

INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM

***1st Meeting of the Advisory Group on Clinical Trial Registration and Reporting
Geneva, Switzerland, 4-5 November 2009***

Meeting Report

Note:

- This report summarises the discussions and advice of the ICTRP's Advisory Group on Clinical Trial Registration and Reporting
- A variety of views were expressed on the topics discussed.
- Formal policies of the ICTRP may differ from those stated here
- Please refer to the ICTRP web site for definitive policies (www.who.int/ictip)

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AGCTRR Terms of Reference

The Terms of Reference of the AGCTRR are:

- To advise on the strategic direction of the ICTRP
- To advise the ICTRP on scientific and technical issues relating to clinical trial registration and reporting
- To advise the ICTRP on the criteria by which a clinical trial registry will be deemed to be assigned the status of WHO Primary Registry
- To advise the ICTRP on the WHO trial registration data set
- To advise the ICTRP on other issues relating to clinical trial registration and reporting

These terms of reference will primarily be achieved electronically by email and teleconference. If the situation warrants it, and resources are available, one face-to-face meeting per year may be held. If held, this meeting will usually take place at WHO Headquarters in Geneva, Switzerland.

1. Reporting Structure

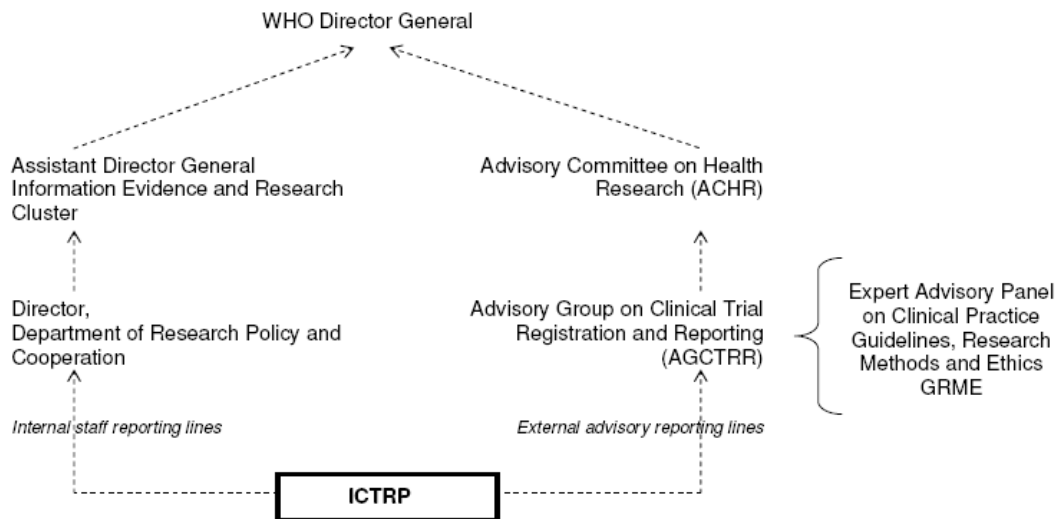
The AGCTRR will report to the WHO Advisory Committee on Health Research (ACHR) which in turn reports to the Director General. It will also report annually through the Expert Panel on Guidelines Research Methods and Ethics (GRME) to the Executive Board. See Appendix 1: Expert Advisory Panel on Clinical Practice Guidelines and Research Methods and Ethics (GRME).

IER/RPC/ICTRP will serve as the Secretariat of the AGCTRR.

2. Criteria for the Selection of Members

Members will be drawn from the GRME. Membership of the AGCTRR is at the invitation of the ICTRP Secretariat. All reasonable efforts will be made to achieve regional balance, gender balance and an appropriate mix of relevant expertise.

- The number of members will be 9-11
- The term of membership will be one year. More than one term may be served.
- The AGCTRR will make recommendations but the authority for final decisions remains with WHO.
- Communication will primarily be by email .
- Meetings will take place by teleconference. It is expected that 3-4 teleconferences will be held each year.
- If necessary, one face-to-face meeting may be held each year.



Participants

Note: Region in parentheses (); Members of previous ICTRP Scientific Advisory Group marked with *

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Report

1. The quality of registered data

The meeting started with a presentation by the ICTRP Secretariat, summarizing the quality issues that have been raised by both an ICTRP evaluation and other evaluations of registered data, some of which have been published elsewhere (see Table 1).

The ICTRP's study examined a random 5% sample of records of clinical trials registered between 17 June 2008 and 17 June 2009 on the ICTRP database. Each record was assessed for the presence of contact information, the presence of intervention specifics in drug trials, and the quality of primary and secondary outcome reporting. The study found that, although key data fields may be populated with data, the quality of many of these entries remains problematic. Contact information is frequently absent, less than 1/3 of scientific titles contain all elements of PICO (Patient/population, intervention, comparison, outcome), specific details on interventions are complete in less than half of intervention arms, and frequently, study design descriptions contradict themselves.

