Developing a register of randomised controlled trials in primary care

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Abstract

***Objective*—To determine the number, nature, site of publication, and feasibility of identifying randomised controlled trials relevant to primary care.**

***Design*—Review of literature using three strategies: approaching journal editors, Medline search, and manual search of individual journals.**

***Setting*—Journals containing publications of studies based in primary care.**

***Main outcome measures*—The number, site of publication, and subject of trials identified.**

***Results*—No journal had a system which enabled identification of all the randomised controlled trials it published. 266 trials relevant to primary care were identified from 110 different journals during 1987-91 by Medline. Of these, only 62 trials were published in primary care journals. Hand searching of seven major primary care research journals showed that between 13% and 38% of the trials had been missed by the Medline search. Of the trials identified, 47 (18%) were concerned with mental disease (including neuroses, tobacco misuse and alcohol misuse) and 43 (16%) were concerned with hypertension.**

***Conclusion*—Given the diversity of publication sources and topics, this supports the need for a centrally based register of randomised controlled trials that may be relevant to primary care overviews in the future.**

Introduction

The randomised controlled trial is widely accepted as the best study design for most types of clinical research. By reducing much of the bias often associated with other design methods such trials can provide more reliable information about the efficacy of an intervention.[1]

Although it is neither possible nor appropriate to use randomised controlled trials to investigate every research question, an increasing number are being published. More trials are being conducted in, or are directly relevant to, primary medical care, but many are published in journals that are not readily accessible to most general practitioners. Consequently, important information from these studies may not reach its target audience.

One strategy to help in overcoming this problem is to include the results of trials in comprehensive and well compiled overviews of clinical topics in published general practice journals. However, there is a danger in accepting the content of review articles at face value. It is important that a systematic approach is used in compiling the review and that all the data have been covered. This was highlighted by recent research into treatments for myocardial infarction.[2] Many of the review articles and text books did not take into account data from all the relevant published randomised controlled trials. Consequently, some of the recommendations overlooked important advances in treatment or effective new preventive measures. Furthermore, some treatments continued to be recommended despite having either no proved effect on mortality or being potentially harmful.[2]

Identifying and synthesising information from all the randomised controlled trials associated with a particular topic is extremely time consuming and labour intensive. Cochrane and others have therefore called for a systematic listing of all randomised controlled trials in all branches of medicine.[3,4] The listing would form a basis for comprehensive overviews of a range of health care topics which could be updated as required. These overviews could be used to help determine future provision of health care.[5] In the United Kingdom a new centre (the Cochrane Centre) has recently been created to facilitate such a process.[4]

Systematic lists of randomised controlled trials exist in only a few branches of medicine.[6] For example, in obstetrics and perinatal medicine there is now a register of published and unpublished trials.[7] The electronic form of this register enables regular updating.[8]

Establishing a systematic list of trials relevant to primary care is difficult since it overlaps with many other disciplines. As a result, trials are likely to be published in a wide range of journals. One possible solution to this problem is to create a register of trials. I did a feasibility study to determine the number, nature, site of publication, and strategies for identifying randomised controlled trials conducted in, or directly relevant to, primary care.

Methods

The main criterion used to determine eligibility for inclusion in the register of randomised controlled trials was that the trial had been carried out in a primary care setting, had been published in a primary care journal, or had results that were directly relevant to the organisation and practice of primary care. In addition all trials had to have included at least two groups and allocation to the groups must have been either by formal randomisation or by a quasirandom method (for example, alternation).

Three strategies were used to identify studies suitable for inclusion in the register.

Search of electronic databases—For this feasibility study I limited the electronic search to Medline between 1987 and 1991 using SilverPlatter on CD-ROM. The box shows terms used in the search. To be included in the register, a trial needed to fulfil criterion 14. I read the abstract of each article identified by the search 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.

Approach to editors—I compiled a list of editors of the specialist primary care journals worldwide using the *Serials Directory*[9] and checked against the list indexed in the *Family Medicine Literature Index* (Famli), which includes journals not on Medline.[10] A standard letter was sent to the editors outlining the project and asking

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Terms used in Medline search to identify randomised controlled trials relevant to primary care

No	
1	Random allocation (medical subject heading—MeSH)
2	Random (text word)
3	Clinical and trial (text word)
4	Prospective or prospectively (text word)
5	Double and blind (text word)
6	Double-blind method (medical subject heading)
7	1 or 2 or 3 or 4 or 5 or 6
8	7 and human
9	General practice (text word)
10	Primary health care (text word)
11	Family medicine (text word)
12	Community medicine (text word)
13	9 or 10 or 11 or 12
14	8 and 13

Criterion 14 had to be satisfied for a trial to enter the register.

