Promoting systematic reviews of randomised controlled trials in primary care

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Abstract The aims of this study were to examine the extent to which review articles currently published in leading peer reviewed primary care journals incorporate reviews of RCTs in a systematic way, and to examine the feasibility of establishing an international register of RCTs conducted in, or relevant to, primary care. A retrospective literature review was undertaken of all review articles published in the seven primary care journals during 1991. The extent to which the reviews had systematically synthesised evidence from RCTs was assessed. Of the 28 review articles identified during 1991, only 2 attempted to quantitatively synthesise data from RCTs. A total of 266 RCTs relevant to primary care were identified from 110 different journals between 1987-1991 using Medline. Of these only 69 trials appeared in primary care journals. However, 13-38 per cent of RCTs in the 7 major primary care journals were only identified by manual searching and had been missed by a Medline search.

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- Silagy CA. Developing a register of randomised controlled trials in primary care. Br Med J 1993; 306: 897-900;
- Silagy CA. An analysis of review articles published in primary care journals. Fam Pract 1993; 10(3): 337-41.

Introduction

Ideally, clinical and policy decisions made in primary care ought to take account of the evidence, where available, about the effectiveness of interventions. Of the various types of evidence to guide this decision making, randomised controlled trials (RCTs) are widely accepted as representing a 'gold standard', since they reduce much of the bias which is often associated with other design methods.[1]

An increasing number of RCTs are conducted in, or directly relevant to, primary medical care. Many of these are published in journals which are not readily accessible to the majority of general practitioners. Consequently, it is possible that important information that could be derived from these studies may not reach its target audience. One strategy to help in overcoming this problem is to include the results of RCTs in comprehensive and well-compiled overviews of clinical topics which are then made readily accessible to general practitioners.

It is important that review articles are constructed in a systematic manner. Those which are not may have a negative effect on provision of health care.[2] A recent analysis of review articles from several leading peer-reviewed journals, about the treatment of myocardial infarction, demonstrated that frequently these articles failed to take into account data from all the relevant published randomised controlled trials which were available at the time.[3] Consequently, some of the recommendations made in the reviews overlooked important advances in therapy or effective new preventive measures. These inconsistencies might have been avoided if the reviews had incorporated a systematic and quantitative method of synthesising all the published evidence from randomised controlled trials available at the time.[3]

Placing the blame for this situation solely on the experts responsible for preparing review articles is not entirely fair. The process of identifying and synthesising information from all the RCTs associated with a particular topic is extremely time-consuming and labour-intensive. *Cochrane* and others have therefore called for the need to establish a systematic listing of all RCTs in all branches of medicine. This could then form a basis to undertake comprehensive systematic reviews in the future.[4,5]

Currently, systematic lists of RCTs exist in very few branches of medicine.[6] Obstetrics and perinatal medicine is the notable exception where there is now a systematically assembled register of relevant RCTs (both published and unpublished) which has been used as a resource for systematic reviews.[7]

No systematic lists exist of RCTs relevant to primary care. Establishing such a list is potentially very difficult since primary care overlaps with many other disciplines. As a result, relevant RCTs are likely to be dispersed across a wide range of journals and a significant effort would be required to identify all of them. One possible solution to this situation is to create a register of RCTs which would hopefully facilitate more ready access to trials published in a wide range of journals.

Prior to establishing an international register of RCTs in primary care, a feasibility study was performed to determine the proportion of primary care review articles which systematically review evidence from RCTs (where appropriate to the subject) and incorporate quantitative techniques to pool this information, and the most effective strategy(s) for identifying RCTs conducted in, or directly relevant to, the discipline of primary care.

Method

To estimate the proportion of review articles which systematically reviewed evidence from RCTs, all the 1991 issues of the following seven peer-reviewed primary care journals were handsearched: The British Journal of General Practice, Family Medicine, Family Practice, Family Practice Research Journal, Journal of the American Board of Family Practice, Journal of Family Practice and Scandinavian Journal of Primary Health Care. Articles which were headed as 'review articles' or

'clinical review' were eligible for inclusion in this part of the study.

