

Cochrane Schizophrenia Group

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Background

Systematic Reviewing, Cochrane, and the Cochrane Collaboration

In 1884, Lord Raleigh, the president of the British Association for the Advancement of Science, stated “If, as is sometimes supposed, science consisted in nothing but the laborious accumulation of facts, it would soon come to a standstill, crushed, as it were, under its own weight Two processes are thus at work side by side, the reception of new material and the digestion and assimilation of the old”¹ When applied to the accumulation of facts on the effects of medical treatments, health care had to wait nearly 100 years for attempt to apply basic epidemiological principles and quantification into the process of reviewing. Beecher² was, perhaps, the first to apply these principles in health with an early review of the effects of placebo. Some years later, in the mid-1970s, Gene Glass, an educational psychologist, added results of similar studies in the hope of quantifying the effects of a treatment.³ Glass defined “meta-analysis” as “the statistical analysis of a large collection of analyses results from individual studies for the purpose of integrating the findings.”^{4,5} Unsurprisingly, in the sensitive area of the psychotherapies, their first and flawed attempts in the new discipline generated controversy.⁶ Critics were quick to point out that drawing conclusions from summation of very different types of therapies, undertaken by practitioners of varied experience, was likely to be inadvisable. Beecher, Glass, Slater, and John Davis in the area of schizophrenia⁷ were all pioneers. Even years later when

the sophistication of systematic reviewing techniques has improved out of all proportion, they are still being criticized for adding “apples and oranges”⁸ but are nevertheless owed a great debt by the rest of medicine.

It was about the same time as the early work of Glass and Davis that Archie Cochrane stated “It is surely a great criticism of our [medical] profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials.”⁹ Cochrane had an interesting history. He was born in Scotland in 1908. In the 1930s, he underwent psychoanalysis with Theodor Reik in Berlin, Vienna, and The Hague, and his first academic article was on this topic and documented a conversation he had had with Freud.¹⁰ Cochrane was a veteran of the International Brigade of the Spanish Civil War and then World War II, but by the 1970s, he directed the Medical Research Council Epidemiology Research Unit, Cardiff, Wales.

Archie Cochrane's challenge led Iain Chalmers, a perinatal epidemiologist working in Oxford in the 1980s, to establish an international collaboration to develop the Oxford Database of Perinatal Trials. In 1987, the year before Cochrane died, he referred to systematic review by Chalmers et al of randomized controlled trials (RCTs) of care during pregnancy and childbirth as “a real milestone in the history of randomized trials and in the evaluation of care” and suggested that other specialties should copy the methods used.¹¹ This encouragement, and the endorsement of his views by others, combined with the vision, energy, and leadership of Chalmers, led to the opening of the first Cochrane Centre (in Oxford, UK) in 1992 and the founding of The Cochrane Collaboration in 1993. The Cochrane Collaboration is now an international not-for-profit and independent organization, dedicated to making up-to-date, accurate information about the effects of health care readily available worldwide.¹² Thousands of reviewers from across the globe produce systematic reviews of health care interventions, and these reviews are regularly maintained and then disseminated in the electronic Cochrane Library. This library is now distributed widely though academic institutions and is increasingly available to the wider public through national subscriptions (<http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME>).

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The Cochrane Schizophrenia Group

Within the Cochrane Collaboration, special interest groups formally register their interest, draw up plans for a hub of the wider collaboration, and formally agree to the governance arrangements now necessary for such a large international organization. In 1994, the Schizophrenia Group was the fourth group to register within the Cochrane Collaboration and the first of the now 5 mental health groups. Jeremy Anderson (then Dunedin, New Zealand), Jair Mari (Sao Paulo, Brazil), and A.E.C. (then Oxford, UK) founded the group. It does seem a long time since the first open meeting held with the support of the organizers of the VIIth Biennial Winter Workshop on Schizophrenia (January 1994, Les Diablerets, Switzerland). After that international endorsement, several invitations to contribute were published and the first reviews emerged.

