POSTNOTE

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Transparency of Clinical Trial Data

Results from many clinical trials are not published or made available. Recently there have been calls for clinical trials data to be made more accessible. This briefing examines ways of achieving greater transparency and the issues that they raise.

Overview

- Clinical trials test the safety and effectiveness of interventions such as drugs, devices or other procedures.
- Historically, trials have been more likely to be published if they are positive, creating a bias in the scientific literature.
- All UK trials must now be registered as a condition of ethical approval.
- There is debate over what information – for example registration details, trial design or patient outcomes – should be released.
- Detailed data give a more accurate overview of the effectiveness of an intervention, but may risk patient re-identification and compromise commercial interests.

Background

The term clinical trial can include:

- trials carried out on potential new drugs in preparation for a regulatory submission
- trials on any medical interventions whether these are drugs, devices or procedures
- other investigations involving people conducted for research purposes such as sleep or psychology studies.

All of the above generate a lot of data. Historically only a small subset of clinical trials has been published in peer-reviewed journals. These were more likely to be studies reporting positive results[1,2,3] such as a beneficial effect for a drug. This has created a publication bias towards positive findings (see Box 1) that may give an overly optimistic view of the likely effectiveness of an intervention.

These factors have led to calls to increase the transparency of clinical trials. One such initiative is the 'AllTrials' campaign. The recently agreed EU Clinical Trials Regulation that comes into force in 2016 will increase transparency and the European Medicines Agency (EMA) has published a new draft transparency policy (Box 4). Many would like to see increased transparency extend to data from all types of clinical research, including trials not done for regulatory purposes. A recent House of Commons Science and Technology Committee report examined the need for increased transparency of clinical trials, while the Public Accounts Committee looked at access to clinical trial data in the context of stockpiling the drug Tamiflu.

This briefing summarises the issues raised by improving the transparency of four different levels of information about clinical trials:

- the registration of outline details of all clinical trials
- the posting of summary level data from all clinical trials
- publication of the long reports produced by a company for regulatory purposes (called clinical study reports)
- making the anonymised individual patient data that all trials produce available to researchers.

Box 1. Publication Bias and Clinical Trials

Published clinical trials are not representative of the total output of clinical research because negative or inconclusive trials often do not get published. Historically, there have been examples of wilful hiding of trials to engineer a false, positive, outcome for an intervention.[4] However, there are a number of other reasons why trials may not be published. For instance, writing up a trial for publication requires a large amount of time and effort. If a trial does not produce a positive result, the incentive to write up the research is reduced, as it is unlikely to be published in a prestigious journal. Clinical trials also generate copious amounts of data. Even if a trial is published then it is usually summarised in a paper of around 10 pages.[5] This means that much of the information is omitted from the final paper.[6]

It may also be harder to publish 'negative' clinical trials as many journals are only interested in publishing research likely to be referenced by other scientists. However, newer journals such as *Trials* and *Journal of Negative Results in Biomedicine* publish well designed studies irrespective of the outcome.[7]

Different Levels of Trial Information

Trial Registration

Researchers conducting clinical trials are increasingly required to register details of the trial in publicly accessible databases. Details of the main national, European and international requirements are summarised in Box 2. Only clinical trials of new drugs are required to be registered in the UK, meaning many trials go unregistered. Following the Science and Technology Committee's recommendation for universal trail registration, the Health Research Authority (HRA) has made trial registration a requirement for ethical approval. Some research funders, publishers and industry associations[8] have similar requirements. The level of detail required varies from one register to another.

There is a wide consensus across academia, industry, and health professionals in favour of clinical trials registration. Registration provides a valuable resource for researchers, clinicians and patients alike at a minimal regulatory cost to those conducting a trial. However, there is debate over:

- **The information to be registered.** The trial protocol, statistical analysis plan and expected completion date could be registered before the trial starts. This would allow the final outcome to be checked against the protocol and make it easier to flag non published trials.
- **Where trials should be registered.** A UK-specific central trial registry may be a useful resource. However, a proliferation of registers imposes a bigger regulatory burden (entering trials into multiple registers) and makes it harder to search for trials.
- **Retrospective registration.** There is debate as to whether there should be a requirement to retrospectively register details and summary results of historical clinical trials. The further back such a requirement goes the greater the administrative burden involved.
- **Ensuring appropriate oversight.** Registration is now required by HRA for ethical approval but there is debate as to whether making it a statutory requirement in the UK would bring further benefits. Additionally, professional bodies could adopt a policy that construes the conduct of unregistered trials as professional misconduct.

