World Health Organization

International Standards for Clinical Trial Registries

The registration of all interventional trials is a scientific, ethical and moral responsibility

ICTRP

International Clinical Trials Registry Platform

International standards for clinical trial registries – Version 3.0

ISBN 978-92-4-151474-3

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Suggested citation. International standards for clinical trial registries – 2nd edition. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Printed in Switzerland

Contents

Contents 2
Contributors and acknowledgements 3
Introduction 4
Responsibilities 6
The Standards 7
1. Content 8
2. Quality and Validity 12
3. Accessibility 15
4. Unambiguous Identification 17
5. Technical Capacity 19
6. Administration and Governance 21
7. The Trial Registration Data Set (TRDS) 23
8. Partner Registries 34
9. Data Interchange Standards 35
Implementation of these Standards 36
Audit 37
Benchmarking 38
The ICTRP Advisory Group 39
Frequently Asked Questions (FAQs) 40
Appendices 41
Appendix A: Study Type 41
Appendix B: Process for ICTRP Registry Application and the ICTRP Advisory Group 42
Glossary 43
Acronyms 45
Document history 46
References 47

Contributors and acknowledgements

These standards were developed as part of the program of work of the World Health Organization's International Clinical Trials Registry Platform. The mission of the WHO International Clinical Trials Registry Platform is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base.

This document was updated by Lisa Askie (Australian and New Zealand Clinical Trial Registry), Ghassan Karam , Samantha Slattery and Vasee Moorthy (WHO Geneva). The previous version was produced and written by Davina Ghersi (WHO, Geneva) and Lisa Askie.

The general requirements of a clinical trial registry (the WHO Registry Criteria) were developed and agreed upon by the ICTRP's Scientific Advisory Group. The starting point for these criteria were the requirements of clinical trial registries published by the International Committee of Medical Journal Editors (ICMJE) *(1)*. These requirements became the criteria that a registry must meet in order to be considered eligible for the status of Primary Registry in the WHO Registry Network.

The specific, detailed standards in this document further define the requirements of each registry criterion. These standards were reviewed by the ICTRP Secretariat and Administrators of Primary Registries in the WHO Registry Network.

These standards were initially developed in consultation with the ICTRP's Best Practice Group, which was composed of the Administrators of selected Primary Registries in the WHO Registry Network. It's membership changed over time and included: Hélène Faure (ISRCTN), Ambujam Nair Kapoor (CTR-I), Abha Aggarwal (CTR-I), Ludovic Reveiz (LatinRec), Taixiang Wu (ChiCTR)), Lisa Askie (ANZCTR), Udaya Ranawaka (SLCTR), Lotty Hooft (NTR), Lakshmi Grama (PDQ), Susanne Jena (DRKS). Input into the development of the standards was also provided by Ghassan Karam, Chris Jones, Hazim Timimi and Maribel Gomez in the ICTRP Secretariat (WHO, Geneva).

Introduction

The International Clinical Trials Registry Platform (ICTRP) is a global initiative that aims to make information about all clinical trials involving human beings publicly available. It was established in 2006 in response to demand from countries through the World Health Assembly for:

> *"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"* {World Health Assembly, 2005 16 /id}

The Secretariat of the ICTRP is housed by the World Health Organization in its headquarters in Geneva and:

- **Publishes the ICTRP Search Portal:** a web site (http://www.who.int/ictrp) and database (http://apps.who.int/trialsearch) that makes it is possible for anyone in the world to search, for free, data provided by clinical trial registries around the world that meet WHO criteria for content and quality. Data on the portal is updated weekly.
- **Supports the WHO Registry Network:** a forum for Registries to exchange information and work together to establish best practice for clinical trial registration and results reporting and the collection of high quality data.
- **Supports countries and regions:** wanting to establish clinical trial registries or policies on trial registration and results reporting. In some cases, these registries will be a catalyst for other capacity-building activity in clinical trial conduct and oversight - particularly ethical and regulatory oversight.

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. The WHO Registry Criteria have been categorized into six main areas:

- Content
- Quality and Validity
- Accessibility
- Unambiguous Identification
- Technical Capacity
- Administration and Governance

Primary Registries in the WHO Registry Network are those that meet all WHO Registry Criteria. Primary Registries meet the requirements of the International Committee of Medical Journal Editors (ICMJE) *(2)*. Partner Registries in the WHO Registry Network must meet most, but not all, of the criteria. Specifically, they are not required to have a national mandate, and they can be limited in scope (for example, to trials in a particular disease or intervention).

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.

Why standards are necessary
The registries in the WHO Registry Network are disparate in remit and functionality. In order to promote harmonisation in the way in which data are collected and validated by these registries and thus ensure a baseline level of data quality, minimum standards need to be determined and implemented. In doing so, participating registries will improve the usability of the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal and ultimately benefit all those looking for and using information about clinical trials.

How these standards will be used by the ICTRP
The standards contained in this document are based on the criteria clinical trial registries must attain in order to be recognised as a Primary Registry in the WHO Registry Network, and must maintain in order to retain that recognition. They are minimum standards and individual registries may choose to impose stricter requirements than those defined in this document. In some instances, ideal standards have also been suggested.

All registries in the WHO Registry Network, and registries applying for Primary or Partner Registry status, must be able to demonstrate that they comply with the standards by:

1. having documented, registry-specific Standard Operating Procedures (SOPs) in place (see also Sections 2.2 and 9); and
2. providing a written commitment to comply with the standards; and
3. updating that commitment on an annual basis along with an update of the WHO Registry Profile; and
4. agreeing to site visits and random audits by the ICTRP Secretariat and/or delegated auditors.

How Registries will use these standards
These standards outline the broad criteria Primary Registries in the WHO Registry Network must fulfil in six main areas: content, quality and validity, accessibility, unambiguous identification, technical capacity and administration and governance.

Primary and Partner Registries in the WHO Registry Network must adapt these broad standards into registry-specific SOPs which detail the way in which each of these standards are operationalized within each registry.

Translation of these standards
These standards have been developed, and will be maintained, in English. Registries may choose to translate these standards into the language/s used by registry staff; however the registry must take responsibility for any translation, and ensure that at least two (2) people have checked and confirmed the accuracy of the translation.

Updating these standards
The intention is to update this standards document every 5 years. Individual standards may be updated on ad hoc basis, depending on need. Any proposed modifications, revisions or additions made in the interim will be discussed at Registry Network meetings. Once a new or modified standard is agreed upon it will be posted to the ICTRP's web site. Registries are advised to regularly check the ICTRP web site to make sure they are part of the discussion around new standards and are using current information.

Other standards
Several other organizations have developed standards that relate either directly or indirectly to those contained in this document. These include the International Committee of Medical Journal Editors (ICMJE) updated statement on trial registration requirements *(3)*; the Declaration of Helsinki *(4)*; and data interchange standards initiatives such as CDISC *(5)*, HL7 *(6)* and others. The standards contained in this document are in accordance with the ICMJE requirements for trial registration.

Responsibilities

There are several parties which have responsibilities in ensuring that we all have access to complete and meaningful information about clinical trials being conducted throughout the world.

Responsibilities of the Registry
A registry accepting trials for registration must make all reasonable efforts to ensure that an individual who is submitting a trial for registration (known as the Responsible Registrant):

i) is a real person
ii) is the appropriate person to be registering the trial, and
iii) provides complete, accurate and meaningful data for each item in the WHO Trial Registration Data Set at the time of initial registration (see The Trial Registration Data Set on page 24).

Registries are also responsible for ensuring they have quality control processes and procedures in place to ensure compliance with all of the minimum international standards defined in this document.

Responsibilities of the Responsible Registrant
The Responsible Registrant is an appropriate representative of the trial's primary Sponsor. The Responsible Registrant is responsible for making sure that the data submitted for each item in the WHO Trial Registration Data Set for a trial are complete, accurate and meaningful at the time the trial is initially registered. They are also responsible for keeping that data up-to-date and compliant with the trial registration and results reporting recommendations/requirements within their own jurisdiction(s).

The Responsible Registrant will 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. (See Unambiguous Identification on page 17) If a trial is, by necessity, registered in more than one registry then the Responsible Registrant is responsible for ensuring that all known identifiers for the trial are included in each registry's record as Secondary Identifiers to facilitate unambiguous identification of the trial.

