# Clinical Research Governance Policy: Trial Registration

## CRGP 05

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**Effective from date:** Dec 2018

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**Version:** 1.0

**Review cycle:** two years from effective date

### PURPOSE

To define what, why and where clinical research studies and trials Sponsored by the University of Nottingham may be publically registered.

### SCOPE

Applicable to all University of Nottingham clinical research staff conducting clinical research, the results of which are intended to be published in peer reviewed scientific journals.
Clinical research is defined as research that is aimed at addressing hypotheses around the diagnosis, treatment or alleviation of the symptoms of disease.

### BACKGROUND

In 2004 the International Committee of Medical Journal Editors (ICMJE) gave notice (Lancet 2004: 364: 911-12) that it will consider a paper for publication of clinical research data only if it has been registered with an appropriate registry before the enrolment of the first participant. The ICMJE confirmed in May 2005 (Lancet 2005: 365: 1827-1829) that this policy was to take effect from July 1st 2005 for all new trials (to be opened after that date).

The ICMJE's goal is to foster a comprehensive, publicly available database of clinical trials. The ICMJE cited that 'A complete registry of trials would be a fitting way to thank the thousands of participants who have placed themselves at risk by volunteering for clinical trials. They deserve to know that the information that accrues from their altruism is part of the public record, where it is available to guide decisions about patient care, and deserve to know that decisions about their care rest on all of the evidence, not just the trials that authors decided to report and that journal editors decided to publish.'

This policy was sanctioned by the WHO (Lancet 2005: 365: 1829-31) with support from the British Government, the MRC and the Wellcome Trust. The WHO strengthened its resolve to achieve global registration of a minimum data set following the Northwick Park incident involving antibody TGN1412.
Around the world, governments have already or are beginning to legislate for mandatory disclosure of all trials. For example, the U.S. Congress, introduced their Fair Access to Clinical Trials (FACT) Act in 2005 as an amendment to their Public Health Service Act to expand their mandate for registration of clinical trials.

### The WHO Registry Platform

The World Health Organization's Technical Consultation on Clinical Trials Registration, April 2005 stated that it would set up an International Clinical Trials Registry Platform (ICTRP) and also outlined the minimum requirements for an individual registry and the data set that it contained. This is a major initiative aimed at standardising the way information on medical studies is made available to the public

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Currently, there are several hundred registers of clinical trials around the world but little coordination among them adding to the complexity and confusion. The Registry Platform seeks to bring participating registers together in a global network to provide a single point of access to the information stored in them.

The WHO Registry Platform is essentially a database to search for registered trials. It is not a trial registry itself, more of a portal to access registries. The Registry Platform project's aims include establishment of the norms and standards upon which international trial registration can take place ethically and scientifically. The main components and objectives of the platform are:

- Norms and standards as to which trials should be registered
- What information needs to be registered
- Who is responsible for registration
- A network of Primary and Associate Registers that meet WHO-specified criteria for quality and acceptability
- A coordinated process for detecting and resolving duplicate registrations, and the assignment of a Universal Trial Reference Number to each unique trial worldwide
- A one-stop search portal for searching registers worldwide

The Registry Platform can be found at:

http://www.who.int/ictrp/network/primary/en/

**What trials or studies should be registered?**
The WHO considers the registration of all interventional trials a scientific, ethical, and moral responsibility. An interventional clinical trial is any research study that prospectively assigns people to one or more health-related interventions (e.g., preventive care, drugs, surgical procedures, behavioural treatments, etc.) in order to evaluate their effects on health-related outcomes or trials that test a clinical hypothesis about health outcomes (e.g., "Is drug X as effective as drug Y in treating heart failure?"); in other words, those trials or studies that could shape the body of evidence about clinical effectiveness or adverse effects.

The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention *and* a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioural treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes. Health outcomes are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE does not define the timing of first participant enrolment, but best practice dictates registration by the time of first participant consent.

Therefore, registration is required of all trials or clinical research *whose primary purpose is to affect clinical practice*. Whether these are early or late trials, trials of marketed or non-marketed products, randomized or un-randomized trials - all should be registered.

**What trials or studies do not need to be registered?**
Excluded from the registration requirement are trials whose primary goal is to assess major unknown toxicity or determine pharmacokinetics (mainly phase 1 trials). These are the early phase trials conducted mainly by the pharmaceutical industries and not Universities.



