- 0.82) (Online supplement Fig. S15.1) and increased 296 cases of successful eradication (RR = 3.58, 95% CI 2.16-5.94) (Online supplement Fig. S15.2) per 1000 patients compared to the control groups.101,102 The quality of overall evidence is low. Another before-and-after controlled study indicated that CRE decolonization was ineffective. The rate of intestinal CRE eradication was comparable between the intervention group receiving decolonization and the control group. The median days to intestinal CRE eradication was 72 days in the decolonization group and 65 days in the control group, respectively.103 SoF available in Online Supplement Table.

Rationale for recommendation: 1) Current evidence indicates that intestinal CRE decolonization may reduce all-cause mortality, but the quality of evidence is low, and the GDG has low certainty on the observed effect. 2) Intestinal CRE decolonization is likely to be cost-effective without prominent negative impact on the consumption of health resources. 3) Based on their clinical experience, the GDG suggests that intestinal CRE decolonization is relatively well acceptable and feasible in clinical settings. The potential obstacle to feasibility is the lack of clinical research evidence on the best decolonization protocol, thus no consensus is available for the time being.

PICO question 16. Should handwashing sink be removed from areas directly related to patient's treatment for the purpose of CRGNB prevention and control?

Recommendation: It is suggested to remove sink from areas directly related to patient's treatment (e.g., ward, treatment room where invasive procedures are performed) under the following conditions (conditional recommendation, low quality evidence): 1) healthcare facilities under construction or reconstruction, where the above recommendation can be incorporated; 2) In existing healthcare facilities, if resources permit, handwashing sinks should be removed from areas directly related to patient's treatment in wards at high risk of CRGNB infection, such as ICUs, neonatal, hematology, burns and other wards where handwashing sink has been installed.

Implementation consideration: 1) Sink/basin dedicated to handwashing can be placed outside the area for patient management, for example, corridor outside the ward, medical staff working areas. 2) For wards at high risk of CRGNB infections and already equipped with a sink, the sink should be removed or relocated as far away from the patient's bedside as possible; If it is not feasible to adjust the location, consider installing a baffle made of smooth, disinfectant resistant and moisture-proof materials on the side of the sink, and the

height should be sufficient to prevent water from splashing out of the baffle. 3) The handwashing sink/basin should be used only for hand hygiene, and should not be used for disposing body fluid and excreta, cleaning equipment and other purposes.

Evidence summary: A 6-year longitudinal observational study (104) in Spain showed that in an ICU, implementation of interventions such as removal of all sinks, implementation of water-safe policy, medical staff hand hygiene, and environmental cleaning reduced annual incidence rate of MDR GNB (K. pneumoniae and P. aeruginosa) infection from 9.15 per 1000 patient-days before removal of sinks to 2.20 per 1000 patient-days after removal of sinks. The spread of resistant bacteria was successfully contained.104 A before- and-after controlled study demonstrated that removal of sinks in ICU and introduction of "water-free patient care" significantly reduced rate of GNB colonization in ICU patients, from 26.3 to 21.6 per 1000 ICU patient-days (RR = 0.82, 95% CI 0.67-0.95). The reduction in GNB colonization rate became more pronounced in patients with a longer ICU-Length of Stay (LOS): from a 1.22-fold reduction (⩽2 days), to a 1.6-fold (⩽5 days; P = 0.002), 2.5-fold (for 10 days; P < 0.001) to a 3.6-fold (14 days; P < 0.001) reduction (105). A quasi-experimental study in Spain investigated the prevalence of non-fermenting gram-negative bacilli in bronchoaspirate samples in ICU before and after sink removal and found that the incidence density ratio decreased significantly from 11.28/1000 to 1.91 isolates/1000 ventilated days (deceased 5.90 times, 95% CI:1.49-51.05, P=.003) (106).

Rationale for recommendation: Contaminated sink promotes spread of drug-resistant bacteria and outbreak of infection in hospital (107). Current evidence shows that removal of handwashing sinks may reduce the risk of transmission and infection of drug-resistant bacteria in ICU, although the quality of evidence is low, indicating uncertainty on the observed effect. However, the GDG believes that benefit of removing handwashing sink may outweigh any potential harm. Feasibility of removing sink varies across hospitals, and likely to incur additional costs, which must be considered when implementing the recommendation.

Conclusions

Antimicrobial resistance (AMR) is a major threat to human health. Healthcare professionals have to address the increasing challenge of CRGNB in clinical practice. This CPG used a rigorous approach to produce 16 recommendations relevant to the diagnosis, treatment, and prevention of CRGNB infection. Its strength includes adherence to the requirement for

trustworthy guideline, and the application of the WHO endorsed GRADE EtD framework which reinforces transparency in this process. The transparency in production and reporting promotes scientific discourse and improves usability of this guideline for clinicians in various settings. The GDG recognizes the lack of high-quality evidence for some recommendations is a limitation of this CPG, but tried to take this in to consideration in forming recommendations. Further studies orientated by clinical problems will be needed to address knowledge gaps and help inform the choice of optimal antimicrobial therapy for CRGNB infections, assess the utility of in vitro testing and infection prevention control measures to predict clinical outcomes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at

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Chapter 5. Knowledge dissemination: training and evidence

Chapter highlights

This Chapter highlights how the author led dissemination of systematic reviewing skills to researchers globally via popular YouTube-based software training and how she helped lead empirical evaluation of micro-blogging techniques (Twitter/Weibo, Wechat) (paper 5). To date, there has been 218,231 viewings of the YouTube tutorial, creating enormous impact for the funder (University of Nottingham) and The Cochrane Collaboration.

Chapter background

Dissemination of the knowledge gained through research is an integral part of research process(27-29). In all areas of public health and medical practise, as well as in sectors as diverse as education, engineering, music, psychology, commerce and agriculture, there is a gap between research and practise(30, 31) and ineffective dissemination is a major contributing factor of this 'translation gap'(32, 33). Researchers have always understood the value of sharing their discoveries and, increasingly, it has become necessary to actively plan dissemination for relevant impact(34).

With the arrival of internet and other digitally networked technologies, the way of disseminating research is also evolving(35). Over the past 20 years most scholarly paper journals have moved online and increasing numbers are solely online. However, during this transformation, these conventional communication tools have generally kept the same features and forms. Digital distribution, however, can take place in a variety of ways outside of conventional channels: social media has grown in popularity among researchers(35), and blogs and wikis have been widely utilised as a particular form of 'open notebook science' for the last decade(36). Millions of people watch Technology, Entertainment, Design (TED) talks on YouTube(37) - the global online video sharing and social media platform. Adopting these platforms and techniques may also result in fresh disciplinary alliances, opening up new options for study, publication and financing(38). Many now consider greater dissemination and involvement of the general public in science to be essential components of open science(38).

Although, Twitter (blocked in China since 2009), and some other platforms are not available in China, the usage of social media is exceptionally high with 91% of Chinese residents using some form of social media. The Twitter-like systems of Weibo and Wechat are popular in

China. Therefore, in the study presented in this chapter we used Twitter for participants outside of China, and weibo or wechat for participants in China. Additionally, this chapter describes how the author led dissemination of systematic reviewing skills to researchers globally via the popular YouTube-based software training and helped to lead the evaluation of micro-blogging techniques (paper 5) to disseminate information to researchers.

YouTube training video

Review Manager (RevMan) is Cochrane's bespoke software for writing Cochrane Reviews. It is offered to both Cochrane and non-Cochrane users free of charge for research use, but for many first-time user tuition is required to successfully navigate the software. The author created animated video tutorials consisting of 43 short video clips, each tackling a focused operation. For example, one clip shows how to enter binary outcome data in to RevMan and another how to export text of a review. These tutorial clips curated into a tutorial series are disseminated free of charge to researchers globally through YouTube. To date, there has been 218,231 viewings from global users, creating enormous impact for the funder (University of Nottingham) and The Cochrane Collaboration, while relieving the reviewers from the repetitive one-to-one software teaching which is demanding of time.

The YouTube training video on using RevMan can be accessed via the following link: https://www.youtube.com/playlist?list=PLpRE0Zu_k-Bwdb4R9rifjRcz7RD30A7Ca.

Social media (paper 5)

Twitter is a well-known, free microblogging social media site that, at the time of this trial, allowed users to post 140-character messages to lists of followers. A hashtag (#), which is used to search by topic, and/or a handle (@), which designates another Twitter user account, may both be present in a tweet. Despite the fact that Twitter (which has been restricted in China since 2009) and certain other sites are unavailable, China has a very high rate of social media usage, with 91% of its population using it, compared to 67% of US Americans. Weibo and Wechat, two platforms similar to Twitter, are the main social media platforms used in China. In 2011, Cochrane Schizophrenia Group began to use Twitter to disseminate findings of their systematic reviews. Their RCT of tweeting links versus not tweeting links of similar paired reviews showed that social media dissemination of reviews nearly tripled unique page visits to each review. A large survey of 4.8 million tweets reported that early morning tweets received most clicks compared to late eventing twits(39). There is peak tweeting activity between the hours of 11:00 and 13:00.

It is in this context that this prospective two-arm, parallel, open randomised controlled trial was carried out to determine if posting structured microblogs of treatment-related evidence on any given workday (Monday–Friday) of the week affects the Google Analytics statistic for 'all page visits' and if that encourages information-seeking behaviour. The author was a major contributing author in this research and coordinated the China/Weibo/Wechat arm of the trial.

Coda

The traditional model of scientists traveling to particular locations to gather knowledge and then disseminating it after they return home is no longer suitable in the age of Big Data. An exabyte (1 billion gigabytes) of digital data is produced every two days, equal to the amount of data generated by all society up to 2003(40). Digital technology has changed the way we access information, and has created a need for researchers to consider user behaviour and disseminate their work more broadly through multiple and non-conventional channels. As demonstrated by the papers in this chapter, modern platforms such as Twitter, Wikipedia and YouTube are more closely linked to our information acquisition behaviour than we realise. Through paper 5, the author argues that creative research dissemination can maximise the impact of research and creates value for both funders and stakeholders.

Reference for paper 5

PAPER 5. Jayaram M, Adams CE, Friedel JS, McClenaghan E, Montgomery AA, Välimäki M, Schmidt L, **Xia** J, Zhao S (2019). Day of the week to tweet: a randomised controlled trial. BMJ Open 9(4): e025380. (PAPER 5. JX as senior author. She led the Weibo and Wechat arm of the trial).

PAPER 5

Day of the week to tweet: a randomised controlled trial[5]

Abstract

Objective To assess the effects of using health social media on different days of the working week on web activity.

Design Individually randomised controlled parallel group superiority trial. setting Twitter and Weibo.

Participants 194 Cochrane Schizophrenia Group full reviews with an abstract and plain language summary web page. There were no human participants.

Interventions Three randomly ordered slightly different messages (maximum of 140 characters), each containing a short URL to the freely accessible summary page, were sent on specific times on a single day. Each of these messages sent on Tuesday, Wednesday, Thursday and Friday was compared with the one sent on Monday.

Outcome The primary outcome was visits to the relevant Cochrane summary web page at 1 week. Secondary outcomes were other metrics of web activity at 1 week.

Results There was no evidence that disseminating microblogs on different days of the working week resulted in any differences in target website activity as measured by Google Analytics (n=194, all page views, adjusted ratios of geometric means 0.86 (95% CI 0.63 to 1.18), 0.88 (95% CI 0.64 to 1.21), 0.88 (95% CI 0.65 to 1.21), 0.91 (95% CI 0.66 to 1.24) for Tuesday–Friday, respectively, overall p=0.89). There were consistent findings for all outcomes. However, activity on the review site substantially increased compared with weeks preceding the intervention.

Conclusion There are no clear differences in the effect when 1 weekday is compared with another, but our study suggests that using microblogging social media such as Twitter and Weibo do increase information-seeking behaviour on health. Tweet any day but do Tweet.

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[5] A reply to this paper has been published as:
Jayaram M, Adams CE, Friedel JS, McClenaghan E, Montgomery AA, Välimäki M, Schmidt L, Xia J, Zhao S (2019). Day of the week to tweet: a randomised controlled trial. BMJ Open 9(4): e025380.

Introduction

The Cochrane Collaboration is a network of researchers, healthcare professionals, patients, carers and people interested in healthcare who largely work for free with altruistic motives to produce systematic reviews of care (1). Cochrane systematic reviews are available in the Cochrane Library (http:// www.cochranelibrary.com/) and can be freely accessed in 101 countries, available to residents of a further 14 countries via subscription paid by respective governments or other organisations. It is also available for purchase at a cost or as open access if authors have paid the article processing charge (2). Each full review has a summary and abstract web page accessible to anyone with internet access (3) (http://www.cochrane.org/). Cochrane Schizophrenia Group (CSzG) sits within this wider Collaboration.

Twitter is a popular (4) free to use microblogging social media platform, which, at the time of the trial, allowed users to send a 140-character message called a tweet to lists of followers. A tweet may contain a hashtag (#), used as a means of searching by topic, and/or a handle (@), which denotes another Twitter user account. Although Twitter (blocked in China since 2009), and some other platforms are not available in China, the usage of social media is exceptionally high with 91% of Chinese residents using some form of social media compared with about 67% of those in the USA (5). The Twitter-like systems of Weibo and Wechat are popular in China (6 7).

In 2011, CSzG began to use Twitter. @ CochraneSzGroup following remains small but at the time of the study was over 1300. Our randomised trial (tweeting links vs not tweeting links of similar paired reviews (8) showed that social media dissemination of reviews nearly tripled the unique page visits to each review and nearly increased threefold the time people spent visiting the Cochrane summaries page when they followed the link via a tweet (9). We subsequently identified a variety of case reports, surveys and case series' conclusions on when to microblog (table 1). Each study stresses the importance of appreciating weekly behaviour patterns when tweeting and how to increase traffic as more tweets mean more visibility. In contrast to other social media such as Facebook, Twitter activity dies down a bit during weekends (10). For studies that compare 1 day of the week against another, conclusions are conflicting as are comparisons between weekday and weekend tweeting. Four support microblogging (tweeting) at the weekend (11–14) and three during the 'working' week (15–17). One large survey of 4.8 million tweets reported that early morning tweets

received most clicks while late evening tweets had more retweets (18). There is peak tweeting activity between the hours of 11:00 and 13:00. The best days and times to microblog in terms of site traffic are likely to differ according to the target audience. For example, tweets for shoppers may be best at the end of the week when most are shopping, and tweets of work-related information may be better during the working week.

Given the above findings, we considered examined our own @CochraneSZGroup account by analysing data from Twitter Analytics (19) for the period 1 June 2015 to 25 October 2015 (figure 1). We found the @ CochraneSZGroup engagement rate to be higher during the working week than at the weekend, with the greatest activity on Thursday and Friday.

Table 1 Past analyses of differences in activity across weekdays

Source	Method	Measuring	Data set	Conclusion
How to get more clicks on Twitter (11)	Case series	CTR*	200 000 tweets	Weekends
Time is on your side (15)	Case series	CTR	Unknown tweets	Weekdays
When are tweets better (12)	Survey	Online users	1000 users	Weekends
Twitter marketing—what results should we expect? (13)	Survey	CTR	20 000 tweets	Weekends
Calculating and improving your CTR (14)	Case report	CTR	3128 tweets	Weekends
When-to-post on social networks (16)	Survey	Engagement	2.5 m tweets	Weekdays
Cascading behaviour in large blog graphs and a model (17)	Case series CTR patterns		21.3 m blog posts	Weekdays
The Biggest Social Media Science Study: What 4.8 million Tweets Say About the Best Time to Tweet (18)	Survey	CTR, time to tweet, engagement with tweet	4.8 m tweets	Variable results

*CTR: Ratio of users who click on a specific link to the number of total users who view a page.
CTR, click-through rate.

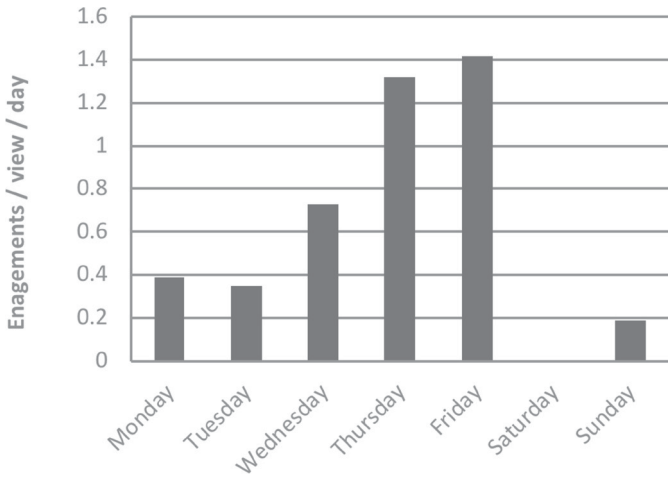

Figure 1 Average engagement* rate (1 June 2015 to 25 October 2015).
*Engagement rate is a broad measure of Twitter activity encompassing CTR and Twitter interactions.

Objective

To evaluate whether structured microblogging of treatment evidence on any particular day of the working week (Monday–Friday) increases the 'all page views' metric recorded by Google Analytics. 'All page views' is the total number of visits to the target page. This generic outcome is routinely collected by the Google Analytics package and has been used in past work.

Methods And Analysis study design

Prospective two-arm, parallel, open randomised controlled trial with an equal allocation. Protocol with full details of the study design has been published elsewhere (20).

Patient and public involvement

Cochrane library and the Cochrane summaries pages are widely accessed by the general population, patients and carers as well as those within the healthcare industry. The research question arose from an interest in ensuring that the information within these webpages is disseminated as widely as possible and that this is done in a manner that is innovative using social media. This process of course has to have an evidence base and hence the idea of conducting a trial to evaluate whether disseminating evidence in this manner works or not. The participants in this trial were not patients, but rather systematic reviews themselves. Hence, patients were not involved in the study. There was no recruitment as such as all the systematic reviews were already published in the Cochrane library and hence the dissemination of results to patients also does not apply. Again for the above reason, the burden of intervention assessment by patients also does not apply. Patients and public were not involved in this trial.

Participants

Participants in this study were published full-text CSzG systematic reviews (date reviews published were between 2000 and 2015) in The Cochrane Library with Plain Language Summary (PLS) which is freely available at www.summaries.cochrane.org. We excluded published protocols for CSzG reviews, any CSzG review not relevant to schizophrenia, unpublished and withdrawn CSzG reviews.

This study was conducted entirely online. The participant PLSs were all available on the Cochrane Library website, the intervention was delivered via two social media platforms (Twitter and Weibo) and outcome data were collected using Google Analytics.

This study did not involve any living participants and used information that is available in the public domain. Participants are systematic reviews rather than people and routine web

activity data were extracted and recorded through Google Analytics. No ethical approval was required (21, 22).

Randomisation

All participating CSzG systematic reviews were identified prior to randomisation. We defined reviews by tertiles of baseline access activity during the 52-week period, 1 January 2015 to 31 December 2015: high (527 to 4023 hits, n=64), medium (232 to 523 hits, n=65) or low (45 to 230 hits, n=65). Reviews were then assigned a unique code, which, along with baseline access activity stratum was supplied to one of the authors (AAM) who generated the random number sequence using a computer and performed randomisation. Stratifying by baseline activity, and using a computer-generated random number sequence, reviews were first allocated to day of the week Monday through Friday then into week number (1–39), and finally, the order in which the three microblogs (title, extract and question) would be released. Tweets had been prepared for all reviews. Allocations were then supplied by AAM to EM and SZ who, independent of other investigators, scheduled tweets for Twitter and Weibo/WeChat. We created two new usernames @CochraneSzFIN (78 followers) and @CochraneSzAuz (74 followers) to disseminate the same tweets in the Finnish language and to Australia in English.

Procedures

For the 10 weeks preceding randomisation, 20 microblogs about research relevant to schizophrenia from Mental (23) were Tweeted in three tweet bundles. Tweets were split evenly to each day of the week. This ensured @CochraneSZGroup was active before the start of the trial as our activity had declined across 2015.

Between 26 January 2016 and 20 October 2016, one review in a day was tweeted in English, Finnish and Mandarin, by the CSzG, three times on the allocated day at 10:30, 13:00 and 15:00 hours local time. These timings are suggested by the SocialBro web tool as when people are likely to be most receptive (24). There is some evidence that multiple postings, 3–4 times a day, of the same or similar tweet can be useful for an international following (25). Each of the three tweets had different text:

- The review title as it appears in www.summaries. cochrane.org, and a shortened URL to the summaries web page.
- A pertinent extract from the results or discussion sections of the abstract, and a shortened URL to the summaries web page.
- An intriguing question or pithy statement directly related to the evidence presented in the abstract and a shortened URL to the summaries web page (see box 1).

box 1 example of the three tweets relating to same review
Tweet 1: #Clozapine combined with different #antipsychotic #drugs for #treatment resistant #schizophrenia http://ow.ly/yaKAU. Tweet 2: How effective is #clozapine in addition to another #antipsychotics at treating 'hard to treat' #schizophrenia? http://ow.ly/yaKAU. Tweet 3: Not clear if combining #clozapine with other #antipsychotics is effective for #treatment resistant #schizophrenia http://ow.ly/yaKAU.

The study was designed to compare the effects of sending this package of tweets on different days of the week, rather than the specific content of the different types of accompanying text, which were formulated in order to appeal to the wide range of followers of the CSzG Twitter page and searchers. To assist the logistics of sending out tweets, we used Hootsuite, a social media management system (26). This free package allows formulation and scheduling of Tweets and is now available in China and integrates with Weibo (27).

Outcomes

The primary outcome was the total number of visits to the relevant Cochrane summary page in the 7 days following the intervention (including the day of tweeting) as reported on Google Analytics. For the primary outcome, repeated views of the same page during a single user session are counted in the total (unique page views are a secondary outcome). The standard free account in Google Analytics produces various reports in real time and data about whom, when and where someone has visited a site as well as how they 'arrived' there (9). In this way, we monitored all traffic to the Cochrane summary page and traffic directly from Twitter. The average half-life of a tweet (with a web link), defined as 'the amount of time at which this link will receive half of the clicks it will ever receive after it's reached its peak', has been estimated as 2.8 hours (28). However, to capture any possible cascade effect of tweeting, we extended the monitoring period to 7 days (29). The secondary outcomes are listed in figure 2 and provide other measures of incoming activity and exiting behaviour. For a glossary of Google Analytics terms, please see ref 20. After the final follow-up period, JSF downloaded data from Google Analytics using Super-metrics (business analytics software) (30) to produce a spreadsheet for analysis.

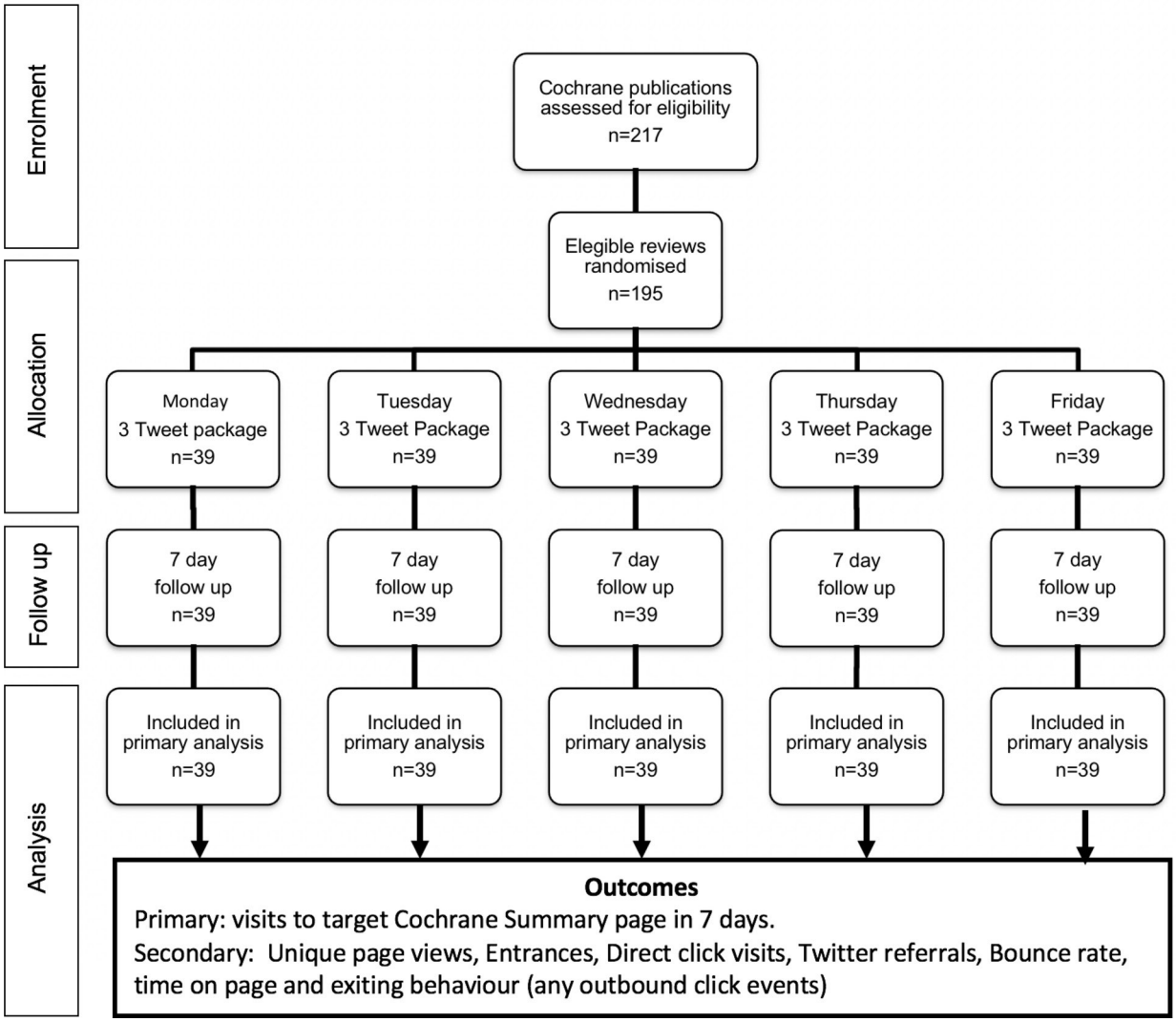

Figure 2 Flow diagram.

Statistical power

The sample size for this study is fixed by the number of published Cochrane reviews within the jurisdiction of the CSzG (n=194). As a multiarm trial (five arms) with no natural control arm for comparison and a log-normal continuous primary outcome, analysis of the primary outcome is by analysis of covariance where the effect size is the ratio of between-arm and residual variances. The detectable (standardised) effect size is calculated using standard sample size software after specifying power, alpha, number of arms and number of observations per arm. This represents the ratio of between-arm and residual variances. In a one-way analysis of variance study, sample sizes of 39, 39, 39, 39 and 39 are obtained from the 5 groups whose means are to be compared. The total sample of 194 achieves 90% power

to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. The detectable standardised effect size assumes a common SD within a group of 1.00. Therefore, the size of the variation in the means is represented by their SD which is 0.28. After taking logs of baseline number of visits for each review, the actual common SD within a group is 0.93. With a standardised detectable effect size of 0.28% and 90% power, this equates to a between-group SD of approximately 0.26 or variance (=SD^2) of approximately 0.07.

Data analysis

We compared baseline access activity of the reviews in each of the five trial arms using descriptive statistics. We analysed all outcomes as continuous, with log transformation for outcomes that were positively skewed. We present descriptive statistics, and measures of effect from linear regression models using Monday as a nominal reference group. For the primary outcome and most secondary outcomes, this estimate of effect is the ratio of geometric means and 95% CIs, adjusted for baseline activity. However, as a multi-arm study with no pairwise comparisons of particular interest, we derived a single p value for each outcome based on a Wald test that the model coefficients for treatment arm are jointly equal to zero. All data were analysed using Stata V.15 statistical software. As the allocated interventions were implemented fully as planned, and there were no missing primary outcome data, we did not conduct any sensitivity analyses.

Results

Following randomisation, 194 reviews were tweeted. Table 2 outlines the baseline review activity for the year before the start of the trial. The minimum and maximum correspond to the least and most viewed reviews by allocated day of the week, respectively. There were no differences between the groups.

For this randomised trial, primary and secondary findings were consistent. Tweeting on any day between Monday and Friday was just as good as any other weekday and no clear advantage over another in terms of ratings of activity as recorded in Google Analytics (table 3). Randomised evidence from our previous trial (31) suggested an approximately threefold increase in activity in the week after disseminating microblogs with hyperlinks. This study provides before-and-after evidence that this level of increase in activity continues to be realistic.

Discussion

Results from this study demonstrate that there was no statistically significant difference between tweeting on Monday or any day of the week for our primary outcome of ‘all page views’. Equally, there were no clear differences found for any of the secondary outcomes.

There are many possibilities why this was so. It is possible that a real effect has failed to be detected in this necessary small trial or the form of the microblogs may not have encouraged differential responses. Perhaps, however, for this type of tweet and Twitter following there is no substantial advantage to microblogging on one working day compared with another.

There was, however, an increase in viewing activity compared with the months prior to the study. This fits with the finding of our previous randomised trial (31). In that 2013–2014 study, the control group had an arithmetic mean of 5.28 'all page views' and this increased in the tweet arm to 13.67. After that trial ended, there was a general increase in baseline activity as evidenced by the data we collected for the year prior to this trial (table 2). Despite this increased baseline activity, tweeting in this study seemed to increase activity by a further threefold. There is a suggestion that interest is increasing and that this has not plateaued. The other comparable variable between the two trials is 'time spent on page'. In this study, time on page was considerably greater than in our first trial (geometric mean 123 vs 76 s).

Much investment is made to disseminate evidence of the effects of healthcare but the strategies by which this is done are rarely investigated. Increasingly, more funding bodies are prioritising dissemination strategies as part of evaluating successful grant applications and decision-making tools are available to support this (32, 33). Medical evidence of enormous impact will disseminate swiftly by every means possible with very little effort beyond the point of disclosure of findings. Maximising impact of most other health evidence does take more effort beyond the publication of the final report. Many choices are available to individuals, institutions and industry and resources limit what can be done but social media is ubiquitous, inexpensive and—as this study continues to suggest—powerful. The first randomised trial in our series illustrated that using a microblog causes nearly a tripling of traffic to a health evidence web page (31). This study supports that finding with the non-randomised before and after hit rates but adds randomised evidence that which day of the week dissemination takes place on does not matter that much. This higher quality evidence does not support the impression we gained form initial routine data analysis (table 1, figure 1) and, again, highlights the value of gaining evidence from randomised trials if possible before embarking on policy based solely on routine data. Perhaps with greater numbers and more power, we would have shown a real difference favouring Monday over the other days as this seemed the only day to have a little more activity than any of the others. This, however, is conjecture and any difference, for this set of evidence, for this following, would be subtle. Our trial tweeted between the hours of 10: 30 and 15: 00 hours local time and this could be a limitation in the local context where it is possible that more professional social media users have sight of it.

However, given the global reach of tweets and access across time zones, we believe the impact of this would be minimal. Perhaps further studies could explore this aspect.

There remain many more questions on which type of social media delivers best impact on health behaviour, and on what content, timing and targeting maximally encourages best evidence to be considered and then implemented. Few techniques or tools have been demonstrated to swiftly influence behaviour of those seeking information on health. Social media are accessible tools and it is possible to evaluate how we use them and then use them in a way that does not waste effort or interest.

Conclusions

Use of social media in an area of healthcare that is not particularly high profile, for dissemination of evidence that is highly specialised to a small following continues to have a genuine effect on increasing indicators of interest—but we have no evidence that use of social media on any particular working day of the week matters. This study continues to support the initial finding from the first randomised trial where the use of social media (Twitter/ Weibo) almost immediately nearly tripled activity on the reviews' summary page. For those interested in wider dissemination of evidence, tweet any working day, but do tweet.

Ethics and dissemination

This study does not involve any living participants and uses information that is available in the public domain. Participants in this study are systematic reviews rather than people. The http://www.cochrane.org/ and the Cochrane Library websites will be the target outcomes and the routine data will be extracted and recorded through Google Analytics. As a result, no ethical approval is required (21,22). Results will be disseminated via Twitter, Weibo and other traditional academic means.

Trial organisation

This study did not have a data monitoring committee or a steering committee.

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Chapter 6. Conclusion

Chapter highlight

This concluding Chapter summarises the work presented in previous chapters. It also highlights the author's other relevant contributions in EBM, as demonstrated by the extensive publication list of systematic reviews of healthcare interventions and her activity in delivering educational workshops and popularisation of evidence-based practice through public engagement. She designed and led the establishment of China Clinical Practice Guideline Alliance (GUIDANCE), which is a pioneering initiative that is changing the landscape of guideline production in China – and it started with small innovative surveys of Chinese databases and loss to follow up.

The body of knowledge created

Evidence synthesis is a type of research technique widely used in EBM that enables researchers to compile all data on research questions. It helps to identify knowledge gaps, provide an evidence base for clinical practice guidelines and gives policymakers and practitioners information to aid decision-making. Policy briefings, systematic reviews, clinical practice guidelines, and many more types of outputs require evidence synthesis. Systematic reviews are a corner stone of EBM and the evidence ecosystem. It is in this context, the author investigated several key issues with significant impact on the reliability of systematic review outputs.

A body of knowledge is created during this journey and through the work presented.

This body of work:

1. Highlights gaps in literature and a wealth of Chinese biomedical literature for systematic reviewers. This contributes to the accumulation of knowledge in the world of evidence synthesis and argues for comprehensive and unbiased inclusion of literature - essential for answering complex health care questions.
2. Provides empirical evidence regarding the credibility threshold for three sets of stakeholders using clinical trials. This unique study begins to address the uncomfortable issue of how loss to follow up erodes credibility of data. Author argues for appropriate planning on dealing with missing data through systematic review protocol; then, building on the finding of Chapter 1 and 2, this work

3. Makes an original contribution to the accumulation of knowledge in a range of clinical questions through critical examination of existing facts and ideas using systematic reviews and in doing so provides new conclusions regarding the care of a range of health conditions and directions for future research;
4. Provides original empirical evidence on effective and creative dissemination of systematic review findings, and research findings in general, which potentially increases research impact, reduce research waste, and minimises translation gap between research and practice; and, finally
5. Utilises the diverse past findings to help produce a suite of systematic reviews to critically examine the existing evidence in clinical management of infections caused by carbapenem-resistant gram-negative bacilli. This resulted in an international clinical practice guideline that will influence the care of patients across the 1.3bn people of China and, potentially around the globe.