The potential benefits of clinical trials registration as related to prevention of publication bias, prevention of selective reporting, and promoting transparency in clinical trials, is undermined by these deficiencies. Potential solutions to address these deficiencies are;

- Clarification of explanatory text in The trial registration data set
- Quality control measures and data recording practices at registries (see separate document: Draft International Standards for Clinical Trial Registries)
- Encouraging enforcement of policies of external organizations on trial registration (eg ICMJE)

Table 1: Manuscripts relevant to the quality of registered data

Appendix 3: CONSORT statement guidance notes
Ottawa Statement on Trial Registration
Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM, 2009. Trial Publication after Registration in ClinicalTrials.gov. A cross-sectional analysis . PLoS Med 6(9): e1000144. doi:10.1371/journal.pmed.1000144
Scherer M, Trelle S. Opinions on registering trial details: a survey of academic researchers . BMC Health Serv Res. 2008 Jan 23;8:18.
Scoggins JF, Patrick DL. The use of patient-reported outcomes instruments in registered clinical trials: Evidence from ClinicalTrials.gov . Contemporary Clinical Trials, V30 (14), 289-292, 2009.
Sekeres M, Gold JL, Chan A-W, Lexchin J, Moher D, et al. 2008 Poor Reporting of Scientific Leadership Information in Clinical Trial Registers . PLoS ONE 3(2): e1610. doi:10.1371/journal.pone.0001610
The Sixth International Congress on Peer Review and Biomedical Publication . September 10-12, 2009. Vancouver, BC, Canada. Abstracts by: <ul style="list-style-type: none"> • Zarin DA, Tse T, Williams RJ: Frequency and nature of changes in peer review outcome measures • Reveiz L et al: Trial registration can be a useful source of information for quality assessment • Huic M et al: Registration Completeness and Changes of Registered Data From ClinicalTrials.gov for Clinical Trials Published in ICMJE Journals After September 2005 Deadline for Mandatory Trial Registration • Scherer et al: Is Protocol Information Recorded in ClinicalTrials.gov Useful for Systematic Reviewers Relying on Conference Abstracts?
Viergever R and Ghersi D. The quality of data on the ICTRP Search Portal of the World Health Organization. Draft manuscript.
Wise J. International trials registry is missing important information, study finds . BMJ 2009;339:b3627

2. The trial registration data set

The poor data quality could be partially related to lack of clarity in the explanatory text for each data item in the WHO Trial Registration Data Set (TRDS). It was therefore agreed that amendments to and clarification of this wording be made. The amended text is documented in Appendix 2: Updated Trial Registration Data Set.

Remarks and AGCTRR recommendations for selected TRDS items

2.0. TRDS 2: Date of registration

Several studies have observed that for a significant number of trials the registration date is later than the trial start date, with median delays of four months (ANZCTR, personal communication) to 10 months (ICTRP study), and in some circumstances by years (Zarin 2009). There is also a need to clarify the date of registration when records on a WHO Partner Registry are included on a WHO Primary Registry.

The AGCTRR recommended that:

- i. The ICTRP continue to monitor this data item to assess if the situation improves or gets worse over time
- ii. When a trial record is uploaded by a WHO Partner Registry onto the database of a WHO Primary Registry, the date of registration should be considered to be the date the trial was registered on the WHO Primary Registry.
 - i. In such cases, the WHO Primary Registry should display both the date of registration in the Primary Registry as well as the date of registration on the Partner Registry.

2.1. TRDS 5: Primary Sponsor

Compliance with completion of this field has improved. In 2005, 8% of records did not identify sponsorship (FDAMA 113 implementation report 2005). All but 1 of 731 records evaluated by the ICTRP provided a sponsor name.

2.2. TRDS 7: Contact for Public Queries

The public and research community must be able to contact persons with general or scientific queries. Several studies have found that email addresses are missing or invalid in up to 61% of records of industry-funded trials (Sekeres 2008, ICTRP study) and 13-29% of other trials (Scherer 2008, Sekeres 2008, ICTRP).

The ICTRP found that telephone numbers were present in less than half of industry sponsored trial records and in approximately 75% of non-industry sponsored trial records.

The AGCTRR recommended that:

- i. All three types of contact details should be registered for the contact for public queries (postal address, email address and telephone number).
- ii. As email addresses frequently change registrants must provide a postal address for the contact for public queries.
- iii. In circumstances where there may be a risk of undue harassment if an individual's name or contact information is publicly disclosed the contact details should be recorded on the registry but not made publicly available.
 - Assessment of the potential risk should be on a case-by-case basis at the discretion of the registry

2.3. TRDS 8: Contact for Scientific Queries

Sekeres et al reported that a Principal Investigator (PI) is not named in the registered records of up to 59% of industry funded trials and 6% of non-industry funded trials (Sekeres 2008). The ICTRP evaluation found that no name at all was documented in 46% of industry funded trials and 6% of non-industry funded trials. Ross et al reported that the name of a PI was absent in 37% of records (Ross 2009).

It has been suggested that scientific leadership should be identified in registered records of clinical trials, for reasons of accountability and transparency (Sekeres et al 2008), although others argue that difficulties with keeping contact names up to date may lead to outdated entries.