A full copy of each review article was obtained and assessed using previously described criteria which are recommended in guidelines for effective information synthesis.[8] These were as follows:

- purpose of review stated;
- sources and methods of the citation search identified;
- provision of criteria for inclusion and exclusion of studies;
- assessment of methodologic validity of material included in the review;
- information synthesised qualitatively;
- quantitatively using a systematic approach within the limits of the available data;
- summary of the main findings;
- provision of specific directives for future research in the area.

Each criterion was assigned 2 points if it was fully and clearly specified, 1 point if it was partially specified and/or not entirely clear or 0 points if it was not specified in the review.

To be eligible for inclusion in the register of RCTs a trial had to have been carried out in a primary care setting or published in a primary care journal or have results which were directly relevant to the organization and practice of primary care medicine. In addition all trials had to meet the following two methodological criteria:

- there must have been at least two groups;
- allocation to the groups must have been either by formal randomization or by a quasi-random method (eg. alternation).

Three strategies were used to identify studies suitable for inclusion in the register: search of electronic data bases, approach of editors, and a manual (hand) searching of journals.

For this feasibility study the electronic search was limited to Medline between 1987 and 1991 using SilverPlatter on CD-ROM. The terms used in the search are shown below:

1 RANDOM ALLOCATION (Medical Subject Heading MeSH)
2 RANDOM (Text Word- TW)
3 CLINICAL AND TRIAL (TW)
4 PROSPECTIVE OR PROSPECTIVELY (TW)
5 DOUBLE AND BLIND (TW)
6 DOUBLE-BLIND METHOD (MeSH)
7 1 or 2 or 3 or 4 or 5 or 6
8 7 and HUMAN
9 GENERAL PRACTICE (TW)
10 PRIMARY HEALTH CARE (TW)
11 FAMILY MEDICINE (TW)
12 COMMUNITY MEDICINE (TW)
13 9 or 10 or 11 or 12
14 8 and 13*
15 CONTROL (TW)*

The print-out of the abstract from each article identified by the search strategy was reviewed manually to identify those that would meet the inclusion criteria. In cases where this was unclear a copy of the full manuscript was obtained and reviewed.

A list of editors of the 'specialist' primary care journals worldwide was prepared using The Serials Directory and checked against the list indexed in FAMLI (which also includes journals not on Medline).[9,10] A standard letter was sent to each editor outlining the project and asking whether their journal has a method of identifying completely and with confidence, all the clinical trials it has ever published. Those who did not respond to the initial request after 2 weeks were followed up by telephone. Those who could not be contacted by telephone received a reminder letter.

All back issues of the seven major primary care research journals previously listed were individually scrutinised by an experienced GP researcher to identify RCTs which met the inclusion criteria.

To allow the number of RCTs obtained from the electronic search to be compared against the number identified by hand searching, the electronic search was extended back to the year in which each of the journals was first included in Medline using the search terms as described above.

The number of RCTs identified was expressed as a proportion of the total number of articles retrieved using each of the specific Medline search strategies employed. This proportion was referred to as the 'yield rate'. Essential frequencies were calculated for the numbers of RCTs published in different journals.

Results

A total of 28 suitable review articles published during 1991 were identified from

Table 1 *Assessment of 28 review articles in the primary care literature during 1991. Rounded percentages*

	Clearly stated (2 points)	Unclear (1 point)	Not stated (0 points)
Purpose	54	25	21
Data sources identified	11	7	82
Data selection	14	7	79
Validity assessment	14	32	54
Qualitative synthesis	32	50	18
Quantitative synthesis	7	4	86*
Summary of findings	14	43	43
Future directions	14	25	61

* In one review article it was inappropriate to include any quantitative synthesis of primary data.