Posting Summary Level Data

Many registers now allow researchers to post brief (summary level) details of the main results of a completed trial. There is no legal requirement for this in the UK, although it is considered best practice.[9,10] There is also widespread support for publishing the summary level results of a trial. This ensures that the published record is complete and reduces the bias in the scientific literature (Box 1). It may also prevent unnecessary research and increase the available information on an intervention.

There is ongoing debate over how best to disseminate summary level data and the oversight mechanisms needed. On this question the Commons Science and Technology Committee favoured publication of summary level data in peer-reviewed journals.

Box 2. Requirements for Trial Registration

World Medical Association's Declaration of Helsinki

The Declaration of Helsinki outlines principles for research involving human subjects. The 7th revision was published in 2013 and contained a section on 'Research Registration and Publication and Dissemination of Results'.[11] It notes that there is an ethical obligation to publish negative, positive or inconclusive findings in a complete and accurate manner and requires researchers conducting a research study involving human subjects to:

- register the study in a "publicly accessible database before recruitment of the first subject"
- give all medical research subjects the "option of being informed about the general outcome and results of the study"
- report and disseminate the study's findings and conclusions.

UK Requirements

The Medicines for Human Use (Clinical Trials) Regulation 2004 regulates the conduct of clinical trials in the UK. It transposed the EU Clinical Trials Directive (2001/20/EC) into UK law and established the UK competent authority (the Medicines and Healthcare products Regulatory Agency, MHRA). It came into force in 2004, before the 2013 revision of the Declaration of Helsinki and requires that clinical trials are conducted in accordance with an earlier version of the Declaration which did not comment on trial registration or publication. There is thus no statutory obligation in UK law to conduct trials in accordance with the 2013 version. The Health Research Authority (HRA) requires trial registration as a condition of ethical approval.[12] While there is an expectation that summary results will also be published this is not a requirement. The Public Accounts Committee recommended that clinical trials data submitted to the MHRA for regulatory purposes should be shared with the National Institute for Health and Care Excellence to aid its appraisal of medicines.

EU Requirements

The EU clinical trials directive requires clinical trials of investigational medicinal products to be registered on the European Clinical Trials database, EudraCT. The latest (2013) version of the database allows summary results to be uploaded.[13] However, the requirement does not apply to academic trials, or trials of other interventions and some clinical trials registered on EudraCT are not viewable by the public. In contrast the US Clinicaltrials.gov register is open, and all trials can be registered on it, from any country. The US Food and Drug Administration require all trials seeking approval to be posted on the register along with a summary of the results at the end of the trial.

Options for oversight to ensure publication are largely similar to those for registration. It has been suggested that all trial sponsors publish their policies on research dissemination. While it may be possible to obtain a commitment to publish as a condition of funding or ethical approval, it is difficult to ensure that it is honoured. It is also difficult to estimate the number of trials that are carried out in the UK that are not registered or published. Data from the German regulator shows that between 2006 and 2011 around 7% of trials conducted for regulatory purposes were not registered or published anywhere in the public domain. No details are available about the proportion of trials submitted to UK or EU regulators that are published in some form.

Clinical Study Reports for Regulators

A Clinical Study Report (CSR) is a document containing all the details of a clinical trial that is submitted to regulators by a company seeking authorisation to market a new product. Detailed guidance on what should be included in a CSR has

been produced by the International Conference on Harmonisation, a collaboration between US, European and Japanese regulators.[14] CSRs can be over a thousand pages long and include detailed descriptions of the study protocols, analysis plans, results and individual patient data. CSRs can be summarised and published in a peer-reviewed journal. The German regulator estimates that 65% of clinical trials that produced a CSR have been published, while the Association of the British Pharmaceutical Industry puts the figure at 89%.[15,16]

Advantages of Making CSRs Available

An independent Cochrane Review of anti-flu drugs led to a dispute about whether the review team could have access to the CSRs for one of the drugs (Tamiflu). CSR access allows researchers to publish summaries of these reports, completing the published record and giving a more accurate overview of a drug's safety and efficacy.[17] The concise nature of journal papers means that a large amount of information is omitted for publication. This may include trial limitations, and information on the harms and efficacy of a drug for different patient groups or endpoints.[18,19] Access to the detailed CSRs allows the quality of a trial to be assessed, and any limitations identified by inspecting the study protocol, statistical analysis plan and detailed results. For example in one of the Tamiflu trials the placebo and the active treatment looked different to each other, potentially biasing the trial. This was only identified by examining the CSR of the trial.[20,21,22]

Disadvantages of Making CSRs Available

Some companies argue that there are two potential concerns over making CSRs more widely available. First, some of the information contained in CSRs may be commercially sensitive, such as details of the manufacturing of the clinical trials material. Second, there is concern that there is a potential for people to abuse this access. For instance those with a vested interest may make improper analyses or come to inappropriate conclusions. This could potentially have an adverse effect on patient care. The Commons Science and Technology Committee noted that it saw no good reason why CSRs submitted to regulators should not be placed in the public domain in a redacted form. It did not support any move to make it mandatory for non-commercial trials to produce a CSR.

