Hong Kong clinical trials published in *Medline* between 1987 and 1996

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The aims of this study were to determine the number of randomised clinical trials where the correspondence address included the words 'Hong Kong' for the years of publication between January 1987 and December 1996, and to study their characteristics: year of publication; disease area; sample size; and correspondence address of the department and institute. MEDLINE EXPRESS was used for the search. A total of 5605 publications were identified, of which only 170 (3.0%) were found to be randomised clinical trials. No significant increase in the proportion of randomised clinical trials could be seen during the decade of publication (P>0.05). Approximately 50% of the trials had a small sample size (fewer than 75 subjects) and most randomised clinical trials were performed in the field of internal medicine, followed by surgery, and obstetrics and gynaecology (total, 69%). The predominant research area was gastrointestinal disease (34%). Despite a relatively high academic output from Hong Kong, the number of randomised clinical trials has not increased much during the decade.

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Introduction

Clinical trials

A clinical trial is defined as a prospective comparative study of human beings involving a therapeutic or diagnostic intervention with a drug, device, or health care product.[1] The clinical trial has a long history, with the earliest recorded account of a comparative study being found in the Old Testament of the Bible, in the first chapter of the Book of Daniel.[2] However, the comparative statistical concept did not emerge until the 14th century and the elements of comparative statistics were first included in a trial in 1662.[3] A classic example of comparative statistics in evaluating a therapeutic intervention was Lind's scurvy trial in 1747.[4]

The concept of using a control group in clinical trials was introduced almost 100 years later, in 1865,[5] when it was realised that the influence of a remedy on the course of a disease could not be judged without comparison with the natural course used as a control. Publications from 1900 to 1930 showed a refinement in experimental design by using a control group.[5] The first clinical trial with a properly randomised control group involved streptomycin in the treatment of pulmonary tuberculosis and was performed by Amberson et al in 1948.[6] This trial included the three main characteristics of clinical trials: concurrent controls; randomisation; and blinding.

In the past, there were very few randomised controlled trials (RCTs), totalling no more than 5% of published clinical studies.[7] Nowadays, RCTs are considered to be among the most legitimate measures for assessing a new drug intended for clinical practice. They also provide solid evidence on which to base patient management and clinical decision making. Besides medical therapies, clinical trials have also been used for the evaluation of surgical therapies and diagnostic tests.[8] Today, the majority of physicians consider RCTs to be the most reliable source of therapeutic information and rank RCTs as an optimum source of evidence.[7,9]

Evidence-based medicine

Evidence-based medicine (EBM) moves the basis for clinical decision making from intuition and un-

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systematic clinical experience to the examination of evidence from clinical research.[10] Consequently, decision making in clinical practice has to be based on research-generated scientific evidence. However, the strength of the evidence depends on the way in which it is obtained. Randomised controlled trials are ranked as the optimum source of evidence by the United States Preventive Services Task Force.[11]

An empirical investigation of methodological quality associated with estimates of treatment effects found that the odds ratios were exaggerated by up to 41% in favour of the new treatment if treatment allocation was inadequately concealed by doctors, and by 17% for trials that were not double-blinded.[12] Other studies show that different study methodologies or designs increase the likelihood of a positive response to therapy. When comparing RCTs in medical therapy, the Mann-Whitney *U* statistic was found to increase by 15% if trials were non-random cross-over and 11% if they were not double-blinded.[13] In surgical therapy, the Mann-Whitney *U* statistic was found to increase by 6% if trials were non-randomised or externally controlled, and to rise to as much as 50% if they were observational studies only.[14] In other general therapies, studies using historical controls claimed a 59% better response than those using randomised controls.[15] A properly designed RCT is therefore the most valid study, and when performed properly, it provides the strongest evidence on which to base a clinical decision. The medical practice based on this decision is consequently a more beneficial and effective one.