* Criterion 14 had to be satisfied in order to meet the entry criteria for the register. Criterion 15 was run independently after the original search to examine the additional yield of RCTs from adding this term.

six of the seven journals. Only the Scandinavian Journal of Primary Health Care did not publish any review articles in 1991. The detailed breakdown of the quality assessment of the articles is shown in *table 1*.

In over 80 per cent of the reviews some effort had been made to synthesise data, at least qualitatively. This was done in a systematic manner in nine of the reviews. However, in five reviews there was no evidence of any qualitative synthesis of information. Attempts to synthesise data quantitatively occurred in even fewer instances. Formal meta-analysis, a recognised form of metrically pooling data, was attempted in only two of the reviews, even though it may have been possible to do so in at least a further eight reviews.

Table 2 *Source of publication of randomised controlled trials (RCTs) related to primary care*

Source	No RCTs published	Rounded % of total
Primary care journals		
Br J Gen Pract	12	5
Fam Med	7	3
Fam Pract	3	1
Fam Pract Res J	3	1
J Am Board Fam Pract	6	2
J Fam Pract	20	8
Scand J Prim Health Care	7	3
Other Journals (3)	4	2
Total	62	23
Public health journals		
Am J Prev Med	4	2
Other Journals (9)	11	4
Total	15	6
Generalist medical journals		
BMJ	17	6
Br J Clin Pract	10	4
Curr Med Res Opin	13	5
JAMA	3	1
J Gen Intern Med	4	2
J Int Med Res	9	3
Lancet	3	1
Med Care	4	2
NZ Med J	4	2
Ugeskr Laeger	7	3
Other Journals (15)	18	7
Total	92	35
Specialist medical journals		
Chemotherapy	4	2
Infection	3	1
Int Clin Psychopharmacol	3	1
J Antimicrob Chemother	4	2
J Cardiovasc Pharmacol	4	2
J Hum Hypert	4	2
J Infect Dis	3	1
Psychopharmacology Berl	4	2
Other Journals (57)	68	26
Total	97	37

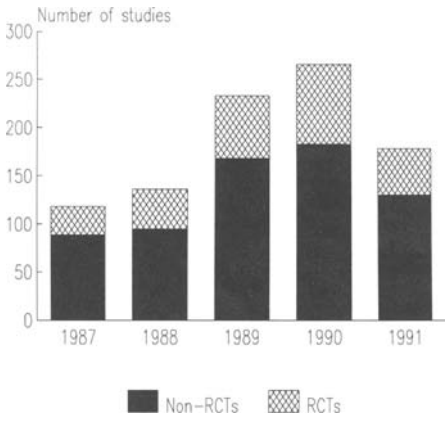

Figure *The number of randomised controlled trials and other studies identified between 1987 and 1991 using criterion 14 from the search strategy*

A total of 931 articles were identified between 1987 and 1991 using the predetermined search terms on Medline. Of these, 28.6 per cent (n=266) met the criteria for inclusion in the register. The number of trials published increased progressively from 1987 to 1990 (*figure*). The apparent slight decline in 1991 probably reflects the fact that the indexing of journals for that year was not yet complete. The trials were published in 110 different journals (*table 2*). Only 23 per cent (n=62) of the RCTs were published in primary care journals; the remainder were found in a wide cross-section of general and specialist medical journals.