Other stakeholders with responsibilities
Comprehensive prospective trial registration and subsequent results reporting is a global effort that requires the assistance of more parties that just Responsible Registrants and the Registries to which they submit their data. Journal editors, ethics committees / institutional review boards (IRBs), regulatory authorities and funding agencies can all play a major role in ensuring complete research transparency by requiring trials under their auspices to be prospectively registered. In this way we can achieve the goal of ensuring that all involved in research in humans accept that the registration of all interventional trials is a scientific, ethical and moral responsibility.

The Standards

The minimum standards which must be attained to satisfactorily meet the requirements of a Primary Registry in the WHO Registry are defined in this document. To apply for, and retain, status as a Primary or Partner Registry in the WHO Registry Network, Registries must fulfil all of the minimum standards.

Unless otherwise stated, the terms “registry” or “registries” refers to Primary Registries in the WHO Registry Network throughout this document.

1. Content

1.1. The Registry will accept prospective registration of interventional clinical trials submitted by Responsible Registrants

For the purposes of registration, an interventional 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. 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-IV trials.

1.1.1. The Registry will register trials before the first participant has been recruited

Prospective registration is registration of a trial before the recruitment of the first participant. Prospective registration is the ideal and is to be encouraged and facilitated whenever possible.

In some countries, legislation allows trial investigators to register their trials within a specific time frame (e.g. within 30 days of the recruitment of the first participant), but after the date of first enrolment. These time frames are a matter for each registry to discuss with the relevant national agency (or agencies). Regardless of any national policies that may exist, trials registered after the date of first enrolment are considered by the ICTRP to be retrospectively registered (see 1.1.2).

Minimum standard:

- Registries must provide clear advice (e.g. in the 'Help' text or by the data item name or label) that prospective registration means that a trial must complete the registration process and have a trial registration number issued before the recruitment of the first participant.
- See also 7.16

1.1.2. The Registry may choose to register trials that have already recruited the first participant

Retrospective registration is registration of a trial after recruitment of the first participant. It is recommended that Registries should allow retrospective registration (see 1.1.1). It is better for trials to be registered retrospectively than not at all. Registries should implement measures to minimise retrospective registration and promote prospective registration as the norm.

Registries may choose to flag all records that are registered retrospectively, or alternatively, flag records registered more than 30 days after enrolment of the first participant.

Minimum standard:

- Registries must query trial registration submissions where registration is sought after the 'date of first enrolment' to ensure that the trial is, in fact, being registered retrospectively.
- Once it has been confirmed that the Responsible Registrant is seeking retrospective registration then Registries may continue with the registration process but should consider alerting register users by displaying a suitable message on these records, e.g. "Note: This trial was registered after enrolment of the first participant".

1.1.3. The Registry may choose to register other types of studies, such as observational studies

Observational studies are those in which the investigator observes rather than influences exposure and disease among participants *(7)*. They include study designs such as case control studies and retrospective cohort studies.

A WHO registration data set for observational studies does not currently exist.

Individual Registries can choose to register observational studies if they wish, but there is no compulsion to do so.

If Registries wish to accept observational studies, they should consider aligning their data collection with recommended standards for reporting non-trial designs (see the Equator web site for lists of standards) *(8)*, and design the relevant fields in their database in accordance with the relevant data interchange standards (eg CDISC/HL7).

Minimum standard:

- There is currently no minimum standard for the registration of observational studies.

1.1.4. The Registry will consider registering all trials submitted by Responsible Registrants

The Registry needs to confirm that the person registering the trial meets the requirements of a Responsible Registrant and is an appropriate representative of the trial's Sponsor. The Responsible Registrant is responsible for ensuring that the trial is properly registered. This includes making sure that the information about a trial is complete, accurate, meaningful and up-to-date.

As stated on page 6, the Responsible Registrant needs to 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 laws and regulations.

Minimum standard:

- Registries must only accept trials submitted by Responsible Registrants. To facilitate this, Registries must ask the person submitting a trial for registration to verify that they meet the terms and conditions for being a Responsible Registrant before being able to proceed to trial registration.
- Registries must use the contact details provided by the Responsible Registrant to verify that those details are correct. As a minimum, Registries must send an email to the address given and receive a reply from that same address. When possible, the telephone number and/or surface mail address will also be verified in a similar fashion.
- All Responsible Registrants must be associated with an institution or organization.
- Registries will obtain institutional contact details (including name and telephone number of the institution) for the Responsible Registrant.

1.1.5. The Registry may choose to accept studies for registration when the data is submitted as an electronic data file (eg as an xml file)

Trial Sponsors are usually required to submit information about their trial to multiple agencies in addition to clinical trial Registries (e.g. National Regulatory Authorities, research ethics committees / institutional review boards, funding agencies, etc). In order to reduce the data entry burden, and potentially reduce data entry errors, Registries should consider accepting information from Responsible Registrants in electronic format. It is suggested that Registries considering this option should accept data provided in the format defined by the CDISC Protocol Representation Model *(9)*.

Minimum standard:

- There is currently no ICTRP minimum standard for electronic data submitted to registries.

1.2. The registry will be open to all prospective registrants (either internationally or within one or more specific countries) *(ICMJE requirement)*

A prospective registrant is any Responsible Registrant wanting to register a trial.

Minimum standard:

- Registries must clearly define which studies they will accept for registration. If registration is restricted in any way (e.g. to specific study designs, conditions or interventions) then these restrictions must be clearly stated on the registry's web site.
- Primary Registries in the WHO Registry Network must be willing and able to accept clinical trials submitted for registration by any Responsible Registrant (meeting the requirements described in section 1.1.3) conducting a trial in the country (or countries) from which the registry has received support from the national government (see section 6.1).
- Primary Registries in the WHO Registry Network may accept trials from Responsible Registrants for registration either directly or via an approved Partner Registry (see section 8).

Note: In exceptional circumstances only (specifically large-scale, multi-country Registries linked to legislation or regulation) Registries may have a limited scope.

1.3. The Registry will be able to collect and publicly display the WHO Trial Registration Data Set (TRDS) *(ICMJE requirement)*.

Minimum standard:

- Registries must be able to collect and display, on a publicly accessible web site, all of the items in the WHO TRDS (see section 7 for details of the TRDS).
- Registries must have quality control procedures in place to ensure all items in the TRDS contain meaningful data.

- Other data items may be collected and displayed at the discretion of the registry. If this is the case then it is recommended that the registry complies with appropriate data interchange standards (e.g. CDISC, HL7).

See also "**Is there a case for exceptions to the requirement that all items in the WHO TRDS be made publicly available?**" on page 40.

1.4. The Registry will make an effort to keep registered information up-to-date.

The users of information in clinical trial Registries need to be aware of how current the information in each record might be. A trial record in a registry will be considered out-of-date when the last update was made more than 12 months previously (and no publication has been recorded).

Minimum standard:

- Registries must permit Responsible Registrants to update information about their trial.
- An audit trail of any changes made to the originally registered TRDS must be made publicly accessible (see section 2.4).

Ideal standard:

- Registries will have a reminder system to facilitate the submission of updated information by the Responsible Registrant. The recommended frequency for updating trial information (and for reminding Registrants to do so) is at least annually.
- Registries will display the date the trial record was last updated so readers will be aware that information contained in trial records may be out of date. Registries may also choose to flag records that are out of date.
- Update reminders will continue to occur annually until the Registrant has recorded meaningful information about the publication of the trial results within the trial record e.g. has listed a citation in a "Publications" field.

1.5. The Registry will <u>never</u> remove a trial once it has been registered.

Minimum standard:

- Registries must never delete a trial record from their database, or remove it from public view, once a registration number has been issued.
- Responsible Registrants must be informed at the time of registration that a trial cannot be deleted once it has been registered.
- Although trial records cannot be deleted, Registries may consider removing a trial record from public view, but in exceptional circumstances only. For example:
    - when it has been proven that the trial is bogus or fraudulent;
    - when the trial has inadvertently been registered twice on the same registry.
- Registries must have clear and transparent processes for dealing with requests to remove a trial record from public view. These will include procedures for:
    - investigating claims of error, fraud or malicious intent
    - documentation of correspondence with all relevant parties
    - consideration of each case by an executive or independent committee
    - notification of the Registrant(s) of the outcome of such proceedings.

