Clinical trials in New Zealand—treading water in the knowledge wave?

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Abstract

Aims To describe the number and type of clinical trials in New Zealand 1998–2003, and to identify the number of trials for which approval was sought in 2003 that were listed with trial registries.

Methods Annual reports (1998–2003) from all regional ethics committees were reviewed for clinical trials. Trials must have been referred to as phase I, II, or III clinical trials; employ descriptors such as randomised controlled trials or controlled trials; or been known to the authors as randomised controlled trials. Trials registers at ClinicalTrials.gov, Current Controlled Trials, NHMRC Clinical Trials Centre, National Cancer Research Network, CenterWatch, Trans-Tasman Radiation Oncology Group, as well as industry registers were searched using keyword identifiers for the trials submitted for ethical review in 2003.

Results Ethics approval was sought for 665 clinical trials (1998, 118 trials; 1999, 91 trials; 2000, 103 trials; 2001, 104 trials; 2002, 108 trials; 2003, 141 trials). The majority of applications (481, 72%) were submitted to either the Auckland or Canterbury committees. 581 (87%) applications were for phase III trials. 522 (78%) applications were for trials involving pharmacological agents, and 115 applications (17%) were for trials involving procedures, processes, or medical devices. The remaining 28 applications (4%) involved interventions such as diet, complementary therapies, or dental care. Of all applications, 332 (50%) were in the fields of cancer, cardiovascular disease, and respiratory disease. Only 45 (32%) of the 141 trials submitted for review in 2003 were listed in a public domain register.

Conclusions The number of randomised controlled trials (RCTs) in New Zealand has not clearly increased in recent years despite the greater than ever need for such evidence. Information currently in the public domain could support registers of clinical trials.
The database only includes trials of some pharmaceutical agents, and like regulatory agencies internationally, the database is not accessible to the public.

No health research in New Zealand can proceed without review by a regional ethics committee. Some details from each of these applications are listed in each committee’s annual report to the Health Research Council. The information contained in these reports is in the public domain and from 2002 the reports were available on the Internet (www.moh.govt.nz).

The objective of this study was to quantify and describe the clinical trials in New Zealand between 1998 and 2003, taking advantage of this publicly available and complete data source.

**Method**

Annual reports for the years 1998–2003 from the regional ethics committees were handsearched by two of the authors (AJ, MW) to identify applications for the conduct of clinical trials.

To be included, trials must have been referred to as either:

- Phase I, II, or III trials;
- Have employed descriptors such as randomised trial, controlled trial, double blind, or parallel group trial, in the title; or
- Have been known to the authors as randomised controlled trials.

Where there was doubt, confirmation was sought using a Google search (www.google.com) or by contacting the principal investigator. Data were collected on the year of first application, the ethics committee, whether it was a multicentre ethics application, the trial name, the applicant’s name, the type of intervention, and the funding source. Identified trials were included only once, and the lead ethics committee was identified from cross-referencing the reports. Trials were excluded if the application had been withdrawn. The health problem being investigated and the type of intervention were inferred by one of the authors (AJ) from the application title.

For trials identified in the 2003 reports, a search for current trial registration was on the following registers: ClinicalTrials.gov, Cancer.gov, Current Controlled Trials (ISRCTN), National Cancer Research Network, NHMRC Clinical Trials Centre Register, International Society of Paediatric Oncology, Trans-Tasman Radiation Oncology Group, CenterWatch, and GlaxoSmithKline. In addition, searches were conducted of industry websites where the industry sponsor was identifiable and a Google search was conducted using keyword terms from the trial title.

**Results**

Ethical approval was sought for 665 clinical trials between January 1998 and December 2003 (Table 1). Approval was sought for 118 trials in 1998, 91 in 1999, 103 in 2000, 104 in 2001, 108 trials in 2002, and 141 trials in 2003. 309 (46%) applications were multicentre ethics applications. The Auckland ethics committees were most frequently the lead committee (143, 46%), followed by Canterbury (86, 27%), Wellington (35, 11%), Waikato (22, 7%), and Otago (9, 3%).

581 (87%) of the applications were for phase III trials, with the remaining trials being phase I (31, 5%) or phase II (53, 8%) clinical trials (Figure 1). The numbers of applications for phase III trials ranged from 87 in 1999 to 109 in 2003. Applications for early phase trials in the years 1998–2002 accounted for 11%, 5%, 12%, 14%, and 8% of applications respectively, but increased to 23% in 2003. Approval for phase I and II trials was most frequently sought in Christchurch (40, 48%) followed by Auckland (23, 27%), and Wellington (10, 13%). Waikato, Otago, Bay of Plenty, and Hawke’s Bay accounted for the remaining trials.
Table 1. Clinical trials by ethics committee and health problem

