Missing trial data – briefing notes.

Doctors need the results of clinical trials to make decisions about which treatment is best. Currently, drug companies and researchers are allowed to withhold the results of clinical trials from doctors and patients if they wish to, alongside other information. This means that we are misled about the benefits and risks of treatments. We can be misled into prescribing an expensive new drug, for example, when in reality an older cheaper one is more effective. Patients are harmed and money is wasted.

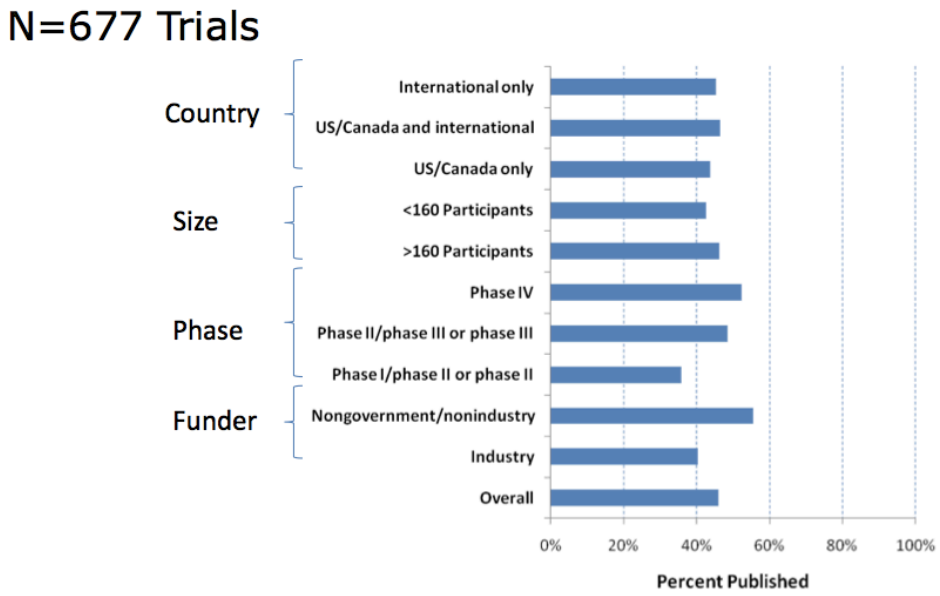
This problem is very well documented, and widely discussed within the profession. Legislators have failed to engage on the issue.

The scale of the problem

The current best estimate is that half of all the clinical trials that have been conducted and completed have never been published in academic journals, and trials with positive results are twice as likely to be published as others. This figure comes from a systematic review conducted in 2010 by the NHS NIHR Health Technology Assessment programme.

http://www.hta.ac.uk/fullmono/mon1408.pdf

This problem occurs for industry and non-industry trials, internationally, at all stages of drug development, and for trials of all sizes.



1. *Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM. Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis. Sim I, editor. PLoS Medicine. 2009 Sep 8;6:e1000144.* http://www.plosmedicine.org/article/info:doi%2F10.1371%2Fjournal.pmed.1000144

The majority of drugs in current use were approved several years ago, and so the rates of missing data over past decades have the greatest detrimental impact on current clinical practice. However, evidence collected since the NHS NIHR HTA review shows that the problem persists at very high rates. Results from individual studies rather than systematic reviews should be interpreted with caution. However, here are three prominent recent studies:

Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. BMJ. 2012 Jan 3;344:d7292. doi: 10.1136/bmj.d7292.

"Among 635 clinical trials completed by 31 December 2008, 294 (46%) were published in a peer reviewed biomedical journal, indexed by Medline, within 30 months of trial completion. The median period of follow-up after trial completion was 51 months (25th-75th centiles 40-68 months), and 432 (68%) were published overall."

"Despite recent improvement in timely publication, fewer than half of trials funded by NIH are published in a peer reviewed biomedical journal indexed by Medline within 30 months of trial completion. Moreover, after a median of 51 months after trial completion, a third of trials remained unpublished."

Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. Ann Intern Med. 2010 Aug 3;153(3):158-66. doi: 10.1059/0003-4819-153-3-201008030-00006.

