Study-Based Registers of Randomised Controlled Trials: The Premise and Increasing Sophistication of Data Supply for Evidence Synthesis

By

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To

The love of my life

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Not all universities in the UK support a PhD for staff candidates. Without approval of such regulations by the University of Nottingham, I couldn't proceed and finish this work.

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Extended Abstract

Summary

Although narrative reviews remain important, overviewing literature often now takes some form of systematic approach. Pivotal to being *systematic* is the searching and, with that, the role of Information Specialists. To offset a common criticism of the time-consuming nature of systematic reviewing, the Information Specialist must evolve real-world solutions for highly sensitive and specific searches and an efficient supply of complete, valid, and accessible data.

This work describes the five-year evolution of a unique and powerful relational study-based register – of randomised controlled trials (RCTs) (Paper 1). Meta-data from 19,964 RCTs have been extracted, and a controlled language created to allow accurate classification and identification of only relevant studies for any given review (Paper 6). This advanced system almost eradicates the need for reviewers of trials to search for themselves, saving the usual waste in review preparation or grant application (Paper 4).

The umbrella term 'meta-data' may include complete datasets – randomised trials' 'big data'. Although increasing numbers of individual patient datasets (IPD) exist, by far the most common data are the qualitative and quantitative information extracted - by hand or machine - from each study's set of publications. To be rigorous, this data extraction process must be possible to verify- with each tiny piece of data being traceable to its source. This should also prevent the continuous repetition of the same data extraction by successive generations of reviewers. Paper 2 describes pioneering work in creating an easy system to make this possible. Paper 3 calls for wide access to publically funded datasets of extracted data from trials. Paper 8 and Paper 9 describe why openness is important for reproducibility and how we could enhance the

reproducibility of systematic reviews and make them a role model for other study designs.

Furthermore, a register working at this level of sophistication lends itself to semi-automation of the systematic reviewing process (Paper 4, Paper 5) and novel uses of these data – including increasing the rigour in the methodology of the analyses of systematic reviews (Paper 5). These registers greatly facilitate new insights into research activity(presented in Paper 7). This paper reports patterns and trends that could support decisions about the future of the register, the process of systematic reviews and the direction of research overall.

This work represents a step-change in the sophistication of the role of Information Specialists in systematic reviewing. The investment of effort of the last half-decade results in a database with unparalleled functionality and completeness, with rich research potential, already relating to reliable, accurate datasets that can be supplied to any person or machine.

The body of work presented in this thesis is a weave of four papers placed within 'background and developing novel methods' – although parts of these papers do also report results and conclusions. Those four 'background' papers lead to another two articles largely reporting results, and finally, three papers focus on 'conclusions and impact on the policy'.

Background and developing novel methods

Paper 1: This introduces the idea of two types of registers to Information Science:

1. Reference-based register - based on the bibliographic data of separate, disconnected, multiple reports of a study; and
2. Study-based register - based on the entire data of one study, including its connected reports and its associated meta-data and bibliographic details; and, within this
    a. Automated study-based register - in which data and meta-data are widely available so that the systematic reviews could start with meta-analysis.

The paper is the first to discuss the necessity, rationale, and steps for the development, utilization and maintenance of study-based registers, as well as the challenges and gains for organizations supporting systematic reviews. Finally, the paper presents an example of structured data in machine-readable XML and human-friendly tabular format encouraging sharing of data, meta-data and the locations of extracted and tabulated data in the original reports.

Paper 2: This follows the arguments from paper one and describes three methods of locating data in the original reports. The paper, for the first time, compares the advantages and disadvantages of each method. The paper develops the argument to describe the practicalities of how actual tabular data records - including meta-data and the exact location of every small piece of qualitative and quantitative

data - were created (work supported by HTA NIHR Programme grant HTA-14/27/02). Paper 2 ends with a call for open access sharing of this type of research data.

Paper 4: This describes using a sophisticated register of trials with a particular focus on saving time/effort/money. The paper describes and quantifies – including through a flow diagram - the processes of how tasks that usually take months to complete can be undertaken [better] in minutes through the use of a well-constructed and maintained study-based register. The paper discusses – and tries to quantify - the avoidable waste in the process of systematic reviewing and a radical approach to study search and screening.

Paper 5: This describes the use of a sophisticated register with a particular focus on novel analysis and easy-to-use quantifiable means of increasing methodological rigour in network meta-analyses. High-grade registers are used not only to identify all relevant studies but also all relevant *comparisons* within those studies. For the first time, this work presents a simple mathematical formula that accurately predicts the number of potential comparisons within a single RCT or, more importantly, a network meta-analysis. For example, a single trial with two interventions generates one comparison; a three-arm trial –three; and an eight-arm trial no less than 28. Many arms exist for potential indirect comparisons within the increasingly prevalent network meta-analyses, and the tested formula accurately enumerates this number. Those embarking on a network meta-analysis can pre-state which potential comparisons are of interest rather than doing this *post hoc*. Where a shortfall in the number of comparisons utilised or reported occurs - this is a considerable opportunity for the inclusion of bias that can be, at least partially guarded against by the use of the *pre hoc* simple formula.

Results

Paper 6: The paper documents the detailed classification of all pharmacological interventions used in all schizophrenia RCTs. Data relating to interventions extracted from 19,964 RCTs were, for the first time, carefully categorised using a [necessarily] novel controlled language derived from WHO ATC. This initiative now allows uniquely accurate searching for intervention with resulting searches of ultra-high, pinpoint accuracy and no redundancy. Quantification of the workload involved in systematically reviewing an area or topic becomes noticeably more accurate, further magnified by the supply of complete datasets.

Paper 7: Using the curated register, I illustrate how new insights into publication, research and care can be gained from even the relatively simple analysis of the now less confused body of trial evidence maintained within the study-based register.

Conclusion and Impact on Policy

Paper 3: To help the move toward full access to all data extracted from trials by people who are publically funded, I planned, instigated, led and coordinated this international and senior collaborative authorship. The paper encouraged the Cochrane Collaboration to develop global policy and take action regarding data sharing, referring to successful examples of such sharing from systematic reviews. This call did help move the argument forward within this largest producer of maintained reviews worldwide (Appendix A).

Paper 8 and 9: Study-based registers can directly assist in the crisis over irreproducibility within research. Systematic review methods do have specific strengths because of the need to use two or three reviewers and through the development of automation. Unlike many who suggest adding new reproducibility

tests into the systematic review process – to increase transparency but also making the process even more time-consuming - I discuss seven suggested strategies to enhance the reproducibility of systematic reviews: pre-registration, open methods, open data, collaboration, automation, reporting guidelines, and post-publication reviews. These two papers complement Paper 3's call for data sharing policy in Cochrane Collaboration. Furthermore, Paper 8 & 9 expand on the idea that, because systematic reviews are often updated and have existing protocols, and also because relevant automation tools are developing or in existence – allowing replication of processes in seconds - systematic reviews can be a role model of reproducibility for other research designs.

References

Paper 1: Shokraneh F, Adams CE. Study-based registers of randomized controlled trials: Starting a systematic review with data extraction or meta-analysis. **BioImpacts** 2017; 7(4): 209-217. https://doi.org/10.15171/bi.2017.25

Paper 2: Shokraneh F, Adams CE. Increasing value and reducing waste in data extraction for systematic reviews: tracking data in data extraction forms. **Systematic Reviews** 2018; 6: 153. https://doi.org/10.1186/s13643-017-0546-z

Paper 3: Shokraneh F, Adams CE, Clarke M, Amato L, Bastian H, Beller E, et al. Why Cochrane should prioritise sharing data. **BMJ** 2018; 362:k3229. https://doi.org/10.1136/bmj.k3229

Paper 4: Shokraneh F, Adams CE. Study-based registers reduce waste in systematic reviewing: discussion and case report. **Systematic Reviews** 2019; 8:129 https://doi.org/10.1186/s13643-019-1035-3

Paper 5: Shokraneh F, Adams CE. A simple formula for enumerating comparisons in trials and network meta-analysis. **F1000Research** 2019; 8:38. https://doi.org/10.12688/f1000research.17352.1

Paper 6: Shokraneh F, Adams CE. Classification of all pharmacological interventions tested in trials relevant to people with schizophrenia: A study-based analysis. **Health Information and Libraries Journal** 2021; [In Press]. https://doi.org/10.1111/hir.12366

Paper 7: Shokraneh F, Adams CE. Cochrane Schizophrenia Group's Study-Based Register of Randomized Controlled Trials: Development and Content

Analysis. **Schizophrenia Bulletin Open** 2020; 1(1): sgaa061. https://doi.org/10.1093/schizbullopen/sgaa061

Paper 8: Shokraneh F. Reducing waste and increasing value through embedded replicability and reproducibility in systematic review process and automation. **Journal of Clinical Epidemiology** 2019; 112: 98-9. https://doi.org/10.1016/j.jclinepi.2019.04.008

Paper 9: Shokraneh F. Reproducibility and replicability of systematic reviews. **World Journal of Meta-Analysis** 2019;7(3):66-71. http://dx.doi.org/10.13105/wjma.v7.i3.66

A Memorandum on the Papers

Paper	Citation	Status (date)	Page
1	Shokraneh F, Adams CE. Study-based registers of randomized controlled trials: Starting a systematic review with data extraction or meta-analysis. **BioImpacts** 2017; 7(4): 209-217. DOI: 10.15171/bi.2017.25	Published 17 Sep. 2017	11
2	Shokraneh F, Adams CE. Increasing value and reducing waste in data extraction for systematic reviews: Tracking data in data extraction forms. **Systematic Reviews** 2018; 6: 153. DOI: 10.1186/s13643-017-0546-z	Published 4 Aug. 2017	39
3	Shokraneh F, Adams CE, Clarke M, Amato L, Bastian H, Beller E, et al. Why Cochrane should prioritise sharing data. **BMJ** 2018; 362:k3229. DOI: 10.1136/bmj.k3229	Published 13 Mar. 2018	49
4	Shokraneh F, Adams CE. Study-based registers reduce waste in systematic reviewing: Discussion and case report. **Systematic Reviews** 2019; 8: 129. DOI: 10.1186/s13643-019-1035-3	Published 28 May 2019	62
5	Shokraneh F, Adams CE. A simple formula for enumerating comparisons in trials and network meta-analysis. **F1000Research** 2019; 8:38. DOI: 10.12688/f1000research.17352.2	Published 9 Jan. 2019	93
6	Shokraneh F, Adams CE. Classification of all pharmacological interventions tested in trials relevant to people with schizophrenia: A study-based analysis. **Health Information and Libraries Journal** 2021; In Press. DOI: 10.1111/hir.12366	Revised 18 Feb. 2021	108
7	Shokraneh F, Adams CE. Cochrane Schizophrenia Group's study-based register of randomized controlled trials: Development and content analysis. **Schizophrenia Bulletin Open** 2020; 1(1): sgaa061. DOI: 10.1093/schizbullopen/sgaa061	Submitted 27 Nov. 2020	137
8	Shokraneh F. Reducing waste and increasing value through embedded replicability and reproducibility in systematic review process and automation. **Journal of Clinical Epidemiology** 2019; 112: 98-9. DOI: 10.1016/j.jclinepi.2019.04.008	Published 23 Apr. 2019	156
9	Shokraneh F. Reproducibility and replicability of systematic reviews. **World Journal of Meta-Analysis** 2019; 7(3): 66-71. DOI: 10.13105/wjma.v7.i3.66	Published 31 Mar. 2019	163

Statement about Joint Authorship

As the second author of seven out of nine manuscripts and adviser of this thesis, I confirm that Farhad Shokraneh is the first, corresponding and the only principal investigator in all nine papers listed in this thesis. Furthermore, two of the manuscripts were single-authored by him.
As the adviser, I have edited parts of his work and commented on some of the pieces. He also has handled the replies to peer-review comments on his own. My contribution to each paper has been between 5% and 10%.

Signature:  Professor Clive E. Adams (Adviser)

Date: Wednesday, 29 May 2019

PAPER 1

Study-based registers of randomized controlled trials: Starting a systematic review with data extraction or meta-analysis

Citation: Shokraneh F, Adams CE. Study-based registers of randomized controlled trials: Starting a systematic review with data extraction or meta-analysis. **BioImpacts** 2017; 7(4): 209-217. DOI: 10.15171/bi.2017.25

PAPER 1

Study-Based Registers of Randomized Controlled Trials

Abstract

Introduction: Despite years of use of study-based registers for storing reports of randomized controlled trials, the methodology used in developing such registers/databases has not been documented. Such registers are integral to the process of scientific reviewing. We document and discuss methodological aspects of the development and use of study-based registers. Although the content is focused on the study-based register of randomized/controlled clinical trials, this work applies to developers of databases of all sorts of studies related to human, animal, cells, genes, and molecules.

Methods: We describe the necessity, rationale, and steps for the development, utilization and maintenance of study-based registers, as well as the challenges and gains for the organizations supporting systematic reviews of the published and unpublished literature.

Conclusion: The ultimate goal of having a study-based register is to facilitate efficient production of systematic reviews providing rapid but accurate evidence for decision-makers. We argue that moving toward study-based registers is an inevitable welcome direction and that infrastructures are ready for such movement.

Introduction

The emergence of specialized organizations creates needs for specific information for decision-making. Developing and maintaining specialized registers or databases is a valuable tool for achieving organizational goals by providing information to support such decision making (Gonzalez, 2002; O'Reilly, 1983).

Specialized bibliographic registers save time by allowing specific and sensitive searches for records of documents of high relevance to the research question (Ingwersen & Järvelin, 2005a).

The Cochrane Collaboration (1993 – present) is an international not-for-profit network of, amongst others, healthcare researchers, practitioners, patients. This Collaboration works to summarize and synthesize available evidence to support informed decision making in healthcare. The Collaboration's main activity is producing high-quality systematic reviews of randomized controlled trials (RCT) (Cochrane Collaboration, 2015a). However, over two decades after its founding, there are still only 6230 reviews published on the Cochrane Library (June 2017), and most are in need of update. Despite the enormous efforts of thousands of researchers, there remain hundreds of thousands of clinically valuable randomized trials not summarized within reviews. The best evidence to support health care decision making is being wasted. It is not an impossible task to provide good coverage of all clinically useful best evidence of the effects of health care in any one sub-speciality, but it is a large task and difficult. Since a systematic review requires a long process including literature searching, de-duplication of search results, screening the search results, obtaining the full text of the reports, putting the publications from the same study together (studification), data extraction and meta-analysis, it has become clear that study-based registers of randomized trials are integral to this task shortening the process for the reviewers to start a review with data extraction or meta-analysis (Tsafnat *et al*., 2013; Tsafnat *et al*., 2014).

From the very start, the Cochrane Collaboration created a specialized register of relevant literature –now called the Cochrane Central Register of Controlled Trials (CENTRAL) – and has disseminated this in Cochrane Library (Higgins, 2008; Manheimer *et al*., 2003; Manheimer *et al*., 2005). CENTRAL is now the largest bibliographic reference-based database of reports of randomized trials

(Dickersin*et al*., 2002; Cochrane Collaboration, 2015b). It is an amalgamation of the individual Cochrane groups' registers which, in turn, are developed from biomedical bibliographic databases such as EMBASE, MEDLINE and other sources such as conference proceedings (Noel-Storr, 2014). In such databases, the publications and the reports from the same study are not linked together and putting the salami of the study back together required massive efforts.

Slow production of update systematic reviews because of the long process (6230 reviews in 20 years) and salami publication of trials were two main problems that lead to the development of study-based registers. In recognition of the value of study-based registers for more efficient review production, the methodology for development, utilization and maintenance of such registers have been documented in this methodology paper.

Objectives

To search the literature for relevant papers on study-based registers.

To report the rationale, methods of development and challenges of study-based registers for which relevant documentation seems remarkably sparse.

To share more than two decades of practical experience in creating and maintaining study-based registers of biomedical literature.

Search methods

We ran a search to find relevant literature and to ensure the novelty of the current paper. Under consideration terminology in this topic is standard, we used the following search strategy on MEDLINE (1946 to Search Date) and EMBASE (1974 to 2017 Week 34) via Ovid SP and updated this search on August 29, 2017:

Search Strategy: ("Study Based" adj (Register* or Database*)).ti,ab.

We also searched all conference abstracts presented in Cochrane meetings. We did not identify any full published paper on study-based registers but did identify

many conference abstracts. We then contacted Cochrane Information Specialists and followed web searching to find all possibly relevant documents for this overview.

Specialized registers

1. Reference-based registers

Within a reference-based register (database), each record usually behaves as a separate independent entity. There is one record for each 'reference' (also referred to as 'citation', 'publication' or 'report'). However, a study may have several reports or publications and hence, several records in the register (Thompson & Macbeth, 2011). For instance, the researchers may conduct one study but report it in several references such as conference abstracts, a dissertation, a poster, journal papers, an online trial registry record in ClinicalTrials.Gov and so on. Although the references are different in format, they all present some or all data from a single study, and each is listed separately within the reference-based register. A reference-based register is the least resource-intensive and simplest register to assemble (Thompson & Macbeth, 2011).

A reference record in a reference-based register may consist of bibliographic information, abstract and indexing fields. This record may also contain a link to the full report of the reference or be the full report in itself (i.e. conference abstract) (Busgeeth *et al*., 2005; Schneck *et al*., 2013). In such a register, the reference record may sometimes contain another link to other references of the same study (Bashir *et al*., 2017) or a study name or unique identifier, such as an online trial registry number (CRS Team, 2013). Such reference records are the backbone of all the major bibliographic biomedical databases such as MEDLINE, and communication between such databases and reference management

packages is usually easy. This type of register may represent the totality of *publishing activity*, but the register is not an accurate representation of the total research activity because of the 'one-to-many' issue of so-called 'salami' publication of one study.

2. Study-based registers

Conducting one study, the researchers usually published their data in more than one paper (Ebrahim *et al*., 2016). It means that one study might have several reports. To represent the whole data, we should find, use and cite the whole study rather than one paper or one reference to the study. For those working in systematic reviewing – summarizing *research* activity rather than *publishing* activity – there is the necessity to work at the study level instead of the reference level. Every time a systematic review is conducted, a study-based register of some sort is created. Recognizing the wastage involved in disassembling these at the end of each review, some Cochrane groups now maintain study-based registers in which all references of one study are linked to a single meta-record called the 'study record' (also referred to as the 'trial record').

The idea of linking related records to one meta-record is not a new concept in information science (Fattahi, 1996), but it is the cornerstone of modern relational databases. A study-based register consists of study records at the most basic level, each of which links to all available references of each study (Altman *et al*., 2014). The further value may be added to the study record by having it contain structured study-specific meta-data such as data about who were the participants, what are healthcare Problems, what are Interventions and Comparator, and what Outcomes have been measured- so-called PICO data (Durao *et al*., 2013; Shokraneh, 2016). These metadata make it possible to run a precise search for the particular intervention relevant to a specific healthcare condition and retrieve all the related trials – and no more – at the click of a button. All the data and their associated meta-data are stored in data tables

(Figure 1-1). One meta-record may also contain information about all relevant references. Even though a reference may have contained similar PICO meta-data, there is no implicit guarantee that data in the one *reference* record accurately represents all activity within the study. A single reference often reports a sub-set of activity within the study.

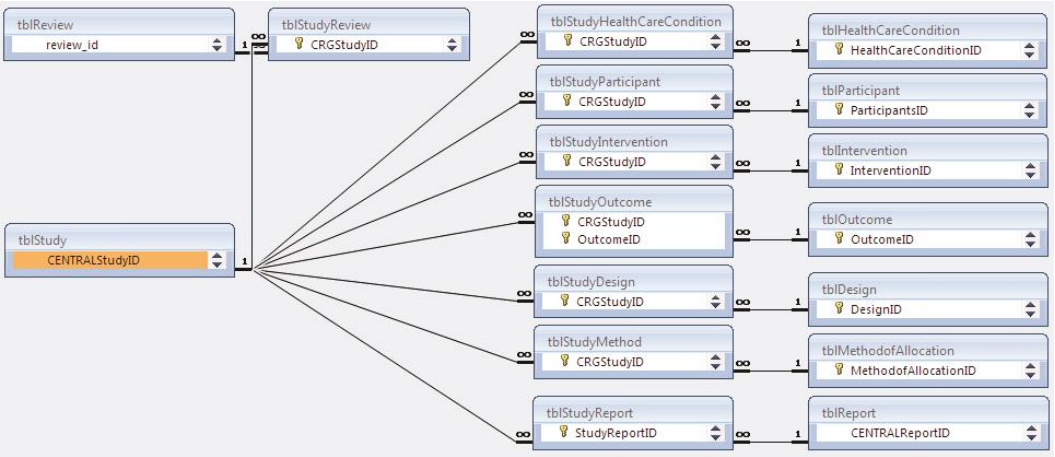

Figure 1-1: Example of the relationships within a real-world study-based register. This figure shows 17 tables out of 34 tables (tbl) within MeerKat, a Microsoft Access-based relational database (Kaur *et al.*, 2009; MeerKat Working Group, 2005; Wright, 2006a). Bibliographic information of each report (in tblReport) is linked to its study (in tblStudy). tblStudy is linked to PICO metadata (in tblHealthCareCondition, tblIntervention, tblOutcome) and to relevant systematic review/s (in tblReview).

The study record can also contain accurate controlled vocabulary (Stoelwinder *et al.*, 2003) describing the comparisons within the study (e.g. drug X versus drug Y for condition Z) with the potential for direct linking to the end review(s) (McDonald *et al.*, 2013). Finally, the study record may also contain all tabulated

data extracted from the full-text reports or the full primary dataset (Table 1-1) (Shokraneh & Adams, 2017).

Table 1-1: A study record containing the metadata, data extracted from a trial report, and the location of the data within the report

Metadata	Data from report(s)				Location
Study Name*	Jahanian 2014				
Reference(s)	1. [Ref. ID 19855] Jahanian AA, Rezaei O, Fadai F, Yaraghchi A. The Effectiveness of Rivastigmine in Reducing Tardive Dyskinesia Symptoms in Patients with Schizophrenia. Iranian Journal of Psychiatry and Clinical Psychology 2014; 20(1): 29-34. 2. [Ref. ID 58435] IRCT2012092910964N1. The effectiveness of Rivastigmine on reducing the symptoms of Tardive dyskinesia in patients with Schizophrenia. Available from [Accessed 29 August 2017]: http://www.irct.ir/searchresult.php?id=10964&number=1				
Characteristics					**Location in PDF****
Methods	Allocation: "randomly assigned" no details reported.				19855PG30C1P3L7
	Blindness: "double blind" no details reported.				19855PG30C1P3L3
	Design: not reported.				
	Duration: "eight weeks".				19855PG31C1P2L4
	Setting: "Razi Psychiatric Center, Tehran, Iran".				19855PG30C1P3L5
Participants	Diagnosis: Patients with schizophrenia and tardive dyskinesia (TD) based on DSM-IV-TR diagnosed by a psychiatrist.				19855PG30C1P3L12-13
	N=40.				19855PG30C1P3L5
	Age: range 18-65 years.				19855PG30C1P3L17
	Sex: not reported.				
Interventions	1. Rivastigmine: dose: 1.5 mg twice daily. N=20.				19855PG30C1P3L7-8
	2. Placebo: no details reported. N=20.				19855PG30C1P3L10
Outcomes	TD symptoms: no improvement (AIMS).				19855PG31C1P2L5
Notes	Sponsorship source: "no financial support".				19855PG33C2P3L1-2
Risk of Bias					
Bias	Support Statement from Report				
Random sequence generation	"Randomly". No details.				19855PG30C1P3L7
Allocation concealment	Not reported.				
Blinding of participants and personnel	"Double blind". No details.				19855PG30C1P3L3
Blinding of outcome assessment	"Double blind". No details.				19855PG30C1P3L3
Incomplete outcome data	Not reported.				
Selective reporting	None. A registered protocol is available (IRCT2012092910964N1).				19855PG30C1P3L1
Other biases	None known.				
Outcome					
	Rivastigmine		Placebo		
	Mean	SD	Mean	SD	
AIMS after Intervention	12.5	7.0	10.3	3.1	19855PG32T2

* This example study has two references

** The first five digits refer to the file name, PG to pages, C to the column, P to paragraph, L to the line, and T to Table.

Rationale

The 'unit of currency' of systematic reviews of health care is the study- not a single reference or a single published paper. The undertaking of a systematic review necessitates creating some sort of study-based list or register, whether it

be by the reviewers or by an Information Specialist. If pre-prepared by the Information Specialist, the final product can be more accurate, save the time of other researchers, and has the potential to be re-used to avoid duplication of effort in the future. Certainly, if the single reference is considered the main unit for systematic reviews, erroneous double or even triple counting of data from various references of a single study is a real danger (Table 1-2). The use of study-based registers decreases this danger – although it does not make it impossible (Huston & Moher, 1996).

Table 1-2: Reasons for assessment and concatenation of all references of one study

Determining relevance	Screening either references or even an individual full-text report of the references may not provide enough information to convince the reviewer that the study meets the inclusion criteria (Leizorovicz *et al*., 1992). Although *references* are assessed, it is the *stud*y that is the unit of analysis.
Over-counting	Treating data from different references of the same study as separate studies will result in over-counting and spurious results (Huston & Moher, 1996; Senn, 2009; Tramer et al., 1997).
Under-counting	Using data from only a selection of references of the study may fail to identify important outcomes in other relevant references of that same study. For example, protocols of studies may report the use of many more outcome measures than are finally reported in any one reference (Altman *et al*., 2014).

1. Reference-based register or study-based register?

Some research groups prefer to keep their trials register at a reference level. However, many in systematic reviewing research have made (what we feel to be) the inevitable move to becoming study-based. In reality, one has to underlie the other. The study-based register should sit over a clean repository of references (Dooley *et al*., 2014; Foxlee *et al*., 2013; Noel-Storr *et al*., 2014).

Moving to a study-based register depends on the research teams' ethos and policies, planning, and available resources. Holding a reference-based register will

save search and de-duplication time. However, a study-based register allows Information Specialists not only to save that searching and de-duplicating time but also it can benefit authors of reviews by providing study records with multiple references already organized at the study level. Study-based registers also have the capacity to save author time by supplying records in which qualitative and numerical data are extracted and referenced.

2. Comparing functionality

Because of the high relevance of screened references to the methodology and healthcare condition, having a specialized reference-based register does increase the sensitivity and specificity of searching for reviews (Ingwersen & Järvelin, 2005a). However, the processes of searching the register, obtaining full-text reports of references, screening search results, checking each reference based on inclusion criteria, assigning references to relevant studies, concatenating data from the same study, and coding information/data to link references to study (Ingwersen & Järvelin, 2005b) takes time – mostly reviewers' time. A study-based register has, to a greater or lesser extent, already undertaken at least some of those tasks moving the expense down the line to Information Specialists who are more skilled in such types of information management.

Making the move

The Cochrane Dementia and Cognitive Impairment Group spent three years converting their specialized register from reference-based to study-based format (Hermans *et al*., 2007). We have found no other estimates of the duration of the switch for other groups in health care. This may seem discouraging, but the initial shift is a matter of days. Fully utilizing functionality does, however, take longer. Any initial investment is offset by the recognition of the daily waste occurring in the systematic reviewing process in discarding efforts of reviewers when supplying data to the next generation of researchers. The past and considerable

efforts in concatenation into study and data extraction are routinely not re-issued. Repeating such efforts of merging (sometimes) hundreds of references into one study is not time-efficient. This merging and extraction of data should, of course, be entirely transparent to future users (study records can potentially hold such tracking information).

As already discussed, a relational database such as a study-based register has the capacity to provide one-to-many relationships so that one study with many reports, but, in addition, conversely, one report referring to data from many studies could be linked and managed easily (many-to-one relationships).

1. Developing a register

The development process of specialized registers is described in Table 1-3. For study-based registers, guidelines should clarify what fields are required (Noel-Storr, 2013a, 2013b) as the study record represents the total research activity in the project, so data may have to be gleaned from different source documents. For example, one reference may record the clinical outcomes of a study. A second reference may record economic data missing from the first reference – but all are brought together in greater or lesser detail in the 'parent' study record (Noel-Storr & Dooley, 2014).

Table 1-3: Levels of specialized registers

Beginners' level or reference-based register	
a.	Setting the scope of the register
b.	Developing running, documenting, and saving the search strategies
c.	De-duplicating and curettage the search results
d.	Screening the search results
e.	Developing minimum dataset for each reference record
f.	Importing the reference records
g.	Maintaining the reference records
h.	Locating the full texts of all reference records
Intermediate level or study-based register	
a.	Developing coding scope and guideline for studies
b.	Coding or extracting general data from each reference
c.	Concatenation, merging and cleaning the study records
d.	Maintaining and updating the study records
Advanced level or automated study-based register	
a.	Classifying the studies under each review title ready to be done
b.	Developing a machine-readable dataset for each study
c.	Extracting all data from each study

Those undertaking systematic reviews already extract qualitative and quantitative information from all relevant references into a study record within their review. These data are often structured, use PICO headings and employ some sort of controlled vocabulary. These data can form the basis of a study record within a register for use by others interested in the area. Maintenance continues as often study records have to be merged. Electronic study-register systems often automatically create a study record for every reference imported (Shokraneh & Adams, 2015). This one-to-one relationship is an understandable default but is inaccurate, and some merging of records will be necessary. This is not usually deleting one record in favour of another, but often the true merging of records to gain the most accurate description of the overall study. If, for example, that third reference of a recognizable study is the economics paper, and the package has

erroneously considered that one reference to be a new unique study, it is important that"

i. the economics outcomes are reported in the 'parent' study record;
ii. other outcomes are not deleted in favour of only economic outcomes; and that
iii. the unneeded *study* record is then deleted, but the economics paper's *reference* record incorporated into the list of citations to that study.

Recognizing references to be from a single study is a skill. Usually, references with the same start time, locations, interventions and the number of participants are identified as references of the same study – although this is not always the case (Huston & Moher, 1996). Recognition of single studies is assisted by using study acronyms or trial registry number, but these, unfortunately, remain the exception rather than the rule. Some software assists this process by pattern recognition within reference records for existing studies. For example, machines can recognize if, in a new reference, authors are identical to those in an existing study, publication dates are very close, interventions and numbers of participants are the same. An Information Specialist on top of her/his topic area quickly gains skills in study recognition. Furthermore, those using references and studies within reviews have to scrutinize all references carefully. Their view of what constitutes a study can be invaluable, save much time and be recycled into the Information Specialist's register.

If all steps are followed based on documented guidelines, it is easy to organize studies into review clusters. For instance, if 11 studies compare 'Intervention A' versus 'Intervention B' for 'Condition C', as coded in fields of the study record, all these studies could be listed under the potential review title 'Intervention A versus intervention B for condition C'. This review cluster is appended to with incoming relevant studies identified by the Information Specialist and, thereafter,

end reviewers need to undertake little or no additional effort searching or screening.

If the full study data extraction is already undertaken, and this is stored within a higher level of study-based register, each study record will consist of a dataset in tabulated format (for readers) and XML-tagged machine-readable format (for software in which each piece of data/information has been linked to its original specific site within the source document). Since we could not identify any structure to cover a study record in a systematic review, Appendix 1-1 demonstrates a proposed XML structure to store extracted study data. A standard tagged, structured, and machine-readable framework can store data right down to the individual patient data level. Structuring for machine readability requires knowledge of the needs of both reviewers and computer scientists and a malleable design to be open to future developments. Much has already been documented regarding such efforts for projects such as Distiller SR, Covidence, and Systematic Review Data Repository (SRDR) (Li *et al*., 2015; Tsafnat *et al*., 2014).

Challenges

1. The concept

The currency of the Information Specialist in health care has, for so long, been the individual reference (1 record for 1 reference) and making the jump to considering studies (1 record to potentially many references of 1 study) as the primary unit of information can be a conceptual challenge. After all, even cursory use of databases such as MEDLINE can cause nagging discomfort that information is being identified for reviewers that is less ordered and sorted than is ideal. For example, searching for CATIE, a large trial acronym, in the title field of MEDLINE will reveal multiple references (170 references at the time of writing). More recently, solutions to this discomfort been conceived, and so the issue is more

acknowledged (Altman *et al*., 2014; Huston & Moher, 1996; Leizorovicz *et al*., 1992; Tramer *et al*., 1997). The process of systematic reviewing does help make this conceptual jump with the use of 'study tags' under which all relevant references are listed.

In a physical library with books, a librarian undertakes collection development, cataloguing, classification and dissemination of information. A reference-based register with just collection development and no coding is the equivalent of maintaining a stack of books with no classification. Whilst 'save the time of the reader' is one of the Five Laws of Library Science (Ranganathan, 1931), 'save the time of the reviewer' is, we argue, best addressed in a study-based register. Also, having a reference-based register 'might work' for some research groups; however, a study-based register 'might work even better', saving time and money for both the Information Specialists and systematic reviewers.

2. Responsibility

In reality, the process of identification of studies is a shared responsibility between Information Specialist and reviewer. Each has different skills to bring to the process. The former has competency in the identification of records and knowledge of what each record should contain. For example, with reference records indexed with study identifiers (e.g. trial registry number), the Information Specialist is in a pivotal position to help the reviewer avoid needless effort in linking references to a study. The reviewer, however, having inspected the detail of each reference, should be able to supply an authoritative study record back to the Information Specialist for their use or for the next reviewer.

Even now, the responsibility for concatenation is shared. However, study-based registers allow this responsibility to be undertaken more easily by the person who maintains the register. The nature of systematic reviewing is that everything is double-checked. By an iterative process, the study record evolves to be an

increasingly accurate report of the primary investigation. To continually pass this responsibility down the line to reviewers creates unnecessary waste and opportunity for inaccuracy.

3. Practicalities

For the gains which we outline above, the development of such a study-based register involves the investment of effort – some pain - often from Information Specialists. Currently, Information Specialists working in systematic reviewing of health care interventions are busy, and the thought of further work and/or responsibility may be unwelcome. However, much current work is inefficient, and we argue that creating a study-based register is an investment. The 'pain' involved makes the role of Information Specialist much more sophisticated and prepares that person to manage a register suitable for the data needs of the 21st century.

Coding of study happens by a shared iterative process as outlined above. Many reference records already contain study codes that can be imported into the study record. For example, the PT field of MEDLINE may contain "Randomized Controlled Trial" – a methodological term relating to the study, or the SI field contains the International Standard Randomized Controlled Trial Number (ISRCTN) – again data that relates to the *study* rather than the reference. These data can be imported automatically into the study record at no cost of time. As reviewers 'use' the study, adding to the complexity but also the utility of the record, more sophisticated data from this investment of effort can be curated and stored ready for the next reviewer.

4. Software

Although there are online clinical trials registers such as ClinicalTrials.Gov, ISRCTN, and WHO International Clinical Trials Registry Platform (including 16 trial registers), however, none of these is study-based register, and none are aimed to

support systematic reviews and provide a very limited number of fields for each study record. Even before the initiation of these sources, in 1995, the Cochrane Stroke Group started using study-based registers, and mental health followed (Adams & Stancliffe, 2002; Cochrane Stroke Group, 2015; Fraser *et al*., 1999; Portfors *et al*., 2002; Thomas & Mclnnes, 1999; Wahlbeck *et al*., 2000). A year after Stroke Group, UK Cochrane Centre supported MeerKat Working Group to develop a study-based register system (Kaur *et al*., 2009; MeerKat Working Group, 2005). In 2003, 10 Cochrane groups were using MeerKat and five other groups considering its use (Kaur *et al*., 2009). By 2005, at least 12 Cochrane groups (out of 37 responses) were maintaining a study-based register on MeerKat, ProCite, Reference Manager or RefTrak (Wright, 2006a, 2006b, 2006c, 2006d). In 2008, Cochrane started developing a new program, Cochrane Register of Studies (CRS), to be used by all groups (Foxlee *et al*., 2010a, 2010b; Foxlee *et al*., 2012; Foxlee, 2008; Malouf *et al*., 2009; Cochrane Collaboration, 2015c). A survey in 2014 showed that 8 out of 29 respondent groups are using a study-based register to some extent (Noel-Storr, 2014).

There are several reference management programs and some study-based register programs. Despite the decision of Cochrane to move to CRS as the only program for managing information on both references and studies, groups do tend to use other programs as well as CRS (Adams *et al*., 2008; Busgeeth *et al*., 2005; Cochrane Dementia and Cognitive Improvement Group, 2014; Cochrane Pregnancy and Childbirth Group, 2015; Cochrane Renal Group, 2005; Cochrane Schizophrenia Group, 2014; Cochrane Stroke Group, 2015; Henderson *et al*., 2002; Higgins, 2003; Hovhannisyan *et al*., 2010; Manheimer *et al*., 2003; Manheimer *et al*., 2005; Monalisa *et al*., 2010; Noel-Storr, 2011; Noel-Storr & Malouf, 2009; Noel-Storr & McShane, 2011; Pienaar *et al*., 2009; Ssemanda *et al*., 2008; Zani *et al*., 2011; Zani *et al*., 2009). Although others have pioneered software for study-based registers (Cochrane Stroke Group, 2015; Fraser *et al*.,

1999), few packages are generic, accessible, or customizable. EndNote, ProCite, and Reference Manager are popular reference management programs that can be modified to include some features of study-based registers. These bibliographic packages do not lend themselves easily to this adaption, and relational databases have considerable advantages. Since the purpose of programs such as EndNote or Reference Manager is not primarily managing studies for systematic reviews, using them in a study-based fashion requires time and effort – and there is an element of fitting a 'square peg in the round hole. Tailor-made relational programs such as MeerKat or RefTrak are much better and potentially more malleable. CRS continues to evolve.

