C. Network of Member Registers

C.1 Network Structure

The Registry Platform seeks to develop common rules and expectations for registers, to achieve the following objectives:

- Achieve the registration of all interventional trials worldwide
- Make it easy for Responsible Registrants[1] and the public to know which registers meet international standards of acceptability
- Ensure that each trial is registered in the fewest number of registers necessary to meet applicable local and regional regulations, and is registered once and only once in any one register

To meet these objectives, the Registry Platform should establish a network of internationally acceptable registers ("Member Registers") that together are comprehensive but that minimize overlap. "Responsible Registrants" can register their trials *directly* or *indirectly* (see below) with Member Registers.

C.1.A Advice on composition of the network

Any register meeting WHO register membership criteria should be eligible to become a Member Register.

Member Registers: We expect that Member Registers will mainly be national or regional registers. Ideally, they will serve non-overlapping communities (defined as those that share language, regulatory, and/or cultural factors), but will agree to cooperate in areas of potential overlap. Individual countries, regions, or international scientific groupings may choose to form partnerships with existing registers or to develop their own registers. In the interests of minimizing the chance of duplicate registration and of conserving resources, the WHO should encourage the formation of the minimum number of Member Registers necessary to serve global needs.

Non-Member Registers: There exist many trial registers worldwide whose organizers may not wish their register to serve as a Member Register, or which may not qualify as a Member Register. These registers may serve other important functions, however. For example, a university may sponsor a register to increase participant recruitment in its own trials, or a disease-specific register may provide a central repository in which investigators can register their trials related to interventions for that disease.

Non-member registers should establish an agreement with a single Member Register to ensure that the trial is affiliated with only one Member Register. Non-member registers that establish a satisfactory formal agreement with a Member Register (criteria to be defined) should be designated Associate [Member] Registers of the WHO Registry Platform. Responsible Registrants may enter the Trial Registration Data Set in a Member Register (*direct registration*) and have that information sent to a non-member register, or the data could be entered first into an Associate Register and then be uploaded to the Member Register (*indirect registration*).

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[1] The "Responsible Registrant" for a trial is either the principal investigator (PI) or the primary sponsor, to be decided by an agreement between the parties. The primary sponsor is "the individual, organization, group or other legal person taking on responsibility for securing the arrangements to initiate, manage and finance a study", and is ultimately accountable for ensuring that the trial is properly registered. For multi-center and multi-sponsor trials, it is the lead PI or lead sponsor who should take responsibility for registration. The responsible registrant should make every reasonable effort to ensure that a trial is registered once and only once in any one register, and that the trial is registered in the fewest number of registers necessary to meet applicable regulations

C.1.B Advice on operation of the network

The WHO should assist the appropriate parties in each member state (e.g., Member Registers, national authorities, journal editors) to issue clear guidance on the appropriate member register for Responsible Registrants in their region. The guidance will change as new Associate Register agreements are formed and as national and regional registers begin operation.

Responsible Registrants should enter the Trial Registration Data Set for an individual trial only once (including multicenter trials). Thereafter, the Trial Registration Data Set for that trial should be exchangeable electronically among all trial registers worldwide.

C.2 Membership Criteria

A draft set of membership criteria was circulated, but there was insufficient time for discussion during the SAG meeting.

D. Trial Deduplication

D.1 Background

One of the goals of the Registry Platform is to provide an unambiguous method for identifying individual trials worldwide. Achieving this goal is complicated because trials may be registered in more than one register, particularly as local regulations may require registration in non-member or multiple registers.

The process of deduplication requires skilled personnel assisted by computer programs that, at best, identify pairs of trials that *might* be duplicates. There is little research or evaluation on the accuracy of these computer systems, or on the overall accuracy of the process. In many cases, a human expert has to contact the providers of the records to resolve uncertainties, a labor-intensive process that can take considerable time. Familiarity with local sponsors, organizations, languages, etc. would be essential in many cases, complicating deduplication efforts for trials conducted in those countries.