The Contribution

The Network

The Cochrane Schizophrenia Group (CSG) has succeeded in building itself into a global independent collaborative network. About 350 like-minded people, from 23 countries, work together to produce a collection of clinically relevant work. This network is open, welcoming, and growing—and is productive of much work other than Cochrane reviews. The CSG tries to ensure its work is relevant to people in low- and middle-income countries, where 80% of people with schizophrenia live. Reviewers from these countries, often working in circumstances of enormous clinical pressure and financial constraint, still find time to work with the CSG. The CSG editors are now from Brazil (Evandro Coutinho; Oswaldo Cruz Foundation, Rio de Janeiro), China (Chunbo Li; Tongji University, Shanghai), Germany (Stefan Leucht; Technische Universität München, Munich), India (Prathap Tharyan; Christian Medical College, Vellore), United Kingdom (Lorna Duggan; St Andrew's Hospital, Northampton) and the United States (John Davis; University of Illinois at Chicago). The CSG's editorial base is now in the University of Nottingham, in the heart of England (<http://szg.cochrane.org/en/index.html>).

The Reviews

Although there is no room for complacency, independent research has shown Cochrane reviews to be considerably more rigorous than what has gone before,¹³ and these maintained reviews are now benchmarks for thoughtful clinicians and policymakers. Of course, many high-quality systematic reviews in the area exist outside of the Cochrane Library, but the Cochrane system does allow for maintenance; as better methods evolve, different perspectives on the data are required and new evidence

comes to light. The CSG has, at this time, 116 maintained reviews on all aspects of care of people with schizophrenia or similar problems. Every 3 months, the numbers of full reviews increase as titles become protocols and protocols a completed into reviews (see Supplementary Table). For full updated list of reviews, please see <http://szg.cochrane.org/en/localrevs.html>.

Topics for reviews are selected by the, largely, volunteer reviewers, although this may involve guidance from an editor. Potential reviewers simply contact an editor, and the title for the review is developed. The agreed title is then discussed by all editors and finally submitted to a central repository for titles in the Cochrane Information Management System. Editors encourage review teams to be compiled of people who may view the topic from different and broad perspectives. Reviewers may request support and training, all of which is freely and widely available. A protocol for the review is drawn up, using the RevMan writing tool (Review Manager—<http://www.cc-ims.net/RevMan>). The protocol is peer reviewed by 2 editors and then sent for external volunteer peer review. Lay review has been found to be of great value, and a system for this is now being established. Once accepted by 2 editors, the protocol is published on the Cochrane Library and, by doing this, made open to general review and peer review. This process is repeated for the full review and updates. All are completed within the freely available RevMan that helps manage text, tables, references, and analyses, and the process of widely dispersed multiple authors and central submission to the editorial base. RevMan has adequate capabilities of analyses for most reviews but additional statistics—such as survival curves—can be undertaken outside of the program, and the results imported and published in this way. Comments and criticisms for these protocols and reviews can be submitted by any reader of the Cochrane Library—the Library includes a direct e-mail system. These comments are addressed, through a Comments Editor, to the relevant reviewer and editor, so valid criticism can help amend and improve the work. In 2006 MedScape's evidence-based medicine service to WebMD Psychiatry, fuelled by the University of McMaster's MORE service (McMaster's Online Rating of Evidence—<http://hiru.mcmaster.ca/more/>) recorded Cochrane reviews in 6 of the top 10 places with CSG reviews coming in at number 1 and 9.

Direct Contributions to the Science of Reviewing

The Science of Information Retrieval. Although the discipline of information retrieval is well established, its systematic application and investigation within mental health was limited. Building a register of trials, as is mandatory for any Cochrane group, affords an opportunity to methodically investigate this area with repercussions for the whole of health care. For example, in the very first

Table 1. Factors That Result in Those Searching Databases Failing to Find Relevant Work

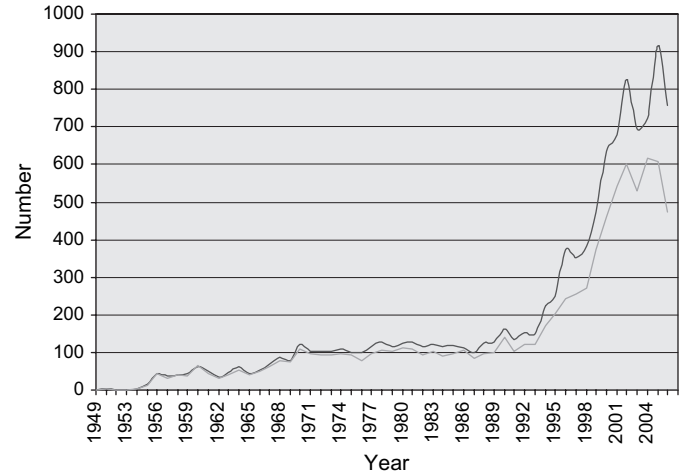
Problems with hardware/software ¹⁴
Inexperience ¹⁵
Indexing
Policy ¹⁵
Inadequacies ¹⁵
Inconsistencies ¹⁶
Language biases ^{17–22}
Currency of contents ¹⁶
Wrong database ²³