The AGCTRR recommended that:

- i. The "contact for scientific queries" has two elements: scientific leadership and scientific contact details. Both should be reported when the trial is registered.
- ii. Scientific leadership should always be identified in registered records of clinical trials, for reasons of accountability and transparency. There should therefore be clearly assigned responsibility for scientific leadership to a named Principal Investigator (PI).
- iii. The PI should be named, and their affiliation and contact details documented, when a trial is registered. This information should be kept up to date.
- iv. ClinicalTrials.gov defines principal investigator (PI) as "the individual who is responsible and accountable for conducting the clinical trial. The PI assumes full responsibility for the treatment and evaluation of human subjects, and for the integrity of the research data and results."
(<http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf>) The ICTRP will adopt this definition.
- v. The PI is ultimately responsible for all aspects of the clinical trial and the record of its registration.
- vi. In circumstances where there may be a risk of undue harassment if an individual's name or contact information is publicly disclosed the contact details should be recorded on the registry but not made publicly available.
 - i. Assessment of the potential risk should be on a case-by-case basis at the discretion of the registry
- vii. The PI may delegate responsibility for dealing with scientific enquiries to a scientific contact for the trial. This scientific contact will be listed in addition to the PI.
- viii. The details for the scientific contact should include email address, postal address and telephone number. The details for the scientific contact may be generic (that is, there does not need to be a named individual): eg a generic email address for research team members qualified to answer scientific queries.
- ix. As email addresses frequently change registrants must provide a postal address for the contact for scientific queries.
- x. The PI remains responsible for the accuracy of registered information and responses to scientific queries.

2.4. TRDS 10: Scientific Title

Two studies have shown deficiencies in scientific title reporting. Huic (2009) reported that 17% of records lacked a scientific title at the time of registration. The ICTRP study found that 4% of records lack a scientific title and all PICO elements (Patient / Population, Intervention, Comparison intervention and Outcome: see <http://www.cebm.net/?o=1036>) were reported in 30% of records.

The AGCTRR recommended that:

- i. It is desirable that the scientific title contain all elements of PICO.
- ii. Information on PICO should be available via the ICTRP website.

2.5. TRDS 12: Health Condition(s) or Problem(s) Studied

This field is reported in "nearly" 100% of records reviewed (Ross 2009).

The AGCTRR recommended that:

- i. Health condition and population studied (TRDS item 14) be listed sequentially on the TRDS page of the ICTRP web site.
- ii. In the case of prevention studies, the potential condition for which the drug/intervention is being developed should be named as the condition. For example, in a trial of Vitamin C for the prevention of the common cold: the condition is "the common cold"
- iii. The ICTRP investigate the need to provide additional guidance on how to indicated the condition or problem studied:
 - a. In Phase I trials
 - b. For trials of public health interventions

2.6. TRDS 13: Interventions

In 2005, nine to ten percent of records provided an incomplete or nonspecific description of the intervention name (FDAMA 2005, Zarin 2005). Although this has decreased to less than two or three percent (Zarin 2005, Huic 2009, Ross 2009, ICTRP) the meaningfulness of the data provided is less certain. The ICTRP study found that in drug trials, for example, fewer than 50% of intervention arms provide information on drug name, dose, frequency, route of administration, and duration of treatment.

The AGCTRR recommended that ICTRP adopt the explanatory text for intervention as documented in Appendix 2: Updated Trial Registration Data Set

2.7. Key Inclusion and Exclusion Criteria

Studies have found that this data field is completed in at least 97% of records (Huic 2009, Ross 2009) but information may be inadequate (as found in 19% of records reviewed by Reveiz 2009).

The AGCTRR recommended that:

- i. The consideration of the equity of trials will require further consultation.
- ii. The term "sex" should be used, not "gender"

2.8. TRDS 15: Study Type

Although study type is reported most in records of registered clinical trials (Ross 2009, Huic 2009), the ICTRP found evidence of contradictory study type descriptions in 9% of records as well as missing information, such as phase of study in drug trials, in 16% of records.

The AGCTRR recommended that:

- i. ICTRP adopt the explanatory text for Study Type as documented in Appendix 2: Updated Trial Registration Data Set
- ii. That registries should collect information on study type in accordance with the description in Appendix 2: Updated Trial Registration Data Set
- iii. For randomized trials, method of allocation concealment and sequence generation should specifically be requested at the time of registration

2.9. TRDS 17: Target Sample Size

Studies of clinical trial registration data have found varying numbers of trials reporting target sample size, ranging from 37% of trials (Huic 2009) to 18% (Ross 2009), or 1.5% (ICTRP).

2.10. TRDS 19: Primary Outcome(s) and TRDS 20: Key Secondary Outcomes
Primary outcomes with a specific measure and a meaningful time frame are registered in only 31-35% of records (Zarin 2005, ICTRP study). The specific instrument used for outcome measurement was reported in 41% of records reviewed by Scoggins (2009).

Up to 80% of records report secondary outcomes at the time of initial trial registration (Huic 2009, Ross 2009, ICTRP study). However, this reporting is considered adequate in a smaller percentage of records (46% of records reviewed by Reveiz 2009 and 32.3% by ICTRP study).