2. Quality and Validity

2.1. The Registry will have processes in place to make sure that registered data is complete and accurate.

The Registry will make all reasonable effort to ensure that the data registered is complete, meaningful and accurate.

This requirement is equivalent to the ICMJE requirement that the Registry will ensure the validity of the registered data. [1] *(ICMJE requirement)*

Minimum standard:

- Registry staff must routinely check all data submitted about a trial for completeness and meaningfulness to ensure that all TRDS fields are populated and comply with the minimum standards contained in this document (see Section 7).
- If one or more items in the TRDS submitted for registration are incomplete or not meaningful, Registries must contact the Responsible Registrant and attempt to obtain complete and meaningful data.
- Registry database systems must apply automated checking procedures (e.g. range checks, logic rules) to data items to facilitate validity checking.
- Registries must have processes in place for deciding whether to register trials where the Responsible Registrant remains non-compliant with requests to provide complete and meaningful data. These may include the following:
    - Registries may choose not to register trials for which complete and meaningful data is not provided.
    - If Registries choose to register trials with incomplete or non-meaningful data then the registry will advise the Responsible Registrant that the trial does not meet international requirements for transparency and of the potential consequences (e.g. the trial may not be acceptable to journal editors).
- Registries must undertake regular internal quality control audits to assess the level of completeness and accuracy of the data collected. Registries may consider making the results of these audits public through publication on the registry's web site or in peer reviewed journals or similar publications.

[1] Note: Accuracy is difficult to ascertain and only possible if the registry has access to trial source documents, including the trial protocol. These standards therefore refer to "meaningfulness" (that is, the information makes sense and complies with the standards outlined in Section 7) rather than accuracy.

2.2. The Registry will have documented Standard Operating Procedures (SOPs). These SOPs will be aligned with the International Standards for Clinical Trial Registries.

Standard Operating Procedures (SOPs) are *"detailed, written instructions to achieve uniformity of the performance of a specific function"* (ICH E6) *(10)*

An SOP is a documented, step-by-step procedure that promotes uniformity in operations. SOPs document the way in which all registry activities are to be performed. They can ensure consistency of the procedures within each registry (that is, all staff perform the same procedures in the same way) and hence facilitate the collection of high data quality.

SOPs are an integral part of a successful quality system because they provide individuals with the information needed to perform a job properly. SOPs also provide guidance in areas in which the exercise of professional judgment is necessary and specify procedures that are unique to each task.

Minimum standard:

- Registries must have written standards for all procedures and processes employed by the registry. These are known as Standard Operating Procedures (SOPs).
- These SOPs must be used to train all staff processing trial registrations to ensure that common standards for ensuring data completeness and meaningfulness are adhered to.
- Internal registry-specific SOPs will be aligned with WHO International Clinical Trial Registry Platform International Standards for Clinical Trial Registration (this document, see Section 9: Implementation).

2.3. The Registry will have processes in place to make sure that people and trials exist

2.3.1. The Registry will make sure that the person registering the trial exists and that they are the appropriate Responsible Registrant

Minimum standard:

- See section 1.1.3.

2.3.2. The Registry will make sure that the trial exists

Minimum standard:

- Registries must obtain written third-party confirmation that a trial exists. Appropriate methods of third party confirmation are:
    - Asking the Responsible Registrant to provide the registry with a copy of approval letters and/or approval numbers from ethics committees, funding agencies or government regulatory authorities
    - The registry communicating with the third party directly in order to obtain this information
- Verbal contact with the Responsible Registrant (e.g. by email or phone) on its own is not sufficient to constitute written third party confirmation of the trial's existence.

Ideal standard:

- Registries will document and display in the trial record whether or not the registry has obtained written third party confirmation of the trial's existence, and the name of the third party/ies from which confirmation was received.

2.4. The Registry will have a publicly accessible audit trail so that changes made to the WHO TRDS for an individual trial can be tracked.

As defined by ICH, an audit trail is documentation that allows reconstruction of the course of events.

Minimum standard:

- Registries must allow Responsible Registrants to update their registered trial records.
- Registries must make available a publicly accessible audit trail of any changes to any TRDS items.
- Registries must implement quality control procedures to ensure any updated information continues to fulfil the standards for each of the TRDS items.
- Registries must use the most up-to-date information as the default display.
- It must be possible to access the TRDS, as originally registered, at all times.

- See also section 1.4.

2.5. The Registry agrees to comply with the International Standards for Clinical Trial Registries (The Standards).

Minimum standard:

- The Registry Administrator will have a thorough working knowledge of the operational aspects of their registry.
- The Registry Administrator will commit themselves to ensuring the all Registry staff are familiar with the standards described in The Standards.
- The Registry Administrator will ensure that their registry-specific SOPs comply with The Standards.
- All Registry staff will be familiar with the contents of The Standards.
- The Registry Administrator will be fluent in English and will attend the regular meetings organized by the ICTRP Secretariat.

3. *Accessibility*

3.1. The Registry will make the WHO TRDS for all registered trials accessible to the public at no charge *(ICMJE requirement)*.

Minimum standard:

- Registries must make the WHO TRDS items for all studies in their register (i.e. the registry database) accessible online at no charge to the end user.
- See also Section 7.

3.2. The Registry will make it possible for the WHO TRDS for all registered trials to be searched electronically *(ICMJE requirement)*.

Minimum standard:

- Registries must enable online electronic searches of text words and phrases via a simple, single search box. As a minimum, it must be possible to search data in both the condition and intervention fields.
- When the results of a trial identified by a search are displayed, all items in the WHO TRDS must be visible.

Ideal standard:

- Registries will provide advanced search options that make it possible for users to conduct more sophisticated searches, and to sort and further refine their search results.

3.3. The Registry will allow Responsible Registrants to submit a trial for registration at any time of day on any day of the week (24 hours a day, seven days a week).

Minimum standard:

- Access to the registry for submission of trial registration data will be available 24 hours a day, seven (7) days a week, subject to a reasonable, minimal period of planned downtime for routine maintenance requirements.

Ideal standard:

- Registries will publish advance notice of planned downtimes at least one (1) week beforehand.

3.4. The Registry will allow their register database to be searched at any time of day on any day of the week (24 hours a day, seven days a week).

Minimum standard:

- Access to the register (i.e. the registry's database) to search for registered trials will be available 24 hours a day, 7 days a week, subject to a reasonable minimal period of planned downtime for routine maintenance requirements.
- See also Section 5.4.

3.5. It is desirable that Registries in the WHO Registry Network also make the WHO TRDS available in the language(s) of the country or countries served by the registry.

The language of registration is English and, as stated previously, Registries are responsible for ensuring that the English language version of the WHO TRDS is complete and meaningful.

Making registered information available in languages other than English increases accessibility and usage of trial registration data. Registries, however, need to be mindful of the data quality and liability issues arising from multi-language trial registration.

Minimum standard:

- Registries accepting and/or displaying trial information in languages others than English must have quality control procedures in place to ensure that all translations are accurate.
- For Registries accepting trial registration records in languages other than English, the TRDS items for all records must also be available in English (see Section 5.1). This can be achieved either by:
    - translation of the original text by the Responsible Registrant, or
    - translation of the original text by the registry.
- Trial records translated into English by the Responsible Registrant must be checked by registry staff against the non-English submission before being accepted for registration. If there is a discrepancy in the translation then it must be checked by a third person and resolution of the discrepancy achieved by consensus.
- Trials records translated by the registry must be checked by at least one other staff member against the original non-English submission before being accepted for registration. If there is a discrepancy in the translation then it must be verified by a third person.
- The responsibility for the accuracy of the translation lies with the person who performed it: either the Responsible Registrant or a member of registry staff.
- Registries that include trial records submitted in languages other than English should make users of the Registry aware of who performed the translation (the Responsible Registrant or Registry staff) of a registered record.
    - Registries may also consider documenting additional information such as the direction of the translation (e.g. from French to English, from English to Chinese)
- If a trial is registered in more than one language then the "Scientific Title", and a language identifier, must be submitted to the ICTRP Search Portal in each language.
    - The title in the additional language(s) will be displayed on the ICTRP Search Portal with the language itself being identified at the end. Example: *Titel van klinische trial (Nederlands/Dutch).*
- A trial is not considered to be registered in compliance with ICTRP requirements until its information is available in English. Any translation required must therefore occur before a registration number and date can be issued.