work the CSG did we found a software commonly used for searching MEDLINE at that time (SilverPlatter) to be faulty. It was, without warning, giving erroneous results.¹⁴ SilverPlatter, always informed of our work and progress, agreed to reissue their product once the fault was fixed. The CSG has investigated each reason why electronic searching may give inaccurate results (see table 1).

Making Reports Accessible. A declining proportion (~50%) of trials in schizophrenia are accessible through MEDLINE or PsycINFO. We have found that the national productivity of trials is more linked with the gross wealth of the nation (gross domestic product—GDP) rather than the absolute numbers of people in the country with schizophrenia.²⁴ It is therefore possible to predict trialing activity per country. It is, eg, entirely predictable that as China's GDP increases, so does its productivity of schizophrenia trials. The emergence of some countries from poverty, combined with increasing Internet access, leads people in countries whose biomedical literature is not well represented in North American databases to create their own bibliographic listings. The CSG, has, for the whole of medicine, investigated many of these new sources of citations and full text and found many to be rich sources of previously unknown trials.^{17–22,23,25} Other researchers have found that trials in general medicine in MEDLINE are more likely to present positive findings than equally high-quality trials by the same authors in their home language indexed outside of this database.²⁶ This study should be replicated for schizophrenia trials.

Piecing Together the Sausage From the Salami. The CSG has a register of all relevant randomized studies. This now incorporates 10 000 reports arranged into 7000 indexed studies (figure 1).

The problem of several references to single studies is a real difficulty for reviewers and clinicians. The impression that there are more data than there really are is frequently given by multiple publications of single trials. The “flat” files seen on the large databases such as MEDLINE are, at best, less helpful than is needed by research-

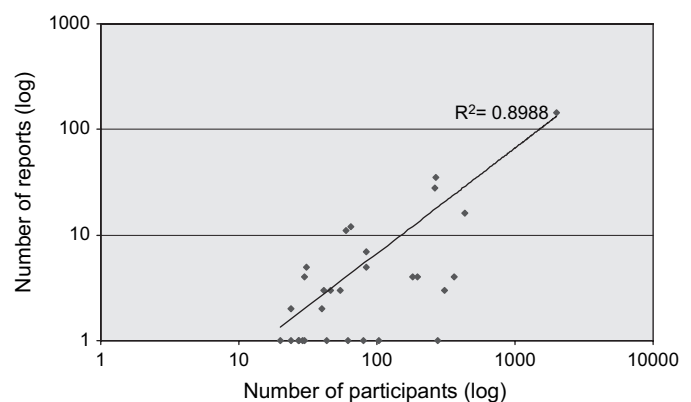


* Reports in red, studies in yellow

Fig. 1. Reports and Studies Across Time. Reports in Red, Studies in Yellow.

ers and clinicians and, at worst, misleading. Those undertaking systematic reviews need to have all relevant information about each *study*, not necessarily records of each individual *report*. For example, the Cochrane review of olanzapine is a major review.²⁷ Much effort was needed to piece together the many slices of salami publications of the same trials (please see “References to Included Studies” in this review). A graph taken from data in this review illustrates the point further (figure 2). The number of people in the study reasonably accurately predicts the number of publications of the study. Ten people randomized—1 publication; 100 people randomized—10 publications; 1000+ people randomized—>100 publications.

