



## All trials registered. All results reported.

*September 2013*

The AllTrials campaign calls for all past and present clinical trials to be registered and their results reported.

Clinical trials are investigations designed to assess the effects – wanted and unwanted - of healthcare interventions in people. The Declaration of Helsinki, which is the World Medical Association’s statement of principles for medical research involving people, states that every investigator running a clinical trial should register it and report its results. Millions of volunteers have participated in clinical trials to help find out more about the effects of treatments on disease, yet that important ethical principle about reporting has been widely ignored. Information on what was done and what was found in these trials could be lost forever to doctors and researchers, leading to bad treatment decisions, missed opportunities for good medicine, and trials being repeated. This is what led to the AllTrials campaign in January 2013, a campaign which is now supported by thousands of individual patients, clinicians and researchers across the world, and by hundreds of organisations representing millions of people.

This document sets out more information about achieving a situation globally where all trials are registered and results reported. It is an achievement that will involve regulators and registries, clinical trial funders, universities and institutes, professional and learned societies and medical journals, patients and researchers.

This document is part of a continuing discussion which many different organisations are working on elaborating further over coming weeks and months. Please email views and contributions to:

[alltrials@senseaboutscience.org](mailto:alltrials@senseaboutscience.org)

### **What trial information needs to be registered and reported?**

There are four levels of information in clinical trial reporting: (1) knowledge that a trial has been conducted, from a clinical trials register; (2) a brief summary of the trial’s results; (3) full details about the trial’s methods and results; (4) individual patient data from the trial.

The AllTrials campaign is concerned with the first three. There are now initiatives in many countries to work out how individual patient data can be shared with other researchers.

## 1. Registration

**In brief: Planned clinical trials should be registered, with a summary of the trial protocol, before the first participant is recruited. Past trials that were not registered should now be registered retrospectively. This is essential if the trial was on medicines or interventions that we currently use (this includes some trials conducted before registries were established).**

Checks on the registration status of published trials, show that around 40% of clinical trials concerning treatments in current use were not registered<sup>1</sup>. This figure does not include unregistered trials that have never been published.

The situation is improving: increasingly, funders and research organisations are insisting that trials are registered and it is a legal requirement for trials on some medicinal products in the EU, USA and five other countries<sup>2</sup>.

The World Health Organization (WHO) has set out a 20 item Trial Registration Data Set<sup>3</sup> of the minimum information that should be included when registering a trial. Registration covers rationale and background to the trial; information on study participants and informed consent; the intervention under investigation, primary and key secondary outcomes; the method of data collection and statistical analysis plans. For further information see the SPIRIT<sup>4</sup> guidelines published in 2013.

Prospective registration is the gold standard for the reasons set out in the 2005 Ottawa Statement<sup>5</sup>. All trials that were not prospectively registered should still be registered now, i.e. retrospectively. This is particularly important for trials conducted to evaluate the efficacy and safety of a treatment in current use, some of which were done before trial registration was possible. Many registrations are incomplete against the WHO data set and registries should advise on which aspects of these could reasonably be completed.

There is no excuse for not registering planned or completed clinical trials. Clinicaltrials.gov is the world's largest register. It accepts registration from anywhere in the world and allows retrospective registration of trials. There are numerous national and regional registries, and others held by funders, institutions and corporations. About 20 of these are collected in the WHO's Registry Network<sup>6</sup>.

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<sup>1</sup> Huser 2013, Freshwater 2013, Killeen 2013, van de Wetering 2012, Jones 2012, Scherer 2012, McGee 2011, Mathieu 2009, Rasmussen 2009

<sup>2</sup> [http://www.who.int/ictrp/trial\\_reg/en/index2.html](http://www.who.int/ictrp/trial_reg/en/index2.html)

<sup>3</sup> WHO Trial Registration Data Set <http://www.who.int/ictrp/network/trds/en/index.html>

<sup>4</sup> SPIRIT 2013 (Standard Protocol Items: Recommendations for Interventional Trials) explanation and elaboration: guidance for protocols of clinical trials <http://www.bmj.com/content/346/bmj.e7586>

<sup>5</sup> Krleža-Jeric K et al for the Ottawa Group 2005 Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa Statement <http://www.bmj.com/content/330/7497/956>

<sup>6</sup> The WHO Registry Network <http://www.who.int/ictrp/network/en/>

The proliferation of registries with different requirements is, though, limiting the usefulness and transparency of reported information. A trial can be registered in multiple registries but the entries are not always connected together. It is not currently possible for researchers or patients to find all trials that have been done on a particular intervention, even if all the trials have been registered somewhere.