"Overall, 362 (66.3%) trials had published results. Industry-funded trials reported positive outcomes in 85.4% of publications, compared with 50.0% for government-funded trials and 71.9% for nonprofit or nonfederal organization–funded trials ($P < 0.001$). Rates of trial publication within 24 months of study completion ranged from 32.4% among industry-funded trials to 56.2% among nonprofit or nonfederal organization–funded trials without industry contributions ($P = 0.005$ across groups)."

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H., Robert M. Califf, M.D., and Nicholas C. Ide, M.S. The ClinicalTrials.gov Results Database — Update and Key Issues. N Engl J Med 2011; 364:852-860March 3, 2011DOI: 10.1056/NEJMsa1012065

"We characterized the 79,413 registry and 2178 results of trial records available as of September 2010. From a sample cohort of results records, 78 of 150 (52%) had associated publications within 2 years after posting."

"ClinicalTrials.gov provides access to study results not otherwise available to the public. Although the database allows examination of various aspects of ongoing and completed clinical trials, its ultimate usefulness depends on the research community to submit accurate, informative data."

There have been no changes to legislation since the 2010 systematic review was conducted.

Failed initiatives

Two major failed initiatives are commonly cited as evidence that the problem no longer exists: (1) journals requiring registration before publication, and (2) FDA legislation requiring results to be posted on clinicaltrials.gov within one year of completion.

(1) Journals requiring registration before publication

ICMJE requirement

Trialists are encouraged to register the existence of their trials publicly, to ensure that there is a clear record of trials in progress. Although this does not guarantee reporting of results, it allows some public scrutiny of whether completed studies have been published.

In 2005, after concern that trial registration was not being used, the International Committee of Medical Journal Editors said they would only publish trials that had been registered at inception. The intention was to force trialists to register trials. There was no public audit of this promise, however and despite widespread intention to adopt this initiative by many journals globally. in 2009 it was shown that half of all trials published after this requirement had been announced had not been properly registered, and a quarter had not been registered at all.

1. *Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials. JAMA. 2009 Sep 2;302(9):977–84.*
http://jama.jamanetwork.com/article.aspx?articleid=184503

Failure of the European Medicines Agency clinical trials register
The EMA was asked to produce a clinical trials register in 2001, and then in legislation in 2004. For many years this 'transparency tool' was held in secret. Since March 2011 the EMA has claimed that it has a publicly accessible register. This is not true. Details of several thousand trials on this register are currently withheld from the public, while the EMA considers whether they should be disclosed. There should be a presumption that details about all trials on the register are to be disclosed.

Furthermore, unlike the US register at Clinicaltrials.gov, information about all Phase 1 trials are held in secret. This is despite the inquiry into the TGN1412 disaster stating that Phase 1 trials should be made publicly available, to prevent harm to trial participants. There is no facility on the EMA register to allow researchers to disclose the existence of their registered Phase 1 trials, even if they wish to do so.

The EMA has also stated on many occasions that it would produce a publicly accessible database of trial results in 2012. They have not done so.

Finally, my anecdotal experience of checking specific trials (BG) is that the contents of the EMA register are often in error, or at least shown to be inconsistent with the contents of other registers when trials have been registered on more than one register.

(2) FDA legislation requiring results to be posted on clinicaltrials.gov within one year of completion

The US government FDA Amendment Act 2007 requires that, for all trials with at least one site in the US researching a currently licensed drug, etc., all results must be posted on the website clinicaltrials.gov within a year of completion of a trial. There was no official public audit of compliance, and no publicly accessible structured data on due dates for results, etc.

An audit was conducted independently and published in the British Medical Journal in 2012. This showed that only one in five trials had met this reporting requirement. Despite this fact, no fine has ever been levied against any company or researcher for failing to post results. Even if a fine had been levied, it would only be $10,000 a day, or $3.65m a year: this is low for a drug company with an annual revenue in the tens of billions, and where global revenue for one blockbuster drug can be in excess of $5 billion.

Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. BMJ. 2012;344:d7373.
http://www.bmj.com/content/344/bmj.d7373

Even if this law had been implemented, it would not have fixed the problem. It would only require publication of trials starting after 2009, whereas prescribers rely on evidence from trials done earlier to make decisions about which current treatment works best. It also misses many trials conducted outside the USA, which is increasingly common now that trials are commonly run by Contract Research Organisations in Brazil, Russia, India, China etc.

Tamiflu and access to Clinical Study Reports.