Responses were received from the editors of 9 of the 10 primary care journals included on Medline which had published at least one clinical trial and 10 of the remaining 22 editors who were responsible for primary care journals not included in Medline. Although supportive of the concept of establishing a register, none of the journals approached currently has a

Table 3 *Comparison of manual vs electronic searching to identify randomised controlled trials (rcts) in primary care. Rounded percentages*

Journal	Search Period	No RCTs identified	RCTs retrieved (rounded percentages)			Additional no RCTs identified by CONTROL†
			Medline*	manually	difference	
British Journal of General Practice‡	1968-1991	77	60 (127)	97	37	5 (52)
Family Medicine	1984-1991	13	62 (46)	100	38	4 (31)
Family Practice	1984-1991	8	88 (50)	100	12	– (28)
Family Practice Research Journal	1986-1991	5	80 (20)	100	20	2 (10)
Journal of the American Board of Family Practice	1988-1991	10	80 (40)	100	20	1 (19)
Journal of Family Practice	1974-1991	67	67 (192)	100	33	8 (165)
Scandinavian Journal of Primary Health Care	1983-1991	24	71 (81)	100	29	0 (40)

* Using criterion 14 from the search term strategy.
† Additional number of RCTs identified by using 'CONTROL' as a Text Word.
‡ Formerly Journal of the Royal College of General Practitioners
Figures in brackets are the total number of citations identified with each Medline Search.

method of systematically identifying all controlled clinical trials it had published, or those which would meet our entry criteria. Two editors had all back issues of their journal manually reviewed to identify the RCTs and one editor provided a Medline print-out from SilverPlatter using the search term 'clinical-trials' to identify studies possibly suitable for inclusion from that particular journal.

The manual search of the seven leading primary care research journals produced 204 RCTs (*table 3*). For four journals (The British Journal of General Practice, Family Medicine, Journal of Family Practice and the Scandinavian Journal of Primary Health Care) the number of RCTs identified in this way was significantly greater than the number detected from the Medline search. In the remaining three journals where the number of RCTs involved were smaller, the discrepancy between the two search methods was not statistically significant. Adding the MeSH term 'control' to the Medline search strategy increased the number of articles identified in The British Journal of General Practice from 127 to 179, but only yielded an additional 5 RCTs. The marginal extra yield was similar in all the other journals except Family Practice and Scandinavian Journal of Primary Care, where none of the additional articles identified were RCTs.

Discussion

Applying a systematic method of assessing review articles to reviews appearing in the peer-reviewed primary care literature, has demonstrated that there is considerable room for improvement. One of the most important and difficult parts of a review article involves actually synthesising the information derived from the primary studies into a coherent message. Usually this is best achieved by a combination of both qualitative and quantitative techniques. Whilst many of the reviews in this series used qualitative techniques, few used quantitative techniques. This may be partly due to the fact that many of the quantitative techniques (such as meta-analysis) are relatively new to medical research, and particularly in a discipline such as primary care.[11] However, they offer the advantage of allowing data to be combined from several smaller studies in order to evaluate the possibility of small effects which may not have been previously recognised.[12] Furthermore, they allow the generalizability and consistency of data to be tested.

An important prerequisite for quantitative synthesis of data is to ensure that all possible primary research (both published and unpublished) has been identified. The second part of this study highlighted the difficulties facing a reviewer trying to identify all the RCTs published each year in primary care. To begin with, the number of RCTs undertaken in the discipline is growing. These trials cover a wide range of clinical topics and are published in an equally diverse range of journals.

Unfortunately, we have demonstrated that there is no ready infrastructure which allows all the RCTs in primary care to be identified with confidence. None of the primary care journals maintain systematic records of such studies. Even though many of the journals are included in Medline, one cannot rely on this electronic data base to identify all published RCTs. In this study, approximately 70 per cent of the articles identified by a comprehensive search strategy were not RCTs. When the search was widened further to include additional MeSH terms the increased yield of RCTs was small in comparison with the number of additional articles that were generated. When the key words attached to the RCTs which had been missed by the Medline search were reviewed, it became clear that with further refinement in the choice of search terms it may have been possible to identify almost 90 per cent of RCTs in these journals.[13] Ideally, if authors use appropriate terminology in the 'methods' section of an article, this should facilitate correct coding of the study as an RCT

at the time of inclusion in an electronic data base, such as Medline. This should help improve the number of RCTs which can be reliably identified. In addition, many of the primary care journals are also indexed on EMBASE. Although we did not have the resources to carry out a combined search on multiple electronic data bases, such an approach may also increase the yield of RCTs.

