

## **Report to the World Health Organization (WHO) on a Plan for International Registration of Controlled Trials**

### **Draft**

This document represents a **draft** of a position paper on this topic. It is a **work-in-progress** and aims to signal the important issues related to the topic. We emphasize that the final document will be developed based on perspectives, comments and suggestions from the various regional consultations to enable critical inputs from regional and country perspectives to be included in the final version.

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### **The need for registers of controlled trials of healthcare interventions**

Doctors and others increasingly turn to practice guidelines for help with diagnosis, prevention, and treatment decisions. Systematic reviews using results from well-conducted controlled trials often provide the most reliable evidence about the effects of healthcare interventions and thus provide crucially important information for guideline development. Systematic reviews represent a summary of effects and effect variation across all relevant research, typically randomized trials, the “gold standard” study design for determining efficacy. Some trial results are not easily accessed, however, either because they have never been published, or because they have been published in sources not generally available or searchable. Because negative results are less likely to be accessible (“publication bias”), the validity and reliability of systematic reviews is threatened. To assure that systematic reviews are unbiased, or at least that the potential for bias can be estimated, the existence of all controlled trials of healthcare interventions should be known.

There are additional compelling reasons to make information about all initiated trials available. When patients and their health care providers know about trials that are open for enrollment, they will be more likely to participate, which in turn will increase the pace at which medical knowledge advances. Current ethical concerns about unpublished research would be addressed as well. Consent forms signed by those who participate in clinical trials usually state that study participants will be contributing to medical knowledge. But if the study results are never made public, no knowledge is gained. Moreover, studies sponsored by industry are more likely than studies with government or other funders to remain unpublished when results are negative, even though industry is gaining financially from public participation. Making the existence of all initiated trials public would allow assessment of the size of the problem, if any, of unpublished findings for a given health question. It would also draw attention to unpublished trials and would

provide indirect pressure to disseminate study findings.

Individuals in academic institutions have long exerted pressure on governments and others to “register” all initiated trials, so that they could be accessed “centrally” (that is, using a single entry portal). Under such a system, the existence of all trials would be known, even if the results were not published or otherwise accessible. The European Science Foundation and others have endorsed registration of all controlled clinical trials, encouraging an international approach to solving the problem. The willingness to work collectively on trials registration is exemplified by the widespread support for the International Standardized Randomized Controlled Trial Number (ISRCTN) assigned by *Current Controlled Trials* to individual studies. The ISRCTN, comparable to the International Standardized Book Number (ISBN) for books, is used to ensure that there is no confusion in identification of individual, stand-alone trials.

Arguments supporting trials registration, use of the ISRCTN, and the need for individual and collective action are detailed in Appendices 1 and 2.

### **A role for the World Health Organization (WHO) in controlled trial registration**

Many small registers of controlled trials have been developed over the years, by public and private groups, but none is comprehensive. Larger registers, such as [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) in the United States, have been developed by governments to alert the public to the clinical trials they fund. *Current Controlled Trials* has developed a ‘metaRegister’ which combines the contents of many of the existing registers, yet it too is inevitably far from comprehensive since coverage by contributing registers is incomplete.

An institution with international authority is needed to promote ‘central’ access to information on all controlled trials and to ensure that each trial has a unique registration number. WHO is the natural leader for such an effort.

On October 7, 2003, a roundtable discussion about WHO’s role in global health research was held at London School of Hygiene and Tropical Medicine (see Appendix 3). Participants included Dr. Jong-Wook Lee, Director General, Dr. Tikki Pang, and Dr. Tim Evans from WHO, as well as key UK-based research investigators, funders, and biomedical journal editors. There was consensus that WHO should take a leadership role in research to strengthen health systems and promote knowledge access and sharing. With regard to issues related to registers of controlled trials, it was recommended that WHO (1) set guidelines for the need for systematic reviews prior to primary research; (2) reaffirm the importance of publishing all results, not just positive ones; and (3) take steps to establish a ‘central’<sup>1</sup> register of trials.

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Note that the notion of a ‘central’ register here and elsewhere in this document refers to a central

As a result of the October 2003 meeting, a Task Force on Knowledge Access and Sharing was formed to brainstorm and suggest the roles WHO could play in the area of a global clinical trials register, and two other areas – improved/'open' access to health and health research information, and the idea of a health research funders' forum with the goal of contributing on these topics to the World Report on Knowledge for Better Health, and to the Mexico Summit on Health Research, November 16-20, 2004. It was agreed that short term plans should aim for a global impact by the end of 2004. The Task Force met for the first time in London on December 8-9, 2003 (see Appendix 4), and recommended the following roles for WHO:

1. WHO should promote an international agenda to capture all controlled trials in a global register and this is a critical priority. WHO is in an excellent position to provide leadership and promote international ownership of the concept. WHO can act as an honest and independent broker and convene a collaborative participatory group of interested parties to develop the concept further.
2. WHO should lend its legal authority to ensure success of the endeavor. Possible instruments available to take this forward include the World Health Assembly resolutions, codes, regulations (eg, international health regulations), framework conventions (eg, the Framework Convention on Tobacco Control), or conventions.
3. A single repository at WHO of all trials should not be the goal at this point. Rather, WHO should play the role of gatekeeper in a trials register network and facilitate communication between 'nodes' (agencies housing individual trials registers). Nodes will agree on a common set of standards and information for the combined trials register. As noted earlier, the 'centralized' register will be a combined register of other registers, but in a dynamic not static sense, existing virtually and not residing in a single place.
4. Initial focus should be on a minimum data set for each register, and an ISRCTN, to be administered centrally through WHO. The originating nodes/agencies should be responsible for updating their registers and for providing more detailed information, if desired.