Meta-analysis is important in the area of EBM. Meta-analysis involves a critical review and the statistical pooling of data from a number of RCTs to draw conclusions—for example, the treatment of gastrointestinal ulcers, the effect of dietary calcium supplementation on blood pressure, and cholesterol-lowering interventions in the secondary prevention of coronary heart disease.[16] To estimate the annual number of meta-analysis–related publications present in *Medline*, the phrase 'meta-analysis' was used to search in the title field.[16] The number of publications involving 'meta-analysis' increased over the study period from about 30 to 200 (a 5.7-fold increase). Meta-analysis has thus become increasingly important over the past decade as a way of pooling the results of various studies. Meta-analysis is an important part of EBM and the analysis is almost exclusively concerned with data from RCTs.

Ethnic differences

In the past decade, many studies have reported ethnic group variations in pharmaceutical response (Table 1)[17-27] and, as a consequence, there is limited mutual acceptance of data from clinical trials carried out in different ethnic populations.[28,29] For example, there are differences in the approved dosage for antihypertensives, anti-arrhythmics, antibiotics, antibacterials, antivirals, antihistamines, and psychotropics used in Japan and in western countries.[30] Instead of accepting data from different ethnic groups, conducting good clinical trials in Asia would provide better, more accurate information on the most appropriate dosing regimens and information on possible side effects, if only local patients were included. Ultimately, conducting more high-quality clinical trials will accelerate the availability of important, better, and safer medical care and health products to patients who are in need of therapy. Asia also provides opportunities for the development of new treatments for diseases such as

Table 1. Some examples of studies of ethnic group differences in pharmaceutical response

Year	Authors	Study findings
1996	Hsu et al[17]	Ethnic differences in immune responses to hepatitis B vaccine
1995	Chan et al[18]	Renal failure is uncommon in Chinese patients with paracetamol poisoning
1993	Zhou et al[19]	Ethnic differences in sensitivity due to differences in plasma binding of propranolol
1993	Zhou et al[20]	Ethnic differences in response to morphine
1992	Katoh et al[21]	Ethnic differences in the primary gene defect at the cytochrome P-450 2D6
1992	Levine et al[22]	Geographic/ethnic differences in human herpes virus-6 antibody patterns
1992	Houghton et al[23]	Pethidine pharmacokinetics after intramuscular dosing
1990	Critchley et al[24]	Ethnic differences in the renal dopamine response to an oral salt load
1987	Kumana et al[25]	Differences in diazepam pharmacokinetics in Chinese and Caucasian populations
1984	Abo et al[26]	Ethnic differences in the lymphocyte proliferative response induced by a murine immunoglobulin G1 antibody, Leu-4, to the T3 molecule
1984	Rudorfer et al[27]	Desipramine pharmacokinetics in Chinese and Caucasian volunteers

hepatitis and nasopharyngeal carcinoma, which are far more common among the local population than they are in other populations.[31,32]

Study objectives

Hong Kong is a major medical centre in Asia with a high academic output. However, much of this research is performed in the area of basic sciences or arises from observational clinical studies without randomisation and/or concurrent controls. The number of good clinical studies, such as RCTs, is not known. The aim of this study was to determine the number and characteristics of RCTs with a correspondence address in Hong Kong that were published in *Medline* between January 1987 and December 1996.

Materials and methods

By means of the MEDLINE EXPRESS computer search technique, RCTs with a Hong Kong correspondence address that were published between 1987 and 1996 were retrieved on 4 April 1997. A computer program, WinSPIRS version 2,[33] was used to process all the retrieved articles downloaded from the *Medline* database. An initial search used the text string 'Hong Kong' in the address field for the publication years 1987 to 1996. A second search within this subset of publications looked for the word 'random' or its synonyms such as 'randomly', 'randomised', 'randomized', 'randomisation', and 'randomization' in the title or abstract. After reading the resulting abstracts, all studies that were not RCTs were identified and excluded. The remaining studies compared two or more medical therapies, surgical operations, interventions, or clinical management. Characteristics, including the year of publication, area of disease, sample size, and correspondence address, were scrutinised and the data were analysed using SAS for Windows Release 6.08.[34]

One possible bias in the searching process was that the correspondence address field might have been missing in *Medline*. For this reason, another computer search was done to estimate the number of publications between January 1987 and December 1996 with the address field completed in the *Medline* database. The address fields of 100 articles randomly selected from each year were examined. The number of articles with complete address fields were then counted.