The AGCTRR recommended that:

- i. Registries be encouraged to implement quality control mechanisms so that more meaningful information on outcomes is registered

2.11. Proposed additional TRDS items

The AGCTRR recommended that no new items be added to the TRDS at this point in time. The following data items may, however, be collected and displayed by individual registries on a voluntary basis. Pilot testing of each of these data items is recommended. Consideration may be given at a future date to making these or other items mandatory.

- i. Lay summaries
- ii. Approvals (including ethics committees and regulatory authorities that have approved the study). A registry may choose to collect a date, a "decision type" (for example, approved, conditional approval, rejection) and a reason for the decision.
- iii. Link to study protocol
- iv. Link to study reports or results

3. The trial registration updating data set

The ICTRP requires WHO Primary Registries to "Endeavour to keep registered information up-to-date". While some fields may be changed during the course of a trial (eg the addition of an outcome; an amendment to the eligibility criteria), there are others that we would expect should be updated on a regular basis.

WHO Primary Registries are also required to "Maintain a publicly accessible audit trail so changes made to the [WHO Trial Registration Data Set](#) for an individual trial can be tracked". All new registries will be required to have this in place before they can become a WHO Primary Registry. Of the existing WHO Primary Registries and Data Providers very few currently have functioning, publicly accessible audit trails in place. The aim is for all registries to have these in place in some form by the end of 2010.

The AGCTRR appreciate the need to balance the requirements for information to maintain transparency in research with the efforts required of registers to maintain audit trails.

The AGCTRR recommended that:

- As a minimum, the following TRDS data items be kept up to date by registries
 - All contact information
 - Recruitment status
 - Countries of recruitment
- If trial was registered before recruitment of the first participant, the actual date of enrolment of the first participant should be recorded when the record is updated.
- Updates should occur at least once each year
- Amendments to registered data must be "trackable" using the registry's audit trail.

4. Issues relating to the Registry Network

WHO Primary Registries meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration. WHO Primary Registries meet the requirements of the [ICMJE](#). The current criteria for WHO Primary Registries are in Appendix 4: WHO Registry Criteria.

WHO Partner Registries meet the same criteria as WHO Primary Registries (ie for content, quality and validity, etc) except they do not need to:

- Have a national or regional remit or the support of government
- Be managed by a not-for-profit agency
- Be open to all prospective registrants (eg, they may be limited to trials in a particular condition or intervention)

From 1 October 2008, all Partner Registries must also be affiliated with either a WHO Primary Registry or an ICMJE approved registry. It is the responsibility of WHO Primary Registries to ensure that their Partner Registries meet [WHO Registry Criteria](#). Partner Registries are becoming more common and now exist in Germany, China and Australia.

Depending on available resources, the intention is to audit registries to ascertain compliance with these criteria and standards. Compliance is currently assessed based on self-report and telephone interview. WHO Primary Registries are now advised that their status is dependent on continuing compliance with the criteria, which will include the need to comply with the International Standards once they have been finalized.

The AGCTRR recommended that:

- The importance of maintaining compliance with WHO Registry requirements be emphasized.
- Primary and Partner Registries that cease to comply with WHO criteria be placed on a time limited probation (suggested time frame of six months). If after this probation period a register remains non-compliant then their status as a WHO Primary Registry should be withdrawn.
- If a registry is on probation then this should be indicated on the ICTRP's web site.

5. Issues relating to language

One of the reasons countries give for wanting to establish a register in their country is the desire to make information about clinical trials available in the language(s) used in that country. As a result, many of the new registries are at least bilingual, including:

- ChiCTR (Chinese Clinical Trials Registry: English and Chinese)
- German Clinical Trials Registry (English and German)
- Iranian Registry of Clinical Trials (English and Farsi)
- The Netherlands National Trial Register (English and Dutch)
- The Japanese Registry Network (English and Japanese)

One of the issues in dual language registries relates to translation. For most registries the process is that, if possible, the registrant should submit the data in both languages. If they are unable to do so then the registry will translate the submission into English. This raises the potential for errors and the International Standards for Clinical Trial Registration need to include standards for checking the accuracy of translation.

The AGCTRR recommended that:

- If a trial is registered in more than one language then the ICTRP Search Portal should import and display the scientific title in both languages.
 - the title in the additional language should be displayed with the language itself being identified at the end.

Example: *Titel van klinische trial (Nederlands/Dutch)*

- When clinical trials are first registered in a language other than English registries should acknowledge this. For example: This data was submitted to the registry in *<language x>* and translated into English by *<the registry / the registrant>*.

6. Reporting the findings of clinical trials

The ICTRP Secretariat presented a summary of the results of a survey "Reporting the Findings of Clinical Trials" presented by the ICTRP Secretariat. There were 562 unique responses, 84 of which were on behalf of an organization. Responses were received from 53 countries and all 6 WHO regions were represented. 99% of responders (including 83 of the 84 organizations) agree with the position of the members of the WHO Registry Platform Working Group on the Reporting of Findings of Clinical Trials that "the findings of all clinical trials must be made publicly available". 84% of all responders indicated that WHO should provide leadership by facilitating the development of international standards for reporting the findings of clinical trials. The need for a globally accepted standard was recognized, as was the need to collaborate with relevant stakeholders including the International Conference on Harmonization (ICH) and CONSORT (Consolidated Standards for Reporting Trials).