<table>
<thead>
<tr>
<th>Field</th>
<th>Auckland N (%)</th>
<th>Waikato N (%)</th>
<th>Wellington N (%)</th>
<th>Canterbury N (%)</th>
<th>Otago N (%)</th>
<th>Other N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer +</td>
<td>53 (19)</td>
<td>15 (31)</td>
<td>34 (46)</td>
<td>60 (29)</td>
<td>11 (35)</td>
<td>7 (22)</td>
<td>180 (27)</td>
</tr>
<tr>
<td>Cardiovascular &amp; stroke</td>
<td>61 (22)</td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>37 (18)</td>
<td>2 (6)</td>
<td>6 (19)</td>
<td>110 (17)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>19 (7)</td>
<td>7 (15)</td>
<td>6 (8)</td>
<td>6 (3)</td>
<td>1 (3)</td>
<td>3 (9)</td>
<td>42 (6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (1)</td>
<td>0</td>
<td>3 (4)</td>
<td>16 (8)</td>
<td>2 (7)</td>
<td>0</td>
<td>25 (4)</td>
</tr>
<tr>
<td>Women’s (health) and maternal</td>
<td>10 (4)</td>
<td>1 (2)</td>
<td>3 (4)</td>
<td>6 (3)</td>
<td>0</td>
<td>0</td>
<td>20 (3)</td>
</tr>
<tr>
<td>Mental health</td>
<td>4 (1)</td>
<td>0</td>
<td>1 (1)</td>
<td>3 (1)</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Other medical specialties +</td>
<td>78 (28)</td>
<td>17 (35)</td>
<td>15 (20)</td>
<td>47 (23)</td>
<td>6 (19)</td>
<td>9 (28)</td>
<td>172 (26)</td>
</tr>
<tr>
<td>Surgical specialties +</td>
<td>28 (10)</td>
<td>2 (3)</td>
<td>6 (8)</td>
<td>14 (7)</td>
<td>5 (16)</td>
<td>4 (13)</td>
<td>59 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (7)</td>
<td>4 (8)</td>
<td>4 (5)</td>
<td>15 (7)</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>46 (7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>276 (42)</strong></td>
<td><strong>48 (7)</strong></td>
<td><strong>74 (11)</strong></td>
<td><strong>204 (31)</strong></td>
<td><strong>31 (5)</strong></td>
<td><strong>32 (5)</strong></td>
<td><strong>665 (100)</strong></td>
</tr>
</tbody>
</table>

*Includes haematologic cancers; +Anaesthesia/pain, Dermatology, Emergency/critical care, Gastroenterology, Haematology (non-cancer), Immunology, Infectious disease, Neonatology, Neurology, Renal, Rheumatology; #Eyes, General/Vascular Surgery, Neurosurgery, Orthopaedics, Transplant, Urology.

Figure 1. Clinical trials by phase and year
The trial intervention was a drug in 522 (78%) trials; a procedure, such as radiotherapy or surgery, in 52 (8%) trials; a process, such as service delivery or education and training, in 35 (5%) trials; and a device in 28 (4%) trials. The intervention in the remaining 28 trials involved complementary therapies, diet, dental care, or interventions that could not be categorised.

Cancer was the most frequently investigated health problem, followed by cardiovascular disease and respiratory disease (Table 1). The 172 applications grouped under medical specialties consisted of anaesthesia and pain (22), dermatology (3), emergency and critical care (5), gastroenterology (35), haematology (non-cancer) (3), immunology (10), infectious diseases (37), neonatology (7), neurology (24), renal (7), and rheumatology (19).

The 59 applications grouped under surgical specialties consisted of eyes (9), orthopaedics (15), general and vascular surgery (8), transplantation (6), urology (20), and neurosurgery (1). Only 45 (32%) of the 141 trials (identified from the 2003 reports) were listed on public domain registers; the most frequent listings were registered on ClinicalTrials.gov (25, 55%), or ISRCTN (10, 22%).

Discussion

Using publicly available information, we have been able to establish a comprehensive database of the clinical trials for which ethical approval was sought between 1998–2003. (The quality of information in earlier ethics committee reports did not support investigation prior to 1998.) Approximately 9 out of every 10 applications were for phase III trials and about 4 out of every 5 applications were for drug trials. Cancer (including haematologic cancers), cardiovascular disease, and respiratory disease were the dominant fields of investigation. Only 1 in 3 of the trials in the most recent ethics committees’ reports were registered.

This list of clinical trials is subject to three main limitations. First, it is likely that we have underestimated the number of trials for which ethical approval was sought, since the descriptors randomised controlled trial, controlled trial, or the phase of the trial must have been present in the application title for the trial to be included in our study. The only exception was where the trial could be identified by other means—e.g. the TeleWalk trial. Use of trial acronyms in ethics applications without descriptors of the study methodology could decrease the accuracy of future efforts to maintain a register of clinical trials. However, this concern will be reduced if ethics committees require applicants to refer to the minimum dataset for clinical trials registration promulgated by the World Health Organization.