One major local journal, the *Hong Kong Medical Journal* (which is not yet included in *Medline*) was also studied for the period from January 1995 to June 1997 to identify locally published RCTs.

Results

Table 2 shows the total number of publications with 'Hong Kong' in the correspondence address field in *Medline* for the years 1987 to 1996. A total of 5605 such publications were identified, of which 170 (3.0%; range, 2.5%-3.8%) were found to be RCTs according to the criteria established for this study. The proportion of randomised trials did not differ significantly over the 10 years of the study (P=0.825, Chi squared test for trend [Table 2]), despite an increasing number of publications from Hong Kong—from 185 to approximately 700 over the decade. But this increase in the total number of publications must be related to the increased number of any kind of publication in *Medline* that had a complete address field. From 1987 to 1989, only 42.0% of 300 randomly selected publications in *Medline* gave full information in the address field, compared with 95.5% of 200 randomly selected publications for the period 1995 to 1996.

Table 2. The total number of publications with 'Hong Kong' in the correspondence address field in *Medline* for the period January 1987 to December 1996

Year of publication	Total No. of articles	No. of clinical trials* (%)†
1996	672	21 (3.1)
1995	736	24 (3.3)
1994	687	17 (2.5)
1993	609	23 (3.8)
1992	598	17 (2.8)
1991	570	14 (2.5)
1990	620	21 (3.4)
1989	540	17 (3.1)
1988	388	11 (2.8)
1987	185	5 (2.7)
Total	5605	170 (3.0)

* Clinical trials were defined as trials that are prospective, randomised, controlled studies comparing two or more medical therapies, surgical operations, interventions, or clinical managements
† P=0.825, Chi squared test for trend

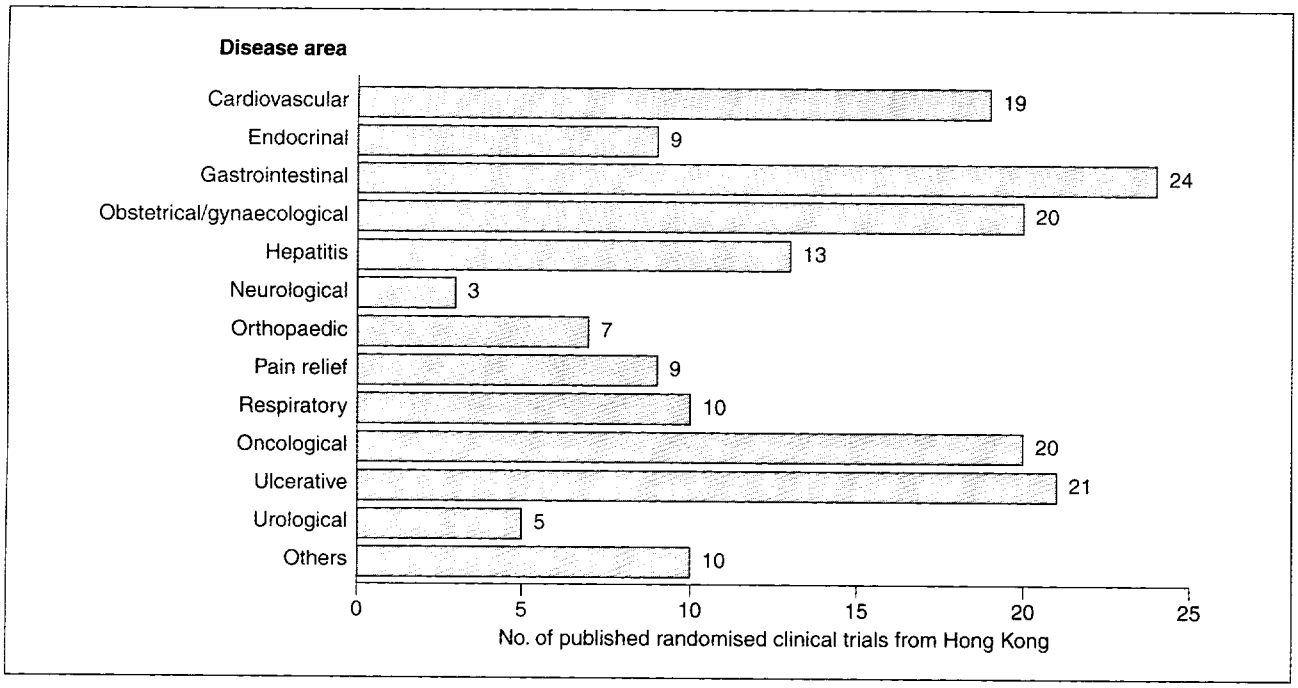


Fig 1. The disease area distribution of Hong Kong randomised clinical trials identified between January 1987 and December 1996