The CSG has led the development of innovative free software, designed for those creating study-based registers where one record can relate to many references (<http://www.cochrane.co.uk/en/newPage1.html>). This software has the capacity to supply full text, extracted data, and sorted studies with their groups of references

**Fig. 2.** Number of Reports of Olanzapine Vs Haloperidol Trials Plotted Against Number of Participants in Each of Those Trials.

and reports. The CSG, supported by the European Union, working with all other mental health groups in the Cochrane Collaboration, has produced the only comprehensive source of mental health trials (PsiTri—<http://psitri.stakes.fi/EN/psitri.htm>). This is in study-based form and is freely accessible on the Web. The CSG register includes unpublished studies, dissertations, work from all over the world and is in both full-text hard and electronic form.

The Statistics of Loss. Loss to follow-up in trials relevant to people with schizophrenia is often large. Although there is no substitute to trying to minimize attrition with good trial design, once a person is lost several things can be done with the data. For continuous data, the technique of taking the last observation before leaving the study (so called last observation carried forward or LOCF) as the outcome is often used by those analysing trials.²⁸ Recent work by CSG collaborators has drawn our attention to the difficulties with this device. For binary data, recent important work, also undertaken in collaboration with the CSG, advances the whole area of how statistics can help in the situation of loss to follow-up.²⁹

Trials

Content, Quality, and Biases. Registers of trials afford opportunities to overview the content and quality of trials in defined sampling frames. For example, despite indexing in leading databases, manual searching of leading journals for randomized trials is still necessary. When a periodical is searched for all such studies, an overview can be undertaken of the trials the journal has published over a protracted period of time. Some time ago, we surveyed trials published in *Archives of General Psychiatry*. On finding how quality and content had not necessarily increased across time and that outcomes were almost invariably positive—suggesting a publishing bias—the then editors of *Archives* reacted generously. They published the work and encouraged its perpetuation and in this way set a standard for medical editors worldwide.³⁰ Taking this idea further, in 1998 the CSG published an overview of all schizophrenia trials on the 50th anniversary of the first randomized trial.³¹ On average, schizophrenia trials were shown to be small, involving people so rigorously diagnosed as to be rare in every day practice, investigating rigid care regimens, and measuring outcomes on hundreds scales of unclear clinical meaning. This article, and its sister study in forensic mental health,³² has been repeatedly used by those calling for a more pragmatic approach to evaluative studies. The study is due repetition to see if we, as a subspecialty, have improved in the last decade. CSG has recently repeated this exercise for schizophrenia trials for particular regions of the world.³³

When CSG collaborators have used the register of trials to investigate aspects of evaluative research in this

area to more depth, they have found worrying signs. For example, it seems that 40% of outcomes in schizophrenia trials are based on scales not validated at their time of use.³⁴ These nonvalidated scales are statistically significantly more likely to yield statistically significant results compared with those that are simply referenced in the original trial. When researchers working in collaboration with the CSG have investigated the effects of industry sponsorship on outcome, they have confirmed that these studies are likely to include a predictable bias.³⁵

Design and Conduct. There are many reasons for undertaking a review—but one is a consuming interest in the area. After undertaking a systematic review, interest is often fed and confidence in undertaking the primary research increased. With the careful scrutiny of the best past evidence, ideas for design, conduct, and reporting of trials are fostered. The CSG was born out of the work of visionary perinatal epidemiologists. Much can still be learnt from their work. The Collaborative Eclampsia Trial, a landmark trial of the 20th century,³⁶ formed the template for the CSG's work in the now 4 TREC trials (TREC acronym stands for Tranquilização Rápida-Ensaio Clínico, translated as Rapid Tranquillisation-Clinical Trial).^{37–40} These pragmatic studies were designed in collaboration with people in low- and middle-income countries for application to their working circumstances and focused on the pharmacological management of acute psychosis-induced aggression. They randomly allocated locally relevant drug management within busy emergency settings and recorded routine clinically relevant outcomes. The designs ensured complete accrual and data acquisition (4 RCTs, total $N = 1232$, >98% follow-up). Recent UK guidelines have noted that “unlike most of the other studies in this review, [the two TREC trials available at the time of this review] were large studies of a high methodological quality.”⁴¹ The TREC studies have been followed by others in the CSG evaluating means of encouraging good outpatient attendance⁴² and of detoxification off illicit opiates in difficult populations.⁴³ CSG reviews, by highlighting the enormous gaps in our knowledge, will continue to spur researchers into action, and many more real-world trials are to be expected. The symbiotic relationship between reviews and trials is also being encouraged from 2 directions. Funding bodies are increasingly encouraging systematic reviews as a prerequisite to trial application,⁴⁴ and good journals recognize that presenting the results of a trial isolated from the totality of evidence is deceptive.⁴⁵