In addition, the AGCTRR considered:

1. The requirements of the FDA Amendment Act in the US (see <http://prsinfo.clinicaltrials.gov/fdaaa.html>)
2. Data repositories being established by various agencies.
 - a. Eg DataCite - International Initiative to Facilitate Access to Research Data (<http://www.datacite.org/>). "The goal of this cooperation is to establish a not-for-profit agency that enables organisations to register research datasets and assign persistent identifiers to them, so that research datasets can be handled as independent, citable, unique scientific objects."
3. The ICJME acknowledgement that reporting of results on a registry's website either to comply with local requirements or in the form of an abstract, 500 words or less, does not constitute prior reporting and will not preclude subsequent publication.
4. Submission made by GlaxoSmithKline (see Appendix 5: Submission made by GlaxoSmithKline)

The AGCTRR recommended that:

- Considering the limited resources available to the ICTRP it should consider not including results reporting on its agenda at this point in time.
- The ICTRP consider facilitating discussion and debate on the issues in this evolving area, taking advantage of technology such as email list serves, scientific blogs, networks and similar.

7. Registration of observational studies

The number of voices advocating in favour of the registration of observational studies (including systematic reviews) is increasing. Many clinical trial registries accept observational studies and, in addition, a number of registers of systematic reviews have been established (completed reviews and review protocols). These include:

- Cochrane Collaboration (Cochrane Database of Systematic Reviews accessible on the Cochrane Library: <http://www.thecochranelibrary.com>)
- Campbell Collaboration (The Campbell Library: <http://www.campbellcollaboration.org/library.php>)
- All Wales Systematic Reviews Register: <http://www.wales.nhs.uk/sites3/page.cfm?orgId=719&pid=22819>
- Registry of Systematic Reviews of Disability and Rehabilitation Research: <http://www.ncddr.org/systematicregistry/about.html>
- Southwest Educational Development Laboratory: <http://www.sedl.org/pubs/catalog/items/dis110.html#>
- Centre for Reviews and Dissemination, York (proposed)

"As any scientific endeavor, an epidemiology study should follow a rigorous scientific process to yield reliable results. A protocol should be available describing the specific hypothesis to be tested, the design, study subject selection, measurement of the risk factor, effect parameter and the statistical analysis that will be carried out. Next, the data collection phase can take place and the statistical analysis can be conducted. All results of the study should be included in the report to be submitted for publication. The report should accurately describe how the study was conducted and should give a detailed description of all the results from the statistical analysis. At this moment it is possible that published articles do not report all study results and the study results can not be weighed against the initial study hypothesis. It is even possible that negative studies are not reported. There is reason to believe that this scientific process is not always maintained and that for instance exploratory analyses are represented as being hypothesis driven. Enhancement of scientific rigor and transparency to observational epidemiological studies will increase their reliability and credibility."

Taken from "[The enhancement of the scientific process and transparency of observational epidemiology studies](#)"

The draft International Standards for Clinical Trial Registries currently state that:

- Registries can choose to register observational studies if they wish, but there is no compulsion to do so.
- There is no recommended standard data set for registering observational studies.

Additional reading

1. Straus S and Moher D. Registering systematic reviews. CMAJ 2009. DOI:10.1503/cmaj.081849
2. STROBE Statement. Strengthening the reporting of observational studies in epidemiology. <http://www.strobe-statement.org/>
3. Stroup DF et al. [Meta-analysis of observational studies in epidemiology](#). JAMA. 2000;283:2008-2012.

Given the increasing interest in the registration of observational studies the ICTRP asked the AGCTRR for advice regarding:

- Should the position apply to all observational studies or a subset (eg systematic reviews)?
- If the ICTRP should support the registration of all or some observational studies, is there a need for an observational studies registration data set?

The AGCTRR advised the ICTRP that:

- It is acknowledged that some clinical trial registries already register observational studies.
- Little (if any) research has been conducted to demonstrate a clear rationale for the ethical, scientific, and moral responsibility to register observational trials.
- At this point in time, mandatory registration of observational trials is not warranted. The possible exception is protocols for systematic reviews.
- The existing WHO trial registration data set (TRDS) is not necessarily applicable or appropriate for observational studies.
- There is a need to establish a registration data set for observational studies. This could be facilitated by WHO in collaboration with appropriate stakeholders and experts.
- Attempts to register observational studies should take advantage of the existing clinical trial registries, when possible.