The disease area distribution of the Hong Kong–based RCTs during the study period is shown in Figure 1. The predominant research area was gastrointestinal diseases (58/170; 34.1%), followed by obstetric and gynaecological diseases, and oncological diseases (each, 20/170; 11.8%). The departmental distribution for these RCTs is shown in Figure 2. Sixty-eight (40.0%) came from the Department of Medicine, 27 (15.9%) from the Department of Surgery, 22 (12.9%) from the Department of Obstetrics and Gynaecology, and the balance came from various other departments. Figure 3 shows the total sample size distribution of the published RCTs identified; 160 (94.1%) of the 170 gave the sample size in the abstracts. Approximately half (73/160; 45.6%) of these had a total sample size of fewer than 75 patients, while only 6.9% had a total sample size of 225 patients or more.

The main institutions given in the address field were The University of Hong Kong (89/170; 52.4%)

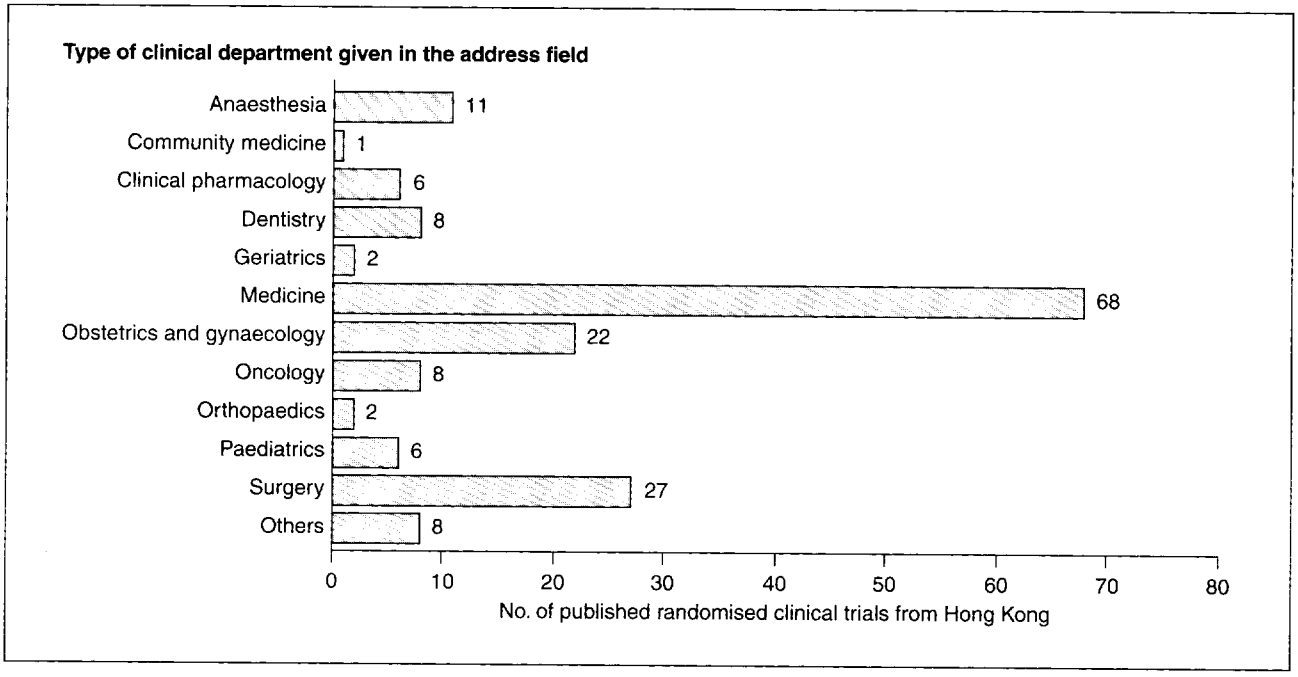


Fig 2. The departmental distribution based on the correspondence address field in *Medline* for Hong Kong randomised clinical trials published between January 1987 and December 1996