The SAG endorses Registry Platform policies that will help to minimize the risk of duplicate trial registration. Platform policy should:

- Clearly identify the Responsible Registrant, and assign to the Responsible Registrant the responsibility for minimizing duplicate registration
- Define what constitutes a unique trial
- Standardize the Trial Registration Data Set to facilitate comparisions between register entries
- Provide a network structure of Member Registers that minimizes the overlap of constituencies, and increases the likelihood that Responsible Registrants register each trial without duplication
- Encourage new Member Registers to develop only if required to meet global registration needs
- Require Member Registers to perform deduplication of entries within their own registers
- Provide Member Registers a forum for sharing and developing best practices on deduplication and quality assurance
- Provide training and capacity building for trial registration worldwide

The SAG believes that the primary preventive strategy against duplicate registration is to assign an identifier to a trial at the earliest possible time, e.g., at the time of submission to the first

ethics review board for that trial. Thereafter, all ethics submissions, participant enrollment, registrations, publications, etc. should use the initially assigned identifier. The logistics of implementing such a system both locally and globally are daunting, however. The SAG suggests that the WHO explore ways to assign a trial identifier as early in the trial registration process as possible, including the potential integration of ethics review and trial registration.

D.1.A Definition of Unique Trial
A trial is considered a "unique" trial if it is conducted according to a single document (the protocol) that describes its objective(s), design, methodology, statistical considerations, and organization. A multi-center trial is one that is conducted according to a single protocol but carried out at more than one site. Even if different versions of the protocol are implemented at each of the sites in a multi-center trial, they are all part of one unique trial and do not constitute separate trials.[2]

D.1.B Implementation of Trial Deduplication
The SAG appreciates the importance of trial deduplication, at the same time as it recognizes the difficulties. The SAG supports the approach of breaking the deduplication task down into two levels:

1. Local Deduplication: The best strategy for deduplication is prevention. Member Registers should verify that each new addition to its own register is not likely to be for a trial that has already been registered *within* that same register. Many existing registers already do local deduplication. All deduplication results should be shared with all involved parties (registers and registrants) so that future duplicate registration may be reduced. Member Registers should exchange information about experiences and approaches, so as to improve their overall deduplication performance.
2. Global Deduplication: No entity currently performs deduplication of register entries *across* registers. The SAG favors the WHO taking on this task, by providing a clearinghouse database for entries from all Member Registers, and working with existing groups who have extensive knowledge and prior experience with deduplication to develop best practices.

In partnership with registers administrators and other experts, the WHO should continue to investigate methods for quicker and more accurate deduplication, including but not limited to computational approaches, data standardization and coding, and manual approaches.

D.1.C Universal Trial Reference Number
Global deduplication will be the responsibility of WHO, which will compare each register entry against entries from all other registers. The SAG considered various approaches to doing this. One possibility is to run a web-based search across all Member registers to identify register entries that appear to be associated with each trial.

A large majority of the SAG endorsed the WHO assigning a Universal Trial Reference Number (UTRN) to each unique trial as determined by the process of global deduplication. This reference number serves a function -- cross-referencing entries across trial registers -- that no existing number does. Varying views were expressed regarding the utility of a UTRN. The majority view was that the overall benefits of having one global reference number for each trial that is determined (as best we can) to be unique outweighs other potential issues related to the introduction of a new number. The minority opinion was that a new number would introduce more confusion than not.

It is unclear how much time the process of global deduplication will take. The WHO should aim for the quickest turnaround possible, combined with the desired level of accuracy. A trial should be considered fully registered when it is registered in the Primary Register, so that assignment of the UTRN will not delay the initiation of recruitment for a trial. The UTRN should be relayed back to all registers and registrants affiliated with the trial.

E. Coding and Data Interchange

E.1 Coding of Trial Registration Data Set Items

Coding the values of key items in the Trial Registration Data Set (e.g., Item 13 Intervention name, Item 12 Health condition or problem studied, and Item 19 Primary Outcome Measure(s)) using standard vocabularies will allow for precise searching, which will be increasingly important as more trials are registered. The WHO should consider coding key fields of the Trial Registration Data Set and returning the coded terms to the Member Registers. The WHO should continue to consult coding experts to develop an approach to maximizing the utility of register entries in Member Registers.

Concern was raised by some SAG members that registering all interventional trials would result in a "clogged system" overwhelmed by many small, early phase studies. The fear was that potential trial participants may search for trials on a particular health condition and identify early phase studies that are not of interest. However, if certain fields in the Trial Data Set are coded using standard vocabulary that has a hierarchy of related concepts (e.g., MeSH), search portals can filter out trials with characteristics typical of early phase studies, and thus filter out unwanted trials.