4. Unambiguous Identification

Clinical trials usually involve participants from more than one institution, and often more than one country. As each country will have its own requirements for clinical trials research conducted within its borders it is possible that single trials could be included on more than one registry database. A further complication is that the data appearing on each registry database about a single trial may differ: for example, the trial title or the countries of recruitment may have been entered differently, or one record may be more up to date than another. The challenge, therefore, is finding a way to unambiguously identify a trial, even though it may have multiple registration records (that is, the trial may appear on more than one registry database).

What Registries and Responsible Registrants can do to facilitate unambiguous identification

- If a trial involves **a single site**, it should not be necessary to register that trial more than once.
- If a trial involves **more than one site in a single country**, it should not be necessary to register that trial more than once.
- If a trial involves **sites in more than one country**, it is possible that the trial will need to be registered more than once in order to meet the ethical, legal or other requirements of each country. If this is the case then it is recommended that:
  - Each trial should have a single point of contact for the trial as a whole, regardless of the countries in which the trial is being conducted. That person should be responsible for the TRDS and for making sure that the same data is provided to each registry.
  - Within each country, before registering the trial, the person who is considering submitting the trial to a registry should first determine if the trial has already been registered on any Primary Registry in the WHO Registry Network or ICMJE approved Registry.
  - If a trial is registered on more than one registry then all known identifiers for the trial should be submitted to each registry as Secondary Identifiers. These include trial registration numbers allocated by other registries.
  - A trial should only be included on more than one registry if it is absolutely necessary.

4.1. The Registry will have in place processes to prevent the registration of a single trial more than once on their database.

Minimum standard:

- Registries must ensure that a trial that has been submitted for registration is not already been included in their register by first searching and checking their own database. Registries must not allow the same trial to be registered more than once on their own database.
- Registries must have policies and procedures to deal with inadvertent duplicate registration of the same trial within their own register. This would involve removal (but not deletion) of the duplicate record from public view (see also section 1.5).
  - If a period of more than 30 days has passed since the time of the duplicate registration then it is recommended that the record not be removed from public view as the registration number is likely to already be in circulation and associated with other documents relating to the trial. In such cases it is preferable that the duplicate records be linked rather than removed from view (including linking of the identifiers), and a note included in each record to inform registry users of the duplication.

4.2. The Registry will 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 UTN, and the unique identifiers allocated by other registries in the WHO Registry Network.

Secondary identifiers include unique identifiers allocated by other Primary Registries, protocol identification numbers assigned by Sponsors or numbers assigned by any other agencies. The UTN is considered to be a key secondary identifier.

Minimum standard:

- Registries must require responsible Registrants to make an entry in the *Secondary Identifiers* field. The field must not be left blank.
- If there are no known secondary identifiers, Registries must require Responsible Registrants to enter 'Nil known' in the *Secondary Identifiers* field.
- The UTN may be entered into either the Secondary Identifiers field or a field designated specifically for collection of the UTN.
    - It is recommended that the UTN be entered into a specifically designated field.

4.3. It is desirable that Primary Registries will search the ICTRP Search Portal and attempt to determine if the trial has already been registered by another Primary Registry in the WHO Registry Network or an ICMJE approved registry.

Minimum standard:

- Registries should attempt to determine whether a submitted trial has been registered in another Primary Registry or an ICMJE approved registry before registration by either:
    - asking the Responsible Registrant to indicate if the trial has already been registered on another Primary Registry, and/or
    - asking the Responsible Registrant to confirm that they have checked the ICTRP search portal to see if a similar trial registration records exist, and/or
    - searching the ICTRP Search Portal themselves
- Registries or Responsible Registrants should search the ICTRP Search Portal using key words in fields such as the title, intervention, Sponsor, source of funding or contact details.
- If matches are found, the relevant *Secondary Identifiers* must be included in the trial record by the Responsible Registrant.

5. Technical Capacity

5.1. The Registry will submit the WHO TRDS for all records on their register, in English, to the WHO ICTRP Central Repository.

Minimum standard:

- Registries must submit the WHO TRDS items for **all records** on their register, in English, to the WHO ICTRP Central Repository. If a registry accepts study types other than interventional trials (i.e. observational studies) these must be provided as well.
- Records must be submitted in the format requested by the WHO ICTRP (e.g. xml file) at regular intervals, the frequency of which will be determined by mutual agreement between the registry and the WHO ICTRP (and at least once per month).
- After the initial data transfer of all records, only new or updated records need be supplied to WHO ICTRP at regular intervals.

5.2. The Registry will have access to a database that is used to store and manage the submitted data.

Minimum standard:

- Registries must use database software and hardware that can guarantee reliable access to registered data and data safety (see Standard 5.5) at all times.
- Registries are not required to develop their own database. They may choose to use a structure or software that is similar to, or the same as, other Primary Registries (see the Data Providers section of the ICTRP website).

5.3. The Registry will have access to adequate information technology support.

Minimum standard:

- Registries must have access to reliable information technology support.
- Registries must have access to:
  - reliable application, database, backup and mail servers
  - good internet connectivity speed
  - sound operating systems
  - appropriate software for servers, desktops and laptops
  - database and web development and maintenance personnel
  - other skilled information technology personnel to support these systems, as required.

5.4. The Registry will have adequate data security and other provisions against data corruption and loss.

Minimum standard:

- Registries must have documented procedures for ensuring adequate data security and other provisions to prevent data corruption and loss. This will include regular database replication and/or back-up (minimum 500 GB data backup capability).

Ideal standard:

- Registries will implement alerts for website downtime, to ensure the registry fulfils the requirements in sections 3.4 and 3.5 regarding 24 hour, seven (7) days a week access.

6. Administration and Governance

6.1. The Registry will 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 (defined as a group of countries and not a group of states within a country).

6.1.1. This requirement is not applicable to Partner Registries (see Section 8).

Minimum standard:

- Registries must be able to provide the ICTRP with evidence of a national or regional remit (as defined in section 6.1). Such evidence will be in the form of a letter of support or other such appropriate documentation from the Ministry of Health or other relevant national or regional agencies.
- Registries must accept prospective trial registration submissions from all prospective registrants covered by their national / regional remit (see also Section 1.2).

6.2. The Registry will publicly disclose ownership, governance structure and not-for-profit status.

Definitions:

- **Ownership**:
  - Legal right of possession; proprietary
- **Governance**:
  - (The World Bank)
  - (United Nations Economic and Social Council)
- **Governance structure**:
  - (IBM)
- **Not-for-profit**:
  - An agency whose purpose is not the generation of profits. A not-for profit agency is one that channels any funds remaining after paying operating expenses back into programs and services rather than sharing profits with owners, shareholders and/or executives.

Minimum standard:

- Registries must publicly disclose their ownership, governance structures and not-for-profit status. This information must be placed in a prominent place on the registry's website.
- Registries must inform the ICTRP as soon as possible if their ownership, governance structures or not-for-profit status change in any way.
- Primary Registries must be managed by a not-for-profit agency.

6.3. The Registry agrees that, should it cease to function, at least the WHO TRDS (original and updated) for all trial records will be transferred to a Primary Registry in the WHO Registry Network.

This will allow Responsible Registrants to keep the trial record up-to-date.

Minimum standard:

- Should a registry cease to function, the registry will transfer at least the WHO TRDS (original and updated) for all trial records to another Primary Registry in the WHO Registry Network.
    - Ideally, all data in the closing registry will be transferred to the registry taking over that registry's function.
- Once transferred, such records would thereafter be owned by the receiving Primary Registry, which would also then be responsible for keeping registered data up-to-date.

6.4. The Registry will have a strategy in place ensure the medium to long term sustainability of the registry

Minimum standard:

- Registries must have a documented business plan that addresses the strategies the registry has in place to address its medium to long term sustainability.

6.5. It is strongly recommended to have only one primary registry per country

Minimum standard:

- It is not recommended to have a primary registry in each and every country. In some cases, regional registries are encouraged to replace national registries, as long as they are sustainable.

