

Joint statement on public disclosure of results from clinical trials

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Inserm

Research Council of Norway

UK Medical Research Council

Médecins Sans Frontières

Epicentre

CEPI

PATH

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Drugs for Neglected Diseases Initiative (DNDi)

Bill and Melinda Gates Foundation

Wellcome Trust

Introduction

The current 2013 Declaration of Helsinki states that “Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.” and that “Researchers have a duty to make publicly available the results of their research Negative and inconclusive as well as positive results must be published or otherwise made publicly available”. In addition to the ethical imperative, poor allocation of resources for product development and financing of available interventions, and suboptimal regulatory and public health recommendations may occur where decisions are based on only a subset of all completed clinical trials.

The signatories of this joint statement affirm that the prospective registration and timely public disclosure of results from all clinical trials is of critical scientific and ethical importance. Furthermore timely results disclosure reduces waste in research, increases value and efficiency in use of funds and reduces reporting bias, which should lead to better decision-making in health.

Within 12 months of becoming a signatory of this statement, we each pledge to develop and implement a policy with mandated timeframes for prospective registration and public disclosure of the results of clinical trials that we fund, co-fund, sponsor or support. We each agree to monitor registration and endorse the development of systems to monitor results reporting on an ongoing basis. We agree to share challenges and progress in the monitoring of these policies. We agree that

transparency is important and therefore the outputs from the monitoring process will be publicly available.

Benefits and costs of requiring public disclosure of results

The benefits of implementing and monitoring policies on public disclosure of results relate to access to more complete information about the results of clinical trials. The benefits are summarised below.

- The current bias in the reporting of results will be reduced allowing for more informed decisions in the following areas:
 - Licensure/marketing authorization (including risk-benefit assessments),
 - Public health policy recommendation on use (including cost-effectiveness), and
 - Financing decisions by public procurement bodies, and multilateral agencies
 - Optimal implementation and delivery
 - Individual treatment choices by doctors and patients
- Research funding allocation will be more efficient (avoiding the current situation, whereby funds may be allocated to answer scientific questions that have already been answered in unreported clinical trials, and waste occurs because learning from previous trials cannot be taken into account in design of current trials)
- The development of interventions will be more efficient
- Ethical requirements for dissemination of information will be met, potentially increasing trust of trial participants in the utility of clinical research
- The scientific state-of-the-art will be based on a more complete cross-section of clinical trial data; in particular the many negative clinical trials will be more available for assessments.

A further benefit is that doctors, professional bodies and the general public will be able to access the results from a larger proportion of clinical trials.

Finally patients seeking enrolment in clinical trials will be able to access results from previously completed clinical trials in their area, as they make decisions on which clinical trials they may wish to seek enrolment into.

There will be modest costs associated with public disclosure of clinical trial results. The costs of disseminating the results of research are a minor component of the overall costs of conducting such research, and results reporting is an essential component of the research enterprise. The resource allocation, public health and scientific benefits - together with the need to meet ethical imperatives - far outweigh the costs.

PROPOSED COMMON ELEMENTS OF AGENCIES' POLICIES ON RESULTS REPORTING

Principles that could be included in harmonized policies on results reporting include the following:

Registration of clinical trials

Before any clinical trial¹ is initiated (at any Phase) its details must be registered in a publicly available, free to access, searchable clinical trial registry complying with WHO's international agreed standards

¹ A clinical trial is defined by WHO as 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.

(www.who.int/ictrp). The clinical trial registry entry must be made before the first subject receives the first medical intervention in the trial (or as soon as possible afterwards). Clinical trial registry records should be updated as necessary to include final enrolment numbers achieved, and the date of primary study completion (defined as the last data collection timepoint for the last subject for the primary outcome measure). If clinical trials are terminated, their status should be updated to note the date of termination, and to report the numbers enrolled up to the date of termination.

Completeness and accuracy of the clinical trial registry records can be a limiting factor for use of information from the registries, and it is encouraged that care is taken to ensure good quality registry entries.

Reporting timeframes for clinical trials

We jointly agree that summary results² of clinical trials should be made publicly available in a timely manner following primary study completion. There are two main modalities for this to occur. By posting to the results section of the clinical trial registry and by journal publication. We will work towards a timeframe of 12 months from primary study completion (the last visit of the last subject for collection of data on the primary outcome) as the global norm for summary results disclosure³. As timelines for publication in a journal are not fully within the control of the sponsor or investigator, this joint statement focuses on use of registries – such as clinicaltrials.gov and EU-CTR - to meet this results disclosure expectation. Publication in a journal is also an expectation, with an indicative timeframe of 24 months from study completion to allow for peer review etc. Access to a sufficiently detailed clinical trial protocol is necessary in order to be able to interpret summary results. Therefore we also encourage development of requirements that the protocols are made publicly available no later than the time of the summary results disclosure as part of the clinical trial registry summary results information (including amendments approved by ethics committees/institutional review boards, and either as uploaded electronic document formats such as pdfs or links to the pdf).

At the time of the initial grant submission, the plan for public disclosure of results should be included, including specific time bound commitments. Reasonable funds to enable compliance with these considerations is a cost eligible item in clinical trial budgets.

Trial ID in clinical trial publication

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.

² “Summary results” here are defined as including the following as a minimum: baseline characteristics, participant flow, primary and secondary outcome measures, and adverse events including all serious adverse events and important anticipated or unanticipated adverse events. An example of a format for providing results: <https://clinicaltrials.gov/ct2/about-site/results>. Note that “summary results” refers to analyses conducted on data, not to primary data disclosure itself. “Summary results” in this statement are synonymous with “key outcomes” in the 2015 WHO statement on public disclosure of results.

³ Agencies retain the right to include flexibility in how this is implemented, including a phase-in period, and allowance of requests for extensions for up to a maximum of 24-36 months from primary study completion for certain pre-licensure trials of regulated products where sponsors certify that product development remains ongoing.

The Trial ID or registry identifier code/number should be included in all publications of clinical trials, and should be provided as part of the abstract to PubMed and other bibliographic search databases for easy linking of trial related publications with clinical trial registry site records. This is essential for linking journal publications with registry records.

Registration and reporting of past trials

Reporting of previous trials realises the value of funding; therefore the contribution made from reporting previous trials, whatever their results, will be considered in the assessment of a funding proposal. When a PI applies for new funding, they may be asked to provide a list of all previous trials on which they were PI within a specified timeframe and their reporting status, with an explanation where trials have remained unreported.

A note on sharing of individual participants' data

As trials are registered, this sets a basis for development of IPD sharing. The benefit of sharing individual participants' data (IPD) and the facilitation of research through greater access to primary datasets is a principle which we consider important. This statement is not directed towards sharing of IPD. However we are all actively engaged with initiatives related to IPD sharing, and support sharing of health research datasets whenever appropriate. We will continue to engage with partners in support of an enabling environment to allow data sharing to maximise the value of health research data. We will support activities that enable the development of explicit ethical and legal frameworks that govern data collection and use and enable development of international norms and standards for sharing of IPD from clinical trials.

A note on open access policies

We are all supporters of open access policies, and consider that publications describing clinical trial results should be open access from the date of publication, wherever possible. Open access fees should be included in clinical trial budget requests, if necessary.

A note on the scope of this statement

While this statement focuses on clinical trials, transparency and reduction of waste and reporting bias are important for other types of research including public health intervention studies, observational studies, implementation research and pre-clinical studies of experimental therapeutics and preventives.

We encourage formative work on development of possible transparency frameworks for these types of research, including how best to develop registries that publicly disclose research studies in the above categories.