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 two weeks were followed up by telephone. Those who could not be contacted by telephone received a reminder letter.

Manual searching—I scrutinised all back issues of seven major primary care research journals to identify randomised controlled trials that met the inclusion criteria. The journals reviewed were *British Journal of General Practice* (formerly *Journal of the Royal College of General Practitioners*), *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*.

To compare the number of randomised controlled trials obtained from the electronic search with the number identified by hand searching, I extended the electronic search back to the year in which each of the journals was first included in Medline. I also examined the effect of increasing the number of trials identified with the Medline search by adding the medical subject heading (MeSH) terms "control" and "clinical-trial" to the original search strategy.

The subject examined in each trial was coded by using the international classification of health care problems in primary care (ICHCPPC).[11] A few supplementary categories were added to cover trials of medical education and health service research.

All trials identified were entered on to a database run with software being developed by the Cochrane Centre. The number of randomised controlled trials identified was expressed as a proportion of the total number of articles retrieved through Medline. Confidence intervals were calculated where appropriate by using the Confidence Interval Analysis (CIA) program.[12]

Results

A total of 931 articles were identified between 1987 and 1991 with the predetermined search terms (box) on Medline. Of these, 266 (28·6%) met the criteria for inclusion in the register (table I). The number of trials published increased progressively from 1987 to 1990. The apparent slight fall in 1991 probably reflects indexing of journals for that year was not yet complete. The trials were published in 110 journals (table II), and only 62 (23%) appeared in primary care journals.

Responses were received from the editors of nine of the 10 primary care journals included on Medline which had published at least one clinical trial, and 10 of the 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 had a method of systematically identifying all controlled clinical trials it had published or those that would meet the study's entry criteria. Two editors had all back issues of their journal manually reviewed to identify the randomised controlled trials and one editor provided a Medline print out from SilverPlatter using the search term "clinical-trials" to identify studies possibly suitable for inclusion.

The manual search of the seven leading primary care research journals produced 204 randomised controlled trials (table III). For four journals (*British Journal of General Practice*, *Family Medicine*, *Journal of Family Practice*, and *Scandinavian Journal of Primary Health Care*) the number of trials identified was greater than the number detected from the Medline search. In the remaining three journals where the number of trials was smaller, the discrepancy between the two search methods was not 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 gave an extra five randomised controlled trials. In the *Journal of Family Practice* the same approach increased the number of articles from 192 to 377 but gave only an extra eight trials. In *Family Medicine*, *Family Practice Research Journal*, and *Journal of the American Board of Family Practice* an extra 31, 10, and 19 articles were identified of which only four, two, and one respectively were randomised controlled trials. In the remaining

TABLE I—*Randomised controlled trials related to primary care retrieved from Medline*

Year	No of studies retrieved*	No (%) of randomised control trials	95% confidence interval (%)
1987	118	29 (25)	17 to 32
1988	136	41 (30)	22 to 38
1989	233	65 (28)	22 to 34
1990	266	83 (31)	26 to 37
1991	178	48 (27)	20 to 34
Total	931	266 (28·6)	25·7 to 31·5

*Studies retrieved using search terms given in box.

TABLE II—*Place of publication of randomised controlled trials related to primary care*

	No (%) published (n=266)
Primary care journals	62 (23)
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)
Others (3)	4 (2)
Public health journals	15 (6)
Am J Prev Med	4 (2)
Others (9)	11 (4)
General medical journals	92 (35)
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)
Others (15)	18 (7)
Specialist medical journals	97 (36)
Chemotherapy	4 (2)
Infection	3 (1)
Int Clin Psychopharmacol	3 (1)
J Antimicrob Chemother	4 (2)
J Cardiovasc Pharmacol	4 (2)
J Hum Hypertens	4 (2)
J Infect Dis	3 (1)
Psychopharmacology (Berl)	4 (2)
Others (57)	68 (26)

TABLE III—*Comparison of manual and electronic searching in identifying randomised controlled trials in primary care*

