Systematic reviews of observational epidemiological studies: new challenges in research synthesis?

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Using a rigorous systematic protocol, systematic reviews synthesize findings from available randomized controlled trials (RCTs)—the gold standard for studies of effectiveness of preventative and therapeutic interventions for particular conditions—on a single research question in order to provide a holistic understanding of the available answers. Such reviews are now widely accepted as a prerequisite for making decisions on clinical interventions and health policy. However, clinicians, programme managers and policy-makers need equally comprehensive and reliable information in a variety of other health care areas in which research designs other than RCTs are used and there is an absence of methods for conducting systematic reviews. These areas include, for example: evaluation of performance of different screening and diagnostic methods and tests (cross-sectional or prospective observational studies); short-and long-term consequences of environmental, behavioural or other risk factors (cohort studies); and assessments of the magnitude of burden of specific conditions (surveys, cross-sectional and other prevalence studies). At the present time there is no mechanism for synthesizing data from these studies in a systematic manner in order to arrive at a comprehensive understanding of the available knowledge. We believe that systematic reviews of these data can greatly improve clinical practice and public health. The challenge lies in developing appropriate methods and systems to do so, just as the Cochrane Collaboration did for systematic reviews of RCTs. In order to understand the scope and the magnitude of the work involved we examine briefly the processes involved in the coming together of The Cochrane Collaboration.

In his famous 1972 book *Effectiveness and Efficiency: Random Reflections on Health Services* published in 1972 (1), Archibald Leman Cochrane underscored the value of using evidence from RCTs in providing reliable data on evidence of health care interventions than other sources of evidence (2). In 1979 he wrote, "It is surely a great criticism of our profession that we have not organized a critical summary, by speciality or subspecialty, adapted periodically, of all relevant randomized controlled trials" (2). This was a direct call for systematic reviews of RCTs. In 1989, Cochrane referred to the two-volume book on systematic reviews of 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 areas of health care should copy the methods used (3). Archie Cochrane's ideas lived on and the first Cochrane centre was opened in Oxford, UK, in 1992 and The Cochrane Collaboration was founded in 1993.

During the past ten years of existence of the Cochrane Collaboration, statisticians, librarians, consumers and health researchers have collaborated in increasing numbers. By 2003 close to 10 000 individuals globally had collaborated to prepare, maintain and disseminate systematic reviews of the effects of health care, leading to

the publication of 1837 systematic reviews and 1344 review protocols in *The Cochrane Library* (October 2003).

The success of The Cochrane Collaboration has motivated even groups outside health care to launch similar initiatives. For example, in 2000 The Campbell Collaboration (C2) was established to prepare, maintain and disseminate systematic reviews of studies of interventions in the social, behavioural and educational fields (4).

The methodological developments in research synthesis have led to substantial advances in critical appraisal and meta-analysis techniques in the past 25 years. Many empirical studies on the science of reviewing and summarizing data from different but similar studies have been published. The Cochrane Collaboration Methods Working Groups have contributed substantially to this field. These studies have alerted the reviewers to potential areas of bias such as publication bias (the tendency to publish results that show differences) and language bias (ignoring work published in languages other than English). Studies on heterogeneity among trials (5), discrepancies between single large trials and meta-analyses of smaller trials (6), have improved the quality of reviews and led to initiatives such as prospective meta-analysis and individual patient data meta-analysis.

As noted earlier, studies of the accuracy of diagnostic and screening tests, rare and long-term adverse effects of drugs, prevalence/incidence of conditions, prognosis of diseases and comprehensive assessment of risk factors are some of the areas where organized efforts to prepare systematic reviews are lacking. Dickersin recently highlighted this gap in observational epidemiology (7). The systematic review concept also applies to animal (8) and laboratory studies. To produce systematic reviews of observational studies a global collaborative effort similar to The Cochrane Collaboration is needed.

Each of the areas mentioned above will present its own special challenges. But at the outset, ways to search the literature, critical appraisal and analytical approaches are important areas to address. For example, one of the most significant contributions of The Cochrane Collaboration has been the establishment of systems for the identification of published RCTs. The handsearching (manual searching page by page) of journals and retrospective re-tagging of articles has identified thousands of published RCTs that were inaccessible. These have been entered into a register of more than 300 000 RCTs, making searching the literature for RCTs easier for individual researchers and librarians (9).

For observational epidemiological studies, the issue of identification of studies appropriate to a particular question and appraisal of their quality pose specific challenges. The World Health Organization recently conducted a systematic review of maternal morbidity and mortality. In this review, more than 60 000 titles and abstracts were screened, but eventually only 2500 published reports were included in the review after critical appraisal. This process could have been much faster and efficient if a system of identifying the specific types of reports was available.

There has been more empirical work on the critical appraisal and meta-analysis techniques for screening/diagnostic tests compared with other observational epidemiological studies. However, the scale of this work is minuscule in comparison to that of The Cochrane Collaboration for the moment.

Given the scope and the magnitude of the work required it is clear that international collaboration at a similar scale to that of The Cochrane Collaboration (7) is needed. The World Health Organization could play a central role in developing a global partnership to fill this gap.

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