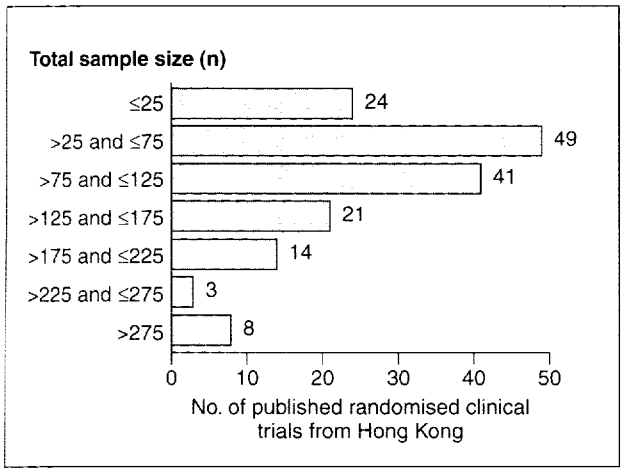
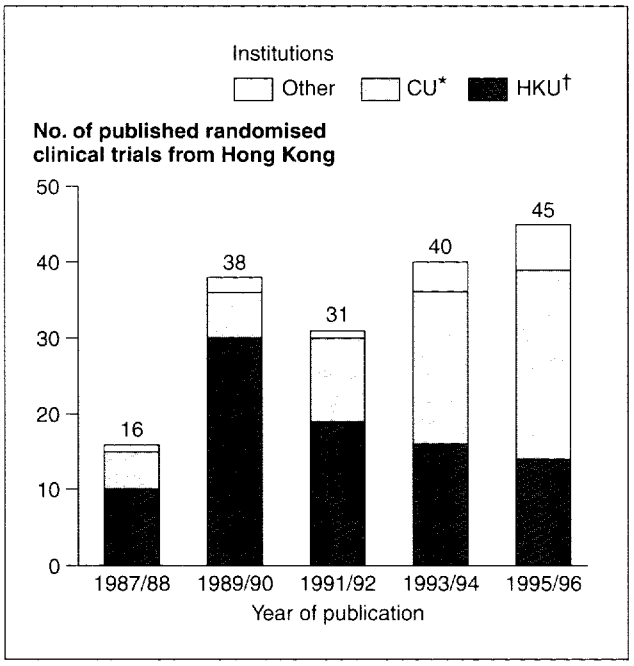


Fig 3. The total sample size distribution of Hong Kong randomised clinical trials identified in *Medline* between January 1987 and December 1996



* CU The Chinese University of Hong Kong
† HKU The University of Hong Kong

Fig 4. The distribution of the institutions given in the *Medline* address field for Hong Kong randomised clinical trials published between January 1987 and December 1996

and The Chinese University of Hong Kong (67/170; 39.4%) [Fig 4]. During the 3 years from 1994 to 1996, the departments of The Chinese University of Hong Kong published 54.8% of the RCTs identified in this study, while the departments of The University of Hong Kong published 33.9% (Table 3). Within this period, the proportion of randomised trials performed by The Chinese University of Hong Kong has been significantly different from that of The University of Hong Kong ($P<0.001$, Chi squared test for trend).

During the past two and a half years, 45 original articles have been published in the *Hong Kong Medical Journal* but none have an RCT design type.

Discussion

This study shows that RCTs represent approximately 3% of the clinical academic output in Hong Kong as identified in terms of the MEDLINE EXPRESS search. No change could be seen in this figure over the past decade. Approximately 50% of the identified RCTs had a small sample size (fewer than 75 subjects). Most of the studies were performed in the field of internal medicine, followed by surgery, and obstetrics and gynaecology (together, 69%). The predominant research area was diseases of the gastrointestinal tract, including ulcers and hepatitis (34%).