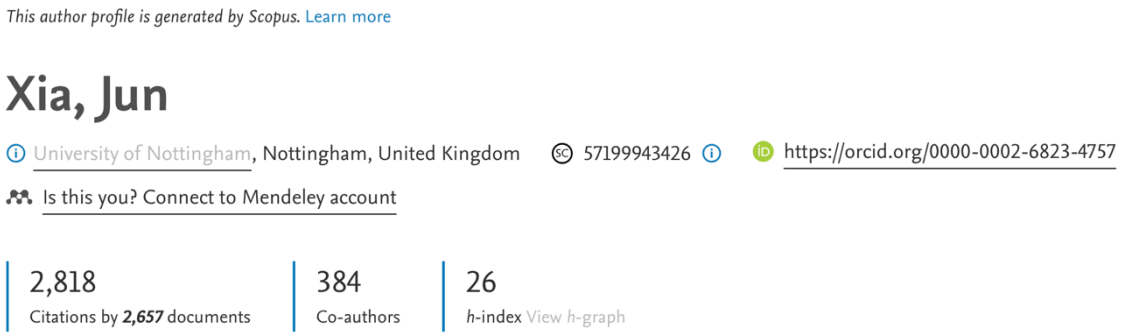
General contribution to EBM and knowledge transfer

Systematic review of healthcare interventions

The author has devoted her research career in evidence-based medicine, particularly in applying the methods of systematic reviews to resolve real-life clinical questions. She has published 49 Cochrane systematic reviews of healthcare interventions across her career (see Appendix 2 for full publication list), critically evaluated existing evidence and generated both new knowledge and new research hypotheses. This work covers multiple clinical areas including, acne, attention-deficit hyperactive disorder, cancer pain, chronic pain, delirium, depression, diabetes, eczema, heterotopic bone formation, liver cancer, lung disease, prostate cancer, schizophrenia, substance misuse and tinnitus. She collaborated with 384 researchers around the world to improve relevance of the review outputs to global users and, consequently, these systematic reviews are widely cited by health research communities around the globe (please refer to Figure 2 below for citation and h-index). A recent report from Sandford University ranked[6] the author in the top 2% of researchers globally in general and internal medicine (https://mp.weixin.qq.com/s/KpkZq-o0I-76fIME_7OdrA).

[6] The list of "World's Top 2% Scientists" is published by a team of experts led by Professor John P. A. Ioannidis at Stanford University. The calculation is based on Scopus author profiles and bibliometric data, using indicators of citations, h-index, co-authorship adjusted hm-index, citations to papers in different authorship positions and a composite indicator. Selected scientists are classified into 22 scientific fields and 176 sub-fields.

Figure 2. Scopus author profile with h-index



Some of these systematic reviews (41) are invited projects by the Cochrane Collaboration to support World Health Organisation (WHO) global guidelines (42). These have significant impact on the care of millions of people residing in the WHO member states. Others (43-46) are commissioned by the National Institute of Health Research (NIHR) to provide timely evidence to inform critical clinical decision-making in the United Kingdom.

The author has made significant contribution in accelerating the development of evidence-based medicine and promoting evidence-based practice in resource-limited settings. This is evidenced by her decade of work in delivering systematic review workshops to clinicians (http://en.review-solutions.cn/trainpic.htm) and in her effort to enhance public understanding of science through open class lectures. She has delivered over 100 workshops to Chinese clinicians. One of her public engagement lectures reached an audience of 964,112 people (see Figure 3 below) in a single session.

Figure 3. 2022 Public engagement lecture and evidence of impact



Changing clinical practice through improving guideline quality

The author established a GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) centre in China, hosted by the University of Nottingham Ningbo China, to provide world-class methodological support to clinical evidence users and clinical practice guideline commissioners. In 2021, the author led the establishment of China Clinical Practice Guideline Alliance (abbreviated as GUIDANCE), which is a multi-disciplinary collaboration platform that brings together guideline commissioners, guideline methodologists, systematic reviewers, and key stakeholders to jointly produce guidelines with relevance to local settings. GUIDANCE is a pioneering initiative, and first of its kind in China. It strictly follows the WHO recommended process (47) and adopts GRADE to assess evidence quality and develop recommendations (48). These guidelines' (49) recommendations are rigorously produced with enhanced relevance to developing economies with limited healthcare resources. For that reason, GUIDANCE collaborates with a NIHR sponsored platform IMPACT (Improving Outcomes in Mental and Physical Multimorbidity and Developing Research Capacity in South Asia; https://www.impactsouthasia.com/) to promote guideline adaptation in South Asian countries. While this initiative helps to reduce research waste, it also benefits partner countries in raising the quality and applicability of their domestic guidelines.

General strength and limitations

The papers presented has shared strengths in their methodological rigorousness, conduct and good reporting standard. Appropriate study design and rigorous conduct is essential for ensuring the internal validity of a study. For example, paper 3 adhered strictly to Cochrane standards of conduct and reporting. The review protocol was peer reviewed by a multi-disciplinary group of experts, including information specialist, statistician, reviewer, and content expert. As a result, the review output benefited from a well-designed and comprehensive literature search, informed by earlier research presented in paper 1, and input from information specialist, which provides a solid foundation for data collection and subsequent analysis. Paper 4 strictly adhered to the requirement for trustworthy guideline, and the application of the WHO endorsed GRADE EtD framework which reinforces transparency in this process. The transparency in production and reporting promotes scientific discourse and improves usability of this guideline for clinicians in various settings. The lack of high-quality evidence for some recommendations is a limitation of this CPG and the guideline panel tried to take this into consideration in forming recommendations.

The lack of high-quality evidence is a general limitation in the systematic review and clinical practice guideline presented in this thesis. It is difficult to draw firm conclusions when we only have low certainty on the observed effects. On the other hand, however, through the systematic reviews we were able to identify gaps in research and generate new hypotheses for future research.

Implications for policy and healthcare practice

Each of the five papers presented in this thesis provide a unique angle of guidance to improved healthcare policy and practice. Paper 1 calls for the attention of the global healthcare researchers and policy makers to the large - and growing - Chinese biomedical literature. The paper appeals for health researchers to consider supplementing mainstream English-language biomedical database searches with other language databases. It calls for information specialists to be aware of – at least - the different Chinese databases, their coverage and utility. In practice, systematic searching of the biomedical literature should consider investigating the value of at least one Chinese database using English and simplified Chinese terms. Until unification of the different Chinese biomedical databases, searches of each are likely to yield many reports of studies not disseminated elsewhere.

Paper 2 suggests that relevant stakeholders, including researchers, fundamentally mistrust results of most drug trials in schizophrenia. This will vary between health specialties, and different trial questions even within the same specialty but remains a largely unexplored issue for all. Adopting a more pragmatic trial design can help address this 'credability' boundary. Paper 3 demonstrated to health policy makers of the lack – almost complete absence - of health economics data concerning routine application of psychoeducation. Much better work should be undertaken in this area to explore the true *costs* of the intervention and variations of approach, such as use of a brief form of psychoeducation or group delivery rather than individual to individual. Paper 3 also had important implications for practice, particularly concerning service users and clinicians. It explains to service users that psychoeducational interventions may initially seem 'off putting' for the person with schizophrenia, but it can reduce relapse, readmission and encourage medication compliance, as well as reduce the length of hospital stay. The reduction in relapse and length of hospital stay with psychoeducational interventions and the increase of medication compliance rate should make it useful for clinicians as a part of their treatment programme. Paper 4 is a guideline document by design, employs all methods researched in the previous studies and provides timely guidance on the management of CRGNB infections mainly for clinicians, and related professionals involved in management of infectious diseases. Paper 5 investigated the effects of using health social media on different days of the working week on web activity. It found no clear differences in the effect when any one weekday is compared with another, but our study suggests that using microblogging social media such as Twitter and Weibo do increase information-seeking behaviour on health.

The collective implication of these 5 papers for policy and healthcare practice is to highlight the importance of systematic evidence review in informing clinical decisions or healthcare policy. The papers provide the research community with tools to improve systematic review methodology and, down the line, all stakeholders with rigorously produced evidence to aid their decision-making.

Future research opportunities

Similarly, each of the five papers identified gaps – sometimes embarrassing gaps - for future research. The systematic reviews found the existing trials are poorly reported, which further diminished the already limited evidence-base. Often, meta researchers were unable to extract useful information from clinical trials due to ambiguous reporting, or omitted information,

such as standard deviation of the mean. Research communities across clinical specialty are encouraged to devote more effort to well-designed, conducted and reported randomised studies in future to promote a healthy evidence ecosystem. Following CONSORT for good reporting of clinical trials more closely would have helped to considerably increase the amount of data available in the systematic review and clinical practice guideline presented in this thesis. Economic data – even the simplest economic data – of expensive treatments were almost entirely absent.

There is a striking gap in research around stakeholders' values and preferences towards healthcare technology and healthcare outcomes. Evidence is also lacking in feasibility and acceptability of healthcare technology. These are critical information in improving the design of our research and relevance of outputs, overall, contributing to the construction of a synergistic evidence ecosystem.

Similarities and differences with other research

This thesis presented five pieces of independent, but interconnected research, each contributing to the efficiency improvement of evidence ecosystem in their unique ways. Since the publication of these research, some themes were repeated and evolved, while others not. The methodological survey of Chinese biomedical databases (chapter 1) took a systematic approach to investigate the databases that host biomedical research published in Chinese language. To our knowledge, to date, this is the only piece of research in this topic area, which has not been repeated. Findings of this research is still valid to current date. The relationship between missing data and credibility of research findings is an ongoing topic in the evidence synthesis community, but the LOSS study presented in chapter 2 is still the only empirical research to date investigated into the relationship between proportion of missing data and user's confidence in research findings. The first GRADE centre was set up in 2012 in China，but the application of GRADE in Chinese guidelines are limited. The guideline presented in Chapter 4 is a milestone of the methodological progress in Chinese clinical practice guideline development, which follows the WHO recommended process and applied GRADE methodology throughout. With the establishment of China Clinical Guideline Alliance (GUIDANCE), and their endorsement of GRADE method, consequently GRADE is increasingly adopted by Chinese guideline developers. Finally, there appears to be a wealth of literature discussing the impact of social media on research dissemination. It is evident that the emergence of social media has changed the ways we communicate information. The

findings of these research are consistent with the findings of Twitter trial presented in Chapter 5, demonstrating the effectiveness of social media platforms in closing the knowledge-to-practice gaps through faster mobilization of scientific findings (50,51,52).

Conclusion

Clinical epidemiology and the 'evidence movement' within healthcare encouraged use of evidence in support of clinical and public policy decision-making. Formal approaches and systematic methods of evidence synthesis evolved swiftly over the same decades. Critical appraisal plus, if indicated and possible, synthesis of the findings of similar research studies in a systematic manner, emerged in its first formal guise in the mid-1970s. Systematic reviews are now carried out in an array of healthcare fields, such as for clinical tests, public health interventions, adverse effects and economic evaluations. There are also varieties of systematic review methods used to address diverse healthcare questions such as issues related to risk factors or accuracy of diagnostic tests. Alongside these developments have been the evolution of ever-more sophisticated techniques to address issues of relevance to systematic reviews of healthcare interventions – such as meta-regression and network meta-analyses. Further, the rigorous methodology and comprehensive assessment of literature of the systematic review is now often used to scope for gaps in knowledge as a guide for future research. The systematic review has a critical role in breaking the silos in evidence echosystem, and providing an environment for primary research to interact and to generate new knowledge and inform future research. Through five publications, the author of this thesis demonstrated her contribution to the advancement of the systematic review methodology, and the development of EBM through applications of evidence.

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Appendix 1. Supplimentary material of paper 3

Published notes

This review has undergone anonymous external peer review by two experts in the field.

Characteristics of studies

Characteristics of included studies

Brief - Both 2004 (131)

Methods	Allocation: randomised - no further description. Blindness: not stated. Duration: 6 months. Setting: Jining Psychiatric Prevention Hospital, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 118. Age: average age ~ 41years (SD ~ 9). Sex: male and female. History: average length of illness ~ 14.5 years (SD ~ 9). Inclusion: living in Jining city district with relative; stabilised condition, BPRS score < 30. Exclusion: patients with heart, liver, renal impairment, drug, or alcohol dependency.
Interventions	1. Family intervention + routine rehabilitation therapy: 60-90 minutes/month, for 6 months in the form of outpatient home visit: familiarise patients with basic knowledge of schizophrenia; provide patients with individualised guidance on communication skills, common drug adverse events and coping strategies, as well as how to recognise early warning signs of relapse; answer family members' enquiries regarding patients behaviour and social functioning; organise seminars for patients and family to exchange experience (two seminars in total run at 2-3 hours each). N = 59. 2. Routine rehabilitation therapy. N = 59.
Outcomes	Social functioning: MRSS, SDSS. Mental state: GWB, SES. Unable to use - Knowledge: increase (unpublished scale). Compliance: (unpublished scale).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, but no detail described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Unclear risk	None obvious.

Brief - Both 2004a (134)

Methods	Allocation: randomised - no further description. Blindness: not stated.

	Duration: 4 weeks. Setting: Jining Psychiatric Prevention Hospital, Shandong, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 146. Age: average age ~ 37 years (SD ~ 11). Sex: male and female. History: length of illness 3 months - 10 years. Inclusion: patients with stabilised psychotic symptoms after systematic anti-psychotic medication, and most cognitive functioning have recovered; without medication side effects; 4) can independently complete questionnaire. Exclusion: patients with either self- or drug-induced depression or anxiety.
Interventions	1. Health belief model: this is delivered in the form of both group and individual therapy – i.e. analyse cause & nature of illness with patients; ii. guide patients to associate recovery with health education; encourage patients to participate in sports, entertainment activities and travel; help patients to develop hobbies; communicate their feelings with nurses or family, friends; 30 minutes/time, 2 times/week for 4 weeks. N = 74. 2. Routine health education. N = 72.
Outcomes	Social functioning: SAS. Mental state: SDS, anxiety and depression incidence rate*.
Notes	*SAS score>51 is considered as having anxiety; SDS score > 51 is considered as having depression.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further description.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

Brief - Group 1995 (36-44)

Methods	Allocation: randomisation in which age, sex, prognosis and medication compliance were balanced by preliminary matching. Randomisation by an independent institution, ZMBT. Blinding: raters were not blind to the treatment conditions except compliance rated by independent raters at 1 year. Duration: 15 weeks and follow-up 5 years. Analysis of drop-outs: withdrawals partially described, modified ITT mentioned (data unclear).
Participants	Diagnosis: schizophrenia (DSM-III-R) with the exception of schizoaffective disorder. N = 191. Age: mean 31.9 years, SD ~ 7.8 years. Sex: male and female. History: 'chronic', outpatients, > 2 acute episodes in last 5 years, illness duration mean 8.3 years (SD 5.7), onset of illness mean ~ 24 years, mean ~ 4 (SD 3.1) hospitalisations, BPRS mean ~ 27 (SD 6.4), GAS mean 55 (SD 10.4), daily neuroleptic dose mean ~ 470 mg CPZ (SD 680).
Interventions	1. Psychoeducational medication training (PT) + leisure time group (LTG) at 7 study centres: 10 sessions in groups of 4-6 patients with one or two

	psychotherapists during 15 weeks. First 5 sessions once a week, next five twice a fortnight. N = 32. 2. PT + key person counselling 10 sessions (KC) + LTG. N = 35. 3. PT + cognitive psychotherapy (CP). N = 34. 4. PT + KC + CP. N = 33. 5. Control group patients attended a structured but unspecific leisure-time group of same length. N = 57.
Outcomes	Relapse. Global functioning: GAS. Unable to use - Medication compliance (no usable data). Mental state: BPRS (no usable data). Qualification for medication self-management (no usable data). Illness-related attitudes: KK-Skala (no usable data). Satisfaction with knowledge (no usable data).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by independent third party.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias)	High risk	Blind rating for readmission (independent criterion as researchers had no influence on this). Relapse data, compliance data and other outcomes where not blindly rated.
Incomplete outcome data (attrition bias)	High risk	44 patients dropped out before start of intervention and were not included in analysis but compared on socio-demographic and other characteristics to trial group.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Brief - Group 1995a (71, 72)

Methods	Allocation: random. Blinding: not reported. Duration: one session and follow-up 1 year. Analysis of drop-outs: withdrawals not described.
Participants	Diagnosis: schizophrenic disorder (DSM-III-R). N = 165. Age: < 15 years 6 patients and > 60 years 2 patients, most between 20-30. Sex: male 69, female 96. History: all poor compliance, 46 patients had depot injection, 30% treated with chlorpromazine, haloperidol or trifluoperazine, 30% chronic.
Interventions	1. Counselling session: by trained hospital pharmacist at discharge in presence of key relative; frequency of drug dosage was reduced to twice a day. N = 85. 2. No counselling: also received routine prescription of medication. N = 80.
Outcomes	Relapse.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	High risk	Not stated.
Incomplete outcome data (attrition bias)	Unclear risk	Not stated concerning total dropout and ITT (intention to treat criteria fulfilled).
Selective reporting (reporting bias)	Low risk	Only compliance and readmission measured and reported.
Other bias	High risk	Control patients were not given as much therapist time.

Brief - Group 1999(63-66)

Methods	Allocation: stratified for gender and for illness duration, randomisation carried out by an independent institution. Blinding: relapse and compliance assessed blindly. Duration: 8 weeks, 1 year follow-up. Analysis of drop-outs: follow-up of withdrawals reported.
Participants	Diagnosis: schizophrenia (F20.2-F20.9) ICD Danish version, OPCRIT. N = 46. Age: median 35.9 years, interquartile range 30.3-39.6 years. Sex: male and female. History: illness duration median 8.2 years, earlier admissions median 5. In treatment at 2 community psychiatric centres.
Interventions	1. Psychoeducational sessions: 8 sessions, using didactic, interactive method standardised with manual for group leaders and booklet for participants; weekly group of 5-8 participants conducted separately for patients and relatives. N = 24. 2. Standard care: psychopharmacological treatment, psychosocial rehabilitation efforts and some supportive psychotherapy. N = 22.
Outcomes	Compliance: non-compliance episodes of 14 days. Relapse. Global functioning: GAF. Mental state: BPRS. Satisfaction: VSSS. Expressed emotion: FQ. Unable to use - Knowledge: (instrument non-validated). Insight: IS (instrument non-validated).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation carried out by an independent institution.

Allocation concealment (selection bias)	Low risk	Patients included before randomisation, given participant numbers, separated from patient identification data. Allocation of patent-numbers to intervention/control done subsequently.
Blinding (performance bias and detection bias)	Low risk	Single blind (assessor blind).
Incomplete outcome data (attrition bias)	Low risk	ITT (Intention treat principle) used.
Selective reporting (reporting bias)	Low risk	ITT (Intention treat principle) used.
Other bias	Low risk	None obvious.

Brief - Group 2003 (137)

Methods	Allocation: randomised - no further description. Blindness: not stated. Duration: 6 months. Setting: ChuXiong Zhou Psychiatric Hospital, YunNan Province, China.
Participants	Diagnosis: schizophrenia (CCMD-2-R). N = 120. Age: average age ~ 37 (SD ~ 10). Sex: male and female. History: average length of illness ~ 13 years (SD ~ 9). Inclusion: not stated.
Interventions	1. Family intervention (psychoeducation): introduce to patients and family basic information about schizophrenia, its treatment and rehabilitation, adverse effects of medication & importance of continuous treatment; guidance on communication & social skills; 1/month for 6 months. N = 68. 2. Routine care. N = 52.
Outcomes	Mental state: BPRS. Unable to use -: Mental state: BPRS sub-scale scores. Behavioural outcome - level of symptoms: SCL-90 sub-scale scores.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, but no randomisation detail described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

Brief - Group 2006 (82)

Methods	Allocation: randomised - no further description. Blinding: not stated. Duration: 8 weeks. Setting: Mental Health Centre of Shantou University, Guangdong, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 60. Age: not stated.

	Sex: not stated. History: not stated. Exclusion: severe physical or other mental illness, drug/alcohol dependent.
Interventions	1. Psychoeducation + standard drug therapy: provide patients with information on cause, development & symptoms of illness, crisis strategy, communication with family member, maintain medication; 30 minutes/session, 1 session/week. N = 30. 2. Standard drug therapy. N = 30.
Outcomes	Compliance with medication. Mental state: BPRS score.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Brief - Group 2007 (127)

Methods	Allocation: randomised - no further description. Blinding: not stated. Duration: 2 weeks + 12 months follow-up. Setting: Pamela Youde Nethersole Eastern Hospital, Hongkong, China.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 81. Age: 18-65 years. Sex: male and female. History: not stated. Exclusion: not stated.
Interventions	1. Psychoeducation: didactic presentation on mental health, schizophrenia, rehabilitation resources, medication management & compliance, relapse prevention & stress management; 50 minutes/session, 10 sessions. N = 44. 2. Routine care. N = 37.
Outcomes	Relapse. Insignt: SAUMD scores. Unable to use - Quality of life: SF-36 (sub-scores only).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Brief - Group 2007a (51)

Methods	Allocation: randomised - by tossing a coin. Blinding: not stated. Duration: 8 weeks + 9 months. Setting: Jinhua Number 2 Hospital, Zhejiang, China.
Participants	Diagnosis: schizophrenia (inpatients). N = 62. Age: mean ~ 35 years, SD ~ 6 years. Sex: male and female. History: not stated. Exclusion: severe physical illness.
Interventions	1. Psychoeducation: background knowledge on schizophrenia; importance of family environment; role of family members; group therapy, one session/week. N = 30. 2. Routine care. N = 30.
Outcomes	Quality of life: FAD, GQOLI-74.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by tossing a coin.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Brief - Group 2007b (83)

Methods	Allocation: randomised. Blinding: not stated. Duration: 8 weeks. Setting: Yangzhou Wutaishan Hospital, Jiangsu Province, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 102. Age: not stated. Sex: not stated. History: not stated. Exclusion: severe physical or other mental illness.
Interventions	1. Psychoeducation + routine drug therapy: provide patients with information on cause, development & symptoms of illness, crisis strategy, communication with family member, maintain medication; 30-60 minutes/week. N = 51. 2. Routine drug therapy. N = 51.
Outcomes	Compliance: with medication. Behaviour: NOSIE score.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.

Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	High risk	PANSS, ITAQ scores measured, but not reported.
Other bias	Low risk	None obvious.

Brief - Group 2009 (130)

Methods	Allocation: randomised. Blinding: not stated. Duration: 3 months treatment + 12 months follow-up. Setting: Hong Kong, China.
Participants	Diagnosis: schizophrenia (DSM -4). N = 73. Age: 18-65 years. Sex: male and female. History: not stated. Exclusion: clients with secondary diagnosis of a mental or physical disorder.
Interventions	1. Psychoeducation + routine care: providing information on cause, development & treatment of schizophrenia, its recovery, relapse & early warning signs; 10 sessions over 3 months. N = 36. 2. Routine care. N = 37.
Outcomes	Knowledge: ITAQ endpoint scale score. Mental state: BPRS endpoint scale score (data skewed). Unable to use - Satisfaction: continuous satisfaction data - unclear from which scale they are derived from. Quality of life: FBIS endpoint scale score, no n number reported, data are skewed.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete data.
Selective reporting (reporting bias)	High risk	Some scale data (SSQ-6, SES) were not reported.
Other bias	Low risk	None obvious.

Brief - Individual 1996 (46)

Methods	Allocation: random - a random numbers table. Blinding: all ratings were carried out by the author, without blinding procedures. Duration: 7 weeks. Analysis of drop outs: withdrawals described.
Participants	Diagnosis: schizophrenia (DSM-III-R). N = 67. Age: mean 45.2 years, SD ~ 13 years. Sex: male 48, female 16.

	History: largely (54/64) community based, chronic, institutionalised population, at least 6 months cumulative antipsychotic drug exposure and clinical stability. Years in institution mean 12.8 (SD 11.8). Education mean 11 y (SD 1.9).
Interventions	1. Single individualised educational session: followed manual guidelines based on psychoeducation literature & principles of general health education. N = 24. 2. Individualised teaching: in 3 education sessions 25-35 minutes/session at weekly interval. N = 23. 3. No education. N = 20.
Outcomes	Compliance: SAI - compliance sub-scale. Knowledge change: UMQ. Insight: SAI. Unable to use - Mental state (no usable data).
Notes	All education was performed by the author RM.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a random numbers table
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	High risk	Open label.
Incomplete outcome data (attrition bias)	Low risk	No incomplete data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Brief - Unclear 2005 (87)

Methods	Allocation: randomised. Blinding: not stated. Duration: 8 weeks intervention + 3 months follow-up. Setting: Kangning Hospital, Shenzhen City, China.
Participants	Diagnosis: schizophrenia (CCMD-3-R). N = 286. Age: mean ~ 32.5 years, SD ~ 17.2 years. Sex: male and female. History: < 10 years. Exclusion: with combined other mental health problem, or if their conditions are obviously deteriorating.
Interventions	1. Psychoeducation: introduce patients to i. background of prescribed medication; ii. importance of taking medication; iii. review on benefit of medication; iv. discussion on schizophrenia as an illness; v. medication management after discharge; frequency 1/week. N = 143. 2. Routine health education: provided as a part of standard care. N = 143.
Outcomes	Compliance: with medication and follow up (leaving the study early). Unable to use - Compliance: with medication continuous data - derived from unpublished scale.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.

Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	High risk	Drop out was excluded in the analysis.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Standard - Both 1996 (58, 59)

Methods	Allocation: randomly assigned - computer generated cards stored in sealed envelopes. Blinding: assessments done by research interviewers blinded to patient's group assignment, not associated with clinical care & instructed not to inquire about patient's treatment. Duration: 18 months. Analysis of drop-outs: withdrawals reported.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-III-R). N = 82. Age: study group mean 33.3 years (SD 8.8), control mean 26 years (SD 9.3). Sex: male 53, female 29. History: outpatients at high risk for relapse, maintained on standard doses of antipsychotic medication, previous hospitalisations study group 2.27(SD 1.29), control 2.64(SD 1.28), participants were included in the study even if they did not comply with the medication.
Interventions	1. Program for relapse prevention: education for patients & family members about process of relapse in schizophrenia & how to recognise prodromal symptoms & behaviours, active monitoring for prodromal symptoms, clinical intervention within 24-48 hours, when prodromal episodes detected, one-hour weekly supportive group or individual therapy emphasising improving coping skills; 90 minutes multifamily psychoeducation groups biweekly for six months and monthly thereafter. N = 41. 2. Treatment as usual: individual 15'-30' biweekly sessions of medication management, symptom monitoring & individual supportive therapy. N = 41.
Outcomes	Compliance. Relapse. Service utilisation: length of hospital stay. Health economic outcomes: costs.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using computer generated random number card.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding (performance bias and detection bias)	Low risk	Single blind.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Standard - Both 2004 (129)

Methods	Allocation: randomised - no further description. Blindness: not stated.

	Duration: 9 months treatment, 1 year follow-up. Setting: Zhu-Ma-Dian City Psychiatric Hospital, Henan Province, China.
Participants	Diagnosis: first episode schizophrenia (CCMD-2-R). N = 86. Age: average age ~ 23 (SD ~ 6). Sex: male and female. History: average length of illness ~ 6.5 months (SD ~ 5.5). Inclusion: without learning disability or severe physical impairment, educated to middle school level minimum; there is at least one carer/relative living with the patient after discharge.
Interventions	1. Family psychological intervention + routine drug therapy: 3 stages, i. familiarise patients & family with knowledge of schizophrenia, information on medication & coping with side effects; 30 minutes/2weeks; ii. crisis intervention & communication skills were demonstrated to patients & family, patient's harmful behaviours corrected; 60 minutes/month; iii. organise seminars for patients & family member to exchange experience; 120 minutes/2 months. N = 43. 2. Routine drug therapy. N = 42.
Outcomes	Compliance: leaving the study early Relapse*. Global state: no clinical improvement**. Mental state: BPRS endpoint score. Unable to use - Satisfaction: FES-CV sub-scale scores.
Notes	* Any one of the following items, 10, 11, 12, 15, 17, in BPRS scored > 3 (inclusive of 3), or BPRS total score > 36 (inclusive of 36) is considered as relapse. ** BPRS total score < 25 (inclusive of 25) is considered as full recovery.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, but further detail provided on randomisation.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	High risk	Drop-out was excluded from final analysis.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

Standard - Both 2006 (61)

Methods	Allocation: randomised. Blinding: not stated. Duration: 3 months. Setting: Taiyuan mental health hospital, Shanxi province, China.
Participants	Diagnosis: schizophrenia (CCMD-2-R). N = 100. Age: mean ~ 48.63 years, SD ~ 1.33 years. Sex: female. History: mean ~ 25.34 years, SD ~ 1.33 years. Exclusion: not stated.

Interventions	1. Psychoeducation + routine drug therapy: introduce to patients and their family basic information about schizophrenia, treatment & rehabilitation, adverse effects of medication & importance of continuous treatment, group therapy; 30 minutes/session, 2 session/week; individual therapy; 15-20 minutes/session, 3 sessions/week. N = 50. 2. Routine drug therapy: N = 50.
Outcomes	Compliance with medication.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Standard - Both 2008 (138, 139)

Methods	Allocation: randomised. Blinding: not stated. Duration: 6 months. Setting: Xiangya Mental Health Centre, Changsha City, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 156. Age: 18-60 years. Sex: male and female. History: mean ~ 4.2 years, SD ~ 1.6 years, Exclusion: severe physical or other mental illnesses.
Interventions	1. Psychoeducation + standard drug therapy: provide patients with information on illness, crisis strategy, communication with family member, maintain medication; 60 minutes/session, 2 sessions/month. N = 79. 2. Standard drug therapy. N = 78.
Outcomes	Compliance: with follow up, with treatment. Mental state: BPRS. Quality of life: FBIS.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	ITT was used.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Standard - Both 2008a (86)

Methods	Allocation: randomised. Blinding: not stated. Duration: 12 weeks. Setting: Wuxi Mental Health Centre, China.

Participants	Diagnosis: schizophrenia (CCMD-3). N = 60. Age: mean ~ 31.2 years, SD ~ 10.4 years. Sex: male only. History: mean ~ 10.2 months, SD ~ 8.5 months. Exclusion: severe physical illness, history of medication allergy.
Interventions	1. Psychoeducation + standard care: provide patients with information on illness, crisis strategy, communication with family member, maintain medication, small group sessions; 2 session/week, 30-60 minutes/session; also big group sessions; 1 session/fortnight, 60-120 minutes/session. N = 30. 2. Standard care. N = 30.
Outcomes	Mental state: BPRS. Unable to use - Behaviour: NOSIE sub-scale score (sub-scale not validated).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not described.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Standard - Both 2008b (126)

Methods	Allocation: randomised using random number table. Blinding: not stated. Duration: 8 weeks treatment + 12 months follow-up. Setting: Rongjun Hospital, Jiangxi Province, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 90. Age: 18-60 years. Sex: not stated. History: < 1 year. Exclusion: severe physical or other mental illness.
Interventions	1. Psychoeducation + standard drug therapy: provide patients with information on causes, development symptoms of illness, crisis strategy, communication with family member, maintain medication; 30 minutes/session, 2 sessions/week. N = 45. 2. Standard drug therapy. N = 60.
Outcomes	Compliance with medication. Relapse. Social functioning: SDSS. Mental state: BPRS
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised with random number table.

Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	High risk	ITT was not used, drop-outs were excluded from analysis.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Standard - Group 1988 (11, 67-69)

Methods	Allocation: random. High and low EE groups were randomised separately, stratified for multiple episodes and presence/absence of residual symptoms. Blinding: at follow-up EE, PSE ratings and assessment of relapse blindly. Duration: 9 months. Analysis of drop-outs: non-participators and withdrawals described.
Participants	Diagnosis: schizophrenia (PSE). N = 83. Age: mean 35.3 years, SD ~ 12.8 years. Sex: male 29, female 54. History: acute case ward patients, first episode 25 patients, mean number of admissions 2.8 (SD 3,6), mean duration ill 6.3 years (SD 7.4), mean time since last admission 1.6 years (SD 3.1), mean days in hospital prior to index admission 91 (SD 149), mean days in hospital (index admission) 35.5 (SD 25); neuroleptic medication - 10 discharged with oral medication only, of 63 on depot injection 24 also received oral neuroleptics.
Interventions	1. Education: 2 sessions high EE-group N = 16, low EE-group. N = 9. 2. Behavioral intervention: symbolic 13 sessions high EE-group. N = 16. 3. Routine treatment: high EE-group N = 16, low EE group N = 10. 4. Behavioral intervention: inactive. N = 16.
Outcomes	Relapse. Expressed emotion: CFI. Unable to use - Compliance: with medication (no usable data). Contact with psychiatric services (no usable data). Social functioning: SAS (no usable data).
Notes	Interventions 1-3 are taken into account. Only high EE group was randomised to intervention 2, therefore have all outcomes of intervention group 2 been compared only to high EE group of control intervention 3.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization stated as stratified but no further information concerning method
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Low risk	Some outcomes (relapse, EE, PSE ratings) are assessed single blind.
Incomplete outcome data (attrition bias)	Low risk	All treatment or assessment dropouts were included in analyses
Selective reporting (reporting bias)	Low risk	None obvious.
Other bias	Low risk	None obvious.

Standard - Group 2004 (88)

Methods	Allocation: randomised - no further description. Blindness: not stated. Duration: 3 months. Setting: Jining Medical College Hospital, Jining City, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 250. Age: average age ~ 30 (SD ~ 9). Sex: male and female. Inclusion: stabilized condition, BPRS rating < 30, not suffer from drug side effect and educated to primary school 11 or above. Exclusion: patients with severe physical illnesses; patients with drug and alcohol dependency.
Interventions	1.Psychoeducation + routine care: information given on i. cause and clinical symptoms; ii. medication management and compliance; iii. side effects & coping strategies; iv. prevention of relapse & recognition of early warning sign; v. control temper & release anger; vi. marriage & having family; viii. recovery; frequency 20-40 minutes each time, 4 times per week for 3 months. N = 125. 2. Routine care only: 3 months. N = 125.
Outcomes	Compliance: with medication*. Mental state: BRPS. Unable to use - Curative effect: did not clarify how categorised result. Behaviour: improvement in hostile behaviour (scales used not stated).
Notes	*Conclusion derived from self-designed questionnaire; divided into compliance, partial compliance and non-compliance.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly divided into two groups, no further detail on randomisation method.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Standard - Group 2005 (89, 90)

Methods	Allocation: randomised - no further description. Blinding: not stated. Duration:21 sessions + 2 years follow-up. Setting: multi-centred, France.
Participants	Diagnosis: schizophrenia (diagnostic standard not stated). N = 220 Sex: not stated. Age: ~ 33 years old. History: not stated. Exclusion criteria: not stated.
Interventions	1. Psychoeducational Soleduc programme + amisulpride: including eight modules concerning disease, assumption of responsibility, neuroleptic

	treatments, course, methods of care & specialised follow-up, reintegration & psychosocial rehabilitation. N = 111. 2. Control group: usual information + amisulpride. N = 109.
Outcomes	Relapse: defined as "a schizophrenia episode leading to hospitalisation whatever its duration".
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised - each participating Centre received a list with randomisation order (from a central study site)
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Unclear risk	No incomplete outcome.
Selective reporting (reporting bias)	Low risk	None obvious.
Other bias	Unclear risk	Control group contained many protocol deviating patients.

