

STANDARD OPERATING PROCEDURE 28

Transparency in Clinical Research Studies

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Version 1.6	25 July 2019	Change of title, addition of information on ensuring research transparency throughout research study
Version 1.5	8 January 2019	Biennial review: Change to new format. Minor amends to text. Web links updated. Addition of requirement to keep registration data up to date.
Version 1.4	4 December 2015	Web links updated. Changes to instructions for using the ISRCTN website.
Version 1.3	25 November 2013	Addition of HRA requirement to register all trials as a condition of favourable ethical opinion.
Version 1.2	23 April 2012	Website links updated. Trial detail requirements for registration updated.
Version 1.1	21 April 2010	Addition of information on free ISRCTN registration for eligible NIHR CRN Portfolio trials.
Version 1.1	31 January 2008	Biennial review: Format change.
Version 1.0	March 2006	

Transparency in Clinical Research Studies

1. Purpose

This Standard Operating Procedure (SOP) describes the requirement for ensuring transparency in clinical research and is applicable to all study staff.

2. Background

Research transparency is central to ethical research practice. Research studies should be registered and the results made public, so that participants are protected from unnecessary research and patients benefit from improved outcomes and care informed by high quality studies.

Research transparency has four key elements:

- registering research
- making the results of research public
- letting research participants know about the results of the research
- making data from studies available for further research.

When applying for approval for a study, it is now expected that researchers have a plan for meeting ethical standards in research transparency. For clinical trials, Research Ethics Committees (RECs) will only give a favourable opinion on the condition that the study is registered on a public database.

When research is carried out openly and transparently, everyone benefits:

- patients and the public can see what research is taking place and access clear information about the results
- patients, service users and carers know about research that is relevant to them, giving them the opportunity to join studies
- health professionals, commissioners, researchers, policy makers and funders can use research findings to make informed decisions.

The Declaration of Helsinki of the World Medical Association states: “Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject”. It is also government policy in the UK to promote registration of clinical trials.

The International Standard Registered Clinical/social Study Number (ISRCTN) register was founded in response to calls for the registration of trials as a condition of publication in a journal, and also in response to the recognition that the results of many trials remain unpublished and, without registration, remain hidden from the scientific record. It is the main database used by UK researchers on which non-Investigational Medicinal Product (IMP) studies are registered.

The ISRCTN is a simple numeric system for the unique identification of Randomised Controlled Trials (RCTs) worldwide. The scheme was formally launched in May 2003 as ‘the first online service that provides unique numbers to RCTs in all areas of healthcare and from all countries around the world’. When the registry was started in the early 2000s, the acronym stood for International Standard Randomised Controlled Trial Number because the scope of the Registry was RCTs. Over the years the scope has been expanded and the acronym now means International Standard Registered

Clinical/sociAl sTudy Number. However the preferred name is simply ISRCTN and not the spelt out version.

All RCTs or studies designed to assess the efficacy of healthcare interventions (both observational and interventional) are eligible to be registered with the ISRCTN scheme. Since September 2013, registration of clinical trials in a publicly accessible database is a condition of continuing favourable ethical approval for all trials.

Registration of non-CTIMPs on a publically accessible database is not a legal requirement, but the trial must be registered in order for written articles to be included in journals and publications belonging to the International Committee of Medical Journal Editors (ICMJE) group.

The ICMJE does not advocate one particular registry, but its member journals will require authors to record their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organisation. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable.

Use of the ISRCTN register fulfils all the criteria for the ICJME.

Other acceptable registries for ICMJE are listed here: <http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/>

Clinical Trials of Investigational Medicinal Products (CTIMPs) must be registered on the EU Clinical Trials Register (European Union Drug Regulating Authorities Clinical Trials (EudraCT) database) as a requirement of their approval by the regulatory authorities. Further details of how to obtain a EudraCT number can be found in SOP 5 'Regulatory Approvals and Communication'.

Alternatively, clinical research may be registered at <http://www.clinicaltrials.gov> (a register of studies in the United States and around the world).

For other types of research, registration is also encouraged wherever possible. It may be possible to register a study through an NHS organisation or a register run by a medical research charity, or publish the study protocol through an open access publisher.

In general, registration is not expected for projects undertaken entirely for educational purposes below doctoral level.