The registration system could be streamlined and standardised internationally. There are now discussions about how to achieve this. Drawing down central information to multiple destinations may be more achievable than drawing it in from multiple sources to a central place, which has so far been the model. A small number of global centres would make it possible to standardise the way the data are structured so that entries can be linked and searched. Another option is to ensure that registries require trials to give all other registries' ID numbers for trials that appear on multiple registers. Both strategies would help to ensure that trials can be linked and tracked from registration to publication of results.

### **Enforcement and Monitoring**

It should be impossible to obtain funding for a trial, including funding from Government, or to sell a product, or to obtain permission to do a clinical trial, without proving registration.

**Regulatory routes:** In some regions the registration requirement has become or will become law for trials related to new marketing authorisation of drugs. The proposed EU Clinical Trials Regulation will require registration as part of approval for any new trial of a medicinal product. The US TEST Act, tabled in 2013, would require trials used to support licensing applications to have been registered before they have started. The FDA Amendments Act 2007 already requires trials with at least one site in the US to be registered within 21 days of the first patient being enrolled. The regulatory and ethical approval processes for clinical trials in every country can be developed to incorporate and monitor compliance with registration.

**Funders:** Applications for reimbursement and funding could include explicit statements that the trials will be registered and results reported. Some funders have already started to do this. Trial registration IDs should be requested and compliance monitored to the best of an organisation's ability. A declaration that all past trials conducted by the investigator were registered could also be requested.

**Journals and professional societies:** The International Committee of Medical Journal Editors (ICMJE) committed in 2005 to publish only reports from trials that had been registered at inception. Requesting the trial number will help to monitor compliance with this more effectively. However, in order to overcome the historic gap in trial registration and reporting, journals should look at how they deal with any previously unreported trials that weren't registered or pre-dated the registration requirement. For the future, journals could also ask for disclosure of registration details of all linked trials and commit to making it clear on a trial report if previously undisclosed trials come to light after publication. Professional bodies and learned societies should make it explicit in their codes of conduct that members must register clinical trials, and they can lobby for this to become an international standard.

## 2. Summary results reporting

**In brief: A summary of results should be publicly available where the trial was registered, within one year of completion of the trial. Summary results from all past trials of medicines currently in use should be made publicly available on a register now. Summary results include information on the primary and any secondary outcomes measured and statistical analysis. This is part of the structured information that global registries should support.**

An audit published in 2012 found that only a fifth of trials registered on [clinicaltrials.gov](http://clinicaltrials.gov) had reported results within one year of completion<sup>7</sup> and different research found that trials which produced negative results are twice as likely to remain unreported than positive trials<sup>8</sup>. Publication of all results will reduce reporting biases and help researchers and policymakers produce more reliable systematic reviews of the safety and effectiveness of medical interventions.

Millions of patients have volunteered for clinical trials in the expectation that the findings generated by their effort will contribute to the body of knowledge about their conditions and future treatments. Publishing results fulfils clinical trialists' ethical responsibility to patients in clinical trials, as set out in the Helsinki Declaration.

Summary results should be posted publicly within a year of the completion of the trial<sup>9</sup> where the trial was registered. Current discussions about registry development are looking at how to provide a clearer timeline of updates made to each entry and to indicate more clearly where information about the results is missing. As well as helping to improve compliance this will raise awareness among investigators about what is expected.

All past trials which have not reported results for medicines in current use should do this now. Registers should provide space for reporting of requests for results by third parties and include a log of requests for overdue information sent to trial sponsors, as well as responses to such requests.