Standard - Group 2006 (47)

Methods	Allocation: randomised - using random number table. Blinding: single blind (assessor blind). Duration: 24 weeks. Setting: University of Medicine and Dentistry of New Jersey, USA.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). N = 71 (+3 dropped out). Age: 22-65 years old. Sex: male and female. History: not stated. Exclusion criteria: patients with comorbid diagnosis of dementia or mental retardation, severely impaired intellectual functioning, or unable/willing to give informed consent, had been exposed to more than one Team Solutions workbook, at risk of suicide are excluded from the study.
Interventions	1. Team solutions + routine care: first 8-week sessions covered understanding illness & recovering from schizophrenia; second 8-week sessions covered understanding treatment & getting best results from medication; third 8-week sessions covered helping prevent relapse & avoiding crisis situations; frequency met twice per day, 2 days per week for 24 weeks. N = 38. 2. Treatment as usual: all aspects of day treatment programmes. N = 33.
Outcomes	Knowledge/attitude: KASQ, RAQ, ROMI. Mental state: PANSS Quality of life/Well-being: GAF-DIS, PGWB. Unable to use - General functioning: GAF - only sub-scale scores reported (sub-scores not validated). Global state: CGI - only sub-scale scores reported (sub-scores not validated). Insight: SUMD (only non-validated sub-scale scores). Knowledge: IAPSRS, TSCKAS (Team Solutions comprehensive knowledge assessment scale) (not clearly validated scale). Compliance: TCI (Treatment Compliance Interview) (not clearly validated scale).

Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised with random number table.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Low risk	Single blind - assessor blind.
Incomplete outcome data (attrition bias)	High risk	Drop-outs were excluded from final analysis.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

Standard - Group 2007 (60)

Methods	Allocation: randomised. Blinding: single blind (assessor blind). Duration: approximately 36 weeks of intervention + 12 months follow-up. Setting: community, Hong Kong, China.
Participants	Diagnosis: Schizophrenia (diagnostic standard not stated). N = 84 families. Age: 22-60 years. Sex: male and female. History: unclear. Exclusion: if family member care for more than one relative with a chronic mental or physical illness.
Interventions	1. Psychoeducation + routine care: 4 stage intervention including - orientation and engagement, educational workshop, therapeutic family role & strength rebuilding; 2 hours/session, 1 session every 2 weeks, 18 sessions. N = 42. 2. Routine care. N = 42.
Outcomes	Relapse/re-admission. Global functioning: SLOF. Mental state: BPRS. Quality of life: FBIS. Service utilisation: length of hospital stays. Unable to use - Family functioning: FAD (usually high score indicate unhealthy family functioning, but author of paper reported high score as indication of better family functioning. When data incorporated (high score = favourable), these caused heterogeneity. We, therefore, think there was some mistake in reporting of these data).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Low risk	Single blind.
Incomplete outcome data (attrition bias)	Low risk	No incomplete data.
Selective reporting (reporting bias)	Low risk	All outcome reported.
Other bias	Low risk	None obvious.

Standard - Group 2008 (79)

Methods	Allocation: randomised. Blinding: not stated. Duration: 6 months. Setting: community, Wuhan city, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 198. Age: 18-60 years. Sex: male and female. History: not stated. Exclusion: severe physical illness.
Interventions	1. Psychoeducation: background knowledge of schizophrenia, importance of medication compliance, medication side effects, ways of expressing feelings & emotion, guidance on family life; frequency 2 per week, group therapy. N = 99. 2. Routine care. N = 99.
Outcomes	Compliance: with medication.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Standard - Individual 03a (132)

Methods	Allocation: randomised - no further description. Blindness: not stated. Duration: 8 weeks. Setting: Psychiatric prevention hospital, Jining City, China.
Participants	Diagnosis: schizophrenia (CCMD-2-R). N = 116. Age: average age ~ 32 years (SD ~ 10). Sex: male and female. History: average history ~ 5.5 years (SD ~ 3.19). Inclusion: stabilised with BPRS < 30, no drug side effects, education > 5 years (inclusive of 5), without heart, liver or renal illnesses or history of drug/alcohol dependency.
Interventions	1. Psychoeducation + routine drug therapy: individualised guidance about onset, nature and symptoms, guided to differentiate before & after treatment, to associate improvement with good medication compliance, counselling when necessary, asked to write reflective diary; 45-60 minutes/session, 2/week. N = 58. 2. Routine drug therapy. N = 58.
Outcomes	Social functioning: SAS. Global state: IPROS. Mental state: BPRS, SDS. Unable to use - Global state: IPROS factor scores (non-validated sub-scale scores).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients randomly divided into two group, no further detail on randomisation.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Unclear risk	Blinding is not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Low risk	No selective reporting.
Other bias	Low risk	None obvious.

Standard - Individual 03b (50)

Methods	Allocation: random (draw lots). Blindness: not stated. Duration: 8 weeks treatment, 2 years follow-up. Setting: Jining Psychiatric Prevention Hospital, Jining City, China.
Participants	Diagnosis: first onset schizophrenia (CCMD-2-R). N = 136. Age: < 50 years (inclusive of 50). Sex: male and female. History: average length of illness ~ 1.4 years (SD ~ 0.8). Inclusion: first onset; never received systematic anti-psychotic treatment before hospitalisation; family members agree the patient to receive at least 8 weeks treatment in hospital. Exclusion: severe physical impairment; drug allergy, or alcohol dependency.
Interventions	1. Routine drug therapy (Clozapine < 300mg/d) + psychoeducation: i. therapist explained symptoms to patients & enlighten them on the difference between now (ill) and before (well), to increase ability to recognise psychotic symptoms; ii. guide patients to associate improvement with good medication compliance & to realize benefit of anti-psychotics; iii. encourage patients to write reflective diary; 30-40 minutes/time, 2-3 times/week for 8 weeks. N = 68. 2. Routine drug therapy (Clozapine < 300mg/d). N = 68.
Outcomes	Compliance: leaving the study early*. Relapse* Knowledge: ITAQ. Mental state: BPRS.
Notes	* Data entered with intention-to-treat method.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by draw lots.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.

Incomplete outcome data (attrition bias)	High risk	Incomplete outcome data at follow-up was excluded from analysis.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

Standard - Individual 03c (48)

Methods	Allocation: randomised with random number table. Blindness: double blind. Duration: 12 weeks treatment + 1 year follow-up. Setting: Jining Veterans' Hospital, Shandong, China.
Participants	Diagnosis: schizophrenia (CCMD-2-R). N = 110. Age: average age ~ 36.5 years (SD ~ 11). Sex: male and female. History: average length of illness ~ 13.5 years (SD ~ 10.5). Inclusion: living with at least one member of the family after discharge. Exclusion: patients with severe physical impairment or mental retardation.
Interventions	1. Conventional psychoeducation + psychological stress education + routine drug therapy: 1.5 hours/week for 12 weeks. N = 37*. 2. Conventional psychoeducation + routine drug therapy: delivered in form of individual therapy, included basic knowledge about schizophrenia, symptoms & causes, encourage patients to write reflective diary; 1 hour/week for 12 weeks. N = 37. 3. Routine drug therapy. 12 weeks. N = 36.
Outcomes	Relapse. ** Global state: NOSIE-30. Mental state: BPRS. Unable to use - Behaviour: NOSIE-30 (non-validated sub-scale scores only). Cognitive function: Simplified Coping Style Questionnaire (not clearly validated).
Notes	*Results of this group is not included in analysis. ** Any of the following items in BRPS, 4, 7, 11, 12, 15, scored > 5, or any combined two items scored > 4 is considered as relapsed.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised with random number table.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Low risk	Double blind.
Incomplete outcome data (attrition bias)	High risk	Addressed in some outcomes, but not others.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

Standard - Individual 93 (70)

Methods	Allocation: random, from a list of 30 patients attending a specialised clinic for young adults, the research team identified with the clinicians those with stable enough clinical state, considered able to attend group therapy. Blinding: knowledge, social functions and symptomatology assessed blindly.

	Duration: 2-3 months. Analysis of drop-outs: withdrawal reported.
Participants	Diagnosis: schizophrenia or schizophreniform or schizoaffective disorder (DSM-III). N = 20. Age: mean ~ 23 years (SD 3.4), range 18-30 years. Sex: male 15, female 5. History: outpatients.
Interventions	1. Medication management group: 3 times per week for 2-3 months. N = 10. 2. Control group. N = 10.
Outcomes	Knowledge: SKQ. Social functions: SAS II. Mental state: BPRS. Increased medication.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation method used: dice.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Low risk	Some outcomes are assessed single blind.
Incomplete outcome data (attrition bias)	Unclear risk	Not stated, but only one subject retired from the study.
Selective reporting (reporting bias)	Low risk	None obvious.
Other bias	Low risk	None obvious.

Standard - Unclear 1988 (74-78, 140-142)

Methods	Allocation: stratification patients with schizophrenia/schizophreniform disorder and schizoaffective disorders, respectively, was based on the average level of pre-hospital functioning rated by RPTS using a cutting score of 3.5 (the median on this scale). Within each of these four groups randomly - no further description Blinding: not reported. Duration: 18 months. Analysis of drop-outs: inadequate description.
Participants	Diagnosis: schizophrenia DSM-III, schizoaffective or schizophreniform disorder. N = 92. Age: mean 27(SD 8.2), range 15-58 years. Sex: male 49, female 43. History: recent admission to the unit, prior episodes 2.1 (SD 2.2), previous admissions 2.0 (SD 2.7), GAS score mean 25.0 (SD 6.2), PRF mean 4 (SD 1.2).
Interventions	1. Inpatient family intervention (IFI): brief family treatment with emphasis on psychoeducation; average number of sessions 8.6, mode 6, 1 or 2 per week during hospitalisation. N = 37. 2. Standard hospital treatment: included medication, individual supportive psychotherapy, occupational therapy & other activities common to hospital treatment. N = 55.
Outcomes	Global functioning: GAS.

	Unable to use - General symptoms: PEF (no usable data). Family attitudes and behaviour: FAI (no usable data). Rehospitalisation: (no usable data). Compliance: with treatment and medication - TMCDS (no usable data). Role functioning: RAPS (no usable data). Negative outcomes (no usable data).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	High risk	Some scale scores were measured, but no mean or SD reported.
Other bias	Low risk	None obvious.

Standard - Unclear 1996 (52-57, 62)

Methods	Allocation: randomised (block randomisation using computer) Blinding: single blind. Duration: 4-5 months and 1 year follow-up. Analysis of drop-outs: withdrawals described and analysed.
Participants	Diagnosis: schizophrenia, schizophreniform disorder, schizoaffective disease (ICD9, DSM-III-R). N = 236. Age: mean 33 years. Sex: male 109, female 127. History: outpatients, GAS mean 49, BPRS mean 42, illness duration mean 7 years, hospitalisations mean 4, first episode 24% of patients.
Interventions	1. Information group: 8 sessions using information booklet. 4 sessions weekly, followed by 4 further sessions at monthly interval. N = 125. 2. Control group. N = 111.
Outcomes	Readmission. Knowledge: KQ. Insight: KK-skala. Expressed emotion: FQ. Negative outcomes. Unable to use - Compliance: with medication (no usable data, continuous data derived from unpublished scale). Mental state: BPRS (no usable data). Social functioning: GAS (no usable data).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Block randomisation using computer.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Low risk	Single blind.
Incomplete outcome data (attrition bias)	Low risk	ITT-analysis and completer analysis performed and drop-out reported.
Selective reporting (reporting bias)	Low risk	None obvious.
Other bias	Low risk	None obvious.

Standard - Unclear 2005 (84)

Methods	Allocation: randomised. Blinding: not stated. Duration: 2 weeks intervention + 2 years follow-up. Setting: Shangqiu number 2 hospital, Henan province, China.
Participants	Diagnosis: schizophrenia (CCMD-2-R). N = 142. Age: 18-55 years. Sex: male only. History: mean ~ 10.2 months, SD ~ 6.5 months. Exclusion: severe physical illness, history of medication allergy.
Interventions	1. Psychoeducation + standard care: provide patients with information on illness, crisis strategy, communication with family member, maintain medication; 12 sessions provided within 2 weeks prior to discharge, 1 hour/session. N = 69. 2. Standard care. N = 73.
Outcomes	Relapse. Unable to use - Mental state: N-BPRS (not published scale).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Unclear risk	No incomplete data.
Selective reporting (reporting bias)	Unclear risk	All measured outcomes reported.
Other bias	Unclear risk	None obvious.

Standard - Unclear 2005a (73)

Methods	Allocation: randomised. Blinding: not stated. Duration: 5 years. Setting: community, Binzhou, Shandong province, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 40. Age: 16-60 years. Sex: male and female. History: 6-20 months. Exclusion: other illnesses.

Interventions	1. Psychoeducation: provide patients with information on causes, development symptoms of illness, crisis strategy, communication with family member, maintain medication; frequency not clear. N = 20. 2. Routine care. N = 20.
Outcomes	Compliance: with medication. Global state: no clinical improvement.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	High risk	BPRS and SOSS score measured but not reported.
Other bias	Low risk	None obvious.

Standard - Unclear 2006 (133)

Methods	Allocation: randomised - no further description. Blinding: not stated. Duration: 1 month intervention + 1 year follow-up. Setting: Tian Shui mental health hospital, Gansu province, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 116. Age: 21-58 years. Sex: male and female. History: not stated. Exclusion: severe physical or other mental illness.
Interventions	1. Psychoeducation + routine care: patients & family members given booklets to read on cause, development & treatment of schizophrenia, relapse & relapse prevention; frequency > 2 times each week for 4 weeks. N = 58. 2. Routine care. N = 58.
Outcomes	Compliance: with follow-up. Relapse. Global state: no clinical improvement. Mental state: SDS, SAS. Satisfaction with care.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Standard - Unclear 2007 (85)

Methods	Allocation: randomised. Blinding: not stated. Duration: 8 weeks. Setting: Shizhu number 2 hospital, Chongqing city, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 100. Age: 17-68 years. Sex: male. History: 4 months to 28 years. Exclusion: severe physical illness.
Interventions	1. Psychoeducation + standard care: provide patients with information on cause, development & symptoms of illness, crisis strategy, communication with family member, maintain medication; 2 sessions/week for 8 weeks. N = 50. 2. Standard care. N = 50.
Outcomes	Compliance: with medication.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Unclear - Both 2001 (143)

Methods	Allocation: randomised - no further description. Blindness: not stated. Duration: 12 weeks. Setting: Psychiatric prevention hospital, Jining City, China.
Participants	Diagnosis: schizophrenia (CCMD-2-R). N = 80. Age: 18-60 years old. Sex: male and female. History/inclusion: duration ill 3 months-10 years, BRPS >/= 36, no severe physical illness, drug/alcohol dependency, heart, liver, renal functioning test normal.
Interventions	1. Psychoeducation + routine drug therapy: intervention given both individually & in groups; individual psychoeducation emphasise on reminding patients to take medication & to receive routine care; group psychoeducation focused on cause of illness & benefit of good medication compliance, prior to discharge focus of intervention on relapse prevention, self-monitoring & returning to family/society; frequency not stated. N = 40. 2. Routine drug therapy only. N = 40.
Outcomes	Knowledge: SAUMD. Unable to use - Knowlege: SAUMD total and factor scores (two groups' data combined and cannot be separated). Mental state: BPRS total and factor scores (two groups' data combined and cannot be separated).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients randomly divided into two groups, no further detail on randomisation.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Unclear - Both 2005 (136)

Methods	Allocation: randomised - no further description. Blindness: not stated. Duration: > 8 weeks (no further detail). Setting: Henan Psychiatric Hospital, Henan Province, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 86. Age: 16-62 years old. Sex: male and female. History: not stated. Exclusion: patients with organic mental health problem, or severe physical impairment.
Interventions	1. Psychoeducation + routine drug therapy: promote treatment compliance, independent living, recognition of psychotic symptoms, analyse causes of illness & effect of medication with patients, associate improvement with good medication compliance; 8 weeks, frequency not stated. N = 43. 2. Routine drug therapy. N = 43
Outcomes	Compliance: with medication.* Knowledge: ITAQ. Mental state: BPRS.
Notes	*Assessment based on nurse observation; divided into compliance, partial compliance and non-compliance.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, without further description.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

Unclear - Both 2007 (85)

Methods	Allocation: randomised with random number table. Blinding: not stated.

	Duration: 1 year. Setting: Xinxiang Mental Health Hospital, Henan Province, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 129 (but only 102 completed study). Age: mean ~ 20.4 years, SD ~ 6 years. Sex: male and female. History: mean ~ 6.5 years, SD ~ 3.2 years. Exclusion: not stated.
Interventions	1. Psychoeducation + standard care: provide patients with information on illness, crisis strategy, communication with family member, maintain medication; sessions held once every 1-2months for 1 year. N = 52. 2. Standard care. N = 50.
Outcomes	Compliance: with medication. Relapse. Mental state: PANSS.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised with random number table.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	High risk	Drop-outs were excluded from analysis.
Selective reporting (reporting bias)	High risk	MRSS was measured but not reported.
Other bias	Low risk	None obvious.

Unclear - Both 2007a (144)

Methods	Allocation: randomised. Blinding: not stated. Duration: unclear. Setting: Rongjun Hospital, Jiangxi Province, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 120. Age: 18-36 years. Sex: male. History: > 2 years. Exclusion: not stated.
Interventions	1. Psychoeducation + standard drug therapy: provide patients with information on causes, development symptoms of illness, crisis strategy, communication with family member, maintain medication; frequency not stated. N = 60. 2. Standard drug therapy. N = 60.
Outcomes	Compliance: with medication.
Notes	Outcome is analysed as short term.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete data.

Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Unclear - Both 2008 (81)

Methods	Allocation: randomised. Blinding: not stated. Duration: intervention period unclear + 6 months follow-up. Setting: inpatients, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 96. Age: unclear. Sex: male and female. History: unclear. Exclusion: not stated.
Interventions	1. Psychoeducation: provide patients with information on causes, development symptoms of the illness, crisis strategy, communication with family member, maintain medication. 40 minutes/session, 1 session/week. N = 48. 2. Routine care. N = 48.
Outcomes	Relapse. Knowledge.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Unclear - Group 1996 (80)

Methods	Allocation: random - no further description. Blinding: not described. Duration: 20 weeks, follow-up 3 months. Analysis of drop-outs: the data is presented for study group attenders, rather than those allocated to groups.
Participants	Diagnosis: schizophrenia (SADS and DSM-III-R). N = 146. Age: not reported Sex: male 92, female 54. History: community based outpatients good depot clinic attenders, illness length 9-14 years.
Interventions	1. Education groups: on 8 geographical areas, each session 90' including break; sessions alternated between information & problem solving; manual outlining the content was given. N = 73. 2. Waiting list. N = 73.
Outcomes	Social functioning: SFS, modified SNS. Quality of life: Heinrichs' scale. Unable to use - Compliance with medication (no usable data). Mental state: BPRS (no data).
Notes	Knowledge + self-esteem assessed but reported elsewhere.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome.
Selective reporting (reporting bias)	Low risk	Everything measured are reported.
Other bias	Low risk	None obvious.

Unclear - Group 2008 (145)

Methods	Allocation: randomised. Blinding: not stated. Duration: 4 weeks. Setting: Zigong Mental Health Centre, Sichuan City, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 100. Age: 15-60 years. Sex: male and female. History: not stated. Exclusion: not stated.
Interventions	1. Psychoeducation + routine care: education on causes, development & treatment of schizophrenia, group therapy; frequency not stated. N = 50. 2. Routine care. N = 50
Outcomes	Behaviour: NOSIE.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Unclear - Individual 2008 (128)

Methods	Allocation: randomised. Blinding: not stated. Duration: length of treatment period unclear + 2 years follow-up. Setting: Henan Zhumadian Mental Health Hospital, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 160. Age: 15-55 years. Sex: male and female. History: 3 months to 6 years. Exclusion: severe physical illness.
Interventions	1. Psychoeducation + routine care: provide patients with information on the illness, crisis strategy, communication with family member, maintain medication. 30 ~ 50 minutes/session, 3 sessions/week. N = 80. 2. Routine care. N = 80.

Outcomes	Compliance: with medication, and follow-up. Mental state: BPRS.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	High risk	Drop outs were excluded from analysis.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Unclear - Unclear 2008 (146)

Methods	Allocation: randomised. Blinding: not stated. Duration: 4 weeks. Setting: Number 6 Renmin Hospital, Hebei Province, China.
Participants	Diagnosis: schizophrenia (CCMD-3). N = 120. Age: mean ~ 20.5 years, SD ~ 7.2 years. Sex: male and female. History: mean ~ 4.6 years, SD ~ 5.6 years. Exclusion: not stated.
Interventions	1. Psychoeducation: provide patients with information on the causes, development symptoms of the illness, crisis strategy, communication with family member, maintain medication. Intervention frequency unclear. N = 60. 2. Routine care. N = 60.
Outcomes	Knowledge. Satisfaction.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	No incomplete data.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.
Other bias	Low risk	None obvious.

Footnotes
Rating scale abbreviations

BPRS - Brief Psychiatric Rating Scale
CGI - Clinical Global Impression
FAD - Family Assessment Device
FBIS - Family Burden Interview Schedule
GAS - Global Assessment Scale

GAF - Global Assessment of Functioning
GQOLI-74 - General Quality of Life Inventory -74
GWB - General Well-being Schedule
IPROS - Inpatient Psychiatric Rehabilitation Outcome Scale
ITAQ - Insight Treatment Attitude Questionnaire
KASQ - Knowledge About Schizophrenia Questionnaire
KK-skala - Krankenheitskonzept Skala
KQ - Knowledge Questionnaire
MRSS - Morningside Rehabilitation Status Scale
NOSIE-30 - Nurse Observation Scale for Inpatient Evaluation-30
PANSS - Positive and Negative Syndrome Scale
PGWB - psychological general well-being scale
QOL - Quality of Life
RAQ - Recovery Attitudes Questionnaire
SAI - Schedule for Assessment of Insight
SAS - Zung Self-Rating Anxiety Scale
SAS II - Social Adjustment Scale II
SAUMD - The Scale to Assess Unawareness of Mental Disorder
SDS - Zung Self-Rating Depression Scale
SDSS - Social Disability Screening Schedule
SES - Rosenberg Self-esteem Scale
SFS - Social functioning schedule
SKQ - Schizophrenia Knowledge Questionnaire
SLOF - Specific Level of Functioning Scale
SNS - Social Networks Schedule
TCI - Treatment Compliance Interview
TSCKAS - Team Solutions comprehensive knowledge assessment scale
UMQ - Understanding of medication questionnaire
VSSS - Verona Service Satisfaction Scale

General abbreviations
DSM - Diagnostic and Statistical Manual of Mental Disorders
EE - expressed emotion
ICD - International Classification of Diseases
ITT - intention to treat
SD - standard deviation
ZMBT - Statistics and Data Center for Clinical Trials at the Institute of Medical Biometry and Informatics

Characteristics of excluded studies

Agara 2007 (147)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia and depressive disorders. Intervention: psychoeducation vs standard care. Outcomes: no usable data - no mean or SD reported, only P values.

Aguglia 2007 (148)

Reason for exclusion	Allocation: random. Participants: schizophrenia. Intervention: Psychoeducation vs standard care. Outcome: no usable data - no mean or SD reported, only P values reported.

An 2005 (149)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation with elements of skill training and token economy vs standard care.

Angunawela 1998 (150)

Reason for exclusion	Allocation: random. Participants: adult general psychiatry patients with schizophrenia 21%, affective disorder 57%, neurotic, personality, other non-psychotic disorder 14% and others 8%. No analyses on diagnostic subgroups. Intervention: patient information leaflet vs usual information.

Azrin 1998 (151)

Reason for exclusion	Allocation: patients matched and randomly assigned. Participants: chronically mentally ill patients: schizophrenia, bipolar and major depressive disorder. No analyses on diagnostic subgroups.

Barnes 2001 (152)

Reason for exclusion	Allocation: planned to be randomised - trial was not conducted in the end.

BaumI 2006 (153)

Reason for exclusion	Allocation: not randomised.

Bechdolf 2005a (154)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: CBT vs psychoeducation.

Bechdolf 2007 (155)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: CBT vs routine care.

Bi 2000 (156)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: health education with elements of training and token economy vs routine care.

Boczkowski 1985 (157)

Reason for exclusion	Allocation: random. Participants: schizophrenia patients.

	Interventions: psychoeducation vs control group. Outcomes: no usable data.

Borell 1995 (158)

Reason for exclusion	Allocation: random. Participants: schizophrenia DSM-III. Interventions: information program versus control waiting list group. Outcomes: no usable data.

Cao 2002 (159)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation vs standard care. Outcome: no usable data - only sub-scale scores were reported.

Castrogiovanni 2006 (160)

Reason for exclusion	Allocation: randomised. Participants: not schizophrenia patients.

Chaplin 1998 (161)

Reason for exclusion	Allocation: random. Participants: diagnosis functional psychosis, not limited to patients with schizophrenia. No analyses on diagnostic subgroups.

Chen 2005 (73)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: health education with elements of training vs standard care.

Cormier 1995 (162)

Reason for exclusion	Allocation: random. Participants: schizophrenia patients. Intervention: psychoeducation (French version of the Medication and Symptom Management Modules) group, two control groups 1) with leisure activities and 2) usual follow-up activities (support therapy with their treating psychiatrist and neuroleptic medication). Outcomes: no usable data.

Dang 2007 (163)

Reason for exclusion	Allocation: randomised. Participants: chronic schizophrenia. Intervention: psychological intervention with elements of independent living skills training.

Degmecic 2007 (164)

Reason for exclusion	Allocation: not stated. Participants: schizophrenia ICD-10. Intervention: psychoeducation versus control group.

Eckman 1992 (165)

Reason for exclusion	Allocation: random. Participants: schizophrenia. Intervention: skills training versus supportive group psychotherapy, not psychoeducation.

Goldman 1988 (166)

Reason for exclusion	Allocation: random. Participants: schizophrenia.

	Interventions: didactic program versus standard ward activities Outcomes: no usable data (means, no standard deviations), number of drop-outs unclear.

Gumley 2003 (167)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: CBT vs treatment as usual.

He 2008 (168)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: CBT vs standard care.

Hogarty 1986 (169)

Reason for exclusion	Allocation: random. Participants: schizophrenia or schizoaffective disorder. Intervention: family intervention with minimal psychoeducation versus social skills training versus combination of family intervention and social skills training versus drug treatment.

Hu 1998 (170)

Reason for exclusion	Allocation: random. Participants: schizophrenia Intervention: insight education + routine drug therapy versus routine drug therapy alone.

Hua 2008 (171)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation with elements of skills training and token economy vs standard care.

Huang 2007 (172)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: health education with elements of CBT and token economy vs standard care.

Kelly 1990 (173)

Reason for exclusion	Allocation: random. Participants: non-psychoses 7-11%, schizophrenia 59-71%, no analyses of diagnostic subgroups.

Kleinman 1993 (174)

Reason for exclusion	Allocation: block randomisation after stratifying for hospital affiliation. Participants: schizophrenia. Intervention: educational process group versus single educational session. No standard care group.

Klingberg 2009 (175)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: CBT vs psychoeducation. Outcome: no numerical data reported. No n numbers for groups.

Kopelowicz 1998 (176)

Reason for exclusion	Allocation: random. Participants: schizophrenia or schizoaffective disorder. Intervention: community re-entry program, not psychoeducation.

Kuipers 1994 (177)

Reason for exclusion	Allocation: random. Participants: schizophrenia and affective disorder. Interventions: structured medication education versus unstructured teaching. No standard care group.

Lester 2004a (178)

Reason for exclusion	Allocation: random. Participants: general practitioners, not people with schizophrenia.

Li 2002 (179)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation vs routine care. Outcome: no usable data - no numerical data reported.

Li 2004 (180)

Reason for exclusion	Allocation: not randomised, case control study.

Liu 2007 (121)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation + standard drug therapy vs standard drug therapy. Outcome: ITAQ and BPRS scale scores. Authors agreed to exclude this study found in 2010 update search, as all of the continuous scale scores are exactly the same (down to the decimal points) as study 'Unclear - both 2005'. Review authors felt this unlikely to be true.

Liu 2008 (181)

Reason for exclusion	Allocation: not randomised, quasi randomisation.

Liu 2008a (182)

Reason for exclusion	Allocation: not randomised, quasi randomisation.

Liu 2008b (183)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: health education with elements of skill training vs routine care.

Li Zheng 2004 (184)

Reason for exclusion	Allocation: random. Participants: schizophrenia. Interventions: problem solving and skills training.

Lv 2005 (185)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation with elements of CBT vs standard care.

Ma 1998 (186)

Reason for exclusion	Allocation: randomisation not mentioned and received open management. Participants: schizophrenia, initial onset.

	Interventions: family intervention versus traditional treatment, not psychoeducation.

Magliano 2006 (187)

Reason for exclusion	Allocation: random. Participants: schizophrenia. Intervention: family psychoeducation with elements of skills training.

Mak 1997 (188)

Reason for exclusion	Allocation: random. Participants: schizophrenia DSM-III outpatients. Intervention: group and individual behavioral family management with psychoeducation provided through printed information versus conventional care. (Psychoeducation component did not involve interaction between information provider and recipients and was thus excluded from the review.)

McGill 1983 (189)

Reason for exclusion	Allocation: random. Participants: PSE schizophrenia. Intervention: complex family therapy intervention versus individual supportive psychotherapy.

Mo 2007 (190)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation with elements of skill training vs standard care.

Motlova 2003 (191)

Reason for exclusion	Allocation: Case Control design. Participants: ICD-10: schizophrenia, schizoaffective disorder and acute psychotic episode with psychotic symptoms. Intervention: the program provided a combination of education about mental illness, family support, crisis intervention, communication and problem-solving skills training.

Pei 2008 (192)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation vs standard care. Outcome: no usable data - data are from sub-scale of NOSIE and another unvalidated scale.

Poplawska 2004 (193)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation vs standard care. Outcome: no usable data (IMHC scale score reported, but the scale is unvalidated).

Rotondi 2005 (194)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: telehealth psychoeducation - a package of care including elements of problem-solving training.

Scocco 2006 (195)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia.

	Intervention: a depot olanzapine trial where one group of patients were told that the drug might cause weight gain - not a psychoeducation programme.

Shin 2002 (196)

Reason for exclusion	Allocation: random. Participants: DSM-IV: schizophrenia, schizoaffective or schizophreniform disorder. Intervention: complex intervention including communication and stress management skills, self-help and community resources.

Song 2008 (197)

Reason for exclusion	Allocation: quasi randomisation.

Su 2007 (198)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation with elements of skill training vs standard care.

Sun 2005 (122)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: CBT vs standard care.

Wang 2004 (199)

Reason for exclusion	Allocation: random. Participants: schizophrenia. Intervention: complex family cognition insight therapy and family intervention and the control group treated with common psychotherapy.

Wang 2007 (200)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: health education with elements of skills training vs standard care.

Wang 2008 (201)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation with elements of music and exercise therapy vs standard care.

Wei 2005 (202)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: CBT vs standard care.

Xiang 2007 (203)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: community re-entry module (a module of a structured social skills training programme) vs psychoeducation.

Xiong 1994 (204)

Reason for exclusion	Allocation: random. Participants: DSM-III-R schizophrenia. Intervention: family intervention with minimal psychoeducation vs standard care.

Xiong 2007 (205)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: health education with elements of social and independent living skills training vs standard care.

Youssef 1987 (206)

Reason for exclusion	Allocation: random. Participants: diagnosis unclear: schizo-affective or affective disorder, data not available for a non-affective subgroup. Intervention: education sessions vs standard care.

Zhang 1994 (207)

Reason for exclusion	Allocation: random. Participants: schizophrenia. Intervention: family intervention with minimal psychoeducation vs standard care.

Zhang 2005 (208)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: psychoeducation with elements of social skill training vs standard care.

Zhang 2006 (209)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: health education with social and independent living skills training vs standard care.

Zheng 2008 (210)

Reason for exclusion	Allocation: randomised. Participants: schizophrenia. Intervention: health education with practical help on social activities and independent living vs standard care.

Zhu 2002 (211)

Reason for exclusion	Allocation: quasi randomisation.

Footnotes
BPRS = Brief Psychiatric Rating Scale
CBT = cognitive behaviour therapy
DSM-III = Diagnostic and Statistical Manual of Mental Disorders, third edition
DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, third edition, revised
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition
ICD-10 = International classification of diseases, tenth revision
PSE = Present State Examination

Characteristics of studies awaiting classification

Aho-Mustonen 2011 (212)

Methods, Participants, Interventions, Outcomes	To be assessed.

Bentall 2001 (123)

Methods	Allocation: unclear.
Participants	Diagnosis: schizophrenia DSM-IV or schizoaffective disorder. N = 228. History: admitted to acute psychiatric wards.
Interventions	1. Compliance intervention (patients educated about benefits of neuroleptic medication). 2. Alliance intervention (structured intervention in which patients are encouraged to rationally appraise the costs and benefits of their neuroleptic medication). 3. Treatment as usual.
Outcomes	1. Attitudes towards neuroleptic as measured by the Drug Attitudes Inventory. 2. Psychotic symptoms as measured by the Positive and Negative Syndromes Scale.
Notes	Further information needed on 'Methods'. Publication being sought.

Day 2000 (124)

Methods	Allocation: unclear.
Participants	Diagnosis: schizophrenia. N = 180-225. History: inpatients on acute psychiatric admission wards presenting with psychotic symptoms, who have been prescribed neuroleptic medication.
Interventions	1. An educational intervention. 2. A collaborative intervention. 3. A control condition.
Outcomes	Compliance with prescribed neuroleptic medication regimens.
Notes	Further information needed on 'methods', publication being sought

Fiorillo 2011 (213)

Methods, Participants, Interventions, Outcomes	To be assessed.

Gassmann 2011 (214)

Methods, Participants, Interventions, Outcomes	To be assessed.

Hegde 2012 (215)

Methods, Participants, Interventions, Outcomes	To be assessed.

ISRCTN32545295 (216)

Methods, Participants, Interventions, Outcomes	To be assessed.

ISRCTN33576045 (217, 218)

Methods, Participants, Interventions, Outcomes	To be assessed.

Jahn 2011 (219)

Methods, Participants, Interventions, Outcomes	To be assessed.

Medalia 2012 (220)

Methods, Participants, Interventions, Outcomes	To be assessed.

Mueser 2012 (221)

Methods, Participants, Interventions, Outcomes	To be assessed.

Navidian 2010 (222)

Methods, Participants, Interventions, Outcomes	To be assessed.

NCT01547026 (223)

Methods, Participants, Interventions, Outcomes	To be assessed.

NCT01601587 (224)

Methods, Participants, Interventions, Outcomes	To be assessed.

Nischk 2011 (225)

Methods, Participants, Interventions, Outcomes	To be assessed.

Nordentoft 1999 b (226)

Methods, Participants, Interventions, Outcomes	To be assessed.

Rabovsky 2012 (227)

Methods, Participants, Interventions, Outcomes	To be assessed.

Ran 2002 (228)

Methods, Participants, Interventions, Outcomes	To be assessed.

Rotondi 2011 (194)

Methods, Participants, Interventions, Outcomes	To be assessed.

Schlosser 2011 (229)

Methods, Participants, Interventions, Outcomes	To be assessed.

Schlosser 2012 (230)

Methods, Participants, Interventions, Outcomes	To be assessed.

Schulze 2011 (231)

Methods, Participants, Interventions, Outcomes	To be assessed.

Sharif 2012 (232)

Methods, Participants, Interventions, Outcomes	To be assessed.

Shaygan 2011 (233)

Methods, Participants, Interventions, Outcomes	To be assessed.