No matter what software or application is used, transition to a study-based register necessitates the acquisition of a skill-set to use the package to full capacity from the study perspective. This transition is helped by practice, training and mentoring.

5. Data ownership

As mentioned before, there are other resources, such as online registries of trials, that do provide some useful data for studies; however, there are certain barriers in terms of copyright and legal issues such as 'who owns the data' (Bierer *et al.*, 2017). Such limitations make it hard to use and share the data openly and import or share them from other resources in study-based registers.

6. Study designs

Since the current development of study-based registers in Cochrane is mainly focused on RCTs/CCTs, and because we work within that organization, we have not discussed involving other study designs. There is, however, a possibility to include all empirical study designs in study-based registers of the future. This may cause new challenges for the development of the registers involving different sets of meta-data. Some Cochrane groups are already considering involving more

diverse study designs in their reviews. However, these other study designs are not a priority for consideration in the technological development of specialized registers. The development of such registers has made it possible to link the studies from pre-clinical sciences to clinical sciences. Such a link could reduce the waste by avoiding clinical trial research where a systematic review of pre-clinical studies about the ineffectiveness of intervention exists (Glasziou & Chalmers, 2015).

Gains

Having a study-based register gives review groups the advantage of knowing with some accuracy how many systematic reviews (or at least comparisons) there are to cover in a topic area – and to more accurately estimate the future workload (McClenaghan *et al*., 2012). Such knowledge allows accurate and efficient prioritization of effort.

Current resources, if used effectively, are sufficient to increase productivity. Using the study as the currency of the Information Specialist, modifying that role within a review group to create and maintain the study-based register, and finally using such a register will greatly increase the pace and efficiency of information exchange.

Information Specialists could then undertake regular – perhaps semi-automated – searches to screen and code and include relevant records within the study register. New references for existing studies would be added to the existing record and, if this study is used within an existing review, the reviewers would be notified. New studies relevant to existing review topics would also cause reviewers to be alerted. Rather than passively waiting for reviewers to request update searches, Information Specialists would be proactive in helping the update. From the ordered study-based register, studies can be linked to topics and be instantly ready for new reviewers. Should data from a study have been

extracted for use in an existing review, these detailed data could be supplied from a sophisticated study-based register in an appropriate format to anyone undertaking a new review necessitating the use of the same study.

Conclusions

The ultimate goal of having a study-based register is to facilitate efficient production of systematic reviews providing rapid but accurate evidence for decision-makers. The future will involve increasing automation. Document optimization now allows much more reliable auto-data extraction (Torres *et al.*, 2015a). Programs already exist for semi-automated data extraction from randomized trials (Tsafnat *et al.*, 2014), and text mining techniques are increasingly sophisticated. The automatic synthesis of data is not far away, perhaps driven by users' needs rather than those of policymakers. Limited automatic write-up of synthesized evidence already exists (Adams *et al.*, 2013; Torres *et al.*, 2015a, 2015b). These next years will see a swift synthesis of best and personalized evidence of the effects of health care in the hands of anyone. At the heart of this exciting prospect should be the role of the Information Specialist – but a role fit for the 21st century and not one that is dated and wasteful. Moving from reference-based register toward study-based register is, we think, inevitable. The infrastructures are ready for such movement.

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Methodology Highlights
What is current knowledge?
• A systematic review is required before starting each biomedical research. • Doing a systematic review is time-consuming, costly and requires training. • To do a systematic review, the review team should search relevant databases with a suitable search strategy, de-duplicate the results, screen the results, obtain the full texts, check the papers against the eligibility criteria of the review, collect the papers relevant to one study under one study name (studifying) and then extract and analyse the data.
What is new here?
• Study-based registers could link the clinical and pre-clinical studies related to the same research question to support the translational research. • Study-based registers save time and cost of systematic review for the research team by skipping the searching, de-duplicating, screening, finding the full texts, criteria checking and studifying steps. The systematic review could start with data extraction or meta-analysis. • There are three different levels of specialized registers, which are now the milestone of automation of systematic reviews.

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PAPER 2

Increasing value and reducing waste in data extraction for systematic reviews: Tracking data in data extraction forms

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PAPER 2

Increasing Value and Reducing Waste in Data Extraction for Systematic Reviews: Tracking Data in Data Extraction Forms[1]

Abstract

Data extraction is one of the most time-consuming tasks in performing a systematic review. Extraction is often recorded onto some sort of form. Sharing completed forms can be used to check the quality and accuracy of extraction or to re-cycle data to other researchers for updating. However, validating each piece of extracted data is time-consuming and linking to the source is problematic.

In this methodology paper, we summarise three methods for reporting the location of data in original full-text reports, comparing their advantages and disadvantages.

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The open peer-review report from one reviewer is available in the following link:

https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-017-0546-z/peer-review

Background

One of the time-consuming tasks in conducting a systematic review is data extraction, and this should be done by at least two researchers to reduce errors (Buscemi *et al*., 2006; Carroll *et al*., 2013). Traditionally, the research team uses a form unto which they enter extracted data. These forms then become the dataset and can be made open access for reuse – a practice that has been encouraged for some time (Wolfenden *et al*., 2016).

Although sharing data extracted from reports is an attractive option, research has identified that – understandably - extraction errors are common (20/34 Cochrane systematic reviews (Jones *et al*., 2005)). Verifying laboriously extracted data, however, necessitates re-locating the text from which the data were extracted in the original report. Such re-locating of each tiny data point in full texts may require the same amount of time that the original review team already spent and is a duplication of effort.

Tracking extracted data to the original source is valuable for checking quality (Jones et al., 2005) and to ensure ease of reuse (Wolfenden *et al*., 2016). In this paper, we highlight three techniques for making the extracted data traceable to the source.

First method: Simple annotation

This method is similar to the citing/referencing system in science/technology literature. We highlight the related data and then annotate a number to it on the original full text and then refer to this number in data extraction form (**Table 2-1, Figure 2-1**).

Table 2-1: Example of using '*simple annotation*' method in data extraction form

Design	Location in PDF
Randomized	1

Although this has the advantage of simplicity, sharing completed data extraction forms will not be helpful without also sharing the same annotated source document. Annotations are valid only in the company of the specific source file that has been used by the research team. Copyright may not allow sharing of the PDF files.

Second method: Descriptive addressing

In this method, the 'address' of each data point is extracted. For example, in the case of PDF files, the structure includes pages, paragraphs, lines, tables, figures, boxes and headlines (Table 2-2, Figure 2-1).

Table 2-2: Example of using '*descriptive addressing*' method in data extraction form

Design	Location in PDF
Randomized	PG2TrialDesignL2

To provide an example of how this may be shared, as a part of a funded project (Adams *et al*., 2015), we extracted data from all randomised trials relevant to the treatment of a disorder of movement and made them available (Adams *et al*., 2017). This has the advantage of being the only PDF-independent method. If the data extraction forms are available, then sharing the PDFs is not required. The readers could access the PDF file from the journal's website and locate the data by following the address.

Third method: Cartesian coordinate system

Every single pixel in a particular PDF file has a unique address. Each word can be identified within a rectangle as a two-dimensional object (**Table 2-3, Figure 2-1**).

This system is similar to – but not the same as – the Global Positioning System (GPS) for geographical location. Whereas GPS has one source document (the Earth) and therefore coordinates are universally applicable, reviewers may be using different PDFs of the same document. One may be a photocopy of the report published within the journal. Another may be the downloaded PDF of the same report. Co-ordinates on one PDF will not tally with another. This method is in its infancy, but with increasing interest from Computer Sciences (Hughes *et al.*, 2014; Nur *et al.*, 2016) and increasing quality and uniformity of PDF, this method is promising for automating data tracking. Coordinates make it possible to link from the data extraction form to the location of the data-point inside the PDF.

Table 2-3: Example of using '*Cartesian coordinate system*' method in data extraction form

Design	Location in PDF
Randomized	264.417999,657.670044,470.810333,657.670044,264.417999,602.998413,470.810333,602.998413

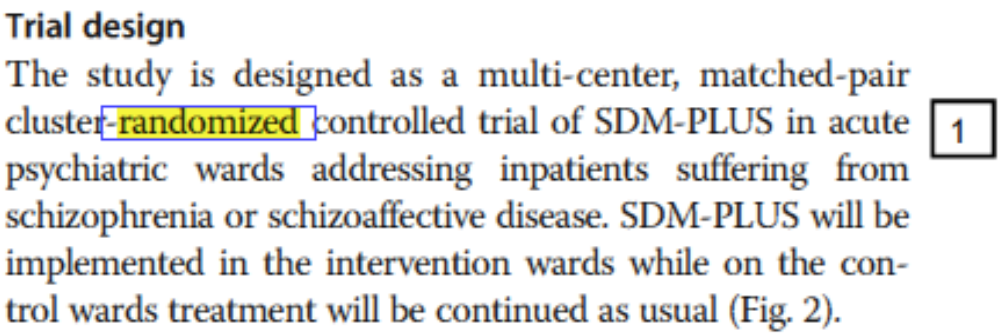

Figure 2-1: Examples of three tracking methods in PDF; the number in the text box is the result of using a *simple annotation* method; the highlighted and linked box is the result of the *Cartesian coordinate system*; Descriptive addressing method does not require PDF file and is based on data extraction forms, we could find the data in PG2TrialDesignL2 (Page 2, Trial Design, Line 2).

Comparing Methods

The first two methods are usable by anyone; the last is computerized and has the potential to be fully automated, but it is not yet available for systematic reviewers. Extraction may be an ongoing process, and update is important. The data systematic reviewers extracted from a study ten years ago are of ongoing value but rarely contained the detail necessitated by modern standards that is now routine. The ease of appending existing data extraction forms is important (Table 2-4).

Table 2-4: Comparing the three methods of tracking extracted data

Methods	Advantages	Disadvantages
Simple annotation	• Available • Easy	• Full texts must be available • Ties user to original highlighted PDF • Difficult to update • Requires PDF editor
Descriptive addressing	• Available • Applicable to any PDF of the same report • Update is possible • No editing required in PDF	• Full texts must be available • Less easy than simple annotation • Uniformity of location definition could be problematic
Cartesian coordinates	• Possibility of hyperlinking from data to report • Possibility of automating data quality check • Ease of update	• Full texts must be available • Piloting – unavailable to wide use

Conclusions

All three methods require access to the original document, so efforts to make research results open-access are of ongoing importance. We think the future is the human-machine interaction and is likely to be driven by Cartesian coordinates relating to uniform PDF reports. The human interface of such a system would be a package to upload or relate to the highest-quality uniformly available PDF to highlight text from which the data are extracted to the form, carrying their coordinates with them via hyperlink. Until that is widely available, we suggest the second method (Descriptive addressing) to locate original source data (see Appendix 2-1).

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PAPER 3

Why Cochrane should prioritise sharing data

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PAPER 3

Why Cochrane Should Prioritise Sharing Data[1]

Open sharing is vital for collaboration, innovation, and reproducibility: Cochrane could show leadership.

Packer (2018) discusses the idea that the one who submits research for public good should be ready to receive a request for data sharing for examination and re-analysis. Tax payers assume that a national agency is checking such data and analysis. Here we discuss Cochrane's practice on data sharing.

Open science, as endorsed by the G7 (G7 Expert Group on Open Science, 2017), includes sharing data, computer code and materials. It is essential for reproducibility, collaboration, and innovation. We support the work of Cochrane, but are concerned Cochrane is not sharing all its reviews' data. These data should be fully accessible for re-use by third parties.

Cochrane, a non-profit private company (Companies House, 2018) and registered charity, produces and maintains systematic reviews in health and social care. Its work is undertaken by a global network of thousands of people (Cochrane Collaboration, 2018a), and its support largely comes from public funding (Cochrane Collaboration, 2018b). Most people producing Cochrane reviews are volunteers, not specifically funded for this work (Tharyan, 2010; Wilson, 2018)and Cochrane encourages 'crowdsourcing' of work (Cochrane Collaboration, 2018c, 2018d; Wallace *et al.*, 2017).

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Cochrane Editorial bases help volunteers obtain study reports and manually extract the wealth of data needed to generate systematic reviews (Shokraneh &Adams, 2017a, 2017b; Wolfenden *et al*., 2016). Cochrane teams use RevMan software (Nordic Cochrane Centre & Cochrane Collaboration, 2014)to produce files in standard format (XML), storing information on the studies, their methods and results for publication in the Cochrane Library.

Benefits of sharing extracted data from trials and systematic reviews are well known, as are the costs of not sharing (Mayo-Wilson *et al*., 2018; Nordic Trial Alliance Working Group on Transparency and Registration, 2015; Uhlir & Schröder, 2007; Wolfenden *et al*., 2016). Sharing maximises transparency, reliability of data extraction, and syntheses. It improves access to data - saving time and money - and opens new avenues of inquiry (Agency for Healthcare Research and Quality, 2015). Sharing is associated with increased citations (Angraal *et al*., 2017), more publications (Piwowar *et al*., 2007), and re-use for new purposes (Nordic Trial Alliance Working Group on Transparency and Registration, 2015).

Structured data from Cochrane should be fully accessible for download, re-use and review (Box 3-1). Currently, they are not. Although Cochrane supports transparency initiatives such as AllTrials (Brown, 2013), and is explicit about this within its policy (Cochrane Collaboration, 2018e), it has no similar clear principles on opening full access to the data within Cochrane reviews. Cochrane does provide access to results data from reviews but, crucially, these cannot be readily re-used; and the available information is an incomplete set of the data generating these reviews. It comes in a technically problematic format and can only be viewed by those with access to the full content of the Cochrane Library (Cochrane Collaboration, 2018f; Cochrane Library, 2018; Soares-Weiser, 2017).

Box 3-1: Structured data and associated metadata

Reference data
- All data from within Cochrane Central Register of Controlled Trials (CENTRAL) excluding copyrighted abstracts (so creating OPEN CENTRAL)
- All data from within Cochrane Register of Studies (CRS) excluding copyrighted abstracts (so creating OPEN CRS)
- Links to 'parent' study
- Links to 'parent' reviews

Study data
- Links to 'child' references
- Links to 'parent' reviews

Characteristics of studies:
- Methods, participants, interventions, outcomes
- Qualitative data on risk of bias
- Quantitative data on outcomes
- Qualitative and quantitative derived data
  - meta-analysis results, grading of quality of outcomes

Small amounts of Cochrane data *have* been released with bespoke arrangements for specific individuals. This sharing is welcome, but there is a lack of an organisational culture, policy, or process regarding data release; there is no appeals process. For example, OpenTrials aggregates all accessible documents on all trials in an open database and makes it free for public re-use (Goldacre & Gray, 2016; Goldacre *et al.*, 2017). Thus far, OpenTrials have been unable to persuade Cochrane to share data for re-use. The Trip Database (Trip Database, 2018) is a searchable library of evidence that asked to re-present structured data from Cochrane but also encountered barriers to access (Brassey, 2016). Open sharing could foster collaborative ecosystems of digital innovation going beyond academic publications, with outputs which might include live, interactive presentations of summaries and results of trials produced by teams around the world, interactive decision support tools and many more.

Cochrane's non-release of data is unlikely to reflect the preferences of funders, publishers, the thousands of Cochrane volunteers, participants in trials, or patients. For example, when asked, 83% of the members of the Cochrane Individual Participant Data (IPD) Meta-analysis Methods Group supported sharing systematic review data via a central repository (recognising that the IPD might require some form of moderated access) (Tudur Smith *et al.*, 2014). Many funders now require that data arising from their grants are shared (Bill & Melinda Gates Foundation, 2018; Medical Research Council, 2018; National Health and Medical Research Council, 2017; National Institute for Health Research, 2018). Cochrane volunteer authors give tacit consent for use of their work within reviews but may not be aware of the restrictions placed on access to the data they worked so hard to prepare (Soares-Weiser, 2017). This is morally and ethically questionable, potentially eroding public trust (Coyne, 2017; Nordic Trial Alliance Working Group on Transparency and Registration, 2015).

This issue of Open Science is now pressing, following recent moves by Cochrane to create more information and become a hub for systematic review data. This has potential to improve evidence and patient care, but while the Cochrane Linked Data Project aims to share re-usable data in some form (Li *et al.*, 2015; Slaughter *et al.*, 2015), as yet, there is no information on how or when this will happen (Cochrane Collaborarion, 2017, 2018g). Furthermore, Cochrane is making efforts towards 'living' systematic reviews, with updates from data in real-time (Elliott *et al.*, 2014). This is important work, but progress is slow. Opening up this work with shared data resources, and collaboration with the open source software community - where all can contribute - would accelerate progress and best reflect the culture of collaboration in science (Box 3-2).

Open data offers a transformative, collaborative future for the systematic review community. Cochrane has enabled a vast workforce to painstakingly extract information for great benefit. Cochrane could act as a hub, harmonising data

collected across groups and sharing these widely, reflecting the collective funding and volunteer workforce that produces them. This could involve the conversion of the morass of free text trial reports into machine-readable curated data, in archived, citable, accessible, inter-operable and re-usable formats, as set out in the FAIR Principles (Data Citation Synthesis Group, 2014; Wilkinson *et al*., 2016). Cochrane could show leadership in supporting innovation and open science for clinical trials with full credit to all data extractors before (Chalmers & Glasziou, 2016) and after review publication (Bierer *et al*., 2017) and, in this way harness the greatest broadest impact. This reflects the exciting current move towards better use of data to produce digital tools of direct value to clinicians rather than academic publications alone.

Open data is a route to success and impact in the 21st century. We have raised these issues with Cochrane (Adams *et al*., 2017), and understand that the organisation is considering whether to commence a process of reviewing its approach to sharing data (Tovey, 2017). We hope that our setting out the benefits of open data is a helpful contribution to open that discussion.

We appreciate Cochrane must focus on making itself sustainable and that open data sharing may be commercially sensitive (Senior Management Team, 2017). However, making Cochrane a champion for openness, transparency and sharing can only be beneficial for the organisation's reputation - and finances. We encourage Cochrane leadership to create a policy that allows open data sharing and to make explicit any concerns they have on open data sharing so that these can be resolved.

Box 3-2: Key messages

- Cochrane could lead and set standards for open data sharing from systematic reviews.
- Availability of data from Cochrane reviews would:
  - give opportunities for collaboration, innovation, scientific replication, novel research and clinical decision making.
  - reduce the considerable waste of the current duplication of effort in systematic reviewing.

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PAPER 4

Study-based registers reduce waste in systematic reviewing: Discussion and case report

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PAPER 4

Study-Based Registers Reduce Waste in Systematic Reviewing: Discussion and Case Report[1]

Abstract

Background: Maintained study-based registers (SBRs) have, at their core, study records linked to, potentially, multiple other records such as references, data sets, standard texts and full-text reports. Such registers can minimise and refine searching, de-duplicating, screening and acquisition of full text. SBRs can facilitate new review titles/updates and, within seconds, inform the team about the potential workload of each task.

Methods: We discuss advantages/disadvantages of SBRs and report a case of how such a register was used to develop a successful grant application and deliver results – reducing considerable redundancy of effort.

Results: SBRs saved time in question-setting and scoping and made rapid production of nine Cochrane systematic reviews possible.

Conclusion: Whilst helping prioritise and conduct systematic reviews, SBRs improve quality. Those funding Information Specialists for literature reviewing could reasonably stipulate the resulting SBR to be delivered for dissemination and use beyond the life of the project.

[1] The open peer-review reports from three reviewers is available in the following link: https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-019-1035-3/peer-review

Background

Time to complete systematic reviews

There is much redundancy in medical research (Chalmers *et al.*, 2014; Chan *et al.*, 2014; Glasziou *et al.*, 2014; Ioannidis *et al.*, 2014; Macleod *et al.*, 2014; Al-Shahi Salman *et al.*, 2014) and systematic reviewing is no exception (Afshari *et al.*, 2017; Annane *et al.*, 2018; Chalmers & Glasziou, 2016; Chevret *et al.*, 2018; Garattini *et al.*, 2016; Handoll & Langhorne, 2015; Lund *et al.*, 2016a; Moller *et al.*, 2018; Nelson, 2016; Roberts & Ker, 2015, 2016; Roberts *et al.*, 2015). Usually, the review team runs searches, removes duplicates, screens titles and abstracts, obtains full-text reports, screens full texts, assembles reports of the same study, extracts data, synthesises them and writes the final report. This process has great potential for waste (Andrade *et al.*, 2017; Rathbone *et al.*, 2015; Tovey, 2015). For systematic reviews the median time from search to publication has improved from 14months in 2008 (Sampson *et al.*, 2008) to 8in 2013 (Beller *et al.*, 2013) (mean time to complete 17 months(Borah *et al.*, 2017); median time between first search and appearance of the review in PubMed was nearly two years (Bramer & Bain, 2017)). The Cochrane Collaboration, a large organisation undertaking and maintaining systematic reviews of health care, largely works with volunteer health care professionals (Tharyan, 2010; Wilson, 2018) and the median time from protocol to review publication was 2.4 years (Tricco *et al.*, 2008). Keeping volunteer authors active on the review and the actual length of the review process are two major challenges to swift reviewing (Turner *et al.*, 2017). Efficiencies are needed.

Current preparation for reviewing

At the start of a new systematic review or an update for an existing systematic review, there is limited knowledge about the quantity of relevant literature.

Although estimation of workload is possible through piloting or scoping searches (Clavisi *et al*., 2013; Hoekstra *et al*., 2017; Otter *et al*., 2017), this requires time and the exact number of relevant studies may remain unclear. This lack of clarity leaves assembled review teams vulnerable. The predicted investment of effort could be:

- Overestimated–and eventually review teams have no or very few studies for their new review or update – with the waste this would incur.
- Underestimated–and the team is eventually surprised and, perhaps, overwhelmed with many relevant studies, with the risk of:
    - Publishing a protocol but finding completion of the review unaffordable or impossible with the resulting wasteful unfinished or empty review.
    - Requesting extensions to funding; and/or
    - Running into delays that may render the final work being immediately out of date.
- Accurately estimated – but what remains unclear is as to whether the investment needed to review/update is warranted by any potential to change what is already known.

Waste in systematic reviewing and information supply

The majority of the literature related to waste in systematic review are either focused on methodology (Afshari *et al*., 2017; Annane *et al*., 2018; Chalmers & Glasziou, 2016; Chevret *et al*., 2018; Garattini *et al*., 2016; Handoll & Langhorne, 2015; Lund *et al*., 2016a; Moller *et al*., 2018; Nelson, 2016; Roberts & Ker, 2015, 2016; Roberts *et al*., 2015) or automation of processes to shorten time-

consuming tasks (Jonnalagadda *et al*., 2015; O'Connor *et al*., 2018; Tsafnat *et al*., 2013; Tsafnat *et al*., 2014). For over two decades, Information Specialists have given practical guidance for waste reduction in systematic reviews (Kirtley, 2014a, 2014b, 2016; Lund *et al*., 2016b; Moher *et al*., 2017; Otter *et al*., 2017). Information Specialists in the Cochrane Collaboration maintain specialized registers to support Cochrane reviews. Some of these registers are highly developed and shorten the systematic review process (Shokraneh & Adams, 2017b).

Study-based registers

Study-based registers (SBRs) are databases in which all records of the same study are linked to one 'parent' report. This study report may contain meta-data extracted from the various 'child' records of that same study. Often building a SBR involves an Information Specialist running searches across major bibliographic databases, de-duplicating, screening for eligibility, and obtaining full text of records. Then there is the process of linking 'child' reports to the 'parent' study record, extracting, cleaning and curating meta-data and maintaining the register with updates. In the case of randomised trials, meta-data for the study may be gleaned from the individual records (e.g. details of participants, interventions, controls and outcomes (PICO)) or, working from the other direction, from the overarching review in which the study has been used (e.g. qualitative or quantitative data incorporated within the review relating to that study). Details of *creating and maintaining* an SBR have been reported elsewhere (Shokraneh & Adams, 2017b).

Aims and objectives

To let us describe how an SBR can be used to almost eliminate certain arduous steps in prospective systematic reviewing. We will illustrate how these steps can

be accomplished in a matter of minutes or seconds and how this approach almost negates the early, inhibiting, and, we argue, wasteful, effort experienced by systematic reviewers. Although some benefits of SBRs have already been reported (Shokraneh & Adams, 2015, 2017b), little has been presented on how SBRs can reduce waste whilst assisting prioritisation of systematic review work (Shokraneh & Adams, 2018).

'Living' study-based registers

With a well-maintained SBR, an Information Specialist can provide the following data in a matter of minutes (stipulation of all estimates are review-specific but a worked example follows):

- The exact number of:
    - studies/related records in a field (e.g. schizophrenia, tardive dyskinesia);
    - studies/related records relevant to a new title or update (e.g. vitamin E for people with tardive dyskinesia);
    - studies/related records relevant to a class of interventions (e.g. cognitive therapy);
    - studies that have/have not already been data-extracted, and the extracted data were available;
    - existing related reviews on a topic – and quantification of studies/related records within each review;
    - comparisons possible to accurately scope existing relevant evidence on a given topic – and quantification of studies/related records within each comparison (Shokraneh& Adams, 2019);

- Alerts to:
    - new studies, records to known studies and novel relevant treatments;
    - research gaps in topic areas devoid of/with a dearth of evidence;
- For the studies
    - Concatenated importable references output of each study or all the relevant studies;
    - Full reports of each study collected into a study folder;
    - Completed data extraction forms of studies where available.

Essentially, an SBR should be 'living'. These 'living' curated registers involve minimal analyses and are maintained by an Information Specialist (Table 4-1). Such registers have been produced by the Cochrane Dementia (ALIOS), Renal/Kidney (maintained within MeerKat), Pregnancy and Childbirth, Stroke (DORIS) and Schizophrenia (within MeerKat) teams for over two decades. For some existing SBRs, there is further developments to add functions to include extracted data from reviews (Shokraneh & Adams, 2017b), links to standard text and to prioritise sharing these data publicly (Shokraneh *et al*., 2018). Unfortunately, CENTRAL and Cochrane Register of Studies (CRS) are, at best, rudimentary SBRs at the time of revising this paper (27th March 2019).

Table 4-1: Saved resource by use of study-based registers by stage of systematic reviewing.

Stage	Prioritisation	Registering new title	Searching	De-duplication	Primary screening	Provision of study reports	Extracting data	Performing analyses	Running an update
Resource saving	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Funder	Reviewers	Librarian	Librarian	Librarian	Librarian	Reviewers	Reviewers	Reviewers
Duplication avoidance	✓					✓	✓		
Empty review anticipation	✓	✓							✓
Timetabling efficiencies		✓							✓
Workload assignment		✓							✓
Reducing incorrect results								✓	

Armed with the information from these sophisticated registers, a potential review team should be able to present a much more accurate estimate of workload before embarking on the grant application or the actual review or update. These registers should make it possible to truncate the period immediately after protocol publication, seeding the systematic review with extracted data and preparing for swift meta-analysis.

A case report from schizophrenia

Cochrane Schizophrenia has maintained an SBR of randomised trials for over two decades (Shokraneh *et al*., 2018). Routine searching identifies records that, with some help from automation, are merged into study reports (examples of studies with 10, 50 or even 100 records are not rare) helping minimise the risk of multiple counting with the systematic review. Meta-data (including number randomized) are part of the study record. Although increasingly automated, this process is facilitated by the Group's Information Specialist (FS). Since search strategies have been saved in bibliographic databases, monthly automatic updates are received through email. Then the Information Specialist spends three days per month for routine processes of updating the register: 1. One day for primary screening of search results and adding references to the register; 2. another day for obtaining full texts and linking them to their references; and finally 3. One last day for indexing the PICO meta-data from each full text and then assembling the separate references of the same study and linking them to that study. This register supports 324maintained systematic reviews.

Using this SBR, prioritisation of work could then proceed with efficiency (**Figure 4-1**) and in line with items 2-6 from module 2 of SPARK, a prioritisation tool for systematic reviews (Akl *et al*., 2017).

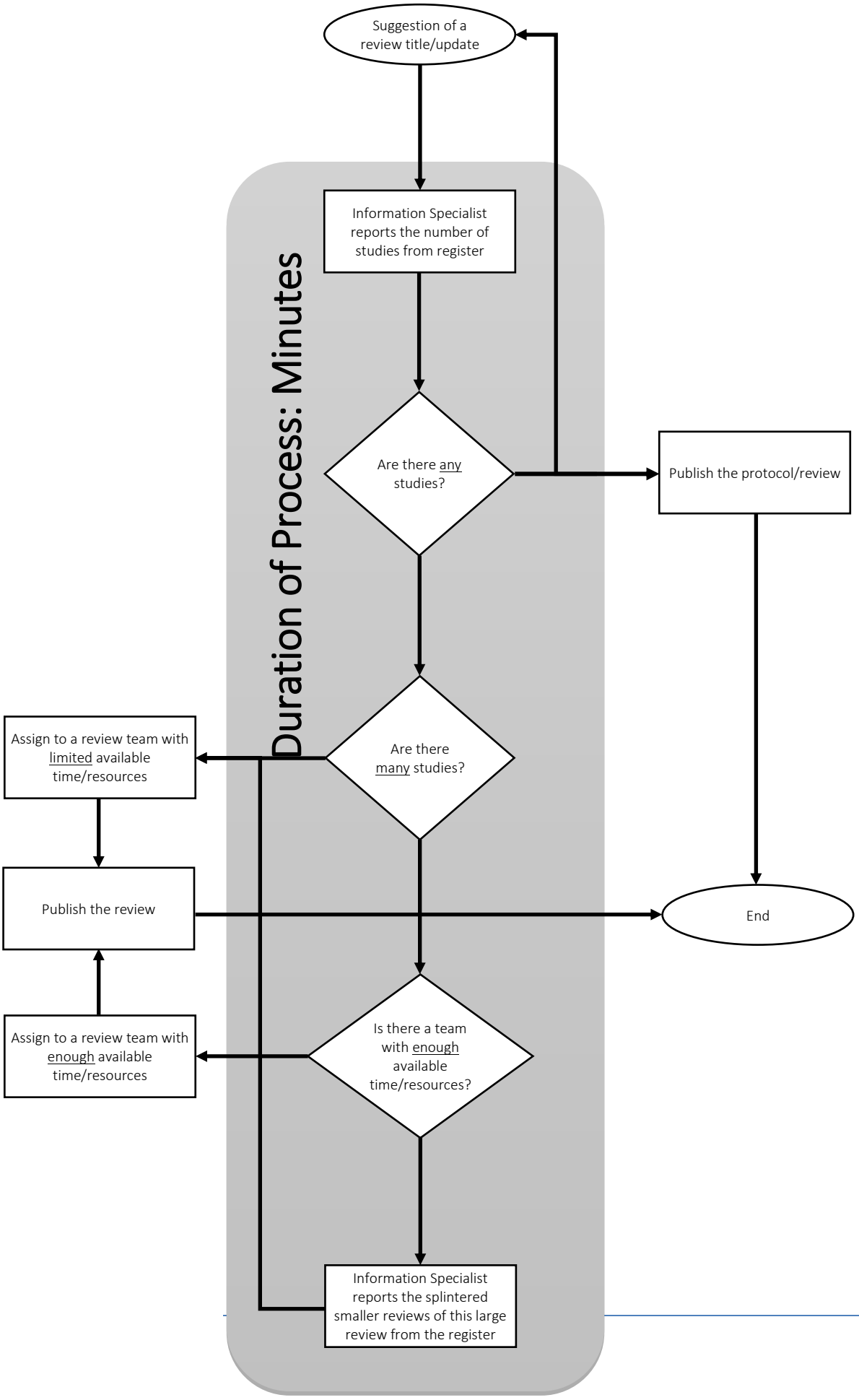

Figure 4-1: The process of systematic reviewing using a study-based register.

Estimates of costs for the grant application

In applying for NIHR UK Health Technology Assessment (HTA) Project Grant (14/27/02) (Adams *et al*., 2015; Adams *et al*., 2017)– a call for reviews relevant to treating people with Tardive Dyskinesia (a problematic adverse effect of antipsychotic drugs) use of the SBR gave clear advantage. Cochrane Schizophrenia's Information Specialist ran a highly specific, highly sensitive search (16th July 2015) in the SBR and identified the exact number of studies relevant to the problem (time spent on task: 8 seconds). This number helped the grant application team provide an accurate assessment of the work to be done – and realistic estimates of costs.

Prediction of the best composition of families of reviews

Tardive Dyskinesia is a condition for which many treatments have been used (Soares *et al*., 1996). Arguments exist for 'lumping and splitting' at all sorts of levels. At the broadest level of 'lumping', the overview could encompass all treatments but this becomes unwieldy and impossible to update. At the finest level of 'splitting' each individual comparison of each treatment could be treated as a separate review. Even in a limited topic area such as Tardive Dyskinesia, this would lead to hundreds of separate reviews. Clearly, there is a balance to be struck. By use of a controlled vocabulary for the meta-data within the SBR, auto-grouping into logical treatment/comparison families for reviews can take place – and, once established, this can take place instantly. This ensures a pragmatic middle road dividing work into clinically logical bite-size reviews for later overviewing if required. Also, the classification of interventions within the register allows reviewing a class of interventions in a review. In the case of Tardive Dyskinesia, 10 separate review groupings were created (Box 4-1) (time spent on task: 2 minutes and 10 seconds). This also helped the grant application team provide an accurate assessment of the output the funders could expect.

Box 4-1: Updated/started Cochrane reviews as a result of NIHR HTA Grant (14/27/02) (Adams *et al*., 2015)

Anticholinergic medication for antipsychotic-induced tardive dyskinesia (Bergman & Soares-Weiser, 2018)
Antipsychotic reduction and/or cessation and antipsychotics as specific treatments for tardive dyskinesia (Bergman & Soares-Weiser, 2018)
Benzodiazepines for antipsychotic-induced tardive dyskinesia (Bergman *et al*., 2018)
Calcium channel blockers for antipsychotic-induced tardive dyskinesia (Essali *et al*., 2018)
Cholinergic medication for antipsychotic-induced tardive dyskinesia (Tammenmaa-Aho *et al*., 2018)
Gamma-aminobutyric acid agonists for antipsychotic-induced tardive dyskinesia (Alabed *et al*., 2018)
Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (Soares-Weiser, Rathbone *et al*., 2018)
Non-antipsychotic catecholaminergic drugs for antipsychotic-induced tardive dyskinesia(El-Sayeh *et al*., 2018)
Pyridoxal 5 phosphate for neuroleptic-induced tardive dyskinesia* (Adelufosi *et al*., 2015)
Vesicular monoamine transporter inhibitors versus placebo for antipsychotic-induced tardive dyskinesia**(Karl *et al*., 2018)
Vitamin E for antipsychotic-induced tardive dyskinesia (Soares-WeiserMaayan *et al*., 2018)

*This review is absent in the published report (Adams *et al*., 2017) because there was no new study.
** This review is absent in the published report (Adams *et al*., 2017) because we became informed and started this review as a result of update search process in SBR.

Prediction of effort needed at data extraction step and saving effort for others

In this particular case, the SBR also contains information on already extracted data. Therefore, the applicants were also informed of exactly how much work has been completed and allowed them to make accurate costing for the necessary remaining efforts (time spent on the task: 8 seconds)—working with such a

register affords applicants opportunities to ensure that their request for funding for this part of the effort can be seen as an investment. The extracted study data can, thereafter, be made available to anyone, thus reducing future duplication of effort (see below).

Supply of documents

SBR systems such as Microsoft Access 'MeerKat' (Kaur *et al*., 2009; MeerKat Working Group, 2005; Wright, 2006) have the capacity to output file batches grouped by review, then sub-grouped into relevant study files, while in turn contain all relevant records and references (time spent on the task: 4 minutes and 43 seconds). In this cause, this procedure allowed those applying for the grant to reassure funders that supply of documents was not an issue and, once the grant was given, to waste no time in acquiring papers and piecing together the studies from 'salami' or multiple publications of the same study.

The future supply of full dataset

In the hope of evolving SBR towards making the level of document supply described above redundant and saving more time in the future - applicants sought and were granted support to extract all data from all randomised studies relevant to Tardive Dyskinesia and to make these data publicly available. This included each part of the data being made traceable to the exact site within the source record (Shokraneh & Adams, 2017a). Any new updates of this will involve supply of documents containing tabulated, reliably and verifiably extracted data (Adams *et al*., 2017).