3. Procedure

3.1 Who

Any member of staff who acts in the capacity of Chief Investigator (CI) is responsible for registering studies, updating as required to ensure the information is up to date, publishing results in a timely fashion, ensuring participants can access results and preparing a plan regarding future data sharing with other researchers. Research sponsors are responsible for ensuring appropriate arrangements are in place.

3.2 When?

The UK Health Research Authority (HRA) expects registration of all clinical trials before the first participant is recruited, in line with researcher and sponsor duties as set out by the World Health

Organisation (WHO), current Declaration of Helsinki and in the UK Framework for Health and Social Care.

Since 30 September 2013 the HRA has identified trial registration as a specific ethical expectation within the existing duties of the sponsor, and it has been a condition of the Research Ethics Committee (REC) favourable opinion, and hence a requirement, to ensure clinical trials are registered. Failure to do so within 6 weeks of the recruitment of the first UK participant is therefore a breach of the favourable ethical opinion unless a request to defer registration has been granted by the HRA and is still valid. This action was to enable the duties of sponsors to be captured as a legal requirement from that point for all clinical trials.

The ICJME states that they will only consider a study for publication if it was registered before the enrolment of the first participant. This policy applies to all studies that started recruiting on or after 1st July 2005. Failure to do so may prevent publication in key journals, such as the BMJ, which actively implement this requirement.

The mandatory requirement to register will apply to clinical trials which fit the definition of at least one of the first four categories listed on the Integrated Research Application System (IRAS) question:

- Clinical trial of an investigational medicinal product (CTIMP),
- Clinical investigation or other study of a medical device,
- Combined trial of an investigational medicinal product and an investigational medical device,
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice.

Sponsors and investigators are not required to make a separate notification to their REC confirming the trial has been registered, but they should do so at the earliest opportunity e.g. if submitting an amendment or progress report.

All registration records must be kept up to date during the conduct of the study and summary results must be uploaded within twelve months of the Notification of the End of the Study to the authorities.

3.3 How?

3.3.1 Study Registration

3.3.1.1 Non-CTIMPs

A study can be registered on the ISRCTN website via: <http://www.isrctn.com/> where full guidance is provided. It is necessary to create an account in order to log in to the system. (If the trial has been adopted onto the National Institute of Health Research (NIHR) Clinical Research Network (CRN) Portfolio of clinical trials, it is not necessary to create a registration as this will be done by the relevant CRN).

A list of the required data items for an ISRCTN application can be found: <http://www.controlled-trials.com/page/definitions>. Guidance on the completion of the form is also available from this website. The application can be saved at any point and returned to at a later time for completion.

Please note that all study registers are publically accessible and there is a requirement to ensure the text used is in lay-persons terms so it is easily understandable.

Contact details are required but note that Sponsors and CIs may request that telephone, fax and email are not displayed in their records. Details are required for administration purposes. Use of a study resource email account is acceptable rather than personal account details.

A fee is usually required to cover the costs of assigning each number. It is a one-off payment and in return the trial record will be hosted permanently in the ISRCTN Register. The ISRCTN website has details of the current rates: <http://www.isrctn.com/page/faqs>

However, the NIHR Clinical Research Network CRN Coordinating Centre has developed a process which enables free ISRCTN registration for all eligible new NIHR CRN Portfolio studies. For more information and to see if your trial is eligible for free registration see the NIHR CRN website: <https://www.nihr.ac.uk/research-and-impact/nihr-clinical-research-network-portfolio/isrctn-registration.htm>

Once confirmation that the study has been adopted onto the Portfolio, the CRN will contact the trial manager/CI with instructions on how to complete the ISRCTN information. The CI or their delegate must then complete the registration and file the email response to confirm the registration details. Trial registration details can be subsequently accessed via: <http://www.controlled-trials.com/>

Ongoing maintenance and updates to the information held in the register is required throughout the duration of the trial to ensure the details remain correct. A summary of results should be uploaded, when available, at the end of the study and within 12 months from primary study completion. More information regarding the expectations for timescales for results upload and publication can be accessed via: <http://www.who.int/ictrp/results/jointstatement/en/>

The ISRCTN website also has instructions on the practicalities of how to update ISRCTN records: <http://www.isrctn.com/page/faqs>

3.3.1.2 CTIMPs

Clinical Trials of Investigational Medicinal Products (CTIMPs), except for Phase 1 trials involving healthy volunteers, must be registered in the EudraCT database and they appear in the EU Clinical Trials Register.