Silverman 2011 (233)

Methods, Participants, Interventions, Outcomes	To be assessed.

Silverman 2011a (234)

Methods, Participants, Interventions, Outcomes	To be assessed.

Smeerdijk 2010 (235)

Methods, Participants, Interventions, Outcomes	To be assessed.

Valencia 2012 (236)

Methods, Participants, Interventions, Outcomes	To be assessed.

Zarafonitis 2012 (237)

Methods, Participants, Interventions, Outcomes	To be assessed.

Characteristics of ongoing studies

Kissling 2007 (125)

Study name	"How can re hospitalisations of patients with schizophrenia be avoided? A comparison between different compliance programs."
Methods	Allocation: randomised. Blinding: open label, placebo control.
Participants	Diagnosis: schizophrenia Age: 18-67 years.
Interventions	1. Psychoeducation by professional vs placebo comparator. 2. Psychoeducation with video vs placebo comparator.
Outcomes	
Starting date	September 2006
Contact information	Dr Werner Kissling Technical University Munich, Germany.
Notes	Estimated completion date: August 2010.

Summary of findings tables

1 ANY FORM OF PSYCHOEDUCATION compared with STANDARD CARE for schizophrenia

ANY FORM OF PSYCHOEDUCATION compared with STANDARD CARE for schizophrenia						
Patient or population: patients with schizophrenia **Settings:** in hospital **Intervention:** ANY FORM OF PSYCHOEDUCATION **Comparison:** STANDARD CARE						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	STANDARD CARE	**ANY FORM OF PSYCHOEDUCATION**				
Compliance: Not compliant with medication Follow-up: 12 months	**Low risk population**[1]		**RR 0.48** (0.31 to 0.75)	282 (3 studies)	⊕⊖⊖⊖ **very low**[2,3,4]	
	200 per 1000	**96 per 1000** (62 to 150)				
	Medium risk population[1]					
	400 per 1000	**192 per 1000** (124 to 300)				
	High risk population[1]					
	800 per 1000	**384 per 1000** (248 to 600)				
Compliance: 2a. With follow-up - loss to follow-up for any reason - long term (by 5 years or more) Follow-up: 12 months	**Low risk population**[1]		**RR 0.77** (0.48 to 1.23)	172 (2 studies)	⊕⊖⊖⊖ **very low**[2,3,4]	
	200 per 1000	**154 per 1000** (96 to 246)				
	Medium risk population[1]					
	400 per 1000	**308 per 1000** (192 to 492)				
	High risk population[1]					
	800 per 1000	**616 per 1000** (384 to 984)				
Compliance: 2b. With follow-up - received intervention but left the study early - long term Follow-up: 12 months	**Low risk population**[1]		**RR 0.63** (0.38 to 1.04)	206 (2 studies)	⊕⊕⊖⊖ **low**[2,4]	
	200 per 1000	**126 per 1000** (76 to 208)				
	Medium risk population[1]					
	400 per 1000	**252 per 1000** (152 to 416)				
	High risk population[1]					
	800 per 1000	**504 per 1000** (304 to 832)				
Relapse: 1. Relapse for any reason - long term Follow-up: 12 months	**Low risk population**[5]		**RR 0.73** (0.62 to 0.85)	790 (6 studies)	⊕⊕⊖⊖ **low**[4,6]	
	200 per 1000	**146 per 1000** (124 to 170)				
	Medium risk population[5]					
	400 per 1000	**292 per 1000** (248 to 340)				
	High risk population[5]					
	800 per 1000	**584 per 1000** (496 to 680)				

Relapse: 2. Relapse with readmission - long term Follow-up: 12 months	**Low risk population**[7]		**RR 0.71** (0.56 to 0.89)	206 (2 studies)	⊕⊕⊖⊖ **low**[2,4]	
	200 per 1000	**142 per 1000** (112 to 178)				
	Medium risk population[7]					
	400 per 1000	**284 per 1000** (224 to 356)				
	High risk population[7]					
	800 per 1000	**568 per 1000** (448 to 712)				
Satisfaction with mental health services: 3. binary outcome - medium term - unsatisfied Follow-up: 12 months	**Low risk population**[1]		**RR 0.4** (0.17 to 0.96)	116 (1 study)	⊕⊕⊖⊖ **low**[2,4]	
	200 per 1000	**80 per 1000** (34 to 192)				
	Medium risk population[1]					
	400 per 1000	**160 per 1000** (68 to 384)				
	High risk population[1]					
	800 per 1000	**320 per 1000** (136 to 768)				
Adverse event: Death - long term Follow-up: 12 months	**Low risk population**[8]		**RR 1.39** (0.24 to 8.11)	344 (2 studies)	⊕⊕⊖⊖ **low**[2,4]	
	10 per 1000	**14 per 1000** (2 to 81)				
	Medium risk population[8]					
	30 per 1000	**42 per 1000** (7 to 243)				
	High risk population[8]					
	50 per 1000	**69 per 1000** (12 to 405)				
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio;						
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.						

Footnotes

[1] Control risk from studies - about 30%

[2] Randomisation poorly described

[3] High heterogeneity not explained by study design, population or interventions

[4] Small sample size - confidence interval around best estimate of effect include both no effect and appreciable benefit/harm

[5] Control risk from studies - about 50%

[6] 50% of the included studies used scientific randomisation methods and provided description of methods, but the other 50% did not describe randomisation methods

[7] Control risk from studies - about 70%

[8] Control risk from studies - about 1%

Additional tables

1 Chinese studies vs full analysis (sensitivity analyses)

Primary outcome	China Experimental	China Control	China RR (CI)	Full analysis Experimental	Full analysis Control	Full analysis RR (CI)
Compliance	19/174	22/172	0.85 (0.48-1.51)	109/488	101/461	1.00 (0.79-1.26)
Relapse	44/353	90/347	0.48 (0.35-0.66)	174/628	22/586	0.7 (0.61-0.81)

Footnotes

2 English studies vs full analysis (sensitivity analyses)

Primary outcome	English Experimental	English Control	English RR (CI)	Full analysis Experimental	Full analysis Control	Full analysis RR (CI)
Compliance	90/314	79/289	1.04 (0.8-1.34)	109/488	101/461	1.00 (0.79-1.26)
Relapse	130/275	132/239	0.85 (0.73-0.99)	174/628	22/586	0.7 (0.61-0.81)

Footnotes

3 Suggested design of study

Methods	Allocation: randomised, fully explicit description of methods of randomisation and allocation concealment. Blinding: single, tested. Setting: community rather than hospital. Duration: 12 weeks treatment, and then follow-up to at least 52 weeks.
Participants	Diagnosis: schizophrenia (ICD). N = 300.* Age: adults. Sex: both.
Interventions	1. Psychoeducation. N = 150. 2. Standard care. N = 150.
Outcomes	General: time to all-cause treatment failure marked by its discontinuation, relapse, general impression of clinician (CGI), career/other, compliance with treatment, healthy days. Mental state: BPRS and PANSS. Global state: CGI (Clinical Global Impression). Quality of life. QOL (Quality of Life Questionnaire). Family burden: FBQ (Family Burden Questionnaire). Social functioning: return to everyday living for 80% of time.* Adverse events: any adverse event recorded. Economic outcomes.
Notes	* Powered to be able to identify a difference of ~ 20% between groups for primary outcome with adequate degree of certainty.

Footnotes

Data and analyses

1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Compliance: 1a. With medication - non-compliance	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 short term	10	1400	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.40, 0.67]
1.1.2 medium term	6	781	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.27, 0.49]
1.1.3 long term	3	282	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.31, 0.75]
1.2 Compliance: 1b. With medication - partial compliance	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 short term	3	472	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.49, 0.85]
1.2.2 medium term	1	118	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.39, 1.18]
1.3 Compliance: 1c. With medication - continuous outcomes - skewed data	1		Other data	No numeric data
1.3.1 single session - average compliance with medication (SAI sub-scale endpoint score, high = favourable)	1		Other data	No numeric data
1.3.2 three sessions - average compliance with medication (SAI sub-scale endpoint score, high = favourable)	1		Other data	No numeric data
1.4 Compliance: 2a. With follow up - loss to follow-up for any reason	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 medium term - loss to follow-up for any reason	8	949	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.79, 1.26]
1.4.2 long term - loss to follow-up for any reason (by 2 years)	3	420	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.62, 1.10]
1.4.3 long term - loss to follow-up for any reason (by 5 years or more)	2	172	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.48, 1.23]
1.5 Compliance: 2b. With follow-up - received intervention but left the study early	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 short term	2	87	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.36, 25.67]
1.5.2 medium term	4	319	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.29, 1.10]
1.5.3 long term	2	206	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.38, 1.04]
1.6 Compliance: 2c. With follow-up - allocated but never accepted treatment	2	213	Risk Ratio (M-H, Fixed, 95% CI)	12.27 [2.58, 58.33]

1.6.1 medium term	2	213	Risk Ratio (M-H, Fixed, 95% CI)	12.27 [2.58, 58.33]
1.7 Relapse: 1. Relapse for any reason	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 medium term	11	1214	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.81]
1.7.2 long term	6	790	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.62, 0.85]
1.7.3 long term (at 5 years follow-up)	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.08]
1.7.4 long term (at 7 years follow-up)	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.42, 0.92]
1.8 Relapse: 2. Relapse with readmission	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.8.1 medium term	2	206	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.56, 1.07]
1.8.2 long term	2	206	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.56, 0.89]
1.9 Knowledge: 1a. Average endpoint scale scores on various knowledge scales	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.9.1 short term - at end of intervention (KQ, high = favourable)	1	75	Mean Difference (IV, Fixed, 95% CI)	-12.00 [-17.67, -6.33]
1.9.2 short term (KASQ, high = favourable)	1	71	Mean Difference (IV, Fixed, 95% CI)	0.20 [-2.12, 2.52]
1.9.3 short term (ITAQ, high = favourable)	3	295	Mean Difference (IV, Fixed, 95% CI)	5.53 [4.56, 6.49]
1.9.4 short term (SKQ, high = favourable)	1	19	Mean Difference (IV, Fixed, 95% CI)	-16.26 [-22.72, -9.80]
1.9.5 medium term (ITAQ, high = favourable)	1	73	Mean Difference (IV, Fixed, 95% CI)	4.83 [1.51, 8.15]
1.9.6 medium term (KASQ, high = favourable)	1	61	Mean Difference (IV, Fixed, 95% CI)	1.60 [-0.84, 4.04]
1.9.7 long term (KQ, high = favourable)	1	75	Mean Difference (IV, Fixed, 95% CI)	-8.00 [-14.64, -1.36]
1.10 Knowledge: 1b. Average change (UMQ, high = favourable, data skewed)	1		Other data	No numeric data
1.10.1 single session psychoeducation	1		Other data	No numeric data
1.10.2 three session psychoeducation	1		Other data	No numeric data
1.11 Knowledge: 2. Average endpoint scores on various insight scales	3	217	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-1.31, 0.93]
1.11.1 short term (SAUMD, high = poor)	2	161	Mean Difference (IV, Fixed, 95% CI)	-0.63 [-1.86, 0.61]
1.11.2 medium term (RAQ, high = poor)	1	56	Mean Difference (IV, Fixed, 95% CI)	1.80 [-0.85, 4.45]
1.12 Knowledge: 3. Average endpoint score on illness-	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

related attitudes - 4 months (KK, high = high expressed)				
1.12.1 confidence in medication	1	75	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-3.21, 0.21]
1.12.2 confidence in physician	1	75	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.73, -0.07]
1.12.3 negative expectations toward medication as such	1	75	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-2.07, 1.07]
1.12.4 susceptibility to illness and to relapse	1	75	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.78, 1.98]
1.12.5 attribution of illness to chance	1	75	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-2.30, 0.90]
1.12.6 attribution of guilt	1	75	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.07, 0.47]
1.12.7 fear of side effects of medication	1	75	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-2.74, -0.46]
1.13 Knowledge: 4. level of knowledge did not improve	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.06, 0.28]
1.14 Behaviour: Average score (NOSIE-30, endpoint, high = poor)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.14.1 short term	2	202	Mean Difference (IV, Fixed, 95% CI)	16.85 [11.90, 21.80]
1.14.2 medium term	1	73	Mean Difference (IV, Fixed, 95% CI)	14.00 [3.03, 24.97]
1.14.3 long term	1	70	Mean Difference (IV, Fixed, 95% CI)	41.33 [31.02, 51.64]
1.15 Social functioning: 1a. Average change scores on various scales - medium term (high = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.15.1 MRSS	1	118	Mean Difference (IV, Fixed, 95% CI)	13.68 [12.51, 14.85]
1.15.2 SDSS	1	118	Mean Difference (IV, Fixed, 95% CI)	1.96 [1.83, 2.09]
1.16 Social functioning: 1b. Average endpoint scores on various scales (high = poor)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.16.1 short term - IPROS	1	116	Mean Difference (IV, Fixed, 95% CI)	-6.64 [-11.02, -2.26]
1.16.2 short term - SAS	3	378	Mean Difference (IV, Fixed, 95% CI)	-8.53 [-10.50, -6.55]
1.16.3 short term - SAS-II	1	19	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.37, 0.17]
1.16.4 short term - SDS	3	378	Mean Difference (IV, Fixed, 95% CI)	-5.60 [-7.55, -3.65]
1.16.5 medium term - SDSS	1	85	Mean Difference (IV, Fixed, 95% CI)	-3.74 [-6.05, -1.43]
1.17 Social functioning 1c. Average SAS, SFS, SNS scale scores - skewed data (low = favourable)	1		Other data	No numeric data

1.18 Global functioning: 1. No clinically significant improvement	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.18.1 short term	2	208	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.32, 1.13]
1.18.2 medium term	2	178	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.43, 0.82]
1.18.3 long term	2	132	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.48, 1.04]
1.19 Global functioning: 2. Average endpoint scale score	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.19.1 short term - (GAF/GAS, high = good)	1	41	Mean Difference (IV, Fixed, 95% CI)	-2.64 [-12.74, 7.46]
1.19.2 short term - (SLOF, high = good)	1	84	Mean Difference (IV, Fixed, 95% CI)	23.60 [11.88, 35.32]
1.19.3 medium term - (GAF/GAS, high = good)	4	321	Mean Difference (IV, Fixed, 95% CI)	-5.44 [-8.51, -2.38]
1.19.4 medium term - (SLOF, high = good)	1	84	Mean Difference (IV, Fixed, 95% CI)	46.40 [34.45, 58.35]
1.19.5 long term (GAS, high = good) - at 2 years	1	59	Mean Difference (IV, Fixed, 95% CI)	-6.70 [-13.38, -0.02]
1.19.6 long term - (GAS, high = good) - at 5 years or more	2	108	Mean Difference (IV, Fixed, 95% CI)	-3.36 [-7.24, 0.52]
1.20 Service utilisation: days in hospital	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.20.1 short term - days in hospital	2	200	Mean Difference (IV, Fixed, 95% CI)	-3.23 [-5.44, -1.01]
1.20.2 medium term - days in hospital	1	84	Mean Difference (IV, Fixed, 95% CI)	-8.40 [-10.44, -6.36]
1.21 Service utilisation: Days in hospital using 'acute services' - during 18 months (data skewed)	1		Other data	No numeric data
1.22 Global state: 1. Average endpoint score - medium term (CGI, high = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.22.1 severity	1	61	Mean Difference (IV, Fixed, 95% CI)	0.50 [0.08, 0.92]
1.22.2 change	1	61	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-1.45, -0.15]
1.23 Global state: 2. Increased medication dose by 25%	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.15, 1.20]
1.24 Global state: 3. Disability - long term	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.13, 0.64]
1.25 Mental state: 1a. Global - continuous - average total endpoint scale scores (high = poor)	17		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.25.1 short term (BPRS)	11	1107	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-1.38, -0.63]
1.25.2 medium term (BPRS)	7	760	Mean Difference (IV, Fixed, 95% CI)	-4.73 [-5.55, -3.91]

1.25.3 medium term (PANSS)	2	163	Mean Difference (IV, Fixed, 95% CI)	-2.52 [-5.01, -0.04]
1.25.4 long term (BPRS - 1 ~ 2 year follow-up)	3	370	Mean Difference (IV, Fixed, 95% CI)	-6.89 [-8.55, -5.23]
1.25.5 long term (BPRS - 7 year follow-up)	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-6.55, 6.15]
1.26 Mental state: 1b. Global - continuous - average change scale scores - medium term (high = good)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.26.1 GWB	1	118	Mean Difference (IV, Fixed, 95% CI)	10.89 [9.82, 11.96]
1.26.2 SES	1	118	Mean Difference (IV, Fixed, 95% CI)	8.00 [7.77, 8.23]
1.27 Mental state: 1c. Global - continuous - average total endpoint scale scores - (BPRS, high = poor, data skewed)	2		Other data	No numeric data
1.28 Mental state: 2a. Specific - binary - specific symptoms - short term	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.28.1 anxiety	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.25, 0.93]
1.28.2 depression	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.25, 0.88]
1.29 Mental state: 2b. Specific - continuous - average endpoint PANSS scores (high = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.29.1 short term - negative symptoms	1	71	Mean Difference (IV, Fixed, 95% CI)	0.40 [-1.98, 2.78]
1.29.2 short term - positive symptoms	1	71	Mean Difference (IV, Fixed, 95% CI)	1.50 [-0.99, 3.99]
1.29.3 medium term - negative symptoms	1	61	Mean Difference (IV, Fixed, 95% CI)	3.10 [0.16, 6.04]
1.29.4 medium term - positive symptoms	1	61	Mean Difference (IV, Fixed, 95% CI)	2.40 [-0.46, 5.26]
1.30 Expressed emotion: Participants with high EE relatives (FQ)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.30.1 short term - at end of interventions	2	282	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.76, 0.94]
1.30.2 medium term - at 9-12 months	1	46	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.64, 1.78]
1.31 Quality of life: Average endpoint scores on various scales (high = favourable)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.31.1 short term - GQOLI-74	1	62	Mean Difference (IV, Fixed, 95% CI)	0.63 [-0.79, 2.05]
1.31.2 short term - PGWB	1	71	Mean Difference (IV, Fixed, 95% CI)	2.00 [-6.08, 10.08]
1.31.3 medium term - GQOLI-74	1	62	Mean Difference (IV, Fixed, 95% CI)	2.13 [1.03, 3.23]

1.31.4 medium term - QOL	1	108	Mean Difference (IV, Fixed, 95% CI)	-9.70 [-17.22, -2.18]
1.31.5 medium term - PGWB	1	61	Mean Difference (IV, Fixed, 95% CI)	2.80 [-5.40, 11.00]
1.32 Quality of life: Average endpoint scores on various scales (high = poor)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.32.1 short term - FAD	1	62	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-5.45, 4.61]
1.32.2 short term - FBIS	1	84	Mean Difference (IV, Fixed, 95% CI)	-4.70 [-7.19, -2.21]
1.32.3 medium term - FAD	1	62	Mean Difference (IV, Fixed, 95% CI)	-6.79 [-11.67, -1.91]
1.32.4 medium term - FBIS	2	241	Mean Difference (IV, Fixed, 95% CI)	-6.24 [-7.80, -4.68]
1.33 Satisfaction with mental health services: 1. Short term - average change score (VSS, high = good)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.33.1 patients' satisfaction	1	32	Mean Difference (IV, Fixed, 95% CI)	-2.15 [-13.96, 9.66]
1.33.2 relatives' satisfaction	1	17	Mean Difference (IV, Fixed, 95% CI)	-8.31 [-29.72, 13.10]
1.34 Satisfaction with mental health services: 2. Average change - at 1 year (VSS Scale, high = good)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.34.1 patients' satisfaction with relatives' involvement - mean change	1	30	Mean Difference (IV, Fixed, 95% CI)	-4.35 [-7.09, -1.61]
1.34.2 relatives' involvement satisfaction	1	21	Mean Difference (IV, Fixed, 95% CI)	-2.17 [-6.11, 1.77]
1.34.3 relatives' efficacy satisfaction	1	24	Mean Difference (IV, Fixed, 95% CI)	-2.16 [-7.29, 2.97]
1.34.4 relatives' intervention satisfaction	1	26	Mean Difference (IV, Fixed, 95% CI)	-3.43 [-9.83, 2.97]
1.35 Satisfaction with mental health services: 3. Binary outcome	2	236	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.12, 0.50]
1.35.1 short term - unsatisfied	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.03, 0.46]
1.35.2 medium term - unsatisfied	1	116	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.17, 0.96]
1.36 Adverse event: Death	4	626	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.31, 4.21]
1.36.1 medium term	2	282	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.13, 6.35]
1.36.2 long term	2	344	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.24, 8.11]
1.37 Economic outcomes: Costs (US$ per person, data skewed)	1		Other data	No numeric data

1.37.1 acute hospital charges	1		Other data	No numeric data
1.37.2 ambulatory charges	1		Other data	No numeric data
1.37.3 total charges	1		Other data	No numeric data

2 SUBGROUP ANALYSES 1. BRIEF PSYCHOEDUCATION/STANDARD PSYCHOEDUCATION vs STANDARD CARE

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Compliance: 1a. With medication - binary outcomes	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1.1 short term - non-compliance - brief	3	448	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.41, 0.96]
2.1.2 short term - non-compliance - standard	4	586	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.25, 0.67]
2.1.3 medium term - non-compliance - brief	1	118	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.05, 0.54]
2.1.4 medium term - non-compliance - standard	4	561	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.32, 0.62]
2.2 Compliance: 2. With follow-up - loss to follow-up for any reason	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2.1 medium term - brief	2	170	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.37, 0.94]
2.2.2 medium term - standard	7	739	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.83, 1.55]
2.2.3 long term (by 2 years) - brief	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.43, 1.15]
2.2.4 long term (by 2 years) - standard	1	136	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.66, 1.42]
2.2.5 long term (by 5 years or more) - brief	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.44, 1.21]
2.2.6 long term (by 5 years or more) - standard	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.28, 3.54]
2.3 Compliance: 2a. with follow-up - received intervention but left the study early	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.3.1 short term - brief	1	67	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.17, 56.70]
2.3.2 short term - standard	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.14, 65.90]
2.3.3 long term - brief	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.33, 1.01]
2.3.4 long term - standard	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.28, 2.52]
2.4 Relapse: Relapse for any reason	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.4.1 relapse - medium term - brief	3	292	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.43, 0.89]

2.4.2 relapse - medium term - standard	6	1011	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.99]
2.4.3 relapse with readmission - medium term - brief	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.59, 1.22]
2.4.4 relapse with readmission - medium term - standard	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.30, 1.21]
2.4.5 relapse - long term - brief	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.59, 1.22]
2.4.6 relapse - long term - standard	5	666	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.59, 0.84]
2.4.7 relapse with readmission - long term - brief	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.64, 1.08]
2.4.8 relapse with readmission - long term - standard	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.35, 0.82]

3 SUBGROUP ANALYSES 2. GROUP PSYCHOEDUCATION/INDIVIDUAL PSYCHOEDUCATION vs STANDARD CARE

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Compliance: 1a. With medication - binary outcomes	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1.1 short term - non-compliance - group	3	412	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.13, 0.52]
3.1.2 short term - non-compliance - individual	2	296	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.39, 1.11]
3.1.3 short term - partial compliance - group	1	250	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.50, 1.16]
3.1.4 short term - partial compliance - individual	1	136	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.41, 0.92]
3.2 Compliance: 2. With follow-up - leaving the study early/loss to follow-up	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.2.1 medium term - received intervention but left the study early - group	2	213	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.25, 1.06]
3.2.2 medium term - received intervention but left the study early - individual	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.14, 65.90]
3.2.3 medium term - loss to follow-up for any reason - group	4	367	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.61, 1.20]
3.2.4 medium term - loss to follow-up for any reason - individual	1	73	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.18, 20.53]
3.2.5 long term - loss to follow-up for any reason (by 2 years) - group	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.43, 1.15]

3.2.6 long term - loss to follow-up for any reason (by 2 years) - individual	2	296	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.63, 1.29]
3.3 Relapse: Relapse for any reason	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.3.1 relapse - medium term - group	4	410	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.57, 0.96]
3.3.2 relapse - medium term - individual	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.19, 1.05]
3.3.3 relapse - long term - group	2	344	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.66, 0.99]
3.3.4 relapse - long term - individual	1	136	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.94]

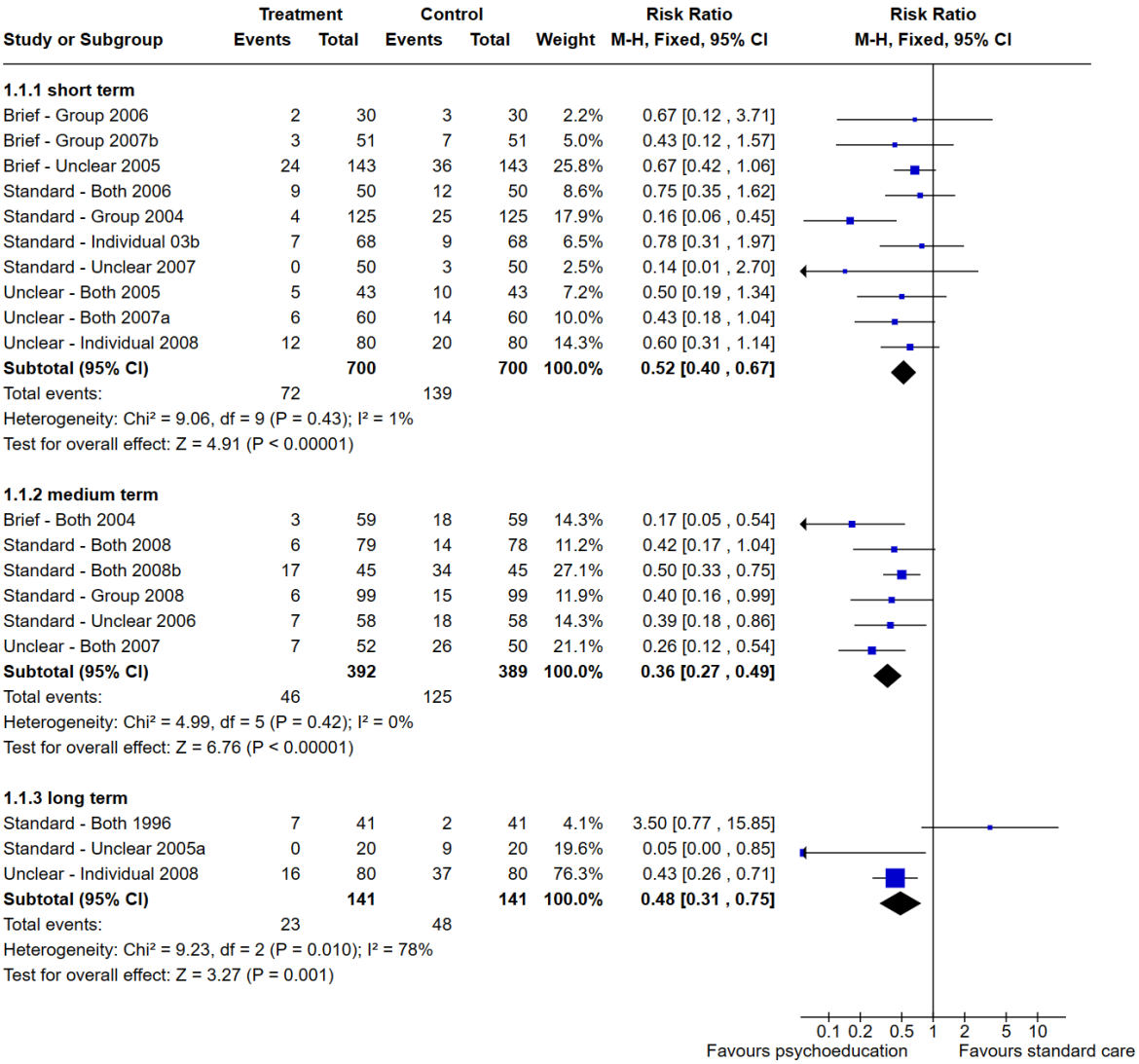
4 SENSITIVITY ANALYSIS - Chinese studies vs non-Chinese studies

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Compliance: 1a. With medication - non-compliance	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1.1 long term	3	282	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.31, 0.75]
4.1.2 long term - Chinese studies	3	282	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.31, 0.75]
4.2 Compliance: 2a. With follow-up - loss to follow-up for any reason	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.2.1 medium term - loss to follow-up for any reason	8	949	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.79, 1.26]
4.2.2 medium term - loss to follow-up for any reason - Chinese studies	8	949	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.79, 1.26]
4.2.3 long term - loss to follow-up for any reason (by 2 years)	3	420	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.62, 1.10]
4.2.4 long term - loss to follow-up for any reason (by 2 years) - Chinese studies	3	420	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.62, 1.10]
4.3 Compliance: 2b. With follow-up - received intervention but left the study early	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.3.1 medium term	4	319	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.29, 1.10]
4.3.2 medium term - Chinese studies	4	319	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.29, 1.10]
4.4 Relapse: 1. Relapse for any reason	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.4.1 medium term	11	1214	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.81]

4.4.2 medium term - Chinese studies	11	1214	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.81]
4.4.3 long term	6	790	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.62, 0.85]
4.4.4 long term - Chinese studies	6	790	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.62, 0.85]

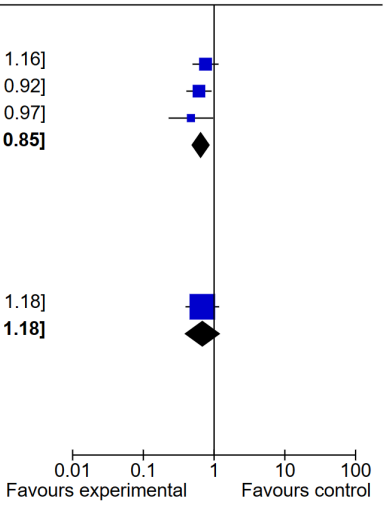
Figures

Analysis 1.1. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 1 Compliance: 1a. With medication - non-compliance.



Analysis 1.2. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 2.

Study or Subgroup	Psychoeducation Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 short term						
Standard - Group 2004	28	125	37	125	41.1%	0.76 [0.50 , 1.16]
Standard - Individual 03b	22	68	36	68	40.0%	0.61 [0.41 , 0.92]
Unclear - Both 2005	8	43	17	43	18.9%	0.47 [0.23 , 0.97]
Subtotal (95% CI)		**236**		**236**	**100.0%**	**0.64 [0.49 , 0.85]**
Total events:	58		90			
Heterogeneity: Chi² = 1.34, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 3.15 (P = 0.002)						
1.2.2 medium term						
Brief - Both 2004	15	59	22	59	100.0%	0.68 [0.39 , 1.18]
Subtotal (95% CI)		**59**		**59**	**100.0%**	**0.68 [0.39 , 1.18]**
Total events:	15		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						



Analysis 1.3. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 3 Compliance: 1c. With medication - continuous outcomes - skewed data.

Compliance: 1c. With medication - continuous outcomes - skewed data

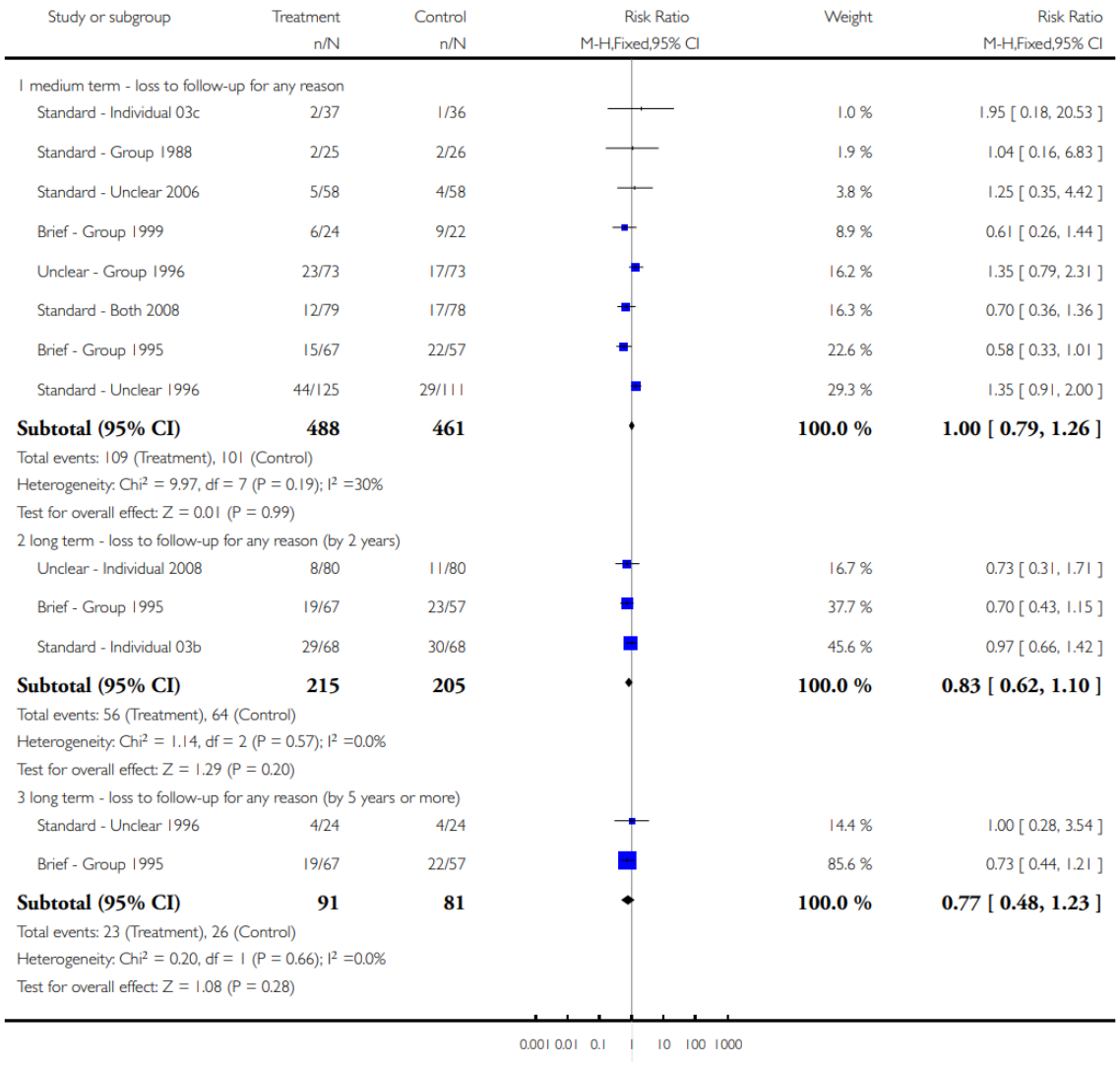
Study	Psychoed. mean	Psychoed. SD	Psychoed. N	Standard care mean	Standard care SD	Standard care N
single session - average compliance with medication (SAI sub-scale endpoint score, high = favourable)						
Brief - Individual 1996	2.6	1.2	22	2.1	1.3	20
three sessions - average compliance with medication (SAI sub-scale endpoint score, high = favourable)						
Brief - Individual 1996	2.18	1.3	22	2.1	1.3	20

Analysis 1.4. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 4 Compliance: 2a. With follow up - loss to follow-up for any reason.