7. The Trial Registration Data Set (TRDS)

Version 1.3.1
For data collected at the time of registration

	Item/Label	Explanatory text	Additional notes and guidance
1	Primary Registry and Trial Identifying Number	Name of Primary Registry, and the unique ID number assigned by the Primary Registry to this trial.	
2	Date of Registration in Primary Registry	Date when trial was officially registered in the Primary Registry.	When a trial record is in a WHO Partner Registry is imported (or otherwise entered) into the database of a WHO Primary Registry, the date of registration is considered to be the date the trial was registered on the WHO Primary Registry. In such cases, the WHO Primary Registry (as well as the Partner Registry) will display both the date of registration in the Primary Registry as well as the date of registration on the Partner Registry.
3	Secondary Identifying Numbers	Other identifiers besides the Trial Identifying Number allocated by the Primary Registry, if any. These include: • The Universal Trial Number (UTN) • Identifiers assigned by the Sponsor (record Sponsor name and Sponsor-issued trial number (e.g., protocol number)). • Other trial registration numbers issued by other Registries (both Primary and Partner Registries in the WHO Registry Network, and other Registries) • Identifiers issued by funding bodies, collaborative research groups, regulatory authorities, ethics committees / institutional review boards, etc. All secondary identifiers will have 2 elements: an identifier for the issuing authority (eg CTN, ISRCTN, ACTRN) plus a number. There is no limit to the number of secondary identifiers that can be provided.	Some Registries may choose to collect the UTN in a separate field.
4	Source(s) of Monetary or Material Support	Major source(s) of monetary or material support for the trial (e.g., funding agency, foundation, company, institution).	
5	Primary Sponsor	The individual, organization, group or other legal entity which takes responsibility for initiating, managing and/or financing a study. The Primary Sponsor is responsible for ensuring that the trial is properly registered. The Primary Sponsor may or may not be the main funder.	This definition is aligned with the ICH definition

	Item/Label	Explanatory text	Additional notes and guidance
6	Secondary Sponsor(s)	Additional individuals, organizations or other legal persons, if any, that have agreed with the Primary Sponsor to take on responsibilities of sponsorship. A Secondary Sponsor may have agreed to: • take on all the responsibilities of sponsorship jointly with the primary sponsor; or • form a group with the Primary Sponsor in which the responsibilities of sponsorship are allocated among the members of the group; or • act as the Primary Sponsor's legal representative in relation to some or all of the trial sites	
7	Contact for public queries	Email address, telephone number and postal address of the contact who will respond to general queries, including information about current recruitment status "Note: The information provided in here is functional and not personal, it is recommended to provide institutional and not personal information. By providing this information the registrant consents that the information provided can or may be published on a public website. Once provided the information cannot be redacted or anonymized as a result of new privacy legislation such as the European General Data Protection Regulation (GDPR)".	All three types of contact details must be registered for the contact for public queries (postal address, email address and telephone number). As email addresses frequently change registrants must provide a postal address for the contact for public queries. 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

	Item/Label	Explanatory text	Additional notes and guidance
8	Contact for scientific queries	There must be clearly assigned responsibility for scientific leadership to a named Principal Investigator (PI). 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. The contact for scientific queries must therefore include: i) Name and title, email address, telephone number, postal address and affiliation of the Principal Investigator, and; ii) Email address, telephone number, postal address and affiliation of the contact for scientific queries about the trial (if applicable). 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. “Note: The information provided in here is functional and not personal, it is recommended to provide institutional and not personal information. By providing this information the registrant consents that the information provided can or may be published on a public website. Once provided the information cannot be redacted or anonymized as a result of new privacy legislation such as the European General Data Protection Regulation (GDPR)”.	Scientific leadership must always be identified in registered records of clinical trials, for reasons of accountability and transparency. There will therefore always be clearly assigned responsibility for scientific leadership to a named Principal Investigator (PI). 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. A PI is defined 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.” (as defined by ClinicalTrials.gov: http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf) The PI is responsible for the accuracy of registered information and responses to scientific queries. 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 must be recorded on the registry but may not be made publicly available. Assessment of the potential risk should be on a case-by-case basis at the discretion of the registry. 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. As email addresses frequently change registrants must provide postal addresses for all contacts.

	Item/Label	Explanatory text	Additional notes and guidance
9	Public title	Title intended for the lay public in easily understood language.	An informative public title will describe the participants, the intervention, the comparator and the main outcome of the study. The scientific title of the study as it appears in the protocol submitted for funding and ethical review can be used.
10	Scientific title	Scientific title of the study as it appears in the protocol submitted for funding and ethical review. Include trial acronym if available.	It is desirable that the scientific title contain all elements of PICO (Participants, Intervention, Comparator and Outcomes).
11	Countries of Recruitment	The countries from which participants will be, are being, or have been recruited at the time of registration.	This data item needs to be kept up to date. Registries will adopt the coded country names listed in ISP-3166-1. If required, local customizations can be adopted by making use of the ISO-3166 user-assigned code elements feature. Adoption of user-assigned codes will be carried out in consultation with the WHO ICTRP Secretariat. See: (http://www.iso.org/iso/country_codes/background_on_iso_3166/customizing_iso_3166-1.htm#user-assigned-code-elements).

	Item/Label	Explanatory text	Additional notes and guidance
12	Health condition(s) or problem(s) studied	Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error). If the study is conducted in healthy human volunteers belonging to the target population of the intervention (e.g. preventive or screening interventions), enter the particular health condition(s) or problem(s) being prevented.	Registries will provide one or more free text fields to enable Responsible Registrants to record the Health Conditions or Problems studied. In addition to free text, controlled vocabularies may be used. These vocabularies can be used by either the Responsible Registrant (to be submitted when the trial is registered), or by the registry (eg registry staff coding the record at the time of registration). Some examples of controlled vocabularies include SNOMED, ICD and MeSH. (See http://healthinformatics.wikispaces.com/Controlled+Medical+Vocabularies+-+CMV) There is currently no single recommended controlled vocabulary. As the ICTRP Search Portal has implemented the UMLS meta-thesaurus it is recommended that Registries implement controlled vocabularies that map to this meta-thesaurus.

	Item/Label	Explanatory text	Additional notes and guidance
13	Interventions	For each arm of the trial record a brief intervention name plus an intervention description. **Intervention Name:** for drugs use generic name; for other types of interventions provide a brief descriptive name. • For investigational new drugs that do not yet have a generic name, a chemical name, company code or serial number may be used on a temporary basis. As soon as the generic name has been established, update the associated registered records accordingly. • For non-drug intervention types, provide an intervention name with sufficient detail so that it can be distinguished from other similar interventions. **Intervention Description:** Must be sufficiently detailed for it to be possible to distinguish between the arms of a study (e.g., comparison of different dosages of drug) and/or among similar interventions (e.g., comparison of multiple implantable cardiac defibrillators). For example, interventions involving drugs may include dosage form, dosage, frequency and duration. If the intervention is one or more drugs then use the International Non-Proprietary Name for each drug if possible (not brand/trade names). For an unregistered drug, the generic name, chemical name, or company serial number is acceptable. If the intervention consists of several separate treatments, list them all in one line separated by commas (e.g., "low-fat diet, exercise"). For controlled trials, the identity of the control arm should be clear. The control intervention(s) is/are the interventions against which the study intervention is evaluated (e.g., placebo, no treatment, active control). If an active control is used, be sure to enter in the name(s) of that intervention, or enter "placebo" or "no treatment" as applicable. For each intervention, describe other intervention details as applicable (dose, duration, mode of administration, etc).	