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The purpose of clinical trial registration is to prevent selective publication and selective reporting of research outcomes, to prevent unnecessary duplication of research effort, to help patients and the public know what trials are planned or ongoing into which they might want to enrol, and to help give ethics review committees considering approval of new studies a view of similar work and data relevant to the research they are considering. Those purposes apply also to research with alternative designs, for example observational studies. For that reason, the ICMJE *encourages* registration of research with non-trial designs, but because the exposure or intervention in non-trial research is not dictated by the researchers, the ICMJE does not require it.

There are some clinical trials or studies whose pre-specified goal is to investigate the biology of disease or to provide preliminary data that may lead to larger, clinically directive trials. The ICMJE directed that each journal editor will have to decide on a case-by-case basis about reviewing unregistered trials in this category. Authors whose trial is unregistered will have to convince the editor that they had a sound rationale when they decided not to register their trial.

Secondary data analyses of primary (parent) clinical trials should not be registered as separate clinical trials, but instead should reference the trial registration number of the primary trial.

**When to register**

Trials should be registered as early as possible in the design and approvals process, and certainly before recruitment of the first participant (a WHO requirement). Some registers may require ethics committee approval before registration.

The Clinical Trial Authorisation application (Annex 1) to the MHRA for permission to conduct a trial that uses Investigational Medicinal Products (CTIMPs) does not require pre-registration for publication purposes but does require registration on the European Database for Regulatory Authorities of Clinical Trials (EudraCT). Please note that the EudraCT number required for ethical and regulatory approval of clinical trials involving IMPs is not a registration for publication purposes per se, but further posting of trial data and the trial results via this portal for inclusion in the EU Clinical Trials Register (EUCTR) is sufficient to meet the ICMJE requirements for publication purposes.

The WHO Registry Platform currently considers ethics approval and trial registration to be separate processes and does not require them to be inter-related. This position may change over time.

The WHO consultation paper, April 2005, also stated that the unique reference number allocated when registering a trial should appear on the trial consent form. Although this is not mandatory at present, it may become mandatory in the future and then you will have to register your trial before you submit your application to an ethics committee in this country.

**Which registry?**

The ICMJE does not advocate one particular registry, but its member journals will require authors to register 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 organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. An acceptable registry must include at minimum the following information:

- a unique identifying number
- a statement of the intervention (or interventions) and comparison (or comparisons) studied
- a statement of the study hypothesis
- definitions of the primary and secondary outcome measures
- eligibility criteria



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- key trial dates (registration date, anticipated or actual start date, anticipated or actual date of last follow-up, planned or actual date of closure to data entry, and date trial data considered complete)
- target number of subjects
- funding source
- and contact information for the principal investigator.

An important element of the plan the ICMJE endorses, is the requirement that such registries are run by none-profit making agencies with standards for the validity of the data they contain. The IMCJE sets outs out its minimum requirements of a suitable registry here:

http://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf

However, if you choose to register your trial with a registry of your choice or the registry as cited by your preferred journal for publication then be aware that should this journal reject your paper then other journals might not recognise your registration, as a valid requirement to publish in their journal.

Please also be aware that for funding purposes there may be specific requirements to register your trial with a specific database. If this is the case please check with the either the holders of that database or the ICMJE that it fulfils the requirements for subsequent publication purposes.

Currently the University of Nottingham is registered as a trial Sponsor at clincialtrials.gov and any trials registered on this website that cite the University of Nottingham as the Sponsor will undergo an authorisation step to confirm that the University is acting as Sponsor. The Head of Research Governance is the contact for that authorisation.

The Head of Research Govenrnance also holds the University of Nottingham account on EudraCT and the responsibility for obtaining a EudraCT number now lies with the Research Governance Team.

**Confidentiality and IP**
Understandably there may be concerns over the disclosure of trial objectives and expected outcomes, particularly for potentially commercially viable products and that such disclosure via a registry could jeopardize academic or commercial competitive advantage if they apply to preliminary trials of new interventions.

In response to such concerns the ICMJE have stated that they will not consider as prior publication the posting of trial results in any registry that meets the above criteria 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).

**Registry Maintenance**
Once your study is registered it is your responsibility to maintain that registry i.e. to update the record in accordance with the timeframe and requirements of that registry. This maintenance includes the final posting of study results. For CTIMPs results should be posted on the EUCTR (via the EudraCT portal) within 12 months of the end of the study as defined in the study protocol.



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