Reports of clinical trial summary results on a register should at least contain the items on a [clinicaltrials.gov](http://clinicaltrials.gov) results page (which includes summary participant information, protocol and amendments, summary results for pre-specified primary and secondary end points, details of adverse events and statistical analyses)<sup>10</sup>. If they don't, they should be supplemented with extra information added to the register the trial was registered on. Results are produced in a variety of formats - in peer reviewed journal papers, clinical study reports in the case of drugs for which marketing authorisation applications are being

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<sup>7</sup> Prayle AP 2012 Compliance with mandatory reporting of clinical trial results on [ClinicalTrials.gov](http://clinicaltrials.gov): cross sectional study <http://www.bmj.com/content/344/bmj.d7373>

<sup>8</sup> Song et al 2010 Dissemination and publication of research findings: an updated review of related biases <http://www.hta.ac.uk/fullmono/mon1408.pdf>

<sup>9</sup> The completion date of a trial is the final date on which data was (or is expected to be) collected.

<sup>10</sup> See Appendix 1 for a suggested list of contents of summary results

made, reports to grant giving bodies, and so on. These may contain all or some of the summary results information required. Links and documents can be uploaded directly onto registers.

Registers currently have different formats for reporting results. Results cannot be uploaded to [clinicaltrials.gov](http://clinicaltrials.gov) as PDFs for example. Ideally every major register could require results to be uploaded in a format that allows the main reported items to be searchable and enables sharing of information between registries. Some registries are curated to ensure there is internal logic in entries. Global registries would certainly have to do this to be useful and manageable.

The ICMJE has stated that prior publication of results on a register is not a barrier to publication in a journal. Journal reports on trials should be linked to the clinical trial unique identifier.

### **Enforcement and Monitoring**

**Regulation:** The US FDA Amendment Act 2007 requires that results must be posted on [clinicaltrials.gov](http://clinicaltrials.gov) within a year of the completion of the trial for all trials with at least one site in the US. The FDA has the power to fine trial sponsors who do not comply but rarely does this. Whether or not a trial is required to post results – or has been granted an extension - is often the subject of legal discussion, and as a consequence there is no clarity about whether a trial is truly overdue by the terms of the Act. The proposed EU Clinical Trials Regulation will require that summary results for every registered trial must be posted within one year of the completion of the trial, and the European Commission is discussing how to enforce this properly. Trial approval bodies in each country should consider expanding their monitoring of reporting, and ensure there is routine and open public audit of compliance for each individual trial.

**Funders:** Trials approval, processes such as marketing authorisation and reimbursement for medicinal products, and applications for funding could require an explicit statement that the results of the trial will be made available on a register within a year of trial's end. Some funders have started this, and begun withholding funds until results are shared. A declaration that results from all past trials conducted by the investigator have been reported could also be required.

**Journals and professional societies:** Journals should state clearly that there are no bars to subsequent publication of a trial report when summary results are posted to a register. A number of journals have supported the Restoring Invisible and Abandoned Trials statement which gives trialists an amnesty of one year to publish results of previously unreported trials<sup>11</sup>. Professional societies should ensure that their professional codes of conduct reflect the requirement to report summary results.

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<sup>11</sup> Restoring invisible and abandoned trials: a call for people to publish the findings *BMJ* 2013;346:f2865  
<http://www.bmj.com/content/346/bmj.f2865>

### 3. A full report

**In brief: Trial sponsors or others who produce a full report for marketing authorisation or any other purpose should make this publicly available. The narrative reports of adverse events and individual patient data in a full report can be redacted and available on request to researchers, in the same way that reports of adverse incidents currently are, with a commitment that no reasonable request will be refused.**

Full reports (Clinical Study Reports or their equivalent in non-commercial settings) contain a large amount of detailed information about the methods, analysis, results and conclusions of a clinical trial<sup>12</sup>. This information is needed to make and to scrutinise decisions about medicines and to assess published summary findings. Clinical Study Reports are produced for regulatory and licensing purposes and follow a standard structure set out by ICH GCP guidelines<sup>13</sup>. An equivalent for researchers who do not plan to produce a Clinical Study Report is any document that complies with the 25-item CONSORT statement on trial reporting.<sup>14</sup> Full reports should be made publicly available when they have been created.