Unfortunately, many primary care journals which publish RCTs are not included in electronic data bases. For example, a manual search of the Canadian Family Physician, which falls into this category, identified 21 RCTs published between 1980 and 1991 (Dunikowski L, Personal Communication). This was one of the main reasons that WONCA (World Organization of National Colleges and Academies of General Practice) supported the development of the FAMLI index of primary care literature.[10] However, FAMLI only covers journal issues published from 1980 onwards and is not sufficiently comprehensive in its coding to be a reliable source of RCTs. For example, between 1987 and 1991 it did not identify any RCTs in the Canadian Family Physician whereas 5 were actually published.

The value of hand searching key journals within a discipline as an integral process in establishing a register of RCTs has been documented previously.[13] Although there is no method of ensuring that all RCTs are identified even with this method, it is clear that many trials which are missed using a Medline search can be identified by hand searching of individual journal issues. In this study the number of extra RCTs identified by hand searching was similar to those reported in other disciplines.[6,14] Although this approach is extremely time-consuming and labour-intensive, it is the only way to identify RCTs from specialist primary care journals which are not included in Medline or other accessible electronic data bases.

Irrespective of the method used to establish a register of RCTs related to primary care several potential limitations must be kept in mind. Firstly, its usefulness will depend on the extent to which it is used to undertake overviews and the degree to which results from these are effectively communicated to their target audience in order to influence clinical practice and health care policy. Determining effective and reliable ways of achieving this remains a challenge. Secondly, there are not RCTs covering every clinical issue. In some instances, it may not be feasible or ethical to conduct an RCT and alternative research designs must be used. Hence, the development of guidelines for effective clinical practice will always need to draw on composite sources of data, of which RCTs are important but not the only one. Thirdly, the tendency to use highly selected study populations in many of the RCTs which have examined the efficacy of new interventions has often made it difficult to extrapolate these results to primary care, where the patients and setting are much more varied. However, with the move towards more pragmatic RCTs which examine the effectiveness of an intervention in the 'real world' this limitation is being redressed.

The recent establishment of the Cochrane Collaboration may help to overcome some of the difficulties raised in this study.[15] For example, the Collaboration, which is international and interdisciplinary in scope, is establishing a central data base of RCTs covering all branches of health care. By primary care collaborating in this process it will avoid the limitations imposed by arbitrary definitions of discipline boundaries, and help overcome some of the resource demands associated with independently establishing a discipline-based register. The Cochrane Collaboration aims to use the register of RCTs as a basis for facilitating preparation and maintenance of up-to-date systematic reviews in all areas of health care. The reviews will then be disseminated to practitioners, allied health workers, and health policy planners in as many countries around the world as possible in a variety of different ways (including electronically, in paper form, through practice guidelines, and in regular bulletins). The task being undertaken by the Cochrane Collaboration is ambitious and, to be successful, must be global in scope. Family physicians, health care workers, research agencies and Governments in all countries should have the opportunity both to participate in, and take advantage of, the results of its work.

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References

1 Sackett DL, Haynes RB, Tugwell P. Clinical epidemiology: a basic science for clinical medicine. Boston, USA: Little, Brown and Company, 1985.

2 Chalmers I. Improving the quality and dissemination of reviews of clinical research. In: Lock S, ed. The future of medical journals. Br Med J 1991; 304: 127-46.

3 Antman EN, Lau J, Kupelnick B, et al. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. JAMA 1992; 268 (2): 240-8.

4 Cochrane AL. Effectiveness and efficiency. Random reflections on health services. London: Nuffield Provincial Hospitals Trust, 1972.