This study aimed to show what proportion of published studies in Hong Kong were RCTs and to identify any increasing trend in this proportion over the past decade. We feel that the study provided useful information for such a research question. However, there are always a number of sources for bias in literature searching, such as those identified by the Cochrane Collaboration.* In the present study, we have not searched through all local journals, abstracts, departmental or governmental reports, or studies reported from non–Hong Kong institutions. But we made one search of 45 original articles published in the *Hong Kong Medical Journal*; none appeared to be of the RCT study design. For this reason, our study is not liable to selection bias. We strongly believe that our results show no clear increase in the proportion of RCTs published in Hong Kong during the past decade.

There has been an increasing global trend for the use of the RCT study design type, since it is recognised as a major source of solid and reliable information for evidence-based medical practice. In many countries, the number of RCTs being undertaken has increased annually. These studies cover a wide range of clinical topics and have been published in diverse journals and electronic databases. For instance, an average of 94 RCTs investigating the treatment of acute myocardial infarction were identified each year from 1989 to 1990.[35] The number of published RCTs in primary care increased progressively from 1987 to 1990.[36] One study assessed the type of clinical research published in the *Journal of the American Medical Association*, the *Lancet*, and the *New England Journal of Medicine* and found that the percentage of RCTs increased from

* http://hiru.mcmaster.ca/cochrane/Need_for_More_Reliable_Reviews_of_Research_Evidence

Table 3. The distribution of the institutions given in the *Medline* address field for Hong Kong randomised clinical trials published between January 1987 and December 1996

	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	Total
CU*	2	3	3	3	3	8	11	9	15	10	67
HKU†	3	7	13	17	10	9	9	7	8	6	89
Other	0	1	1	1	1	0	3	1	1	5	14

* CU The Chinese University of Hong Kong
† HKU The University of Hong Kong

31% to 70% (P<0.003) while case series decreased from 30% to 4% (P<0.0001).[37] Thus, RCTs have become widely used, but these kinds of figures usually underestimate the actual number of ongoing RCTs. Moreover, some RCTs are not published in international journals either because of non-significant results or because they are published in local journals. As a result, some organisations such as the Department of Health in the United Kingdom register all trials in a database from the planning stage of the study rather than after the study reaches publication.[36] The *Lancet* assesses protocols of randomised intervention studies and publicises a list of accepted protocols; the journal also makes a provisional commitment to publication of main clinical data after the study is finished. All of these steps are taken to increase the quality of clinical research and to reduce publication bias such as the reporting of significant study results only.

Randomised controlled trials are regarded as important and prestigious not only by virtue of their being accepted for publication in highly rated international journals, but also because they provide the best evidence for clinical practice. A good example of this is the Cochrane Collaboration, which is an international network of individuals and institutions. It consists of review groups and specialties sharing an interest in a particular topic. Starting in the 1980s, the Cochrane Collaboration began to prepare, maintain, and disseminate a systematic, contemporary review of RCTs of health care using the most reliable evidence from all sources. Each collaborative review group is currently responsible for maintaining about 600 systemic reviews of RCTs each year. All health care areas that have been evaluated by RCTs will be covered. Between 200 and 300 new reports of trials are released annually and disseminated through the Cochrane Database of Systematic Review. The Cochrane Collaboration has also established a central database of RCTs covering all branches of health care, rather than a separate database for each discipline. This database is distributed on-line and on CD-ROM. Hence, the results of research assessing the effects of health care are more readily available to those who want to improve their decision making and are accessible to a larger clinical population.

Currently, most data collected about RCTs are based on studies conducted in North America, Europe, and Australia, so the subjects are usually Caucasians. More Asian RCTs are needed since some diseases are more specific for the region and have not yet been studied in RCTs. Another important reason for performing Asian RCTs is the increasing evidence of ethnic group differences in pharmaceutical response.[17-27] Unfortunately, despite a relatively high academic output in Hong Kong, RCTs have not increased much during the decade. Academic and government institutions need to initiate and promote RCTs in Hong Kong to facilitate important health care promotion. This has occurred in Singapore in the past 3 years; extra government funding has been given to the National Medical Research Council to run RCTs and various short courses in clinical trials research methodology at the National University of Singapore.

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