Journal	Search period	Total No identified	No (%) identified by Medline*	No (%) identified manually	Difference in No (%) retrieved (manual–Medline)
Br J Gen Pract (formerly *J R Coll Gen Pract*)	1968-91	77	46 (60)	75 (97)	29 (37)
Fam Med	1984-91	13	8 (62)	13 (100)	5 (38)
Fam Pract	1984-91	8	7 (88)	8 (100)	1 (12)
Fam Pract Res J	1986-91	5	4 (80)	5 (100)	1 (20)
J Am Board Fam Pract	1988-91	10	8 (80)	10 (100)	2 (20)
J Fam Pract	1974-91	67	45 (67)	67 (100)	22 (33)
Scand J Primary Health Care	1983-91	24	17 (71)	20 (100)	3 (29)

*Using criterion 14 from the search term strategy shown in box.

two journals none of the additional articles identified were randomised controlled trials. Adding the MeSH explosion term "clinical-trials" to the original search strategy identified only one additional trial from the *Scandinavian Journal of Primary Health Care* and none from the other six journals.

Blood pressure problems, in particular hypertension, were the most common subject of study and accounted for 43 (16%) of the trials. Interventions for neuroses and stopping smoking constituted 27 (10%) and 17 (6%) respectively, while urinary tract infection and respiratory tract infection each accounted for a further 15 (6%). A sizeable proportion of the trials did not include pharmacological interventions. For example, 11 (4%) were controlled evaluations of different aspects of health service provision and 17 (6%) assessed different preventive care strategies. Even among the trials on hypertension and neuroses seven (16%) and five (19%) respectively included non-pharmacological interventions.

Discussion

This feasibility study has shown that increasing numbers of randomised controlled trials are undertaken in primary care each year. These trials cover a wide range of clinical topics and are published in an equally diverse range of journals. This makes it difficult for busy practitioners to access the information contained in these studies, even though many have important implications for managing patients. No infrastructure exists that allows all the randomised controlled trials in primary care to be identified. None of the primary care journals maintain systematic records and even though many of the journals are included in Medline, electronic searching did not identify all published trials.

Use of appropriate terminology in the methods section of an article should facilitate correct coding of the study as a randomised controlled trial when it is entered into an electronic database such as Medline. This should help improve the number of trials that can be reliably identified. In my study about 70% of the articles identified by a comprehensive search strategy were not randomised controlled trials. When the search was widened to include additional MeSH terms the increased yield of randomised controlled trials was small compared with the number of additional articles that were generated. Restricting the search to only randomised controlled trials that included the terms "general practice," "primary care," "family medicine," or "community medicine" as text words, may have missed some trials eligible for inclusion. However, excluding these terms from the search resulted in 11 311 publications being identified for 1991 alone.

MANUAL SEARCHING

Unfortunately, many primary care journals that publish randomised controlled trials are not included in electronic databases. For example, a manual search of the *Canadian Family Physician*, which falls into this category, identified 21 trials published between 1980 and 1991 (L Dunikowski, personal communication). This was one of the main reasons that the World Organisation 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 its coding is not sufficiently comprehensive to be a reliable source of randomised controlled trials. For example, it did not identify any randomised controlled trials in the *Canadian Family Physician* during 1987-91, although five were published.

Although there is no method of ensuring that all randomised controlled trials are identified, many trials that are missed by a Medline search can be identified by hand searching. In my study the proportion of trials identified only by hand searching was as high as 37% (in the case of *British Journal of General Practice*). These figures are similar to those reported in other disciplines.[6,13]

PROBLEMS WITH PRIMARY CARE REGISTER

One concern about the comprehensiveness of any register of randomised controlled trials is how to ensure that unpublished (but completed) trials are also included. There are many reasons why trials may remain unpublished apart from poor methodology, and failure to include them in an overview may significantly affect the outcome.[14] Although I did not examine the extent of non-publication of randomised controlled trials in primary care research, studies in other disciplines have found appreciable numbers.[15] One solution would be to extend the register to include trials from the time of starting rather than waiting until they reach publication.[15] Registers of randomised controlled trials, including those in progress, already exist for certain types of cancer[16] and antiplatelet therapy.[17] The Department of Health is encouraging regional health authorities to initiate registers covering all types of research undertaken in a field from the time of starting through to completion and publication.

A further concern is defining what constitutes a primary care trial. Many of the clinical areas for which overviews are urgently required (such as the management of common respiratory illness, otitis media, low back pain, stopping smoking, and approaches to promoting disease prevention) could include trials in settings other than primary care. Furthermore, the concept of what constitutes primary care and where it is delivered differs considerably among countries. Hence, it may be appropriate to include trials from general practice in Britain alongside those conducted in a community hospital in another country if the type of patient and severity of disease are similar.