When registered, each trial is issued with a unique EudraCT number which identifies the protocol and trial throughout its lifespan. The number must be quoted on ethics approval and clinical trials authorisation forms.

To begin the registration process and get a EudraCT number, trial details must be completed on the website: <https://eudract.ema.europa.eu/eudract-web/components/eudractnumber/eudractNumber.faces?showHome=false>

To create a clinical trial application and add initial required information, follow the instructions on the EMA's website: https://eudract.ema.europa.eu/help/Default.htm#cshid=/eudract/create_eudract_no.htm

Full details of the requirements to prepare the record can be found: https://eudract.ema.europa.eu/help/Default.htm#eudract/purpose_cta_ov.htm

The application must then be validated before it is entered onto the EU Clinical Trials Register.

3.3.2 Making the results of research public

For drug trials other than adult phase I trials, it is mandatory that results are made publicly available within 12 months of study completion (as defined in the study protocol).

It is a good practice requirement that results from non-CTIMPs are also made publicly available within 12 months of study completion. This applies no matter whether the results are positive, negative, neutral or inconclusive.

The International Committee of Medical Journal Editors (ICMJE) does not consider as prior publication the posting of trial results in any registry if results are limited to a brief (500 word) structured abstract or tables (to include trial participants enrolled, baseline characteristics, primary and secondary outcomes, and adverse events). For further details see: <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>

For studies managed by WCTU, the QA team will alert study teams three months prior to the reporting deadline (with additional prompts as required until the actions are completed). If results are not published in the required timelines, the issue will be escalated to the WCTU Director who will ensure appropriate actions are taken.

Summary results including key outcomes should be posted to the results section of the register(s) where the research project is registered.

If the register used does not have a results section, the results should be posted on a free-to-access, publicly available, searchable institutional website of the sponsor, funder or chief investigator.

Where the main findings are also to be submitted for publication in a journal, this should be done within 12 months of study completion, to be published through an open-access mechanism in a peer-reviewed journal.

Key outcomes of CTIMPs and trial protocols must be made publically available within 12 months of primary study completion.

Individuals must register on the EMA system to become a results user and have the ability to post results. To register follow the instructions: <https://eudract.ema.europa.eu/help/Default.htm#eudract/register.htm>

Clinical trial results can be posted once they are considered complete. In order to post results they must also be valid. If results are not valid, when you try to post them error messages are displayed. Result-related information can be posted to EudraCT in one, or both ways:

- Full data set by entering the information using the web interface, or by uploading an XML file using the web interface.
- Summary attachment(s) by uploading one or more files (e.g. PDF) using the web interface.

For full instructions see:

https://eudract.ema.europa.eu/help/Default.htm#eudract/posted_results.htm

3.3.3 Letting research participants know about the results of the research

The HRA have developed guidance to explain how and what information should be provided to study participants, their legal representatives, consultees, relatives or close friends (as applicable), at the end of a study.

See SOP 7 'Participant Information and Consent' for full details.

3.3.4 Making data from studies available for further research.

It is a good practice requirement that the data and any tissue collected for a research project are made accessible with appropriate safeguards.

The ICMJE require the following as conditions of consideration for publication of a clinical trial report in member journals:

- As of 1 July 2018 manuscripts submitted to ICMJE journals that report the results of clinical trials must contain a data sharing statement as described below.
- Clinical trials that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration.
- The ICMJE's policy regarding trial registration is explained at www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html.
- If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record.
- Data sharing statements must indicate the following: whether individual deidentified participant data (including data dictionaries) will be shared; what data in particular will be shared; whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.); when the data will become available and for how long; by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism).

See SOP 22 'Publication and Dissemination' for more details on data sharing.

For studies funded by the NIHR, expectations around data sharing have been published:

<https://www.nihr.ac.uk/about-us/who-we-are/our-policies/sharing-of-research-data.htm>

List of Abbreviations

CI	Chief Investigator
CRN	Clinical Research Network
CTIMP	Clinical Trial of an Investigational Medicinal Product
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EMA	European Medicines Agency
HRA	Health Research Authority
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
ISRCTN	International Standard Registered Clinical/social Study Number
NIHR	National Institute for Health Research
QA	Quality Assurance
R&IS	Research & Impact Services
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SOP	Standard Operating Procedure
WCTU	Warwick Clinical Trials Unit
WHO	World Health Organisation