preventive drugs sold in rich countries that would be used to fund treatment pharmaceuticals in poor countries. This could help to flatten both arms of the J curve and thereby benefit people in both rich and poor countries.

Contributors and sources: IH has been a general practitioner in the same inner city practice in London for nearly 30 years. The ideas in this article arose from thinking and reading around the experience of caring for patients in this context and were first presented at the 31st Annual Meeting of the North American Primary Care Research Group in October 2003.

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Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa statement (part 1)

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Registering of trials is essential to make sure all results are publicly available and that ethical obligations to participants are met

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Recent evidence of selective reporting of results has eroded public and academic confidence in publications of clinical trials, leading to renewed calls for trial registration.[1–5] The dangers of non-disclosure of trial results, although described for years, sparked an international furore last spring after the publication of two systematic reviews on the effects of selective serotonin reuptake inhibitors for childhood depression.[1 6] Subsequent legal proceedings[7] and policy statements by journal editors,[8 9] medical associations,[10] and industry[11] have recognised the importance of trial registration. The rationale for registering trials is well known (box 1).[12 13] Most importantly, the contribution to social good that justifies research on human participants is not realised when resulting knowledge remains invisible.

As an interested and neutral party that has been registering the trials that it funds,[14] the Canadian Institutes of Health Research hosted an open meeting on 4 October 2004 in Ottawa, Canada, to foster international consensus on trial registration. The resulting Ottawa statement aims to establish internationally recognised principles for registration (box 2). The full statement is on bmj.com, but here we highlight and discuss some of the key principles. A statement on how to implement these principles (part 2) is still in development.

Box 1: Rationale for registration of clinical trials

Ethical

- Respect the investigator-participant covenant to contribute to biomedical knowledge by making trial methods and results public
- Provide global open access to information
- Reduce unnecessary duplication of invested research resources through awareness of existing trials
- Assure accountability with regard to global standards for ethical research
- Enable monitoring of adherence to ethical principles and process

Scientific

- Increase the reliability and availability of evidence on which healthcare decisions are based
- Improve trial participation
- Increase opportunities for collaboration
- Ensure transparency of trial design and methods
- Provide open review of protocols to improve trial quality and refine methods
- Provide means for identification and prevention of biased under-reporting or over-reporting of research
- Accelerate knowledge creation

Summary of principles

The mandatory registration of all trials has three components:

- Obtaining an internationally unique identification number (unique ID)
- Registering the original protocol along with subsequent amendments
- Registering the trial results.

P+ *Members of the Ottawa Group and the full statement are on bmj.com*

Box 2: Outline of the Ottawa statement, part 1 (principles)

- Objective
- Definitions
- Rationale for international trial registration
- Types of trials to be registered
- Elements of registration
- Principles relating to:
  Unique identification number
  Protocol registration
  Registration of trial results
- Organisation and language of registries
- Responsibilities of involved parties

Public release of registered information should occur, as a principle, at specific stages of a trial (figure). Sponsors, principal investigators, journals, and ethics committees all have certain responsibilities to ensure comprehensive registration of trials.

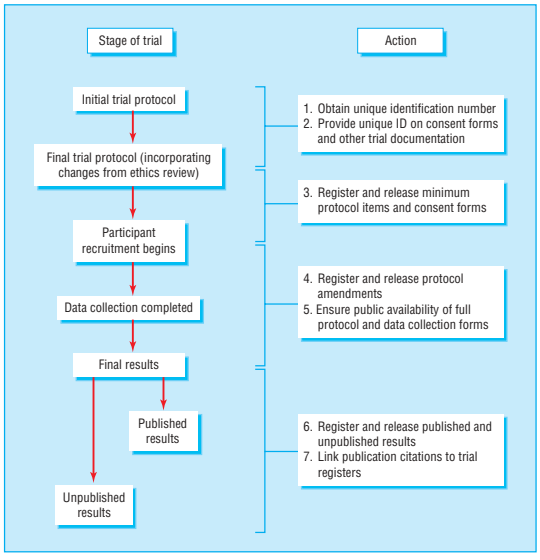
Key principles

Three of the key principles in the statement have been the subject of much debate, and we discuss the rationale behind them in more detail below.

Registering all types of trials

"Protocol information and results from all trials related to health or healthcare—regardless of topic, design, outcomes, or market status of interventions examined—should be registered and publicly available."