Review: Psychoeducation for schizophrenia

Comparison: 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE

Outcome: 4 Compliance: 2a. With follow up - loss to follow-up for any reason



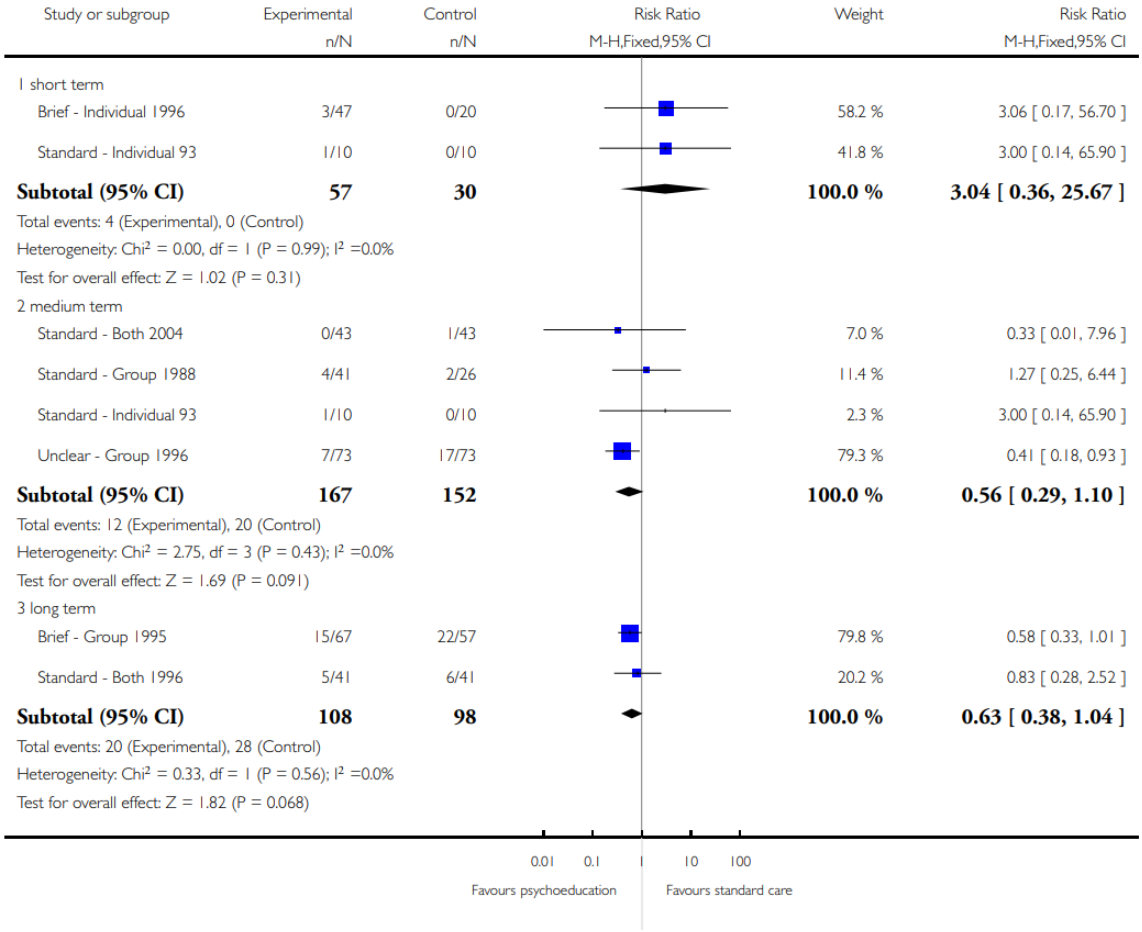
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 medium term - loss to follow-up for any reason					
Standard - Individual 03c	2/37	1/36		1.0 %	1.95 [0.18, 20.53]
Standard - Group 1988	2/25	2/26		1.9 %	1.04 [0.16, 6.83]
Standard - Unclear 2006	5/58	4/58		3.8 %	1.25 [0.35, 4.42]
Brief - Group 1999	6/24	9/22		8.9 %	0.61 [0.26, 1.44]
Unclear - Group 1996	23/73	17/73		16.2 %	1.35 [0.79, 2.31]
Standard - Both 2008	12/79	17/78		16.3 %	0.70 [0.36, 1.36]
Brief - Group 1995	15/67	22/57		22.6 %	0.58 [0.33, 1.01]
Standard - Unclear 1996	44/125	29/111		29.3 %	1.35 [0.91, 2.00]
Subtotal (95% CI)	**488**	**461**		**100.0 %**	**1.00 [0.79, 1.26]**
Total events: 109 (Treatment), 101 (Control)					
Heterogeneity: Chi^2 = 9.97, df = 7 (P = 0.19); I^2 =30%					
Test for overall effect: Z = 0.01 (P = 0.99)					
2 long term - loss to follow-up for any reason (by 2 years)					
Unclear - Individual 2008	8/80	11/80		16.7 %	0.73 [0.31, 1.71]
Brief - Group 1995	19/67	23/57		37.7 %	0.70 [0.43, 1.15]
Standard - Individual 03b	29/68	30/68		45.6 %	0.97 [0.66, 1.42]
Subtotal (95% CI)	**215**	**205**		**100.0 %**	**0.83 [0.62, 1.10]**
Total events: 56 (Treatment), 64 (Control)					
Heterogeneity: Chi^2 = 1.14, df = 2 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 1.29 (P = 0.20)					
3 long term - loss to follow-up for any reason (by 5 years or more)					
Standard - Unclear 1996	4/24	4/24		14.4 %	1.00 [0.28, 3.54]
Brief - Group 1995	19/67	22/57		85.6 %	0.73 [0.44, 1.21]
Subtotal (95% CI)	**91**	**81**		**100.0 %**	**0.77 [0.48, 1.23]**
Total events: 23 (Treatment), 26 (Control)					
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 1.08 (P = 0.28)					

Analysis 1.5. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 5 Compliance: 2b. With follow-up - received intervention but left the study early.

Review: Psychoeducation for schizophrenia

Comparison: 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE

Outcome: 5 Compliance: 2b. With follow-up - received intervention but left the study early

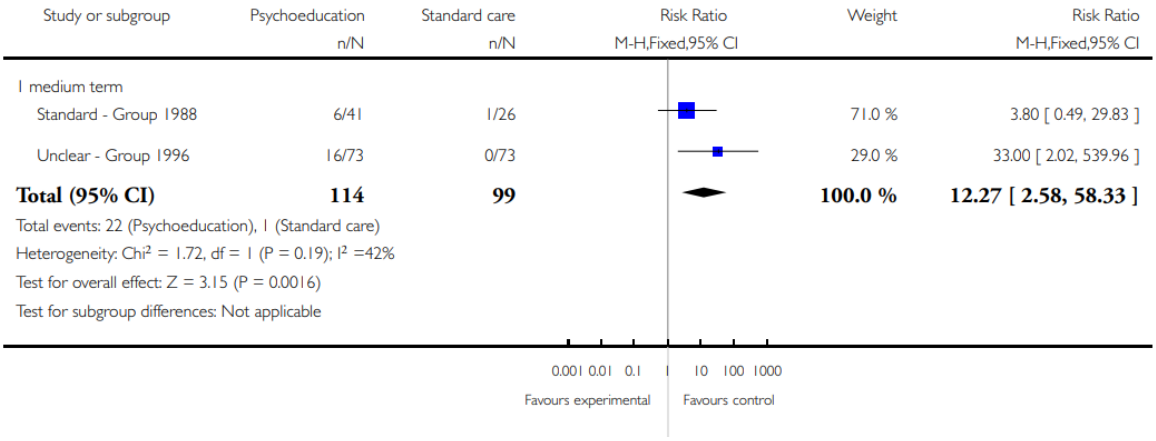


Analysis 1.6. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 6 Compliance: 2c. With follow-up - allocated but never accepted treatment.

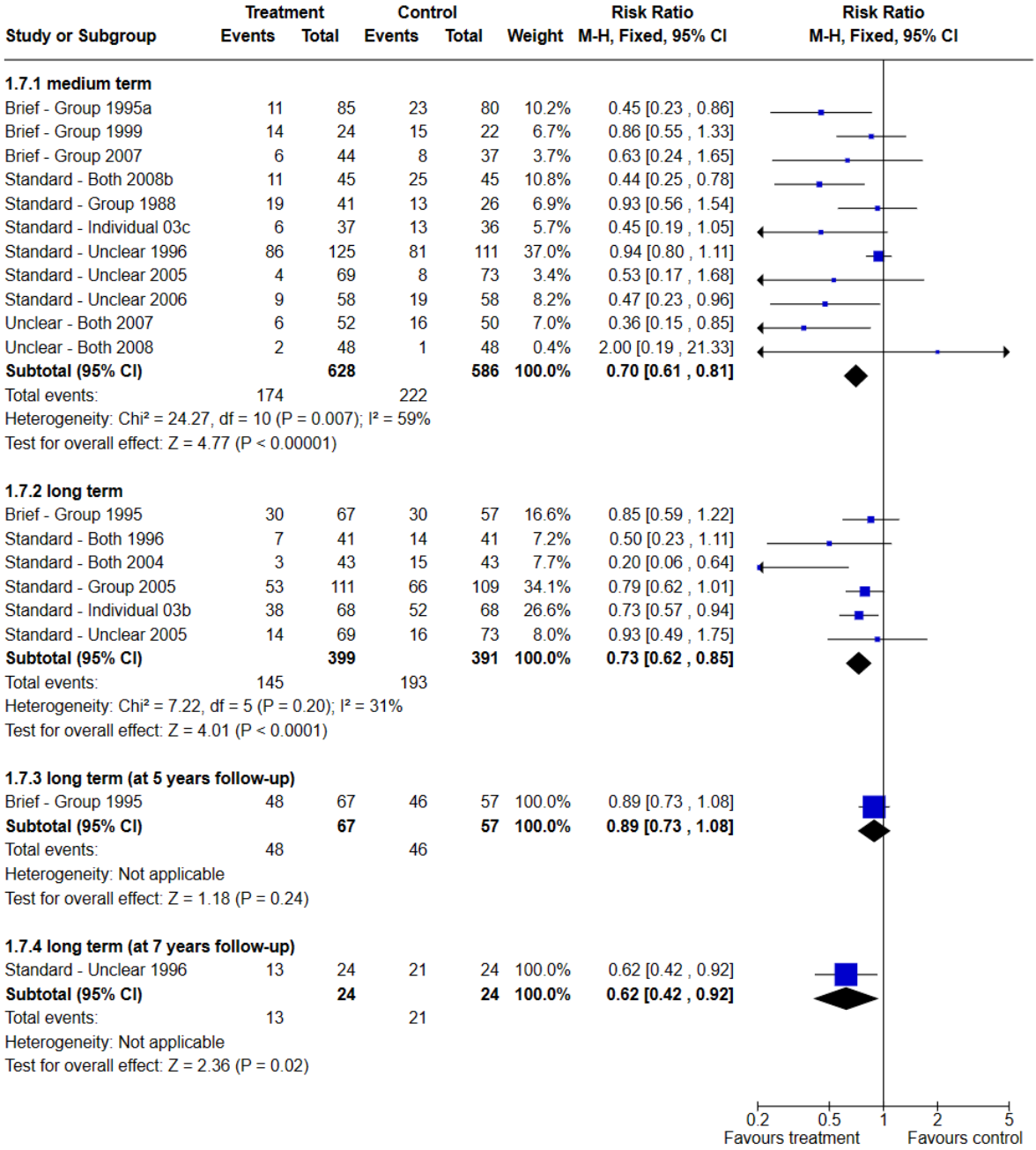
Review: Psychoeducation for schizophrenia

Comparison: 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE

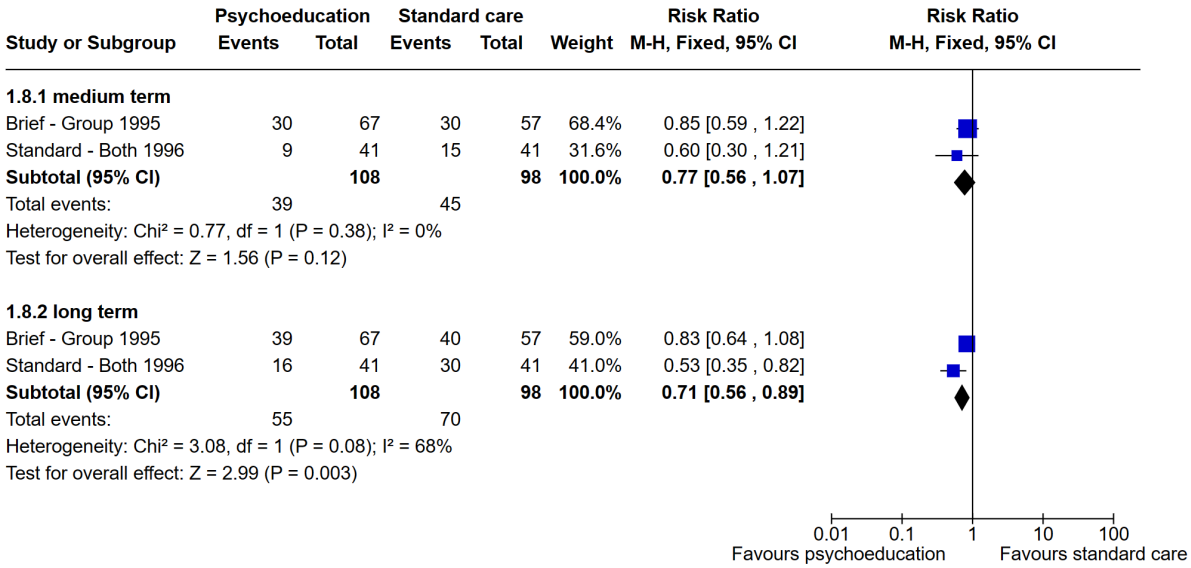
Outcome: 6 Compliance: 2c. With follow-up - allocated but never accepted treatment



Analysis 1.7. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 7 Relapse: 1. Relapse for any reason.

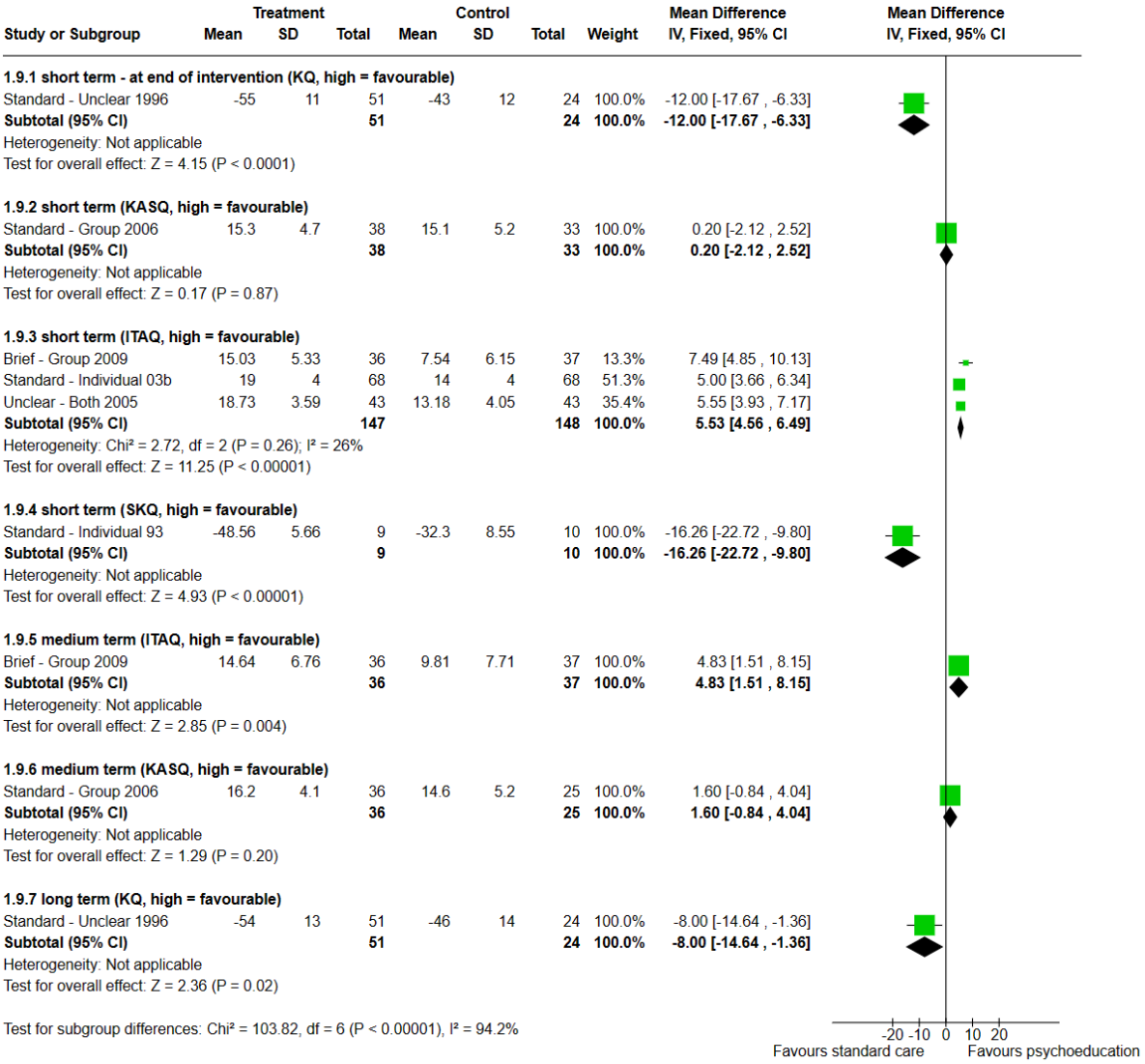


Analysis 1.8. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 8 Relapse: 2. Relapse with readmission.



Analysis 1.9. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 9.

Knowledge: 1a. Average endpoint scale scores on various knowledge scales.
Review: Psychoeducation for schizophrenia
Comparison: 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE
Outcome: 9 Knowledge: 1a. Average endpoint scale scores on various knowledge scales



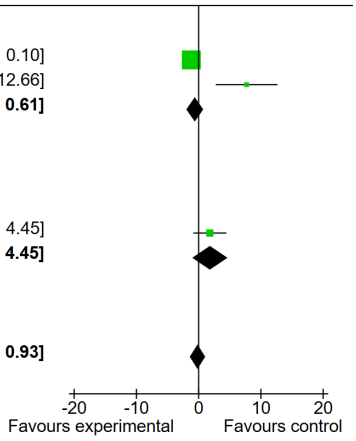
Analysis 1.10.Comparison I ANY FORM OF PSYCHOEDUCATION VS STANDARD CARE, Outcome 10Knowledge: Ib. Average change (UMO, high = favourable, data skewed).

Knowledge: 1b. Average change (UMQ, high = favourable, data skewed)

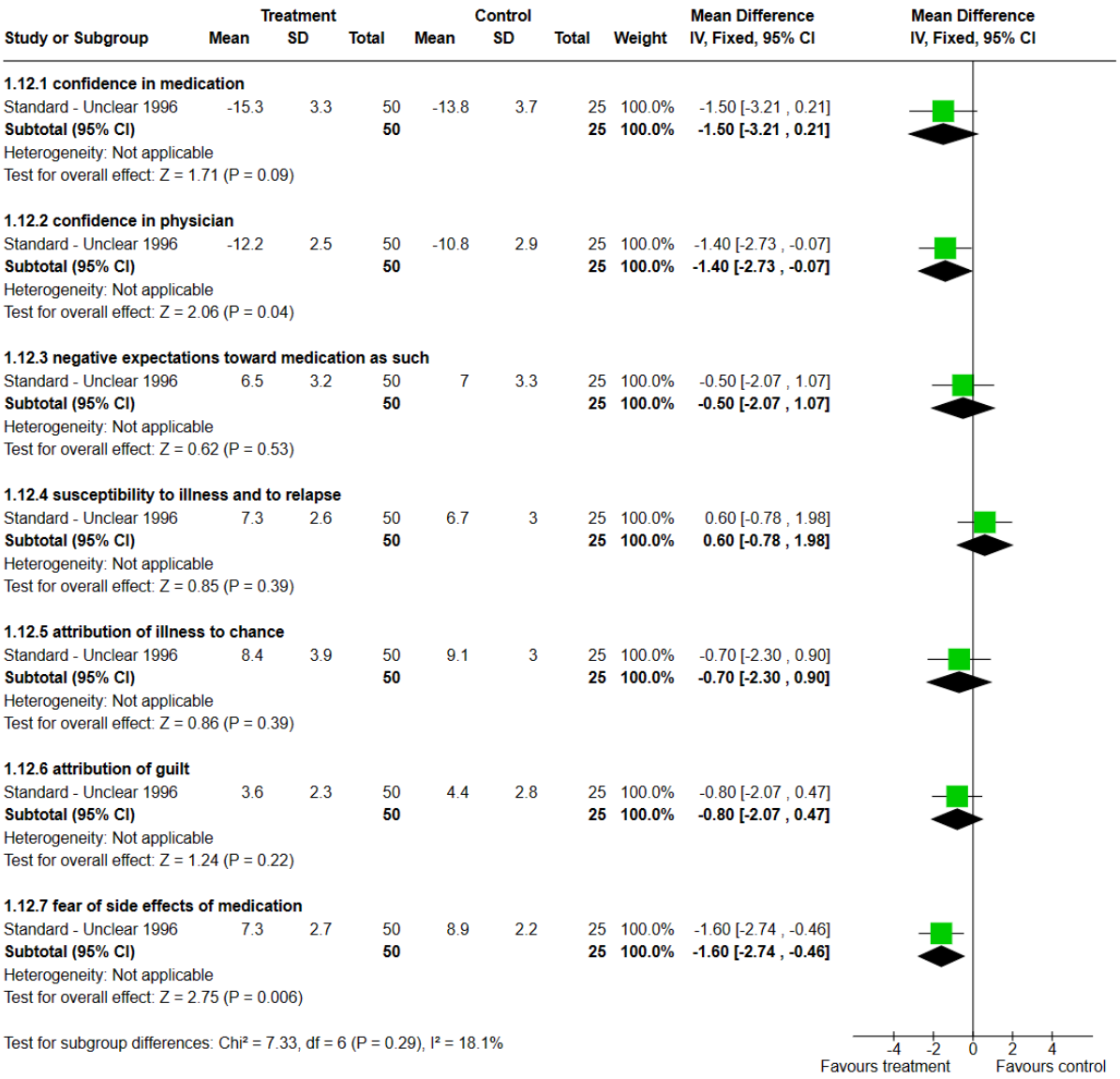
Study	Psychoed. mean	Psychoed. SD	Psychoed. N	Standard care mean	Standard care SD	Standard care N
single session psychoeducation						
Brief - Individual 1996	6.4	5.9	22	1.0	2.8	20
three session psychoeducation						
Brief - Individual 1996	15.00	7.4	22	1.0	2.8	20

Analysis 1.11. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 11 Knowledge: 2. Average endpoint scores on various insight scales.

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
1.11.1 short term (SAUMD, high = poor)									
Brief - Group 2007	6.77	2.56	44	7.95	3.2	37	76.9%	-1.18 [-2.46 , 0.10]	
Unclear - Both 2001	22.5	9.6	40	14.8	12.8	40	5.1%	7.70 [2.74 , 12.66]	
Subtotal (95% CI)			**84**			**77**	**82.1%**	**-0.63 [-1.86 , 0.61]**	
Heterogeneity: Chi² = 11.55, df = 1 (P = 0.0007); I² = 91%									
Test for overall effect: Z = 0.99 (P = 0.32)									
1.11.2 medium term (RAQ, high = poor)									
Standard - Group 2006	28.6	4.1	33	26.8	5.5	23	17.9%	1.80 [-0.85 , 4.45]	
Subtotal (95% CI)			**33**			**23**	**17.9%**	**1.80 [-0.85 , 4.45]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.33 (P = 0.18)									
Total (95% CI)			**117**			**100**	**100.0%**	**-0.19 [-1.31 , 0.93]**	
Heterogeneity: Chi² = 14.20, df = 2 (P = 0.0008); I² = 86%									
Test for overall effect: Z = 0.33 (P = 0.74)									
Test for subgroup differences: Chi² = 2.65, df = 1 (P = 0.10), I² = 62.2%									



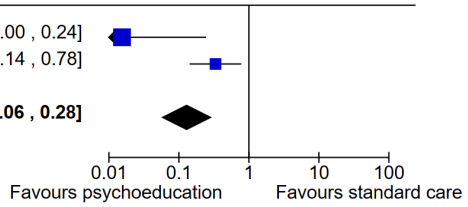
Analysis 1.12. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 12 Knowledge: 3. Average endpoint score on illness-related attitudes - 4 months (KK, high = high expressed).



Analysis 1.13. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 13 Knowledge: 4. level of knowledge did not improve.

Study or Subgroup	Psychoeducation Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Unclear - Both 2008	0	48	32	48	64.4%	0.02 [0.00 , 0.24]
Unclear - Unclear 2008	6	60	18	60	35.6%	0.33 [0.14 , 0.78]
Total (95% CI)		**108**		**108**	**100.0%**	**0.13 [0.06 , 0.28]**
Total events:	6		50			

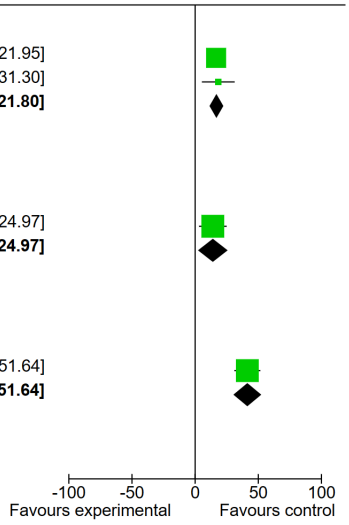
Heterogeneity: Chi² = 7.06, df = 1 (P = 0.008); I² = 86%
Test for overall effect: Z = 5.11 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 14 Behaviour: Average score (NOSIE-30, endpoint, high = poor).

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.14.1 short term								
Brief - Group 2007b	145.6	14.7	51	129	12.8	51	85.5%	16.60 [11.25 , 21.95]
Unclear - Group 2008	150.36	33.96	50	132.04	32.24	50	14.5%	18.32 [5.34 , 31.30]
Subtotal (95% CI)			**101**			**101**	**100.0%**	**16.85 [11.90 , 21.80]**
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%								
Test for overall effect: Z = 6.68 (P < 0.00001)								
1.14.2 medium term								
Standard - Individual 03c	188.34	24.38	37	174.34	23.43	36	100.0%	14.00 [3.03 , 24.97]
Subtotal (95% CI)			**37**			**36**	**100.0%**	**14.00 [3.03 , 24.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.50 (P = 0.01)								
1.14.3 long term								
Standard - Individual 03c	182.62	23.62	35	141.29	20.25	35	100.0%	41.33 [31.02 , 51.64]
Subtotal (95% CI)			**35**			**35**	**100.0%**	**41.33 [31.02 , 51.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.86 (P < 0.00001)								

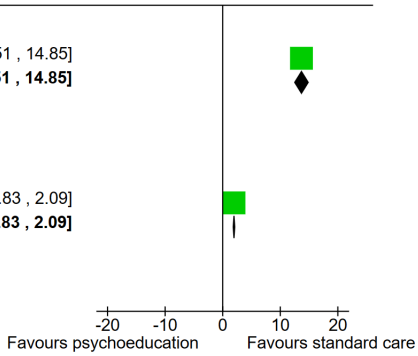
Test for subgroup differences: Chi² = 19.13, df = 2 (P < 0.0001), I² = 89.5%



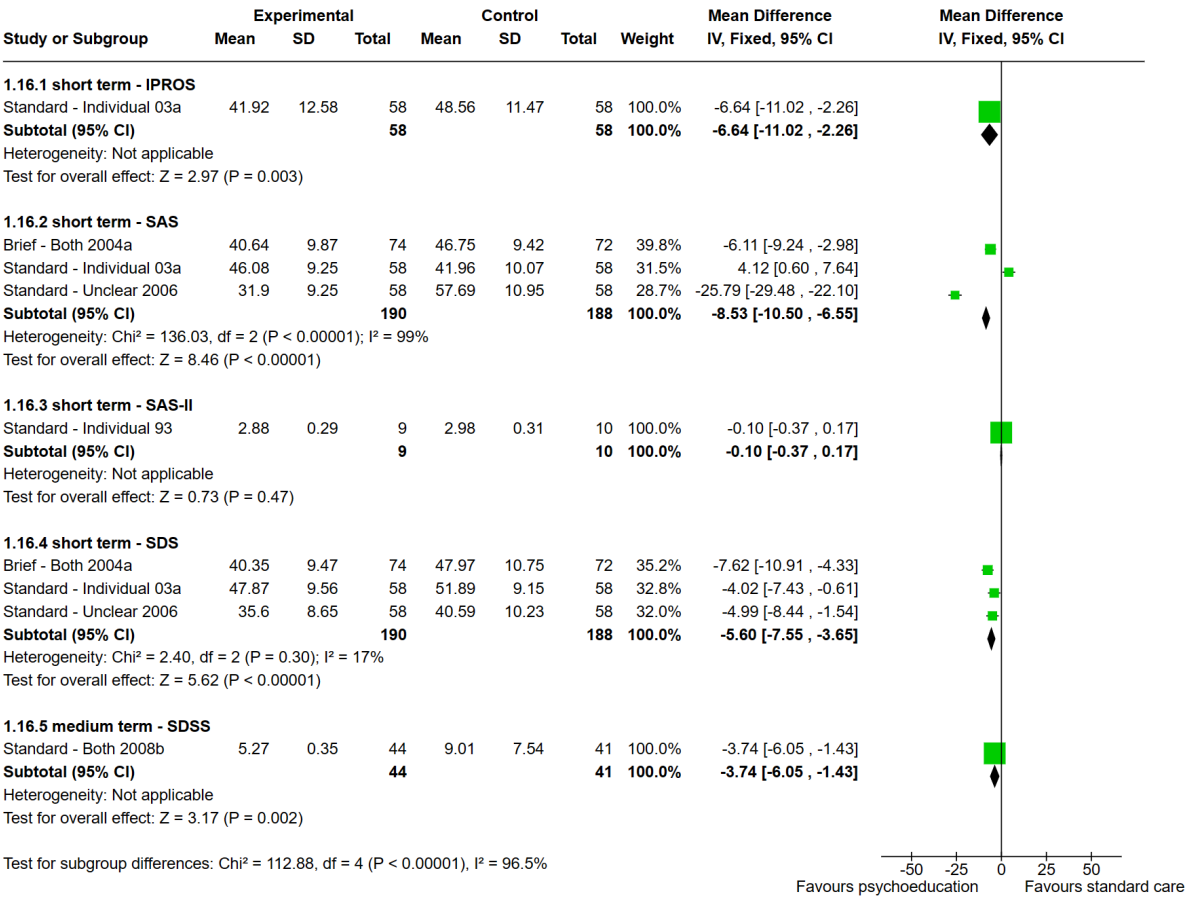
Analysis 1.15. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 15 Social functioning: 1a. Average change scores on various scales - medium term (high = poor).

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.15.1 MRSS								
Brief - Both 2004	15.07	3.67	59	1.39	2.73	59	100.0%	13.68 [12.51 , 14.85]
Subtotal (95% CI)			**59**			**59**	**100.0%**	**13.68 [12.51 , 14.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 22.97 (P < 0.00001)								
1.15.2 SDSS								
Brief - Both 2004	2.25	0.45	59	0.29	0.22	59	100.0%	1.96 [1.83 , 2.09]
Subtotal (95% CI)			**59**			**59**	**100.0%**	**1.96 [1.83 , 2.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 30.06 (P < 0.00001)								

Test for subgroup differences: Chi² = 382.76, df = 1 (P < 0.00001), I² = 99.7%



Analysis 1.16. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 16 Social functioning: 1b. Average endpoint scores on various scales (high = poor).

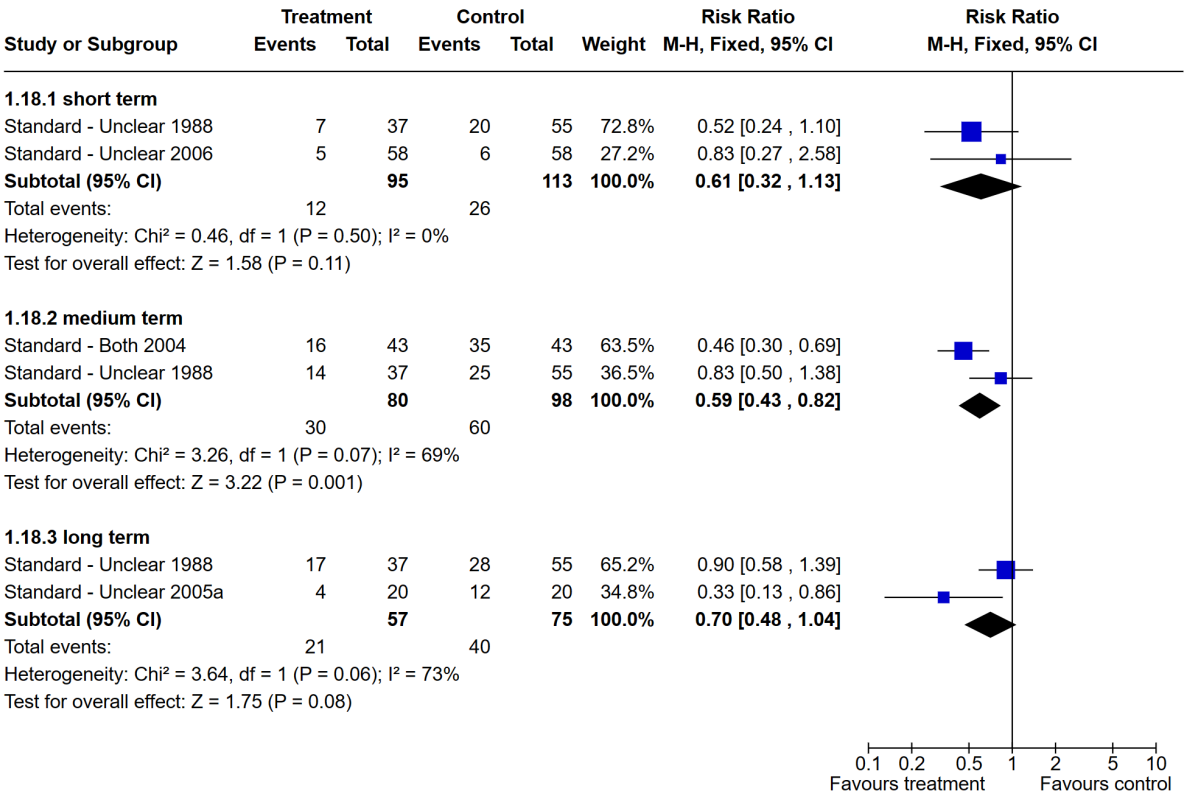


Analysis 1.17. Comparison I ANY FORM OF PSYCHOEDUCATION V STANDARD CARE, Outcome l7Social functioning lc, Average SAS, SFS, SNS scale scores - skewed data (low = favourable).

