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Clinical trials in New Zealand—an update

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Abstract

Aims To describe clinical trial activity in New Zealand for the period 2005–2009 and estimate the number of trials that were listed on World Health Organization-compliant trials registers.

Methods Clinical trials were identified from the annual reports (2005–2009) of the six Health and Disability Ethics Committees. To be included, trials must have been referred to as phase I, II, III or IV trials; or included key descriptors in the title; or have been known to the authors as randomised controlled trials. Key trial characteristics were obtained from searching trials registers or through contact with the investigators.

Results 900 clinical trials were approved in the period 2005–2009 (average 180 per year). The Multi Region ethics committee received most of the applications (379, 42%) followed by the Northern X (190, 21%) and Northern Y (151, 17%). 621 (69%) trials were late phase trials (average 124 per year) and 279 (31%) were early phase trials (average 56 per year). Most trials involved a drug (651, 72%). Trials that recruited infants, children or adolescents accounted for just 68 trials (8%). The most frequent conditions targeted were cancer (163, 18%), cardiovascular disease (125, 14%) and respiratory disease (83, 9%). 532 (59%) trials were commercially sponsored and 335 (37%) were non-commercial. Merck Sharp & Dohme were the single most frequent commercial sponsor (50, 9% of commercial trials) and the Health Research Council the single most frequent non-commercial sponsor (70, 21% of non-commercial trials). 758 (84%) trials could be identified as being listed on a WHO-compliant trials registry. Non-commercially sponsored trials had lower rates of registration (278, 83%) than commercially sponsored trials (480, 90%).

Conclusions Clinical trial activity in New Zealand has increased compared with the period 1998–2003 and early phase activity accounted for most of the increase. There has been a dramatic rise in trials registration and the commercial sector has been more compliant with the International Committee of Medical Journal Editors' statement on trials registration than the non-commercial sector.

In 2010 the New Zealand Health Select Committee investigated the clinical trial landscape in order to consider ways to better coordinate nationwide approaches, remove barriers, streamline processes and measure performance.[1] Several submissions to the Health Select Committee noted the lack of any routinely collected or reported metrics on clinical trial activity in New Zealand. Information regarding clinical trial activity in New Zealand is scarce with no information published since a previous report by one of the authors in 2005.[2]

Measures of clinical trial activity can facilitate accurate estimates of the economic value of the activity, enable comparisons to be made between levels of trial activity

and known areas of disease burden, and identify the impact of policy and process changes. Thus it seems desirable that clinical trial activity be aggregated, if not routinely, then at least with some regularity.

No clinical trial can proceed without ethics committee review and the Health and Disability Ethics Committees publish annual reports on their website that list the studies submitted for their consideration. These details, although limited, are generally sufficient to determine whether a study was a clinical trial. The original intent of this investigation was to describe trial activity from 2004, but the reorganisation of ethics committees adversely affected the reporting for that year.

Therefore, the aim of this study was to describe clinical trial activity in New Zealand 2005–2009 and estimate compliance to the International Committee of Medical Journal Editors' (ICMJE) statements on trials registration.[3 4]

Methods

Annual reports from the six Health and Disability Ethics Committees in New Zealand for the years 2005–2009 were downloaded from the Committees' website. The reports were handsearched by one of the authors (VC) to identify applications for ethical approval for clinical trials.

To be included, trials must have been referred to as phase I, II, III or IV trials; or have contained the key descriptors randomised trial, controlled trial, double blind, placebo or trial in the title; or have been known to the authors to be randomised controlled trials. Pilot studies were only included if they were randomised pilot trials. Where there was uncertainty as to whether an application related to a trial, further information was sought from the applicant or obtained by internet searching.

Trials were not included if the application had been declined or withdrawn. The ethics committee reports were independently reviewed by the second author (AJ) to ensure complete data collect.

Information was extracted from the reports on the year of application, the committee from which approval was sought, the phase of the trial, the type of intervention, the condition being targeted, the population group sought for the trial, trial registration and the sponsor or funder. Trial registers that met the World Health Organization (WHO) Minimal Registration Data Set were searched either through the WHO International Clinical Trials Registry Platform or by directly accessing the register (*clinicaltrials.gov*, the Australia New Zealand Clinical Trials Registry or Current Controlled Trials).

