Prospective registration of clinical trials

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The news that the Editorial Board of the Australian Journal of Physiotherapy is moving to require that trials submitted for publication provide evidence of prospective registration in a publicly-accessible register is welcome as it indicates that specialist journals are now following the lead of the International Committee of Medical Journal Editors. In September 2004, the Committee decreed that from 1 July 2005 all trials submitted for publication in the world’s major medical journals must have registered key details of the trial’s design in a publicly-accessible register before the first participant was enrolled (DeAngelis et al 2004).

Reasons

Why have these journal editors, and now the Editorial Board of the Australian Journal of Physiotherapy, taken this position, ie, why is the prospective registration of trials important? The Declaration of Helsinki (World Medical Association 1964), established after World War II to protect the rights of human research subjects, states that the design of all studies should be publicly available. Despite this, we now know that the results of a substantial proportion of studies are not published at all (Dickersin and Rennie 2003). Making clinical or policy decisions based on only a subset of the complete evidence-base can result in very different conclusions being drawn (Simes 1986). This ‘publication bias’ can have serious consequences as the recent exposure of incomplete reporting of drug trials has highlighted (Jureidini et al 2004, Whittington et al 2004). In the wake of such scandals, researchers have, perhaps not surprisingly, recently felt the force of increasing public mistrust in their activities (Godlee 2005, Martinson et al 2005). One way in which trust could be enhanced would be for the public to be reassured that the existence and main design features of all trials were disclosed at their inception, and that these details were kept permanently on record. In doing so, it would be possible to compare what researchers initially planned to do with what they ultimately reported and published.

In addition to enhancing public trust in research, there are many other reasons to encourage prospective trial registration. If clinicians and potential participants are able to identify studies that are currently open to recruitment there may well be increased participation in trials. Funders would also benefit by being able to direct resources to areas identified as having a limited evidence base. Those who summarise the main trial results of trials by searching across the worldwide network of trial registers. Work is well under way to achieve this goal.

Requirements

Australia has played, and will continue to play, a leading role in these worldwide trials registration activities. The major recent initiative was the establishment, in July 2005, of the online Australian Clinical Trials Registry (www.actr.org.au). Australians now have a place where they can register their studies as well as find out about clinical trial activity in our region. The Australian registry accepts studies with all types of designs, all types of interventions, and from all regions. In January 2006, the International Committee of Medical Journal Editors acknowledged that the Australian registry fulfilled their requirements for an acceptable register for both data and administration criteria (ICMJE 2006). The Australian Clinical Trials Registry is governed by a high-level external Advisory Board with wide stakeholder representation. Current funding is via a five year National Health and Medical Research Council Enabling Grant.

The International Committee of Medical Journal Editors have stated that the studies which should be registered include ‘all research projects which prospectively assign human subjects to intervention and concurrent comparison/control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include any intervention used to modify a health outcome. This definition includes drugs, surgical procedures, devices, behavioural treatments,
process of-care changes, and the like.’ They require trials to be registered at, or before, enrolment of the first participant (DeAngelis et al 2004).

Additionally, in November 2005 the WHO International Clinical Trials Registry Platform recommended the registration of all interventional clinical trials, including early phase uncontrolled trials in patients or healthy volunteers (WHO 2005). They also state that all registration data items should be publicly disclosed at the time of registration. Certain groups, in particular the pharmaceutical industry, have argued that in some circumstances revealing information such as details of the intervention to be tested, may put companies at a competitive disadvantage if rivals know about novel new treatments before a product is ready for licensing. However, after extensive public consultation, the WHO has declared it does not support any mechanism for delayed disclosure of data items. Both the International Committee of Medical Journal Editors and WHO have outlined 20 specific data items as being the minimal information that must be provided to satisfy trial registration criteria (DeAngelis et al 2004, WHO 2006). These are data items that would enable the public to reasonably discern what the trial was about and include information on the trial’s participants, interventions, outcomes, sample size, funder(s), contact persons, and other design features.

