

THE OTTAWA STATEMENT, PART 2

Principles of operationalisation for international trial registration ¹

1 OBJECTIVES

To define principles of operationalisation for international registration of protocol information and results from human trials of healthcare interventions. The following topics are addressed:

- Unique ID
- Minimum protocol items
- Certification criteria for registries
- Search portal
- Trial results (to be addressed at later date).

2 UNIQUE ID

2.1 OS1 (Ottawa Statement, Part 1) Principle: Every trial should have a Unique ID assigned by a single international source prior to participant enrolment. The Unique ID should be verifiable and have built-in error-detecting logic, and should appear on all trial documentation.

2.2 Rationale:

- Enables unique identification of individual trials and their publications even if they are registered in multiple registries with multiple IDs;
- Enables global checking for duplication across multiple certified registries rather than within a single registry;
- Minimizes potential confusion introduced by multiple IDs from different registries;
- Easily recognizable;
- Internationally uniform.

Options	Advantages	Disadvantages
1. Global body assigns Unique ID	<ul style="list-style-type: none"> ▪ Neutral, global origin (e.g. WHO) ▪ Allows for secondary IDs 	<ul style="list-style-type: none"> ▪ Resources required for development and maintenance
2. Existing registry assigns Unique ID	<ul style="list-style-type: none"> ▪ Utilizes existing systems (eg, ISRCTN, clinicaltrials.gov) ▪ Allows for secondary IDs 	<ul style="list-style-type: none"> ▪ May not be perceived as truly global, neutral, or inclusive (e.g. country-specific, RCTs only) ▪ How to decide which registry to use?

¹ based on The Ottawa Group Meetings in Portland (May 2005) and in Melbourne October 24, 2005, and between; (35 participants in Portland and in 54 Melbourne meeting)

2.3 Proposal

2.3.1 Global Unique ID number should be assigned under the aegis of an international, neutral, non-profit organization.

2.3.2 As part of a quality assurance mechanism prior to assigning a Unique ID, the organization should obtain and maintain a linked record of basic protocol information to identify duplicate ID requests for the same trial.

2.3.3 The World Health Organization (WHO) seems to be the most natural body to be trusted with this work. The WHO proposed Universal Trial Reference Number (UTRN) may become a proper candidate for a global Unique ID.

3 MINIMUM PROTOCOL ITEMS

3.1 **OS1 Principle:** Registered protocol items should be sufficient to enable critical appraisal of trial methodology and statistical analyses.

3.2 **Operationalisation:** Feasibility needs to be considered.

3.3 Possible starting points

- Data items proposed for global system: WHO, endorsed by International Committee of Medical Journal Editors (ICMJE);
- Data items in registries such as ISRCTN and clinicaltrials.gov.

3.4 WHO minimum dataset

- A 20-item dataset was developed during WHO stakeholders meeting in April 2005
- Some stakeholders suggested delayed release of five items (**in bold**) that could be considered sensitive for competitive reasons.
 - a. Unique trial number
 - b. Trial registration date
 - c. Secondary IDs
 - d. Funding source(s)
 - e. Primary sponsor
 - f. Secondary sponsor(s)
 - g. Responsible contact person
 - h. Research contact person
 - i. Title of the study
 - j. **Official scientific title**
 - k. Ethics approval
 - l. Condition
 - m. **Intervention(s)**
 - n. Key inclusion and exclusion criteria
 - o. Study type
 - p. Anticipated trial start date
 - q. **Target sample size**

- r. Recruitment status
- s. **Primary outcome**
- t. **Key secondary outcomes**

3.5 Proposal

- 3.5.1 We commend and support the efforts by WHO and ICMJE to define a list of minimum protocol items during the introductory stages of trial registration. However, registration and public release of **all** 20 WHO items are necessary but insufficient for transparency according to Part 1 of the Ottawa Statement.
- 3.5.2 Delayed release of specified items (escrow) is unacceptable for several reasons:
 - Unclear what criteria would be used to determine when escrow would be allowed;
 - The five items are important for trial participants and their advocates for deciding participation in the trial;
 - The five items are necessary to avoid duplication of research;
 - Escrow does not rebuild public trust in clinical research.

3.6 Proposed Ottawa Group protocol items

- 3.6.1 Unique ID
- 3.6.2 Secondary ID(s)
- 3.6.3 Funding source(s)
- 3.6.4 Primary sponsor
- 3.6.5 Secondary sponsor(s)
- 3.6.6 Coordinating / principal investigator
- 3.6.7 Responsible contact person
- 3.6.8 Official scientific title
- 3.6.9 Lay title
- 3.6.10 Acronym
- 3.6.11 Trial website
- 3.6.12 Short lay description (text)
- 3.6.13 Key dates
 - a. Registration date
 - b. Ethics approval
 - c. Recruitment started
 - d. Recruitment ended
 - e. Follow-up ended
 - f. Trial stopped
 - g. Trial extended
 - h. Primary analysis completed
- 3.6.14 Ethics approval
 - a. Name of ethics board (REB/IRB) for the primary site in each country
 - b. REB trial approval number
 - c. Date of issuing
- 3.6.15 Coordinating center(s)
- 3.6.16 Recruitment center locations