Tamiflu (oseltamivir) is a drug the UK government has spent £500m stockpiling. The manufacturer, Roch,e is currently withholding important information about trials on this drug from the Cochrane Collaboration, the large international non-profit academic collaboration that produces for doctors and patients rigorous systematic reviews of reliable evidence on the effects of drugs and other forms of healthcare interventions.
http://www.plosmedicine.org/article/info:doi%2F10.1371%2Fjournal.pmed.1001201
http://www.bmj.com/tamiflu

Tamiflu is not an isolated case, and the evidence above shows that this problem is widespread throughout the whole of medicine. Tamiflu is the most thoroughly documented case because of the extent of the research by the Cochrane Acute Respiratory Infections Group.

There is one specific issue here: for several Tamiflu trials, while there are brief summaries available in the public domain, these do not contain sufficient information to make an informed judgement about the reliability of the trials, and whether they were methodologically rigorous. This is why the Cochrane researchers have sought access to the full Clinical Study Reports. Roche have publicly promised in writing that they would share these documents, in December 2009, but have since refused to do so. Their recent suggestion that they would convene a committee to look at this issue addresses none of the relevant issues around transparency and they continue to withhold data.

www.bmj.com/tamiflu

After a finding of maladministration from the EU Ombudsman in 2010 - in which the EMA was found to have made false claims in their reasons for withholding Clinical Study Reports from researchers - the EMA made a commitment to release more CSRs, on request. However the Agency does not hold the full CSRs on Tamiflu.

Researchers and industry are not the only ones at fault:

- *Universities* have failed to ensure that contracts with companies sponsoring trials run by academics allow the academics to publish the results of trials, regardless of whether the company is happy with them.
- *Ethics committees* that approve research projects have failed to protect patients, because they have not insisted that researchers publish results, and they do not check to see if researchers are withholding the results of previously approved trials. This may currently be being addressed by the Health Research Authority.
- *Medical membership bodies* have failed to act on this issue, and have failed (with one exception) to state publicly that withholding the results of clinical trials is research misconduct.

These all represent opportunities to help address the problem of missing results for future trials.

It is also worth noting that non-publication of trial results presents a major ethical breach: patients participate in research, experiencing inconvenience and sometimes risk, in the belief that their participation will improve our understanding of which treatment works best. If the results of trials are withheld, then the participants have been misled.

Journals

Researchers and industry sometimes claim that medical journals will not publish negative trial results. This was a modest problem in another era of medicine, but was fixed a decade ago. The most current NHS NIHR HTA systematic review found that journals were not the barrier to publication. With the advent of open access journals where the business model is not dependent on the need to sell subscriptions to high profile "positive" papers, there are now several open-access academic journals – such as the open-access journal Trials, and journals from the Public Library of Science - that will publish trials regardless of whether the results are positive. Academic journals are no longer any barrier to publishing trial results; they are no barrier to posting results on clinicaltrials.gov; and they are no barrier to sharing Clinical Study Reports. In addition, because the papers are open acess they can be read and scrutinized by everyone at no cost.

Why do doctors need to see results as well as regulators?

A medicine does not simply "work" or "not work". Some drugs work very well, some work less well than other drugs, but are still better than nothing. A medicines regulator decides if a drug should go on the market at all, and they have a low bar for approval. This is good: we need some less effective drugs to come on the market. For example, a patient may have idiosyncratic side effects from the best available drug for their condition, in which case it is useful to have a less effective drug to try next.

Doctors and patients need all the information about all the clinical trials that have been conducted on drugs (and other treatments) in order to make informed decisions. A clinical decision ("should this patient receive this drug?") is very different to a regulator's decision ("overall, is it in the interests of society that this drug should be on the market for use at all?").

Furthermore, regulators can sometimes miss important problems with medicines. For example, as with Tamiflu, the problems with the drugs Vioxx and Rosiglitazone - both now taken off the market - were spotted by academics and clinicians rather than regulators. This is not because regulators are incompetent: these are difficult problems, so it is good to have many eyes working on them. It is also good for patients if the evidence behind regulators' decisions can be independently assessed, to ensure regulators have made good decisions.

Data on individual patients who have participated in clinical trials

This is a separate issue but also important. Better systems for sharing clinical trial data about individual patients would create more transparency, permit more accurate assessments of drugs by doctors and patients, and enable more accurate identification of any subgroups of patients who might respond to a treatment less or more well than average.