E.2 Data Interchange Standards

Responsible Registrants will enter the Trial Registration Data Set only once, and that thereafter, the information should be exchangeable electronically among all relevant data systems. To achieve this data interchange, the Registry Platform should define a data interchange standard reflecting the Trial Registration Data Set, but only after due diligence in exploring and harmonizing with related information standards that already exist. These standards include those by HL-7, CDISC, and the BRIDG group, EMEA, and others from both the commercial and non-profit sectors. Care should also be taken to set the technical complexity of the standard at a level appropriate to need, and to provide technical assistance to registers (e.g., from developing countries) that may not have the technical expertise to implement the data interchange standard.

Glossary

Interventional Clinical Trial	Any research study that prospectively assigns human participants or groups of humans to one or more health-related intervention to evaluate the effect on outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioral approaches, process-of-care changes, preventive care, diagnostic procedures.
Data Interchange Standard	A set of rules for sending information between machines. Includes agreement and standardization on the concepts exchanged (e.g., "primary sponsor"), and agreement and standardization on the structure of the actual message that is exchanged.
Deduplication	The process of determining whether two sets of trial information belong to the same trial or whether they belong to 2 *unique trials* (see below). Deduplication can happen within registers (local deduplication), as well as among registers (global deduplication).
Direct Registration	Occurs when a Responsible Registrant submits the Trial Registration Data Set of a trial to a Member Register for the purpose of registering that trial
Indirect Registration	Occurs when a Responsible Registrant submits the Trial Data Set of a trial to an Associate Member Register, which then forwards that Data Set to the appropriate Member Register for registration of that trial
Member Register	A register that meets all Registry Platform criteria for international acceptability. Member Registers belong to the Network of Member Registers.
Primary Register	The Member Register in which a trial is first registered.
Responsible Registrant	The "Responsible Registrant" for a trial is either the principal investigator (PI) or the primary sponsor, to be decided by an agreement between the parties. The primary sponsor is "the individual, organization, group or other legal person taking on responsibility for securing the arrangements to initiate, manage and finance a study" (as defined in Trial Registration Data Set), and is ultimately accountable for ensuring that the trial is properly registered. For multi-center and multi-sponsor trials, it is the lead PI or lead sponsor who should take responsibility for registration. The responsible registrant should make every reasonable effort to ensure that a trial is registered once and only once in any one register, and that the trial is registered in the fewest number of registers necessary to meet applicable local and regional regulations.
Standard Vocabulary	A set of terms covering a domain of knowledge (e.g., medicine) that can be used as a shared way to describe that domain of knowledge. The terms may be related to each other in meaningful ways.

Unique ID	A unique identifier assigned by a register to each of its entries to identify individual register entries. With local deduplication, the register-issued unique ID will usually relate to a single, unique trial. However, if that trial is also registered in another register, the trial will also have another register-issued unique ID assigned by the other register. Thus, a register-issued ID will usually relate to a single, unique trial within that register but a single, unique trial may have more than one register-issued unique ID.
Unique Trial	A trial is considered a single trial if it is conducted according to a single document (the protocol) that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. A multi-center trial is one that is conducted according to a single protocol but carried out at more than one site. Even if different versions of the protocol are implemented at each of the sites in a multi-center trial, they are all part of one trial and do not constitute separate trials
UTRN	Universal Trial Reference Number, a number that the WHO Registry Platform issues for each trial deemed to be unique across Member Registers. The UTRN would be used to cross-reference entries for that same trial across multiple registers. Each single, unique trial will have one UTRN, and each UTRN will relate to a single, unique trial worldwide.