Updating

Cochrane recommends biennial update for reviews (Higgins *et al*., 2011) but this timing is not always appropriate. Excessive updating wastes resource while

inadequate updating could result in outdated or incomplete evidence being used (Jaidee *et al*., 2010). While there are methods to detect if updating a review could change the current conclusion/practice, almost all require an awareness of the available 'unused' relevant literature (Akl *et al*., 2017; Barrowman *et al*., 2003; Bastian *et al*., 2011; Chalmers & Haynes, 1994; Chung *et al*., 2012; Cohen, 2008; Cohen *et al*., 2009, 2012; Dalal *et al*., 2012; Doyle *et al*., 2005; Garner *et al*., 2016; Garritty *et al*., 2010; Hoomans *et al*., 2012; Martinez Garcia *et al*., 2017; Martinez Garcia *et al*., 2015; Meremikwu *et al*., 2011; Mickenautsch & Yengopal, 2013; Moher *et al*., 2007, 2008; Newberry *et al*., 2013; Pattanittum *et al*., 2012; Sampson, 2009; Shekelle *et al*., 2014a, 2014b; Shojania *et al*., 2007; Sutton *et al*., 2009; Takwoingi *et al*., 2013; Tugwell *et al*., 2013; Waters *et al*., 2003), and some degree of screening and data checking to allow an informed decision. Within a well-constructed and maintained study register, this investment has already been made.

The up-side

As the grant (Adams *et al*., 2015) was drawing to a close and the reviews were being completed, on the 26th April 2017, the SBR allowed the Information Specialist to run a final 'just-before-submission' update search limiting to not-already-identified records (time spent on the task: 13 seconds). Just before publication, this search was used to inform the team that seven of the 10 reviews were fully current but two needed to be updated with a total of five new studies. This allowed the grant holders to efficiently update the reviews just pre-publication to ensure they held fully current information.

The down-side

This search also identified two new drugs (Valbenazine and Deutetrabenazine) entering the market specifically for treatment of people with Tardive Dyskinesia. These new compounds, unrelated to others, necessitate a new review outside of

what was supported by the grant (Karl *et al.*, 2018). Unlike decades ago when SBRs did not exist or were not sophisticated, it is now almost impossible to fail to identify a newly emerging treatment. This saves further waste in systematic reviews through inclusiveness of all treatments from all classes.

Feasibility of study-based registers

Although it seems exciting to start a systematic review with extraction of data, the workload creating an SBR should not be underestimated. The investment of time is a frequent concern. Is it possible for all evidence-synthesis groups to maintain an SBR and what are the necessary requirements in creating such a register?

The short answer is that every systematic review is, in itself, a small SBR. Frequently at completion of any given review, these small registers (reviews) are rendered unusable to others or disassembled necessitating the next interested group of reviewers to have to repeat the construction. This is an avoidable waste when collating all the data within a related group of reviews constitutes the embryonic SBR.

In Box 4-2, we itemise the time and resource required for establishing and maintaining our broad-based schizophrenia SBR.

Box 4-2: Characteristics of the study-based database in this study

Volume	**Records:**	~20,000 studies ~30,000 references/reports
	PICO meta-data:	~230 healthcare conditions; ~2,700 interventions*; ~13,700 outcomes
Variety	**Standard protocols** for meta-data:	for references (RIS); for studies
Veracity	**Document coverage**	
	Type:	Any
	Language	All
	Date/time:	Any
	Geography	Worldwide
	Publication status:	Published/unpublished
	Status of study:	All**
	Reliability	
	Two independent Information Specialists checked data.	
Velocity	**Information Specialist**	screens 1000-2000 references per month; adds 100-200 eligible references to register.
Value	**Software**: Free. **Current number of maintained systematic reviews:** 324. **Retracted studies:** retraction/correction linked into study record. **Reproducibility and replicability:** all SBR's review-specific steps can be repeated within seconds (Shokraneh, 2019). **Prioritising:** sensitive/specific direction of effort **Human Resources:** skilled Information Specialist Establish register one year (F/T) 2-3 years (P/T 50%) Maintain register one day/week	

* *Structured, controlled language (e.g. WHO ATC)*

** Finished/Ongoing/Awaiting/Terminated/Unclear

Conclusions

Small SBRs, in the form of completed reviews, are increasingly prevalent. We maintain that there is a strong argument for creation of broad-based healthcare study-based registers linked to records containing data, text and other relevant information. Not to use already compiled data is wasteful and not to invest to create the SBR is passing cost – and waste - down the line to reviewers. Information specialist investment is already happening – repeatedly. We argue that focus and direction of this investment would avoid the ongoing unnecessary duplication of effort.

We reported one example of the potential of SBRs for grant application. This is one amongst many. The 'living' property of this register allowed the Information Specialist with his/her more sophisticated role – to become an integral – and useful - part of the review team.

Finally, the SBR promoted more sophisticated sharing of data from this project facilitating the not-so-distant full automation of living systematic reviews.

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PAPER 5

A simple formula for enumerating comparisons in trials and network meta-analysis

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PAPER 5

A Simple Formula for Enumerating Comparisons in Trials and Network Meta-Analysis[1]

Abstract

We present use of a simple formula to calculate the number of pairwise comparisons of interventions within a single trial or network meta-analyses. We used the data from our previous network meta-analysis to build a study-based register and we enumerated the direct pairwise comparisons from the trials therein. We then compared this with the number of comparisons predicted by use of the formula and finally with the reported number of comparisons (indirect or direct) within the network meta-analysis. A total of 133 trials of 8 interventions were selected which included 163 comparisons. The network of these showed 16 unique direct comparisons. The formula predicted an expected 28 indirect or direct comparisons and this is the number that was indeed reported. The formula produces an accurate enumeration of the potential comparisons within a single trial or network meta-analysis. Its use could help transparency of reporting should a shortfall occur between comparisons actually used and the potential total.

[1] The open peer-review reports from two reviewers is available as following:
Broderick J. Peer Review Report For: A simple formula for enumerating comparisons in trials and network meta-analysis [version 2; peer review: 2 approved]. **F1000Research** 2019, 8:38 (https://doi.org/10.5256/f1000research.18976.r43427)
Soomro GM. Peer Review Report For: A simple formula for enumerating comparisons in trials and network meta-analysis [version 2; peer review: 2 approved]. **F1000Research** 2019, 8:38 (https://doi.org/10.5256/f1000research.18976.r44117)

Introduction

The pairwise comparisons reported within each randomized controlled trial are being documented in study-based registers (Shokraneh & Adams, 2017). This lends itself to accurate indexing and enumeration of these comparisons within the studies and then subsequent supply of immediate, highly sensitive and highly specific search results to those wishing to investigate one or more particular comparisons within systematic reviews and meta-analyses or overviews and network meta-analysis (Shokraneh & Adams, 2017, 2018).

To gain a perspective on the absolute effectiveness of a treatment it is ideal to compare all the existing medications with placebo and for relative effects with each other in pairwise comparison trials. However, some of the pairwise comparisons of the medications have not been tested within trials at all. Finally, even if some of the possible pairwise comparisons have been directly tested within trials not all may be eligible for inclusion in a network meta-analysis (Li *et al.*, 2011). This leaves a gap between the research that has been done and the research that should or could have been undertaken and finding this highlights gaps in the fair testing of treatments (Evans *et al.*, 2011).

A two-arm trial will generate one pairwise comparison. A three-arm trial, however, will generate three, and a six-arm study, 15 pairwise comparisons. It is easy to lose track of how many comparisons one study can generate. This is more likely when it comes to the many direct, indirect or mixed comparisons within a network. This paper describes a simple formula for enumerating the possible number of comparisons within a single trial or planned network meta-analysis in advance.

Methods

The formula

Based on the following formula, where n is the number of arms in a single study or network of interventions, N is the number of pairwise comparisons:

$$N=(n*(n-1))/2$$

Where n > 0;

n is a natural number;

Then every intervention is compared to every other intervention except itself so: n*(n-1);

Because N is a bidirectional comparison (X vs. Y = Y vs. X) so: (n*(n-1))/2;

This is an established formula from combinatorics for calculating number of pairs for a number of items in a set.

The networks of 2 to 10 interventions will create networks in shapes of line, triangle, rectangle, pentagon, hexagon, heptagon, octagon, nonagon and decagon, respectively. A visual proof of a network of five interventions and (5*(5-1))/2=10 pairwise comparisons is presented in **Figure 5-1**.

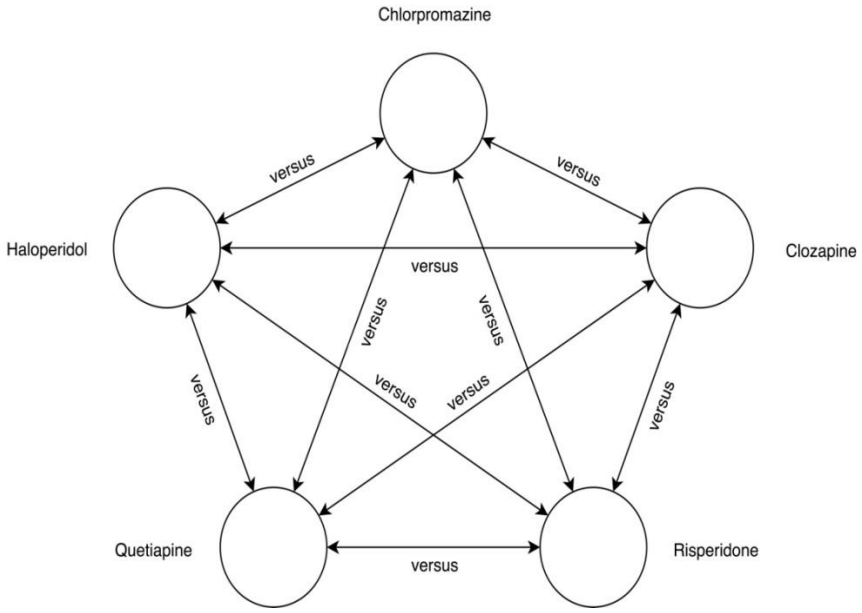

Figure 5-1: Network of five interventions and (5*(5-1))/2=10 pairwise comparisons

Adding any new intervention to the trial or network will create n-1 new pairwise comparisons. For example, where there are 6 arms in a trial—or 6 nodes in network meta-analysis—there will be (6*(6-1))/2=15 comparisons; adding a new intervention (6+1=7) will create 7-1=6 new pairwise direct comparisons in an individual trial and 6 direct or indirect comparisons in a network meta-analysis. Although this formula has been used for other purposes such as Metcalfe's law in telecommunication, its use in the current context is novel.

Testing the formula: working back from existing network meta-analyses

We used the open data (Cipriani, 2018) from our previously published network meta-analysis (Cortese *et al.*, 2018) to re-create and enumerate the comparisons

within the network. Using the direct comparisons reported in the trials within the network, we applied the formula and then compared the number of potential or expected comparisons (formula-derived) and the actual or observed number reported within the network analysis.

Results

Number of direct and indirect comparisons

We built a small study-based register based—thus avoiding the pitfall of multiple counting—containing all 133 included studies in our previous network meta-analysis (Cortese *et al*., 2017, 2018). These trials reported comparisons from 8 interventions. Using our formula, 8 interventions should create 28 unique comparisons: (8*(8-1))/2=28 (Figure 5-2).

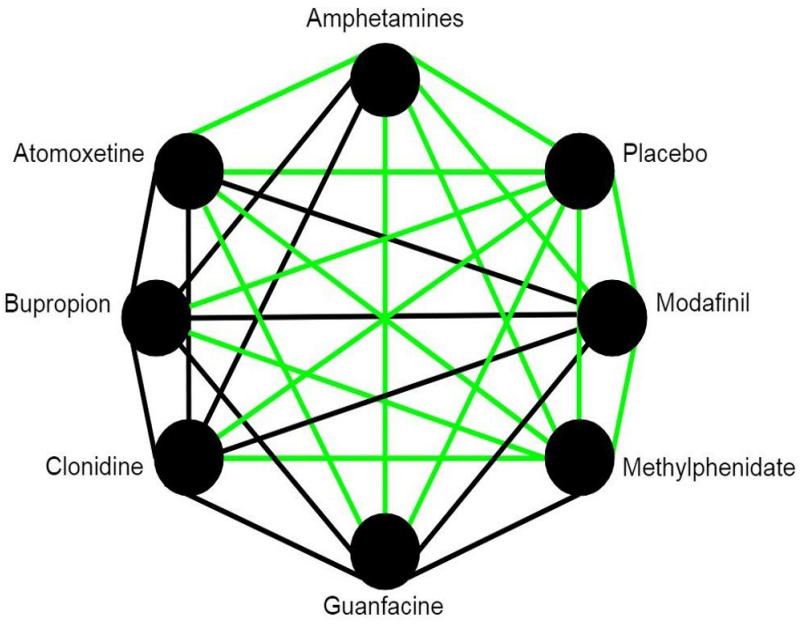

Figure 5-2: All the possible unique bidirectional comparisons of 8 ADHD medications. Only 16 out of 28 comparisons have been directly compared in trials (green lines).

Reported comparisons within the trials

We extracted the separate intervention arms from the open data to re-create the direct comparisons from within trials. The trials had either two or three arms so each study could create either two or three comparisons. As a result, the 133 studies had 163 comparisons, the majority of which were duplicated. After removing these duplicates, this created 16 unique direct comparisons with between 1 and 47 studies per comparison for 8 interventions (Table 5-1). These 16 observed comparisons are 57% of the 28 expected by use of the formula above.

Table 5-1: Direct comparisons extracted from trials and their associated studies

Comparison	Number of studies	Study tag
Amphetamines vs. Atomoxetine	1	Wigal 2005 (SLI381-404, NCT00506727)
Amphetamines vs. Guanfacine	1	Taylor 2001
Amphetamines* vs. Methylphenidate	6	Coghill 2013 (SPD489-325); Efron 1997; Plizka 2000; SPD489-405 (NCT01552915); SPD489-406 (NCT01552902);Stein 2011 (NCT00393042)
Amphetamines vs. Modafinil	1	Taylor 2000
Amphetamines vs. Placebo	21	Adler 2008b (NRP104.303, NCT00334880); Adler 2013 (SPD489-403, NCT01101022); Biederman 2002 (SLI 381-301); Biederman 2007 (NRP104-301, NCT00248092); Biederman 2012 (2008P000971, NCT00801229); Coghill 2013 (SPD489-325); Findling 2011 (SPD 489-305, NCT00735371); Frick 2017 (SPD465-303, NCT00152022); Kay 2009a; Paterson 1999; Plizka 2000; Spencer 2001; SPD489-405 (NCT01552915); SPD489-406 (NCT01552902);Spencer 2006 (SLI381-314, NCT00507065); Spencer 2008 (SPD465-301, NCT00150579); Stein 2011 (NCT00393042); Taylor 2000; Taylor 2001; Weisler 2006 (SLI381-303); Winhusen 2010 (NCT00253747)
Atomoxetine vs. Guanfacine	1	Hervas 2014 (SPD503-316, NCT01244490, EudraCT: 2010- 018579-12)
Atomoxetine vs.	8	Bedard 2015 (NCT00183391); Newcorn 2008 (B4Z-MC-LYBI); Sangal 2006 (B4Z-

Methylphenidate		US-LYAV); Schulz 2012; Spencer 2002a (B4Z-MC-HFBD); Spencer 2002b (B4Z-MC-HFBK); Wang 2007 (NCT00486083, B4Z-MC-LYBR (6934)); Weisler 2012 (NCT00880217)
Atomoxetine vs. Placebo	41	Adler 2008a (B4Z-MC-LYBV, NCT00190931); Adler 2009a (B4Z-US-LYDQ, NCT00190879); Adler 2009b (B4Z-US-LYCU. NCT00190736); NCT00190736); Allen 2005 (B4Z-MC-LYAS); Arnold 2006; Bain 2013 (NCT00429091); Bangs 2007 (B4Z-MC-LYAX); Bangs 2008 (B4Z-MC-LYBX, NCT00191698); Block 2009 (B4Z-US-LYCC, NCT00486122); Dell'Agnello 2009; Dittman 2011; Durell 2013 (B4Z-US-LYDZ, NCT00510276); Gau 2007 (B4Z-TW-S010, NCT00485459); Geller 2007 (B4Z-US-LYBP); Goto 2017 (B4ZJE-LYEE, NCT00962104); Harfterkamp 2012 (NCT00380692); Hervas 2014 (SPD503-316, NCT01244490, EudraCT: 2010- 018579-12); Kay 2009b; Kelsey 2004 (B4Z-US-LYBG); Lin 2016 (NCT00917371); Martenyi 2010 (B4Z-MW-LYCZ, NCT00386581); McRae-Clark 2010 (R21DA018221, NCT00360269); Michelson 2001 (B4Z-MC-LYAC); Michelson 2002 (B4Z-MC-LYAT); Michelson 2003a; Michelson 2003b; Montoya 2009 (B4Z-XM-LYDM, NCT00191945); Newcorn 2008 (B4Z-MC-LYBI); Spencer 1998; Spencer 2002a (B4Z-MC-HFBD); Spencer 2002b (B4Z-MC-HFBK); Sutherland 2012 (NCT00174226); Svanborg 2009 (B4Z-SO-LY15, EUCTR2004-003941-42-SE, NCT00191542); Takahashi 2009 (B4Z-JE-LYBC, NCT00191295); Wehmeier 2012 (B4Z-SB-LYDV, NCT00546910); Weisler 2012 (NCT00880217); Weiss 2005 (B4Z-MC-LYAW); Wietecha 2013 (NCT00607919); Wilens 2008 (B4Z-MC-LYBY, NCT00190957); Wilens 2011 (NCT00528697); Young 2011 (B4Z-US-LYCW, NCT00190775)
Bupropion vs. Methylphenidate	2	Jafarinia 2012; Moharari 2012 (IRCT201012295500N1)
Bupropion vs. Placebo	4	Casat 1989; Reimherr 2005; Wilens 2001; Wilens 2005 (NCT00048360)
Clonidine vs. Methylphenidate	4	Connor 2000; Kurlan 2002; Palumbo 2008 (NCT00031395); van der Meere 1999
Clonidine vs. Placebo	5	Jain 2011 (NCT00556959); Kurlan 2002; Palumbo 2008 (NCT00031395); Singer 1995; van der Meere 1999
Guanfacine vs. Placebo	12	Biederman 2008 (SPD503-301, NCT00152009); Connor 2010 (SPD503-307, NCT00367835); Hervas 2014 (SPD503-316, NCT01244490, EudraCT: 2010- 018579-12); Kollins 2011 (SPD503-206, NCT00150592); McCracken 2016; NCT01069523; Newcorn 2013 (SPD503-314, NCT00997984); Rugino 2014 (NCT01156051); Sallee 2009 (SPD503-304, NCT00150618); Schahill 2001 (NCT00004376); Taylor 2001; Wilens 2015 (SPD503-312, EUCTR2011-002221-21, NCT01081132)
Methylphenidate vs. Modafinil	1	Amiri 2008
Methylphenidate vs. Placebo	47	Abikoff 2009; Adler 2009c (CR011560, NCT00326391); Biederman 2006a (subsample of NCT00181571); Biehl 2016; Bron 2014; Buitelaar

		1996; Casas 2013 (EudraCT: 2007-002111-82); Childress 2009 (CRIT124E2305, NCT00301236); Coghill 2013 (SPD489-325); Cook 1993; CRIT124DUS02; Dopfner 2003; Findling 2008 (NCT00444574); Ginsberg 2012 (EUCTR2006-002553-80-SE); Goodman 2016 (NCT00937040); Greenhill 2002; Greenhill 2006b (CRIT124E2301); Grizenko 2012; Herring 2012 (NCT00475735); Huss 2014 (CRIT124D2302, EUCTR2010-021533-31-DE, NCT01259492); Kooij 2004; Kurlan 2002; Lin 2014 (NCT00922636); Medori 2008 (LAMDA-I EUCTR2004-000730-37, NCT00246220); Newcorn 2008 (B4Z-MC-LYBI); Palumbo 2008 (NCT00031395); Philipsen 2015 (EUCTR2006-000222-31-DE, ISRCTN54096201); Plizka 2000; Reimherr 2007; Rosler 2009; Schrantee 2016 (NTR3103, EUCTR2010-023654-37-NL); Simonoff 2013 (ISRCTN683849); SPD489-405 (NCT01552915); SPD489-406 (NCT01552902); Spencer 1995; Spencer 2002a (B4Z-MC-HFBD); Spencer 2002b (B4Z-MC-HFBK); Spencer 2005; Spencer 2007 (CRIT124E2302); Stein 2011 (NCT00393042); Takahashi 2014 (NCT01323192); Taylor 1987; van der Meere 1999; Weisler 2012 (NCT00880217); Wender 2011; Wigal 2004; Wigal 2015 (NCT01239030)
Modafinil vs. Placebo	8	Arnold 2014 (C1538/2027/AD/US, NCT00315276); Biederman 2005 (Study 311 Cephalon); Biederman 2006b; Greenhill 2006a (Study 309 Cephalon); Kahbazi 2009; Rugino 2003; Swanson 2006; Taylor 2000

* Amphetamines include Lisdexamfetamine.

Direct comparisons eligible for network meta-analysis

Among five networks reported in the final paper, the number of comparisons in these five network meta-analyses, however, varies from 6 (for 3 networks) to 11 (for 1 network) and 13 (for 1 network) (**Figure 5-3**). As visualized in **Figure 5-3**, only 21.42% to 46.42% of comparisons were eligible for pairwise meta-analysis (**Table5-2**).

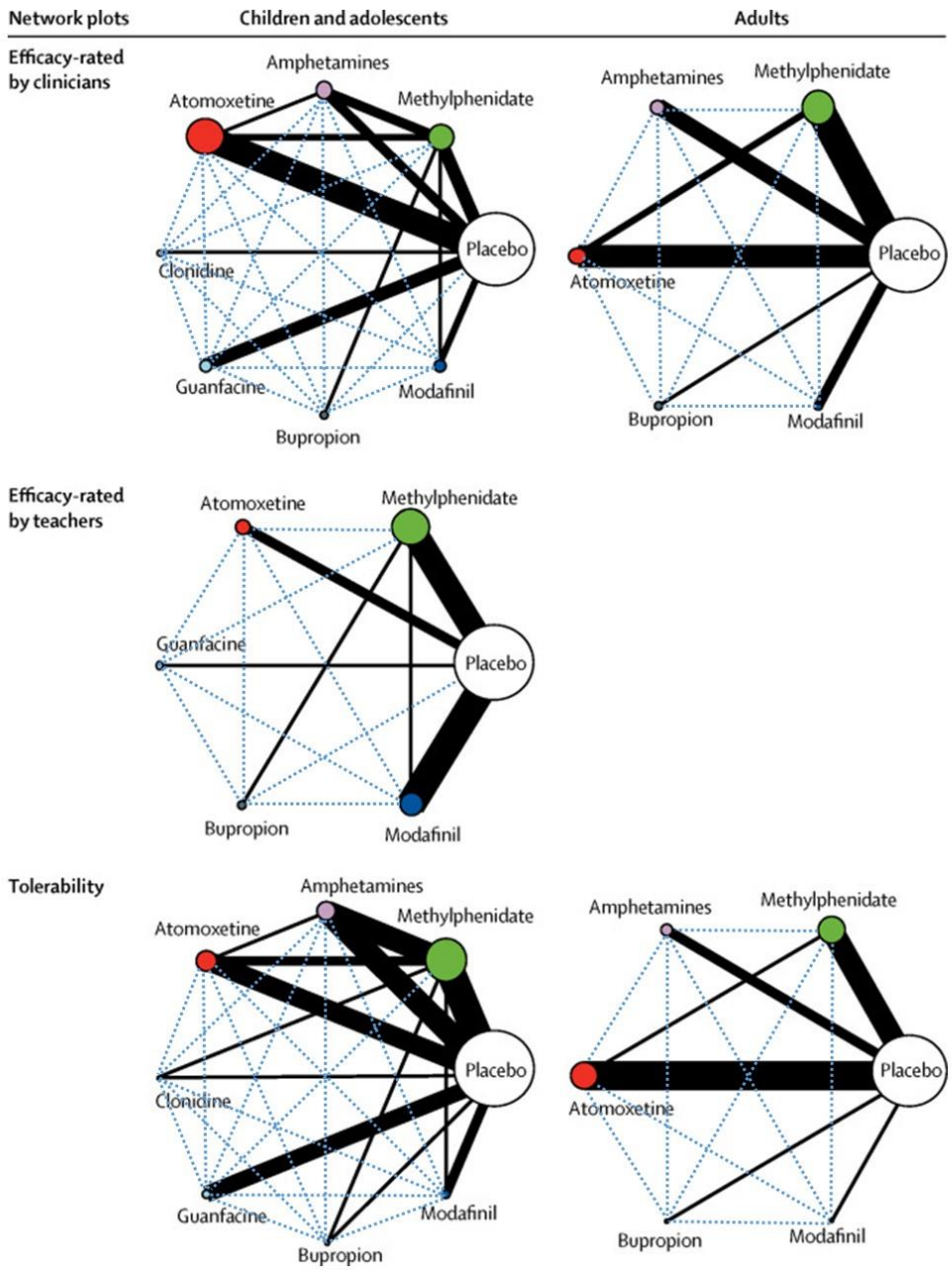

Figure 5-3: Direct and indirect comparisons in the network meta-analysis of 8 interventions for primary outcome. Dark lines are eligible comparisons for pairwise meta-analysis, added dotted blue lines show indirect comparisons. This image has been modified from Cortese *et al*. (2018) under Creative Commons Attribution License (CC BY).

Table 5-2: Comparisons from the body of evidence

Source of comparisons	Type of comparisons		Eligibility for analyses		# of comparisons	% of comparisons
	Direct	Indirect	Eligible	Ineligible		
Formula	√	√	√	√	**28=**(8*(8-1))/2	100.00
Randomised trials	√	×	√	√	**16** (Table 5-1)	57.14
Pairwise meta-analysis	√	×	√	×	**6-13** (Figure 5-3)*	21.42 to 46.42
Network meta-analysis	√	√	√	√	**28** (Figure 5-2)	100.00

* There are five networks in Figure 5-3 and each has 6, 11, or 13 eligible comparisons. Three out of 16 comparisons from trials have not been included in any of five network plots.

Comparisons in network meta-analysis plots

From Figure 5-3, we can calculate that about 42% of comparisons expected through use of the formula have not been tested directly in trials. This is a direct evidence-gap. The number of missing comparisons varies between nine out of 15 in three networks with six interventions, 17 out of 28 in one network with eight interventions, and 15 out of 28 in another network with eight interventions (Figure 5-3). However, all 28 comparisons expected by use of the formula were utilized and reported within the network meta-analysis. It is possible that some of the comparisons predicted by the formula would have been deemed ineligible—either by adherence to a network review protocol or through post hoc exclusions—but this was not the case in this particular review (Figure 5-4). This diagram shows that only some of the comparisons from trials in study-based register could be included in pairwise meta-analysis. In addition, the number of comparisons in network meta-analysis (calculated by formula) is larger and inclusive of all the comparisons in the network of interventions and includes all

the possible unique comparisons even if the comparisons are not in trials or in pairwise meta-analysis.

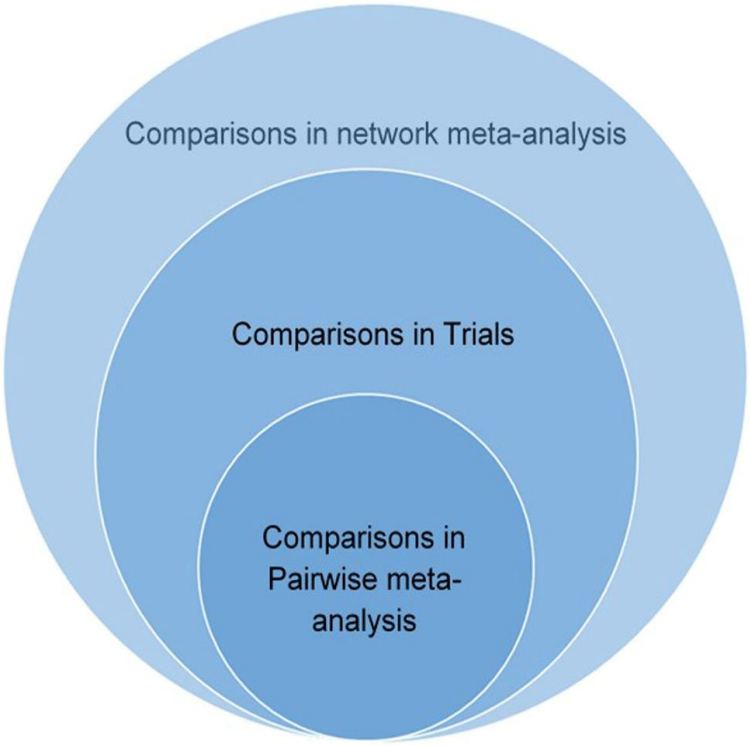

Figure 5-4: Venn diagram showing the coverage of comparisons by the network meta-analysis (from formula), and pairwise meta-analysis (from network plots), and trials (from study-based register)

Discussion

This formula can be employed when estimating the total number of comparisons (direct and indirect combined) theoretically possible within a proposed network meta-analysis. It would be possible that there would sometimes be a discrepancy between the number of comparisons theoretically possible and those actually employed within any given network meta-analysis. The formula would highlight

this for researchers and readers and, before and after analyses, facilitate descriptions of why particular comparisons have not been included.

Conclusion

The formula produces an accurate enumeration of the potential comparisons within a single trial or network meta-analysis.

Any shortfall between the full potential of the data and the actual number of comparisons within a network meta-analysis should be possible to explain through reference to pre-stipulated eligibility criteria or post hoc exclusions.

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PAPER 6

Classification of all pharmacological interventions tested in trials relevant to people with schizophrenia: A study-based analysis

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PAPER 6

Classification of All Pharmacological Interventions Tested in Trials Relevant to People with Schizophrenia: A Study-Based Analysis

I have neither the ability, knowledge, time, or space to classify all present-day therapies. All I feel capable of is a rough classification …

Archie Cochrane, 1971

Abstract

Background: Systematic reviews are time-consuming. Information Specialists are maintaining study-based registers to facilitate efficient conduct of these types of reviews. Classification of study-level meta-data - such as interventions – can result in much more accurate searches, saving time in the early steps of systematic reviewing.

Objective: To classify all pharmacological interventions from all schizophrenia trials.

Methods: We used Cochrane Schizophrenia's Study-Based Register as the source of trials, Emtree and MeSH for synonyms, AdisInsight and CT.gov for research drugs and WHO ATC for marketed drugs.

Results: One third of tested interventions on patients with schizophrenia are pharmacological (816; belonging to 106 clinical classes) with antipsychotic drugs being the most researched (15.1%). Only 528 of these medications are listed in WHO ATC. Around one third of these drug interventions are seen only in research

(236; from 21 pharmacological/biochemical classes). Within the pharmacological evaluations we identified 28 'qualifiers' including dose, route, and timing of drug delivery.

Conclusion: Classification of medication interventions from trials requires use of many sources of information none of which are inclusive of all drugs. The limitations of these sources should be understood. Classification of non-pharmacological interventions is now a priority.

Key Messages for librarians – practice, policy, future research

- Classification of interventions can help systematic reviews to start with data extraction.
- WHO ATC is limited with a major gap for regional drug information from non-English speaking world - specifically drugs discovered in Japan.
- Current searches based on the *known* drug names and synonyms may not retrieve all the relevant studies but only the studies from English-speaking world.
- Drugs used in research are not being comprehensively indexed anywhere.
- Most interventions for people with schizophrenia tested in trials are not medications and these should be a priority for future classification.

Background

To test the effects of new drugs, researchers often use the randomised controlled trial (RCT) study design. In these studies, participants are randomly assigned to different treatment groups. After a period of follow-up, outcomes are compared (Clarke *et al*., 2019). Related studies are often repeated to increase the certainty and applicability of findings. All relevant evidence from trials helps inform policy and clinical decisions and systematic reviews of the RCTs help this happen. To *conduct* a systematic review researchers follow a process that may include some or all these steps (Higgins & Green, 2011):

1. Searching all relevant databases;
2. Screening the title and abstract of search results for review eligibility;
3. Obtaining full reports of potentially eligible search results;
4. Screening full reports to identify the included studies;

5. Concatenating multiple reports of the same study to avoid multiple counting;
6. Extracting quantitative and qualitative data from included studies;
7. Analysing data; and
8. Writing the final report.

Information Specialists' involvement in systematic reviewing improves the quality of searches (Koffel & Rethlefsen, 2016; Meert, Torabi, & Costella, 2016). During the past 25 years – with the development of specialised registers in the Cochrane Collaboration – the role of the Information Specialist has developed to involve screening and the development of subject-specific reference-based bibliographic registers of RCTs (Metzendorf & Featherstone, 2018). Furthermore, emergence of study-based registers, a sub-type of specialised registers, upgraded the Information Specialists' role to Data Scientists (Shokraneh & Adams, 2019). In study-based registers, all references or reports of the same study even its sibling reports (Hamad 2012) such as pre-trial intervention development or post-trial qualitative or economic studies are linked to their study record – the meta-record (Shokraneh & Adams, 2017). It is then possible to search *study* fields (e.g. health care condition, interventions, outcomes – so-called PICO (Shokraneh, 2016)) in addition to reference fields (e.g. title, abstract, etc.). If the reference-based registers were like a stack of books in one subject area with no classification, a study-based database could be compared to an organised library with a classification system based on PICO (Shokraneh & Adams, 2019). For this level of organisation to be useful, however, PICO meta-data has to be extracted from each study using existing or new controlled vocabularies.

While Medical Subject Headings (MeSH), Excerpta Medica Tree (Emtree), and other controlled vocabularies are used to assist information retrieval, a rigorous controlled vocabulary based on the PICO meta-data has not yet been published. This paper addresses this deficit for pharmacological interventions relevant to

people with schizophrenia. Such classifications can increase precision and recall to 100% (Ingwersen & Järvelin, 2005). Then, by the time a review team is supplied with studies, the Information Specialist has completed the first five steps outlined above and time-saving [waste-reduction] is considerable (Shokraneh & Adams, 2019).

Objective

This work reports the development steps of a classification schema for the tested pharmacological interventions in RCTs of people with schizophrenia and shares this classification publicly.

Methods

Source of data: Cochrane Schizophrenia Group's Study-Based Register of Trials

This database was started nearly 30 years ago (Adams & Gelder, 1994) to facilitate the systematic review process in the Cochrane Schizophrenia Group. Currently, it supports running the searches for over 300 maintained Cochrane reviews (increasing at rate of 25-30/year). This database is being maintained using the MeerKat 1.6 computer program and details of this register are described elsewhere (Cochrane Schizophrenia Group, 2019).

Timeline and resource

This research took place between 17 December 2014 and 6 January 2019 by a full-time Information Specialist.

Piloting

In December 2014, the database already contained 9200 intervention labels for the approximately 18,500trials. It seemed unlikely that a new intervention was tested in every second study. Investigating only interventions starting with the letter 'A' showed that over half were duplicates undetected by the machine because of:

- [Human] errors in spelling;
- Differences between American and British spelling;
- Unique entry of synonyms/brand names rather than use of generic name;
- Indexing aspects of *administration* or *actions* rather than the drug itself.

Despite the attempted development of a standard protocol for indexing PICO meta-data in April 2004 as part of the PsiTri project (EU-PSI Coding Manual Working Group, 2004) there was clearly a problem in consistency.

Data cleaning

To solve these problems, FS corrected spelling errors, separated the interventions from intervention qualifiers (subheadings) and made sure a single preferred controlled term was employed instead of multiple synonyms of the same drug. The project then required development of a controlled vocabulary and classification system in order to facilitate the process of systematic reviewing.

Current subjective classification in titles of Cochrane reviews

FS initially relied on the author-led classification within Cochrane Schizophrenia's existing systematic reviews. These 324 reviews, although the largest sample of maintained systematic reviews in existence, still cover only a subset of pharmaceutical approaches tested in trials. Currently, classification from titles

would generate many omissions. In addition, even within these titles, there are inconsistencies and synonyms. Clearly, a controlled vocabulary is needed.

Choice of objective controlled vocabulary

FS investigated AdisInsight, Emtree, MeSH, and British National Formulary, and World Health Organisation's Anatomical Therapeutic Chemical (WHO ATC) for their indexing of drugs starting with the letter 'A'.

- AdisInsight - the most comprehensive source for recent research drugs (sourcing part of its data from ClinicalTrials.Gov);
- BNF - suggested practical *clinical* classes for some drugs but coverage was limited.
- Emtree and MeSH - solely useful in identifying different synonyms of old research drugs because of their longevity - not good at identifying drugs used outside Western Europe and the English speaking world;
- WHO ATC - the best available option for approved, marketed drugs;

None of these controlled vocabularies covered all 'A' drug interventions in the register of trials. Because it is a priority for Cochrane reviews to support clinical practice, the decision was taken to use WHO ATC. For every compound, FS indexed generic drug name, WHO ATC code, clinical class, and pharmacological action class or chemical structure/group class. Where the intervention in RCT referred to more than one drug (i.e. a class of drugs), FS used an asterisk after the term to indicate this (see Appendix).

Theoretical Context

The classification scheme in this paper is partly following the Practicalist approach to knowledge organization (Hjørland 2016a) because of using WHO ATC which is being updated centrally and is stable. On the other hand, the classification used

by the systematic reviewers in Cochrane reviews follows Consensus-based approach as agreed among experts (Hjørland 2016a). We also utilised a facet-analytic approach in the current classification because we were compelled to classify all reported interventions and their facets – such as route of administration, dosage, and, in some cases, flavour – from each trial. Many trials are using a combination of interventions and some compare an aspect (facet) of one intervention (i.e. oral versus injection). Although Hjørland (2016b) verifies the strong position of this approach for being the 'most explicit' and 'pure theoretical approach', we found it practical to classify single-intervention trials using this approach to cover the compared facets of one intervention between two patient groups.