The Australian Clinical Trials Registry possesses other features such as being searchable, free-of-charge, and having quality control procedures in place. Currently trial registration in Australia is voluntary. If registrants choose to register their trial on the Australian registry, they must provide meaningful information for each of the 20 minimum data items and these will all be made publicly available at the time of registration. ‘Meaningful information’ involves not just writing ‘procedure A vs procedure B’ as a description of the interventions being tested in the trial. Registrants are required to provide sufficient detail so that readers can understand what the trial is really about. For example, a meaningful description of the intervention might be ‘group circuit class compared to one-to-one physiotherapy’. It is the responsibility of the trial Sponsor to ensure the quality, accuracy, and currency of the data lodged on the registry. A trial Sponsor is defined as ‘an individual, company, institution or organisation that takes responsibility for the initiation, management and/or financing of a clinical trial.’ (TGA 2001). Trial Sponsors wishing to register their trial on the Australian registry, register as a ‘user’ and, once verified, are able to enter, save, and then submit their data for registration. The information is checked by registry staff for duplication, accuracy, and completeness before registration.

Challenges

Whilst the establishment of the Australian Clinical Trials Register has been an important step forward, achieving a complete and comprehensive system of prospective trial registration is not without its challenges.

One of the main challenges is ensuring that all trials are registered. At present, whilst the requirement of the International Committee of Medical Journal Editors is a major incentive for researchers to register their trials, the fact remains that trial registration in Australia is voluntary. Hence we have no way of knowing whether the 1200 trials registered on the Australian registry to date represent all, some, or only a small proportion of the clinical trials being undertaken nationally. The most effective way to ensure registration of all trials informing health care practice would be to make trials registration a condition of Ethical approval. We have proposed a simple mechanism for achieving this without increasing the workload of Ethics Committees. This model is currently being considered in a review of several key documents relating to the conduct of clinical trials in Australia: the National Statement (2006), the Australian Code for the Responsible Conduct of Research (2006) and the National Ethics Application Form (2006).

A related challenge is to ensure that the data submitted to the registry are meaningful and accurate. The Australian Clinical Trials Registry has quality control procedures in place that allow discussion with the registrant between data submission and prior to trial registration to clarify any potential errors and ensure completeness of the mandatory data items. If a registrant refuses to complete a mandatory data field with meaningful information, trial registration will not be permitted. Other registries, such as ClinicalTrials.gov (www.clinicaltrials.gov), have found that some Sponsors did not provide meaningful detail for some data items such as the primary outcome (Zarin et al 2006).

One final challenge is the task of minimising duplicate entries both within and across trial registers. This task is easier said than done. The Australian Clinical Trials Registry is working closely with the WHO and other major registers around the world to share experience and technical expertise to ensure that these challenges are overcome. The aim is to facilitate a system whereby anyone looking for trials related to a certain condition can access a one-stop search portal which will look within and across registers and provide a short-list of potential trials and their details within seconds.

The establishment of the Australian Clinical Trials Registry in 2005 has been a major milestone for trials registration in Australia. However, much is still to be done and we have plans for continuous improvement of the current facility including more advanced search functionality and the ability to update some data fields whilst still retaining the original dataset as registered. A comprehensive series of stakeholder consultations was undertaken in the latter part of 2006 to help identify how users would like the registry to operate both now and in the future.

Summary

The WHO International Clinical Trials Registry Platform has stated that the prospective registration of clinical trials is an ‘ethical, scientific and moral obligation’ for those undertaking research on humans. Australia has taken this obligation seriously with the establishment of the Australian Clinical Trials Registry, an online database of clinical trials being undertaken throughout the country that is accessible to all. Efforts continue to ensure that all clinical trials are registered at inception and that the public can be reassured that researchers will be transparent and accountable in disclosing the results of their research activities.

References


Documents


Statement regarding registration of clinical trials from the Editorial Board of Australian Journal of Physiotherapy

This journal is moving towards requiring that clinical trials whose results are submitted for publication in Australian Journal of Physiotherapy are registered. From January 2008, all clinical trials submitted to the journal must have been registered prospectively in a publicly-accessible trials register. We will accept any register that satisfies the International Committee of Journal Editors requirements. Authors must provide the name and address of the register and the trial registration number on submission.