Scientific Advisory Group – Full List of Board Members (19)

as of November, 2005

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- **Janet Wale**, Cochrane Consumer Network (CCNet), Burwood, VIC, Australia
- **Deborah Zarin**, ClinicalTrials.gov, Bethesda, Maryland, United States of America

FACT SHEET（抄訳）

ClinicalTrials.gov への登録：
Public Law 110-85, Title VIII で定めるところによる

2007 年 9 月 27 日に公衆衛生法を改正する公法 110-85 が施行され、ClinicalTrials.gov に登録すべき試験の種類が拡大された。それとともに、提出すべき登録項目が増え、結果情報の提出が必要になった他、法に従わない場合の罰則も定められた。新たに登録が必要になった事項には、2007 年 12 月 26 日が締切のものもある。結果情報の提出要件は、近日中に示される予定。

1．　一般的要求事項

A.　ClinicalTrials.gov に登録が必要な臨床研究（適用対象となる臨床研究）

・　医薬品・生物由来製品の研究：FDA 規制の対象となる医薬品等の比較対照試験。ただし、Phase I 試験を除く。

・　医療機器の研究：FDA 規制の対象となる機器の医療効果を見るための比較試験。ただし、小規模なフィージビリティ試験及び小児市販後調査を除く。

B.　試験登録の責任は誰にあるか。

1．　臨床試験のスポンサー　又は、

2．　臨床試験の主任研究者としてスポンサー等から指名された者

C.　求められるデータ

適用対象となる臨床試験を登録する際に、責任ある当事者は、記述的、募集、場所、連絡先、管理情報を提出しなければならない。主要・副次的指標、試験開始日、目標症例数が新たに要件に含まれることになった。

2．　ClinicalTrials.gov への登録のタイミング

一般に、適用対象となる臨床試験の責任ある当事者は、2007 年 12 月 26 日又は最初の患者の組み入れから 21 日後のいずれか遅い方までに、必要な情報を提出しなければならない。

例外：(a) 2007 年 9 月 27 日時点で実施中の臨床試験で、重篤又は致死的な疾患又は症状を含まないものについては、2008 年 9 月 27 日までに登録する。
(b) 重篤又は致死的な疾患又は症状を含む試験で、2007 年 9 月 27 日以前に開始されたもの、及び 2007 年 12 月 26 日以前に完了したものは、新法施

行前に行われていた登録要件の対象となることはあっても、新規要件の対象にはならない。

3．　登録しなかった場合の罰則

適用対象となる臨床試験を登録しなかった場合の、責任ある当事者への罰則は重大で、民事上の罰金刑及び連邦から資金提供を受けて行っている試験の場合は、研究費の保留又は返還を含む。2007年12月26日以降、連邦医薬品食品化粧品法第505条、510(k)条、515条、520(m)条、又は公衆衛生法第351条に基づきFDAに提出される申請書又は報告書については、適用条項を遵守している旨の証明書の添付が必要となる。

11/09/07

FACT SHEET (Available at http://prsinfo.clinicaltrials.gov/)

Registration at ClinicalTrials.gov: As required by Public Law 110-85, Title VIII

On September 27, 2007, a U.S. law was enacted that expands the types of clinical trials that must be registered in ClinicalTrials.gov, increases the number of data elements that must be submitted, and also requires submission of results data. There are penalties for non-compliance with the law. This fact sheet addresses the new registration requirements, some of which have reporting deadlines beginning on **December 26, 2007.** Information about the requirement to submit results data will be forthcoming.

1. General Requirements for Registration

A. Clinical Trials That Must be Registered at ClinicalTrials.gov ("Applicable Clinical Trials")

- Trials of Drugs and Biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation [1]
- Trials of Devices: Controlled trials with heath outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric postmarket surveillance [2]

B. Who is Responsible for Trial Registration? ("Responsible Party") [3]

1. The sponsor of the clinical trial [4]; - *OR* -
2. The principal investigator (PI) of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the PI is responsible for conducting the trial and has sufficient data rights.

C. Required Data Elements -

The Responsible Party must submit descriptive, recruitment, location, contact, and administrative information when registering an applicable clinical trial [5]. More data elements are required than under prior U.S. law, and these new requirements include primary and secondary outcome measures, start date, and target number of subjects.

2. Timing of Registration at ClinicalTrials.gov

In general, the Responsible Party for an applicable clinical trial must submit required information by the later of 12/26/**2007** or 21 days after the first patient is enrolled [6].

Exceptions: (a) data for trials "ongoing" as of 9/27/2007 that do ***not*** involve a "serious or life threatening disease or condition" must be submitted by 9/27/**2008** [7], [8];
(b) trials that involve a "serious or life threatening disease or condition", are initiated before 9/27/07, and have a "completion date" prior to 12/26/2007 [9] are not subject to the new requirements, although they may be subject to other laws.