	Item/Label	Explanatory text	Additional notes and guidance
14	Key Inclusion and Exclusion Criteria	Inclusion and exclusion criteria for participant selection, including age and sex. Other selection criteria may relate to clinical diagnosis and co-morbid conditions; exclusion criteria are often used to ensure patient safety. If the study is conducted in healthy human volunteers not belonging to the target population (e.g., a preliminary safety study), enter "healthy human volunteer".	This requirement is aligned with the CONSORT definition. See also http://www.consort-statement.org/consort-statement/3-12---methods/item4a_participants/
15	Study type	Study type consists of: 1. Type of study (interventional or observational) 2. Study design including: • Method of allocation (randomized/non-randomized) • Masking (is masking used and, if so, who is masked) • Assignment (single arm, parallel, crossover or factorial) • Purpose 3. Phase (if applicable) For randomized trials: the allocation concealment mechanism and sequence generation will be documented.	See Appendix A on page 49 for more details. For more information on blinding (or masking) go to: http://www.consort-statement.org/consort-statement/3-12---methods/item11a_blinding/ For more information on allocation concealment mechanism go to: http://www.consort-statement.org/consort-statement/3-12---methods/item9_randomisation-allocation-concealment-mechanism/ For more information on sequence generation go to: http://www.consort-statement.org/consort-statement/3-12---methods/item8a_randomisation-sequence-generation/
16	Date of first enrolment	Anticipated or actual date of enrolment of the first participant.	If the anticipated date is provided at the time of registration then the actual date should be recorded when the record is updated. Some Registries may use the label "trial start date". If so, it should be made clear to Registrants (via 'Help' text or other documents) that this field must contain the date the first participant was enrolled.

	Item/Label	Explanatory text	Additional notes and guidance
17	Sample size	1. Target sample size at registration. 2. Final enrolment number.	Number of participants that the trial plans to enrol in total. This should be completed at the time of registration and updated subsequently should changes to the target sample size be made. Country- or site-specific sample size targets may be provided separately. Final enrolment number actually achieved. This should include all participants actually enrolled in the trial, regardless of any attrition subsequent to enrolment. This field should be completed once the trial's recruitment phase has been completed.
18	Recruitment status	Recruitment status of this trial: • Pending: participants are not yet being recruited or enrolled at any site • Recruiting: participants are currently being recruited and enrolled • Suspended: there is a temporary halt in recruitment and enrolment • Complete: participants are no longer being recruited or enrolled • Other	This data item needs to be kept up to date.
19	Primary Outcome(s)	Outcomes are events, variables, or experiences that are measured because it is believed that they may be influenced by the intervention. The Primary Outcome should be the outcome used in sample size calculations, or the main outcome(s) used to determine the effects of the intervention(s). Most trials should have only one primary outcome. For each Primary Outcome provide: 1. The name of the outcome (do not use abbreviations) 2. The metric or method of measurement used (be as specific as possible) 3. The time point(s) of primary interest Example: Outcome Name: Depression Metric/method of measurement: Beck Depression Score Timepoint: 18 weeks following end of treatment	The time point is <u>not</u> the same as study duration or period of follow-up.

	Item/Label	Explanatory text	Additional notes and guidance
20	Key Secondary Outcome(s)	Secondary outcomes are outcomes which are of secondary interest or that are measured at timepoints of secondary interest. A secondary outcome may involve the same event, variable, or experience as the primary outcome, but measured at timepoints other than those of primary interest. As for Primary Outcomes, for each Secondary Outcome provide: 1. The name of the outcome (do not use abbreviations) 2. The metric or method of measurement used (be as specific as possible) 3. The time point(s) of interest	
21	Ethics Review	1. Status of approval by at least one named ethics review committee (Not approved, Approved, Not Available). 2. Date of approval 3. Name and contact details of Ethics committee(s) (Contact details: address, phone, email)	All three types of contact details must be registered for the ethics review committee contact for public queries (postal address, email address and telephone number). The details may be generic (that is, there does not need to be a named individual): e.g. a generic email address for a representative of the ethics committee to answer queries. As email addresses frequently change registrants must provide a postal address for the ethics review committee contact for public queries. In circumstances where there may be a risk of undue harassment if contact information is publicly disclosed, the contact details must be recorded on the registry but may not be made publicly available. Assessment of the potential risk should be on a case-by-case basis at the discretion of the registry. In cases where a clinical trial is reviewed by more than one ethics committee, the information for each committee should be provided.
22	Completion Date	The date on which the final data for a clinical study were collected (commonly referred to as, "last subject, last visit"). .	

	Item/Label	Explanatory text	Additional notes and guidance
23	Summary Results	Within 12 months of the study completion date, trials should include, at a minimum, summary results or a link to summary results within the trial registration record. Summary results should include the following: **1. Date of posting of results summaries** **2. Date of the first journal publication of results** **3. URL hyperlink(s) related to results and publications** 4. **Baseline Characteristics**: Data collected at the beginning of a clinical study for all participants and for each arm or comparison group. These data include demographics, such as age and sex, and study-specific measures. Templates may be found from organizations such as clinicaltrials.gov, EQUATOR network, or CONSORT) 5. **Participant flow**: Information to document the progress and numbers of research participants through each stage of a study in a flow diagram or tabular format. (often in tabular format, but pdf uploads possible) 6. **Adverse events**: An unfavorable change in the health of a participant, including abnormal laboratory findings, and all serious adverse events and deaths that happen during a clinical study or within a certain time period after the study has ended. This change may or may not be caused by the intervention being studied. 7. **Outcome measures**: A table of data for each primary and secondary outcome measure and their respective measurement of precision (eg a 95% confidence interval) by arm (that is, initial assignment of participants to arms or groups) or comparison group (that is, analysis groups), including the result(s) of scientifically appropriate statistical analyses that were performed on the outcome measure data, if any. 8. **URL link to protocol file(s) with version and date** (e.g. pdf documents of consent forms, statistical analysis plans, participant information sheets) **9. Brief Summary**	Provide the date that any results information (publication or summary results) were made publicly accessible on the registry. For interpretation, it is important that the final clinical trial protocol (methods) is available together with the summary results

	Item/Label	Explanatory text	Additional notes and guidance
24	Data Sharing Plan	1. Whether individual de-identified participant data will be shared (Yes, No, Undecided). 2. Additional description regarding data sharing plan. • What data in particular will be shared. • Whether additional documents related to the trial will be shared (e.g., protocols, statistical plans, consent forms). • When the data will be available. • For what purpose the data can be used. • By what mechanisms the data may be made available.	Per ICMJE guidelines, clinical trials commencing enrolment after 1 January 2019 must include a data sharing plan in the trial's registration record.
Additional data items required			
A1	URL	The unique URL of the trial record in the primary registry database.	Allows the ICTRP search portal to provide links to source record.
Optional data items for collection by the registries			
B1	Lay Summary	Short description of the primary purpose and background of the study followed by a description of the included participants, interventions to be tested and outcomes to be measured. Include a brief statement of the study hypothesis. This should be written in language intended to be read and understood by the lay public. Do not include the entire protocol; do not duplicate information recorded in other data elements.	
B2	Approvals	Oversight entities that have approved the trial (or to which the trial has been submitted for approval). These include ethics committees and regulatory authorities. For each approving entity the name of the entity, the date and status of the approval should be reported.	

Previous versions of the TRDS

8. Partner Registries

8.1. Primary Registries in the WHO Registry Network will have the capacity to partner with other Registries.

Minimum standard:

- Primary Registries must be willing and able to form partnerships with other Registries that do not themselves fulfil the criteria for a Primary Registry in the WHO Registry Network on the basis of
  - lacking a national / regional remit
  - not being open to all prospective registrants
  - not being publicly accessible, or
  - for other legitimate reasons.
- Primary Registries must list all approved Partners Registries on their own website and on the WHO ICTRP Primary Registry Profile form which is publicly displayed on the WHO ICTRP website.

8.2. Primary Registries in the WHO Registry Network will ensure that potential Partner Registries meet WHO minimum standards requirements.

Minimum standard:

- Before agreeing to accept trial registration records from Partner Registries, Primary Registries in the WHO Registry Network must work with the WHO ICTRP Secretariat to ensure potential Partner Registries meet all the WHO minimum standards requirements for Primary Registries other than those listed in 8.1. This includes ensuring potential Partner Registries fulfil minimum standards for data content, quality and validity and have documented SOPs (see Sections 1 and 2).