8. *Is there a case for exceptions?*

The ICTRP has been asked by some registries to adjudicate on cases where they have been requests by Responsible Registrants not to make information about their clinical trials publicly available. The reasons given include:

- That registering the trial details could compromise the study
- The law in the country prevents the trial from being publicly registered
 - Eg FDAAA requirement for device trials

The ICTRP currently advises registries that:

- It is ultimately the decision of the registry as to whether the a trial will be registered with information missing or under-reported
- When trials are incompletely registered it is recommended that as much information as possible regarding the decision not to provide pieces of information be publicly documented (eg in a comments field)
- Registrants should be advised that a decision to register the trial with information missing means that it does not meet international requirements for transparency and may result in journals that comply with ICMJE requirements refusing to consider it for publication
- If a registry is prevented by law from making registered information on some trials public (eg device trials on ClinicalTrials.gov) then registrants are advised that they will also need to register the trial on another WHO Primary Registry if they wish to meet ICTRP and ICMJE requirements

The AGCTRR:

- Considered the case studies tabled and agreed that, for none of the cases put forward, was there a case for selective disclosure.
- Could not identify or envision circumstances when registering a trial could compromise the integrity of a trial, or where selective disclosure would be acceptable.
- Registries should not issue waivers to registrants, even if an Ethics Board has approved aspects of non-disclosure within the protocol.
- Reminds peer reviewers and ICJME journals of the need to check trial registry entries as part of the peer review process to ensure that complete, meaningful trial registration has taken place.
- Agreed with the ICTRP's advice that device trials affected by the FDAAA "lock box" requirement be registered on a WHO Primary Registry as well as ClinicalTrials.gov in order to ensure they meet international requirements for transparency.

9. *Miscellaneous issues and other business*

9.0. Endorsements

The ICTRP, and the AGCTRR, is often asked to endorse activities external to WHO. The ICTRP itself is unable to endorse external activities.

The AGCTRR encourages groups interested and engaged in activities relating to trial registration - such as those that could lead to improvements in the quality of clinical trial protocols, and research into publication bias and selective reporting. The AGCTRR, however, is not able to endorse any of these activities.

9.1. Fraud

The AGCTRR discussed the responsibilities of the clinical trial register when made aware of investigations of fraudulent research or when fraudulent activities have occurred.

The AGCTRR recommended that:

- In the circumstance where a PI is under investigation or has been found to commit fraud, an indication in the trial record on a registry is recommended.
- The trial record should be immediately updated if an ethics committee (or IRB or similar) has withdrawn its approval of a trial. In such cases an explanation of the reason for withdrawal of approval should be disclosed on the record in the trial register.

Appendices

Appendix 1: Expert Advisory Panel on Clinical Practice Guidelines and Research Methods and Ethics (GRME)

Objective

To ensure that the Guidelines Review Committee (GRC), Research Ethics Review Committee (ERC) and International Clinical Trials Registry Platform (ICTRP) of WHO receive the best possible technical guidance and support on the methodological and ethical aspects of health research.

Terms of Reference

- Advise on the methodological and ethical aspects of health research.
- Advise on current scientific and technical issues and developments related to the creation and utilization of health research evidence.
- Suggest guidelines for minimum standards for the conduct and reporting of health research and practice guidelines performed by the Organization.
- Provide ad-hoc advice on specific technical and policy issues relevant to the 3 activities when requested by the Organization.
- To strengthen and promote collaboration between WHO and appropriate international and national agencies; such as the Cochrane Collaboration, the CONSORT group, etc.
- Give advice on any other matters relevant to the strategies and activities to be carried out in the context of the objective set out above.

Functions

- The WHO Expert Advisory Panel on Clinical Practice Guidelines and Research Methods and Ethics will be composed of individuals with expertise in the design, conduct, analysis, reporting, synthesis, interpretation, publication, dissemination or implementation of research evidence in health.
- The Panel is being established primarily to support the activities of the WHO Guidelines Review Committee, the WHO Research Ethics Review Committee and the WHO International Clinical Trials Registry Platform.
- Advice will usually be sought and received via email correspondence and/or telephone or teleconference communication.
- Technical Advisory Groups: These will be utilized if and as required as one-off groups to address specific needs.
- Individual Panel members may also be invited to advise other WHO Units or Departments.
- Technical Advisory Groups: These will be utilized if and as required as one-off groups to address specific needs.

Criteria for Selection of Experts

Individuals invited to join the Expert Advisory Panel on Clinical Practice Guidelines and Research Methods and Ethics (GRME) will be scientists of high international standing in the fields of biostatistics, clinical trials, systematic reviews, evidence-based practice guidelines and similar.

They will have:

1. appropriate academic training and relevant experience
2. proven scientific excellence and/or technical excellence in one or more of the abovementioned fields
3. international experience and/or recognition
4. gender balance and geographical distribution
5. balance between established experts and younger promising scientists

Administration

- The Secretariat will be based in the Department of Research Policy and Cooperation (RPC/IER)

About the Functions

WHO Guideline Review Committee (GRC)

In response to concerns about the quality of WHO guidelines, and following up on recommendations by the Advisory Committee on Health Research (ACHR) and resolution EB120.R15 of the 120th Session of the Executive Board it was decided to establish the WHO Guidelines Review Committee (GRC). The GRC is responsible for developing and implementing standards and procedures for guideline development that ensure that WHO guidelines are consistent with internationally accepted best practice, including appropriate use of evidence.

WHO Research Ethics Review Committee (ERC)

The WHO Research Ethics Review Committee, is responsible for reviewing the ethical aspects of WHO supported research proposals involving human participants. The Committee plays an important role in ensuring that WHO supported research is conducted in an ethical manner which respects the rights of research participants and recognizes the responsibilities of researchers.