Individual Patient Data

Individual patient data (IPD) is the raw data from a clinical trial that has been processed to remove obvious identifying features such as names, addresses and telephone numbers. In practice IPD from historical non-commercial trials are unlikely to have been preserved. Archiving of IPD in a form that remains accessible and useful presents a number of challenges (see Box 3).

Advantages of Making IPD available

There are a number of arguments for making IPD available. First, IPD from similar trials can be combined and used to give a summary result for all the trials.

Box 3. Archiving and Data Preservation

There is a regulatory requirement to archive data from commercial clinical trials. However, archiving data in a way that allows them to be retrieved, used and shared at a later date presents a number of challenges.[23] These include:

- Providing appropriate documentation that describes what each part of the dataset is and how it is coded. This ensures that clinical trial data are usable once retrieved.
- Using an appropriate format. Using a basic format such as plain text increases the usefulness of the data. In contrast, storing data in proprietary formats limits the number of people who could reuse the data. It also makes the data more resilient to future changes in software, as some proprietary formats may cease to be supported.

An Institute of Medicine workshop on sharing clinical research data suggested that a global standard for storage of clinical data would aid further analysis. The Clinical Data Interchange Standards Consortium is working towards creating these global standards to facilitate research that combines results from many trials.[24]

This can be hard to do with only the summary data. For example it would be impossible to combine two clinical trials using only the summary data if one trial looked at three year survival and one at seven year survival. However, if IPD data were made available it would be possible to combine the three year survival information for both trials.[20]

IPD could also be used to answer new research questions. For example if a licensed drug is suspected of increasing the risk of an adverse reaction, then it may be possible to address this using existing trial data. Further, researchers could look at whether an intervention performed differently in different populations such as older and younger people. Further, making data available to researchers increases the chances of error identification and reduces the potential for selective reporting.

Disadvantages of Making IPD Available

Key arguments against making IPD available include the possibility of inappropriate reanalysis (see CSR), and the potential for individual patients to be identified, raising issues of patient consent and confidentiality with the risk increasing in patients with a rare disease. Some companies are concerned that this would release commercially sensitive information if for example the data reveals any proprietary information. The Commons Science and Technology Select Committee favoured restricted access to IPD using a gatekeeper model (see below).

Making Better use of Information

Storing and Managing IPD

Researchers may want to use IPD to verify results, carry out new analyses or answer new research questions. One model for accessing IPD is to make it available through a trusted third party known as a gatekeeper.[23] This decreases the risk of re-identification and protects commercial interests. There are different gatekeeper models. Some require applicants to provide proof of their identity and agree not to attempt to re-identify individuals. Others require details of the intended research such as statistical analysis plans for an independent scientific review.

Box 4. The European Medicines Agency Policy on Transparency
The European Union is currently in the process of replacing the EU clinical trials directive with the clinical trial regulation. A primary aim of this regulation is to increase the transparency of clinical trials data. The European Medicines Agency (EMA) has stated that it will enable access to full data sets by interested parties and has consulted widely on how to achieve this. It hosted a workshop on clinical trials data and transparency in 2012 and established advisory groups on patient confidentiality, data formats, rules of engagement, good analysis practice and legal aspects. In June 2013, EMA published a draft policy for consultation on publication and access to clinical trials data. It has considered responses to the consultation and agreed key principles for implementing the new policy; these will be discussed at the EMA Board meeting in March 2014.

Safe Havens

Gatekeepers can provide different levels of access to IPD. One model is to make it available through a safe haven. A safe haven is a computer environment that allows data analysis but prevents the data from being extracted and re-identified. One of the advantages of making IPD available through a safe haven is that it allows data from different trials to be combined in order to improve the quality of the evidence for or against an intervention. Restricting the movement of data into a safe haven impacts upon the type of analysis that can be carried out. Companies such as GSK have created their own safe havens to provide researchers access to its data. More recently, Roche has started to make some of its clinical trials data available through a collaborative safe haven.