Sources of synonyms and dealing with non-marketed drugs

During a drug's life cycle, a drug may have a chemical name, research names, a generic name, and brand names. These names also reflect different phases of drug development (Scutti, 2016). Although WHO ATC is the most comprehensive source of classification of marketed drugs, it does not support search for synonyms. FS, therefore, used Emtree (inclusive of MeSH terms) for this and, in all cases, recorded the generic name, later using WHO ATC to find the drug's class name, tree and number.

For drugs not in the WHO ATC:

1. AdisInsight was used to cover recent drugs in RCTs; then
2. ClinicalTrials.Gov searched to cover recent drugs not in AdisInsight; then
3. Google searched (inclusive of Google Books) to cover old drugs; and finally
4. Classes suggested/claimed within the RCT reports used to cover drugs unclassified in other sources.

For a *marketed* drug not within WHO ATC, the same data as for marked drugs were recorded, with the nearest possible WHO ATC code and the uncertainty in last digits and letter was expressed by use of question marks '?'.

Drugs not on enter the market and their development status

We considered a drug to be a 'drug only used in research' if it met the following criteria:

- Not listed in WHO ATC; and
- Despite searching current major relevant resources no wide use was identified for the drug.

During the indexing process, FS recorded the last used name of the drug, development status, potential clinical class, and potential pharmacological action or chemical structure/group (Table 6-1).

Table 6-1: Development status of drugs

Development Status		Description
Currently marketed for clinical practice	WHO	Listed in WHO ACT.
	Non-WHO	Not listed in WHO ACT.
	If not marketed	
Drugs used in research†	Developing-Adis	Status 'developing' in RCT cited in AdisInsight.
	Developing-CT.Gov	Status 'developing' in RCT cited in ClinicalTrials.Gov.
	Developing	Used as research drug after 2000 in at least one RCT.‡
	If not marketed but clearly stopped	
Stopped	Stopped-Adis	Status 'stopped' in RCT cited in AdisInsight.
	Stopped-CT.Gov	Status 'stopped' in RCT cited in ClinicalTrials.Gov.
	Post-Marketing Withdrawal§	Originally marketed and then withdrawn from market.
	Stopped	Not used after 2000 in any RCT.
	If not marketed, not researched, nor stopped	
Unclear	Unclear-Adis	No report of RCTs cited in AdisInsight.
	Not Available	No traceable evidence about the development state.
	Not Marketed	No traceable country of market.

†Drugs may have established use for other conditions.
‡We used the year 2000 as arbitrary break-point.
§ 'Market' refers to *legal* market for *humans* - some drugs are considered as illicit drugs, doping drugs (abused in humans and in horse-racing), and some are still being used in veterinary medicine.

Double-checking

During cleaning of data it became clear that some interventions were missing from the original Cochrane Schizophrenia Group's Register of study records. Human errors are inevitable in a task of this size but these errors make searches unreliable. FS double-checked all indexing and, in the case of discrepancy or complexity, consulted a specialist psychiatrist.

Indexing principles

We indexed what patients had been 'randomised to' although this was not always straightforward. For example, sometimes participants were randomised to a combination of drugs or two different doses of the same drug. In these cases, we applied qualifiers as learnt from pilot study. We also tried to follow the indexing principles:

- *Literary Warranty* (Rodriguez, 2008): the drug enters the classification system if it has been used in one of the treatment arms (or as part of the randomised treatment) in one or more RCTs.
- *Co-ordination* (Bachrach & Charen, 1978): when impossible to describe an intervention using a single index term more than one concept or qualifiers were used to describe the intervention.
- *Multiplicity* (Bachrach & Charen, 1978): indexing covered all interventions in the randomised arms- even if the drug was not specific or was not a major part of the treatment.
- *Specificity* (Bachrach & Charen, 1978): indexing focused on the most specific intervention rather than broad classes.

In rare cases, pragmatic decisions had to be made. For example, where researchers have randomised people to a *class* of drug –without naming the specific compounds– drug-level indexing was impossible.

Results

Existing classification within the systematic reviews

After nearly 30 years of working still only 10% of RCTs have been included in systematic reviews produced by the Cochrane Schizophrenia Group – but, limited though this is, these trials are likely to represent a subset of comparisons that are considered important by clinicians, policymakers, researchers and consumers of care. This was the starting point for the classification of pharmacological interventions (summarised in Table 6-2) and identified 19 classes of drugs. Thirteen classes, however, were based on pharmacological action of drugs, three on clinical action and the last three based on chemical group/structure.

Table 6-2: Classification of pharmacological interventions as described in Cochrane schizophrenia reviews

#	Class of Intervention	Nature of Class
1	Acetylcholinesterase inhibitors	Pharmacological Action
2	Amphetamines	Chemical Group/Structure
3	Anticholinergics	Pharmacological Action
4	Antidepressants	Clinical Action
5	Antiglucocorticoid and related treatments	Pharmacological Action
6	Antioxidants	Pharmacological Action
7	Antipsychotics	Clinical Action
7.1	Atypical antipsychotics=New generation antipsychotics	Clinical Action
7.1.1	Newer atypical antipsychotics	Clinical Action
7.2	Typical antipsychotics=First-generation antipsychotics	Clinical Action
7.2.1	Low-potency first-generation antipsychotics	Clinical Action
8	Benzodiazepines	Chemical Group/Structure
9	Beta-adrenergic-blocking agents (beta blockers)	Pharmacological Action
9.1	Central action beta-blockers	Pharmacological Action
10	Calcium channel blockers	Pharmacological Action
11	Gamma-aminobutyric acid agonists	Pharmacological Action
12	Glutamatergic drugs	Pharmacological Action
13	HMG-CoA reductase inhibitors (statins)	Pharmacological Action
14	Mood stabilisers	Clinical Action
15	Non-antipsychotic catecholaminergic drugs	Pharmacological Action
16	Polyunsaturated fatty acid supplementation	Chemical Group/Structure
17	Selective noradrenaline reuptake inhibitors	Pharmacological Action
18	Vesicular monoamine transporter inhibitors	Pharmacological Action

One third of tested schizophrenia treatments are drugs

After cleaning 9,200 interventions, 2,792 remain. About one third (816) are pharmacological interventions, 71% of which are on the market (Table 6-3).

Table 6-3: Development status of pharmacological interventions from schizophrenia RCTs

Development status		Number (% of total)	
Currently marketed†	WHO	528 (65.0)	580 (71.1)
	Non-WHO	52 (6.4)	
Drugs used in research‡	Developing-Adis	33 (4.0)	45 (5.5)
	Developing-CT.Gov	5 (0.6)	
	Developing	7 (0.9)	
Stopped	Stopped-Adis	72 (8.8)	150 (18.4)
	Stopped-CT.Gov	1 (0.1)	
	Post-Marketing withdrawal§	13 (1.6)	
	Stopped	64 (7.8)	
Unclear	Unclear-Adis	29 (3.9)	277 (34.0)
	Not Available	25 (3.0)	
	Not Marketed	223 (27.3)	

†Either for clinical practice or use as products consumed by humans.
‡Research for the purpose of clinical practice for people with schizophrenia.
§ 'Market' refers to *legal* market for *humans* - some drugs are considered as illicit drugs, doping drugs (abused in humans and in horse-racing), and some are still being used in veterinary medicine.

Most (65%) have been classified in WHO ATC (528 drugs). In addition, 52 drugs were not present in WHO ATC but are in the market (Table 6-4). Most of these 52 are used as chemical food additives; however, some of them were country-

specific drugs such as Blonanserin, Spiperone, Perospirone, and Timiperone (Japan).

Table 6-4: Non-WHO marketed pharmacological agents from Schizophrenia RCTs (sorted by clinical class)

Intervention	Code	Clinical Class	Pharmacological Action/Chemical Class
Sydnocarb	N06B???	Agents Used for ADHD and Nootropics	Dopamine Uptake Inhibitors
Benserazide	N04BA??	Anti Parkinson Drugs	Dopaminergic Agents
Deutetrabenazine	N07XX??	Anti Parkinson Drugs	Vesicular Monoamine Transporter 2 Inhibitors
Hopantenic Acid	N04????	Anti Parkinson Drugs	Not Available
Mepiprazole	N05AX??	Antidepressants	Phenylpiperazine Derivatives
Tandospirone	N06AB??+N05BE??	Antidepressants+Anxiolytics	Serotonin Reuptake Inhibitors
Latrepirdine	R06AX??	Antihistamines for Systemic Use	Acetylcholinesterase Inhibitors
Sulfadoxine	J01ED??	Antimalarials	Long-Acting Sulfonamides
Blonanserin	N05AX??	Antipsychotics	Not Available
Carpipramine	N05AD??	Antipsychotics	Butyrophenone Derivatives
Clocapramine	N05AX??	Antipsychotics	Imidobenzyl Derivatives
Clotepine (Clorotepine)	N05AX??	Antipsychotics	Perathiepin Derivatives
Nemonapride	N05AL??	Antipsychotics	Benzamides
Oxyprothepin	N05AX??	Antipsychotics	Not Available
Perlapine	N05AH??	Antipsychotics	Diazepines, Oxazepines, Thiazepines and Oxepines
Perospirone	N05BE??	Antipsychotics	Azaspirodecanedione Derivatives
Spiperone	N05AD??	Antipsychotics	Butyrophenone Derivatives
Timiperone	N05AD??	Antipsychotics	Butyrophenone Derivatives
Delorazepam	N05BA??	Anxiolytics	Benzodiazepine Derivatives
Cereobiogen	A03AX??	Drugs for Functional Gastrointestinal Disorders	Not Available
Silicon Dioxide	A03AX13	Drugs for Functional Gastrointestinal Disorders	Not Available
Chromium Picolinate	A10X???	Drugs Used in Diabetes	Not Available
Lodenafil Carbonate	G04BE??	Drugs Used in Erectile Dysfunction	Phosphodiesterase Type 5 Inhibitors
Berberine	V06D???	General Nutrients	Not Available
Caffeic Acid	V06D???	General Nutrients	Not Available
Carnosine	V06D???	General Nutrients	Not Available
Epigallocatechin Gallate	V06D???	General Nutrients	Not Available
Essential Fatty Acids*	V06D???	General Nutrients	Not Available
Gamma-Aminobutyric Acid	V06D???	General Nutrients	Not Available
Gastrodin	V06D???	General Nutrients	Not Available
Glucuronolactone	V06D???	General Nutrients	Not Available
Lecithin	V06D???	General Nutrients	Not Available
Linoleic Acid	V06D???	General Nutrients	Not Available
Magnesium Glutamate	V06D???	General Nutrients	Magnesium Compounds
Magnesium Threonate	V06D???	General Nutrients	Not Available
Protoporphyrin Disodium	V06D???	General Nutrients	Not Available
Quercetin	V06D???	General Nutrients	Not Available
Saccharin	V06D???	General Nutrients	Not Available
Sodium Butyrate	V06D???	General Nutrients	Not Available
Sodium Glutamate	V06D???	General Nutrients	Amino Acids
Succinic Acid	V06D???	General Nutrients	Not Available
Tetrahydropalmatine	V06D???	General Nutrients	Not Available
Penehyclidine	N05CM??	Hypnotics and Sedatives	Anticholinergic Agents
Arginine Aspartate	B05XB??	I.V. Solution Additives	Amino Acids
Creatine	B05XB??	I.V. Solution Additives	Amino Acids
Phenylalanine	B05XB??	I.V. Solution Additives	Amino Acids

Taurine	B05XB??	I.V. Solution Additives	Amino Acids
Theanine	B05XB??	I.V. Solution Additives	Amino Acids
Tyrosine	B05XB??	I.V. Solution Additives	Amino Acids
Batyl Alcohol	V06D???	Not Available	Not Available
Levamlodipine Maleate	C08CA??	Not Available	Calcium Channel Blockers
Dyhydroprogesterone	G03????	Sex Hormones and Modulators of the Genital System	Selective Estrogen Receptor Modulators

WHO ATC classes

There are 13 major anatomical categories in WHO ATC and, predictably, most (49.3 %) of the drugs in the Cochrane Schizophrenia Register belong to the Nervous System Drugs. At the finer 'clinical class' level, these drugs belong to 106 classes – the antipsychotics being the most researched (15.1%). WHO ATC also provides a 'pharmacological action and/or chemical structure' class (Table 6-5). Drugs may affect more than one receptor and have more than one pharmacological action. FS grouped the major pharmacological mechanism of action of research drugs into 21 major categories of either pharmacological action or biochemical group. Over 40% of research drugs target one or more Serotonin, Dopamine, Acetylcholine, and GABA A receptors.

Table 6-5: Classes of pharmacological interventions in schizophrenia RCTs

Anatomical physiological systemic class	M
Alimentary tract and metabolism	74
Anti-infectives for systemic use	24
Anti-neoplastic and immunomodulating agents	12
Anti-parasitic products, insecticides and repellents	8
Blood and blood forming organs	19
Cardiovascular system	61
Genito-urinary system and sex hormones	21
Hormonal preparations, excl. sex hormones and insulins	10
Musculo-skeletal system	11
Nervous system	286
Respiratory system	18
Sensory organs	4
Various	32

Clinical class	M	RD
Acid related disorders drugs	12	0
Addictive disorders drugs	7	1
ADHD drugs and nootropics	20	1
Analgesics	19	1
Anesthetics	15	2
Anti-bacterials	13	0
Anti-dementia drugs	7	4
Anti-depressants	43	12
Anti-emetics and anti-nausea drugs	0	1
Anti-epileptics	19	3
Anti-histamines	8	0
Anti-hypertensives	13	1
Anti-malarials	8	0
Anti-mycobacterials	5	0
Anti-neoplastics	0	1
Anti-obesity drugs	7	0
Anti-Parkinsonism drugs	27	17
Anti-psychotics	80	113
Anxiolytics	18	6
Constipation drugs	5	0

Pharmacological class	M*	RD*
Adrenergic receptor antagonists	0	3
Alkaloids	9	0
Amino acids	9	4
Amino acids/monoamine oxidase inhibitors	0	6
AMPA receptor modulators	0	4
Antiadrenergic agents	11	0
Anticholinergic agents	18	3
Anticholinesterases	8	0
Barbiturates	7	0
Benzodiazepines	25	0
Benzamides	8	0
Beta blocking agents	14	0
Butyrophenone derivatives	13	7
Calcium channel blockers	7	0
Diazepines, oxazepines, thiazepines, oxepines	7	0
Dihydropyridine derivatives	6	0
Dopaminergic agents	15	35
Fatty acid derivatives	5	0
GABA-a receptor modulators	0	10
Glutamate receptor modulators	0	8

		Convulsants	0	1	Glycine transporter inhibitors	0	7
		Diabetes drugs	11	0	HMG CoA reductase inhibitors	6	0
		Diagnostic agents	6	0	Indole derivatives	5	0
		Gastrointestinal disorders (functional) drugs	7	1	Monoamine oxidase inhibitors	22	0
		General nutrients	20	0	Muscarinic receptor agonists	0	3
		Hormones - other	6	0	Neurokinin antagonists	0	3
		Hormones - sex and modulators	20	0	Neurotransmitter receptor modulators	0	3
		Hypnotics and sedatives	25	6	Nicotinic acetylcholine receptor modulators	0	11
		I.V. solution additives	8	0	NMDA receptor agonists/antagonists	0	6
		Immunosuppressants	5	0	Opioid anesthetics	8	3
		Lipid modifying agents	10	0	Phenothiazines	21	6
		Metabolites	0	2	Phosphodiesterase inhibitors	0	5
		Muscle relaxants	7	0	Serotonin receptor agonists/antagonists	10	40
		Ophtalmologicals	5	0	Sigma receptor agonists/antagonists	0	3
		Vitamins	14	0	Sympathomimetics	10	0
		Unclear	0	65	Tertiary amines	7	0
					Thioxanthene derivatives	5	0
					Unclear	0	61
TOTALS	580		470	238		256	231

* M – Marketed drug RD – Drug used only in research

Qualifiers (subheadings)

The most frequently used 'qualifiers' from the perspective of systematic reviews were used to develop the main set employed in the final classification (Table 6-6).

Table 6-6: Qualifiers of pharmacological interventions used in Cochrane Schizophrenia systematic reviews or RCTs

Qualifier Type			Example			Source
Chemical	binder		fluphenazine enanthate	*vs*	fluphenazine decanoate	RCT
	duration of action		long-acting	*vs*	short-acting	
	isomer		cis-	*vs*	trans-	
Cost			free	*vs*	full cost	
Delivery	injection depth		20mm	*vs*	50mm	
	injection site		gluteal	*vs*	deltoid injection	
	tablet		orally disintegrating tablet	*vs*	standard tablet	
	with meals		fasting	*vs*	With food	
Dose	change	↓	decreasing	*vs*	maintaining dose	Cochrane review
		↑	increasing dose	*vs*	maintaining dose	
	oral/IM/IV		10 mg	*vs*	20 mg	
	plasma level titration		low	*vs*	high	RCT
Form	brand		brand	*vs*	generic	
	flavour		strawberry	*vs*	vanilla	
	size of tablet		small	*vs*	large	
Polypharmacy	Antipsychotic		monotherapy	*vs*	polypharmacy	Cochrane review
	decrease		maintaining	*vs*	decreasing numbers	
	instigate	Other drugs	polypharmacy (combination)	*vs*	treatment as usual	
Regimen	as required		as required	*vs*	treatment as usual	
	instigation		immediate	*vs*	delayed	RCT
	intermittent		3 days per week	*vs*	all week	Cochrane review
	maintenance		continuation	*vs*	discontinuation	
	switching		switching	*vs*	maintaining	
	switching - method		sudden	*vs*	tapering off	
Route			oral	*vs*	injection	RCT
Timing	frequency		once a day	*vs*	twice a day	
	periodicity		three weeks	*vs*	six weeks	
	time of day		morning	*vs*	evening	

One third of tested schizophrenia drugs are not on the market

There were 236 pharmacological interventions developing, in unclear development state or stopped (29% of RCT-tested schizophrenia drugs). The majority of research drugs were targeting nervous system and were purported antipsychotics, anti-Parkinson agents, and antidepressants. The clinical purpose of 65 of these drugs (27.5%) is not available.

As available in Appendix 6-1, only 19 of these drugs (8%) were withdrawn post-marketing (Methitural, Phencyclidine, Benzquinamide, Flurothyl, Lysergic Acid Diethylamide (LSD), Picrotoxin, Benactyzine, Etryptamine, Pheniprazine, Azacyclonol, Carphenazine, Mepazine, and Piperacetazine). The rest either are still being researched, stopped, or are in unclear development state.

Qualitative results

We already discussed the benefits of a study-based register for preventing errors in systematic reviewing (Shokraneh & Adams, 2017; Shokraneh & Adams, 2019). However, the current experience adds two additional errors that could be prevented because of the use of a study-based register:

- *Misjudgement of development status:* without full availability of all reports of study, it is easy for systematic reviewers to misclassify the status of the study as 'ongoing' - where details are incomplete and not enough to include or exclude a study in a review. We found that standardisation of interventions led to much merging of what we had previously thought of as separate studies into one. The better indexing resulted in more accurate concatenation and complete study records so that a more

informed decision could be made about how to use the study data within the review.

- *Exclusion because of unknown intervention names:* systematic review authors search for all *known* drug names - as they – and even the Information Specialists working with them - are unaware of the unknown names of the same drug. Clearly, there are many names for even very widely used compounds that are unfamiliar to many. Use of generic names for indexing, at the study level, helps avoid failing to identify studies which originate from places using very unfamiliar drug names.

Discussion

This research is the first effort to classify pharmacological interventions tested within a defined group of RCTs. The source of RCTs – the Study-Based Register of the Cochrane Schizophrenia Group – has coverage from 1949 (the date of the very first RCT (Kitzinger *et al*., 1949)) to the present and contains any document type or language. Accessing this comprehensive database affords opportunity to categorise all drugs tested in one important corner of health care. Information Specialists with intimate knowledge of a certain medical speciality can classify the relevant interventions and have the best chance of keeping abreast of the changing names of drugs. Having said this, this study found important trials that buried in the register for over two decades that had not been included in relevant reviews because the brand name of the drug was unknown in Western medicine.

Heterogeneous pharmacogenetic profile of two patients can contribute to the treatment response for certain outcome on certain receptor more than the other. If we add the different states and stages of psychosis development among the patients with schizophrenia and complexity of dealing with negative, positive and cognitive symptom domains of schizophrenia (Steeds 2015), we should also consider the heterogeneity caused by targeting an aspect of illness (symptoms, state or stage of illness (Lieberman and Fall 2018), and co-morbidities), an aspect of patient population (age, sex, and genetics), an aspect of intervention (receptor, dosage, route of and administration), a specific outcome or adverse effect (weight gain), a specific setting (low-income country, emergency department, and outpatients). Altogether, such heterogeneities in PICOS elements could be the reason for developing so many pharmacological agents for treating people with schizophrenia.

Classifications should be used in their own context (Bowker 1998). I identified many medications in WHO ATC with anatomical classes *irrelevant* to

schizophrenia yet the pharmacological action *was* relevant. My classification system was developed to be used in the contexts of interventions from trials of people with schizophrenia and any use for other purposes may require modifications. The materials used as the source of interventions were the RCTs reported by medical researchers and the classification systems used to standardise the collected interventions – just like other medical classification systems – were not necessarily designed based on clinicians' or systematic reviewers' needs (Bowker and Star 1991). While WHO ATC classifies Lithium as antipsychotic drug, none of the systematic reviews of antipsychotic drugs includes Lithium. The reviewers refer to Lithium as Mood Stabilizer, a class of drugs that has no place in WHO ATC. To meet both WHO ATC class and reviewers' need, we kept both classes working in parallel.

Are systematic reviewers the good classifiers?

Although the Cochrane reviewers' titles were a good starting point, it is clear that no available classification system has been followed. Some titles are based on clinical effect, others on pharmacological class and, in some cases, there were duplicate terms for describing the same concept (i.e. typical antipsychotics and first generation antipsychotics); the latter concept being not a true class of drug but more one imposed by industry with pecuniary interests. It is not clear that the titling of Cochrane reviews has to be this inconsistent. It is important to communicate clearly the target of the review in terms that make the work easy to identify and access. In this, classification can help. It may be that, in general, the title of the Cochrane review should use generic drug names or pharmacological classes as default. Titling of Cochrane Overviews, however, may be best to favour either pharmacological classes or/and clinical class.

What qualifies as qualifier?

Useful qualifiers of pharmacological interventions for systematic reviews have been ignored in all classification systems. The Schizophrenia Group's Information Specialist had to develop the list of qualifiers for both existing reviews and, looking towards the future, as yet un-reviewed RCTs. We considered a concept/aspect as a 'qualifier' when people were randomised to an 'aspect' or facet of the same drug – for example, timing of when the same drug is given, generic vs. trade forms of the same compound. Before the end of this classification effort, there was little information on what aspects of the drugs have been targeted and tested in RCTs. Now we are aware that from size and flavour of the pill to the depth of the injection are being tested in RCTs and each of these qualifiers can be the target of the next systematic reviews.

Problems with using the WHO ATC

Unlike International Classification of Diseases (ICD) where the industry – insurance companies, industrial firms, and pharmaceutical companies – had an influence on the classification (Bowker and Star 1991), the classes such as atypical/typical and first/second generations were not listed in WHO ATC. The only use of 'generations' – which is relevant and valid – is for classifying Cephalosporins (a class of antibiotics).

Although WHO ATC is currently the best available classification for our purpose, it does have important limitations (Merabti *et al.*, 2011). Our study found some more limitations:

- Duplicates: WHO ATC does contain many duplicates. This is not only where a drug is classed - justifiably - in two places but genuine duplication of the same drug appearing in the search results more than once with the same class code.

- No ordered hierarchy: For example, after the overarching anatomical class, the next class down is sometimes clinical, sometimes pharmacological and sometimes a chemical structure or group.
- Listed drugs limited by assignment to anatomical class: For example, a drug listed under 'ophtalmologicals' is being used by people with schizophrenia not because of this anatomical class but because of its pharmacological [anticholinergic] action. As a result, the anatomical classification will appear odd for those using the classification for condition-specific indexing.
- Synonyms: It is not possible to search synonyms of drugs.
- Spelling: WHO ATC relies on European spelling of the generic drug name (i.e. amfetamine not amphetamine) and there is no function to recognise potential differences in spelling when searching.
- Different binders of the same drug not covered: For example, the important distinction between Zuclopenthixol *acetate* and Zuclopenthixol *decanoate* is not made.
- Marketed drugs: WHO ATC largely – but not entirely comprehensively (see below) - relies on drugs already at market. It does not list experimental or upcoming drugs or classes.
- Geographical bias: it is largely based on drugs from Western countries.

Marketed non-WHO ATC drugs

There are marketed schizophrenia drugs in China, Czech Republic and Japan that are not on WHO ATC. These omissions may reflect some degree of a language barrier to entry on WHO ATC. A highly specific indexing project such as this one is able to identify such omissions but is also vulnerable to them. For example, Japan's ICHUSHI bibliographic database is currently inaccessible to Cochrane Schizophrenia Group and may contain more trials of other drugs unknown to the

West. With illnesses such as schizophrenia, for which care must be tailored depending on many variables including individual response – however idiosyncratic – every potential drug treatment is an important addition to the armoury.

One third of schizophrenia drugs are not on the market

Overall, there is poor reporting of the reasons why drugs had not reached the market. Where AdisInsight reports that a drug had ceased being tested, it gives no reason. It may be that these drugs were ineffective or toxic. This should be reported to prevent more trials. Other drugs may have been effective but not been brought to market for reasons of finance and business strategy (Bannister, Adams, & Shokraneh, 2019). This also should be made clear for once the chemical goes off patent it could be produced as another treatment for this difficult illness.

Receptors targeted by non-marketed drugs

The dopamine (D) hypothesis, accepted among many schizophrenia researchers, explains that hypostimulation of D1 receptor and hyperstimulation of D2 are respectively responsible for negative and positive symptoms of schizophrenia (Jones & Buckley, 2006). This hypothesis has been refined and we know that there are many other receptors involved in schizophrenia. Accurate classification of the drugs could extend to receptor blockade profiles. This is crudely undertaken by grouping pharmacologically (phenothiazines, butyrophenones etc.) but, once indexing is accurate and the receptor targeting known, each compound could be given receptor weighting. Modelling these to the trial outcomes could generate hypothesis for new drug design.

We suggest that the classification of pharmacological agents should not be binary – or monothetic in classification terminology – and that these interventions fit better a fuzzy classification system (Bowker 1998) because of their

pharmacological action on two or more receptors with different percentage of occupancy in each type of receptor.

Limitations

I have taken a comprehensive approach in including all schizophrenia RCTs regardless of their language, date of publication, types of the documents, or publication status. However, I consider that the search methods for databases are not very accurate and we are unable to search all information sources in all languages. It is likely that we have missed some trials.

Regardless of double and triple checking of the content and classification in our register, we always have the possibility for human errors. However, this is a living database and living classification system. When a new aspect or an intervention is being added to the register not only do we have to check and amend the new aspect to all new prospective content but also to the retrospective content in the database. It is likely that the main items of our classification that may change across time are facets or aspects because, currently, there is no standard to follow or consensus regards reporting or documentation.

Conclusion

Critics of Cochrane reviews often cite the production time as a problem (Turner *et al.*, 2017) – with good reason. On average, it takes 2.4 years to conduct a Cochrane review – with eight hours for screening every 1000 search results (Higgins & Green, 2011). A comprehensive specialised study-based database with classified indexing makes it possible to run searches with almost 100% precision

and recall within seconds (Shokraneh & Adams, 2019), almost eliminating screening time.

FS invested much time in testing various options whilst developing the practical classification system described above. It is likely that most other areas of health care will also take this road. Many lessons were learnt and mistakes made which it is hoped, this paper will go some way to help others avoid. Only one third of tested treatments for people with schizophrenia are drugs. Non-pharmacological interventions are more common. The next classification effort should target non-drug therapies.

To avoid more chaos in knowledge organisation by adding a new classification system (Bowker and Star 1999), we did our best to rely on existing classification systems – at least initially. We found that the current systems to be pragmatic but, predictably, imperfect. Suggestions for the existing classifications are 1. Keep up-to-date as fast as possible, missing a new effective interventions may cost lives; 2. Cover old interventions, some may be effective but forgotten; 3. Focus on facets and aspects of interventions and fuzzy classes rather binary classes.

Data sharing

Following the call for sharing data from Cochrane efforts (Shokraneh *et al.*, 2018), the data produced as the results of current classification activity is available as appendix and upon request from the author.

To make our register and this classification (datasets, element sets, and value vocabularies) usable and linkable in web of data, we need to put it on the web in a machine-readable structured format under non-proprietary format – CSV format using Creative Commons Licenses – and to use open standards for data interchange on the web and finally to link it to other data. Currently, we have

shared our data in CSV and Excel format under Creative Commons License in Open Science Framework that makes our classification a three-star rather than five-star linked data (Berners-Lee 2016). Like any other structured data, such linked data may also face challenges related to quality of data including but not limited to becoming out of date, being incomplete, having inconsistencies and inaccuracies (Rula *et al*. 2016). Such movement for our register requires skills that I do not currently have – although we are on the journey to acquire them.

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PAPER 7

Cochrane Schizophrenia Group's study-based register of randomized controlled trials: Development and content analysis

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PAPER 7

Cochrane Schizophrenia Group's Study-Based Register of Randomized Controlled Trials: Development and Content Analysis

Abstract

Background: Study-based registers facilitate systematic reviews through shortening the process for review team and reducing considerable waste during the review process. Such a register also provides new insights about trends of trials in a sub-specialty.

Objective: This paper reports development and content analysis of Cochrane Schizophrenia Group's Study-Based Register.

Methods: The randomised controlled trials were collected through systematic searches of major information sources. Data points were extracted, curated and classified in the register. We report associations and trends using regression analyses in Microsoft Excel and we used GIS mapping (GunnMap 2) to visualise the geographical distribution of the origin of schizophrenia trials.

Results: Although only 17% of trials were registered, the number of reports from registered trials is steadily increasing and registered trials produce more reports. Clinical trial registers are main source of trial reports followed by sub-specialty journals. Schizophrenia trials have been published in 23 languages from 90 countries while 105 nations do not have any published/registered schizophrenia trials. Only 9.7% of trials were included in at least one Cochrane review. Pharmacotherapy is main target of trials while trials targeting psychotherapy are increasing in a continuous rate. The number of people randomised in trials is on average 114 with 60 being the most frequent sample size.

Conclusion: The register provides accurate information about the number of studies per interventions or per pairwise comparison for systematic reviews.

Curated datasets within the register uncover new patterns in data that have implications for research, policy and practice for testing new interventions in trials or systematic reviews.

Introduction

Systematic reviews provide evidence for informed clinical decision-making (Bello *et al.*, 2015; Oliver, Dickson & Bangpan, 2015). However, production of systematic reviews involves several time-consuming steps. These include searching for studies, screening search results, obtaining full text of relevant studies, screening that full text, linking reports of the same study to one record, extracting and analysing data, and writing the final report (Higgins & Green, 2011). The average time from instigation to completion of a systematic review of treatment is 2.4 years (Tricco *et al.*, 2008), and the average cost $300,000 (Lau, 2019). Having all relevant studies identified and held in a register helps researchers set relevant questions, and considerably aids reduction of reviewing time (Shokraneh & Adams, 2019a).

Many specialised registers are reference-based. These include the bibliographic information and abstract of each report. However, some registers are upgraded to the level of being study-based. In this type of register, the *study* is the principal record and each study record contains extracted meta-data (such as participant, interventions, comparators, and outcome information – so-called PICO) (Shokraneh, 2016) and is linked to one or more reference/report (Wright, 2006b). Such a register helps minimise miscounting of studies for meta-analysis, avoid null-study reviews or large unmanageable reviews, shortens search time to seconds, facilitates relevancy/eligibility and discrepancy checks, and detects evidence gaps. Furthermore, having this type of register allows reviewers to accurately estimate workload and save time and increase efficiency (Shokraneh & Adams, 2015, 2017, 2018, 2019).

The Cochrane Collaboration (Cochrane Collaboration, 2015a) has long recognised the advantage of maintaining registers of trials (Lefebvre *et al.*,

2013) and many Cochrane condition-specific groups developed sophisticated registers to include all the relevant studies (Noel-Storr, 2014). Cochrane Schizophrenia is a group that maintains a study-based register of randomised trials.

Objective

To report the development of Cochrane Schizophrenia's Study-Based Register of Trials and produce a summary of its content at both study and reference level.

Materials and methods

Source of the content

In 1994 (Adams & Gelder, 1994), we set out the argument for the need for a register of trials relevant to people with schizophrenia. The work has been ongoing since generating much original informatics research (Glasziou & Aronson, 2017).

The register's core is based on regular systematic searching of the following databases:

- AMED, BIOSIS, CENTRAL, CINAHL, ClinicalTrials.Gov, Embase, ISRCTN, MEDLINE, PubMed, WHO ICTRP (monthly);
- ProQuest Dissertations and Theses (quarterly)
- Four major Chinese databases from SinoMed, CNKI, VIP, and WANFANG (annual)

The register also includes records identified through searching local/national databases, hand-searches of relevant conferences, grey literature, checking references of relevant studies and non-Cochrane systematic reviews, and contacting researchers, authors and drug companies. There are no limitations on language, document type, time/date or publications status. Details of the search strategies for every database are reproduced elsewhere (Shokraneh, 2018). This register, compiling records from all sources, now supports all

Cochrane systematic reviews of interventions for people with schizophrenia and related disorders. It is central to a one-stop-shop searching service.

Content eligibility criteria

The register contains reports. A 'report' is any source (journal article, book chapter, conference abstract, dissertation, poster or presentation in conference, trial registry record, email/tweet from trialists, etc.). Reports may be published or unpublished status and associated with completed, ongoing or terminated studies.

Each report meets the following two criteria to enter the register:

- It should be that of a randomised controlled trial or a controlled clinical trial where randomisation is unclear or implied; and
- It should report participants relevant to people with schizophrenia or related disorders (non-affective psychotic disorder, schizoaffective disorder, schizophreniform, schizotypy, akathisia, tardive dyskinesia, delusional disorder, persistent audio-visual hallucinations, population at risk of psychosis, serious mental illness, dual diagnosis and poorly-defined serious mental illness) (Lieberman & First, 2018). These participants are mostly people with a relevant condition or problem but could also be relatives, caregivers, or even inanimate items relevant to schizophrenia. Participants do not include animals (physiological studies) or healthy people (physiological or Phase I studies).

Processing the content

The Information Specialist (FS) screens the report's title and abstract – a process increasingly aided by automation (Stark *et al.*, 2014). If the report meets the eligibility criteria, the full text is acquired. When there is doubt about eligibility, the full text is still acquired. The full text is inspected and, if eligible, FS adds the report is added to the register, receiving a link to a new study or an existing study.

PICO metadata for each study is then extracted, standardised and added to the register. This metadata, assisted by use of specific controlled vocabularies

(Shokraneh & Adams, 2019b) allows highly accurate searches in addition to the usual much less specific usual bibliographic searches within title and abstract. As more information about references or studies become available during processing (status in a systematic review, author communications, new records, data or meta-data, corrections, deletions etc.), the reference and study records are updated and appended.

We are unclear ourselves about the Information Specialist's processing time for each study. It varies from between only a few minutes (the great majority) to an hour. Records have to be maintained in the light of new evidence. For example, a five year follow up paper appears of a known study and new links and outcomes may have to be added to the original study record.

Software

In the early days (1992), this register used ProCite – a powerful reference management programme (Rosenberg, 1995) – to create a basic study-based register. ProCite was, however, a flat database unable to really link reference records to a study record and does not have the powerful and necessary functions of a relational database (Shokraneh & Adams, 2017). In 2000, the Cochrane Collaboration supported creation of MeerKat, a free Microsoft Access-based program running on Windows OS (v7 and lower) (Kaur *et al.*, 2009; MeerKat Working Group, 2005; Wright, 2006a). This tailored program uses Visual Basic macros and Microsoft Access forms to automate repetitive tasks and has a clear user-friendly graphical user interface (GUI). Behind the GUI data and meta-data are stored in a linked relational database (Wright, 2006a). This supports links from reference to study records and from the study records to PICO meta-data using one-to-many relationships (Kaur *et al.*, 2009). MeerKat supports all the functions required for a study-based register and has potential to evolve into the type of register that supports 'living' systematic reviews (Shokraneh & Adams, 2017).

In 2008, Cochrane Collaboration started developing the Cochrane Register of Studies (CRS) (Cochrane Collaboration, 2015b) to bring together all registers within Cochrane from across all of health care. This supported some functions

of a study-based register. The desktop version used H2 - another relational database management system developed in Java environment. CRS' main benefit was synchronisation of the registers to Cloud and its web-based version had great potential to support linked data initiatives and create data-based products. The CRS team created a module that was able to upload the MeerKat database and transfer records to tables in CRS.