As stated in the WHO Manual, the ERC's function is "to provide ethical review of research projects involving human participants funded or otherwise supported by WHO and to approve, reject, or modify research proposals submitted to it. The Committee shall be guided by the Declaration of Helsinki, the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, and supplemented by other internationally accepted statements of ethical guidance adopted by the Committee. The Committee may also consider and provide advice to the Organization on any matter of general policy relating to ethical aspects of research involving human participants."

The International Clinical Trials Registry Platform (ICTRP)

In November 2004, at the Ministerial Summit on Health Research, those present called for action by "*All major stakeholders, facilitated by WHO secretariat, to establish a platform linking a network of international clinical trials registers to ensure a single point of access and the unambiguous identification of trials.*" (The Mexico Statement on Health Research). This was further expanded on during the 58th World Health Assembly (WHA 58.34) held on 25th May 2005. The global scientific community, international partners, the private sector, civil society, and other relevant stakeholders were called upon to "establish a voluntary platform to link clinical trials registers in order to ensure a single point of access and the unambiguous identification of trials with a view to enhancing access to information by patients, families, patient groups and others".

ICTRP staff collaborate with stakeholders on the development and implementation of policies and procedures related to improving access to information about clinical trials. This information includes protocol information registered prospectively (before the first participant is recruited) through to reporting the findings of a trial once it has been completed. The ICTRP stakeholders include health care consumers, biomedical journal publishers, ethics review committees, funding agencies, health care policy makers, trial sponsors (including the pharmaceutical and device industries), regulatory agencies and the various trial registries that exist (or are being established) in countries or regions. That is, all those involved in the production and utilization of health research evidence.

The GRC, ERC and ICTRP are all supported administratively by the RPC department in the IER Cluster.

Appendix 2: Updated Trial Registration Data Set

This document can be obtained from the ICTRP web site: www.who.int/ictrp/network/trds

Appendix 3: CONSORT statement guidance notes

This document can be obtained from the CONSORT web site: www.consort-statement.org

Appendix 4: WHO Registry Criteria

Any registry that enters clinical trials into its database prospectively (that is, before the first participant is recruited) and meets the WHO Registry Criteria, or that is working with ICTRP towards meeting these criteria, can be part of the WHO Registry Network.

WHO Primary Registries meet specific for content, quality and validity, accessibility, unique identification, technical capacity and administration. WHO Primary Registries meet the requirements of the ICMJE.

Data Providers are responsible for a database that is used by one or more registries.

- Data Providers provide data to WHO for inclusion in the ICTRP Search Portal.
- The ICTRP will accept trial records from Data Providers if it is satisfied that those trial records have been created and managed in a manner that is consistent with the WHO Registry Criteria.

The following definitions are also available on the ICTRP web site: <http://www.who.int/ictcp/glossary/en/index.html>

Clinical Trial

For the purposes of registration, a clinical trial is 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. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. This definition includes [Phase I to Phase IV trials](#).

Clinical Trial Register

The formal record of an internationally agreed minimum amount of information about a clinical trial ([trial registration data set](#)). This record is usually stored in and managed using a database.

Clinical Trial Registry

The entity that houses the clinical trial register. It is responsible for ensuring the completeness and accuracy of the information the register contains, and that the registered information is used to inform health care decision making.

Application Process

Registries interested in becoming a WHO Primary Registry need to submit a completed Registry Profile. The profile is based on the Requirements for a WHO Primary Registry. The profile is evaluated and the WHO ICTRP Secretariat contact the applicants to seek clarification and obtain more detailed information on technical issues, if required. When all issues have been addressed to the satisfaction of the ICTRP Secretariat, and the Registry is considered eligible to become a WHO Primary Registry, a Request to Consider Establishing a WHO Primary Registry is submitted to the Assistant Director General (ADG) of the Information, Evidence and Research (IER) Cluster.

Applicants are informed of the result of the request to the ADG in writing. If applications are rejected, or a decision is deferred, an explanation is given to the applicants.

WHO Registry Criteria (Version 2.1, April 2009)

Content

- Accept prospective registration of interventional clinical trials submitted by Responsible Registrants.
- Be open to all prospective registrants (ICMJE)
- Be able to collect and publicly display the WHO Trial Registration Data Set (ICMJE)
- Endeavour to keep registered information up-to-date.
- Never remove a trial once it has been registered.

Quality and Validity

- Have a mechanism in place to ensure the validity of the registered data (ICMJE)
- Maintain a publicly accessible audit trail so changes made to the WHO Trial Registration Data Set for an individual trial can be tracked.
- Participate in the development of the International Standards for Clinical Trials Registries

Accessibility

The WHO Trial Registration Data Set for all registered trials will:

- Be accessible to the public at no charge (ICMJE)
- Be electronically searchable (ICMJE)
- Be available in English

Unique Identification

- Have in place processes to prevent the registration of a single trial more than once on their register
- Facilitate the retrospective linking (or bridging) on the WHO Search Portal of a single trial registered with more than one registry by entering secondary identifiers. This includes the UTRN, and the unique identifiers allocated by other WHO Primary Registries.

Technical Capacity

- Submit the WHO Trial Registration Data Set for all records on their registry, in English, to the Central Repository.
- Have access to a database that is used to store and manage the submitted data.
- Be able to demonstrate that they have access to adequate information technology support.
- Have adequate security and other provisions against data corruption/loss, including but not limited to a backup server and database.