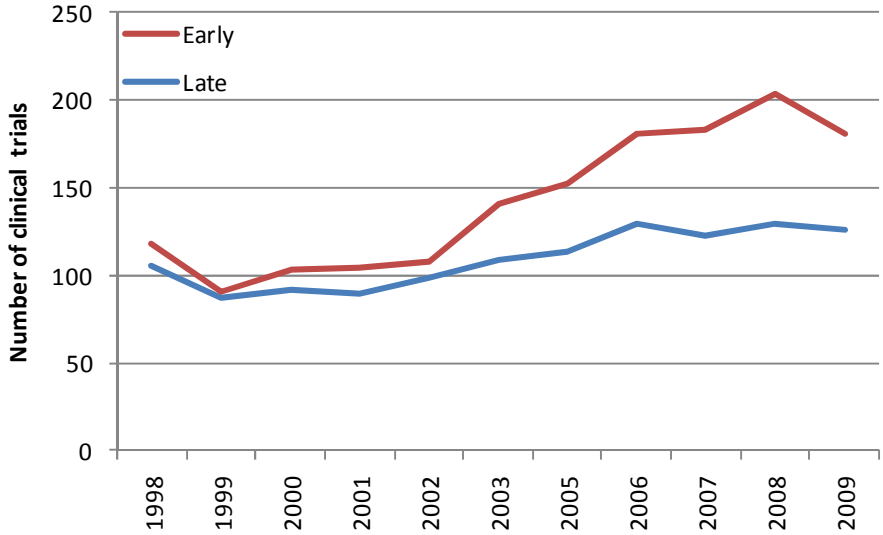
Early phase trials were those identified as phase I, II or pilot randomised controlled trials. Phase I or II trials need not have used random allocation. Late phase trials were those that self-identified as phase III or IV trials and must have used random allocation. If the phase of the trial was unable to be identified from internet searches or the trial title, it was categorised as late phase. Each trial was assigned to one of 26 condition categories. If a trial fell into two or more categories it was coded according to the greatest perceived contribution to one category.

A random sample of 10% of the data extract was independently reviewed by a second author (AJ) to ensure accuracy of content and agreement with condition categorisations. Although agreement was 93%, all condition categorisations were then reviewed by the second author for accuracy and consistency.

Results

Ethical approval was sought for 900 clinical trials conducted in New Zealand between January 2005 and December 2009. Trial activity increased within the 5-year period: there were 152 trials in 2005, 181 trials in 2006, 183 trials in 2007, 203 trials in 2008 and 181 trials in 2009 (Figure 1) giving an annual average of 180 trials per year. The trials were predominantly late phase (621 trials, 69%, average 124/year) with 279 trials (31%, average 56/year) being described as phase I or phase II clinical trials (61 and 189 respectively) or pilot randomised trials (29).

Figure 1. Contribution (cumulative) of early and late phase trials 2005–2009 compared to data from previous report 1998–2003.[2] Note data not available for 2004



The multi-region ethics committee received the largest proportion of applications in the 5-year period, with 379 (42%) of trials falling under this committee's jurisdiction (table 1). Northern X reviewed 190 applications (21%), Northern Y reviewed 151 applications (17%), Central reviewed 71 applications (8%), Upper South reviewed 61 applications (7%) and Lower South reviewed 48 applications (5%).

A similar pattern was evident with both early and late phase trials, which were most frequently reviewed by the multi-region ethics committee (Early: 112, 40%. Late: 267, 43%), followed by the Northern X (Early: 65, 23%. Late: 125, 23%) and Northern Y committees (Early: 44, 16%. Late: 107, 17%). The pattern varied slightly with the Upper South (Early: 29, 10%. Late: 32, 5%), Central (Early: 20, 7%. Late: 51, 8%), and Lower South committees (Early: 9, 3%. Late: 39, 6%). Early phase trials increased from 25% of trial activity in 2005 to 30% of trial activity in 2009, with peak activity in 2008.