Some people have argued against requiring registration of early or post-marketing exploratory trials and uncontrolled trials, citing the need to protect commercial interests for interventions under development.[11 15] Such trial designs may also be deemed less important for registration because they rank lower in the hierarchy of evidence to guide healthcare decisions. Furthermore, pharmaceutical companies have suggested restricting the registration of results to commercially available drugs because many researched drugs never make it to market and cannot affect healthcare.



General time line for process of trial registration

However, these arguments ignore the fundamental ethical obligations to research participants. Most importantly, the potential risks of their voluntary participation, which exist in any type of trial, are justified primarily by the presumed social good resulting from the creation of publicly accessible knowledge. This social contract to accurately disseminate information and results from all trials takes precedence over commercial or other interests. A decision not to bring an intervention to market—whether for economic or scientific reasons—does not invalidate this ethical obligation to participants and has little bearing on the importance of knowledge gained from trials. For example, information gained in early trials about an ineffective or harmful intervention that has not been marketed should be made publicly known to avoid unnecessary and potentially harmful duplication by other researchers.

Several additional justifications exist for including all trials. Certain interventions and uncommon diseases are less amenable to controlled study designs. The best evidence for these interventions is thus limited to less rigorous designs such as prospective case series. Even so, information from exploratory and uncontrolled trials can be clinically important for generating future hypotheses and for documenting potential harms and preliminary efficacy data. Despite supporting registration of results from all hypothesis testing trials of market approved drugs, the pharmaceutical industry has offered to report results from early exploratory trials only if they are deemed to be medically important.[11 15] This is, however, no different from what happens now with exploratory trials. The conflict between disclosure and commercial or other interests must be avoided by mandating registration for all trials on approved and unapproved interventions; voluntary disclosure is inherently subjective.

Timing of public release of protocol information

"The public should have cost-free access to the Unique ID, minimum protocol items, and consent forms prior to participant enrolment. Registered amendments should be made publicly available as they occur."

Concerns have been raised over the public release of commercially sensitive information and intellectual property contained in trial protocols, such as trade secrets and novel methods or hypotheses. Competitors could use registered information to their advantage. Likewise, other academic researchers could use detailed protocol information to complete and publish a similar study earlier.

However, details of the trial have to be publicly available before recruitment to fully inform potential participants about the nature of the study. Protection of trade secrets can be a legitimate concern, but detailed pipeline information on interventions and research from the preclinical phase to the market phase is already available through various subscription websites.[16–18] Thus, public release of protocol information does not pose a new threat to commercial interests. Furthermore, specific details about an intervention's design properties need not necessarily be registered, so trade secrets would be uncompromised. With regards to protecting novel ideas, protocol

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Summary points

Registration and early public release of accurate information about all trials is necessary to fulfil an ethical obligation to participants

Although protection of commercial and other interests is important, the social contract with participants should take precedence

All trial results should be registered and publicly available, along with sufficient protocol information to enable critical assessment of their validity

The Ottawa Group will continue to foster international dialogue on the principles of trial registration and their implementation

registration will establish a form of intellectual property by publicly documenting methods and their date of registration.

Registering unpublished results

"At a minimum, results for outcomes and analyses specified in the protocol (as approved by the institutional review boards/independent ethics committees), as well as data on harms, should be registered regardless of whether or not they are published."

Much debate has focused on the use of unpublished results that are not peer reviewed.[19 20] If such results are produced with incorrect analyses or biased methods, they may be inappropriately interpreted and applied. Therefore, when citing registered results, it is important to continue to draw a distinction between peer reviewed and non-peer reviewed data. As an additional safeguard against potential misuse of invalid registered results, the public availability of protocol details in the register will enable critical appraisal of trials' methods and analyses. Finally, we should, of course, remember that peer review is not infallible and does not in itself guarantee validity.[21 22]

Next steps

We now have the opportunity to shape the transition to a new framework of health research based on transparency, full disclosure, and collaboration. In the coming year, the evolving Ottawa Group (currently consisting of over 80 individuals and organisations from five continents) will continue to consult broadly about the most effective and practical ways to enact these principles in a coordinated fashion worldwide.

Difficult decisions will have to be made related to timely and feasible implementation of the principles. Those who wish to contribute further to the Ottawa statement are invited to become involved (www.ottawagroup.ohri.ca). The group will meet in Portland, US, on 22 May 2005 during the 26th annual meeting of the Society for Clinical Trials to discuss how these principles can be put into practice.

Already, a group assembled by the World Health Organisation to guide development of global trial registration[23] has used an earlier draft of the statement to shape its plans. We encourage other stakeholders to do the same and contribute to public discussion of this important issue.

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