Administration and Governance

- Have at least a national remit, and the support of government within the country (or region) to act as the Primary Registry for that country (or region).
- Publicly disclose ownership, governance structure and not-for-profit status.
- Be managed by a not-for-profit agency (ICMJE)
- Should a register cease to function the register agrees that at least the WHO Trial Registration Data Set (original and updated) for all trial records will be transferred to a Primary Register or appropriate alternative.

Appendix 5: Submission made by GlaxoSmithKline

**Items for Consideration by the World Health Organization
Advisory Group on Clinical Trial Registration and Reporting (AGCTRR)
From GlaxoSmithKline (GSK)
October 2009**

Introduction

Prescribing information provides the authoritative, interpretation of the large and complex sets of data from clinical development programs and must continue to guide appropriate use of medicines. Clinical trial results registers and databases can, however, can provide a valuable additional channel for the public disclosure of clinical trial results to supplement information in the scientific literature and prescribing information. Public disclosure via the registration of results ensures that results are in the public domain whether or not they are accepted for publication. GlaxoSmithKline has pioneered these registers – we were the first company to launch an internet-based clinical trial results repository providing result summaries from all our clinical trials of marketed medicines.

By comparison with protocol registration, the challenges associated with universal public disclosure of trial results through study results databases are more complex by many orders of magnitude, and depend upon a careful understanding of the intended audience(s) with the recognition that the findings of clinical research are inherently complex in nature.

As clinical research transparency continues to evolve, a number of significant issues will need to be thoughtfully and proactively addressed. For example

1. The types of studies that should be posted
2. When the results of these studies should be posted
3. Ensuring there are not multiple and different summaries posted of the same study
4. Providing context and interpretation with the result summaries

1. Which Studies

Similar to protocol registration, we believe it is important that the results of all types of clinical research are disclosed via internet-based repositories. We have always included phase I studies and we are now extending this to include all our observational studies and meta-analyses that evaluate our medicines. For terminated compounds we have registered result summaries from phase III studies of discontinued compounds and phase II studies when the termination is related to a safety issue. We recognize that information from terminated research programmes can help inform the scientific community about the most productive areas of research to progress and help to reduce unnecessary patient exposure to similar compounds in clinical trials. We have therefore decided to extend this commitment to all our studies of terminated compounds.

2. Timing of Disclosure

We believe that it is important that the results studies are made available at the time of approval so the information is in the public domain and can therefore be used to supplement the prescribing information. Disclosure prior to approval is not relevant in this regard. For results of terminated research programs we disclose results within 12 months of the termination.

3. Multiple posting

There are a number of results registers. There is a risk that different registers will require different data sets. This will create a significant burden for sponsors in posting the information and keeping it current. Moreover this risks giving a confusing picture in the public domain about the results of a single trial. The use of consistent data fields in different registers (e.g., based on the synopsis described in ICH 3 guideline¹) provides a good basis for a longer term goal of bringing different registers together in a searchable format. While we recognize that different national solutions may vary, we support a consistent, well-defined data set for results reporting, and feel that such consistency will best serve the interest of physicians and patients.

4. Context and Interpretation

The challenge is to provide results in a manner that is useful to academic researchers interested in generating/evaluating research hypotheses and payers who may use the information for reimbursement/formulary decisions, while also making the results comprehensible to healthcare practitioners, who may be less familiar with clinical research, and to patients. Results posting alone does not, in our view, make the results of clinical research available to relevant medical or patient communities in meaningful ways and therefore it does not, in isolation, meet the objective of advancing medical care and medical science. These postings on the internet should be seen as a supplement but not a replacement for the need to publish studies in peer-reviewed journals. To that end, we aim to publish clinical research of our medicines as more comprehensive manuscripts in peer-reviewed journals that are indexed by online search engines. When studies are not published, we will provide context and interpretation on our register of results summaries.

Providing context and interpretation with textual summaries for all studies does not appear to be appropriate outside the traditional journal peer-review process. Who would write the summaries? Would summaries produced by a pharmaceutical industry study sponsor be universally viewed as not being misleading or promotional? How would any differences be addressed in summaries provided by the sponsor and regulators? Using independent organizations/ writers to produce these summaries, however, comes with its own set of challenges including: who will review the accuracy of the summaries; how will disagreements on summary content be adjudicated; and can/should indemnification against legal action be provided to the summary authors?. Moreover, it can be difficult to summarize the results of a single trial in a way that has meaning for patients. Rather, it is the cumulative evidence base from a number of research studies that may provide value for patients. Summaries of this cumulative evidence base are already produced in the form of package inserts and patient information leaflets. Would summaries of individual trials provide added value and benefit? When patient information leaflets are available, perhaps a link or reference could be provided as part of the study results summary.

¹ ICH represents the pharmaceutical regulatory authorities and industry from the United States, European Union, and Japan. Its guidelines are developed via a consensus process and are incorporated into the regulatory requirements of those regions. The E3 synopsis is concise and should contain numerical data illustrating results, not just text or p-values.