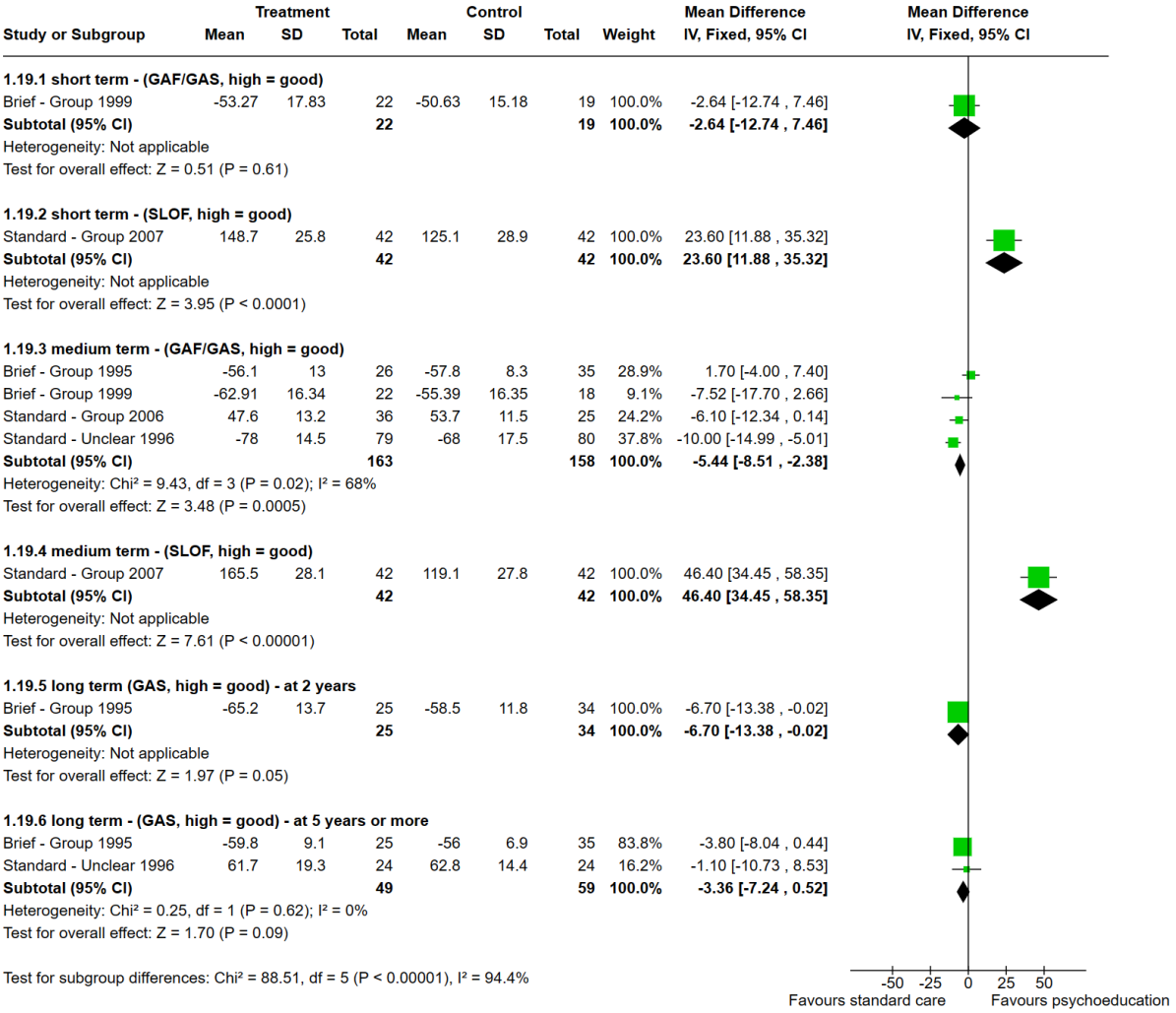
Social functioning 1c. Average SAS, SFS, SNS scale scores - skewed data (low = favourable)

Study	Scale	Experimental N	Exp. mean + SD	Control N	Control mean + SD
Unclear - Group 1996	Social Adjustment Scale II at end of study	52	2.40 + 1.30	62	2.60 + 1.30
Unclear - Group 1996	Social Functioning Schedule score at 3 months	50	2.00 + 1.10	58	2.50 + 1.20
Unclear - Group 1996	To-tal number of con-tacts (SNS, modi-fied): post treatment	52	16.80 + 8.60	60	13.10 + 10.30
Unclear - Group 1996	Total number of contacts (SNS, modified): at 3 months follow-up	50	17.50 + 10.70	56	13.50 + 10.80

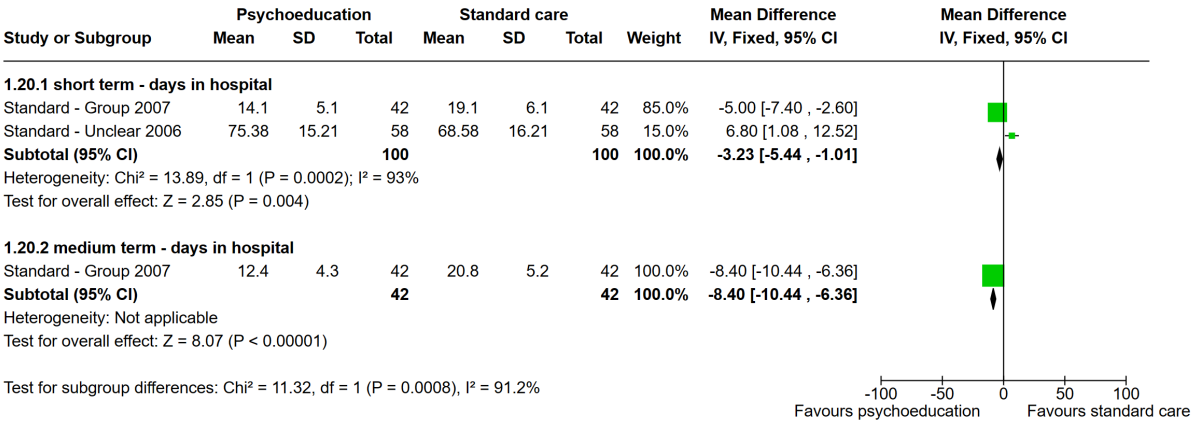
Analysis 1.18. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 18 Global functioning: 1. No clinically significant improvement.



Analysis 1.19. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 19 Global functioning: 2. Average endpoint scale score.



Analysis 1.20. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 20 Service utilisation: days in hospital.

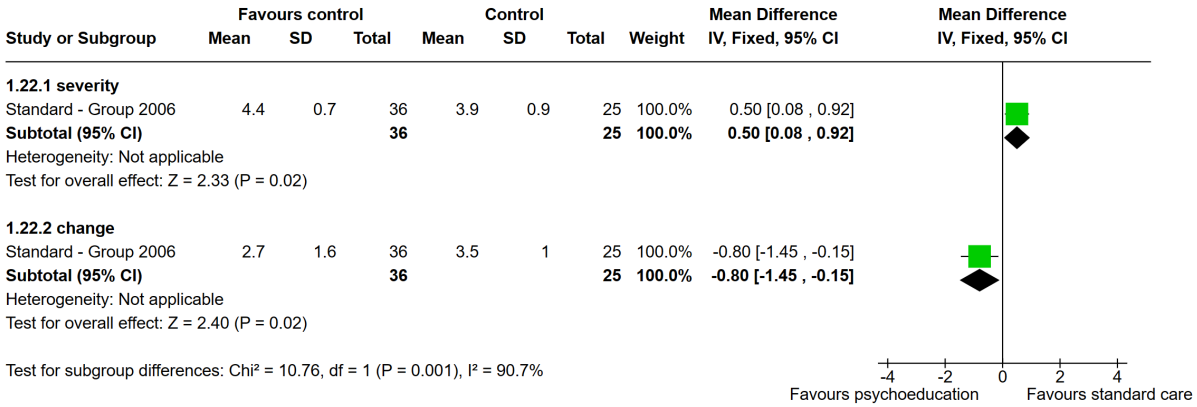


Analysis 1.21. Comparison I ANY FORM OF PSYCHOEDUCATION Vs STANDARD CARE, Outcome 2iService utilisation: Days in hospital using 'acute services' during 18 months (data skewed).

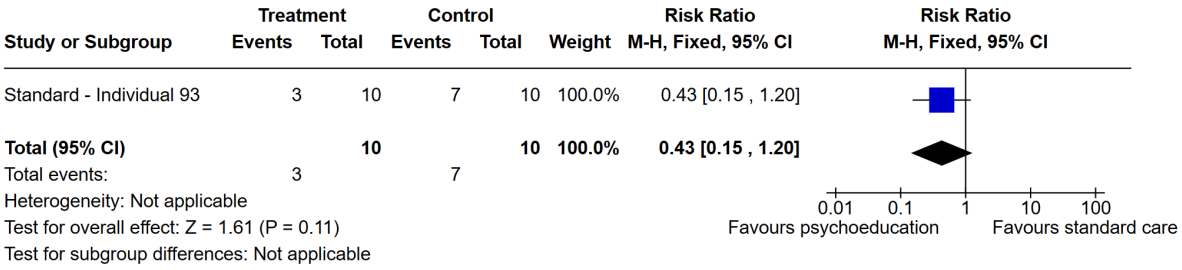
Service utilisation: Days in hospital using 'acute services' - during 18 months (data skewed)

Study	Psychoed. mean	Psychoed. SD	Psychoed. N	Standard care mean	Standard care SD	Standard care N
Standard - Both 1996	37.2	33.3	41	27.9	12.6	41

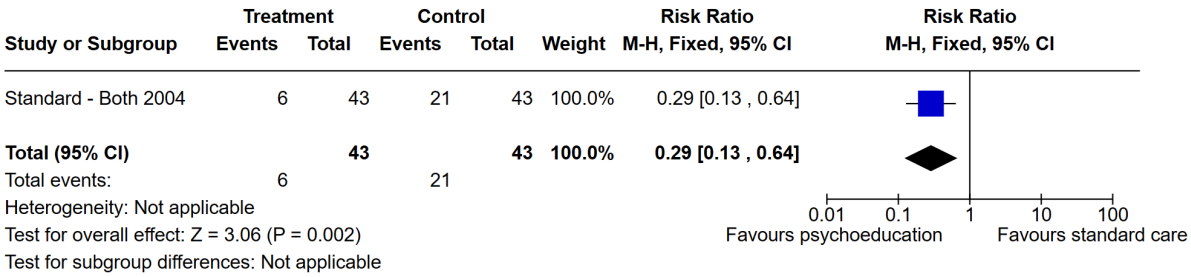
Analysis 1.22. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 22 Global state: 1. Average endpoint score - medium term (CGI, high = poor).



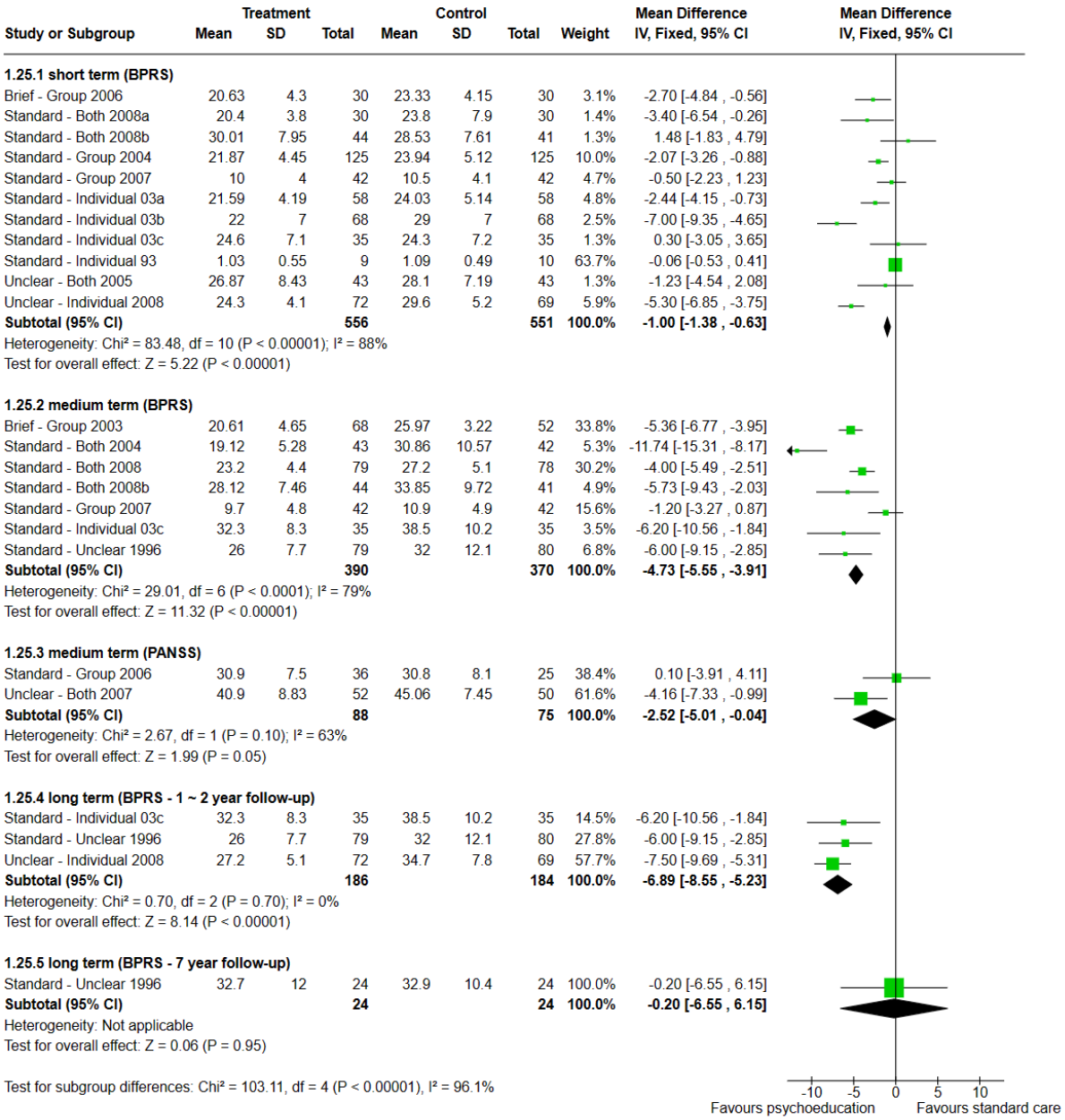
Analysis 1.23. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 23 Global state: 2. Increased medication dose by 25%.



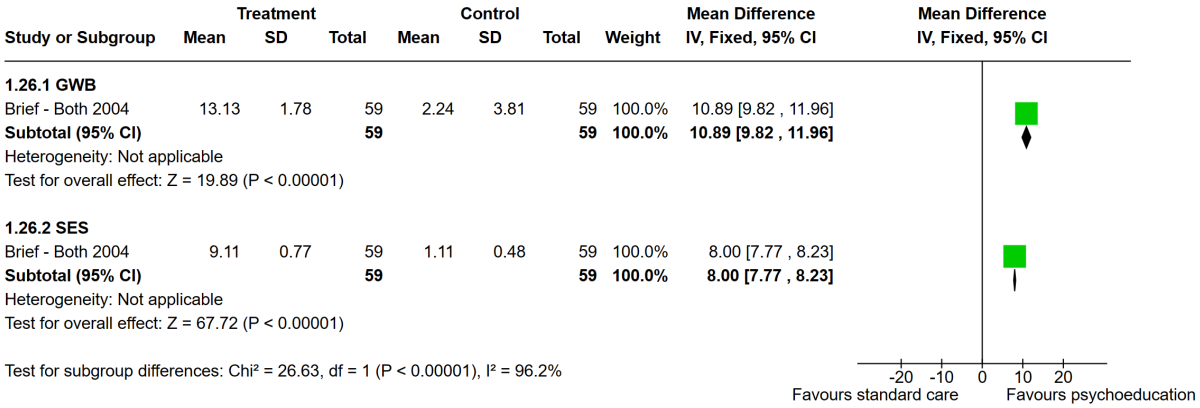
Analysis 1.24. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 24 Global state: 3. Disability - long term.



Analysis 1.25. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 25 Mental state: 1a. Global - continuous - average total endpoint scale scores (high = poor).



Analysis 1.26. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 26 Mental state: 1b. Global - continuous - average change scale scores - medium term (high = good).

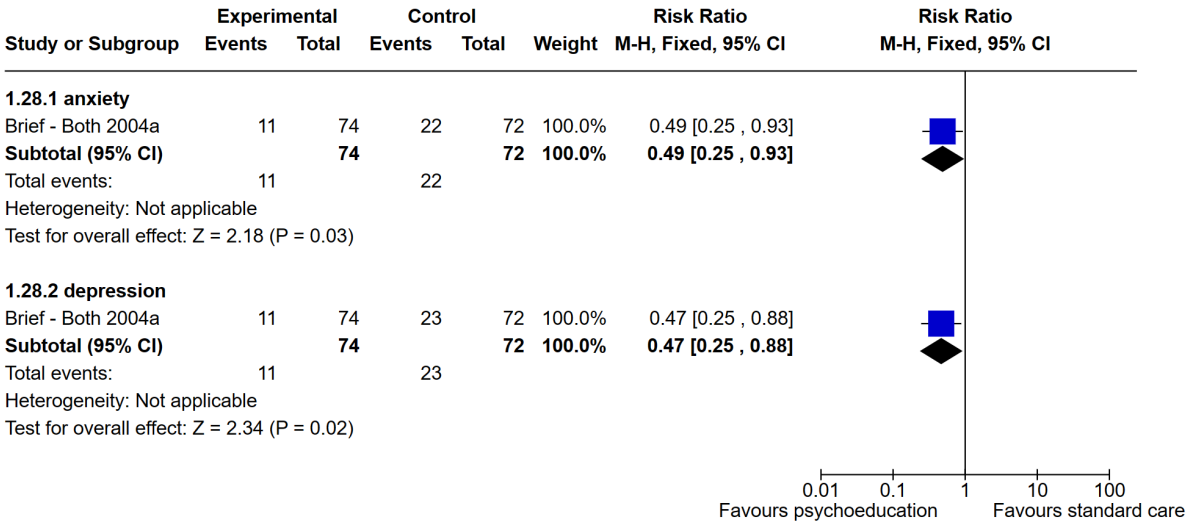


Analysis 1.27.Comparison I ANY FORM OF PSYCHOEDUCATION VS STANDARD CARE, Outcome 27Mental state: Ic, Global - continuous - average total endpoint scale scores - (BPRS, high = poor, data skewed).

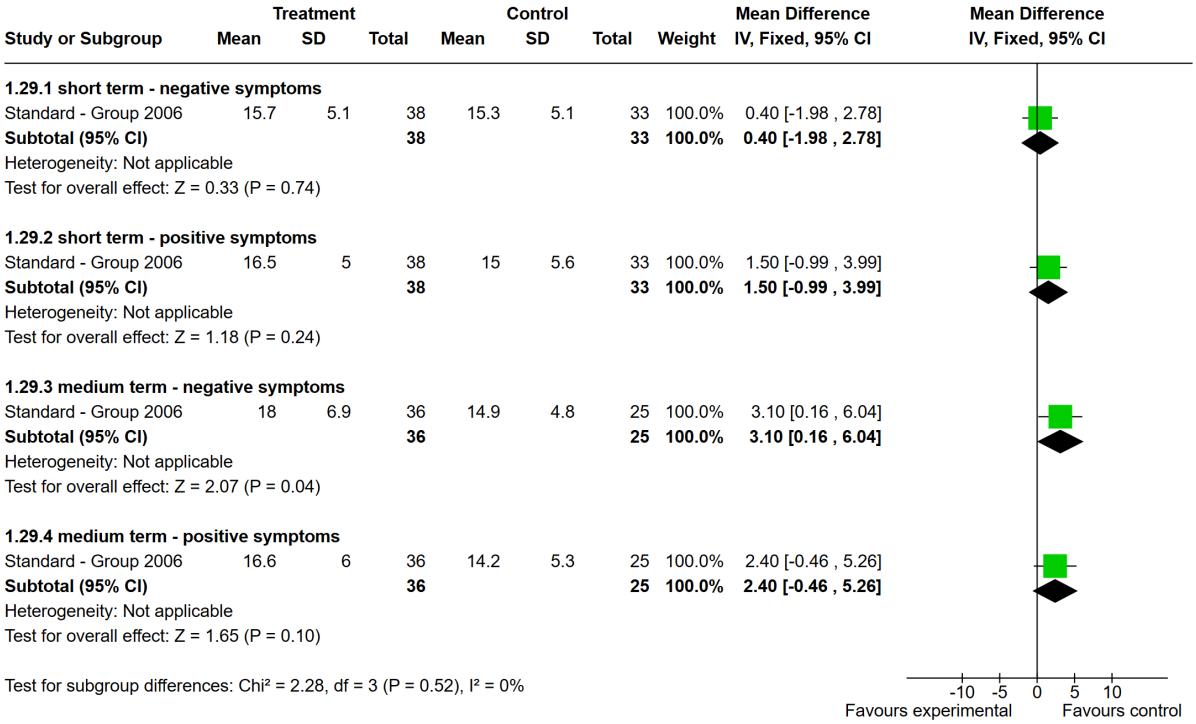
Mental state: 1c. Global - continuous - average total endpoint scale scores - (BPRS, high = poor, data skewed)

Study	Length of follow-up	Psychoed. N	Exp. mean + SD	Control N	Control mean + SD
Brief - Group 1999	at end of study (8 weeks)	22	11.41±7.91	19	13.50±9.54
Brief - Group 1999	at 1 year	22	8.86±6.19	18	10.50±7.37
Brief - Group 2009	at end of study (3 months)	36	5.69±7.91	37	8.81±9.58
Brief - Group 2009	at 1 year	36	4.5±5.11	37	8.81±9.12

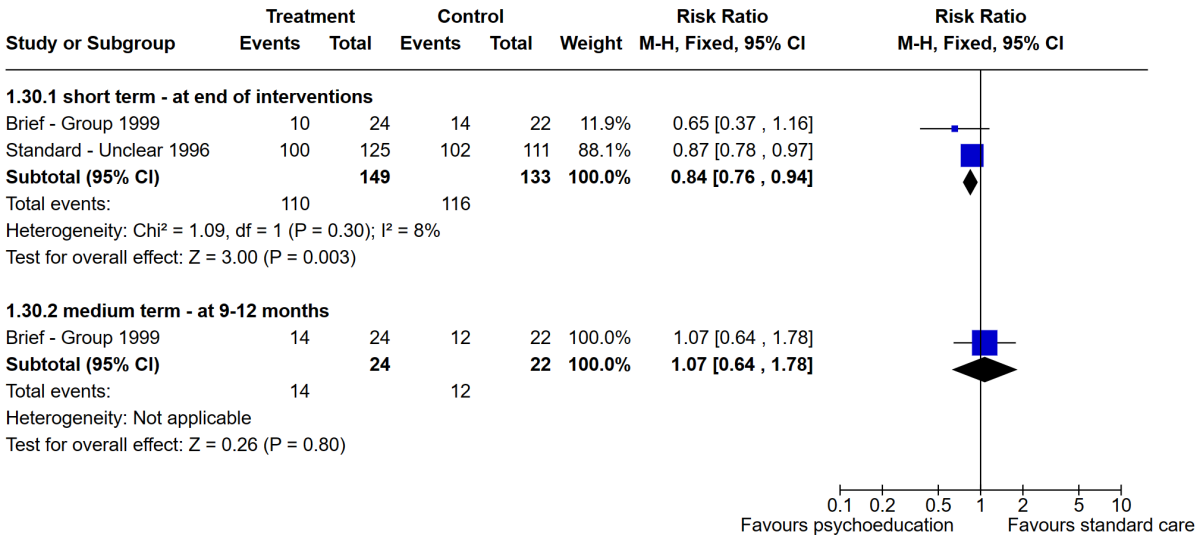
Analysis 1.28. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 28 Mental state: 2a. Specific - binary - specific symptoms - short term.



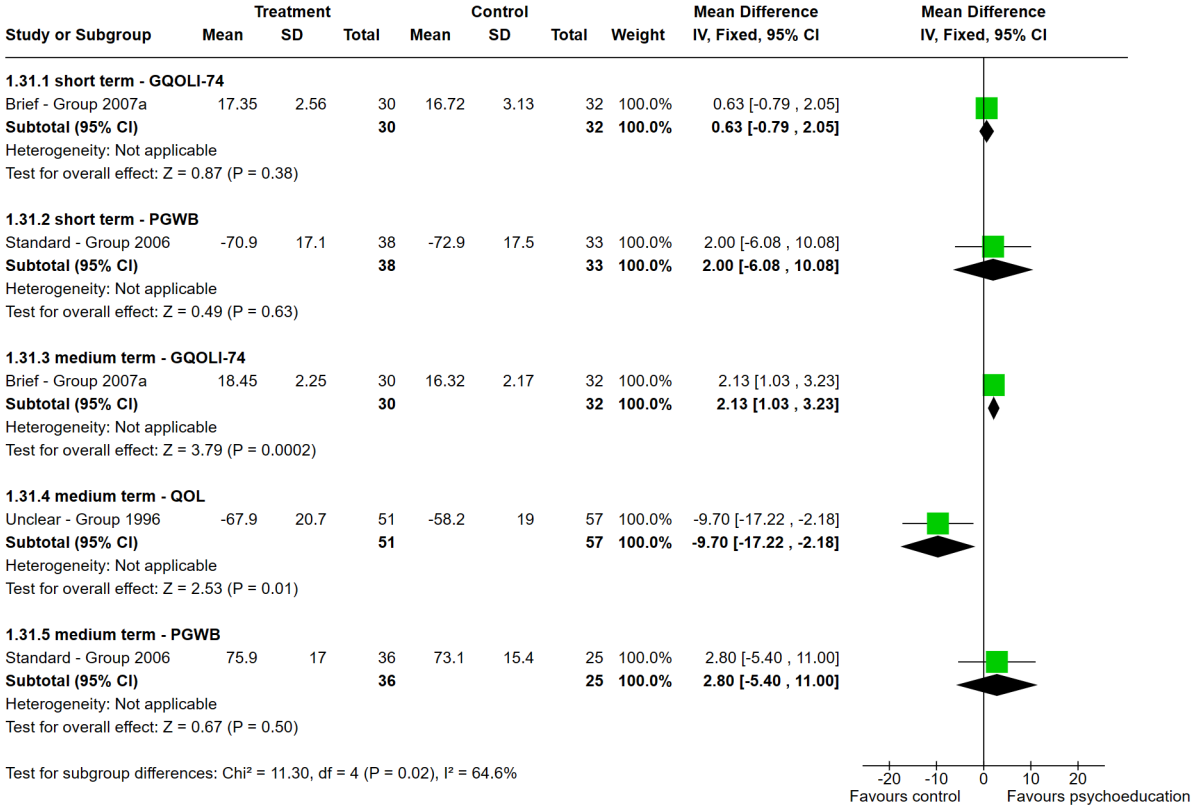
Analysis 1.29. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 29 Mental state: 2b. Specific - continuous - average endpoint PANSS scores (high = poor).



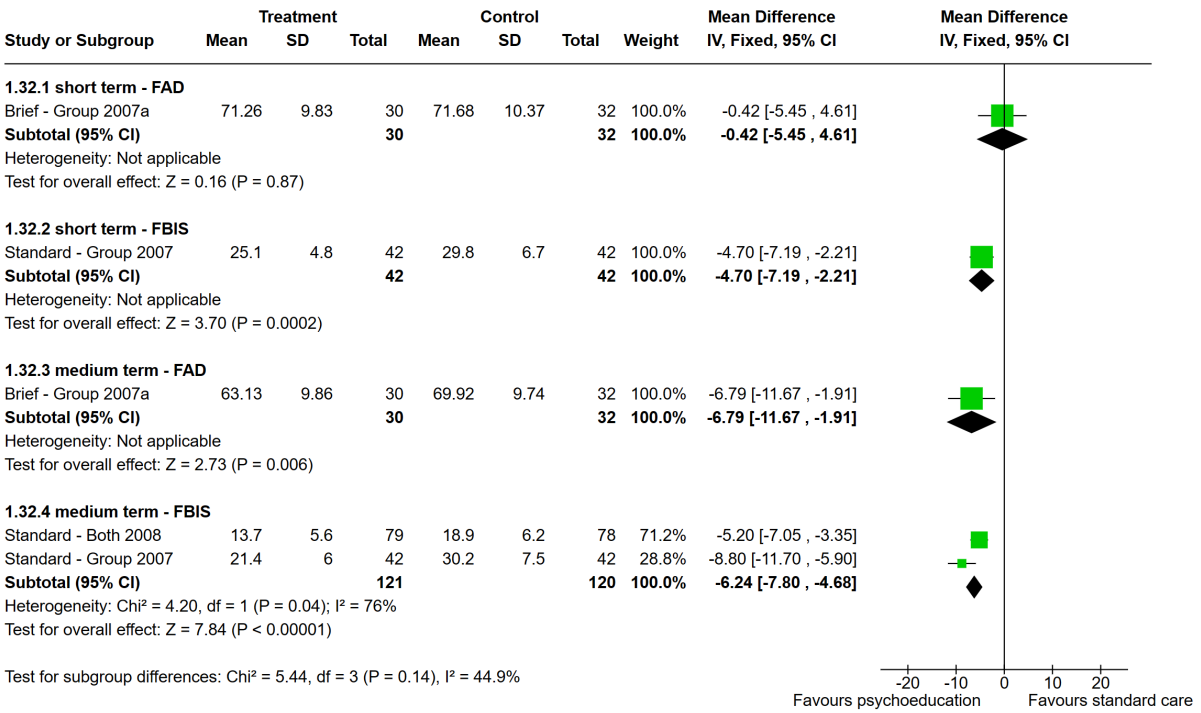
Analysis 1.30. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 30 Expressed emotion: Participants with high EE relatives (FQ).



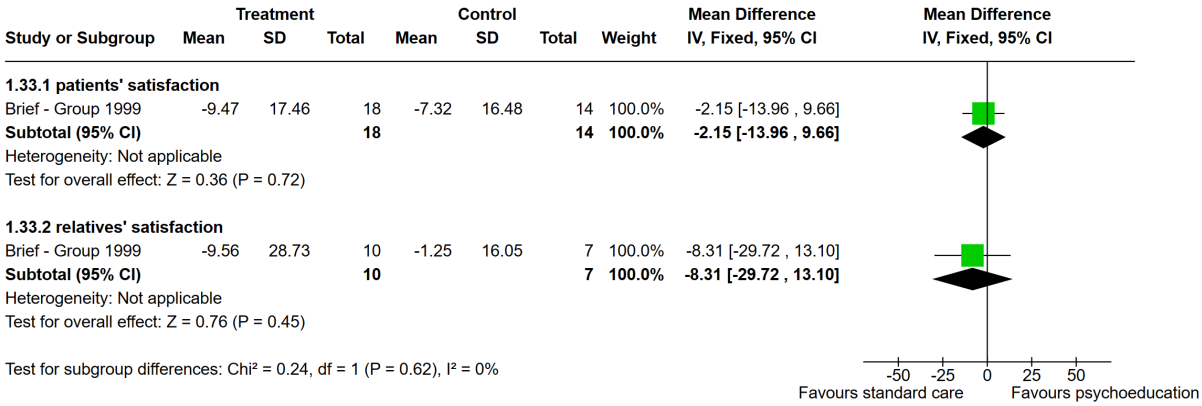
Analysis 1.31. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 31 Quality of life: Average endpoint scores on various scales (high = favourable).



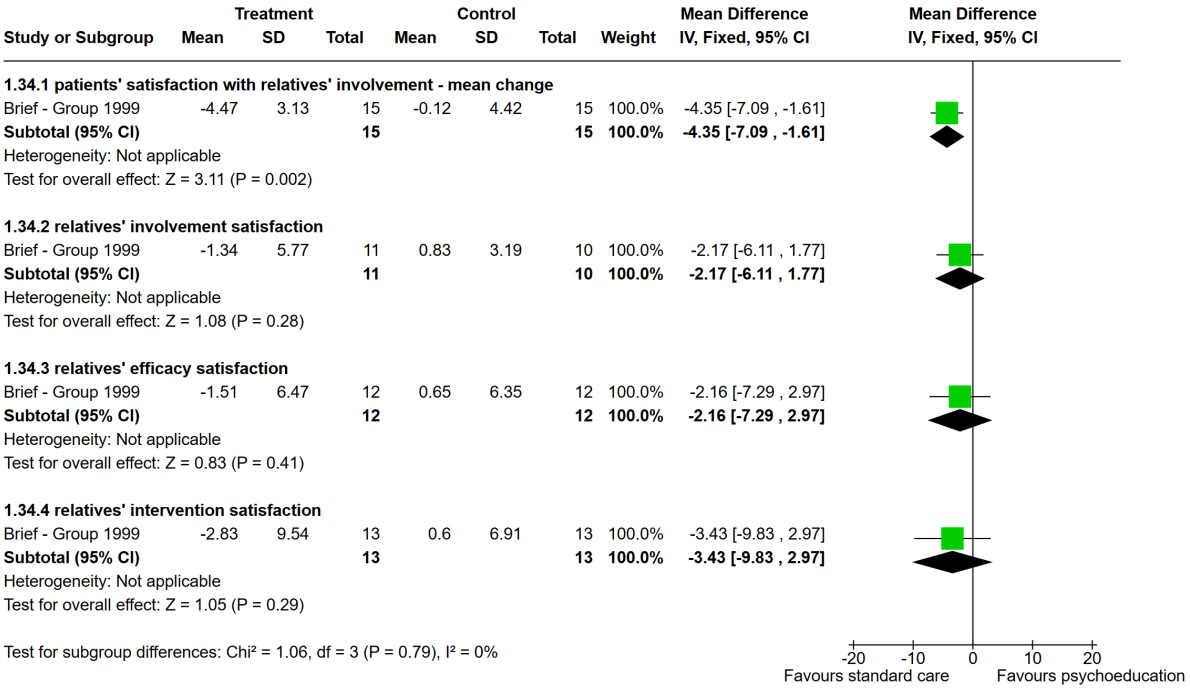
Analysis 1.32. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 32 Quality of life: Average endpoint scores on various scales (high = poor).