In 2012, our team decided to move from MeerKat to CRS. By September 2014, however, after much effort, this move had to be aborted for several reasons:

- Dysfunction: CRS did not supporting the basic functions of a study-based register;
- Malfunction: desktop CRS was slow and often failed to work (Java black screen);
- Slow development: CRS's development phases were slow – even now its web-based version does not support many study-based register functions;
- Time: a task that took a few minutes to complete through the automated functions of MeerKat required half a day of manual work in CRS.

Currently, Cochrane groups, working with standard non-relational bibliographic databases or reference-based registers are able to use CRS' web version while its core functionality continues to develop. Since December 2014, FS maintains the register using MeerKat 1.6 (Shokraneh, 2018).

Structured data and meta-data set

For each reference record, there is bibliographic information, abstract and full text. For every study record there are the links to references, status of the study, duration of intervention, country of origin, age group, gender, and number of participants, healthcare problems (major, minor, state and stage), randomised interventions, outcomes, trial registration numbers and status in Cochrane reviews.

Data analysis

We briefly summarise the content of Cochrane Schizophrenia's register - both reference and study level - using tables and figures. Analyses at the reference level provide information on sources of trials and publication trends. At the study level, we use GIS mapping (GunnMap 2 (Gunn, 2019)) to visualise the

geographical distribution of the origin of schizophrenia trials. Finally, as illustration, we report associations at the study level using regression analyses in Microsoft Excel.

Results

Study to report ratio

On 22 May 2019, the register includes 27,861 reports from 19,964 studies (ratio of 1:1.4). The average number of reports per study is 1 (mode 1, range 1 – 174). The multiple publications are not common for Chinese trials (ratio ≈1:1) compared with English (1:1.03 English) with trials originating from the USA commonly disseminating results in more than one report (ratio 1:1.73). Trials which are registered, obtaining, for example, an ISRCTN, are commonly published more than once (ratio 1:1.86).

Sources of trial reports

Clinical trial registries are rich sources of schizophrenia trial reports as are the conference proceedings published within journals such as *Schizophrenia Bulletin*. A mixture of specialist and general journals, proceedings, thesis listings follow in the top 20 sources. Chinese journals are increasingly prevalent in this list (Table 7-1).

Table 7-1. Top 20 source of schizophrenia trial reports

Source	Count
Clinical Trials Registries	2597
Schizophrenia Research	1482
Schizophrenia Bulletin	787
Medical Journal of Chinese People's Health (中国民康医学)*	670
Proceedings of Annual Meetings of American Psychiatric Association	625
European Neuropsychopharmacology	531
American Journal of Psychiatry	436
Biological Psychiatry	360
Journal of Clinical Psychiatry	337
British Journal of Psychiatry	334
Journal of Clinical Psychiatry (临床精神医学杂志)	312
National Research Register	305
Dissertations	299
Neuropsychopharmacology	276
China Journal of Health Psychology (中国健康心理学杂志)	275
Early Intervention in Psychiatry	274
Journal of Clinical Psychopharmacology	274
Journal of Clinical Psychosomatic Diseases (临床心身疾病杂志)	273
Archives of General Psychiatry	263
Psychopharmacology Bulletin	224

* The name of this journal was Medical Journal of Chinese Civil Administration (中国民政医学杂志) till the end of 2002.

The language of reports

There are 27,861 references in the register in 23 languages with Chinese and then English leading (**Figure 7-1**).

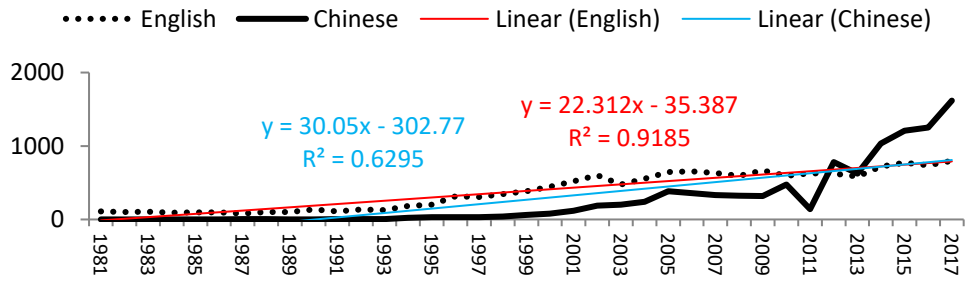

Figure 7-1. The language and count of references added to the register based on the publication year

Reports from registered trials

Only 4,840 reports (17.4% of all reports) belong to registered trials and only 2,597 trials (13% of all studies) were registered. The trend of reporting from registered trials is increasing (**Figure 7-2**).

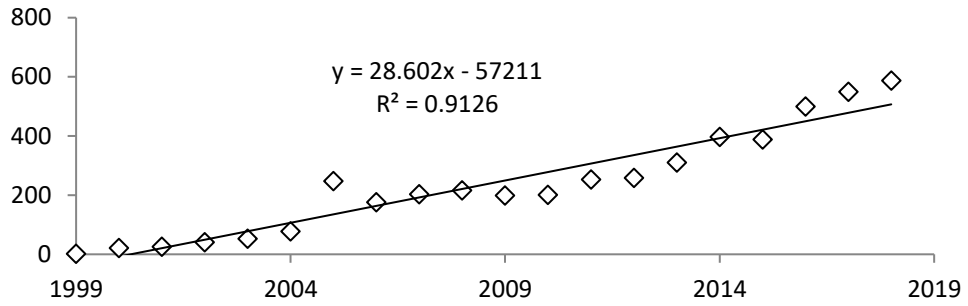

Figure 7-2. Trend in reporting from registered trials

Just over one quarter of trials from the USA are registered compared with only 1.75% from China.

Country of origin for studies

The trials involved participants from 90 countries with authors originating from those nations (multi-country trials (424) were assigned to more than one country) (Figure 7-3). Only China (8542), United States of America (4188), United Kingdom (1024), Canada (541), and Germany (533) had more than 500 trials. Australia, Japan, Netherlands, India, Iran, Israel, Spain, and France have between 200 and 500 studies. Forty countries have between 10 to hundred trials and 30 countries with less than 10 trials and 105 nations do not seem to have published any trials (Appendix 7-1).

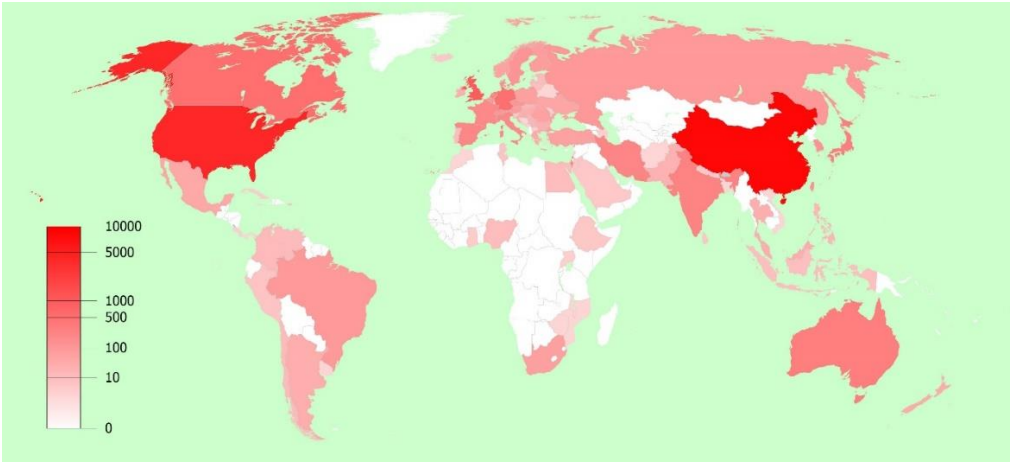

Figure 7-3. Geographical distribution of schizophrenia trials

Inclusion in Cochrane reviews

Only 1950 studies (9.7%) are included in a Cochrane schizophrenia review. On the other hand, 3030 studies (15.2%) are listed as excluded – so have been considered but found not to be eligible – and a further 3778 (19%) as awaiting assessment or as ongoing studies (147; 0.7%). There is overlap among these categories across different reviews, but, in total, 7089 studies (35.5%) have been listed in a Cochrane schizophrenia review. Currently it is unclear how many of the excluded, awaiting assessment and ongoing studies could never be included in a review and how many hold useful information on the effects of care of people with schizophrenia which, one day, should find a place in an appropriate review.

Type of interventions in trials

Pharmacotherapy interventions make up one third of indexed and coded interventions within the register (Shokraneh and Adams, 2019). However, the proportion of studies evaluating these drugs is, by far, greater than the percentages devoted to psychotherapy approaches (Figure 7-4).

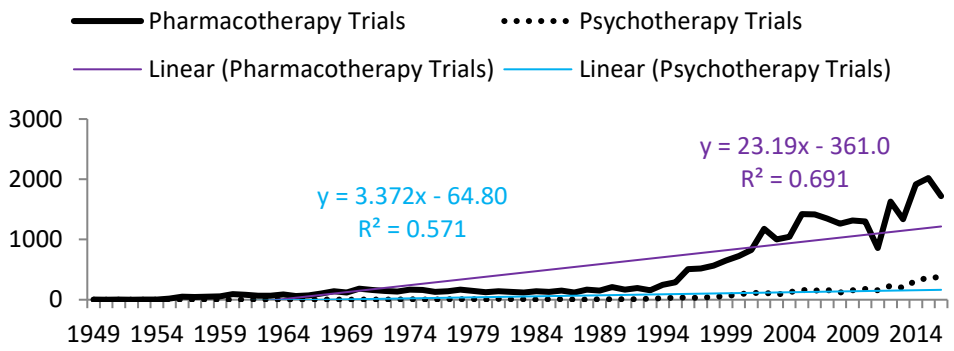

Figure 7-4. Type of interventions in trials over time

Number of randomised participants

This number of people randomised within the studies varies between zero (for terminated trials) to 25,210 (Ferebee, 1964) (average 114 SD=±334; median=72; mode=60) (For cluster-randomised studies we count numbers of clusters rather than numbers of individuals within those clusters).

Discussion

This register of studies is the largest, most comprehensive database of evaluative studies relevant to the care of people with schizophrenia ever assembled. Its structure and indexing afford opportunity for analyses to obtain insights into biases in research production, and prediction of the future from the patterns of the past.

Salami publication

It is understandable – and laudable – that these studies often have multiple reports. They are important pieces of work. The trial register report often heralds the full published protocol, the conference presentation, the final journal article, the thesis, and the five year follow up. But studies with hundreds of papers are hard to justify. At some point, we argue, multiple publication, most commonly seen in big 'Western' pharmaceutical trials, strays out of the realm of *convincing* the readership, into a *confusion* of evidence, and finally even a *corrupt* practice - flooding journals, ousting other studies, and undertaking such a degree of repetition that findings could be mistaken for truth (Bartsch *et al*., 2004).

Where to search for schizophrenia trials

An analysis of top 20 sources of trials reports shows that clinical trial registries are the main source of schizophrenia trial reports. This could be a sign to us and other sub-specialties, that the current practice of initially searching large bibliographic databases such as Embase and MEDLINE as main sources of trials for systematic reviews (Higgins & Green, 2011) is less valuable. The list of top journals then helps guide hand searching activities. The National Library of Medicine (US) which produces the dataset used in PubMed and MEDLINE, by policy, do not index abstracts from conferences. The journal *Schizophrenia Research* is a particularly rich source of trial reports within the Cochrane register precisely because it reports conference proceedings – none of which are in MEDLINE.

The appearance of four Chinese journals among top 20 also is in line with the rise of South East Asian trials (Chakrabarti *et al.*, 2007). Interestingly, the National Research Register (Roberts, 1998) used to be a valuable source of trial reports before the current clinical trial registers. However, this source is no longer available (National Institute for Health Research, 2019) encouraging our practice of holding a copy of every trial report – as sources may disappear – perhaps especially from the online world.

China on rise

The trend illustrates that production of Chinese language randomised trials is now double that of those published in English. The significant lag in starting undertaking 'local' evaluative studies, the enormous population and hence health care need, and probably, above all, the burgeoning economy will be fuelling this activity (Chen, 2017). However, less rigorous governance, cheaper cost of recruiting patients and a relentless drive for research publication that, despite stringent measures (Cyranoski, 2007), can lead to production of dishonest work could be other reasons for such an increase. We, however, could not find any evidence of the latter claim. Just like Purgato *et al.*(2012), we support including Chinese trials in systematic reviews to make the findings more generalisable to Chinese people and the use of sensitivity analyses where doubt remains. For certain topics, such as the value of traditional Chinese medicine or acupuncture, trials from China predominate (Cohen *et al.*, 2015; Wu *et al.*, 2013).

World contribution to schizophrenia trials

Although economics – rather than public health need - is a considerable driver for evaluative research in schizophrenia (Moll *et al.*, 2003) the picture becomes increasingly nuanced. China started late but now produces more trials than any other country. When researchers are given freedom to question – albeit in a still highly constrained environment - they do and relish doing so. The high-income USA, the UK, Canada, and Germany are the next leaders producing schizophrenia trials. In the 200-500 second cluster, apart from India and Iran, all countries are in the high income bracket again,

economics being *the* potent driver of research. However, the presence of Iran and Israel, with their similar number of trials, highlights other issues. These nations have little similarity in their income or population (Iran – middle, heavily sanctioned, income, 81m population; Israel – high income, 9m population). Persian Gulf countries enjoy income from oil resources but this does not seem to encourage them to invest in schizophrenia research – economics is clearly not the sole driver. Iran, with its now constrained income, currently directs investment internally and into research. Israel, on the other hand, with its relatively small population, is a major producer of schizophrenia trials. Here income, the investment of pharmaceutical industry, the culture of rigorous enquiry and strong support from other high-income nations may help drive it to be so productive.

There is a yawning gap in evaluative research in Africa and many ex-soviet countries – at least for people with schizophrenia. The presence of 'local' trials in systematic reviews with findings homogeneous to studies from other settings reassures readers that findings are, indeed, locally applicable. Whilst authorities in Moscow may resent and resist influence from the USA in internal affairs, the care of 1% of the Russian population with schizophrenia is likely to be heavily dependent on studies undertaken in New York, Detroit or Houston. Good evaluative studies are needed set in the many different traditions and services of care provision across the world. War, disaster and poverty make trials difficult – but not impossible (Abbas *et al.*, 2018; Bell & Donnay, 2015). In times of great austerity the only equitable way to provide care is through randomisation (Salomone, 2012). Corruption is also a major hindrance to productive questioning. The African nations, some of which are wealthy and stable, are not serving their collective 1.2bn population well in terms of evaluative research for the 1% who suffer from the often erosive effects of schizophrenia (Utoblo *et al.*, 2019).

Proportion of trials in systematic reviews

Only about 10% of schizophrenia trials have been included and their data used in over 300 Cochrane schizophrenia systematic reviews produced across the

last 25 years. A further 25%, however, have been inspected and considered for inclusion. We do not know what proportion of this quarter are relevant yet redundant studies – perhaps due to poor reporting. Individual reviews often cite this as a problem and a research waste (Roberts & Ker, 2015, 2016; Tovey, 2015). However, a sizable proportion of this 25% is also likely to be good, clearly-reported randomised studies with, as yet, no place in a maintained systematic review. There remains much work to do before all high-grade data relevant to the effects of care of people with schizophrenia is liberated from the 'printed' page/website into 'live' reviews. The pace of inclusion of studies highlighted by this analysis would suggest that among the solutions to this enormous lag-time are maintenance of good trial registers paired with much more review automation (Tsafnat *et al*., 2014).

Targeted treatments

The dominance of pharmacotherapy trials probably reflects the great investment of industry in this sub-speciality. We do not know the trend of independently funded pharmaceutical studies, but we suspect this very skewed pattern of trialling reflects an unhealthily close reliance on industry (Fibiger, 2012). The necessary academic and clinical collaboration may well have become too dependent (Palmer & Chaguturu, 2017). The steady increase in psychotherapy studies is encouraging but it is important to avoid thinking that such studies are not just as prone to the same potent biases that affect trials undertaken by industry (Dragioti *et al*., 2015).

Number of randomised participants

The mode size of trials is 60. This has not changed across time (Miyar & Adams, 2013; Thornley & Adams, 1998). There are important and, correctly, influential exceptions to this rule, but, on average, the size of study relevant to people with schizophrenia is, and remains, very small. For a clear important 15-20% difference in a binary outcome – such as' getting better' - to be confidently highlighted within a comparative study to conventional levels of statistical significance, sample sizes need to be around 300 for a two-arm study (Altman, 1991). Most trials fall well short of this size. Then proxy

measures are used. These often take the form of scale measures use of which frequently makes the conduct of the trial complex. Scales, valuable within research, are rarely used in real working life. Their use is commonly accompanied by considerable attrition (Dumville, Torgerson, & Hewitt, 2006), they are often fine-grain categorical in nature rather than truly continuous (Campbell *et al*., 1995), report skewed data which are problematic to analyse (Delucchi & Bostrom, 2004) and often near impossible to interpret for the clinician, policy maker let along patient (Higgins & Green, 2011). There remains a strong argument for design of large real-world randomised trials recording simple important and understandable outcome of clinical utility (Weinfurt *et al*., 2017).

The size of the trials usually depends on the phase of trial and the available fund to run the trial. For example the first RCT of a new medication has usually a small sample size because of safety and tolerability concerns. The second trial could be a bit larger to identify the optimum dosage of the drug and the third trial has more patients but still has small sample size to test the efficacy. When clinical efficacy confirmed in first RCT then there might be more small size trials to compare the new treatment with the best existing treatments in the market rather than placebo. Only after showing promising results from such comparisons a large multi-centre or multi-country RCT could be confirmed by the funder and still each country may run their own small sample size trial to make sure the new treatments still is effective in the new geography with environmental, characteristics and pharmacogenetics of the new population. Funding bodies usually cannot risk funding a trial with large sample size without having some assurance from small sample size trials. Furthermore, unawareness of researchers in following guidelines in sample size calculation, indention of new outcome measure for research setting with no or little implications to clinical setting, and challenges of recruiting and retaining patients with mental illnesses could be added to the list of reasons for small samples sizes. When the number of treatments increases, it may not be possible to run large RCTs for all treatment and the best alternative is to

conduct a systematic review and run a meta-analysis of studies with small sample sizes to save the resources. Of course, this alternative has its own problems.

Future plans

The Cochrane Schizophrenia Group's Study-Based Register of Trials is currently an offline resource while we are trying to find support to make it a free publicly accessible online resource and to share the data from within the systematic reviews following FAIR guidelines and supporting the reproducibility initiatives (Page *et al.*, 2018; Shokraneh, 2019).

The obvious next evolution of the Cochrane Schizophrenia Register is towards facilitating live reviewing. In such reviews extracted data from each study are available to users querying the data, auto-generating entirely up-to-the-minute results, perhaps tailored to users' health care values, in their 'home' languages (Torres Torres & Adams, 2017). Moving the register online, auto-data extraction from PDF reports (Nur *et al.*, 2016), and employing data stripping programmes (such as RAPTOR (Schmidt *et al.*, 2019)) can assist appending more datasets to the study records. This then lends itself to automatic analysis and writing in multiple languages (such as that seen with RevManHAL (Torres Torres & Adams, 2017)). All this has to come in the near future (Tsafnat *et al.*, 2014).

Conclusion

Only a few groups across the earth hold and maintain a study-based register of randomised trials. The benefits of investment in this work are enormous and immediately reap benefits in terms of avoidance of the waste prevalent in the processes of systematic reviewing (Shokraneh & Adams, 2019a). Cochrane Schizophrenia's Register is world-leading. It affords great, ever more sophisticated, opportunity for reviewers of trials, those wishing to study (and, hopefully, improve) research practice, and Information and Computer Scientists helping evolve more review automation

Data Sharing

All data used in this paper are in Appendix 7-1 so that the audience could repeat the analyses and see the detailed numerical data.

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PAPER 8

Reducing waste and increasing value through embedded replicability and reproducibility in systematic review process and automation

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PAPER 8

Reducing Waste and Increasing Value through Embedded Replicability and Reproducibility in Systematic Review Process and Automation

Clovis Mariano Faggion Jr. points out a serious problem starting a valuable discussion suggesting two approaches to facilitate the reproducibility of the systematic reviews (Faggion, 2019). Because performing systematic reviews is already time-consuming (Sampson *et al.*, 2008) and resource-consuming (Borah *et al.*, 2017), it is arguable how adding more steps – such as reproducibility testing that requires even more time and human resources – could reduce waste, and increase value, compared to excluding some steps (Shokraneh & Adams, 2017a). Here, I discuss how the replicability of methods and reproducibility of results (RMRR) have been embedded within the systematic reviewing and how "semi-automation" and "sharing" could solve RMRR issues (Shokraneh, 2019a).

The masterminds who developed the process of systematic reviewing considered involving at least between two or three people in screening and data extraction steps. Although the purpose of double-checking could be to reduce the errors (Buscemi *et al.*, 2006; Carroll, Scope, & Kaltenthaler, 2013), it also means the screening and data extraction are being repeated or replicated by at least one other member of the team to ensure the reproducibility of the same results in each step; when there are discrepancies, either these two members reconsider the decision for the third time or they ask a third member's opinion. These two steps enjoy RMRR as embedded within the methodology. But how do we know if what has been said in the systematic review has actually been done? We usually trust the researchers but using the existing online semi-automated platforms that document the steps of the systematic reviews (Beller *et al.*, 2018; O'Connor *et al.*, 2018;

Tsafnat*et al*., 2013; Tsafnat *et al*., 2014; van Altena, Spijker, & Olabarriaga, 2018) could help transparency if the team shared the processes and methods openly, and shared the results in a findable, accessible, interoperable, and reusable format as advised by FAIR principles (Wilkinson *et al*., 2016). This is not the best practice right now (Shokraneh *et al*., 2018) but we have what it takes to do the systematic reviews once without being worried about RMRR. That is also a requirement in the update step.

Following the protocol and sharing the data (Shokraneh & Adams, 2017b; Wolfenden *et al*., 2016), on the other hand, the meta-analysis step—based on established math embedded within software programs—can be repeated conveniently. It only leaves the vulnerable search step behind. I intentionally kept the search, the first step, to discuss last.

- Like meta-analysis the search is rooted in computerised systems with certain differences:
- Unlike the computer programs for meta-analysis, the databases are not freely accessible to develop the search strategies or to repeat them;
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (RISMA) mandates reporting of search strategy for at least one database (Moher *et al*., 2009), so RMRR is possible for only one database not all the databases;
- Last but not least, even if the authors decide to be generous in reporting the search strategies for all databases, they do not share the search results (Shokraneh *et al*., 2018). The main excuse for not sharing the search results is that the abstracts are copyrighted; however, it is and was always possible to share the search results excluding the copyrighted abstract after deduplication in RIS (RefMan/Reference Manager) format.

Apart from those review teams who have the privilege of using a study-based register to conduct a register-based study (Shokraneh & Adams, 2017a), the search step is the weakest point in terms of RMRR in evidence synthesis (Shokraneh, 2019b).

Although many follow PRISMA guideline in reporting the systematic reviews, it is not currently the primary purpose of PRISMA to ensure the viability of RMRR in systematic reviews. My suggestion is for PRISMA 2019 to include items that enforce the scientific principles of RMRR through public data/methods sharing based on FAIR principles and using the online automated platforms where they support public accessibility to documented processes, methods, and data as recommended within seven available strategies for reproducibility of systematic reviews (Shokraneh, 2019b).

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PAPER 9

Reproducibility and replicability of systematic reviews

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PAPER 9

Reproducibility and Replicability of Systematic Reviews[1]

Abstract

Irreproducibility of research causes a major concern in academia. This concern affects all study designs regardless of scientific fields. Without testing the reproducibility and replicability, it is almost impossible to repeat the research and gain the same or similar results. In addition, irreproducibility limits the translation of research findings into practice where the same results are expected. To find the solutions, the Interacademy Partnership for Health gathered academics from established networks of science, medicine and engineering around a table to introduce seven strategies that can enhance reproducibility: pre-registration, open methods, open data, collaboration, automation, reporting guidelines, and post-publication reviews.

The current editorial discusses the generalisability and practicality of these strategies to systematic reviews and claims that systematic reviews have even a greater potential than other research designs to lead the movement toward the reproducibility of research. Moreover, I discuss the potential of reproducibility, on the other hand, to upgrade the systematic review from review to research. Furthermore, there are references to the successful and ongoing practices from collaborative efforts around the world to encourage systematic reviewers, the journal editors and publishers, the organisations

[1] The open peer-review reports from three reviewers is available in the following links:
https://www.f6publishing.com/Forms/Manuscript/Tracking/QualityTrackReport.aspx?TrackId=2666
https://www.f6publishing.com/Forms/Manuscript/Tracking/QualityTrackReport.aspx?TrackId=2672
https://www.f6publishing.com/Forms/Manuscript/Tracking/QualityTrackReport.aspx?TrackId=2709

linked to evidence synthesis, and the funders and policymakers to facilitate this movement and to gain the public trust in research.

Core tip

Reproducibility increases the practicality of the research findings and gains public trust in research. The ongoing developments in the automation of systematic reviews, availability of pre-registration platform, dealing more with secondary data or anonymised primary data, the collaboration culture among the organisations who produce systematic reviews, and finally having an update step that mandates replicability are all reasons that systematic reviews have the potential to lead the movement toward reproducibility among other research designs. Meanwhile, reproducibility can help systematic reviews to be considered as research design rather than a literature review.

Introduction

Systematic reviews are at high levels of evidence hierarchy in clinical practice (Phillips *et al*., 2009). People involved in healthcare systems usually use systematic reviews in research, policy, and practice (Chalmers & Fox, 2016), trusting the reproducibility of the results when implemented (Ahmad *et al*., 2010). At the same time, some criticise that systematic reviews are literature reviews, not research (Campbell, 2004; Petticrew, 2001). To utilise the systematic reviews in practice and to call them research studies, we need reproducibility testing; to ensure the reproducibility of a systematic review, it is important to design, record and report systematic reviewing in a transparent and reproducible way and to prioritise and fund reproducible reviews (Page *et al*., 2018). Some suggest that a team independent from the original team can repeat the systematic reviews to ensure reproducibility (Faggion, 2019). Since conducting systematic reviews is already time-consuming (Sampson *et al*., 2008) and resource-consuming (Borah *et al*., 2017), it is arguable how adding more steps, such as a reproducibility test that requires more time and resources, could reduce waste and increase value.

In the context of this paper, reproducibility means re-conducting the same study, using the same methods and data by a different researcher or team. Replicability is re-doing the same study to gather new data or to recollect the data (Patil, Peng, & Leek, 2016).

To provide solutions for irreproducibility, the Interacademy Partnership (IAP) for Health introduced seven strategies to enhance the reproducibility practice in science (The Interacademy Partnership for Health, 2016). This editorial discusses the progress of using these strategies in the systematic reviewing process and calls for collaboration in all system levels to enhance the reproducibility of systematic reviews.

Strategy 1: Pre-Registration

Currently, the prospective registration of systematic review protocols in PROSPERO, a register of systematic review protocols, is recommended (Stewart, Moher, & Shekelle, 2012). Compared to clinical trials with at least 17 registries (World Health Organization, 2019), there is only one register for systematic reviews; however, unlike clinical trials, it is not yet mandatory to register systematic reviews prospectively (Booth & Stewart, 2013). Today, PROSPERO covers only 30,000 records of conducted, ongoing, awaiting, and abandoned review family (less than a third of 100,000 systematic reviews in MEDLINE) (Page, Shamseer, & Tricco, 2018). It does not support a quality control mechanism (Booth *et al*., 2012), and it lacks a rigorous follow-up procedure for abandoned systematic reviews (Andrade *et al*., 2017). To look on the bright side, there is an association between the registration of the published reviews and the quality of these reviews (Sideri, Papageorgiou, & Eliades, 2018). Allocating more resources to this register, training and encouraging the systematic reviewers to register their reviews, and making the pre-registration a standard for bias control will push reproducibility theory towards practice.

Strategy 2: Open Methods

Researchers should share search strategies for all databases (Koffel & Rethlefsen, 2016) and analytical codes for meta-analysis (Goldacre, 2016) as part of the methods of systematic reviews. Following the prospective registration and publication of the protocol, the researchers and the research audiences could assess the reproducibility and detect if any variation from the protocol might have important implementation messages for research, policy and practice (Stewart *et al*., 2012). This practice is not just to test the reproducibility but also to replicate another analysis or a new update for the

systematic review. None of these is possible without access to all search strategies and statistical codes for meta-analysis.

Strategy 3: Open Data

Search results (excluding copyrighted abstract and database-specific meta-data) in Research Information Systems (RIS) format (Shokraneh, 2018) and extracted data and meta-data from the studies are the main resulting dataset during the systematic reviewing (Haddaway, 2018; Shokraneh *et al.*, 2018; Wolfenden *et al.*, 2016). Access to open data from systematic reviews makes it possible to re-screen the search results, de-duplicate the update searches, re-run the meta-analyses, and test the reproducibility of searching, screening, and data analysis steps. Besides, these data will have more value if shared beside their associated meta-data following FAIR guidelines (findable, accessible, inter-operable, and reusable) (Wilkinson *et al.*, 2016). There have already been calls for sharing the data from systematic reviews, but there is no policy or action in place (Haddaway, 2018; Shokraneh *et al.*, 2018; Wolfenden *et al.*, 2016). Sharing the data from all systematic reviews can lead to data-driven innovations with the potential for knowledge discovery and saving the waste of resources.

Strategy 4: Collaboration

Collaboration among research teams on a small or large scale increases the chance for more expert input. It enhances the practice of detecting and correcting errors (Academy of Medical Sciences *et al.*, 2015, 2016). Sharing the data among collaborators or interested research groups could bring together the data and resources for re-analysing the same data (Goldacre, 2016) or innovations (Shokraneh *et al.*, 2018) that are impossible without such

collaboration. It is not good practice to hold the data for years, hoping to receive funding or innovating while sharing could result in faster innovation, receiving credits or collaboration in grant applications (Academy of Medical Sciences *et al*., 2015, 2016). It also raises the morality and mortality question of whether it is ethical to hold the data when sharing it could lead to decisions that can save public resources and lives and reduce waste. The data extracted from other primary research for systematic reviews cannot be owned by the systematic reviewers or organisations producing systematic reviews.

Strategy 5: Automation

International Collaboration for the Automation of Systematic Reviews (ICASR) produces an annual report of progress for automating systematic reviews (Beller *et al*., 2018; O'Connor *et al*., 2018, 2019). This collaboration seems to understand well that automation is a key for reproducibility and follows Vienna Principles that also emphasise the replicability of automation activities and sharing program codes for wider use by the community (Beller *et al*., 2018). The value of automation becomes more evident by looking at reports of human errors in systematic reviews in the searching (Sampson & McGowan, 2006) and data extraction steps (Buscemi *et al*., 2006). The service provided by machine can speed this process and reduce the waste caused by human errors via standardisation of practices such as statistical analysis or systematic review write-up steps (O'Connor *et al*., 2019; Tsafnat *et al*., 2014). Despite all technological development, systematic reviewers have underused automation tools (van Altena, Spijker, & Olabarriaga, 2018). Currently, Systematic Review Data Repository (SRDR) (Li *et al*., 2015), EPPI-Reviewer (Park & Thomas, 2018), Study-Based Registers (Shokraneh & Adams, 2017), and Evidence Pipeline as semi-automated systems have the potential to evolve into automated systems for systematic reviews.

Strategy 6: Reporting Guidelines

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher *et al*., 2009) now celebrates a decade of being used in the reporting step of systematic reviews. Major journals enforce systematic reviewers to follow the PRISMA family guidelines in reporting. Such reporting guidelines are helping researchers to report certain items for publications, and it is not their primary purpose to advocate reproducibility (Page *et al*., 2018). There is an update of PRISMA 2019 in progress that will include more items, and some of these items can optimise reproducibility practice (Page *et al*., 2018).

Strategy 7: Post-Publication Review

Pre-publication peer-reviews are limited to a few people, while post-publication reviews give a chance for a wider audience to appraise and comment on some aspect of the research. Post-publication activities take many forms, including letters to the editor, commentary, blogs, and other social media posts (Academy of Medical Sciences *et al*., 2015). These reviews are separate and independent from the original research, and the only connection is through a link or citation. As a result, it is hardly possible to find all these reviews integrated into one place. This problem expands when there are retractions to the original systematic reviews, or the findings are published in salami of papers. Such post-publication reviews, however, are encouraged – in particular for systematic reviews – because they can be taken into account in the following updates of the current systematic review. Having an update step in the development of systematic reviews, unlike other published literature, is a unique advantage of systematic reviews allowing the reviewers

to correct their mistakes and errors or consider adding new data or a new aspect to the review.

Open Process: Embedded Reproducibility in Agreement Checks

In addition to these strategies, it is also important not to overlook the process of systematic reviewing and its connection to reproducibility. The routine practice in systematic reviews involves at least two researchers in the screening and data extraction steps to reduce human errors (Buscemi *et al.*, 2006; Carroll, Scope, & Kaltenthaler, 2013) through double-checking of the decision and to reach an agreement. Such agreement sometimes requires a discussion between two reviewers or inviting comments from another, usually a senior researcher. It means the decision on the eligibility of studies or data extraction accuracy is being replicated twice or three times. Since this process itself is replicating part of the review and has value for improving the reproducibility, some of the automation and semi-automation systems allow the researchers to document the process of double- and triple-checking within the system, but for transparency purposes, this needs to be shared as well. In other words, the process should be documented and shared publicly.

Systematic Reviews as a Role Model for Other Research Designs

Systematic reviews have the great potential to lead the reproducibility practice among the rest of the study designs in scientific fields because:

A. Having an update step allows the systematic reviews to be corrected and helps in advancing 'living systematic reviews';

B. Making unique progress in automation of systematic reviews helps researchers to save time and resources in every step of systematic reviewing;

C. Provision of protocol and methods facilitates the replication of systematic review in the update step.

To make such a role model, the organisations – whose main activity includes producing systematic reviews – should collaborate on developing policies on reproducibility and sharing data and methods from within the systematic reviews. On the other hand, these organisations have their own journal platforms, and the journal publishers themselves need to engage in this policy development. To avoid a meta-waste, *Cochrane Database of Systematic Reviews*, *Systematic Reviews* journal, *World Journal of Meta-Analysis*, *JBI Database of Systematic Reviews and Implementation Reports*, and *Environmental Evidence* now have a great opportunity to come together and set the bars on the reproducibility of systematic reviews.

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Thesis Summary

Paper	Title	Rationale and key outcomes
1	Study-based registers of randomized controlled trials	**Rationale**: Salami publication may lead in undercounting and over-counting of studies in meta-analysis, or misjudgement of relevancy in systematic reviewing. On the other hand, systematic reviewing is time-consuming and a resource-intensive process and semi-automation has the potential for great saving of time. Study-based registers target both salami publication and issues of time/resource waste. **Key outcomes**: There was no academic research or literature review on the topic. The paper covers history and methodology of developing and maintaining study-based registers, their structure, rationale, functionality, and the challenges and opportunities that study-based registers bring.
2	Increasing value and reducing waste in data extraction for systematic reviews	**Rationale**: There is no standard practice for recording the location of extracted data in study data extraction forms in systematic reviews. **Key outcomes**: The paper describes three possible methods to locate data in original documents and discusses advantages and disadvantages of each of the

		methods. It also encourages sharing of extracted data with a link to an appendix facilitating practicing of one of the data-locating methods.
3	Why Cochrane should prioritise sharing data	**Rationale**: Accessing large structured data could facilitate meta-research and meta-analysis and lead to discovering new relations and patterns within the data. If data has been collected using public resources – this also raises ethical and legal concerns. Cochrane Collaboration, as a supported organisation by public funding, has no clear policy on sharing data. **Key outcomes**: This widely authored paper draws attentions to Cochrane's unclear policies on sharing data. Describing the rationale and benefits of sharing the data, the papers calls for action and describes the structured data that could be shared from within Cochrane reviews. A reply by Editor in Chief of the Cochrane Library shows interest in developing such a policy.
4	Study-based registers reduce waste in systematic reviewing	**Rationale**: Study-based registers are not widely understood – even among systematic reviewers. This paper tries to show the advantages of these registers with a particular focus on saving resources and time in grant application and updating reviews. **Key outcomes**: The register can save months of work for a systematic review

		team through providing accurate estimate of workload, possible review titles, lists of new treatments whilst supplying existing data thus shortening the early steps of systematic reviews to minutes if not seconds.
5	A simple formula for enumerating comparisons in trials and network meta-analysis	**Rationale**: Study-based registers are a source of accurate data which then can be used to improve the systematic reviewing process. As part of extracting meta-data from each study, the Information Specialist creates 'X vs. Y' comparisons for every randomised trial. When the trial has multi-arms, it is easy to lose the track of number of pairwise comparisons. The formula – adopted from elsewhere - provides accurate number of comparisons given the accurate number of trial arms. Importantly, this formula also has implications for network meta-analysis to detect the evidence gap in network plots. **Key outcomes**: the formula provides the accurate estimate of number of pairwise comparisons from a trial or in a network meta-analysis. Its use also highlights the gap between the existing evidence and the evidence presented in network meta-analysis showing the proportion of the evidence that has reported – and the proportion that has not.
6	Classification of all pharmacological interventions tested in trials relevant	**Rationale**: Single pharmacological intervention may have many names and systematic reviewers sometimes target a group of drugs rather than two drugs.

	to people with schizophrenia	Having all pharmacological interventions classified can save massive time in searching and provide accurate number of studies with no 'false positive' results. Key outcomes: The paper presents the first classification of pharmacological interventions and their qualifiers from all schizophrenia trials. It uses several sources to show that no existing system is comprehensive and even WHO ATC is limited. One third of schizophrenia drug treatments are not in the market.
7	Cochrane Schizophrenia Group's Study-Based Register of Randomized Controlled Trials	Rationale: A curated study-based register is a dataset that holds potential for novel insights. The paper reports use of structured meta-data at both reference and study-level and presents new insights into publication and research practice. Key outcomes: Trials registers are the main source of randomised trial reports relevant to people with schizophrenia - followed by speciality journals, conference, proceedings, Chinese journals, and dissertation. Production of schizophrenia trials depends on inter-related factors some of which are discussed through illustrations supported by register analyses. Trials remain so small that clinically meaningful outcomes my well fail to be identified because of the study design. Reports of registered trials are becoming more prevalent every year and pharmaceutical research predominates. Only 10% of schizophrenia studies are included Cochrane schizophrenia – although another 25% have been

		considered and not been possible to include.
8	Reducing waste and increasing value through embedded replicability and reproducibility in systematic review process and automation	**Rationale**: It has been suggested that there should be new 'reproducibility tests' added to the process of systematic reviewing. Taking into account that systematic reviews are already time-consuming, it is argued that we should follow other routes for reproducibility practice in systematic reviews. **Key outcomes**: Reproducibility is embedded within the methodology of systematic reviewing. Two or three reviewers check screening and data extraction. Furthermore, automation of some steps of the systematic review process can help the researchers to repeat steps - if the data and methods are shared – in a matter of seconds. The paper makes suggestions for PRISMA and leads on to Paper 9 – which introduces practical routes to reproducibility.
9	Reproducibility and replicability of systematic reviews	**Rationale**: Problems with not being able to reproduce findings affects all of science and systematic reviews are no exception. **Key outcomes**: The paper lists seven strategies – often facilitated by use of the study-based register - for enhancing the reproducibility of systematic reviews with the potential for making systematic reviews the role model for other research designs in scientific integrity.