- 3.6.17 Recruitment status
- 3.6.18 Eligibility criteria
 - a. Inclusion criteria
 - b. Exclusion criteria
- 3.6.19 Controlled (yes/no) - If yes:
 - a. Study design: parallel group, crossover, cluster, factorial
 - b. Number of arms
 - c. Randomized or not
 - If randomized, generation of the allocation sequence
 - If randomized, allocation concealment
 - d. Masking / blinding - If yes, who is blinded
 - e. Other design features
- 3.6.20 Framework (superiority, non-inferiority, equivalence - to be further elaborated)
- 3.6.21 Trial objectives
- 3.6.22 Disease/condition
- 3.6.23 Interventions by study groups and duration
- 3.6.24 Target sample size
- 3.6.25 Primary outcome(s) and time point of measurement
- 3.6.26 Secondary / additional outcomes and time point of measurement for each (including subgroup analyzes and adverse events)
- 3.6.27 Trial phase (phase I, II, III, or IV) if relevant

The Ottawa Group will define additional essential items, such as

- Other elements of study design
- Reference to systematic review(s) justifying the trial
- Consent forms
- Full protocol
- Justification of comparator in control groups, justification of interventions (dosage, duration, frequency, etc)
- Contracts and financial arrangements.

4 ACCEPTABLE REGISTRIES

- 4.1 **OS1 Principle:** Registered information must be presented at least in English and also preferably in the major language(s) of the region where the main study site/ sites is/ are located.
- 4.2 **Rationale:** Ensure high-quality, unbiased registries, containing internationally agreed minimal dataset at minimum, and enable mutual comparison and control of multiple registration (de-duplication).
- 4.3 **Proposal**
 - 4.3.1 A trial registration requirement is considered fulfilled only when a trial is registered in an internationally acceptable/ certified registry. A single search portal should exist to link these registries.

4.3.2 Criteria for registry certification

- a. Displays global Unique ID in addition to registry-specific ID(s)
- b. Records minimum protocol items irreversibly with amendments and finalised items and dates of each
- c. Language
 - The registered information must be presented at least in English and also preferably in the major language(s) of the region where the main study is located.
 - The relationship between international register in English and national registries in language(s) of the region is to be further elaborated.
- d. Broad scope of acceptable (certified) registry
 - Accepts all types of clinical trials
 - Not restricted by study design, disease, or intervention type
 - May be country-specific or international.
- e. Registration fee, if requested, must be based on ability to pay
- f. Accessible to the public at no charge
 - Public access to all registered fields should be provided free-of-charge on the worldwide web.
- g. Committed and independent governance structure
 - Commitment to registration
 - Independent oversight governing board.
- h. Electronically searchable.
- i. Quality-checking mechanism (for duplication, completeness, and meaning)
 - Must have system to verify the completeness and quality of information entered into each data field
 - All fields must be completed at point of registration, except for date of ethics approval, which may be submitted at a time of approval.
- j. Transparency with regards to conflicts of interest
 - Definition: Set of conditions in which judgment concerning a primary interest (e.g. complete registration of minimum protocol items for all trials) has the potential to be unduly influenced by a secondary interest.
 - Governance and structure of a certified registry should have procedures in place to promote trust, including
 - Avoiding major, potential, perceived conflicts of interest:
 - financial
 - intellectual
 - political
 - Avoiding predominance of single interest.

5 SEARCH PORTAL

- 5.1 OS1 Principle:** To facilitate efficient searching, multiple international, national, or regional registers should be linked.

5.2 Operationalization: Single global search portal should be developed to retrieve details of trials from certified registries.

5.3 Proposal:

5.3.1 Single global search portal should be developed to retrieve details of trials from certified registries free of charge.

5.3.2 Criteria for coordination:

- a. Perceived as neutral
- b. Sustainable infrastructure
- c. Committed and independent governance structure
- d. Independent oversight governing board
- e. Transparency with regards to conflicts of interest
 - Definition: Set of conditions in which judgment concerning a primary interest (e.g. complete registration of minimum protocol items for all trials) has the potential to be unduly influenced by a secondary interest.
 - Governance and structure of a certified registry should have procedures in place to promote trust, including
 - Avoiding major, potential, perceived conflicts of interest:
 - financial
 - intellectual
 - political
 - Avoiding predominance of single interest.

6 NEXT STEPS

- Continued open consultation via website
 - Finalise list of protocol items
 - Results
- Drafting of Ottawa Statement, Part 2
- Collection of signatories
- Submission for publication
- Anticipated next meeting for operationalisation of registration of trial results: Dublin October 2006 (during the 14th Cochrane Colloquium).