758 (84%) trials could be identified as listed on a WHO-compliant trials register, with *clinicaltrials.gov* being the most frequent site of registration (498, 55%) followed by the Australia and New Zealand Clinical Trials Register (250, 28%). The percentage of trials registered was highest at 88% (134) in 2005, but fell in the following years to 82% (148) in 2006, 84% (154) in 2007, 82% (167) in 2008 and 86% (155) in 2009. 278 (83%) of non-commercial trials and 480 (90%) of commercial trials were registered; the only year non-commercial trials exceeded commercial trials being registered was in 2005 (Table 3).

Table 1. Clinical trials by year and phase for each ethics committee

Region	2005 N (%)		2006 N (%)		2007 N (%)		2008 N (%)		2009 N (%)	
	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late
Multi-region	16 (42)	47 (41)	19 (37)	54 (42)	32 (53)	57 (46)	25 (34)	59 (46)	20 (36)	50 (40)
Northern X	7 (18)	33 (29)	12 (23)	22 (17)	16 (27)	23 (19)	17 (23)	23 (18)	13 (24)	24 (19)
Northern Y	5 (13)	19 (17)	10 (19)	18 (14)	8 (13)	25 (20)	13 (18)	21 (16)	8 (15)	24 (19)
Central	3 (8)	5 (4)	6 (12)	10 (8)	3 (5)	9 (7)	5 (7)	10 (8)	3 (5)	17 (13)
Upper South	7 (18)	5 (4)	4 (8)	12 (9)	1 (1)	3 (2)	7 (9)	5 (4)	10 (18)	7 (6)
Lower South	–	5 (4)	1 (2)	13 (10)	–	6 (5)	7 (9)	11 (9)	1 (2)	4 (3)
Total	38 (25)	114 (75)	52 (29)	129 (71)	60 (33)	123 (67)	74 (36)	129 (64)	55 (30)	126 (70)
	152		181		183		203		181	

Table 2. Clinical trials by year approved and condition

Variables	2005 N (%)	2006 N (%)	2007 N (%)	2008 N (%)	2009 N (%)	Total N (%)
Cancer +	35 (23)	32 (18)	30 (16)	34 (16)	32 (18)	163 (18)
Cardiovascular ++	24 (16)	33 (18)	26 (14)	28 (14)	14 (8)	125 (14)
Respiratory	10 (7)	22 (12)	17 (9)	18 (9)	16 (9)	83 (9)
Gastroenterology	17 (11)	4 (2)	15 (8)	16 (8)	12 (7)	64 (7)
Diabetes	10 (7)	11 (6)	18 (10)	11 (5)	12 (7)	62 (7)
Neurology	5 (3)	8 (4)	7 (4)	7 (3)	10 (6)	37 (4)
Mental health	5 (3)	8 (4)	4 (2)	7 (3)	9 (5)	33 (4)
Anaesthesia/pain	4 (3)	6 (3)	7 (4)	8 (4)	8 (4)	33 (4)
Haematology (non-cancer)	3 (2)	5 (3)	7 (4)	7 (3)	6 (3)	28 (3)
Rheumatology	3 (2)	7 (4)	7 (4)	6 (3)	5 (3)	28 (3)
Women's health	8 (5)	1 (1)	7 (4)	1 (1)	7 (4)	24 (3)
Ophthalmology	6 (4)	3 (2)	2 (1)	4 (2)	8 (4)	23 (3)
Infectious diseases	2 (1)	4 (2)	6 (3)	3 (2)	7 (4)	22 (2)
Emergency/critical care	2 (1)	4 (2)	6 (3)	4 (2)	5 (3)	21 (2)
General/vascular surgery	1 (1)	6 (3)	3 (2)	7 (3)	4 (2)	21 (2)
Orthopaedics	2 (1)	5 (3)	4 (2)	5 (3)	4 (2)	20 (2)
Neonatology	3 (2)	4 (2)	2 (1)	5 (3)	2 (1)	16 (2)
Dermatology	1 (1)	1 (1)	1 (1)	7 (3)	2 (1)	12 (1)
Renal	–	–	3 (2)	4 (2)	4 (2)	11 (1)
Urology	1 (1)	3 (2)	2 (1)	3 (2)	2 (1)	11 (1)
Dental	–	2 (1)	3 (2)	3 (2)	2 (1)	10 (1)
Gerontology	2 (1)	1 (1)	1 (1)	2 (1)	–	6 (1)
Immunology	–	1 (1)	1 (1)	1 (1)	2 (1)	5 (1)
Transplant	2 (1)	2 (1)	1 (1)	–	–	5 (1)
Other *	2 (1)	3 (2)	1 (1)	6 (3)	4 (2)	16 (2)
Unknown	4 (3)	5 (3)	1 (1)	5 (2)	4 (2)	19 (2)
Total	**152 (17)**	**181 (20)**	**183 (20)**	**203 (23)**	**181 (20)**	**900 (100)**