Contribution to Knowledge, Policy, and Practice

Cochrane Schizophrenia Group's Study-Based Register of randomised controlled trials is the main contribution of this thesis to knowledge. The content added to the register between mid-2013 and mid-2019 (6 years) is more than the content added between 1993 and mid-2013 (20 years). Although it was expected that we should hire more human resources to deal with such workload, the classification and standardization of the content in this register saved huge amount of time for the Information Specialist so more human resource was not required. Paper 4 discusses details of how this came about and its advantages. This dataset was shared with three research groups in the USA and the UK for machine-learning and automation purposes and two teams from Australia and Belgium requested us to help them in piloting study-based register system for their organizations. This register is one of the best specialised registers, if not the best, among Cochrane groups in terms of quality of data and implementing and creating a classification system that serves the editorial base and review teams and saves resources for funders.

As detailed in Paper 4, this register saves time in all steps of systematic reviewing, either it is registering a new review title or updating a review. Accurate prediction of the number of studies to be reviewed helps both editorial base and review team to decide if they want to proceed with the title based on the available resources. It happens that the classification in the register informs the reviewers about a new comparison that have not been reviewed or suggests breaking a large review into smaller but manageable reviews. Furthermore, shortcutting stages such as screening save time for the reviewers. Paper 2 and 4 are representing a successful grant application fed by workflow estimation from this register. In addition to all, having all reports of one study in one place saves the time in identifying pieces of puzzle and saves the time for checking for Ongoing and Awaiting Classification studies. Information Specialist does not require building long search strategies and the search time is between seconds and minutes for a typical Cochrane review.

Study-based registers, in some form or other, have been used in science and the scientific literature for over two decades but there was no clear description of them in the literature.

For the first time, this work describes this technology in detail and explains and discusses the rationale, methodology, advantages, and challenges. Whilst undertaking this work, and as a logical progression of it, I organised calls for policies on data sharing and reproducibility. The work used methods of literature reviewing, case studies, cataloguing and classification, critical thinking, data and meta-data collection and curation, data analysis and data visualisation in meta-research to demonstrate the capabilities of study-based registers.

As a result of this work, a formula is published to assist the bourgeoning area of network meta-analysis and the largest producer of maintained systematic reviews on the planet is reconsidering its policy on data sharing. Also, as a direct result of this work, Cochrane Schizophrenia, based in the University of Nottingham, now holds one of the most sophisticated sources of trial evidence in existence and is a common point of contact for anyone in the world interested in evaluation of care provided for people with schizophrenia.

Multi-Disciplinary Methodology

The current thesis is covering multi-disciplinary topics included but not limited to:

- Clinical Sciences (Schizophrenia, Pharmacotherapy, and Epidemiology);
- Computer Science (Data Science and Database Management);
- Information Science (Knowledge Organization and Information Retrieval and Storage);
- Scientific Communications (Systematic Reviews).

Research methods and techniques used in the current thesis were borrowed from all the aforementioned disciplines:

- Computer Science: Database and Software Development (Paper 1 and 7), Meta-Data Scheme Development (Paper 6), Text Analysis (Paper 6 and 7), Dataset Development (Paper 1, 2, and 7), Database Migration (Paper 7), Data Waste and Recycling Data (Paper 2), Process Mining (Paper 4), Pilot Study (Paper 2, 4, and 5)

- Health Services Research: Feasibility Study (Paper 2 and 4), Case Study (Paper 2 and 4), Economic Study (Paper 4)
- Library and Information Science: Systematic Review (Paper 1), Scientometrics (Paper 7), Classification Development (Paper 6), Methods Research (Paper 1, 2, and 5), Policy Research (Paper 3, 8, and 9)
- Philosophy: Action Research (Paper 1, 2, 4, 5, 6, and 7)
- Qualitative Research: Content Analysis (Paper 6 and 7)
- Quantitative Research (in Epidemiology): Cross-Sectional or Population-Based or Register-Based Study (Paper 7), Meta-Research (Paper 6 and 7), Trend Analysis (Paper 7), Correlational Study (Paper 7), Validation and Reliability Study (Paper 6 and 7), Geographical Mapping Study (Paper 7)
- Statistics: Formula Development and Testing (Paper 5)

Recommendations

Systematic review groups already curate their data sets into study-based registers – essentially their completed systematic reviews. These micro-registers should not be disassembled on completion of the review but should be made public in order to be maintained and not re-invented next time a review is to be created or updated.

Institutions producing systematic reviews should maintain study-based registers.

Information Specialists training should include modules on creation and management of study-based registers with career progression through to Data Scientists.

Movement toward Open Synthesis as part of Open Science movement should continue and involve Open Data, Open Access, Open Source, and Open Methodology.

Future Directions/Outstanding Questions

Being aware of challenges of linked open data, I will continue to learn new skills to move MeerKat online making it free, publicly accessible, crowd-'sourceable' and usable.

Stand-alone study-based registers will be moved towards cloud computing and web-based platforms. Although Cochrane's CRS is a web-based and cloud-based system, it does not support study-based functions that save time and resources for review teams. We hope Cochrane policies shift towards supporting Cochrane systematic review teams to facilitate their needs in data management.

Cochrane Schizophrenia is well-placed to continue to lead development of innovative systems of data supply so that, amongst many other things, best treatment evidence can be supplied to the coal-face of care in a truly swift informative way.

Although we discussed the economy of study-based register in terms of time and human resources, we did not compare the study-based register with traditional approach in supplying the evidence for systematic reviews. We are developing the protocol of an ongoing study, out of scope of the current thesis, to quantify the economic benefit of study-based register in comparison with traditional approach.

Conclusion

This research introduced study-based registers and shared practical experience in database development and management. Cochrane Schizophrenia now holds a reliable, clean and structured dataset to support its daily work. This register saves time for research teams shortening the systematic review process and reducing errors and waste. The register solves the issues of salami publications and retracted/corrected records. In addition, it provides a classification for interventions that facilitates a search with a remarkable 100% precision and recall – now a reality rather than a dream for any information retrieval system. This register can be a gold standard for machine learning and information retrieval systems, cross-language retrieval and text analysis.

The current work was a journey that started from the daily practice of an Information Specialist and involved many levels of methodological and data science skills – including dissemination of the work and petitioning for more open policies on data-sharing. The impact of this work continues daily within Cochrane Schizophrenia and its [current] 324 maintained reviews, the Cochrane Collaboration's policies and within the international evidence synthesis community who seek reproducible systematic reviews and automation.

In terms of professionalism, the Information Professionals, across various levels of their career, pose different ranges of skills. They have to update the existing skill set or learn new ones to survive and evolve. Technological developments have already and repeatedly challenged Information Professionals and every time Information Professionals have turned the challenges into opportunities. When the internet was emerging, a librarian coined the phrase 'surfing the internet' and the librarians looked to the internet and web as media holding information so it was they who developed catalogues and resources to make it useful and usable. Later, when search engines such as Yahoo and Google were evolving, librarians were integral in helping develop subject directories and assessing the relevancy ranking. Information Scientists recognized that the tools were changing – although the principles were stable. They adapted and learnt new skills – this process must continue.

Two decades before emergence of evidence-based medicine as a new paradigm in 1970s, clinical librarians started bringing evidence to doctors in clinical settings when no one talked of evidence-based medicine. When evidence synthesis started, the librarian moved from searching library catalogues to searching databases with the search syntax – the language of databases. Now is the era of automation and semi-automation of evidence synthesis it is time for information professionals to not only learn programming languages but also to join the automation initiatives. Machines need supervised and semi-supervised sets to learn from. Information Professionals can supervise these sets and run the machines. Books, the internet, and databases are only media holding knowledge, information and data. It is time for Informational Professionals to develop again and move towards data science.

Appendices

Appendix 1-1

File Name: Structure of a Randomized Controlled Trial Study in XML Format

File Description: Following data could be copied and saved with .xml extension and could be opened/edited using any XML Editor. This structure tries to present a machine-readable format for a study record.
Citation: Please cite the main paper

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Appendix 2-1

Additional file 1: A data extraction form based on real data using *Descriptive addressing* method

Study Name	**Jahanian 2014**				
Reference	[Ref. ID 19855] Jahanian AA, Rezaei O, Fadai F, Yaraghchi A. The Effectiveness of Rivastigmine in Reducing Tardive Dyskinesia Symptoms in Patients with Schizophrenia. Iranian Journal of Psychiatry and Clinical Psychology 2014; 20(1): 29-34.				
Characteristics					**Location in PDF***
Methods	Allocation: "randomly assigned" no details reported.				19855PG30C1P3L7
	Blindness: "double blind" no details reported.				19855PG30C1P3L3
	Design: not reported.				
	Duration: "eight weeks".				19855PG31C1P2L4
	Setting: "Razi Psychiatric Center, Tehran, Iran".				19855PG30C1P3L5
Participants	Diagnosis: Patients with schizophrenia and tardive dyskinesia (TD) based on DSM-IV-TR diagnosed by a psychiatrist.				19855PG30C1P3L12-13
	N=40.				19855PG30C1P3L5
	Age: range 18-65 years.				19855PG30C1P3L17
	Sex: not reported.				
Interventions	1. Rivastigmine: dose: 1.5 mg twice daily. N=20.				19855PG30C1P3L7-8
	2. Placebo: no details reported. N=20.				19855PG30C1P3L10
Outcomes	TD symptoms: no improvement (AIMS).				19855PG31C1P2L5
Notes	Sponsorship source: "no financial support".				19855PG33C2P3L1-2
Risk of Bias					
Bias	Support Statement from Report				
Random sequence generation	"Randomly". No details.				19855PG30C1P3L7
Allocation concealment	Not reported.				
Blinding of participants and personnel	"Double blind". No details.				19855PG30C1P3L3
Blinding of outcome assessment	"Double blind". No details.				19855PG30C1P3L3
Incomplete outcome data	Not reported.				
Selective reporting	Outcomes have been reported based on the registered protocol IRCT2012092910964N1.				19855PG30C1P3L1
Other biases	None known.				
Outcome					
	Rivastigmine		Placebo		
	Mean	SD	Mean	SD	
AIMS after Intervention	12.5	7.0	10.3	3.1	19855PG32T2

*In this example, the first five digits refer to the file name, PG to pages, C to the column, P to paragraph, L to the line, and T to Table.

Appendix 6-1

Table A-6-1-1: Research drugs tested in schizophrenia trials

Intervention	Potential Clinical Class	Claimed Mechanism of Actions	Development Status	Market
Monoamine	Not Available	Amino Acid Derivatives	Developing	Not Marketed
R209130	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists	Developing	Not Marketed
Stepholidine	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists+Dopamine D1 Receptor Agonists	Developing	Not Marketed
Muscimol	Anti Parkinson Drugs	GABA A Receptor Agonists	Developing	Not Marketed
Sarcosine	Not Available	Glycine Transporter 1 Inhibitors	Developing	Not Marketed
meta-Chlorophenylpiperazine	Metabolites	Phenylpiperazine Derivatives	Developing	Not Marketed
SKL 15508	Not Available	Alpha7 Nicotinic Acetylcholine Receptor Agonists	Developing-Adis	Not Marketed
APN 1125	Psycholeptics-Antipsychotics	Alpha7 Nicotinic Acetylcholine Receptor Agonists	Developing-Adis	Not Marketed
Encenicline	Psycholeptics-Antipsychotics	Alpha7 Nicotinic Acetylcholine Receptor Agonists	Developing-Adis	Not Marketed
Nelonicline	Psycholeptics-Antipsychotics	Alpha7 Nicotinic Acetylcholine Receptor Agonists	Developing-Adis	Not Marketed
VQW 765	Psycholeptics-Antipsychotics	Alpha7 Nicotinic Acetylcholine Receptor Agonists	Developing-Adis	Not Marketed
JNJ 39393406	Drugs Used in Addictive Disorders-Drugs Used in Nicotine Dependence	Alpha7 Nicotinic Acetylcholine Receptor Modulators	Developing-Adis	Not Marketed
PF 04958242	Psycholeptics-Antipsychotics	AMPA Receptor Modulators	Developing-Adis	Not Marketed
TAK 831	Psycholeptics-Antipsychotics	D Amino Acid Oxidase Inhibitors	Developing-Adis	Not Marketed
ALKS-3831	Psycholeptics-Antipsychotics	Dopamine D1 Receptor Antagonists+Dopamine D2 Receptor Antagonists+Opioid mu Receptor Antagonists+Serotonin 2A Receptor Antagonists	Developing-Adis	Not Marketed
Lu AF35700	Psycholeptics-Antipsychotics	Dopamine D1 Receptor Antagonists+Serotonin 2A Receptor Antagonists+Serotonin 6 Receptor Antagonists	Developing-Adis	Not Marketed

ASP 4345	Psycholeptics-Antipsychotics	Dopamine D1 Receptor Modulators	Developing-Adis	Not Marketed
RP 5063	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Agonists+Dopamine D3 Receptor Agonists+Dopamine D4 Receptor Agonists+Serotonin 1A Receptor Agonists+Serotonin 2A Receptor Agonists+Serotonin 2B Receptor Antagonists+Serotonin 6 Receptor Antagonists+Serotonin 7 Receptor Antagonists	Developing-Adis	Not Marketed
Evenamide	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists+Serotonin 2 Receptor Antagonists	Developing-Adis	Not Marketed
TV 46000	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists+Serotonin 2A Receptor Antagonists	Developing-Adis	Not Marketed
F 17464	Psycholeptics-Antipsychotics	Dopamine D3 Receptor Antagonists+Serotonin 1A Receptor Agonists	Developing-Adis	Not Marketed
Lumateperone	Psycholeptics-Antipsychotics	Dopamine Receptor Modulators+Serotonin 2A Receptor Antagonists	Developing-Adis	Not Marketed
Basmisanil	Psycholeptics-Antipsychotics	GABA A Alpha 5 Receptor Modulators	Developing-Adis	Not Marketed
BI 425809	Psycholeptics-Antipsychotics	Glycine Transporter 1 Inhibitors	Developing-Adis	Not Marketed
TAK 041	Not Available	GPR139 Protein Agonists	Developing-Adis	Not Marketed
Pomaglumetad Methionil	Psycholeptics-Antipsychotics	Metabotropic Glutamate Receptor 2 Agonists+Metabotropic Glutamate Receptor 3 Agonists	Developing-Adis	Not Marketed
Talnetant	Drugs for Functional Gastrointestinal Disorders	Neurokinin 3 Antagonists	Developing-Adis	Not Marketed
Nicotinamide Adenine Dinucleotide	Not Available	Nicotinamide Adenine Dinucleotide Modulators	Developing-Adis	Not Marketed
Apimostinel	Psychoanaleptics-Antidepressants	NMDA Receptor Agonists	Developing-Adis	Not Marketed
Deudextromethorphan	Psycholeptics-Antipsychotics	NMDA Receptor Antagonists	Developing-Adis	Not Marketed
Curcumin	Psycholeptics-Antipsychotics	Not Available	Developing-Adis	Not Marketed
MK 8189	Psycholeptics-Antipsychotics	Not Available	Developing-Adis	Not Marketed
BI 409306	Psycholeptics-Antipsychotics	Phosphodiesterase 9A Inhibitors	Developing-Adis	Not Marketed
Lu AF11167	Psycholeptics-Antipsychotics	Phosphoric Diester Hydrolase Inhibitors	Developing-Adis	Not Marketed
SEP 363856	Psycholeptics-Antipsychotics	Serotonin 1A Receptor Agonists	Developing-Adis	Not Marketed
Roluperidone	Psycholeptics-Antipsychotics	Serotonin 2A Receptor Antagonists	Developing-Adis	Not Marketed

TAK 058	Psycholeptics-Antipsychotics	Serotonin 3 Receptor Antagonists	Developing-Adis	Not Marketed
AVN 211	Psycholeptics-Antipsychotics	Serotonin 6 Receptor Antagonists	Developing-Adis	Not Marketed
Rimcazole	Psycholeptics-Antipsychotics	Sigma Receptor Antagonists	Developing-Adis	Not Marketed
DAAOI-2	Not Available	D Amino Acid Oxidase Inhibitors+NMDA Enhancing Agents	Developing-CT.Gov	Not Marketed
BE	Not Available	Not Available	Developing-CT.Gov	Not Marketed
GlyT-1 Inhibitor-1	Not Available	Not Available	Developing-CT.Gov	Not Marketed
Lipopolysaccharide	Not Available	Not Available	Developing-CT.Gov	Not Marketed
MS14	Not Available	Not Available	Developing-CT.Gov	Not Marketed
Clomacran	Psycholeptics-Antipsychotics	Acridane Derivative	Not Available	Not Marketed
Alanine	Not Available	Amino Acids	Not Available	Not Marketed
AL 1021	Psycholeptics-Antipsychotics	Butyrophenone Derivatives	Not Available	Not Marketed
Biriperone	Psycholeptics-Antipsychotics	Butyrophenone Derivatives	Not Available	Not Marketed
BP 4897	Not Available	Dopamine D3 Receptor Agonists	Not Available	Not Marketed
CF 25-397	Anti Parkinson Drugs	Dopamine Receptor Agonists+Ergot Derivatives	Not Available	Not Marketed
Butaclamol	Psycholeptics-Antipsychotics	Dopamine Receptor Antagonists	Not Available	Not Marketed
Capuride	Antiepileptics	Not Available	Not Available	Not Marketed
Amphenidone	Not Available	Not Available	Not Available	Not Marketed
B.W.203	Not Available	Not Available	Not Available	Not Marketed
BAY 2591	Not Available	Not Available	Not Available	Not Marketed
BC 347	Not Available	Not Available	Not Available	Not Marketed
BL KR140	Not Available	Not Available	Not Available	Not Marketed
Choline	Not Available	Not Available	Not Available	Not Marketed
CI 383	Not Available	Not Available	Not Available	Not Marketed

CI 515	Not Available	Not Available	Not Available	Not Marketed
Cosaldon Retard	Not Available	Not Available	Not Available	Not Marketed
Cyprodenate	Not Available	Not Available	Not Available	Not Marketed
Dihydroarteannuin	Not Available	Not Available	Not Available	Not Marketed
Iomazenil	Not Available	Not Available	Not Available	Not Marketed
Isofloxythepin	Not Available	Not Available	Not Available	Not Marketed
Cyclopregnol	Psycholeptics-Antipsychotics	Not Available	Not Available	Not Marketed
Des-Enkephalin-Gamma-Endorphin	Psycholeptics-Antipsychotics	Not Available	Not Available	Not Marketed
Des-Tyrosine-Gamma-Endorphin	Psycholeptics-Antipsychotics	Not Available	Not Available	Not Marketed
Hydroxyphenamate	Psycholeptics-Anxiolytics	Not Available	Not Available	Not Marketed
Ethybenztropine	Anti Parkinson Drugs	Anticholinergic Agents	Stopped	Not Marketed
Piroheptine	Anti Parkinson Drugs	Anticholinergic Agents	Stopped	Not Marketed
EMD 16139	Not Available	Benzoquinolizine Derivative	Stopped	Not Marketed
CI 601	Not Available	Butyrophenone Derivatives	Stopped	Not Marketed
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Clofluperol	Psycholeptics-Antipsychotics	Butyrophenone Derivatives	Stopped	Not Marketed
Halopemide	Psycholeptics-Antipsychotics	Butyrophenone Derivatives	Stopped	Not Marketed
Tybamate	Psycholeptics-Anxiolytics	Carbamate Derivatives	Stopped	Not Marketed
Trebenzomine	Psychoanaleptics-Antidepressants	Chromanamine Derivatives	Stopped	Not Marketed
Metiapine	Psycholeptics-Antipsychotics	Dibenzothiazepine	Stopped	Not Marketed
Pinoxepin	Psycholeptics-Antipsychotics	Dibenzoxepine Derivatives	Stopped	Not Marketed
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Propylnorapomorphine	Anti Parkinson Drugs	Dopamine Receptor Agonists	Stopped	Not Marketed

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Reduced Haloperidol	Metabolites	Phenylpiperidines	Stopped	Not Marketed
Sedaltine	Psycholeptics-Anxiolytics+Hypnotics and Sedatives	Poly-Pharmaceutical Preparation	Stopped	Not Marketed
Glaziovine	Hypnotics and Sedatives	Proaporphine Alkaloids	Stopped	Not Marketed
Piquindone	Psycholeptics-Antipsychotics	Pyrroloisoquinoline Derivatives	Stopped	Not Marketed
2-methyl-3-orthotolyl-4-quinazinolone	Hypnotics and Sedatives	Quinazolone Derivatives	Stopped	Not Marketed
MK 212	Psycholeptics-Anxiolytics	Serotonin 5-HT2c Receptor Agonists	Stopped	Not Marketed
Noxiptiline	Psychoanaleptics-Antidepressants	Serotonin and Norepinephrine Reuptake Inhibitors	Stopped	Not Marketed
U-22,394a	Psycholeptics-Antipsychotics	Tryptamine Derivatives	Stopped	Not Marketed
Preladenant	Anti Parkinson Drugs	Adenosine A2 Receptor Antagonists	Stopped-Adis	Not Marketed
Levafetamine	Not Available	Adrenergic Receptor Agonists+Central Nervous System Stimulants+Neurotransmitter Modulators	Stopped-Adis	Not Marketed
ICI 118551	Not Available	Alpha 1 Adrenergic Receptor Antagonists+Beta 2 Adrenergic Receptor Antagonists (Beta Blocking Agents)	Stopped-Adis	Not Marketed
Idazoxan	Psychoanaleptics-Antidepressants	Alpha 2 Adrenergic Receptor Antagonists	Stopped-Adis	Not Marketed
Ispronicline	Not Available	Alpha4 Beta2 Nicotinic Receptor Agonists	Stopped-Adis	Not Marketed
Bradanicline	Psycholeptics-Antipsychotics	Alpha7 Nicotinic Acetylcholine Receptor Agonists	Stopped-Adis	Not Marketed
GTS 21	Psycholeptics-Antipsychotics	Alpha7 Nicotinic Acetylcholine Receptor Agonists	Stopped-Adis	Not Marketed

AZD 0328	Anti Dementia	Alpha7 Nicotinic Acetylcholine Receptor Agonists	Stopped-Adis	Not Marketed
CX 516	Not Available	AMPA Receptor Agonists+AMPA Receptor Antagonists+Glutamate Agonists	Stopped-Adis	Not Marketed
Farampator	Psycholeptics-Antipsychotics	AMPA Receptor Agonists+Glutamate Agonists	Stopped-Adis	Not Marketed
Oglufanide	Not Available	Angiogenesis Inhibitors+Immunomodulators	Stopped-Adis	Not Marketed
Drinabant	Psycholeptics-Antipsychotics	Cannabinoid Receptor CB1 Antagonists	Stopped-Adis	Not Marketed
RS 86	Not Available	Cholinergic Receptor Agonists	Stopped-Adis	Not Marketed
L 745870	Psycholeptics-Antipsychotics	D4 Dopamine Receptor Antagonists	Stopped-Adis	Not Marketed
Dihydrexidine	Anti Parkinson Drugs	Dopamine D1 Receptor Agonists	Stopped-Adis	Not Marketed
SDZ 208912	Not Available	Dopamine D2 Receptor agonists+Dopamine D2 Receptor Antagonists	Stopped-Adis	Not Marketed
Norclozapine	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Agonists+Dopamine D3 Receptor Agonists+Muscarinic M1 Receptor Agonists+Serotonin 2A Receptor Inverse Agonists	Stopped-Adis	Not Marketed
Sarizotan	Anti Parkinson Drugs	Dopamine D2 Receptor Agonists+Serotonin 1A Receptor Agonists	Stopped-Adis	Not Marketed
Bifeprunox	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Agonists+Serotonin 1A Receptor Agonists	Stopped-Adis	Not Marketed
PF 00217830	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Agonists+Serotonin 1A Receptor Agonists+Serotonin 2A Receptor Antagonists	Stopped-Adis	Not Marketed
Raclopride	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists	Stopped-Adis	Not Marketed
Savoxepin	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists	Stopped-Adis	Not Marketed
UH 232	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists+Dopamine D3 Receptor Antagonists	Stopped-Adis	Not Marketed
Pridopidine	Anti Parkinson Drugs	Dopamine D2 Receptor Antagonists+Glutamate Modulators+Sigma-1 Receptor Agonists	Stopped-Adis	Not Marketed
SLV 313	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists+Serotonin 1A Receptor Agonists	Stopped-Adis	Not Marketed
ABT 925	Psycholeptics-Antipsychotics	Dopamine D3 Receptor Antagonists	Stopped-Adis	Not Marketed
Sonepiprazole	Psycholeptics-Antipsychotics	Dopamine D4 Receptor Antagonists	Stopped-Adis	Not Marketed
Fananserin	Psycholeptics-Antipsychotics	Dopamine D4 Receptor Antagonists+Serotonin 2 Receptor Antagonists	Stopped-Adis	Not Marketed

Balaperidone	Not Available	Dopamine D4 Receptor Antagonists+Serotonin 2A Receptor Antagonists	Stopped-Adis	Not Marketed
PF 06412562	Anti Parkinson Drugs	Dopamine Receptor Agonists	Stopped-Adis	Not Marketed
Preclamol	Psycholeptics-Antipsychotics	Dopamine Receptor Agonists	Stopped-Adis	Not Marketed
OPC 4392	Psycholeptics-Antipsychotics	Dopamine Receptor Antagonists	Stopped-Adis	Not Marketed
BL 1020	Psycholeptics-Antipsychotics	Dopamine Receptor Antagonists+GABA Receptor Agonists	Stopped-Adis	Not Marketed
MK 0777	Not Available	GABA A Alpha 2 Receptor Agonists+GABA A Alpha 3 Receptor Agonists	Stopped-Adis	Not Marketed
Alpidem	Psycholeptics-Anxiolytics	GABA A Receptor Agonists	Stopped-Adis	Not Marketed
CI 966	Antiepileptics	GABA Uptake Inhibitors	Stopped-Adis	Not Marketed
Siagoside	Not Available	Gangliosides	Stopped-Adis	Not Marketed
AZD 8529	Psycholeptics-Antipsychotics	Glutamate Modulators	Stopped-Adis	Not Marketed
Org 25935	Not Available	Glycine Transporter 1 Inhibitors	Stopped-Adis	Not Marketed
AMG 747	Psycholeptics-Antipsychotics	Glycine Transporter 1 Inhibitors	Stopped-Adis	Not Marketed
Bitopertin	Psycholeptics-Antipsychotics	Glycine Transporter 1 Inhibitors	Stopped-Adis	Not Marketed
GSK 1018921	Psycholeptics-Antipsychotics	Glycine Transporter 1 Inhibitors	Stopped-Adis	Not Marketed
PF 03463275	Psycholeptics-Antipsychotics	Glycine Transporter 1 Inhibitors	Stopped-Adis	Not Marketed
GSK 239512	Psycholeptics-Antipsychotics	Histamine H3 Receptor Antagonists	Stopped-Adis	Not Marketed
MK 0249	Psycholeptics-Antipsychotics	Histamine H3 Receptor Antagonists	Stopped-Adis	Not Marketed
Pavinetant	Not Available	Hormone Modulators+Neurokinin 3 Receptor Antagonists	Stopped-Adis	Not Marketed
ADX 71149	Psycholeptics-Antipsychotics	Metabotropic Glutamate Receptor 2 Modulators	Stopped-Adis	Not Marketed
TS 032	Psycholeptics-Antipsychotics	Metabotropic Glutamate Receptor Agonists	Stopped-Adis	Not Marketed
Davunetide	Anti Dementia	Microtubule-Associated Protein Modulators	Stopped-Adis	Not Marketed
Xanomeline	Psycholeptics-Antipsychotics	Muscarinic M1 Receptor Agonists+Muscarinic M4 Receptor Agonists	Stopped-Adis	Not Marketed
Leteprinim	Not Available	Nerve Growth Factor Modulators	Stopped-Adis	Not Marketed
Osanetant	Psycholeptics-Antipsychotics	Neurokinin 3 Antagonists	Stopped-Adis	Not Marketed
MK 0557	Not Available	Neuropeptide Y5 Receptor Antagonists	Stopped-Adis	Not Marketed
Meclinertant	Psycholeptics-Antipsychotics	Neurotensin Antagonists	Stopped-Adis	Not Marketed
ABT 288	Psycholeptics-Antipsychotics	Neurotransmitter Receptor Modulators	Stopped-Adis	Not Marketed

MK 5757	Not Available	Not Available	Stopped-Adis	Not Marketed
ASP 6981	Psycholeptics-Antipsychotics	Not Available	Stopped-Adis	Not Marketed
Fluperlapine	Psycholeptics-Antipsychotics	Not Available	Stopped-Adis	Not Marketed
Panamesine	Psycholeptics-Antipsychotics	Opioid Receptor Antagonists	Stopped-Adis	Not Marketed
Balipodect	Psycholeptics-Antipsychotics	Phosphodiesterase 10A Inhibitors	Stopped-Adis	Not Marketed
FRM 6308	Psycholeptics-Antipsychotics	Phosphodiesterase 10A Inhibitors	Stopped-Adis	Not Marketed
Mardepodect	Psycholeptics-Antipsychotics	Phosphodiesterase 10A Inhibitors	Stopped-Adis	Not Marketed
OMS 643762	Psycholeptics-Antipsychotics	Phosphodiesterase 10A Inhibitors	Stopped-Adis	Not Marketed
Ipsapirone	Psycholeptics-Anxiolytics	Serotonin 1A Receptor Agonists	Stopped-Adis	Not Marketed
Eltoprazine	Psycholeptics-Antipsychotics	Serotonin 1A Receptor Agonists+Serotonin 1B Receptor Agonists	Stopped-Adis	Not Marketed
Ritanserin	Not Available	Serotonin 2 Receptor Antagonists	Stopped-Adis	Not Marketed
Eplivanserin	Not Available	Serotonin 2 Receptor Antagonists+Serotonin 2A Receptor Antagonists	Stopped-Adis	Not Marketed
Volinanserin	Psycholeptics-Antipsychotics	Serotonin 2A Receptor Antagonists	Stopped-Adis	Not Marketed
Vabicaserin	Psycholeptics-Antipsychotics	Serotonin 2C Receptor Agonists	Stopped-Adis	Not Marketed
Zacopride	Psycholeptics-Antipsychotics	Serotonin 3 Receptor Antagonists	Stopped-Adis	Not Marketed
Tiospirone	Psycholeptics-Antipsychotics	Serotonin Receptor Antagonists	Stopped-Adis	Not Marketed
SR 31742A	Psycholeptics-Antipsychotics	Sigma Receptor Agonists	Stopped-Adis	Not Marketed
IHBG-10	Not Available	Not Available	Stopped-CT.Gov	Not Marketed
7 Meota	Anti Parkinson Drugs	Acetylcholinesterase Inhibitors	Unclear-Adis	Not Marketed
Huperzine A	Anti Parkinson Drugs	Acetylcholinesterase Inhibitors+NMDA Receptor Antagonists	Unclear-Adis	Not Marketed
Facinicline	Anti Dementia	Alpha7 Nicotinic Acetylcholine Receptor Agonists	Unclear-Adis	Not Marketed
AVL 3288	Psycholeptics-Antipsychotics	Alpha7 Nicotinic Acetylcholine Receptor Modulators	Unclear-Adis	Not Marketed
Cattle Encephalon Glycoside and Ignotin	Not Available	Amino Acids+Gangliosides+Hypoxanthines+Nucleic Acids+Peptides	Unclear-Adis	Not Marketed
D-Serine	Not Available	Amino Acids+Glycine NMDA-Associated Agonists	Unclear-Adis	Not Marketed
2 Deoxy D Glucose	Antineoplastics	Antimetabolites+Glucose Modulators	Unclear-Adis	Not Marketed
Pregnenolone	Not Available	Corticosteroids for Systemic Use	Unclear-Adis	Not Marketed
OSU 6162	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Agonists+Serotonin 2A Receptor Agonists	Unclear-Adis	Not Marketed

JNJ 37822681	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists	Unclear-Adis	Not Marketed
Mazapertine	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists	Unclear-Adis	Not Marketed
SB 773812	Psycholeptics-Antipsychotics	Dopamine D2 Receptor Antagonists+Serotonin 2A Receptor Antagonists	Unclear-Adis	Not Marketed
Ganaxolone	Antiepileptics	GABA A Receptor Agonists	Unclear-Adis	Not Marketed
Gaboxadol	Not Available	GABA A Receptor Agonists	Unclear-Adis	Not Marketed
Guanabenz	Antihypertensives	Immunostimulants	Unclear-Adis	Not Marketed
FPF-1070	Not Available	Neuron Stimulants	Unclear-Adis	Not Marketed
Zicronapine	Psycholeptics-Antipsychotics	Neurotransmitter Receptor Modulators	Unclear-Adis	Not Marketed
NSA 789	Anti Dementia	Not Available	Unclear-Adis	Not Marketed
Phosphatidylcholine	Anti Parkinson Drugs	Not Available	Unclear-Adis	Not Marketed
Dihomo Gamma Linolenic Acid	Not Available	Not Available	Unclear-Adis	Not Marketed
Fenretinide	Not Available	Not Available	Unclear-Adis	Not Marketed
Resveratrol	Not Available	Not Available	Unclear-Adis	Not Marketed
RO 5545965	Not Available	Not Available	Unclear-Adis	Not Marketed
Sulforaphane	Not Available	Not Available	Unclear-Adis	Not Marketed
AMG 581	Psycholeptics-Antipsychotics	Not Available	Unclear-Adis	Not Marketed
Beta-Endorphin	Analgesics	Opioid Receptor Agonists	Unclear-Adis	Not Marketed
Idalopirdine	Psycholeptics-Antipsychotics	Serotonin 6 Receptor Antagonists	Unclear-Adis	Not Marketed
AUT 00206	Psycholeptics-Antipsychotics	Shaw Potassium Channel Modulators	Unclear-Adis	Not Marketed
MK 8998	Psycholeptics-Antipsychotics	T Type Calcium Channel Antagonists	Unclear-Adis	Not Marketed
Methitural	Anesthetics	Barbiturate Derivatives	Developing	Post-Marketing Withdrawal
Benactyzine	Psychoanaleptics-Antidepressants	Anticholinergic Agents	Stopped	Post-Marketing Withdrawal
Picrotoxin	Not Available	GABA A Receptor Antagonists	Stopped	Post-Marketing Withdrawal