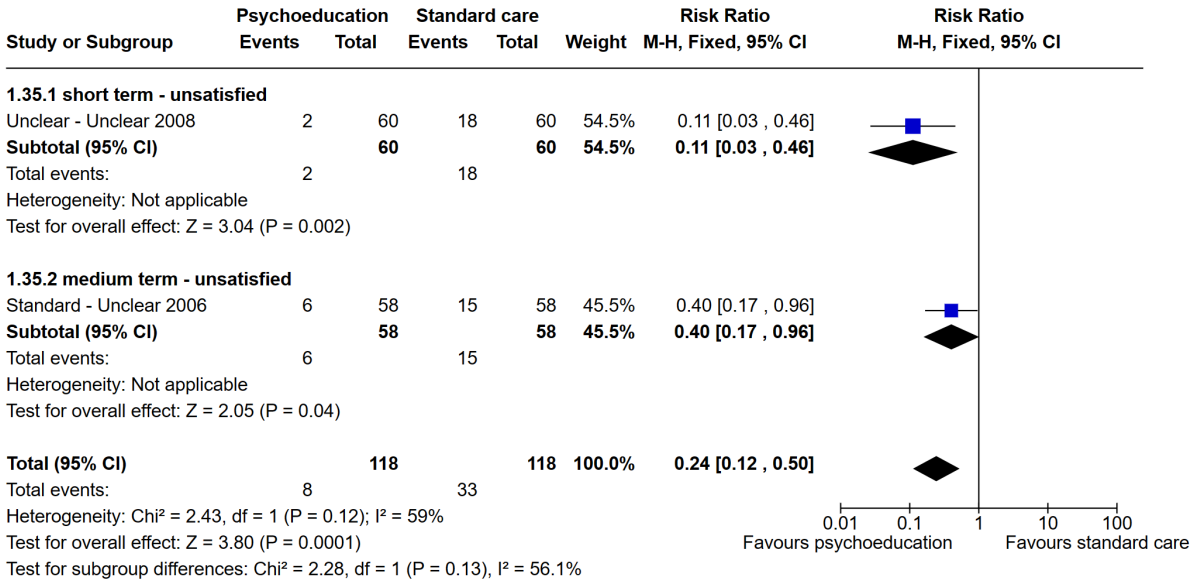
Analysis 1.33. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 33 Satisfaction with mental health services: 1. Short term - average change score (VSS, high = good).



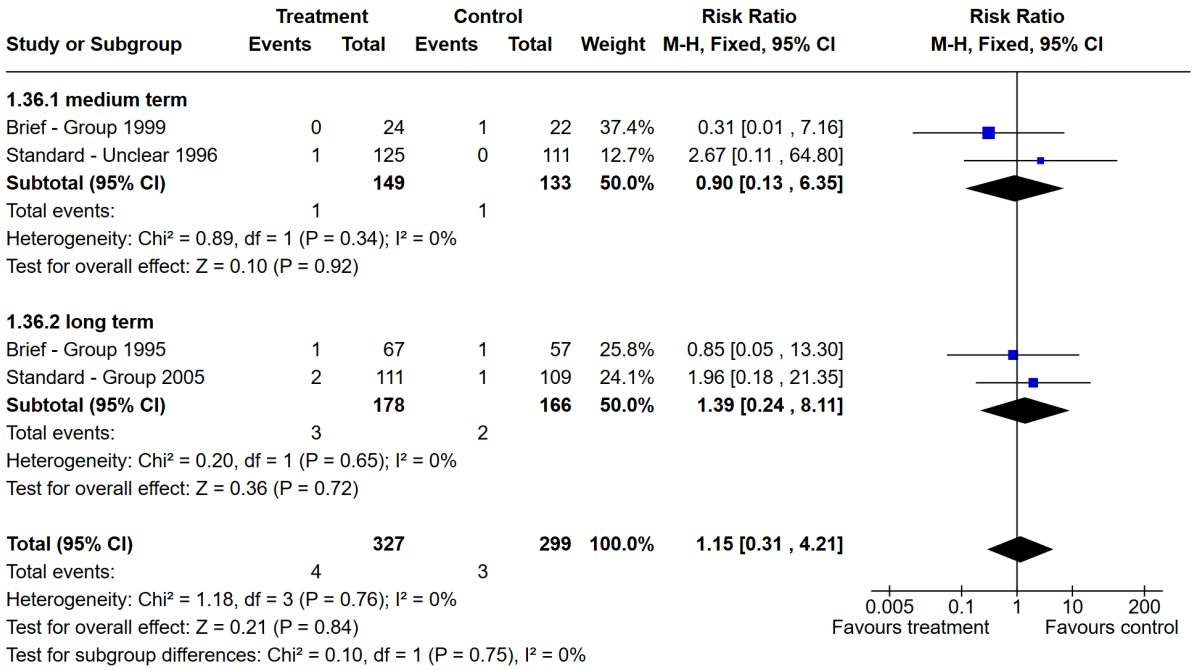
Analysis 1.34. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 34 Satisfaction with mental health services: 2. Average change - at 1 year (VSS Scale, high = good).



Analysis 1.35. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 35 Satisfaction with mental health services: 3. Binary outcome.



Analysis 1.36. Comparison 1 ANY FORM OF PSYCHOEDUCATION vs STANDARD CARE, Outcome 36 Adverse event: Death.



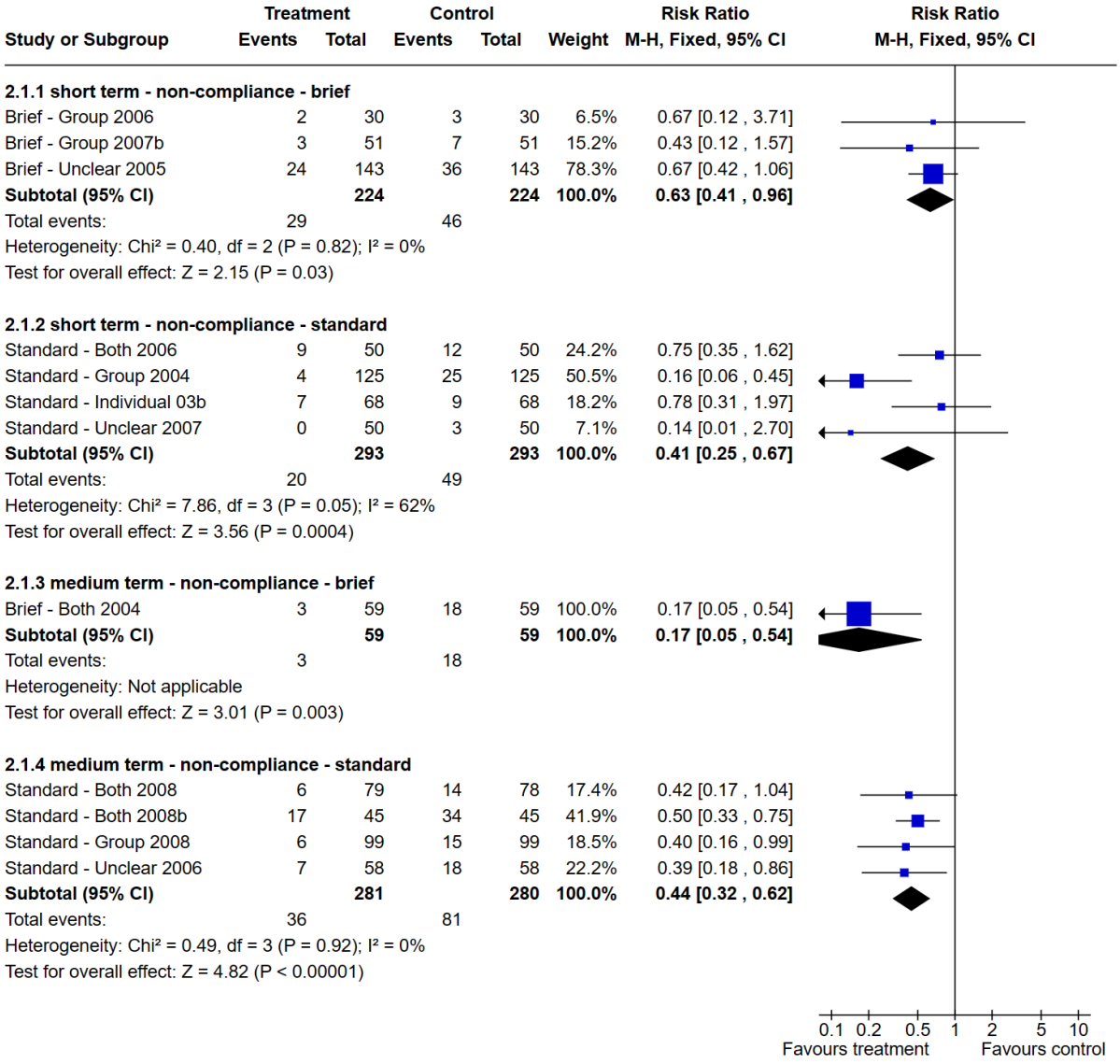
Analysis 1.37 Comparison I ANY FORM OF PSYCHOEDUCATION s STANDARD CARE, Outcome 37 Economic outcomes: Costs (USs per person, data skewed).

Economic outcomes: Costs (US$ per person, data skewed)

Study	Psychoed. mean	Psychoed. SD	Psychoed. N	Standard care mean	Standard care SD	Standard care N
acute hospital charges						
Standard - Both 1996	6537	17248.0	41	7863	12038	41
ambulatory charges						
Standard - Both 1996	6488	4332.8	41	5212	3500.1	41
total charges						
Standard - Both 1996	13025	16358.4	41	13075	12000	41

Analysis 2.1. Comparison 2 SUBGROUP ANALYSES 1. BRIEF PSYCHOEDUCATION/STANDARD

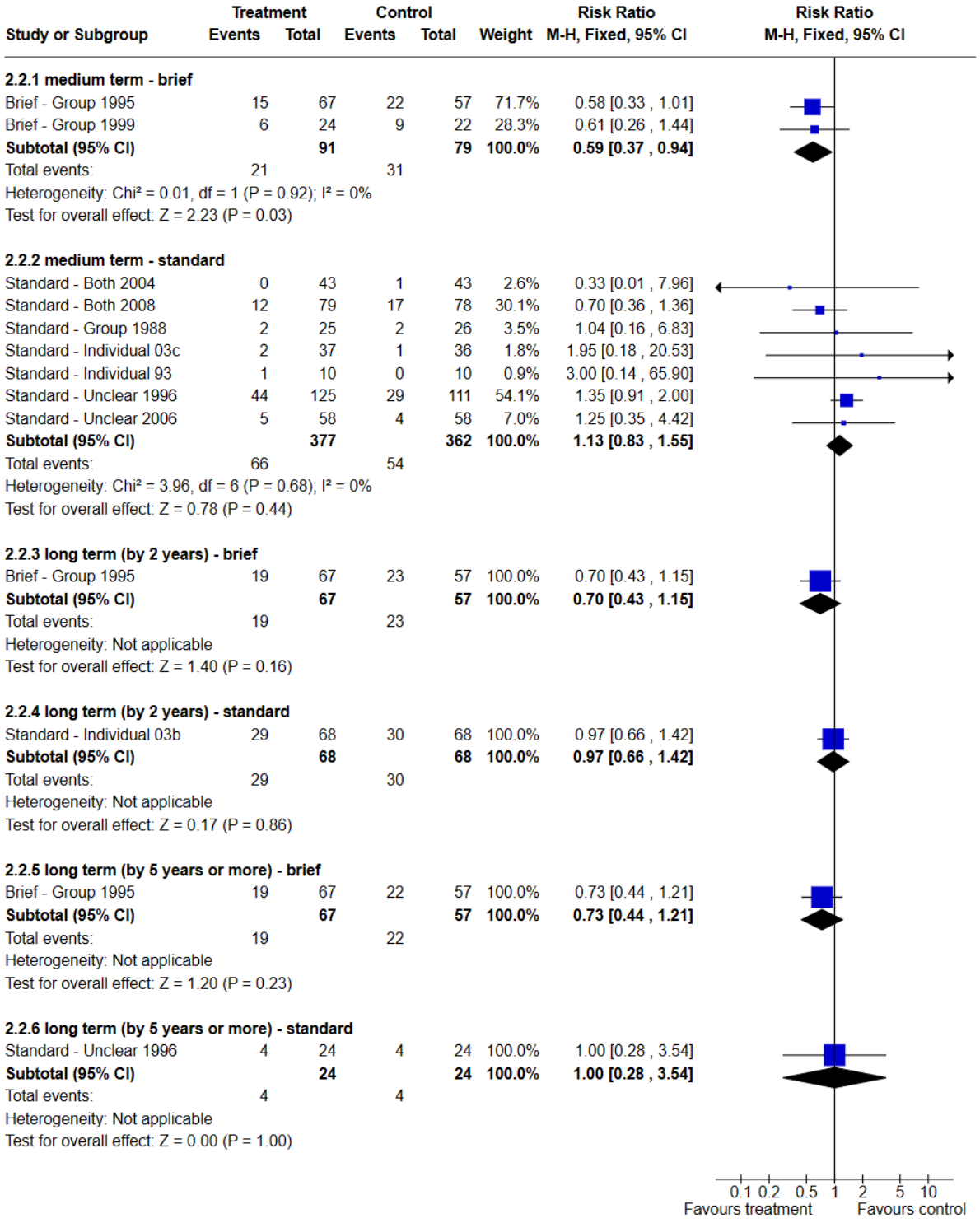
PSYCHOEDUCATION vs STANDARD CARE, Outcome 1 Compliance: 1a. With medication – binary outcomes.



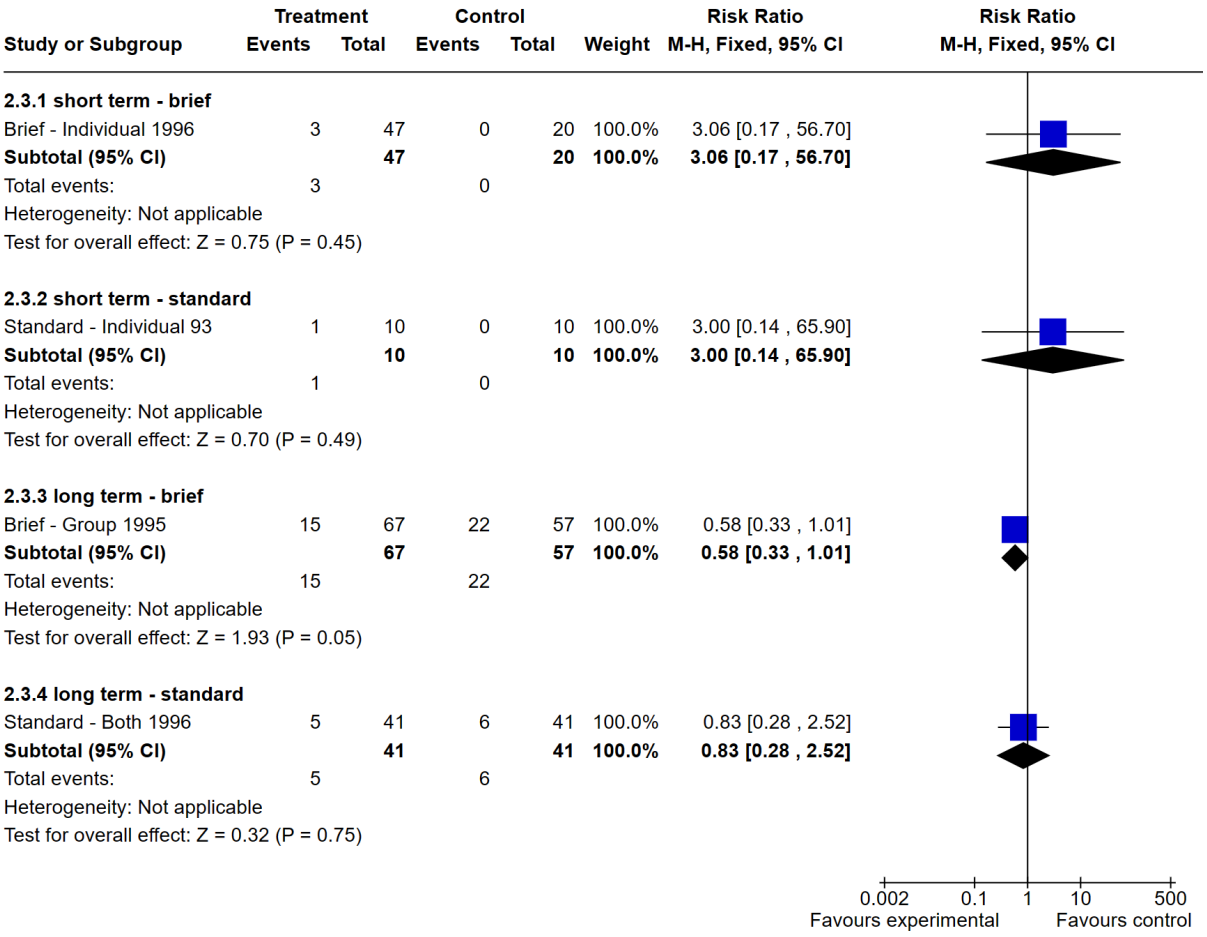
Analysis 2.2. Comparison 2 SUBGROUP ANALYSES 1. BRIEF

PSYCHOEDUCATION/STANDARD

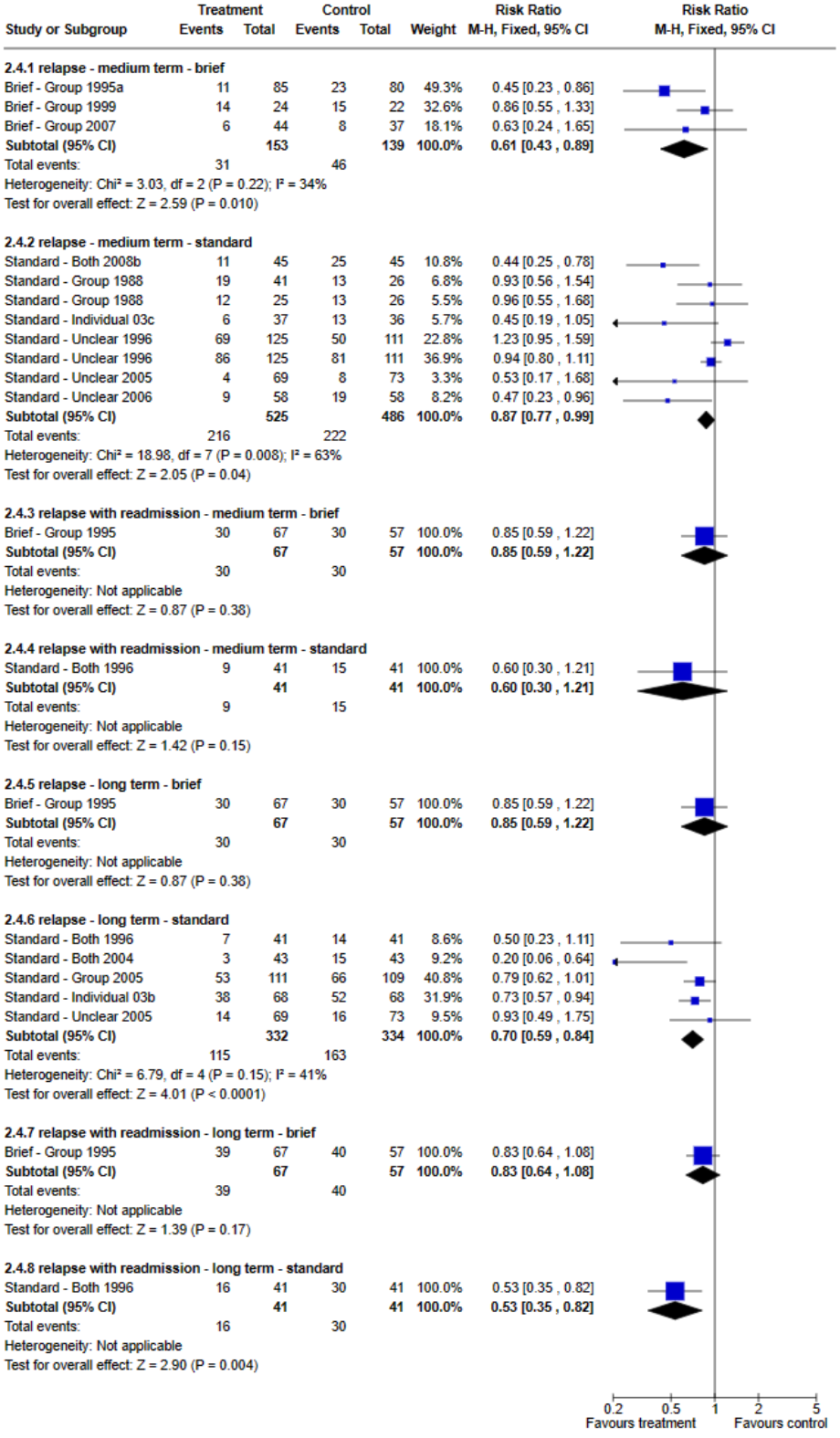
PSYCHOEDUCATION vs STANDARD CARE, Outcome 2 Compliance: 2. With follow-up - loss to follow-up for any reason.



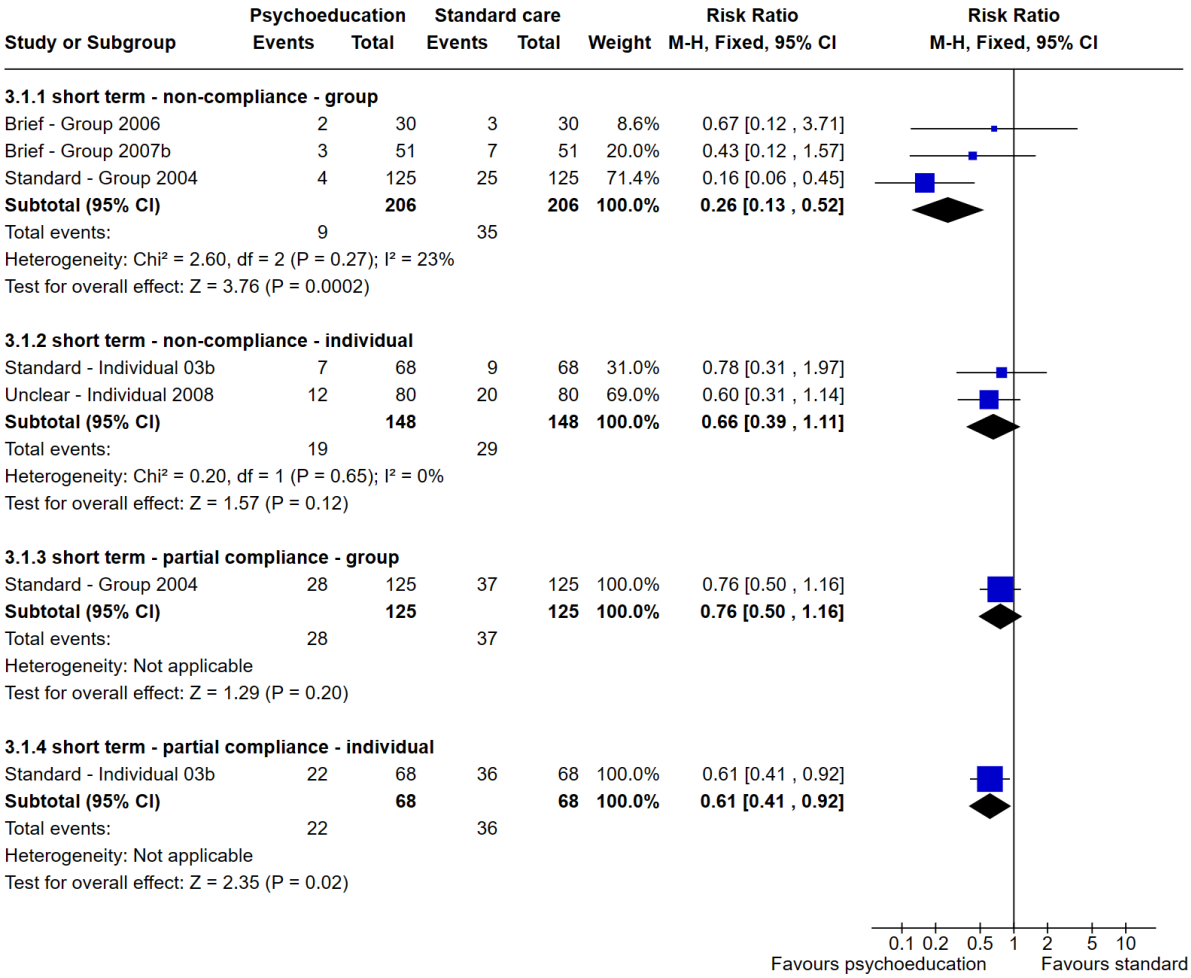
Analysis 2.3. Comparison 2 SUBGROUP ANALYSES 1. BRIEF PSYCHOEDUCATION/STANDARD PSYCHOEDUCATION vs STANDARD CARE, Outcome 3 Compliance: 2a. with follow-up – received intervention but left the study early.



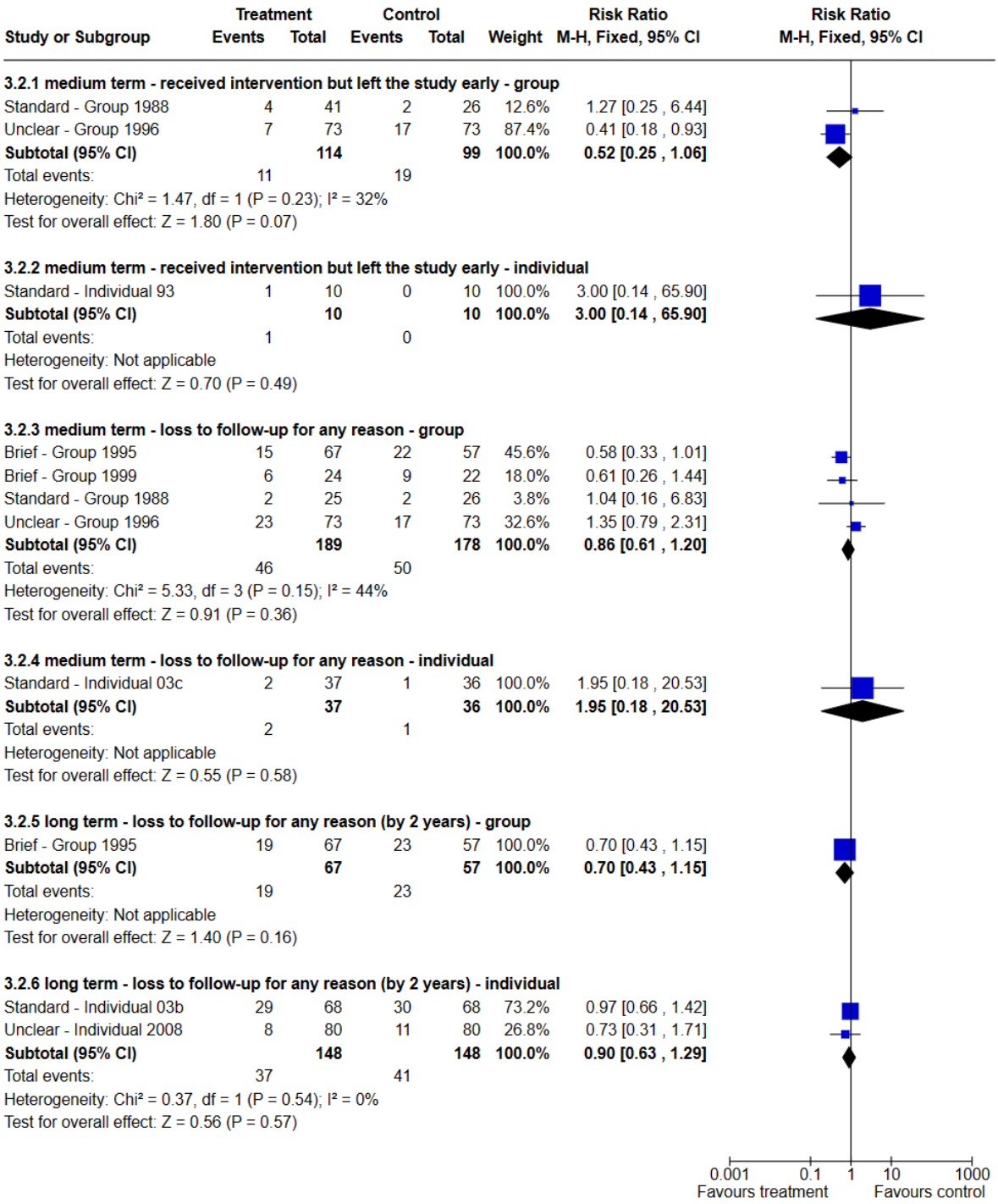
Analysis 2.4. Comparison 2 SUBGROUP ANALYSES 1. BRIEF PSYCHOEDUCATION/STANDARD PSYCHOEDUCATION vs STANDARD CARE, Outcome 4 Relapse: Relapse for any reason.



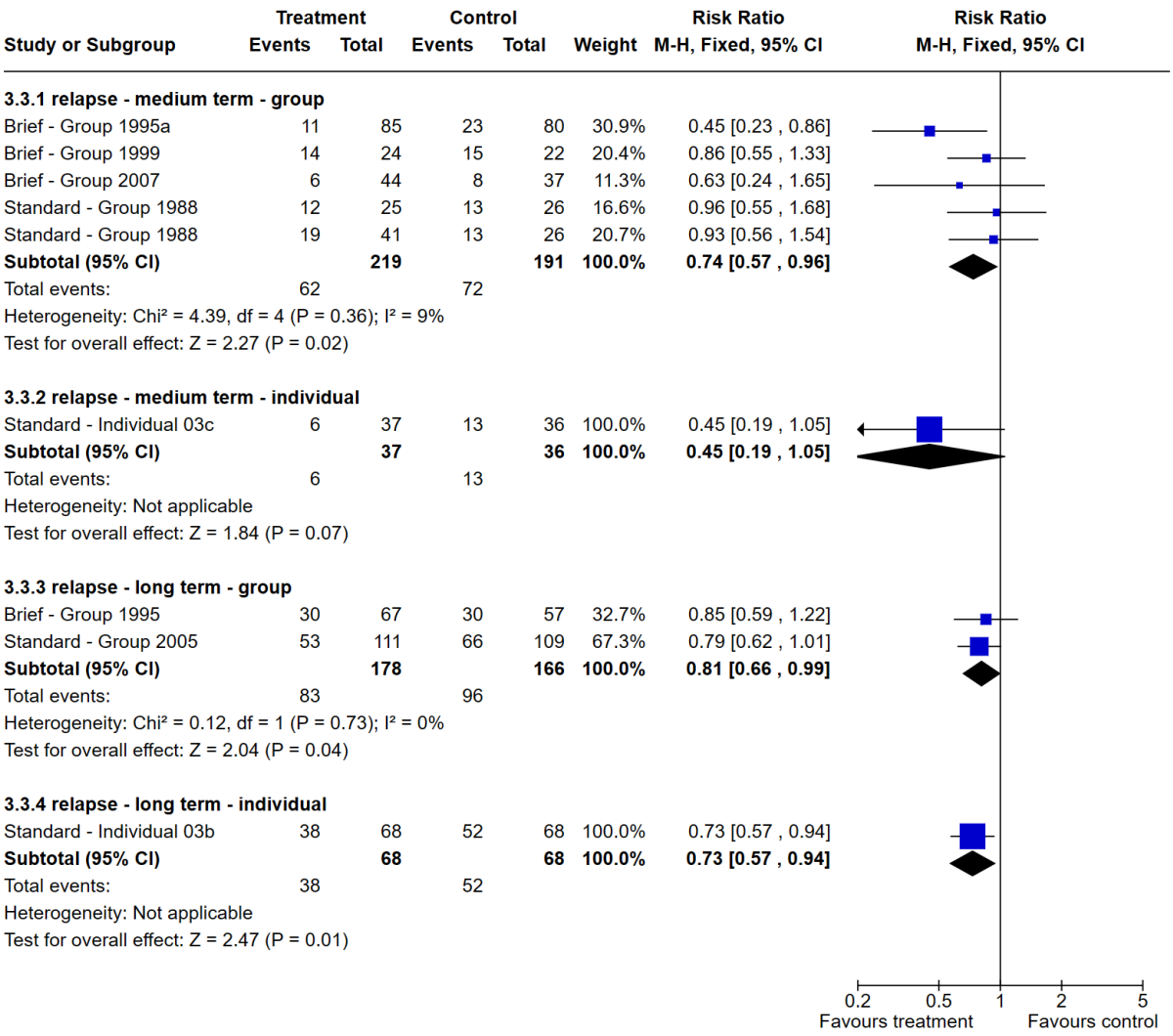
Analysis 3.1. Comparison 3 SUBGROUP ANALYSES 2. GROUP PSYCHOEDUCATION/INDIVIDUAL PSYCHOEDUCATION vs STANDARD CARE, Outcome 1 Compliance: 1a. With medication – binary outcomes.



Analysis 3.2. Comparison 3 SUBGROUP ANALYSES 2. GROUP PSYCHOEDUCATION/INDIVIDUAL PSYCHOEDUCATION vs STANDARD CARE, Outcome 2 Compliance: 2. With follow-up - leaving the study early/loss to follow-up.

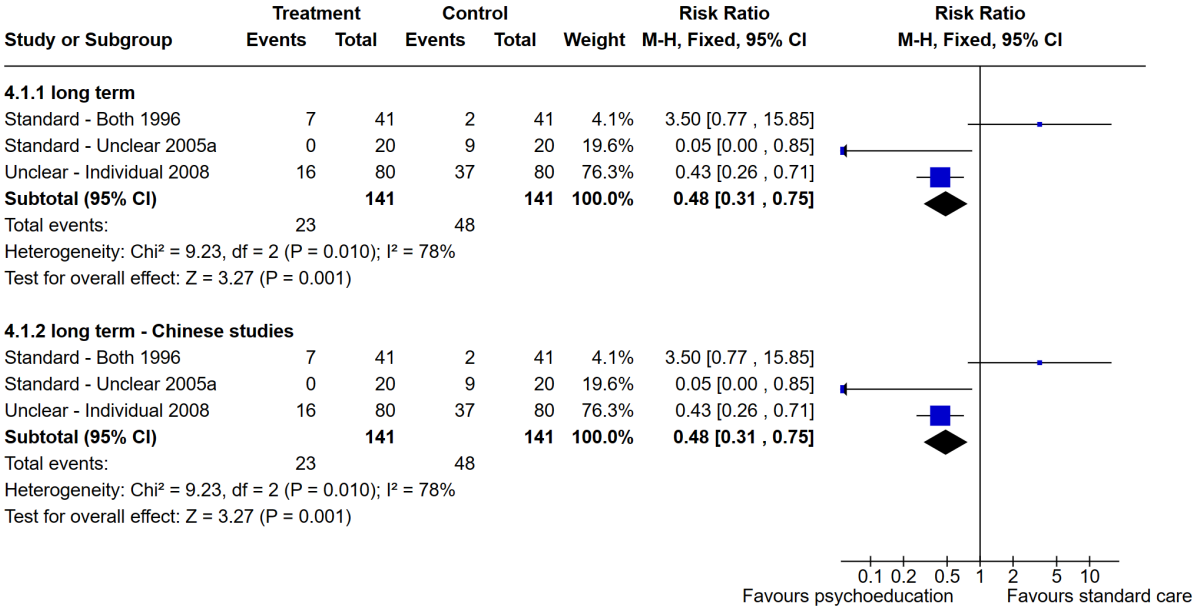


Analysis 3.3. Comparison 3 SUBGROUP ANALYSES 2. GROUP PSYCHOEDUCATION/INDIVIDUAL PSYCHOEDUCATION vs STANDARD CARE, Outcome 3 Relapse: Relapse for any reason.