[+] Included haematological cancers; [++] Included cardiac surgery and interventional cardiology; [*] Included herbal, dietary, injury prevention, education, physiotherapy, sports science, sleep disorder, and health services delivery interventions and other endocrine diseases.

Table 3. Trial registration, by year, for non-commercial and commercial trials (excluding 33 trials where sponsorship could not be determined)

Registered	2005 N (%)		2006 N (%)		2007 N (%)		2008 N (%)		2009 N (%)	
	Public	Industry	Public	Industry	Public	Industry	Public	Industry	Public	Industry
Yes	55 (98)	79 (92)	57 (84)	91 (88)	47 (76)	107 (92)	61 (79)	106 (88)	58 (81)	97 (92)
No	1 (2)	7 (8)	11 (16)	13 (12)	15(24)	10 (8)	16 (21)	14 (12)	14 (19)	8 (8)
Total	**142**		**172**		**179**		**197**		**177**	

The sponsor could be identified in 867 (96%) trials either directly from the annual report or from a trials register. 532 (59%) trials were funded by industry or other private sponsors (commercially sponsored) and 335 (37%) by public research funders, government agencies or research charities. The largest single commercial contributor to trial activity was Merck with 50 trials (9% of commercial activity), followed by Roche (48, 9%), GSK (41, 8%) and Novartis (28, 5%).

The largest single non-commercial sponsor was the Health Research Council of New Zealand, providing funding for 70 trials (21% of non-commercial activity). Universities (both New Zealand and overseas universities) were the sponsor for 41 trials (12%), while district health boards or other health providers sponsored 37 trials (11%), and government ministries or other government agencies sponsored 17 trials (5%). The remaining 170 trials (51% of non-commercial activity) were sponsored by research trusts or charities within New Zealand and from overseas.

The largest single condition category investigated was cancer followed by cardiovascular disease (including stroke) and respiratory diseases (table 2). The target populations recruited were adults in 631 trials (70%), infants in 29 trials (3%), children in 22 trials (2%) and adolescents in 7 trials (1%).

Ten trials (1%) targeted both children and adolescents, while 60 trials (7%) allowed all ages entry (20) or had age criteria that allowed a mix of children, adolescents and adults to be recruited but within specified age ranges (40). The target population could not be identified in the remaining 141 trials (16%).

The intervention was a drug in 651 (72%) trials compared with a process such as education, training or service delivery in 108 (12%) trials, a procedure such as radiation therapy or surgery in 55 (6%) trials, and a device in 49 (5%) trials. The interventions in the remaining 37 (4%) trials included dietary interventions, alternative therapies or were unable to be determined.

Discussion

The number of trials undertaken in New Zealand in 2005-2009 has increased to an average of 180 trials per year, up from an average of 111 per year in 1998-2003.[2] Growth that appeared to have started in 2003 has been sustained. Much of the increase is due to early phase activity, with 300% increase in activity from an average of 14 trials per year in 1998-2003. The proportion of trials that could be identified as being listed on a WHO-compliant register has also increased to 84%, up from 32% in 2003.[2]

Internationally, this study remains the only nationwide stock take of all clinical trial activity, with the exception of a similar exercise undertaken in by one of the authors in 2004.[2] The national organisation of the health and disability ethics committees, an overarching operating standard, with standardised national application form and annual reporting facilitates such a stock take. Other national surveys have been limited to non-commercial trials only or examined clinical trial registers for specific country codes.[5 6]

This study demonstrates once more that ongoing monitoring of trial activity in New Zealand is possible, especially if information currently reported by ethics committees is used. Such an activity could be undertaken be the relevant ministries, such as the Ministry of Health or the Ministry of Research, Science and Technology. With very little added effort, information that clearly identifies ethics applications as pertaining to a clinical trial, the phase of the trial, whether it is registered or not and where, could be included in the ethics committees' annual reports for aggregation by a ministry.