MULTIDISCIPLINARY REGISTER

The recent initiative of the NHS research and development programme in establishing the Cochrane Centre may help to overcome some of the difficulties raised in this study. The centre aims to establish a central database of randomised controlled trials covering all branches of health care rather than separate databases for individual disciplines. Including primary care as one of the modules within the Cochrane Centre

database, managed by a core group of general practitioners, will allow the inclusion criteria and search strategies to be modified as required. Electronic searching of databases could use comprehensive strategies to identify any randomised controlled trial, without having to try to limit the search to those relevant to a specific discipline. Manual searching of journals could be shared across different disciplines, thereby reducing the need for researchers to maintain coverage of journals outside their own discipline that might contain relevant studies. Such an infrastructure would make regular updating of the register easier.

A collaborative approach with researchers from specialist, hospital based disciplines would also allow overviews of clinical topics to be addressed from the perspectives of both primary and secondary care. In some cases it might be possible to highlight the differences in intervention outcomes from different settings. It should also make it easier to establish that review articles and meta-analyses cover all the relevant data.

LIMITATIONS

Irrespective of the method used to establish a register of randomised controlled trials 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. Determining effective and reliable ways of achieving this remains a challenge. Secondly, for some clinical issues it may not be feasible or ethical to conduct a randomised controlled trial and alternative research designs must be used. Guidelines for effective clinical practice will always need to draw on composite sources of data, not just randomised controlled trials. Thirdly, the tendency to use highly selected study populations in many of the randomised controlled trials that examine the efficacy of new interventions has made it difficult to extrapolate these results to primary care, where the patients and setting are more varied. The move towards more pragmatic randomised controlled trials that examine the effectiveness of an intervention in the "real world" should help to overcome this problem.

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RESEARCH THAT CHANGED MY PRACTICE

Always look a gift horse in the mouth

In my day doctors were cautious in their investigation of patients and careful about the application of the results. Well trained in wet chemistry from our early teens, we had no illusions about its constraints. As budding clinicians, we soon learnt that there were differences between the normal range in the textbook and that for our laboratory. Emergency after hours estimations would involve exercise of the higher criticism: the results of estimations carried out after midnight by charming colleagues might require to be discounted in the light of clinical acumen. That was wet chemistry.

Two other developments came slowly to the laboratory. Electrochemical methods transferred from science to medicine, and automation of wet chemistry and optoelectronic techniques occurred to reduce human involvement. We were too unfamiliar with the electronics to evaluate the new machines and accepted the technology at print out value.

I transformed from physician to anatomy research assistant in an academic department engaged in the correlation of finger tip sweating with circulating catecholamine. I was generously offered a little bench space, a method, reagents, and apparatus in the department of pharmacology. Now the best item was the measuring apparatus, at the heart of which were electronics capable of measuring the amount of light emitted after excitation by ultraviolet radiation. Machinery that inspired confidence. It was carefully calibrated with various concentrations of standard catecholamine and estimation was simplicity itself.

Considerate use of another department's facilities required you to fit in. On being told that the apparatus was free, you set to and got through the work promptly. I completed several runs of analyses, and to my delight the expected results emerged. Successive measurements of concentrations of catecholamine showed, as predicted from the hypothesis, a smooth dose response curve developing. But here began the lesson. Lulled into the state of absentmindedness induced by this easy method, I inserted the specimens to be estimated and jotted down the dial's readings, noting that they followed the anticipated increase.

Unfortunately for the hypothesis, but fortunately for my long term education, I subsequently discovered that I had inserted the specimens on this occasion in the reverse order. Thus was I taught an important lesson in the use of electronic gadgetry: that machinery can take a long time to warm up and is fallible.

At the cost of what would have been my first (shared) publication, this lesson stood me in good stead during my subsequent career. As an epidemiologist, although introduced to increasingly sophisticated and powerful generations of computers, I was never again a pushover for electronics. Reverting to the healthy scepticism about all data and methods of measurement and analysis of my early clinical days, I was saved many an embarrassment—and, more importantly, obviated the clinical mayhem that would have resulted from the belief that the less human involvement the less the chance of error.—GILLIAN GREENBERG *is a retired consultant clinical epidemiologist in London*