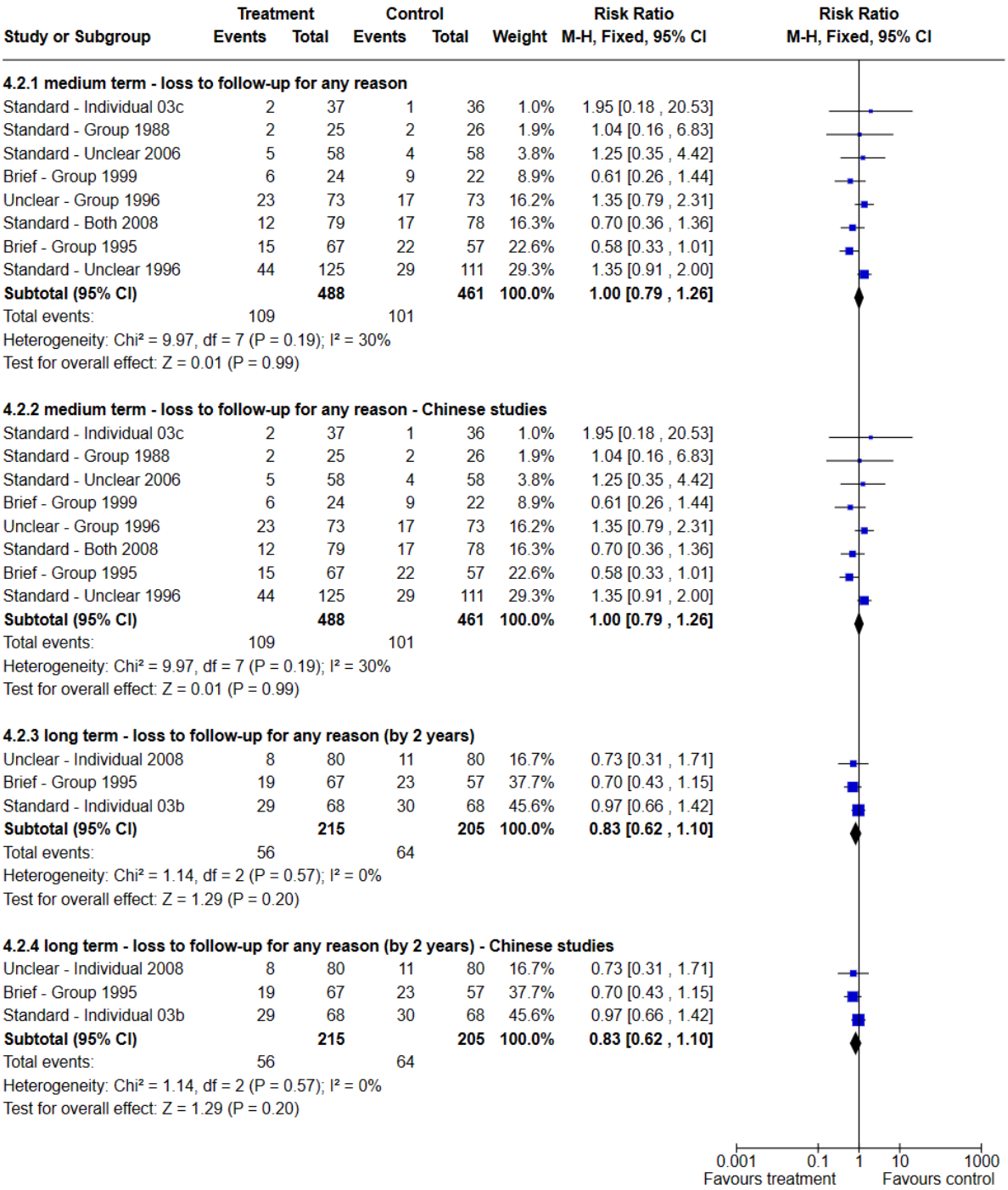
Analysis 4.1. Comparison 4 SENSITIVITY ANALYSIS - Chinese studies vs non-Chinese studies, Outcome 1

Compliance: 1a. With medication - non-compliance.



Analysis 4.2. Comparison 4 SENSITIVITY ANALYSIS - Chinese studies vs non-Chinese studies, Outcome 2

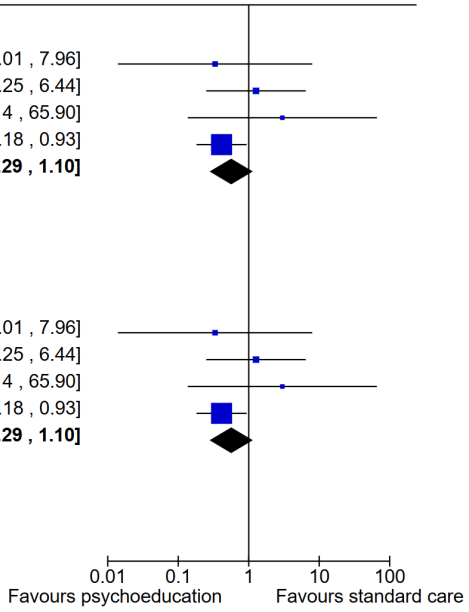
Compliance: 2a. With follow-up - loss to follow-up for any reason.



Analysis 4.3. Comparison 4 SENSITIVITY ANALYSIS - Chinese studies vs non-Chinese studies, Outcome 3

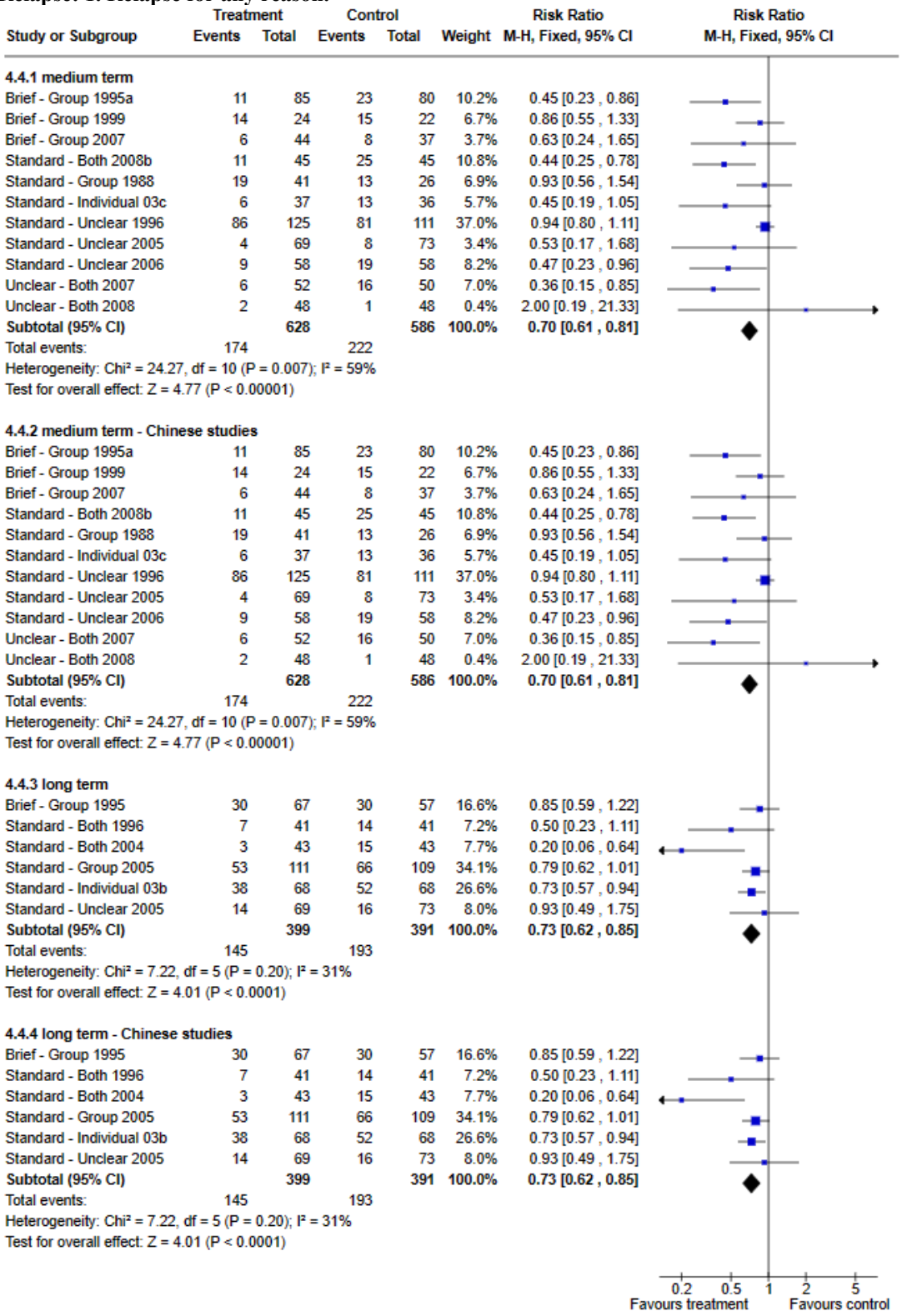
Compliance: 2b. With follow-up - received intervention but left the study early.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 medium term						
Standard - Both 2004	0	43	1	43	7.0%	0.33 [0.01 , 7.96]
Standard - Group 1988	4	41	2	26	11.4%	1.27 [0.25 , 6.44]
Standard - Individual 93	1	10	0	10	2.3%	3.00 [0.14 , 65.90]
Unclear - Group 1996	7	73	17	73	79.3%	0.41 [0.18 , 0.93]
Subtotal (95% CI)		**167**		**152**	**100.0%**	**0.56 [0.29 , 1.10]**
Total events:	12		20			
Heterogeneity: Chi² = 2.75, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.69 (P = 0.09)						
4.3.2 medium term - Chinese studies						
Standard - Both 2004	0	43	1	43	7.0%	0.33 [0.01 , 7.96]
Standard - Group 1988	4	41	2	26	11.4%	1.27 [0.25 , 6.44]
Standard - Individual 93	1	10	0	10	2.3%	3.00 [0.14 , 65.90]
Unclear - Group 1996	7	73	17	73	79.3%	0.41 [0.18 , 0.93]
Subtotal (95% CI)		**167**		**152**	**100.0%**	**0.56 [0.29 , 1.10]**
Total events:	12		20			
Heterogeneity: Chi² = 2.75, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.69 (P = 0.09)						



Analysis 4.4. Comparison 4 SENSITIVITY ANALYSIS - Chinese studies vs non-Chinese studies, Outcome 4

Relapse: 1. Relapse for any reason.



Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 medium term						
Brief - Group 1995a	11	85	23	80	10.2%	0.45 [0.23 , 0.86]
Brief - Group 1999	14	24	15	22	6.7%	0.86 [0.55 , 1.33]
Brief - Group 2007	6	44	8	37	3.7%	0.63 [0.24 , 1.65]
Standard - Both 2008b	11	45	25	45	10.8%	0.44 [0.25 , 0.78]
Standard - Group 1988	19	41	13	26	6.9%	0.93 [0.56 , 1.54]
Standard - Individual 03c	6	37	13	36	5.7%	0.45 [0.19 , 1.05]
Standard - Unclear 1996	86	125	81	111	37.0%	0.94 [0.80 , 1.11]
Standard - Unclear 2005	4	69	8	73	3.4%	0.53 [0.17 , 1.68]
Standard - Unclear 2006	9	58	19	58	8.2%	0.47 [0.23 , 0.96]
Unclear - Both 2007	6	52	16	50	7.0%	0.36 [0.15 , 0.85]
Unclear - Both 2008	2	48	1	48	0.4%	2.00 [0.19 , 21.33]
Subtotal (95% CI)		**628**		**586**	**100.0%**	**0.70 [0.61 , 0.81]**
Total events:	174		222			
Heterogeneity: Chi² = 24.27, df = 10 (P = 0.007); I² = 59%						
Test for overall effect: Z = 4.77 (P < 0.00001)						
4.4.2 medium term - Chinese studies						
Brief - Group 1995a	11	85	23	80	10.2%	0.45 [0.23 , 0.86]
Brief - Group 1999	14	24	15	22	6.7%	0.86 [0.55 , 1.33]
Brief - Group 2007	6	44	8	37	3.7%	0.63 [0.24 , 1.65]
Standard - Both 2008b	11	45	25	45	10.8%	0.44 [0.25 , 0.78]
Standard - Group 1988	19	41	13	26	6.9%	0.93 [0.56 , 1.54]
Standard - Individual 03c	6	37	13	36	5.7%	0.45 [0.19 , 1.05]
Standard - Unclear 1996	86	125	81	111	37.0%	0.94 [0.80 , 1.11]
Standard - Unclear 2005	4	69	8	73	3.4%	0.53 [0.17 , 1.68]
Standard - Unclear 2006	9	58	19	58	8.2%	0.47 [0.23 , 0.96]
Unclear - Both 2007	6	52	16	50	7.0%	0.36 [0.15 , 0.85]
Unclear - Both 2008	2	48	1	48	0.4%	2.00 [0.19 , 21.33]
Subtotal (95% CI)		**628**		**586**	**100.0%**	**0.70 [0.61 , 0.81]**
Total events:	174		222			
Heterogeneity: Chi² = 24.27, df = 10 (P = 0.007); I² = 59%						
Test for overall effect: Z = 4.77 (P < 0.00001)						
4.4.3 long term						
Brief - Group 1995	30	67	30	57	16.6%	0.85 [0.59 , 1.22]
Standard - Both 1996	7	41	14	41	7.2%	0.50 [0.23 , 1.11]
Standard - Both 2004	3	43	15	43	7.7%	0.20 [0.06 , 0.64]
Standard - Group 2005	53	111	66	109	34.1%	0.79 [0.62 , 1.01]
Standard - Individual 03b	38	68	52	68	26.6%	0.73 [0.57 , 0.94]
Standard - Unclear 2005	14	69	16	73	8.0%	0.93 [0.49 , 1.75]
Subtotal (95% CI)		**399**		**391**	**100.0%**	**0.73 [0.62 , 0.85]**
Total events:	145		193			
Heterogeneity: Chi² = 7.22, df = 5 (P = 0.20); I² = 31%						
Test for overall effect: Z = 4.01 (P < 0.0001)						
4.4.4 long term - Chinese studies						
Brief - Group 1995	30	67	30	57	16.6%	0.85 [0.59 , 1.22]
Standard - Both 1996	7	41	14	41	7.2%	0.50 [0.23 , 1.11]
Standard - Both 2004	3	43	15	43	7.7%	0.20 [0.06 , 0.64]
Standard - Group 2005	53	111	66	109	34.1%	0.79 [0.62 , 1.01]
Standard - Individual 03b	38	68	52	68	26.6%	0.73 [0.57 , 0.94]
Standard - Unclear 2005	14	69	16	73	8.0%	0.93 [0.49 , 1.75]
Subtotal (95% CI)		**399**		**391**	**100.0%**	**0.73 [0.62 , 0.85]**
Total events:	145		193			
Heterogeneity: Chi² = 7.22, df = 5 (P = 0.20); I² = 31%						
Test for overall effect: Z = 4.01 (P < 0.0001)						

Risk Ratio M-H, Fixed, 95% CI

0.2 0.5 1 2 5

Favours treatment Favours control

ADDITIONAL TABLES

Table 1. Chinese studies vs full analysis (sensitivity analyses)

Primary outcome	China Experimental	China Control	China RR (CI)	Full analysis Experimental	Full analysis Control	Full analysis RR (CI)
Compliance	19/174	22/172	0.85 (0.48-1.51)	109/488	101/461	1.00 (0.79-1.26)
Relapse	44/353	90/347	0.48 (0.35-0.66)	174/628	22/586	0.7 (0.61-0.81)

Table 2. English studies vs full analysis (sensitivity analyses)

Primary outcome	English Experimental	English Control	English RR (CI)	Full analysis Experimental	Full analysis Control	Full analysis RR (CI)
Compliance	90/314	79/289	1.04 (0.8-1.34)	109/488	101/461	1.00 (0.79-1.26)
Relapse	130/275	132/239	0.85 (0.73-0.99)	174/628	22/586	0.7 (0.61-0.81)

Table 3. Suggested design of study

Methods	Allocation: randomised, fully explicit description of methods of randomisation and allocation concealment. Blinding: single, tested. Setting: community rather than hospital. Duration: 12 weeks treatment, and then follow-up to at least 52 weeks
Participants	Diagnosis: schizophrenia (ICD). N = 300.* Age: adults. Sex: both.
Interventions	1. Psychoeducation. N = 150. 2. Standard care. N = 150.
Outcomes	General: time to all-cause treatment failure marked by its discontinuation, relapse, general impression of clinician (CGI), career/other, compliance with treatment, healthy days. Mental state: BPRS and PANSS. Global state: CGI (Clinical Global Impression). Quality of life. QOL (Quality of Life Questionnaire). Family burden: FBQ (Family Burden Questionnaire). Social functioning: return to everyday living for 80% of time.* Adverse events: any adverse event recorded. Economic outcomes.
Notes	* Powered to be able to identify a difference of ~ 20% between groups for primary outcome with adequate degree of certainty

Sources of support

Internal sources

- Department of Psychiatry, Porvoo Hospital, Finland
- Department of Psychiatric Demography, Institute of Basic Psychiatric Research, University Hospital of Aarhus, Denmark

External sources

- Finnish Office for Health Technology Assessment (FinOHTA), Finland

Feedback

Appendices

1 Methods section of original review

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials. Quasi-randomised trials, using, for example, alternation as the method of randomisation, were excluded.

Types of participants

People suffering from severe non-affective mental disorders such as schizophrenia and schizophreniform, schizoaffective or schizotypal disorders, and including those with multiple diagnoses.

Types of interventions

1. All didactic interventions of psychoeducation or patient teaching involving individuals or groups were included. Psychoeducational interventions were defined as any group or individual programme involving interaction between information provider and patient. These programmes address the illness from a multidimensional viewpoint, including familial, social, biological and pharmacological perspectives. Patients are provided with support, information and management strategies. Programmes of 10 sessions or less were considered as 'brief', and 11 or more as 'standard' for the purposes of this review. Interventions including elements of behavioural training, such as social skills or life skills training, as well as education performed by patient peers, were excluded from this review. Staff education

studies were also excluded.

2. Standard care was defined as the normal level of psychiatric care provided in the area where the trial was carried out.

Types of outcome measures

Primary outcomes

1. Patient compliance, defined as:

1.1 compliance with medication;

1.2 compliance with follow-up.

2. Relapse.

Secondary outcomes

1. Level of knowledge:

1.1 improvement of understanding of his/her illness and need for treatment;

1.2 level of knowledge about expected and undesired effects of medication.

2. Behavioural outcomes:

2.1 level of psychiatric symptoms;

2.2 symptom control skills;

2.3 problem-solving skills;

2.4 social skills.

3. Family members' level of knowledge:

3.1 family members' understanding of medication and psychiatric illness.

4. Service utilisation:

4.1 use of outpatient treatment;

4.2 length of hospitalisation.

5. Health economic outcomes:

5.1 treatment costs.

Data collection and analysis

1. Selection of trials

The search for trials was performed independently by two reviewers. Potentially relevant abstracts were identified and full papers were assessed for inclusion and methodological quality. Any disagreement was resolved by discussion.

2. Quality assessment

Trials were allocated to three quality categories by each reviewer, as described in the Cochrane Collaboration Reviewers' Handbook (Clarke 2000). When disputes arose as to which category a trial was allocated, again, resolution was attempted by discussion. When this was not possible and further information was necessary to clarify into which category to allocate the trial, data was not entered and the trial was allocated to the list of those awaiting assessment. Only trials in Category A or B were included in the review.

3. Data management

3.1 Data extraction

This was performed independently by at least two reviewers and the authors of trials were contacted to provide missing data where possible.

3.2 Intention-to-treat analysis

Data were excluded from studies where more than 50% of participants in any group were lost to follow-up. A sensitivity analysis was performed to assess the impact of this decision. In studies with less than 50% dropout rate, withdrawals were considered as negative outcome.

4. Data analysis

4.1 Binary data

For binary outcomes an estimation of the relative risk (RR) and its 95% confidence interval (CI) was calculated. The weighted number needed to treat statistic (NNT) was also calculated. The chi-squared test for heterogeneity was used to establish heterogeneity, as well as visual inspection of graphs. When heterogeneity ($P < 0.1$) occurred, the reviewers tried to establish if there were reasons for true heterogeneity. If studies were found to be comparable in spite of heterogeneous outcomes, a random effects model was used in statistical calculations.

4.2 Continuous data

4.2.1 Skewed data: continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, the following standards were applied to all data before inclusion: i. standard deviations and means were reported in the paper or were obtainable from the authors; ii. when a scale started from a finite number (such as 0), the standard deviation, when multiplied by 2, was less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution (15)). Endpoint scores on scales often have a finite start and end point and this rule can be applied to them.
4.2.2 Summary statistic: for continuous outcomes a weighted mean difference (WMD) or a standardised mean difference (SMD) between groups was estimated. Again, if heterogeneity was found a random effects model was used. A post-hoc decision was made to pool the GAF scale (22) and its virtually similar earlier version, the GAS scale (23), using WMD statistics.
4.2.3 Valid scales: continuous data from rating scales were included only if the measuring instrument had been described in a peer-reviewed journal and the instrument was either a self-report or completed by an independent rater or relative (not the therapist).
4.2.4 Endpoint versus change data: where possible, endpoint data were presented and if both endpoint and change data were available for the same outcomes, then only the former were reported in this review.

5. Addressing publication bias
Data from all identified and selected trials were entered into a funnel graph (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias (33).

6. Sensitivity analyses
A sensitivity analysis was performed to assess the impact of the reviewers' decision to exclude trials with more than 50% loss of participants.

2 2001 Search

2001 update (12)
To update this review the searches were repeated in January 2001 and in May 2001. The search in January 2001 yielded 213 citations and 235 in May 2001, of which both 200 were quickly rejected as not relevant for the following mutually exclusive reasons: duplicate references, not a randomised controlled trial, participants were not people with schizophrenia,

the intervention was not psychoeducation defined as interaction between information provider and patient or the control intervention was not standard care defined as the normal level of psychiatric care provided in the area where the trial was carried out. No new trials were identified for the comparison of psychoeducation vs. standard care. In this process four ongoing studies were recognised by the reviewers to be relevant and were included in the section of ongoing studies. Six papers awaiting assessment were translated and rejected as not relevant, one study (162) was moved to the excluded studies section due to lack of usable data. Secondary reports of included studies were found and added to the list of references.

The total number of studies that matched with the reviewers' inclusion criteria closely enough to be mentioned in either the included studies or excluded studies section was 28. One paper is awaiting assessment until the additional information is obtained. The review cites 18 studies dating from 1983 to 1998 in the excluded studies section and 10 studies dating from 1988 to 1999 in the included studies section. The results of the review have not changed.

3 1999 Search

Original 1999 search (12)
The original searches in 1999 yielded 583 electronic records, of which 495 were rejected during the first inspection. The other 88 papers were ordered, inspected and 58 were quickly rejected as not relevant. The remaining 30 papers were considered. During this process a further four studies were recognised by the reviewers to be relevant.

4 2010 Search

Update 2010 - Cochrane Schizophrenia Group Trials Register (February 2010)
We searched the register using the phrase:

[*Psychoeducat* in interventions of STUDY]

This register is compiled by systematic searches of major databases, handsearches and conference proceedings (see Group Module).

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Appendix 2. Evidence to Decision Framework

QUESTION

Should polymyxin combination vs. polymyxin monotherapy be used for CRO?	
POPULATION:	People with CRO infection
INTERVENTION:	Polymyxin combination
COMPARISON:	Polymyxin monotherapy
MAIN OUTCOMES:	Mortality; Treatment failure; Pathogen eradication failure; Adverse events-Any AE; Adverse events -acute kidney injury; Adverse events - liver dysfunction; Adverse events - discontinuation of therapy due to AE; Adverse events -reversible renal dysfunction; Adverse events -irreversible renal dysfunction.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The global spread of carbapenem-resistant Enterobacteriaceae (CRE) has been observed over the past two decades (Nordmann 2011, Schwaber 2008). CRE are currently the leading cause of hospital outbreaks worldwide. Infection with these drug-resistant bacteria is associated with high morbidity and mortality, especially in patients with severe underlying diseases or admitted to intensive care units (ICUs) (Baran 2016).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		

				Anticipated absolute effects* (95% CI)	
				Risk with Colistin	Risk difference with Colistin+Other
Mortality				Study population	

	779 (5 RCTs)	⊕⊕⊕◯ Moderate[a,b]	**RR 0.97** (0.84 to 1.13)	470 per 1,000	**14 fewer per 1,000** (75 fewer to 61 more)
Treatment failure	578 (5 RCTs)	⊕⊕⊕◯ Moderate[a,c]	**RR 0.82** (0.72 to 0.93)	Study population	
				659 per 1,000	**119 fewer per 1,000** (185 fewer to 46 fewer)
Pathogen eradication failure	779 (5 RCTs)	⊕⊕◯◯ Low[a,b,c]	**RR 0.81** (0.67 to 0.98)	Study population	
				392 per 1,000	**74 fewer per 1,000** (129 fewer to 8 fewer)
Adverse events - acute kidney injury (RIFLE)	82 (1 RCT)	⊕⊕◯◯ Low[d]	**RR 0.76** (0.46 to 1.26)	Study population	
				487 per 1,000	**117 fewer per 1,000** (263 fewer to 127 more)
Adverse events - liver dysfunction	82 (1 RCT)	⊕⊕◯◯ Low[d]	**RR 0.76** (0.25 to 2.28)	Study population	
				154 per 1,000	**37 fewer per 1,000** (115 fewer to 197 more)
Adverse events - reversible renal dysfunction	60 (1 RCT)	⊕⊕◯◯ Low[d]	**RR 0.75** (0.18 to 3.07)	Study population	
				133 per 1,000	**33 fewer per 1,000** (109 fewer to 276 more)
Adverse events - irreversible renal dysfunction	60 (1 RCT)	⊕⊕◯◯ Low[d]	**RR 1.00** (0.07 to 15.26)	Study population	
				33 per 1,000	**0 fewer per 1,000** (31 fewer to 475 more)

a. Downgrade by 0.5 level due to ROB: there are high risk areas with high risk of missing data.
b. Downgrade by 1 level due to imprecision: low incidence of events.
c. Downgrade 1 due to inconsistency: heterogeneity exists.
d. Downgrade by 2 levels due to imprecision: low incidence of events and wide confidence intervals.

AYDEMIR 2021: Duration of pathogen eradication(d),mean±SD: 3.1±0.5; 4.5±1.7.
Mangoni 2013: Length of hospitalization, d (Median IQR):41 (26–61); 44 (27–59).

Undesirable Effects

How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		All of the impairments are in non-critical indicators, and the quality of evidence is low or very low, it shows a relatively small degree of impairment, and is therefore judged to be minimally impaired

				Anticipated absolute effects* (95% CI)	
				Risk with Colistin	**Risk difference with Colistin+Other**
Adverse events-Any AE	209 (1 RCT)	⊕⊕◯◯ Low[a]	**RR 1.07** (0.73 to 1.55)	Study population	
				333 per 1,000	**23 more per 1,000** (90 fewer to 183 more)
Adverse events - discontinuation of therapy due to AE	406 (1 RCT)	⊕◯◯◯ Very low[a,b]	**RR 1.27** (0.29 to 5.60)	Study population	
				15 per 1,000	**4 more per 1,000** (11 fewer to 70 more)

a. Downgrade by 2 levels due to imprecision: low incidence of events and wide confidence intervals.
b. Downgrade by 0.5 level due to ROB: there are high risk areas with high risk of missing data.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The quality of the body of evidence for the critical outcome was moderate, and the quality of the body of evidence for some of the other important outcomes was low or very low. The main reasons for the downgrading of the body of evidence were the small sample sizes of the studies, the low number of events, the low precision of the intervention effect values, and the risk of bias due to missing data in some of the studies.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability	No included study	The guideline expert group judged the convergence of value preferences among all stakeholders based on clinical practice experience.

○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Desirable: Compared to CMS monotherapy, in every 1000 patients receiving CMS combination therapy there might be on average 14 fewer deaths (RCT=5, N=779, RR=0.97, 95% CI 0.84 – 1.13,moderate-quality evidence), probably on average 119 fewer treatment failure(RCT=5, N=578, RR=0.82, 95% CI 0.72 – 0.93, moderate-quality evidence), might be on average 74 fewer cases of pathogen eradication failure (RCT=5， N=779, RR=0.81, 95% CI 0.67 – 0.98, low-quality evidence), might be on average 117 fewer acute kidney injury (RCT=1, N=82, RR=0.76, 95% CI 0.46 – 1.26, low-quality evidence), might be on average 37 fewer liver dysfunction（RCT=1, N=82, RR=0.76, 95% CI 0.25 – 2.28, low-quality evidence), might be on average 33 fewer reversible renal dysfunction（RCT=1, N=60, RR=0.75, 95% CI 0.18 – 3.07, low-quality evidence). Undesirable: Compared to CMS monotherapy, in every 1000 patients receiving CMS combination therapy there might be on average 23 more adverse events (not reported specific AE) (RCT=1, N=209, RR=1.07, 95% CI 0.73 – 1.55, very low-quality evidence), there might be on average 4 more discontinuation of therapy due to AE (RCT=1, N=406, RR=1.27, 95% CI 0.29 – 5.60, low-quality evidence).	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	No included study	The direct cost of treatment with polymyxins and the other drugs they need to be combined with may be higher, e.g., tigecycline, meropenem. The doses routinely used are also relatively high. There is therefore the potential for increased health resource use, but the panel group was less certain about this judgment.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No included study	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No included study	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No included study	The guideline panel group cited clinical practice experience as evidence of good physician and patient acceptance of polymyxin combination regimens during clinical care, and even a greater preference for combinations at times.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No included study	Polymyxin has good clinical accessibility in mainland China and does not require additional staff training or safety monitoring, etc., for implementation, so the panel considered its feasibility to be good.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

Polymyxin combination therapy is recommended as a preferential choice over monotherapy for treating CRGNB infections in patients who requires polymyxin treatment (strong recommendation, moderate-quality evidence).

Justification

1) The benefit of polymyxin combination therapy may outweigh any potential harm, compared to polymyxin monotherapy in the treatment of CRGNB infections, evidenced by lower rates of mortality, treatment failure, and eradication failure. 2) In vitro antimicrobial synergy tests demonstrated synergistic effect of polymyxin combinations on CRGNB (22). 3) Several colistin-based combinations have been shown in vitro to prevent the emergence of the resistant

sub-populations, but its clinical impact needs further investigation

Subgroup considerations

None

Implementation considerations

1) Patients' renal function should be monitored during polymyxin treatment. The GDG encourages therapeutic drug monitoring (TDM) to be performed for polymyxin where possible. 2) The ototoxic and nephrotoxic drugs (including antimicrobial agents) should be avoided in combination with polymyxin. 3) Polymyxin carbapenem combination may be suggested for treatment of CRGNB infections if meropenem MIC is 8 mg/L for CRE or 32 mg/L for CRAB, and with an extended-infusion of meropenem for 3h (9,10). 4) The dose unit of polymyxin is expressed in different ways, so attention should be paid to the correct conversion of dosage. There are two ways to express the dosage of colistin methanesulfonate (CMS): international unit (U) and colistin base activity (CBA) in mg (an active unit, not a mass unit). Dose conversion: 1 million U z 80 mg mass CMS z33 mg CBA; polymyxin B sulfate: 1 mg = 10000 U; colistin sulfate: 1 mg z 22700 U.

Monitoring and evaluation

None

Research priorities

Several colistin-based combinations have been shown in vitro to prevent the emergence of the resistant sub-populations, but its clinical impact needs further investigation

Appendix 3. Career-time peer reviewed publications

Peer Reviewed Publications List

1. Zhou L, Lu H, Song Z, Lyu B, Chen Y, Wang J, Xia J, Zhao Z; on behalf of Helicobacter Pylori Study Group of Chinese Society of Gastroenterology. 2022 Chinese national clinical practice guideline on Helicobacter pylori eradication treatment. Chin Med J (Engl). 2022 Dec 20;135(24):2899-2910. http://doi:10.1097/CM9.0000000000002546. PMID: 36579940.
2. Effectiveness, safety, initial optimal dose, and optimal maintenance dose range of basal insulin regimens for type 2 diabetes: A systematic review with meta-analysis (in press)
3. Sereda M, Xia J, Scutt P, Hilton MP, El Refaie A, Hoare DJ. Ginkgo biloba for tinnitus. Cochrane Database of Systematic Reviews 2022, Issue 11. Art. No.: CD013514. http://doi:10.1002/14651858.CD013514.pub2. Accessed 18 November 2022.
4. Mitter P, De Crescenzo F, Loo Yong Kee K, Xia J, Roberts S, Chi W, Kurtulumus A, Kyle SD, Geddes JR, Cipriani A. Sleep deprivation as a treatment for major depressive episodes: A systematic review and meta-analysis. Sleep Med Rev. 2022 May 26; 64:101647. http://doi:10.1016/j.smrv.2022.101647. Epub ahead of print. PMID: 35700677.
5. Zhang YQ, Lu L, Xu N, Tang X, Shi X, Carrasco-Labra A, Schünemann H, Chen Y, Xia J, Chen G, Liu J, Liu B, Wang J, Qaseem A, Jing X, Guyatt G, Zhao H. Increasing the usefulness of acupuncture guideline recommendations. Bmj. 2022; 376: e070533. http://doi.org/10.1136/bmj-2022-070533.
6. Yao X, Xia J, Jin Y, Shen Q, Wang Q, Zhu Y, McNair S, Sussman J, Wang Z, Florez ID, Zeng XT, Brouwers M. Methodological approaches for developing, reporting, and assessing evidence-based clinical practice guidelines: a systematic survey. J Clin Epidemiol. 2022; 146: 77-85. http://doi.org/10.1016/j.jclinepi.2022.02.015.
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8. Fabbri LA-O, Moss S, Khan FA-O, Chi W, Xia J, Robinson K, Smyth AA-O, Jenkins GA-O, Stewart IA-O. Parenchymal lung abnormalities following hospitalisation for COVID-19 and viral pneumonitis: a systematic review and meta-analysis. Thorax. 2022(1468-3296 (Electronic)):1-11. http://doi.org/10.1136/thoraxjnl-2021-218275.

9. The Society of Breast Cancer of China Anti-Cancer Association. Chinese expert consensus recommendations for management of bone health in female patients with early breast cancer (2022 edition). CHINA ONCOLOGY (Chinese Edition). 2022;32(3):274-86. http://doi.org/10.19401/j.cnki.1007-3639.2022.03.011.
10. Yuan Y, Wang Y, Xia J, Liu H, Liu J, Li D, Wang R, Cao H, Sang H. Topical, light-based, and complementary interventions for acne: an overview of systematic reviews. Cochrane Database of Systematic Reviews [Internet]. 2021; (11). Available from: https://doi.org//10.1002/14651858.CD014918.
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12. Scattoni ML, Starace F, de Girolamo G, Xia J. An Italy-China Collaboration for Promoting Public Mental Health Recommendations During the COVID-19 Pandemic. Front Public Health. 2021; 9:640205. http://doi.org/10.3389/fpubh.2021.640205.
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