Sharing data is very valuable because it facilitates more accurate estimates of the effects of interventions. This is well demonstrated by the work of the Early Breast Cancer Trialists' Collaborative Group, which has conducted highly

accurate and informative systematic reviews and meta-analyses using individual patient data from a large pool of clinical trials to inform breast cancer treatment supported by research funding agencies around the world.

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. The Lancet. 2011 Nov;378(9804):1707–16. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)61629-2/abstract

Analyses such as this present challenges in ensuring confidentiality for individual patients (although these can be overcome, and the work of the YODA data sharing project at Yale presents one interesting early proposal of how to manage these issues). This is a different issue, however, to claiming confidentiality about the existence and results of the trials themselves, and withholding information about their conduct.

Existing promises to share clinical trial data

GSK has indicated it will share data on Relenza, its influenza treatment, with the Cochrane Acute Respiratory Infections Group working on Tamiflu. It has been widely and incorrectly reported that this data has already been shared. In fact, no data has yet been shared, negotiations continue, and these have already taken many days of work, requiring senior research contracts specialist and lawyers at the University of Oxford. The company has expressed the expectation that material will be kept confidential and secret by the Oxford research team. Such a stance prevents "reproducibility," which calls for data sets to be made available for verifying published findings and conducting alternative analyses.

GSK has also offered to share more data from its earlier phases of drug development, to enhance collaboration and innovation. Again, this has not yet happened, and it is unclear what the processes will entail.

The EMA has indicated that it intends to share individual patient data given to them as part of the licensing process for a drug (which is not all trials on that drug). It is presently unclear how this will work. At the EMA meeting to discuss options, industry representatives made clear that they felt industry should be allowed to control access to data and to decide who would be allowed to inspect the data. It was also suggested that this transparency should only be permissible for trials starting in 2014 or later.

Because drugs continue to be used for many decades, this will do nothing for the evidence base of currently used treatments, and will have little impact for a decade, if not longer. This is especially the case since many of the most widely used drugs have been on the market for some time, and good treatments continue to be used for as long as they are the best in their class.

What needs to change?

All involved parties need to work to ensure that *all results of all clinical trials – past and future - on all treatments in current use* are available to doctors and patients, so that they can make informed decisions about treatments. At present, although this problem is thoroughly documented and ongoing, many in industry seek to deny it exists. NICE, regulators, and medical membership bodies have all failed to accept ownership of the problem or show leadership in addressing it.

This problem can be addressed through many means.

We are not experts in legislation. We are not aware of any UK legislation requiring the results of all trials on all drugs in current use to be made available. There is legislation requiring disclosure of adverse events and other monitoring of clinical trials within the UK, and regulation for "good clinical practice" in the conduct of trials, by the MHRA. This legislation does not address biased under-reporting of clinical trials and should not be confused with the issue of missing results.

In Germany, the equivalent of NICE (IQWiG) has developed a reputation for requiring high standards of evidence before recommending the use of drugs, and has also refused to allow drugs to be used until companies have disclosed all trial results to them, which IQWiG has then made public. It is through this mechanism that we have become aware of major problems with currently used drugs. This more robust approach could and should be replicated in the UK. One option is to insist that a treatment can only be used by the NHS if all information about all trials conducted on it are made publicly available to doctors and patients; or that a company's treatments can only be used by the NHS if all information about all trials on all their drugs are made publicly available.

The current form of the draft EU Clinical Trials Regulation is extremely weak, and does not adequately address the problem of missing results. This must be addressed urgently as the Regulation will be considered by the European Parliament over the next 6 months.

Research ethics committees must address publication bias for all future trials by insisting on commitment to publication, and publicly monitoring and auditing compliance. We believe that the current head of the Health Research Agency may be moving towards requiring this position. Ethics committees could also insist on evidence of publication of researchers' previous trials before giving permission for additional research.

Journals can commit to a similar policy undertaken by the BMJ, whereby 'trials of drugs and medical devices will be considered for publication only if the authors commit to making the relevant anonymised patient level data available on reasonable request.'

Finally, Universities should insist on the rights of access to data and to publish results in all collaborative contracts.

Summary

This problem is ongoing, and has not been fixed.