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compilation of registers that depends on computer systems and networks of actual registers, not any 'real' place where all registers are located. That is, individual registers with similar data structures will be joined in a 'register' defined by the user who is searching the register, say for all ongoing trials of treatment of HIV/AIDS.



5. WHO should ensure that the trials it sponsors are registered before taking on global advocacy.

Action items:

- Set example by registering WHO trials
- Develop a 'white' or position paper on issues related to development of the clinical trials register
- Convene a meeting with major funders to present the ideas and proposal for concrete action
- Form a collaborative participatory group to develop and implement key ideas.

### **What needs to be done next**

Both short and long term plans should be developed. For reasons of time, the short term plans should largely be pursued within WHO and must be completed by the November 2004 meeting in Mexico. These include:

1. Develop a register of all controlled trials supported by WHO, using assigned ISRCTNs. This will serve to increase knowledge within WHO about what is required by such efforts, and will increase the persuasiveness of any recommendations or requirements instituted by WHO in respect of its member states.
2. Publish of an article outlining WHO's plans for a centralized trials register, in the *WHO Bulletin* if possible, with concurrent publication of an editorial in the *Lancet*,
3. Develop a prototype showing how a trials register can be useful to multiple end users (eg, health professionals, researchers, funders and consumers). Several possibilities exist, for example, (1) the WHO Reproductive Health Library could be supplemented with a trials register of reproductive trials, and (2) following the Reproductive Health Library model, a WHO Vaccines Library could be developed showcasing the WHO Vaccines Trial Registry, perhaps merged with trials identified by the Cochrane Vaccine Field, and including systematic reviews and other potentially useful information.

Longer term plans will depend on the advice of a collaborative participatory group ('Trial Registration Advisory Group'), to be convened by WHO. The Advisory Group should have broad representation from leaders at WHO as well as other stakeholders, including researchers, journal editors, funders, practitioners, and consumers. Members should include those with experience and knowledge related to trials registers as well as those who support the objectives

but have little direct knowledge. Together they should represent a diverse group of countries and constituencies. Representation from developing countries is particularly important.

The proposed Trial Registration Advisory Group should be small enough to be nimble and move quickly, yet large enough to ensure that its advice will be respected and acted on. One way to achieve this would be to convene a small Advisory Group (about 10 representatives, both men and women, from diverse constituencies, such as developing and developed countries) and several working groups. The working groups would be chaired by Trials Registration Advisory Group members but would also include other members as needed.

For example, the Trial Registration Advisory Group could choose to convene the following working groups, among others:

- A funders' forum to decide on the mechanism for supporting the WHO trials register and to approach potential partners
- A group to make policy and oversee implementation regarding the unique numbering scheme for trial registration
- A group to agree on the minimal dataset for registers
- A group to provide advice on methods for ensuring broad compliance with registration by participating countries
- A design team to work with computer systems experts to implement the 'virtual' register of individual participating registers.
- A group to evaluate the most appropriate regulatory/'legal' instrument

The Trial Registration Advisory Group should be convened as early as possible in the Project planning process. Because of the time it typically takes to convene expert groups, it is unlikely they will be able to provide collective advice on the short term objectives listed here. Individuals can be consulted by WHO, however, before the first Advisory group meeting.

To be able to move expeditiously, the Trial Registration Advisory Group would initially meet by telephone and in person at least quarterly. Working groups would have their own schedule of meetings. The chair of the Trial Registration Advisory Group would work closely with a team at WHO, over at the least the initial five years of the project. A project timeline with benchmarks should be drafted by the chair and WHO before the first Advisory Group meeting, and this should be endorsed (with modifications, as needed) by the Group at their first meeting. The timeline should be reviewed periodically and amended if necessary.

## Specific recommendations

Although the details of the Project should be worked out by WHO in conjunction with the Trial Registration Advisory Group, I have specific recommendations on the following:

- The types of trials to be included in the WHO register
- The unique trial numbering system
- The organizing principle for the 'centralized' trials register
- The responsibility for trial registration and updating
- The minimal dataset.

The WHO trials register will include controlled trials in which:

the individuals or other units followed in the trial were assigned prospectively and in parallel to one of two or more forms of healthcare using random allocation or other method designed to reduce bias in the intervention assignment.

This definition was selected to omit single group trials and others performed in the early stages of drug or device development (that is, phase I and some phase II studies), about which privacy for proprietary reasons is understandable.

A unique numbering system for individual trials will be the backbone of the WHO register. Without it, it will not be possible to identify trials appearing in multiple registers. The existing ISRCTN system is appealing in that it has been used successfully by trialists in several countries. If the WHO register extends its scope beyond randomized trials, as I recommend, and the ISRCTN system were to be used, entry criteria would need to be expanded and perhaps the name amended, to reflect the eligibility criteria.

As noted earlier, the overarching concept for the WHO register is that it should represent a 'centralized', but virtual, compilation of registers.

Assuring that all trials are registered and assigned an internationally unique trial number, and that individual trials registers are kept updated will not be WHO's responsibility. Rather it will be the responsibility of the member countries contributing registers. Some countries will use the legal system to mandate centralized trial registration (for example legislation similar to that used in the United States to require registration of HIV/AIDS trials and trials of serious and life threatening diseases). Others will rely on regulations that mandate registration through ethics committees (as seen in Germany and the Netherlands). Other countries will need to implement new systems for registration, depending on local practice, resources, and existing systems.

Standardized information about each trial included in the register should be the smallest amount deemed necessary for a trial's identification ('the minimal dataset'). Existing models for a minimal dataset are in use by *Current Controlled Trials* and ClinicalTrials.gov, among others, and should be consulted as a starting point by the Advisory Group.

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