Keeping Up-To-Date

Electronic Publication. The CSG, working within the wider Cochrane Collaboration, has helped move the whole ethos of electronic publication forward. Dissemination on the Web now has the advantage of reaching

a very wide readership. This advantage is increasingly exploited by the traditional journals such as the *Schizophrenia Bulletin*. However, a key advantage to electronic dissemination is the capacity for currency of content. This is not exploited by the traditional journals. Good reviews can be published anywhere but the time lag from submission to print can still be considerable and lead to dissemination of misleading and outdated results. For example, in August 1994, one of the founding editors of the CSG, Jair Mari, published a major systematic review on the effects of family intervention for schizophrenia.⁴⁶ A month later Mari and Streiner⁴⁷ published their substantially updated review in the very first Cochrane Library. Their article had taken time to be peer reviewed and fully published; new trials had emerged in this fast moving field and materially changed the findings. This time lag with its potential for publication of outdated and even misleading reviews is not a thing of the past. Cochrane reviews, however, have the potential to swiftly incorporate new data or valid criticism.

Derivative Publications, Guidelines. The CSG has considerable input into some of the now numerous derivative publications assisting clinicians keep up-to-date. For example, CSG's coordinating editor was, for a period, employed with the BMJ publishing group helping produce *Clinical Evidence*—a regularly maintained series of evidence-based synopses.⁴⁸ These types of publications assist busy clinicians keep on top of evidence. The *Schizophrenia Bulletin's* recent initiative in producing a Cochrane Corner is another way of drawing attention to the fast moving field of evidence of the effects of care for people with schizophrenia or related disorders.⁴⁹ The CSG has also been pleased to be involved in the production of national evidence-based guidelines. It is not a coincidence that the first large national guideline from the National Institute of Clinical Excellence in England and Wales was for the acute care of people with schizophrenia.^{49,50} The Centre for Reviews and Dissemination in York, UK, worked closely with the editorial base of the CSG during the technology appraisal for these guidelines.

The Future

Back in 1884, Lord Rayleigh stated that managing the “accumulation of facts” is “... work in which discovery and explanation go hand in hand, in which not only are new facts presented, but their relation to old ones is pointed out” [but work] “which deserves, but, I am afraid, does not always receive, the most credit.”¹

There is much yet to do because, still, little credit is given to the importance of having our textbooks, meetings, and lectures on treatment based on use of some explicit methods. Mental health researchers, however, have a (fine) tradition of self-doubt. As a consequence, we have led the introduction of blinding into fair tests of

interventions,⁵¹ the adoption of randomized trials as a means of evaluation,³¹ and pioneered systematic reviews.³ In the next years, the CSG will continue to assist opinion leaders who do have that healthy self-doubt and feed their need for up-to-date high-grade evidence in the form of up-to-date systematic reviews and relevant trials.

The CSG is actively planning and experimenting with new techniques of dissemination in order to better reach clinicians and recipients of care or their carers. Certainly, with national (Australia, India, Ireland, Latin America, New Zealand, Norway, Poland, Sweden, United Kingdom), regional (Canada), and state (United States—Wyoming) provision of the Cochrane Library, usage of CSG reviews outside of the usual academic or health care setting is increasing. The CSG's output must evolve to assist everyone to have swift access to yet more clearly presented relevant data.

In the next decade, searching for trials relevant to schizophrenia should become more centralized, with specialist databases such as the Cochrane Library's CENTRAL register of trials⁵² and PsiTri.⁵³ With forward thinking funders, researchers, companies, and editors insisting on the adoption of International RCT Numbers piecing together the single study from multiple publication could become easier. This, along with data-mining techniques,⁵⁴ and increasing openness of industry (eg, <http://www.lillytrials.com/index.html>) should help create databases that are truly representative of the evaluative research in specific areas of health care. The CSG is encouraging these initiatives.

The CSG will continue to help find out where the best evidence for treatment effects is and where it is lacking. Where there are important omissions, we will try to help fill those gaps.

Supplementary Material

Supplementary table is available at <http://schizophreniabulletin.oxfordjournals.org>.

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