New Zealand is thought to provide an environment conducive to increasing clinical trial activity: it is a resourceful and innovative society, has a reputation for conducting world class research, and can produce results on time, with added cost benefits when the New Zealand dollar is weak against other currencies.[7] These factors are reflected New Zealand's contribution to clinical trial publications per million population over the last 60 years (791/million), which puts New Zealand at number three after Sweden and Denmark.[8]

Similarly, New Zealand's biomedical research publications per million population 1990–2000 (309.2) are on par with that of the United Kingdom (310.4) although well short of Sweden (714.3) and the USA (451.2).[9] Although it is not possible to compare all clinical trial activity, the average number of non-commercial trials conducted in New Zealand during 2005–2009 that were non-commercially sponsored was 67 per year, comparable to the 66.5 per year conducted in the United Kingdom during 1980–2002.[5] There is no doubt that New Zealand is a small player in clinical trial activity, but it does punch above its weight.

The increase in trials being registered from 32% in 2003 to 84% in 2005–2009 can only be ascribed to the announcement by the ICMJE that trials seeking publication in member journals had to be prospectively registered on a register compliant with the WHO Minimal Registration Data Set.[4] Previous attempts to encourage registration, such as legislative requirements in trials for life-threatening or serious conditions, had little effect.[10] That 100% of trials conducted in New Zealand were not registered cannot be explained by the increase in early phase activity. Industry appears to be more compliant with trials registration than the non-commercial sector and the commercial sector accounts for the greater proportion of early phase trials in New Zealand (38% of commercial trials compared to 22% of non-commercial trials).

Although industry was hesitant to ascribe voluntarily to trials registration, citing commercial sensitivity,[11] our findings suggest industry has overcome such reservations. The report of the health select committee inquiry into improving the environment for clinical trials recommended that trials conducted in New Zealand be registered with the Australia New Zealand Clinical Trials Register (ANZCTR).[12] However, a possible barrier has arisen as the Health Research Council (HRC) is no longer assisting with funding the ANZCTR, even though the HRC recommends

registering on the ANZCTR. Alternative sources of public funding from New Zealand are needed if this register is to be maintained.

Clinical trials are defined by the WHO as being "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."[3] As such the WHO expectation is that any trial from phase I onwards should be registered, although that consideration was relaxed by the ICMJE 2005 statement.[4]

Ethics committees have a role in continuing improvement in trials registration. The current national application form does ask if it is intended to register a clinical trial, but there is no hint of necessity. If ethics committees were to require trial registration prior to releasing ethical approval, non-commercial sector performance would improve. Such an improvement would be unlikely to influence approval times for commercially-sponsored trials given industry's already excellent record in trials registration.

This study was subject to three limitations. First, the number of clinical trials for which ethical approval was sought may have been underestimated despite our best efforts. If a study did not include adequate descriptors to identify it as a trial or could not be identified as such from internet searching it was excluded from selection. Second, we did not determine where the trial took place. While locality organisations are included for each trial approval in the ethics committees' reports, it was not always possible to determine where the trial was undertaken from such locality reports and thus the information was not collated for analysis. However, we have reported information by ethics committee, which allows some approximation of trial activity at a regional level. Third, the ethics committee annual reports do not specify if trials progress from approval to completion. While this study details applications for ethical approval for trials, it therefore does not definitively detail the number of trials initiated in New Zealand, as some trials may have failed to recruit participants.

Conclusion

There has been an increase in clinical trial activity since 2005 and much of this increase is due to increased early phase activity. There has been a dramatic increase in the proportion of trials registered, with commercially-sponsored trials being more compliant with registration. Ethics committees could improve the compliance of the non-commercial sector with trials registration by requiring evidence of trial registration prior to providing ethical approval.

Competing interests: None declared.

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