5 Chalmers I, Dickersin K, Chalmers TC. Getting to grips with Archie Cochrane's agenda. Br Med J 1992; 305: 786-8.

6 Chalmers I, Hetherington J, Nedwick M, et al. The Oxford database of perinatal trials. Developing a register of published reports of controlled trials. Controlled Clin Trials 1986; 7: 306-24.

7 Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford, England: Oxford University Press, 1985.

8 Mulrow CD. The medical review article: state of the science. Ann Intern Med, 1987; 106: 485-8.

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1982; i: 494-6.
21 Ruth VJ, Raivio KO. Perinatal brain damage: predictive value of metabolic acidosis and the Apgar score. Br Med J 1988; 297: 24-7.
22 Silverman F, Suidan J, Wasserman J, et al. The Apgar score: is it enough? Obstet Gynecol 1985; 66: 331-6.
23 American academy of pediatrics, committee on fetus and newborn. Use and abuse of the Apgar score. Pediatrics 1986; 78: 1148-9.
24 Catlin EA, Carpenter MW, Brann BS, et al. The Apgar score revisited: influence of gestational age. J Pediatr 1986; 109: 865-8.
25 Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. Pediatrics 1981; 68: 36-44.
26 Levene ML, Sands C, Grindulis H, Moore JR. Comparison of two methods of predicting outcome in perinatal asphyxia. Lancet 1986; I: 67-8.
27 Low JA, Galbraith RS, Muir DW, et al. The relationship between perinatal hypoxia and newborn encephalopathy. Am J Obstet Gynecol 1985; 152: 256-60.
28 Winkler CL, Hauth JC, Tucker M, et al. Neonatal complications at term as related to the degree of umbilical artery acidemia. Am J Obstet Gynecol 1991; 164: 637-41.
29 Dijxhoorn MJ, Visser GHA, Huisjes HJ, et al. The relationship between umbilical pH values and neonatal neurological morbidity in full term appropriate-for-dates infants. Early Hum Dev 1985; 12: 33-42.
30 Nelson KB, Leviton AL. How much of neonatal encephalopathy is due to birth asphyxia? AJDC 1991; 145: 1325-31.
31 Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. Arch Neurol 1976; 33: 696-705.
32 Fenichel GM. Hypoxic-ischemic encephalopathy in the newborn. Arch Neurol 1983; 40: 261-6.
33 Robertson C, Finer N. Term infants with hypoxic-ischemic encephalopathy: outcome at 3.5 years. Dev Med Child Neurol 1985; 27: 473-84.
34 Amiel-Tison C, Ellison P. Birth asphyxia in the fullterm newborn: early assessment and outcome. Dev Med Child Neurol 1986; 28: 671-82.
35 Veenhoven RH, Groenendaal F, Eken P, De Vries LS. Onderzoekmethoden ter bepaling van neurologische prognose en therapeutische interventie bij voldragen pasgeborenen met asfyxie. Ned Tijdschr Geneeskd 1993; 137: 10-4.
36 Meijer van Putten JB. Verloskunde bijna onmogelijk door schadevergoedingen. Ned Tijdschr Geneeskd 1993; 137: 1899.

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Continued

9 The Serials Directory. An International Reference Book, 4th Edition (Volume 2). Birmingham, USA: Ebsco Publishing, 1990.
10 FAMLI. Family medicine literature index. World Organisation of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians. London, Ontario: 1980-91.
11 Silagy CA. Developing a register of randomised controlled trials in primary care. Br Med J 1993; 306: 897-900.
12 Peto R. Why do we need systematic overviews of randomised trials? Stat Med 1987; 6: 233-40.
13 Jadad AR, McQuay HJ. Searching the literature. Br Med J 1993; 306: 66.
14 Dickersin K, Hewitt P, Mutch L, et al. Perusing the Literature. Comparison of MEDLINE searching with a perinatal trials database. Controlled Clin Trials 1985; 6: 306-17.
15 Anonymous. Cochrane's legacy (Editorial). Lancet 1992; 340: 1131-2. ■