8.3. Primary Registries will have procedures in place to enable exchange of data with Partner Registries.

Minimum standard:

- Primary Registries must develop mechanisms for accepting data from Partner Registries or other appropriate data providers.
- Primary Registries must establish a Memorandum Of Understanding (MOU) or other such agreements with each of their Partner Registries or other data providers that address issues such as technical specifications of data provision (file structures, method of data transfer etc), frequency of data provision, ownership of records, quality assurance procedures, responsibility and procedures for updating trial registration information, measures to prevent unnecessary duplication, payment of fees by Registrants (if applicable), arrangements should either the Partner Registry or the Primary Registry cease operations, and any other relevant issues.
- Primary Registries must agree the area of coverage/responsibility of their Partner Registries or other data providers (such as geographical location, health condition, intervention type, etc) and incorporate this into their SOPs and instructions to Registrants to avoid any confusion or unintentional duplicate registration.
- Primary Registries must record the identification number and date of registration in the Partner Registry within the trial record on the Primary Registry.
- Primary Registries must identify records that have been sourced from Partner Registries or other data providers so users are aware of the data source.
- Before announcing Partner Registries, Primary Registries must have successfully imported data into the Primary Registry.

9. Data Interchange Standards

9.1. Exchanging data with the Central Repository

Unless otherwise agreed to, Primary Registries in the WHO Registry Network must provide data for inclusion in the ICTRP Central Repository in the format defined in the document "WHO Trial Registration Data Set: data format required for sending records to the central repository"

9.2. Future data interchange standards

It is strongly recommended that Registries considering making modifications to (or redeveloping) their database should adopt the data definitions in the CDISC Protocol Representation Model (8). This will improve our ability in the future to exchange data between Registries and Responsible Registrants, and between Registries and the WHO ICTRP Central Repository.

9.3. Meta-thesaurus

There is currently no single recommended controlled vocabulary. As the ICTRP Search Portal has implemented the UMLS meta-thesaurus it is recommended that Registries implement controlled vocabularies that map to this meta-thesaurus.

Implementation of these Standards

To apply for, achieve and retain the status of a Primary (or Partner) Registry in the WHO Registry Network, Registries must comply with all the minimum standards outlined in Sections 1-9 of this document.

The main aim of the minimum standards is to promote harmonisation in the way data are collected and validated by different trial Registries, and hence to ensure a minimum standard for the quality of registered data. This will improve the usability of the WHO ICTRP Search Portal, and the reliability of the data it contains, and will therefore benefit all those seeking information about clinical trials.

The implementation of the minimum standards will occur in the following ways:

- The minimum standards in this document will apply to all Primary and Partner Registries.

- Registries in the WHO Registry Network that cease to comply with WHO criteria will be placed on a time limited probation. If after this probation period a register remains non-compliant then their status as a WHO Primary (or Partner) Registry will be withdrawn.

- All Primary and Partner Registries in the WHO Registry Network not meeting the minimum standards by 31st January 2019 may be placed on probation.

- If a registry is on probation then this will be indicated on the ICTRP's web site.

- Registries will be required to adapt and apply the minimum standards to their local settings i.e. the minimum standards will provide Registries with the framework for the creation of registry-specific Standard Operating Procedures (SOPs) that outline specific processes and procedures relevant to each individual registry, to ensure each of the minimum standards are fulfilled by each registry.

- Each registry will be required to produce written SOPs that document how each of the minimum standards are fulfilled by that registry. These SOPs will be required to be submitted to the WHO ICTRP upon request at any time and/or as part of a random audit process or site visit.

- Each registry will be required to provide a written commitment to comply with the minimum standards and agree to site visits and random audits by the ICTRP Secretariat and/or delegated auditors.

- All Registries in the WHO Registry Network will be monitored by the ICTRP Registry Application and Monitoring Group (IRAMG), which will annually review the updated Registry Profile forms of each Registry.

- All Registries should conduct regular internal audits and monitor their continued compliance with the Standards, as well as their own SOPs.

Audit

The intention is for the ICTRP to audit registries to ascertain compliance with the standards described in this document. Various types of audit will be conducted:

1. Self-audit: Registries conduct their own, internal audits to determine if processes and procedures are being complied with, and adjustments made if necessary.
2. Self-report: Registries will be asked to update their Registry Profile on an annual basis and return it to the ICTRP Secretariat. This form will be used by the RAMG to monitor continued compliance with ICTRP criteria.
3. Site visit: A small audit team will visit a registry and examine all processes and procedures.
    3.1. Audits are required for all new primary and partner registries and for primary registries who are having a major change in their structure or their operating procedures.
    3.2. Audits will be conducted in the same fashion for all Registries in the WHO Registry Network.
    3.3. The primary registry will cover the cost of one person from the audit team. These costs include the travel cost and the accommodation cost.
    3.4. The audit will be on average for one full working day for each registry divided equally between the administrative and the IT functions. The IT audit should include a visit to the data center. If the data center is not located in the same location, the ICTRP auditor should be informed at least a week before the audit date, and the registry will organize a separate site visit to the data center location.
    3.5. An audit sheet is sent to the registry and it is expected to be filled and returned to ICTRP at least one week before the audit date. This sheet will help preparing the audit.
    3.6. After the audit, a report will be established and sent with the audit sheet and other documentation to the ICTRP advisory group for the final review.
    3.7. An audit is typically valid for a period of five years.

Benchmarking

> "Benchmarking is a process that enables comparison of inputs, processes or outputs between institutions (or parts of institutions) or within a single institution over time."
>
> ((Analytic Quality Glossary))

The proposed benchmarks below are being proposed to promote discussion amongst registries regarding:

- Which processes and procedures within a registry might it be appropriate to benchmark
- What the appropriate benchmark might be for each activity listed

These benchmarks have been drawn from the experience of some Registries, as well as the evaluation of registered records performed by the WHO ICTRP and presented at the 2009 of the Advisory Group on Clinical Trial Registration and Reporting *(11).*

For example: 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).

Activity	**Benchmark**
Time from submission to initial response by registry (registration if no queries, or request for more information if there are queries)	Within 5 working days of submission
Prospectively registered trials	At least 50% of all trials will be registered before recruitment of the first participant No more than 25% of all trials will be registered more than 1 month after recruitment of the first participant
Registered records are updated	At least once each year
Completed clinical trials report results	Within 12 months of completion (last data collection point of last participant).
Proportion of registered trials on a register that are out-of-date	75%
Provision of data to ICTRP Central Repository	At least once each month

The ICTRP Advisory Group

The purpose of the ICTRP Advisory Group is to advise WHO of major strategic development of the International Clinical Trials Registry Platform in order to strengthen accountability and transparency in the conduct of clinical research and dissemination of results generally, and in particular for clinical trials. The purpose of the group is also to recommend whether registries should be designated, or continue to be designated, as Primary Registries in the WHO Registry Network.

The group will:

- Review major challenges in global clinical trial registration, and provide strategic advice to WHO in this area.
- In order to strengthen accountability and transparency of clinical research, and to improve public confidence in research, identify gaps and opportunities in the area of registration of research at national and global level, and advise WHO on priority issues in relation to research registration.
- Support implementation and advocacy for WHO transparency and accountability standards in clinical research
- Review report by the ICTRP Secretariat on the applications from registries for Primary Registry status and make a recommendation for or against the application
- Assess the report by the Secretariat on any changes to a registry's profile that may impact on their continuing eligibility for Primary Registry status.
- Once each year, monitor Primary Registries to evaluate and make recommendations regarding their continuing eligibility for Primary Registry status.
- Advise the ICTRP Secretariat whether a Primary Registry should be placed on probation

If a registry has been placed on probation, determine whether adequate progress has been made to address the identified problem, or whether their status as a Primary Registry should be withdrawn

Frequently Asked Questions (FAQs)

Is there a case for exceptions to the requirement that all items in the WHO TRDS be made publicly available?

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 posted (e.g. FDAAA requirement for device trials)

Answer

- The Advisory Committee on Clinical Trial Registration and Reporting:
    - determined that there is not a case for selective disclosure of any trials
    - could not identify or envision circumstances when registering a trial could compromise the integrity of a trial, or where selective disclosure would be acceptable
    - advised that Registries should not issue waivers to registrants, even if an Ethics Board has approved aspects of non-disclosure within the protocol.
- It is ultimately the decision of the individual 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

What should a registry do when one or more investigators on a registered clinical trial are being investigated for fraud?

Answer

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.

How many primary registries can a single country have?

Answer

It is highly recommended not to have more than one registry per country. Ideally, there shouldn't be registries in all countries but primary registries are encouraged to accept registrations from other countries and especially from countries that don't have a registry.