There have been calls for regulators such as EMA and MHRA or bodies such as the HRA to operate safe havens. However, EMA data are confined to regulatory submissions on new drugs, and the HRA would be restricted to UK trials data. The ideal situation would be a European or global repository in which the data from all clinical trials could be deposited, and access provided by the gatekeepers.

Patient Consent

An important consideration is whether the re-use and sharing of data is in line with what the trial participants consented to. This is a particular issue for past trials for which consent has already been given and where data sharing may not have been explicitly mentioned in the consent process. For future trials, the details of data sharing could be included in the informed consent. Alternatively, trial participants could give consent to a trusted third party such as a gatekeeper to decide on their behalf whether their data should be shared.

Patient Confidentiality

Patients entrust their sensitive information with medical research teams under the premise that it will be kept confidential. Where individual patient data are shared outside of the research group it may be de-identified to protect patient confidentiality. The de-identification process is a balance between protecting patient information and maintaining the usefulness of the data.

In practice, it is relatively straightforward to redact data such as names, addresses, contact details and gene sequences that can be used to directly identify individuals.[25] However, individuals can also be identified by combining data. For instance, combining knowledge of someone's sex, age, ethnicity and medical condition may allow identification of an individual, particularly if they have a rare condition.[26]

When Should the Information Become Available?

Many researchers suggest that summary results should be published within a year of the last visit of the last patient and the patient level data made available at the same time. However, some have described this as unworkable.[27] A distinction may need to be drawn between commercial and non-commercial trials, for example by making data for commercial trials available at the time of regulatory submission.

An additional question relates to how much historical data to make available. Medicine will continue to rely upon current interventions for a long period and thus the more data that becomes available on them the stronger the evidence base becomes. However, going back and making historical data available is likely to require a significant amount of resources. The Commons Science and Technology Committee noted that the retrospective publication of past trials data would be desirable, but was unlikely to be achievable given the time and resources available. It was not in favour of unrestricted publication of IPD because of concerns over patient confidentiality and consent. Rather it saw value in giving specific individuals controlled access to IPD in safe havens managed by gatekeepers.

Endnotes

1 Simes RJ, *Journal of Clinical Oncology*, 4 (10), 1529-41, 1986
2 Hopewell S eta al, *Cochrane Database of Systematic Reviews*, 1, 1-23, 2009
3 Bourgeois FT et al, *Ann Intern Med*, 153, (3) 158-66, 2010
4 Kondro W et al, *CAMJ*, 170 (8), 1211, 2004
5 Doshi P and Jefferson T, *BMJ Open*, 3 (2), e002496 , 2013
6 Wieseler B et al, *PLoS Med*, 10(10), e1001526, 2013
7 www.trialsjournal.com/about. [Accessed 14 10 2013]
8 "*Principles for Responsible Clinical Trial Data Sharing*" EFPIA, 2013
9 Schulz KF et al, *BMJ*, 340 (c332), 698-702, 2010
10 *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*, ICMJE, 2013
11 *Declaration of Helsink*i, World Medical Association, 1964 (amended 2013)
12 *Trial registration to be condition of the favourable REC opinion*, HRA, 10/9/13
13 Press Release 10/WC500151974.pdf, EMA 11 October 2013
14 *Structure and content of clinical study reports*, ICH E3 - 30 11, 1995
15 Gordon D et al, *N Engl J Med*, 369, 1926-34, 2013
16 House of Commons Science and Technology Committee, Ev103, 2013
17 Doshi P et al, *BMJ*, 346, f2865, 2013
18 Kmietowicz Z, *BMJ*, f6179, 347, 2013
19 Rogers JVE et al, *BMJ*, f3981, 346, 2013
20 Goldacre B, *Bad Pharma: How drug companies mislead doctors and harm patients*, London: Fourth Estate, 2012
21 http://youtube/CU3PsTd5Bg0?t=13m5s. [Accessed 01 November 2013]
22 Jefferson T et al, *Cochrane Library Review*, CD008965, 2012
23 *Science as an Open Enterprise*, The Royal Society, 2012
24 *Mission & Principles*, Clinical Data Interchange Standards Consortium, 2013
25 *Final advice to the European Medicines Agency from the clinical trial advisory group on Clinical trial data formats*, EMA,April 2013
26 Hrynaszkiewicz I et al, *Trials*, 11 (9), 1-5, 2010
27 Meinert CL, *BMJ*, 347 (f6449), 1-2, 2013

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