Second, it was not possible to discern from the ethics committee reports whether the identified trials proceeded from approval to completion. Therefore we cannot determine the actual number of trials that have been conducted in New Zealand over the 6-year period. Third, the ethics committees did not all report the same information; only the Canterbury committee reported the sponsor or funding source, and 6 of the 14 committees did not report the name of the principal investigator.

Our findings are significant for three reasons. First, we have shown that it is possible to obtain from public domain records some of the minimal information necessary to maintain a register of clinical trials in New Zealand. Such high-level information clearly does not constitute a threat to commercial sensitivity (a common counter to the call for trial registers). Maintaining or participating in such a register could facilitate
comparison of research efforts in New Zealand with the population health objectives of the New Zealand Health Strategy. For instance, smoking is the leading modifiable risk factor for lost healthy life-years, yet approval was sought for only two smoking-related trials in the 6-year period. Similarly, mental ill-health causes 25% of all years lost-to-disability, but accounted for less than 2% of applications for clinical trials.

Second, the number of RCTs for which approval was sought has not clearly increased, despite RCTs being considered most reliable method for determining which interventions are effective. A key factor here may be the size of New Zealand’s investment in health research—until recently the per capita funding in New Zealand was about half that of Australia. Likewise, the percentage of New Zealand Government health research expenditure (0.036% GDP) was less than 40% of the OECD average (0.10% GDP). There was an encouraging increase in clinical trials in 2003 (exclusively due to more phase I and II trials), but it remains to be seen if this is sustained.

The number of publications tagged randomised controlled trial in Medline has increased by an average of 8% per annum for 1998–2003, but information on trends regarding trials in different countries is very sparse. Despite extensive searching and contact with international experts, we have not been able to obtain any information on overall levels of or trends in clinical trial activity in countries such as Australia, Britain, Canada, or the United States. The only published information is from Hong Kong where the number of clinical trials certificates issued per annum has doubled for the period 1998–2002. Pacific Rim nations such as Hong Kong, China, Taiwan, and Singapore are working to make themselves more attractive to the clinical trials industry, as they recognise the scientific, economic, and health benefits of such activity. These nations regard Australia and New Zealand as competitors for trials.

Third, we have shown that reliance on regulatory agencies as a source of information for a trials register would miss at least one in five clinical trials in New Zealand. Agencies, such as MedSafe or the Therapeutic Goods Administration, are only responsible for trials involving medicines, and more than 20% of the ethics applications were for trials involving non-pharmacological interventions such as devices, supplements, or health services research.

Trial registration is becoming accepted as good research practice. A broad alliance of agencies are pursuing the goal of ensuring information from trials is in the public domain: the World Health Organisation and the European Union require registration of industry sponsored trials; the US requires registration of drug trials for life-threatening or serious clinical conditions; and funders in the United Kingdom and Canada require trials to be registered before grants can be uplifted. In addition, the International Committee of Medical Journal Editors now require the registration of trials as a precondition of consideration for publication. Although previously less receptive to the notion of trial registration, public disclosure of adverse events, like those associated with selective serotonin reuptake inhibitors in childhood depression, have wrought some changes in the pharmaceutical industry. For instance, GlaxoSmithKline is now placing results of its trials in the public domain and others seem likely to follow. These forces should make explicit which trials are completed, encourage publication of completed trials and increase the chances that decisions are based on all evidence. However, simply establishing trials registers will not increase publication rates.
We have proposed elsewhere that ethics committees are an ideal source of information for trials registration.\textsuperscript{19} No investigation proceeds to study start-up without ethical approval. It would be a relatively simple matter for New Zealand ethics committees to require evidence of trial registration prior to releasing ethics approval. Alternatively, the ethics committees could submit the information themselves to trials registers.

There is an increasing community that believe ethics committees have a role in ensuring the dissemination of the results of research they approve.\textsuperscript{20,21} Failing to publish trials or delayed publication is relatively common,\textsuperscript{4,22,23} with a lack of time a commonly cited reason.\textsuperscript{22} The primary intention of efforts to ensure all trials are registered is to guarantee that information about trials having been conducted is in the public domain. Triallists could then be contacted to contribute their data to meta-analyses. Thus, prospective mandatory registration of randomised controlled trials has been proposed as a means of preventing erroneous or harmful conclusions being made on the effect of treatments.\textsuperscript{15,24,25}

A New Zealand public record that contributed to meta-registers such as mRCT at \url{www.controlled-trials.com} should ensure that the results played a part in future syntheses of evidence, even if the trial had not been not published.

Conclusions

The number of applications to conduct RCTs in New Zealand has changed little in the last 6 years, and there are marked gaps in areas of public health importance. Information placed in the public domain by ethics committees would support a register of trials, and such committees are the optimum source of such information, since other sources could only capture a limited subset of trials. By making trials registration mandatory, and creating a national clinical trials register or contributing to an international register, New Zealand would continue to make significant contributions to effectiveness in healthcare.

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