Full reports sometimes contain narrative descriptions of adverse events experienced by trial participants. This information is important to understanding the trade off between risks and benefits of a treatment. These paragraphs may contain identifiable patient information which may need to be redacted. These paragraphs should be available on request to researchers who provide a protocol of their study plan, with no reasonable request refused by the academic or company who authored the report. This is similar to the system for releasing the full narrative descriptions in spontaneous reports of possible adverse events to prescribed medications, reported by doctors and patients to regulators through the Yellow Card<sup>15</sup> scheme in the UK.

Clinical Study Reports also contain line by line individual patient data on all participants in one carefully specified section. **We do not call for individual patient data to be made publicly available** though there are extensive discussions at present on how this information could be shared where it is of value to research. The EU Ombudsman has ruled that it is not a significant burden to remove individual patient data from full reports before public sharing. Some organisations (GSK) have committed to making all of their reports publicly available, with this information redacted. Others (Roche) have committed to providing this information on demand.

#### **Enforcement and Monitoring**

Regulation: The proposed EU Clinical Trials Regulation will contain guidance that no information in a clinical study report should be considered commercially confidential once a decision about marketing

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<sup>12</sup> Doshi & Jefferson, 2012 Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. *BMJ Open* <http://bmjopen.bmj.com/content/3/2/e002496.full>

<sup>13</sup> [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E3/E3\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf)

<sup>14</sup> <http://www.consort-statement.org/consort-statement/overview0/>

<sup>15</sup> Yellow Card Scheme – MHRA <https://yellowcard.mhra.gov.uk>

authorisation has been made. The European Medicines Agency's transparency policy is to release any full report it holds on request. Other regions should adopt a similar approach.

#### **4. Individual patient data**

**The AllTrials campaign is not calling for individual patient data to be made publicly available.**

There are currently initiatives in many countries looking at how to improve sharing of this level of information for the benefit of future research. This offers significant opportunities, such as: improving the accuracy of estimates of benefits from a treatment, through individual patient data meta-analyses; and identifying subgroups of patients who respond better, or worse, to a specific treatment. Patient groups, medical research funders and trialists have raised concerns about the inability to reuse past research. They are keen to develop consent protocols that will optimise the ability to reuse findings, and want legislators to look at whether new data protection regulations impose unnecessary burdens and restrictions on reuse of past research.

The AllTrials campaign is an initiative of Bad Science, *BMJ*, Centre for Evidence-based Medicine, Cochrane Collaboration, James Lind Initiative, *PLOS* and Sense About Science and is being led in the US by Dartmouth's Geisel School of Medicine and the Dartmouth Institute for Health Policy & Clinical Practice. It was launched in January 2013 to call for all clinical trials to be registered and results reported.

[www.alltrials.net](http://www.alltrials.net)

## Appendix 1: Content of the summary of the results of a clinical trial, as set out in Annex IIIa of proposed regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use

### 1. Trial information:

- a) Study identification
- b) Identifiers
- c) Sponsor details
- d) Paediatric regulatory details
- e) Result analysis stage
- f) General information about the trial including: a structured summary of trial design, methods, results, and conclusions; scientific background and explanation of rationale; specific objectives or hypotheses.
- g) Population of trial subjects with actual number of subjects included in the trial

### 2. Subject disposition:

- a) Recruitment
- b) Pre-assignment Period
- c) Post-assignment Periods

### 3. Baseline Characteristics:

- a) Baseline Characteristics (Required) Age
- b) Baseline Characteristics (Required) Gender
- c) Baseline Characteristics (Optional) Study Specific Characteristic

### 4. End Points:

- a) Endpoint definitions
- b) End Point #1\*

Statistical Analyses

- c) End Point #2,

Statistical Analyses

\*Information shall be provided for as many end points as defined in the protocol.

### 5. Adverse Events:

- a) Adverse events information
- b) Adverse event reporting group
- c) Serious Adverse Events
- d) Non-serious adverse event

### 6. More Information:

- a) Global Substantial Modifications
- b) Global Interruptions and re-starts
- c) Limitations & Caveats

### 7. The protocol and its subsequent modifications