Pheniprazine	Psychoanaleptics-Antidepressants	Monoamine Oxidase Inhibitors	Stopped	Post-Marketing Withdrawal
Phencyclidine	Anesthetics	NMDA Receptor Antagonists	Stopped	Post-Marketing Withdrawal
Etryptamine	Psychoanaleptics-Antidepressants	Non-Selective Serotonin Receptor Agonist	Stopped	Post-Marketing Withdrawal
Benzquinamide	Antiemetics and Antinauseants	Not Available	Stopped	Post-Marketing Withdrawal
Flurothyl	Convulsants	Not Available	Stopped	Post-Marketing Withdrawal
Lysergic Acid Diethylamide (LSD)	Not Available	Not Available	Stopped	Post-Marketing Withdrawal
Azacyclonol	Psycholeptics-Antipsychotics	Not Available	Stopped	Post-Marketing Withdrawal
Carphenazine	Psycholeptics-Antipsychotics	Phenothiazine Derivatives	Stopped	Post-Marketing Withdrawal
Mepazine	Psycholeptics-Antipsychotics	Phenothiazine Derivatives	Stopped	Post-Marketing Withdrawal
Piperacetazine	Psycholeptics-Antipsychotics	Phenothiazines with Piperidine Structure	Stopped	Post-Marketing Withdrawal

Table 6-1-2: Marketed pharmacological interventions tested in schizophrenia trials

Intervention	Status	Code	Main Category	Clinical Class	Pharmacological Action/Chemical Class
Arginine Aspartate	Non-WHO-Marketed	B05XB??	Blood and Blood Forming Organs	I.V. Solution Additives	Amino Acids
Batyl Alcohol (Batilol)	Non-WHO-Marketed	V06D???	Various	Not Available	Not Available
Benserazide	Non-WHO-Marketed	N04BA??	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-DOPA Decarboxylase Inhibitors
Berberine	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Blonanserin	Non-WHO-Marketed	N05AX??	Nervous System	Psycholeptics-Antipsychotics	Not Available
Caffeic Acid	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Carnosine	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Carpipramine	Non-WHO-Marketed	N05AD??	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Cereobiogen	Non-WHO-Marketed	A03AX??	Alimentary Tract and Metabolism	Drugs for Functional Gastrointestinal Disorders	Not Available
Chromium Picolinate	Non-WHO-Marketed	A10X???	Alimentary Tract and Metabolism	Drugs Used in Diabetes	Not Available
Clocapramine	Non-WHO-Marketed	N05AX??	Nervous System	Psycholeptics-Antipsychotics	Imidobenzyl Derivatives
Clotepine (Clorotepine)	Non-WHO-Marketed	N05AX??	Nervous System	Psycholeptics-Antipsychotics	Perathiepin Derivatives
Creatine	Non-WHO-Marketed	B05XB??	Blood and Blood Forming Organs	I.V. Solution Additives	Amino Acids

Delorazepam	Non-WHO-Marketed	N05BA??	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Deutetrabenazine	Non-WHO-Marketed	N07XX??	Nervous System	Anti Parkinson Drugs	Vesicular Monoamine Transporter 2 Inhibitors
Dyhydroprogesterone	Non-WHO-Marketed	G03????	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Selective Estrogen Receptor Modulators
Epigallocatechin Gallate	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Essential Fatty Acids*	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Gamma-Aminobutyric Acid	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Gastrodin	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Glucuronolactone	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Hopantenic Acid	Non-WHO-Marketed	N04????	Nervous System	Anti Parkinson Drugs	Not Available
Latrepirdine	Non-WHO-Marketed	R06AX??	Respiratory System	Antihistamines for Systemic Use	Acetylcholinesterase Inhibitors+NMDA Receptor Antagonists
Lecithin	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Levamlodipine Maleate	Non-WHO-Marketed	C08CA??	Cardiovascular System	Not Available	Calcium Channel Blockers-Dihydropyridine Derivatives
Linoleic Acid	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Lodenafil Carbonate	Non-WHO-Marketed	G04BE??	Genito Urinary System and Sex Hormones	Drugs Used in Erectile Dysfunction	Phosphodiesterase Type 5 Inhibitors

Magnesium Glutamate	Non-WHO-Marketed	V06D???	Various	General Nutrients	Magnesium Compounds
Magnesium Threonate	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Mepiprazole	Non-WHO-Marketed	N05AX??	Nervous System	Psychoanaleptics-Antidepressants	Phenylpiperazine Derivatives
Nemonapride	Non-WHO-Marketed	N05AL??	Nervous System	Psycholeptics-Antipsychotics	Benzamides
Oxyprothepin	Non-WHO-Marketed	N05AX??	Nervous System	Psycholeptics-Antipsychotics	Not Available
Penehyclidine	Non-WHO-Marketed	N05CM??	Nervous System	Psycholeptics-Hypnotics and Sedatives	Anticholinergic Agents
Perlapine	Non-WHO-Marketed	N05AH??	Nervous System	Psycholeptics-Antipsychotics	Diazepines, Oxazepines, Thiazepines and Oxepines
Perospirone	Non-WHO-Marketed	N05BE??	Nervous System	Psycholeptics-Antipsychotics	Azaspirodecanedione Derivatives
Phenylalanine	Non-WHO-Marketed	B05XB??	Blood and Blood Forming Organs	I.V. Solution Additives	Amino Acids
Protoporphyrin Disodium	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Quercetin	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Saccharin	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Silicon Dioxide	Non-WHO-Marketed	A03AX13	Alimentary Tract and Metabolism	Drugs for Functional Gastrointestinal Disorders	Not Available
Sodium Butyrate	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available

Sodium Glutamate	Non-WHO-Marketed	V06D???	Various	General Nutrients	Amino Acids
Spiperone	Non-WHO-Marketed	N05AD??	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Succinic Acid	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Sulfadoxine	Non-WHO-Marketed	J01ED??	Antiinfectives for Systemic Use	Antiprotozoals-Antimalarials	Long-Acting Sulfonamides
Sydnocarb	Non-WHO-Marketed	N06B???	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Dopamine Uptake Inhibitors
Tandospirone	Non-WHO-Marketed	N06AB??+N05BE??	Nervous System	Psychoanaleptics-Antidepressants+Psycholeptics-Anxiolytics	Azaspirodecanedione Derivatives+Selective Serotonin Reuptake Inhibitors
Taurine	Non-WHO-Marketed	B05XB??	Blood and Blood Forming Organs	I.V. Solution Additives	Amino Acids
Tetrahydropalmatine	Non-WHO-Marketed	V06D???	Various	General Nutrients	Not Available
Theanine	Non-WHO-Marketed	B05XB??	Blood and Blood Forming Organs	I.V. Solution Additives	Amino Acids
Timiperone	Non-WHO-Marketed	N05AD??	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Tyrosine	Non-WHO-Marketed	B05XB??	Blood and Blood Forming Organs	I.V. Solution Additives	Amino Acids
Flumazenil	WHO-Marketed	V03AB25	Various	All Other Therapeutic Products	Antidotes
Methionine	WHO-Marketed	V03AB26	Various	All Other Therapeutic Products	Antidotes
Nalorphine	WHO-Marketed	V03AB02	Various	All Other Therapeutic Products	Antidotes

Oxygen	WHO-Marketed	V03AN01	Various	All Other Therapeutic Products	Medical Gases
Ethanol	WHO-Marketed	V03AZ01	Various	All Other Therapeutic Products	Nerve Depressants
Norethandrolone	WHO-Marketed	A14AA09	Alimentary Tract and Metabolism	Anabolic Agents-Anabolic Steroids	Androstan Derivatives
Oxymetholone	WHO-Marketed	A14AA05	Alimentary Tract and Metabolism	Anabolic Agents-Anabolic Steroids	Androstan Derivatives
Prasterone	WHO-Marketed	A14AA07	Alimentary Tract and Metabolism	Anabolic Agents-Anabolic Steroids	Androstan Derivatives
Paracetamol	WHO-Marketed	N02BE01	Nervous System	Analgesics	Anilides
Analgesics*	WHO-Marketed	N02	Nervous System	Analgesics	Not Available
Cannabinoids*	WHO-Marketed	N02BG10	Nervous System	Analgesics	Not Available
Cannabis	WHO-Marketed	N02BG10	Nervous System	Analgesics	Not Available
Pentazocine	WHO-Marketed	N02AD01	Nervous System	Analgesics	Opioids-Benzomorphan Derivatives
Butorphanol	WHO-Marketed	N02AF01	Nervous System	Analgesics	Opioids-Morphinan Derivatives
Morphine	WHO-Marketed	N02AA01	Nervous System	Analgesics	Opioids-Natural Opium Alkaloids
Opium	WHO-Marketed	N02AA02	Nervous System	Analgesics	Opioids-Natural Opium Alkaloids
Buprenorphine	WHO-Marketed	N02AE01	Nervous System	Analgesics	Opioids-Oripavine Derivatives

Fentanyl	WHO-Marketed	N02AB03	Nervous System	Analgesics	Opioids-Phenylpiperidine Derivatives
Acetylsalicylic Acid	WHO-Marketed	N02BA01	Nervous System	Analgesics	Salicylic Acid and Derivatives
Salsalate	WHO-Marketed	N02BA06	Nervous System	Analgesics	Salicylic Acid and Derivatives
Sodium Salicylate	WHO-Marketed	N02BA04	Nervous System	Analgesics	Salicylic Acid and Derivatives
Dihydroergotamine	WHO-Marketed	N02CA01	Nervous System	Analgesics-Antimigraine Preparations	Ergot Alkaloids
Lisuride	WHO-Marketed	N02CA07	Nervous System	Analgesics-Antimigraine Preparations	Ergot Alkaloids
Methysergide	WHO-Marketed	N02CA04	Nervous System	Analgesics-Antimigraine Preparations	Ergot Alkaloids
Eletriptan	WHO-Marketed	N02CC06	Nervous System	Analgesics-Antimigraine Preparations	Selective Serotonin (5HT1) Agonists
Naratriptan	WHO-Marketed	N02CC02	Nervous System	Analgesics-Antimigraine Preparations	Selective Serotonin (5HT1) Agonists
Zolmitriptan	WHO-Marketed	N02CC03	Nervous System	Analgesics-Antimigraine Preparations	Selective Serotonin (5HT1) Agonists
Hexobarbital	WHO-Marketed	N01AF02	Nervous System	Anesthetics-Anesthetics, General	Barbiturates, Plain
Methohexital	WHO-Marketed	N01AF01	Nervous System	Anesthetics-Anesthetics, General	Barbiturates, Plain
Thiopental	WHO-Marketed	N01AF03	Nervous System	Anesthetics-Anesthetics, General	Barbiturates, Plain
Desflurane	WHO-Marketed	N01AB07	Nervous System	Anesthetics-Anesthetics, General	Halogenated Hydrocarbons

Sevoflurane	WHO-Marketed	N01AB08	Nervous System	Anesthetics-Anesthetics, General	Halogenated Hydrocarbons
Alfaxalone	WHO-Marketed	N01AX05	Nervous System	Anesthetics-Anesthetics, General	Not Available
Etomidate	WHO-Marketed	N01AX07	Nervous System	Anesthetics-Anesthetics, General	Not Available
Ketamine	WHO-Marketed	N01AX03	Nervous System	Anesthetics-Anesthetics, General	Not Available
Propofol	WHO-Marketed	N01AX10	Nervous System	Anesthetics-Anesthetics, General	Not Available
Sodium Oxybate	WHO-Marketed	N01AX11	Nervous System	Anesthetics-Anesthetics, General	Not Available
Alfentanil	WHO-Marketed	N01AH02	Nervous System	Anesthetics-Anesthetics, General	Opioid Anesthetics
Remifentanil	WHO-Marketed	N01AH06	Nervous System	Anesthetics-Anesthetics, General	Opioid Anesthetics
Prilocaine	WHO-Marketed	N01BB04	Nervous System	Anesthetics-Anesthetics, Local	Amides
Cocaine	WHO-Marketed	N01BC01	Nervous System	Anesthetics-Anesthetics, Local	Esters of Benzoic Acid
Levamisole	WHO-Marketed	P02CE01	Antiparasitic Products, Insecticides and Repellents	Anthelmintics-Antinematodal Agents	Imidazothiazole Derivatives
Anticholinergic Agents*	WHO-Marketed	N04A	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents
Orphenadrine	WHO-Marketed	N04AB02	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents-Ethers Chemically Close to Antihistamines
Benzatropine	WHO-Marketed	N04AC01	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents-Ethers of Tropine or Tropine Derivatives

Etybenzatropine	WHO-Marketed	N04AC30	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents-Ethers of Tropine or Tropine Derivatives
Biperiden	WHO-Marketed	N04AA02	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents-Tertiary Amines
Dexetimide	WHO-Marketed	N04AA08	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents-Tertiary Amines
Mazaticol	WHO-Marketed	N04AA10	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents-Tertiary Amines
Metixene	WHO-Marketed	N04AA03	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents-Tertiary Amines
Procyclidine	WHO-Marketed	N04AA04	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents-Tertiary Amines
Profenamine	WHO-Marketed	N04AA05	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents-Tertiary Amines
Trihexyphenidyl	WHO-Marketed	N04AA01	Nervous System	Anti Parkinson Drugs	Anticholinergic Agents-Tertiary Amines
Entacapone	WHO-Marketed	N04BX02	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents
Tolcapone	WHO-Marketed	N04BX01	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents
Amantadine	WHO-Marketed	N04BB01	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-Adamantane Derivatives
Levodopa	WHO-Marketed	N04BA01	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-Dopa and Dopa Derivatives
Levodopa and Decarboxylase Inhibitor*	WHO-Marketed	N04BA02	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-Dopa and Dopa Derivatives
Apomorphine	WHO-Marketed	N04BC07	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-Dopamine Agonists

Bromocriptine	WHO-Marketed	N04BC01	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-Dopamine Agonists
Pergolide	WHO-Marketed	N04BC02	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-Dopamine Agonists
Piribedil	WHO-Marketed	N04BC08	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-Dopamine Agonists
Pramipexole	WHO-Marketed	N04BC05	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-Dopamine Agonists
Rasagiline	WHO-Marketed	N04BD02	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-Monoamine Oxidase B Inhibitors
Selegiline	WHO-Marketed	N04BD01	Nervous System	Anti Parkinson Drugs	Dopaminergic Agents-Monoamine Oxidase B Inhibitors
Anti Parkinson Drugs*	WHO-Marketed	N04	Nervous System	Anti Parkinson Drugs	Not Available
Folic Acid	WHO-Marketed	B03BB01	Blood and Blood Forming Organs	Antianemic Preparations	Folic Acid and Derivatives
Ferrous Sulfate	WHO-Marketed	B03AA07	Blood and Blood Forming Organs	Antianemic Preparations	Iron Preparations
Hydroxocobalamin	WHO-Marketed	B03BA03	Blood and Blood Forming Organs	Antianemic Preparations	Vitamin B12 (Cyanocobalamin and Analogues)
Erythropoietin	WHO-Marketed	B03XA01	Blood and Blood Forming Organs	Antianemic Preparations-Other Antianemic Preparations	Not Available
Ajmaline	WHO-Marketed	C01BA05	Cardiovascular System	Antiarrhythmics, Class Ia	Not Available
Lidocaine	WHO-Marketed	C01BB01+N01BB02	Cardiovascular System	Antiarrhythmics, Class Ib+Anesthetics	Amides
Neomycin	WHO-Marketed	J01GB05	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Aminoglycoside Antibacterials-Other Aminoglycosides

Sulfamethoxazole and Trimethoprim*	WHO-Marketed	J01EE01	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Combinations of Sulfonamides and Trimethoprim, Incl. Derivatives
Sulfadiazine	WHO-Marketed	J01EC02	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Intermediate Acting Sulfonamides
Azithromycin	WHO-Marketed	J01FA10	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Macrolides
Erythromycin	WHO-Marketed	J01FA01	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Macrolides
Cefazolin	WHO-Marketed	J01DB04	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Other Beta-Lactam Antibacterials-First Generation Cephalosporins
Ceftriaxone	WHO-Marketed	J01DD04	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Other Beta-Lactam Antibacterials-Third Generation Cephalosporins
Ciprofloxacin	WHO-Marketed	J01MA02	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Quinolone Antibacterials-Fluoroquinolones
Levofloxacin	WHO-Marketed	J01MA12	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Quinolone Antibacterials-Fluoroquinolones
Moxifloxacin	WHO-Marketed	J01MA14	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Quinolone Antibacterials-Fluoroquinolones
Demeclocycline	WHO-Marketed	J01AA01	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Tetracyclines-Tetracyclines
Minocycline	WHO-Marketed	J01AA08	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Tetracyclines-Tetracyclines
Trimethoprim	WHO-Marketed	J01EA01	Antiinfectives for Systemic Use	Antibacterials for Systemic Use	Trimethoprim and Derivatives
Dronabinol	WHO-Marketed	A04AD10	Alimentary Tract and Metabolism	Antiemetics and Antinauseants	Not Available
Granisetron	WHO-Marketed	A04AA02	Alimentary Tract and Metabolism	Antiemetics and Antinauseants	Serotonin (5HT3) Antagonists

Ondansetron	WHO-Marketed	A04AA01	Alimentary Tract and Metabolism	Antiemetics and Antinauseants	Serotonin (5HT3) Antagonists
Tropisetron	WHO-Marketed	A04AA03	Alimentary Tract and Metabolism	Antiemetics and Antinauseants	Serotonin (5HT3) Antagonists
Phenobarbital	WHO-Marketed	N03AA02	Nervous System	Antiepileptics	Barbiturates and Derivatives
Clonazepam	WHO-Marketed	N03AE01	Nervous System	Antiepileptics	Benzodiazepine Derivatives
Carbamazepine	WHO-Marketed	N03AF01	Nervous System	Antiepileptics	Carboxamide Derivatives
Oxcarbazepine	WHO-Marketed	N03AF02	Nervous System	Antiepileptics	Carboxamide derivatives
Progabide	WHO-Marketed	N03AG05	Nervous System	Antiepileptics	Fatty Acid Derivatives
Tiagabine	WHO-Marketed	N03AG06	Nervous System	Antiepileptics	Fatty Acid Derivatives
Valproic Acid	WHO-Marketed	N03AG01	Nervous System	Antiepileptics	Fatty Acid Derivatives
Valpromide	WHO-Marketed	N03AG02	Nervous System	Antiepileptics	Fatty Acid Derivatives
Vigabatrin	WHO-Marketed	N03AG04	Nervous System	Antiepileptics	Fatty Acid Derivatives
Phenytoin	WHO-Marketed	N03AB02	Nervous System	Antiepileptics	Hydantoin Derivatives
Antiepileptics*	WHO-Marketed	N03A	Nervous System	Antiepileptics	Not Available
Beclamide	WHO-Marketed	N03AX30	Nervous System	Antiepileptics	Not Available

Cannabidiol	WHO-Marketed	N03AX24	Nervous System	Antiepileptics	Not Available
Gabapentin	WHO-Marketed	N03AX12	Nervous System	Antiepileptics	Not Available
Lamotrigine	WHO-Marketed	N03AX09	Nervous System	Antiepileptics	Not Available
Levetiracetam	WHO-Marketed	N03AX14	Nervous System	Antiepileptics	Not Available
Pregabalin	WHO-Marketed	N03AX16	Nervous System	Antiepileptics	Not Available
Topiramate	WHO-Marketed	N03AX11	Nervous System	Antiepileptics	Not Available
Zonisamide	WHO-Marketed	N03AX15	Nervous System	Antiepileptics	Not Available
Allopurinol	WHO-Marketed	M04AA01	Musculo-Skeletal System	Antigout Preparations	Preparations Inhibiting Uric Acid Production
Amino Acids*	WHO-Marketed	B02AA	Blood and Blood Forming Organs	Antihemorrhagics	Antifibrinolytics
Carbazochrome	WHO-Marketed	B02BX02	Blood and Blood Forming Organs	Antihemorrhagics	Other Systemic Hemostatics
Phytomenadione	WHO-Marketed	B02BA01	Blood and Blood Forming Organs	Antihemorrhagics	Vitamin K
Diphenhydramine	WHO-Marketed	R06AA02	Respiratory System	Antihistamines for Systemic Use	Aminoalkyl Ethers
Doxylamine	WHO-Marketed	R06AA09	Respiratory System	Antihistamines for Systemic Use	Aminoalkyl Ethers
Astemizole	WHO-Marketed	R06AX11	Respiratory System	Antihistamines for Systemic Use	Not Available

Cyproheptadine	WHO-Marketed	R06AX02	Respiratory System	Antihistamines for Systemic Use	Not Available
Alimemazine	WHO-Marketed	R06AD01	Respiratory System	Antihistamines for Systemic Use	Phenothiazine Derivatives
Promethazine	WHO-Marketed	R06AD02	Respiratory System	Antihistamines for Systemic Use	Phenothiazine Derivatives
Cyclizine	WHO-Marketed	R06AE03	Respiratory System	Antihistamines for Systemic Use	Piperazine Derivatives
Methyldopa	WHO-Marketed	C02AB	Cardiovascular System	Antihypertensives	Antiadrenergic Agents, Centrally Acting
Clonidine	WHO-Marketed	C02AC01	Cardiovascular System	Antihypertensives	Antiadrenergic Agents, Centrally Acting-Imidazoline Receptor Agonists
Guanfacine	WHO-Marketed	C02AC02	Cardiovascular System	Antihypertensives	Antiadrenergic Agents, Centrally Acting-Imidazoline Receptor Agonists
Moxonidine	WHO-Marketed	C02AC05	Cardiovascular System	Antihypertensives	Antiadrenergic Agents, Centrally Acting-Imidazoline Receptor Agonists
Deserpidine	WHO-Marketed	C02AA05	Cardiovascular System	Antihypertensives	Antiadrenergic Agents, Centrally Acting-Rauwolfia Alkaloids
Reserpine	WHO-Marketed	C02AA02	Cardiovascular System	Antihypertensives	Antiadrenergic Agents, Centrally Acting-Rauwolfia Alkaloids
Mecamylamine	WHO-Marketed	C02BB01	Cardiovascular System	Antihypertensives	Antiadrenergic Agents, Ganglion Blocking Secondary and Tertiary Amines
Prazosin	WHO-Marketed	C02CA01	Cardiovascular System	Antihypertensives	Antiadrenergic Agents, Peripherally Acting-Alpha Adrenoreceptor Antagonists
Debrisoquine	WHO-Marketed	C02CC04	Cardiovascular System	Antihypertensives	Antiadrenergic Agents, Peripherally Acting-Guanidine Derivatives
Nitroprusside	WHO-Marketed	C02DD01	Cardiovascular System	Antihypertensives	Arteriolar Smooth Muscle, Agents Acting on-Nitroferricyanide Derivatives

Diazoxide	WHO-Marketed	C02DA01	Cardiovascular System	Antihypertensives	Arteriolar Smooth Muscle, Agents Acting on-Thiazide Derivatives
Pargyline	WHO-Marketed	C02KC01	Cardiovascular System	Antihypertensives	MAO Inhibitors
Metirosine	WHO-Marketed	C02KB01	Cardiovascular System	Antihypertensives	Tyrosine Hydroxylase Inhibitors
Inosine	WHO-Marketed	G01AX02	Genito Urinary System and Sex Hormones	Antiinfectives and Antiseptics, Excl. Combinations with Corticosteroids	Not Available
Celecoxib	WHO-Marketed	M01AH01	Musculo-Skeletal System	Antiinflammatory and Antirheumatic Products-Antiinflammatory and Antirheumatic Products, Non Steroids	Coxibs
Meclofenamic Acid	WHO-Marketed	M01AG04	Musculo-Skeletal System	Antiinflammatory and Antirheumatic Products-Antiinflammatory and Antirheumatic Products, Non Steroids	Fenamates
Penicillamine	WHO-Marketed	M01CC01	Musculo-Skeletal System	Antiinflammatory and Antirheumatic Products-Specific Antirheumatic Agents	Penicillamine and Similar Agents
Cycloserine	WHO-Marketed	J04AB01	Antiinfectives for Systemic Use	Antimycobacterials-Drugs for Treatment of Tuberculosis	Antibiotics
Rifabutin	WHO-Marketed	J04AB04	Antiinfectives for Systemic Use	Antimycobacterials-Drugs for Treatment of Tuberculosis	Antibiotics
Rifampicin	WHO-Marketed	J04AB02	Antiinfectives for Systemic Use	Antimycobacterials-Drugs for Treatment of Tuberculosis	Antibiotics
Rifapentine	WHO-Marketed	J04AB05	Antiinfectives for Systemic Use	Antimycobacterials-Drugs for Treatment of Tuberculosis	Antibiotics
Isoniazid	WHO-Marketed	J04AC01	Antiinfectives for Systemic Use	Antimycobacterials-Drugs for Treatment of Tuberculosis	Hydrazides
Ketoconazole	WHO-Marketed	J02AB02	Antiinfectives for Systemic Use	Antimycotics-Antimycotics for Systemic Use	Imidazole Derivatives

Itraconazole	WHO-Marketed	J02AC02	Antiinfectives for Systemic Use	Antimycotics-Antimycotics for Systemic Use	Triazole Derivatives
Rituximab	WHO-Marketed	L01XC02	Antineoplastic and Immunomodulating Agents	Antineoplastic Agents	Monoclonal Antibodies
Bexarotene	WHO-Marketed	L01XX25	Antineoplastic and Immunomodulating Agents	Antineoplastic Agents	Not Available
Vorinostat	WHO-Marketed	L01XX38	Antineoplastic and Immunomodulating Agents	Antineoplastic Agents	Not Available
Meglumine Antimonate	WHO-Marketed	P01CB01	Antiparasitic Products, Insecticides and Repellents	Antiprotozoals-Agents against Leishmaniasis and Trypanosomiasis	Antimony Compounds
Amodiaquine	WHO-Marketed	P01BA06	Antiparasitic Products, Insecticides and Repellents	Antiprotozoals-Antimalarials	Aminoquinolines
Chloroquine	WHO-Marketed	P01BA01	Antiparasitic Products, Insecticides and Repellents	Antiprotozoals-Antimalarials	Aminoquinolines
Hydroxychloroquine	WHO-Marketed	P01BA02	Antiparasitic Products, Insecticides and Repellents	Antiprotozoals-Antimalarials	Aminoquinolines
Artemether	WHO-Marketed	P01BE02	Antiparasitic Products, Insecticides and Repellents	Antiprotozoals-Antimalarials	Artemisinin and Derivatives, Plain
Artemisinin	WHO-Marketed	P01BE01	Antiparasitic Products, Insecticides and Repellents	Antiprotozoals-Antimalarials	Artemisinin and Derivatives, Plain
Pyrimethamine	WHO-Marketed	P01BD01	Antiparasitic Products, Insecticides and Repellents	Antiprotozoals-Antimalarials	Diaminopyrimidines
Cilostazol	WHO-Marketed	B01AC23	Blood and Blood Forming Organs	Antithrombotic Agents	Platelet Aggregation Inhibitors Excl. Heparin
Dipyridamole	WHO-Marketed	B01AC07	Blood and Blood Forming Organs	Antithrombotic Agents	Platelet Aggregation Inhibitors Excl. Heparin
Betahistine	WHO-Marketed	N07CA01	Nervous System	Antivertigo Preparations	Not Available

Cinnarizine	WHO-Marketed	N07CA02	Nervous System	Antivertigo Preparations	Not Available
Flunarizine	WHO-Marketed	N07CA03	Nervous System	Antivertigo Preparations	Not Available
Famciclovir	WHO-Marketed	J05AB09	Antiinfectives for Systemic Use	Antivirals for Systemic Use-Direct Acting Antivirals	Nucleosides and Nucleotides Excl. Reverse Transcriptase Inhibitors
Valaciclovir	WHO-Marketed	J05AB11	Antiinfectives for Systemic Use	Antivirals for Systemic Use-Direct Acting Antivirals	Nucleosides and Nucleotides Excl. Reverse Transcriptase Inhibitors
Hymecromone	WHO-Marketed	A05AX02	Alimentary Tract and Metabolism	Bile Therapy	Not Available
Dopamine	WHO-Marketed	C01CA04	Cardiovascular System	Cardiac Stimulants Excl. Cardiac Glycosides	Adrenergic and Dopaminergic Agents
Norfenefrine	WHO-Marketed	C01CA05	Cardiovascular System	Cardiac Stimulants Excl. Cardiac Glycosides	Adrenergic and Dopaminergic Agents
Dexfenfluramine	WHO-Marketed	A08AA04	Alimentary Tract and Metabolism	Centrally Acting Antiobesity Products	Not Available
Fenfluramine	WHO-Marketed	A08AA02	Alimentary Tract and Metabolism	Centrally Acting Antiobesity Products	Not Available
Lorcaserin	WHO-Marketed	A08AA11	Alimentary Tract and Metabolism	Centrally Acting Antiobesity Products	Not Available
Mazindol	WHO-Marketed	A08AA05	Alimentary Tract and Metabolism	Centrally Acting Antiobesity Products	Not Available
Sibutramine	WHO-Marketed	A08AA10	Alimentary Tract and Metabolism	Centrally Acting Antiobesity Products	Not Available
Cortisone	WHO-Marketed	H02AB10	Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	Corticosteroids for Systemic Use	Glucocorticoids
Dexamethasone	WHO-Marketed	H02AB02	Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	Corticosteroids for Systemic Use	Glucocorticoids

Prednisolone	WHO-Marketed	H02AB06	Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	Corticosteroids for Systemic Use	Glucocorticoids
Fludrocortisone	WHO-Marketed	H02AA02	Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	Corticosteroids for Systemic Use	Mineralocorticoids
Dextromethorphan	WHO-Marketed	R05DA09	Respiratory System	Cough and Cold Preparations-Cough Suppressants, Excl. Combinations with Expectorants	Opium Alkaloids and Derivatives
Acetylcysteine	WHO-Marketed	R05CB01	Respiratory System	Cough and Cold Preparations-Expectorants, Excl. Combinations with Cough Suppressants	Mucolytics
Ceruletide	WHO-Marketed	V04CC04	Various	Diagnostic Agents-Tests for Bile Duct Patency	Not Available
Sincalide	WHO-Marketed	V04CC03	Various	Diagnostic Agents-Tests for Bile Duct Patency	Not Available
Pancreozymin (Cholecystokinin)	WHO-Marketed	V04CK02	Various	Diagnostic Agents-Tests for Pancreatic Function	Not Available
Secretin	WHO-Marketed	V04CK01	Various	Diagnostic Agents-Tests for Pancreatic Function	Not Available
Protirelin	WHO-Marketed	V04CJ02	Various	Diagnostic Agents-Tests for Thyreoidea Function	Not Available
Rubidium (82Rb) Chloride	WHO-Marketed	V09GX04	Various	Diagnostic Radiopharmaceuticals-Cardiovascular System	Not Available
Glutamic Acid	WHO-Marketed	A09AB01	Alimentary Tract and Metabolism	Digestives, Incl. Enzymes	Not Available
Tolvaptan	WHO-Marketed	C03XA01	Cardiovascular System	Diuretics	Vasopressin Antagonists
Bumetanide	WHO-Marketed	C03CA02	Cardiovascular System	Diuretics-High Ceiling Diuretics	Sulfonamides, Plain

Spironolactone	WHO-Marketed	C03DA01	Cardiovascular System	Diuretics-Potassium Sparing Agents	Aldosterone Antagonists
Cimetidine	WHO-Marketed	A02BA01	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders	H2 Receptor Antagonists
Famotidine	WHO-Marketed	A02BA03	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders	H2 Receptor Antagonists
Nizatidine	WHO-Marketed	A02BA04	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders	H2 Receptor Antagonists
Ranitidine	WHO-Marketed	A02BA02	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders	H2 Receptor Antagonists
Omeprazole	WHO-Marketed	A02BC01	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders	Proton Pump Inhibitors
Pantoprazole	WHO-Marketed	A02BC02	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders	Proton Pump Inhibitors
Aluminium Hydroxide	WHO-Marketed	A02AB01	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders-Antacids	Aluminium Compounds
Magnesium Hydroxide	WHO-Marketed	A02AA04	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders-Antacids	Magnesium Compounds
Magnesium Silicate	WHO-Marketed	A02AA05	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders-Antacids	Magnesium Compounds
Sodium Bicarbonate	WHO-Marketed	A02AH	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders-Antacids	Not Available
Pirenzepine	WHO-Marketed	A02BX03	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders-Drugs for Peptic Ulcer and Gastro Oesophageal Reflux Disease	Not Available
Proglumide	WHO-Marketed	A02BX06	Alimentary Tract and Metabolism	Drugs for Acid Related Disorders-Drugs for Peptic Ulcer and Gastro Oesophageal Reflux Disease	Not Available

Naloxone	WHO-Marketed	A06AH04	Alimentary Tract and Metabolism	Drugs for Constipation	Peripheral Opioid Receptor Antagonists
Phenolphthalein	WHO-Marketed	A06AB04	Alimentary Tract and Metabolism	Drugs for Constipation-Contact Laxatives	Not Available
Senna Glycosides*	WHO-Marketed	A06AB06	Alimentary Tract and Metabolism	Drugs for Constipation-Contact Laxatives	Not Available
Mannitol	WHO-Marketed	A06AD16	Alimentary Tract and Metabolism	Drugs for Constipation-Osmotically Acting Laxatives	Not Available
Sorbitol	WHO-Marketed	A06AD18	Alimentary Tract and Metabolism	Drugs for Constipation-Osmotically Acting Laxatives	Not Available
Alosetron	WHO-Marketed	A03AE01	Alimentary Tract and Metabolism	Drugs for Functional Gastrointestinal Disorders	Serotonin Receptor Antagonists
Glycopyrronium Bromide	WHO-Marketed	A03AB02	Alimentary Tract and Metabolism	Drugs for Functional Gastrointestinal Disorders	Synthetic Anticholinergics
Propantheline	WHO-Marketed	A03AB05	Alimentary Tract and Metabolism	Drugs for Functional Gastrointestinal Disorders	Synthetic Anticholinergics
Cisapride	WHO-Marketed	A03FA02	Alimentary Tract and Metabolism	Drugs for Functional Gastrointestinal Disorders-Propulsives	Not Available
Metoclopramide	WHO-Marketed	A03FA01	Alimentary Tract and Metabolism	Drugs for Functional Gastrointestinal Disorders-Propulsives	Not Available
Ipratropium Bromide	WHO-Marketed	R03BB01	Respiratory System	Drugs for Obstructive Airway Diseases	Anticholinergics
Roflumilast	WHO-Marketed	R03DX07	Respiratory System	Drugs for Obstructive Airway Diseases	Not Available
Theophylline	WHO-Marketed	R03DA04	Respiratory System	Drugs for Obstructive Airway Diseases	Xanthines
Acamprosate	WHO-Marketed	N07BB03	Nervous System	Drugs Used in Addictive Disorders-Drugs Used in Alcohol Dependence	Not Available

Disulfiram	WHO-Marketed	N07BB01	Nervous System	Drugs Used in Addictive Disorders-Drugs Used in Alcohol Dependence	Not Available
Nalmefene	WHO-Marketed	N07BB05	Nervous System	Drugs Used in Addictive Disorders-Drugs Used in Alcohol Dependence	Not Available
Naltrexone	WHO-Marketed	N07BB04	Nervous System	Drugs Used in Addictive Disorders-Drugs Used in Alcohol Dependence	Not Available
Nicotine	WHO-Marketed	N07BA01	Nervous System	Drugs Used in Addictive Disorders-Drugs Used in Nicotine Dependence	Not Available
Varenicline	WHO-Marketed	N07BA03	Nervous System	Drugs Used in Addictive Disorders-Drugs Used in Nicotine Dependence	Not Available
Methadone	WHO-Marketed	N07BC02	Nervous System	Drugs Used in Addictive Disorders-Drugs Used in Opioid Dependence	Not Available
Terazosin	WHO-Marketed	G04CA03	Genito Urinary System and Sex Hormones	Drugs Used In Benign Prostatic Hypertrophy	Alpha Adrenoreceptor Antagonists
Acarbose	WHO-Marketed	A10BF01	Alimentary Tract and Metabolism	Drugs Used in Diabetes-Blood Glucose Lowering Drugs, Excl. Insulins	Alpha Glucosidase Inhibitors
Metformin	WHO-Marketed	A10BA02	Alimentary Tract and Metabolism	Drugs Used in Diabetes-Blood Glucose Lowering Drugs, Excl. Insulins	Biguanides
Phenformin	WHO-Marketed	A10BA01	Alimentary Tract and Metabolism	Drugs Used in Diabetes-Blood Glucose Lowering Drugs, Excl. Insulins	Biguanides
Exenatide	WHO-Marketed	A10BJ01	Alimentary Tract and Metabolism	Drugs Used in Diabetes-Blood Glucose Lowering Drugs, Excl. Insulins	Glucagon Like Peptide 1 (GLP 1) Analogues
Liraglutide	WHO-Marketed	A10BJ02	Alimentary Tract and Metabolism	Drugs Used in Diabetes-Blood Glucose Lowering Drugs, Excl. Insulins	Glucagon Like Peptide 1 (GLP 1) Analogues
Pramlintide	WHO-Marketed	A10BX05	Alimentary Tract and Metabolism	Drugs Used in Diabetes-Blood Glucose Lowering Drugs, Excl. Insulins	Not Available
Gliclazide	WHO-Marketed	A10BB09	Alimentary Tract and Metabolism	Drugs Used in Diabetes-Blood Glucose Lowering Drugs, Excl. Insulins	Sulfonylureas