3. Penalties for Failure to Register

Penalties for responsible parties who fail to register applicable clinical trials are significant and may include civil monetary penalties [10] and, for federally-funded trials, the withholding or recovery of grant funds [11]. Starting December 26, 2007, any application or report submitted to FDA under sections 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act or under section 351 of the Public Health Service Act will need to include certification of compliance with any applicable provisions [12].

FACT SHEET

Registration at ClinicalTrials.gov:
As required by Public Law 110-85, Title VIII

ENDNOTES

1. "`(iii) APPLICABLE DRUG CLINICAL TRIAL-

`(I) IN GENERAL- The term `applicable drug clinical trial' means a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act. [The Public Health Service Act]

`(II) CLINICAL INVESTIGATION- For purposes of subclause (I), the term `clinical investigation' has the meaning given that term in section 312.3 of title 21, Code of Federal Regulations (or any successor regulation).

`(III) PHASE I- For purposes of subclause (I), the term `phase I' has the meaning given that term in section 312.21 of title 21, Code of Federal Regulations (or any successor regulation)."

[PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(1)(A)(iii)]

2. "`(ii) APPLICABLE DEVICE CLINICAL TRIAL- The term `applicable device clinical trial' means--

`(I) a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and

`(II) a pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act."

[PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(1)(A)(ii)]

3. "`(ix) RESPONSIBLE PARTY- The term `responsible party', with respect to a clinical trial of a drug or device, means--

`(I) the sponsor of the clinical trial (as defined in section 50.3 of title 21, Code of Federal Regulations (or any successor regulation)); or

"`(II) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under this subsection for the submission of clinical trial information."

[PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(1)(A)(ix)]

4. Under 21 C.F.R. 50.3, "Sponsor" is defined as "a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators."

5. "`(ii) CONTENT- The clinical trial information required to be submitted under this paragraph for an applicable clinical trial shall include--

`(I) descriptive information, including--
`(aa) a brief title, intended for the lay public;
`(bb) a brief summary, intended for the lay public;
`(cc) the primary purpose;
`(dd) the study design;
`(ee) for an applicable drug clinical trial, the study phase;
`(ff) study type;
`(gg) the primary disease or condition being studied, or the focus of the study;
`(hh) the intervention name and intervention type;
`(ii) the study start date;
`(jj) the expected completion date;
`(kk) the target number of subjects; and
`(ll) outcomes, including primary and secondary outcome measures;

`(II) recruitment information, including--
`(aa) eligibility criteria;
`(bb) gender;
`(cc) age limits;
`(dd) whether the trial accepts healthy volunteers;
`(ee) overall recruitment status;
`(ff) individual site status; and
`(gg) in the case of an applicable drug clinical trial, if the drug is not approved under section 505 of the Federal Food, Drug, and Cosmetic Act or licensed under section 351 of this Act, specify whether or not there is expanded access to the drug under section 561 of the Federal Food, Drug, and Cosmetic Act for those who do not qualify for enrollment in the clinical trial and how to obtain information about such access;

`(III) location and contact information, including--
`(aa) the name of the sponsor;
`(bb) the responsible party, by official title; and
`(cc) the facility name and facility contact information (including the city, State, and zip code for each clinical trial location, or a toll-free number through which such location information may be accessed); and

`(IV) administrative data (which the Secretary may make publicly available as necessary), including--
`(aa) the unique protocol identification number;
`(bb) other protocol identification numbers, if any; and
`(cc) the Food and Drug Administration IND/IDE protocol number and the record verification date."

[PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(2)(A)(ii))]

6. "`(C) DATA SUBMISSION- The responsible party for an applicable clinical trial, including an applicable drug clinical trial for a serious or life-threatening disease or condition, that is initiated after, or is ongoing on the date that is 90 days after, the date of the enactment of the Food and Drug Administration Amendments Act of 2007, shall submit to the Director of NIH for inclusion in the registry data bank the clinical trial information described in of subparagraph (A)(ii) not later than the later of--

`(i) 90 days after such date of enactment;

`(ii) 21 days after the first patient is enrolled in such clinical trial; or