Appendices

Appendix A: Study Type

Study type is a multi-dimensional concept, and registers may or may not collect each dimension and, if they do so, collect them in different formats. Our suggestion is that study design be split into type of study, study design and phase. Study design is itself a multi-dimensional concept so it has itself been split into allocation, masking, control, assignment and purpose. These sub-items are based on existing terms used by ClinicalTrials.gov.

In the short term, registers will be asked to provide the WHO Search Portal with 3 aggregated fields: type of study, study design (a single text field containing as much information as collected by the register) and phase (usually only applicable to drug trials). In the future, it would be suggested that registries work towards collecting this data in separate, coded fields which will ultimately improve the search capacity of the WHO Search Portal.

Aggregated item	**Individual field**	**Response options**
Type of study	Type of study	• interventional • observational
Study design	Allocation	• N/A: single arm study • randomized controlled trial • non-randomized controlled trial
	Masking	• open (masking not used) • blinded (masking used) Note: Registries may choose to collect data on who is masked (the subjects, therapist or clinician, assessor or data analyst) and/or use the terms double blind or single blind.
	Control	• placebo • active • uncontrolled • historical • dose comparison
	Assignment	• single • parallel • crossover • factorial • sequential • other
	Purpose	• treatment • prevention • diagnostic • supportive care • screening • health services research • basic science • device feasibility • other
Phase	Phase	• N/A • 0 (exploratory trials) • 1 • 1-2 • 2 • 2-3 • 3 • 4

As these fields and response options are based on the definitions used by ClinicalTrials.gov, more details for each is provided in Part 2 of this appendix.

Appendix B: Process for ICTRP Registry Application and the ICTRP Advisory Group

From 1st July 2011, all registries wanting to apply for the status of Primary Registry in the WHO Registry Network will need to complete a Registry Profile form and submit it, along with other relevant documentation (including the letter of support from the relevant authority) to the ICTRP Secretariat.

- An application will include:
    - A completed Registry Profile form
    - A letter of support from the relevant national agency (eg Ministry of Health)
    - Evidence that the registry has been able to successfully submit an xml file to the ICTRP
    - An IT infrastructure form
- The ICTRP Advisory Group will:
    - Determine if a new registry should be awarded Primary Registry status
    - Assess whether existing Primary Registries are continuing to comply with requirements
    - Determine if an existing registry should have their Primary Registry status withdrawn
- Membership of the ICTRP Advisory Group is to be renewable on a 2-year basis
- ICTRP Advisory Group meetings will be held using online conferencing facilities, or teleconference
- The ICTRP Secretariat will:
    - Assess submissions for completeness and meaningfulness, and resolve any queries, before the submission is considered by the ICTRP Advisory Group.
    - Arrange the teleconference meeting and take and circulate minutes
    - Obtain Assistant Director General clearance
    - Inform the submitting registry of the result of their submission
    - Publish the Registry Profile of the ICTRP web site (new and updated)

Glossary

Note: some definitions in this Glossary are derived from (ICH E6 Good Clinical Practice: Consolidated Guideline)

Term	Definition
Audit	A systematic and independent examination of clinical trials registry related activities and documents to determine whether the registry is complying with the required standards.
Audit trail	Documentation that allows reconstruction of the course of events. (Ref: ICH E6) A record showing who has accessed a computer system and what operations he or she has performed during a given period of time. Audit trails are useful both for maintaining security and for recovering lost transactions. Most accounting systems and database management systems include an audit trail component. In addition, there are separate audit trail software products that enable network administrators to monitor use of network resources. (http://www.webopedia.com/TERM/A/audit_trail.html, accessed 31st Oct 2017)
Clinical trial	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.
Complete	Data for every item in the TRDS has been provided
Flag	To flag a trial record Registries may publish a message or a symbol in the record to indicate that it does (or does not) meet a particular requirement. Flag: "To mark or identify with or as if with a flag <*flagged* potential problems in the proposal>" (http://www.merriam-webster.com/dictionary/flag)
Meaningful	The data provided for each item in the TRDS fulfils WHO requirements for that field, is logical and sensible (see The Trial Registration Data Set).
Multicentre trial	A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator. (Ref ICH E6)
Officially registered	A trial is officially registered once all queries have been resolved to the satisfaction of the registry to which it has been submitted, and a Registration Number has been assigned.

Out-of-date	A registered trial record is considered out of date if it has not been updated within the previous 12 months.
Protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. (Ref ICH E6)
Protocol Amendment	A written description of a change(s) to or formal clarification of a protocol. (Ref ICH E6)
Responsible Registrant	An appropriate representative of the trial's primary Sponsor. The Responsible Registrant is responsible for ensuring that the trial is properly registered. The primary Sponsor may or may not be the primary funder. The responsible registrant will 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. (see http://www.who.int/ictrp/glossary/en/index.html)
Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. (from ICH E6)
Standard	1. Something set up and established by authority as a rule for the measure of quantity, weight, extent, value, or quality (http://www.merriam-webster.com/dictionary/standard) 2. A rule or principle that is used as a basis for judgment (http://dictionary.reference.com/browse/standard) 3. An average or normal requirement, quality, quantity, level, grade, etc. (http://dictionary.reference.com/browse/standard)
Standard Operating Procedures	Detailed, written instructions to achieve uniformity of the performance of a specific function. (ICH E6)
Trial site	The location(s) where trial-related activities are actually conducted. (ICH E6)
WHO Central Repository	The data repository that houses records supplied by Registries in the WHO Registry Network and which is accessed when searching the WHO ICTRP search portal

Acronyms

Acronym	Complete Term
ANZCTR	Australian and New Zealand Clinical Trials Registry
CDISC	Clinical Data Interchange Standards Consortium (http://www.cdisc.org/)
ChiCTR	Chinese Clinical Trial Registry
CRiS	Clinical Research Information Service (Republic of Korea)
CTR-I	Clinical Trials Registry - India
DRKS	Deutsches Register Klinischer Studien (German Clinical Trials Register)
EU-CTR	European Union Clinical Trials Register
GCP	Good Clinical Practice
HL7	Health Level 7 (http://www.hl7.org/)
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICTRP	International Clinical Trials Registry Platform
IRCT	Iranian Registry of Clinical Trials
ISRCTN	International Standardised Randomised Controlled Trial Number
JPRN	Japan Primary Registries Network
NTR	The Netherlands National Trial Register
PACTR	Pan African Clinical Trials Registry
ReBec	Brazilian Clinical Trials Registry / Registro Brasileiro de Ensaios Clinicos
RePec	Peruvian Clinical Trials Registry
RPCEC	Cuban Public Registry of Clinical Trials
SLCTR	Sri Lanka Clinical Trials Registry
SOP	Standard Operating Procedure
TCTR	Thai Clinical Trials Register
TRDS	Trial Registration Data Set
UMLS	Unified Medical Language System
UTN	Universal Trial Number
WHO	World Health Organization
XML	Extensible Markup Language

Document history

Date	Details
30th September 2010	Version 1.0 approved by ICTRP Secretariat
11th October 2010	Version 1.0.1 incorporates minor changes resulting from consultation with Registry Network
11-12th November 2010	Version 1.0 tabled at Registry Network meeting
31st December 2010	Compliance with Version 1.0 required by all new Registries submitting applications for membership of the WHO Registry Network
31st December 2010	Deadline for existing Registries in the WHO Registry Network to develop plan for compliance with Version 1.0 by 30th June 2011
30th June 2011	Deadline for compliance by all Registries in the WHO Registry Network with Version 1.0
31st December 2010	Release of Version 2.0 of the Standards
31st May 2011	Release of Version 2.1 of the Standards (revised version corrects some minor errors in version 2.0, and adds information on the revised application and monitoring process)
December 2017	Drafting of Version 3.0 of the Standards
October 2018	Release of Version 3.0 of the Standards

References

1. ICMJE. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. JAMA 2005.
2. http://www.who.int/ictrp/network/criteria_summary/en/index.html
3. http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html
4. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
5. http://www.cdisc.org
6. http://www.hl7.org
7. https://www.cdc.gov/OPHSS/CSELS/DSEPD/SS1978/Glossary.html#studyObservational
8. http://www.equator-network.org/
9. http://www.cdisc.org/protocol
10. http://ichgcp.net/1-glossary
11. http://www.who.int/ictrp/about/agctrr2009/en/index.html

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