Pioglitazone	WHO-Marketed	A10BG03	Alimentary Tract and Metabolism	Drugs Used in Diabetes-Blood Glucose Lowering Drugs, Excl. Insulins	Thiazolidinediones
Rosiglitazone	WHO-Marketed	A10BG02	Alimentary Tract and Metabolism	Drugs Used in Diabetes-Blood Glucose Lowering Drugs, Excl. Insulins	Thiazolidinediones
Insulin	WHO-Marketed	A10A	Alimentary Tract and Metabolism	Drugs Used in Diabetes-Insulins and Analogues	Not Available
Papaverine	WHO-Marketed	G04BE02	Genito Urinary System and Sex Hormones	Drugs Used in Erectile Dysfunction	Not Available
Sildenafil	WHO-Marketed	G04BE03	Genito Urinary System and Sex Hormones	Drugs Used in Erectile Dysfunction	Not Available
Tadalafil	WHO-Marketed	G04BE08	Genito Urinary System and Sex Hormones	Drugs Used in Erectile Dysfunction	Not Available
Tamoxifen	WHO-Marketed	L02BA01	Antineoplastic and Immunomodulating Agents	Endocrine Therapy	Hormone Antagonists and Related Agents-Anti Estrogens
Nutrients without Phenylalanine*	WHO-Marketed	V06CA	Various	General Nutrients-Infant Formulas	Not Available
Hypothalamic Hormones (Thyroid Releasing Hormone)	WHO-Marketed	H01C	Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	Hypothalamic Hormones	Not Available
Hypothalamic Hormones (Thyrotropin Releasing Hormone)	WHO-Marketed	H01C	Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	Hypothalamic Hormones	Not Available
Lysine	WHO-Marketed	B05XB03	Blood and Blood Forming Organs	I.V. Solution Additives	Amino Acids
Magnesium Sulfate	WHO-Marketed	B05XA05	Blood and Blood Forming Organs	I.V. Solution Additives	Electrolyte Solutions
Filgrastim	WHO-Marketed	L03AA02	Antineoplastic and Immunomodulating Agents	Immunostimulants	Colony Stimulating Factors

Interferons*	WHO-Marketed	L03AB	Antineoplastic and Immunomodulating Agents	Immunostimulants	Interferons
Cridanimod	WHO-Marketed	L03AX18	Antineoplastic and Immunomodulating Agents	Immunostimulants	Not Available
Canakinumab	WHO-Marketed	L04AC08	Antineoplastic and Immunomodulating Agents	Immunosuppressants	Interleukin Inhibitors
Siltuximab	WHO-Marketed	L04AC11	Antineoplastic and Immunomodulating Agents	Immunosuppressants	Interleukin Inhibitors
Tocilizumab	WHO-Marketed	L04AC07	Antineoplastic and Immunomodulating Agents	Immunosuppressants	Interleukin Inhibitors
Methotrexate	WHO-Marketed	L04AX03	Antineoplastic and Immunomodulating Agents	Immunosuppressants	Not Available
Fingolimod	WHO-Marketed	L04AA27	Antineoplastic and Immunomodulating Agents	Immunosuppressants-Selective Immunosuppressants	Not Available
Sulfasalazine	WHO-Marketed	A07EC01	Alimentary Tract and Metabolism	Intestinal Antiinflammatory Agents	Not Available
Glucose	WHO-Marketed	B05CX01	Blood and Blood Forming Organs	Irrigating Solutions	Other Irrigating Solutions
Glycine	WHO-Marketed	B05CX03	Blood and Blood Forming Organs	Irrigating Solutions	Other Irrigating Solutions
Fenofibrate	WHO-Marketed	C10AB05	Cardiovascular System	Lipid Modifying Agents	Fibrates
Atorvastatin	WHO-Marketed	C10AA05	Cardiovascular System	Lipid Modifying Agents	HMG CoA Reductase Inhibitors
Fluvastatin	WHO-Marketed	C10AA04	Cardiovascular System	Lipid Modifying Agents	HMG CoA Reductase Inhibitors
Lovastatin	WHO-Marketed	C10AA02	Cardiovascular System	Lipid Modifying Agents	HMG CoA Reductase Inhibitors

Pravastatin	WHO-Marketed	C10AA03	Cardiovascular System	Lipid Modifying Agents	HMG CoA Reductase Inhibitors
Rosuvastatin	WHO-Marketed	C10AA07	Cardiovascular System	Lipid Modifying Agents	HMG CoA Reductase Inhibitors
Simvastatin	WHO-Marketed	C10AA01	Cardiovascular System	Lipid Modifying Agents	HMG CoA Reductase Inhibitors
Ezetimibe	WHO-Marketed	C10AX09	Cardiovascular System	Lipid Modifying Agents	Not Available
Omega-3-Triglycerides Incl. Other Esters and Acids*	WHO-Marketed	C10AX06	Cardiovascular System	Lipid Modifying Agents	Not Available
Calcium Carbonate	WHO-Marketed	A12AA04	Alimentary Tract and Metabolism	Mineral Supplements	Calcium
Calcium Gluconate	WHO-Marketed	A12AA03	Alimentary Tract and Metabolism	Mineral Supplements	Calcium
Minerals*	WHO-Marketed	A12	Alimentary Tract and Metabolism	Mineral Supplements	Not Available
Zinc Sulfate	WHO-Marketed	A12CB01	Alimentary Tract and Metabolism	Mineral Supplements	Zinc
Baclofen	WHO-Marketed	M03BX01	Musculo-Skeletal System	Muscle Relaxants	Not Available
Botulinum Toxin	WHO-Marketed	M03AX01	Musculo-Skeletal System	Muscle Relaxants	Not Available
Suxamethonium	WHO-Marketed	M03AB01	Musculo-Skeletal System	Muscle Relaxants-Muscle Relaxants, Peripherally Acting Agents	Choline Derivatives
Atracurium	WHO-Marketed	M03AC04	Musculo-Skeletal System	Muscle Relaxants-Muscle Relaxants, Peripherally Acting Agents	Other Quaternary Ammonium Compounds
Cisatracurium	WHO-Marketed	M03AC11	Musculo-Skeletal System	Muscle Relaxants-Muscle Relaxants, Peripherally Acting Agents	Other Quaternary Ammonium Compounds

Mivacurium Chloride	WHO-Marketed	M03AC10	Musculo-Skeletal System	Muscle Relaxants-Muscle Relaxants, Peripherally Acting Agents	Other Quaternary Ammonium Compounds
Rocuronium Bromide	WHO-Marketed	M03AC09	Musculo-Skeletal System	Muscle Relaxants-Muscle Relaxants, Peripherally Acting Agents	Other Quaternary Ammonium Compounds
Phenylpropanolamine	WHO-Marketed	R01BA01	Respiratory System	Nasal Preparations-Nasal Decongestants for Systemic Use	Sympathomimetics
Benazepril	WHO-Marketed	C09AA07	Cardiovascular System	Not Available	Agents Acting on the Renin Angiotensin System-ACE inhibitors, Plain
Enalapril	WHO-Marketed	C09AA02	Cardiovascular System	Not Available	Agents Acting on the Renin Angiotensin System-ACE inhibitors, Plain
Losartan	WHO-Marketed	C09CA01	Cardiovascular System	Not Available	Agents Acting on the Renin Angiotensin System-Angiotensin II Receptor Blockers (ARBs), Plain
Telmisartan	WHO-Marketed	C09CA07	Cardiovascular System	Not Available	Agents Acting on the Renin Angiotensin System-Angiotensin II Receptor Blockers (ARBs), Plain
Ademetionine	WHO-Marketed	A16AA02	Alimentary Tract and Metabolism	Not Available	Amino Acids and Derivatives
Labetalol	WHO-Marketed	C07AG01	Cardiovascular System	Not Available	Beta Blocking Agents-Alpha and Beta Blocking Agents
Bupranolol	WHO-Marketed	C07AA19	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Non Selective
Carteolol	WHO-Marketed	C07AA15	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Non Selective
Nadolol	WHO-Marketed	C07AA12	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Non Selective
Oxprenolol	WHO-Marketed	C07AA02	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Non Selective

Pindolol	WHO-Marketed	C07AA03	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Non Selective
Propranolol	WHO-Marketed	C07AA05	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Non Selective
Atenolol	WHO-Marketed	C07AB03	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Selective
Betaxolol	WHO-Marketed	C07AB05	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Selective
Celiprolol	WHO-Marketed	C07AB08	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Selective
Esmolol	WHO-Marketed	C07AB09	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Selective
Landiolol	WHO-Marketed	C07AB14	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Selective
Metoprolol	WHO-Marketed	C07AB02	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Selective
Practolol	WHO-Marketed	C07AB01	Cardiovascular System	Not Available	Beta Blocking Agents-Beta Blocking Agents, Selective
Diltiazem	WHO-Marketed	C08DB01	Cardiovascular System	Not Available	Calcium Channel Blockers-Benzothiazepine Derivatives
Isradipine	WHO-Marketed	C08CA03	Cardiovascular System	Not Available	Calcium Channel Blockers-Dihydropyridine Derivatives
Nifedipine	WHO-Marketed	C08CA05	Cardiovascular System	Not Available	Calcium Channel Blockers-Dihydropyridine Derivatives
Nilvadipine	WHO-Marketed	C08CA10	Cardiovascular System	Not Available	Calcium Channel Blockers-Dihydropyridine Derivatives
Nimodipine	WHO-Marketed	C08CA06	Cardiovascular System	Not Available	Calcium Channel Blockers-Dihydropyridine Derivatives

Verapamil	WHO-Marketed	C08DA01	Cardiovascular System	Not Available	Calcium Channel Blockers-Dihydropyridine Derivatives
Immunoglobulins*	WHO-Marketed	J06B	Antiinfectives for Systemic Use	Not Available	Immunoglobulins
Ubidecarenone	WHO-Marketed	C01EB09	Cardiovascular System	Not Available	Not Available
Tiopronin	WHO-Marketed	G04BX16	Genito Urinary System and Sex Hormones	Not Available	Not Available
Pitolisant	WHO-Marketed	N07XX11	Nervous System	Not Available	Not Available
Riluzole	WHO-Marketed	N07XX02	Nervous System	Not Available	Not Available
Tetrabenazine	WHO-Marketed	N07XX06	Nervous System	Not Available	Not Available
Valbenazine	WHO-Marketed	N07XX13	Nervous System	Not Available	Not Available
Nitric Oxide	WHO-Marketed	R07AX01	Respiratory System	Not Available	Not Available
Metergoline	WHO-Marketed	G02CB05	Genito Urinary System and Sex Hormones	Not Available	Prolactine Inhibitors
Acetazolamide	WHO-Marketed	S01EC01	Sensory Organs	Ophtalmologicals-Antiglaucoma Preparations and Miotics	Carbonic Anhydrase Inhibitors
Physostigmine	WHO-Marketed	S01EB05	Sensory Organs	Ophtalmologicals-Antiglaucoma Preparations and Miotics	Parasympathomimetics
Atropine	WHO-Marketed	S01FA01	Sensory Organs	Ophtalmologicals-Mydriatics And Cycloplegics	Anticholinergics
Methylscopolamine	WHO-Marketed	S01FA03	Sensory Organs	Ophtalmologicals-Mydriatics And Cycloplegics	Anticholinergics

Rimonabant	WHO-Marketed	A08AX01	Alimentary Tract and Metabolism	Other Antiobesity Drugs	Not Available
Neostigmine	WHO-Marketed	N07AA01	Nervous System	Parasympathomimetics	Anticholinesterases
Pyridostigmine	WHO-Marketed	N07AA02	Nervous System	Parasympathomimetics	Anticholinesterases
Buphenine	WHO-Marketed	C04AA02	Cardiovascular System	Peripheral Vasodilators	2 Amino 1 Phenylethanol Derivatives
Ergoloid	WHO-Marketed	C04AE01	Cardiovascular System	Peripheral Vasodilators	Ergot Alkaloids
Buflomedil	WHO-Marketed	C04AX20	Cardiovascular System	Peripheral Vasodilators	Not Available
Nicotinic Acid	WHO-Marketed	C04AC01+C10AD02	Cardiovascular System	Peripheral Vasodilators+Lipid Modifying Agents	Nicotinic Acid and Derivatives
Orlistat	WHO-Marketed	A08AB01	Alimentary Tract and Metabolism	Peripherally Acting Antiobesity Products	Not Available
Oxytocin	WHO-Marketed	H01BB02	Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	Posterior Pituitary Lobe Hormones	Oxytocin and Analogues
Desmopressin	WHO-Marketed	H01BA02	Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	Posterior Pituitary Lobe Hormones	Vasopressin and Analogues
Vasopressin	WHO-Marketed	H01BA01	Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	Posterior Pituitary Lobe Hormones	Vasopressin and Analogues
Donepezil	WHO-Marketed	N06DA02	Nervous System	Psychoanaleptics-Anti Dementia Drugs	Anticholinesterases
Galantamine	WHO-Marketed	N06DA04	Nervous System	Psychoanaleptics-Anti Dementia Drugs	Anticholinesterases
Ipidacrine	WHO-Marketed	N06DA05	Nervous System	Psychoanaleptics-Anti Dementia Drugs	Anticholinesterases

Rivastigmine	WHO-Marketed	N06DA03	Nervous System	Psychoanaleptics-Anti Dementia Drugs	Anticholinesterases
Tacrine	WHO-Marketed	N06DA01	Nervous System	Psychoanaleptics-Anti Dementia Drugs	Anticholinesterases
Ginkgo Folium	WHO-Marketed	N06DX02	Nervous System	Psychoanaleptics-Anti Dementia Drugs	Not Available
Memantine	WHO-Marketed	N06DX01	Nervous System	Psychoanaleptics-Anti Dementia Drugs	Not Available
Moclobemide	WHO-Marketed	N06AG02	Nervous System	Psychoanaleptics-Antidepressants	Monoamine Oxidase A Inhibitors
Iproniazide	WHO-Marketed	N06AF05	Nervous System	Psychoanaleptics-Antidepressants	Monoamine Oxidase Inhibitors, Non-Selective
Isocarboxazid	WHO-Marketed	N06AF01	Nervous System	Psychoanaleptics-Antidepressants	Monoamine Oxidase Inhibitors, Non-Selective
Nialamide	WHO-Marketed	N06AF02	Nervous System	Psychoanaleptics-Antidepressants	Monoamine Oxidase Inhibitors, Non-Selective
Phenelzine	WHO-Marketed	N06AF03	Nervous System	Psychoanaleptics-Antidepressants	Monoamine Oxidase Inhibitors, Non-Selective
Tranylcypromine	WHO-Marketed	N06AF04	Nervous System	Psychoanaleptics-Antidepressants	Monoamine Oxidase Inhibitors, Non-Selective
Amineptine	WHO-Marketed	N06AA19	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Amitriptyline	WHO-Marketed	N06AA09	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Amoxapine	WHO-Marketed	N06AA17	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Clomipramine	WHO-Marketed	N06AA04	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors

Desipramine	WHO-Marketed	N06AA01	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Doxepin	WHO-Marketed	N06AA12	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Imipramine	WHO-Marketed	N06AA02	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Maprotiline	WHO-Marketed	N06AA21	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Melitracen	WHO-Marketed	N06AA14	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Nortriptyline	WHO-Marketed	N06AA10	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Opipramol	WHO-Marketed	N06AA05	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Protriptyline	WHO-Marketed	N06AA11	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Trimipramine	WHO-Marketed	N06AA06	Nervous System	Psychoanaleptics-Antidepressants	Non-Selective Monoamine Reuptake Inhibitors
Agomelatine	WHO-Marketed	N06AX22	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Antidepressants*	WHO-Marketed	N06A	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Bupropion	WHO-Marketed	N06AX12	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Duloxetine	WHO-Marketed	N06AX21	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Mianserin	WHO-Marketed	N06AX03	Nervous System	Psychoanaleptics-Antidepressants	Not Available

Minaprine	WHO-Marketed	N06AX07	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Mirtazapine	WHO-Marketed	N06AX11	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Nefazodone	WHO-Marketed	N06AX06	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Oxitriptan	WHO-Marketed	N06AX01	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Reboxetine	WHO-Marketed	N06AX18	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Tianeptine	WHO-Marketed	N06AX14	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Trazodone	WHO-Marketed	N06AX05	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Tryptophan	WHO-Marketed	N06AX02	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Venlafaxine	WHO-Marketed	N06AX16	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Viloxazine	WHO-Marketed	N06AX09	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Vortioxetine	WHO-Marketed	N06AX26	Nervous System	Psychoanaleptics-Antidepressants	Not Available
Citalopram	WHO-Marketed	N06AB04	Nervous System	Psychoanaleptics-Antidepressants	Selective Serotonin Reuptake Inhibitors
Escitalopram	WHO-Marketed	N06AB10	Nervous System	Psychoanaleptics-Antidepressants	Selective Serotonin Reuptake Inhibitors
Fluoxetine	WHO-Marketed	N06AB03	Nervous System	Psychoanaleptics-Antidepressants	Selective Serotonin Reuptake Inhibitors

Fluvoxamine	WHO-Marketed	N06AB08	Nervous System	Psychoanaleptics-Antidepressants	Selective Serotonin Reuptake Inhibitors
Paroxetine	WHO-Marketed	N06AB05	Nervous System	Psychoanaleptics-Antidepressants	Selective Serotonin Reuptake Inhibitors
Sertraline	WHO-Marketed	N06AB06	Nervous System	Psychoanaleptics-Antidepressants	Selective Serotonin Reuptake Inhibitors
Amfetamine	WHO-Marketed	N06BA01	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Centrally Acting Sympathomimetics
Armodafinil	WHO-Marketed	N06BA13	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Centrally Acting Sympathomimetics
Atomoxetine	WHO-Marketed	N06BA09	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Centrally Acting Sympathomimetics
Dexamfetamine	WHO-Marketed	N06BA02	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Centrally Acting Sympathomimetics
Lisdexamfetamine	WHO-Marketed	N06BA12	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Centrally Acting Sympathomimetics
Metamfetamine	WHO-Marketed	N06BA03	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Centrally Acting Sympathomimetics
Methylphenidate	WHO-Marketed	N06BA04	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Centrally Acting Sympathomimetics
Modafinil	WHO-Marketed	N06BA07	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Centrally Acting Sympathomimetics
Pemoline	WHO-Marketed	N06BA05	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Centrally Acting Sympathomimetics
Aniracetam	WHO-Marketed	N06BX11	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Not Available
Citicoline	WHO-Marketed	N06BX06	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Not Available

Idebenone	WHO-Marketed	N06BX13	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Not Available
Meclofenoxate	WHO-Marketed	N06BX01	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Not Available
Oxiracetam	WHO-Marketed	N06BX07	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Not Available
Pipradrol	WHO-Marketed	N06BX15	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Not Available
Piracetam	WHO-Marketed	N06BX03	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Not Available
Vinpocetine	WHO-Marketed	N06BX18	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Not Available
Caffeine	WHO-Marketed	N06BC01	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Xanthine Derivatives
Propentofylline	WHO-Marketed	N06BC02	Nervous System	Psychoanaleptics-Psychostimulants, Agents Used for ADHD and Nootropics	Xanthine Derivatives
Amisulpride	WHO-Marketed	N05AL05	Nervous System	Psycholeptics-Antipsychotics	Benzamides
Benzamide	WHO-Marketed	N05AL	Nervous System	Psycholeptics-Antipsychotics	Benzamides
Levosulpiride	WHO-Marketed	N05AL07	Nervous System	Psycholeptics-Antipsychotics	Benzamides
Remoxipride	WHO-Marketed	N05AL04	Nervous System	Psycholeptics-Antipsychotics	Benzamides
Sulpiride	WHO-Marketed	N05AL01	Nervous System	Psycholeptics-Antipsychotics	Benzamides
Sultopride	WHO-Marketed	N05AL02	Nervous System	Psycholeptics-Antipsychotics	Benzamides

Tiapride	WHO-Marketed	N05AL03	Nervous System	Psycholeptics-Antipsychotics	Benzamides
Benperidol	WHO-Marketed	N05AD07	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Bromperidol	WHO-Marketed	N05AD06	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Butyrophenone	WHO-Marketed	N05AD	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Droperidol	WHO-Marketed	N05AD08	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Fluanisone	WHO-Marketed	N05AD09	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Haloperidol	WHO-Marketed	N05AD01	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Melperone	WHO-Marketed	N05AD03	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Moperone	WHO-Marketed	N05AD04	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Pipamperone	WHO-Marketed	N05AD05	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Trifluperidol	WHO-Marketed	N05AD02	Nervous System	Psycholeptics-Antipsychotics	Butyrophenone Derivatives
Asenapine	WHO-Marketed	N05AH05	Nervous System	Psycholeptics-Antipsychotics	Diazepines, Oxazepines, Thiazepines and Oxepines
Clotiapine	WHO-Marketed	N05AH06	Nervous System	Psycholeptics-Antipsychotics	Diazepines, Oxazepines, Thiazepines and Oxepines
Clozapine	WHO-Marketed	N05AH02	Nervous System	Psycholeptics-Antipsychotics	Diazepines, Oxazepines, Thiazepines and Oxepines

Loxapine	WHO-Marketed	N05AH01	Nervous System	Psycholeptics-Antipsychotics	Diazepines, Oxazepines, Thiazepines and Oxepines
Olanzapine	WHO-Marketed	N05AH03	Nervous System	Psycholeptics-Antipsychotics	Diazepines, Oxazepines, Thiazepines and Oxepines
Quetiapine	WHO-Marketed	N05AH04	Nervous System	Psycholeptics-Antipsychotics	Diazepines, Oxazepines, Thiazepines and Oxepines
Fluspirilene	WHO-Marketed	N05AG01	Nervous System	Psycholeptics-Antipsychotics	Diphenylbutylpiperidine Derivatives
Penfluridol	WHO-Marketed	N05AG03	Nervous System	Psycholeptics-Antipsychotics	Diphenylbutylpiperidine Derivatives
Pimozide	WHO-Marketed	N05AG02	Nervous System	Psycholeptics-Antipsychotics	Diphenylbutylpiperidine Derivatives
Lurasidone	WHO-Marketed	N05AE05	Nervous System	Psycholeptics-Antipsychotics	Indole Derivatives
Molindone	WHO-Marketed	N05AE02	Nervous System	Psycholeptics-Antipsychotics	Indole Derivatives
Oxypertine	WHO-Marketed	N05AE01	Nervous System	Psycholeptics-Antipsychotics	Indole Derivatives
Sertindole	WHO-Marketed	N05AE03	Nervous System	Psycholeptics-Antipsychotics	Indole Derivatives
Ziprasidone	WHO-Marketed	N05AE04	Nervous System	Psycholeptics-Antipsychotics	Indole Derivatives
Lithium	WHO-Marketed	N05AN01	Nervous System	Psycholeptics-Antipsychotics	Lithium
Antipsychotics*	WHO-Marketed	N05A	Nervous System	Psycholeptics-Antipsychotics	Not Available
Aripiprazole	WHO-Marketed	N05AX12	Nervous System	Psycholeptics-Antipsychotics	Not Available

Brexpiprazole	WHO-Marketed	N05AX16	Nervous System	Psycholeptics-Antipsychotics	Not Available
Cariprazine	WHO-Marketed	N05AX15	Nervous System	Psycholeptics-Antipsychotics	Not Available
First Generation Antipsychotics*	WHO-Marketed	N05A	Nervous System	Psycholeptics-Antipsychotics	Not Available
Iloperidone	WHO-Marketed	N05AX14	Nervous System	Psycholeptics-Antipsychotics	Not Available
Mosapramine	WHO-Marketed	N05AX10	Nervous System	Psycholeptics-Antipsychotics	Not Available
Paliperidone	WHO-Marketed	N05AX13	Nervous System	Psycholeptics-Antipsychotics	Not Available
Phenothiazines*	WHO-Marketed	N05A	Nervous System	Psycholeptics-Antipsychotics	Not Available
Pimavanserin	WHO-Marketed	N05AX17	Nervous System	Psycholeptics-Antipsychotics	Not Available
Prothipendyl	WHO-Marketed	N05AX07	Nervous System	Psycholeptics-Antipsychotics	Not Available
Risperidone	WHO-Marketed	N05AX08	Nervous System	Psycholeptics-Antipsychotics	Not Available
Second Generation Antipsychotics*	WHO-Marketed	N05A	Nervous System	Psycholeptics-Antipsychotics	Not Available
Zotepine	WHO-Marketed	N05AX11	Nervous System	Psycholeptics-Antipsychotics	Not Available
Acepromazine	WHO-Marketed	N05AA04	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Aliphatic Side Chain
Chlorpromazine	WHO-Marketed	N05AA01	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Aliphatic Side Chain

Levomepromazine	WHO-Marketed	N05AA02	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Aliphatic Side Chain
Promazine	WHO-Marketed	N05AA03	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Aliphatic Side Chain
Triflupromazine	WHO-Marketed	N05AA05	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Aliphatic Side Chain
Acetophenazine	WHO-Marketed	N05AB07	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperazine Structure
Butaperazine	WHO-Marketed	N05AB09	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperazine Structure
Fluphenazine	WHO-Marketed	N05AB02	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperazine Structure
Perazine	WHO-Marketed	N05AB10	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperazine Structure
Perphenazine	WHO-Marketed	N05AB03	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperazine Structure
Phenothiazines with Piperazine Structure*	WHO-Marketed	N05AB	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperazine Structure
Prochlorperazine	WHO-Marketed	N05AB04	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperazine Structure
Thiopropazate	WHO-Marketed	N05AB05	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperazine Structure
Thioproperazine	WHO-Marketed	N05AB08	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperazine Structure
Trifluoperazine	WHO-Marketed	N05AB06	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperazine Structure
Mesoridazine	WHO-Marketed	N05AC03	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperidine Structure

Periciazine	WHO-Marketed	N05AC01	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperidine Structure
Pipotiazine	WHO-Marketed	N05AC04	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperidine Structure
Thioridazine	WHO-Marketed	N05AC02	Nervous System	Psycholeptics-Antipsychotics	Phenothiazines with Piperidine Structure
Chlorprothixene	WHO-Marketed	N05AF03	Nervous System	Psycholeptics-Antipsychotics	Thioxanthene Derivatives
Clopenthixol	WHO-Marketed	N05AF02	Nervous System	Psycholeptics-Antipsychotics	Thioxanthene Derivatives
Flupentixol	WHO-Marketed	N05AF01	Nervous System	Psycholeptics-Antipsychotics	Thioxanthene Derivatives
Tiotixene	WHO-Marketed	N05AF04	Nervous System	Psycholeptics-Antipsychotics	Thioxanthene Derivatives
Zuclopenthixol	WHO-Marketed	N05AF05	Nervous System	Psycholeptics-Antipsychotics	Thioxanthene Derivatives
Buspirone	WHO-Marketed	N05BE01	Nervous System	Psycholeptics-Anxiolytics	Azaspirodecanedione Derivatives
Alprazolam	WHO-Marketed	N05BA12	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Bromazepam	WHO-Marketed	N05BA08	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Camazepam	WHO-Marketed	N05BA15	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Chlordiazepoxide	WHO-Marketed	N05BA02	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Clobazam	WHO-Marketed	N05BA09	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives

Diazepam	WHO-Marketed	N05BA01	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Etizolam	WHO-Marketed	N05BA19	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Halazepam	WHO-Marketed	N05BA13	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Lorazepam	WHO-Marketed	N05BA06	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Oxazepam	WHO-Marketed	N05BA04	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Potassium Clorazepate	WHO-Marketed	N05BA05	Nervous System	Psycholeptics-Anxiolytics	Benzodiazepine Derivatives
Meprobamate	WHO-Marketed	N05BC01	Nervous System	Psycholeptics-Anxiolytics	Carbamates
Hydroxyzine	WHO-Marketed	N05BB01	Nervous System	Psycholeptics-Anxiolytics	Diphenylmethane Derivatives
Mephenoxalone	WHO-Marketed	N05BX01	Nervous System	Psycholeptics-Anxiolytics	Not Available
Benzodiazepine Derivatives*	WHO-Marketed	N05BA+N05CD	Nervous System	Psycholeptics-Anxiolytics+Hypnotics and Sedatives	Benzodiazepine Derivatives
Chloral Hydrate	WHO-Marketed	N05CC01	Nervous System	Psycholeptics-Hypnotics and Sedatives	Aldehydes and Derivatives
Amobarbital	WHO-Marketed	N05CA02	Nervous System	Psycholeptics-Hypnotics and Sedatives	Barbiturates, Plain
Pentobarbital	WHO-Marketed	N05CA01	Nervous System	Psycholeptics-Hypnotics and Sedatives	Barbiturates, Plain
Secobarbital	WHO-Marketed	N05CA06	Nervous System	Psycholeptics-Hypnotics and Sedatives	Barbiturates, Plain

Brotizolam	WHO-Marketed	N05CD09	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Derivatives
Estazolam	WHO-Marketed	N05CD04	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Derivatives
Flunitrazepam	WHO-Marketed	N05CD03	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Derivatives
Flurazepam	WHO-Marketed	N05CD01	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Derivatives
Midazolam	WHO-Marketed	N05CD08	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Derivatives
Nitrazepam	WHO-Marketed	N05CD02	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Derivatives
Triazolam	WHO-Marketed	N05CD05	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Derivatives
Eszopiclone	WHO-Marketed	N05CF04	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Related Drugs
Zaleplon	WHO-Marketed	N05CF03	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Related Drugs
Zolpidem	WHO-Marketed	N05CF02	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Related Drugs
Zopiclone	WHO-Marketed	N05CF01	Nervous System	Psycholeptics-Hypnotics and Sedatives	Benzodiazepine Related Drugs
Melatonin	WHO-Marketed	N05CH01	Nervous System	Psycholeptics-Hypnotics and Sedatives	Melatonin Receptor Agonists
Ramelteon	WHO-Marketed	N05CH02	Nervous System	Psycholeptics-Hypnotics and Sedatives	Melatonin Receptor Agonists
Dexmedetomidine	WHO-Marketed	N05CM18	Nervous System	Psycholeptics-Hypnotics and Sedatives	Not Available

Methaqualone	WHO-Marketed	N05CM01	Nervous System	Psycholeptics-Hypnotics and Sedatives	Not Available
Methylpentynol	WHO-Marketed	N05CM15	Nervous System	Psycholeptics-Hypnotics and Sedatives	Not Available
Valnoctamide	WHO-Marketed	N05CM13	Nervous System	Psycholeptics-Hypnotics and Sedatives	Not Available
Methyprylon	WHO-Marketed	N05CE02	Nervous System	Psycholeptics-Hypnotics and Sedatives	Piperidinedione Derivatives
Scopolamine	WHO-Marketed	N05CM05+S01FA02	Nervous System	Psycholeptics-Hypnotics and Sedatives+Ophtalmologicals	Mydriatics and Cycloplegics-Anticholinergics
Bemegride	WHO-Marketed	R07AB05	Respiratory System	Respiratory Stimulants	Not Available
Nikethamide	WHO-Marketed	R07AB02	Respiratory System	Respiratory Stimulants	Not Available
Pentetrazol	WHO-Marketed	R07AB03	Respiratory System	Respiratory Stimulants	Not Available
Testosterone	WHO-Marketed	G03BA03	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Androgens-3 Oxoandrosten (4) Derivatives
Cyproterone	WHO-Marketed	G03HA01	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Antiandrogens-Antiandrogens, Plain
Estrogen	WHO-Marketed	G03C	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Estrogens
Conjugated Estrogens*	WHO-Marketed	G03CA57	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Estrogens-Natural and Semisynthetic Estrogens, Plain
Estradiol	WHO-Marketed	G03CA03	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Estrogens-Natural and Semisynthetic Estrogens, Plain
Diethylstilbestrol	WHO-Marketed	G03CB02	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Estrogens-Synthetic estrogens, Plain

Gonadotropin Hormone	WHO-Marketed	G03GA	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Gonadotropins
Mifepristone	WHO-Marketed	G03XB01	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Progesterone Receptor Modulators
Norethisterone	WHO-Marketed	G03DC02	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Progestogens-Estren Derivatives
Medroxyprogesterone	WHO-Marketed	G03DA02	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Progestogens-Pregnen (4) Derivatives
Progesterone	WHO-Marketed	G03DA04	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Progestogens-Pregnen (4) Derivatives
Raloxifene	WHO-Marketed	G03XC01	Genito Urinary System and Sex Hormones	Sex Hormones and Modulators of the Genital System	Selective Estrogen Receptor Modulators
Liothyronine Sodium	WHO-Marketed	H03AA02	Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	Thyroid Hormones	Not Available
Anethole Trithione	WHO-Marketed	A16AX02	Alimentary Tract and Metabolism	Various Alimentary Tract and Metabolism Products	Not Available
Sodium Benzoate	WHO-Marketed	A16AX11	Alimentary Tract and Metabolism	Various Alimentary Tract and Metabolism Products	Not Available
Thioctic acid	WHO-Marketed	A16AX01	Alimentary Tract and Metabolism	Various Alimentary Tract and Metabolism Products	Not Available
Pentosan Polysulfate Sodium	WHO-Marketed	C05BA04	Cardiovascular System	Vasoprotectives-Antivaricose Therapy	Heparins or Heparinoids for Topical Use
Monoxerutin (Oxerutins)	WHO-Marketed	C05CA02	Cardiovascular System	Vasoprotectives-Capillary Stabilizing Agents	Bioflavonoids
Vitamin B Complex	WHO-Marketed	A11EA	Alimentary Tract and Metabolism	Vitamins	Not Available
Vitamin B6	WHO-Marketed	A11DB	Alimentary Tract and Metabolism	Vitamins	Not Available

Vitamins*	WHO-Marketed	A11	Alimentary Tract and Metabolism	Vitamins	Not Available
Vitamin C (Ascorbic Acid)	WHO-Marketed	A11GA01	Alimentary Tract and Metabolism	Vitamins-Ascorbic Acid (Vitamin C), Plain	Not Available
Calcium Pantothenate	WHO-Marketed	A11HA31	Alimentary Tract and Metabolism	Vitamins-Other Plain Vitamin Preparations	Not Available
Inositol	WHO-Marketed	A11HA07	Alimentary Tract and Metabolism	Vitamins-Other Plain Vitamin Preparations	Not Available
Pyridoxal Phosphate	WHO-Marketed	A11HA06	Alimentary Tract and Metabolism	Vitamins-Other Plain Vitamin Preparations	Not Available
Pyridoxine (Vit B6)	WHO-Marketed	A11HA02	Alimentary Tract and Metabolism	Vitamins-Other Plain Vitamin Preparations	Not Available
Riboflavin (Vit B2)	WHO-Marketed	A11HA04	Alimentary Tract and Metabolism	Vitamins-Other Plain Vitamin Preparations	Not Available
Tocopherol (Vit E)	WHO-Marketed	A11HA03	Alimentary Tract and Metabolism	Vitamins-Other Plain Vitamin Preparations	Not Available
Retinol (Vit A)	WHO-Marketed	A11CA01	Alimentary Tract and Metabolism	Vitamins-Vitamin A, Plain	Not Available
Thiamine (Vit B1)	WHO-Marketed	A11DA01	Alimentary Tract and Metabolism	Vitamins-Vitamin B1, Plain	Not Available
Colecalciferol	WHO-Marketed	A11CC05	Alimentary Tract and Metabolism	Vitamins-Vitamin D and Analogues	Not Available
Dihydrotachysterol	WHO-Marketed	A11CC02	Alimentary Tract and Metabolism	Vitamins-Vitamin D and Analogues	Not Available

Appendix 7-1

Table 7-1-1: Number of trials per country

Country	Count
China	8542
United States of America	4188
United Kingdom	1024
Canada	541
Germany	533
Australia	318
Japan	306
Netherlands	268
India	256
Iran	231
Israel	224
Spain	215
France	200
Italy	197
Denmark	136

South Korea	127
Taiwan	120
Sweden	114
Switzerland	111
Czech Republic	110
Russia	102
Belgium	97
Brazil	93
Austria	80
Finland	77
Poland	67
South Africa	65
Turkey	63
Romania	59
Norway	56
Ukraine	48
Hong Kong*	44
Mexico	43
Greece	38

Hungary	34
New Zealand	34
Argentina	32
Croatia	31
Malaysia	28
Thailand	28
Bulgaria	26
Ireland	26
Pakistan	23
Republic of Serbia	19
Singapore	17
Slovakia	17
Philippines	16
Colombia	14
Venezuela	13
Chile	12
Estonia	12
Egypt	11
Latvia	11

Nigeria	11
Portugal	10
Puerto Rico	10
Indonesia	9
Lithuania	9
Yugoslavia	9
Peru	6
Tunisia	6
Ethiopia	5
Jordan	5
Sri Lanka	5
Iceland	4
Nepal	4
Saudi Arabia	4
Slovenia	4
Cuba	3
Ghana	3
Azerbaijan	2
Costa Rica	2

Kuwait	2
Lebanon	2
Moldova	2
Republic of Macedonia	2
Uganda	2
Afghanistan	1
Bahrain	1
Bangladesh	1
Belarus	1
Bosnia and Herzegovina	1
Jamaica	1
Malawi	1
Montenegro	1
Morocco	1
Mozambique	1
Panama	1
Uruguay	1
Vietnam	1
Zimbabwe	1

*Hong Kong mapped on China as default in GunnMap 2 software program.