

## How many clinical trials are left unpublished?

We may never know the answer to this question. In some ways, maybe it doesn't matter. Even one clinical trial left unreported is unacceptable.

There have been attempts to produce an estimate for publication rates of clinical trials. This is a challenging area to research, by definition unpublished research is hard to identify. There are many imperfect ways to go about it. Each piece of research has to be looked at in terms of its design: what subset of clinical trials did it look at, where were they conducted, did it look at completed or ongoing trials, at trials that had been registered or did it look wider than that, over what time period? We also have to ask how each piece of research defined 'reported' as this varies a lot too; is a trial counted as reported if some results from it are included in a conference talk, a journal paper or shared with a regulator? Or is reported taken to mean the trialists complied with the CONSORT guidelines<sup>1</sup> on the minimum information required for proper reporting of clinical trials and the time frame set down by the US and new EU laws?

We may never know one vital piece of information: the number of clinical trials that have been carried out. Without this number (our denominator) we'll probably never be able to generate a precise proportion of trials that are unreported. We will only be able to put precise numbers on publication rates of some subsets of recently carried out trials. Taking this into account and from an overview of the literature (again, taking the various limitations and shortcomings of individual studies into account) "around half" is as close as we can reasonably say at the moment. It is clearly not a statistic, and we wouldn't advocate trying to roll up the results of all the studies listed below to produce something spuriously precise. We hope more studies and reviews are under way and we're talking to the world's biggest registers about how to extract more reliable information. However, note this, around half summarises where it looks as though we are on the studies done on treatments in use today. It is not a number that is uniquely scandalous or the cause of bad medicine. We should be scandalised to learn that the results of 20% of studies on treatments prescribed today are hidden. Or 10%.

We *hope* that around half of trials are reported. Looking at things globally, which we as a campaign have to, and given that you'd expect better behaviour in the most regulated places (US and EU) but those are the places where most of the research into this has been done, around half is probably an optimistic estimate.

Everyone who has studied this area has had to make some decisions and assumptions about how to count trials and characterise them as reported. Before we go through that research, it will be useful to go through some of reasons this is a uniquely challenging area of research:

## How do we count all clinical trials that have been done?

Unfortunately, there isn't a master list of all clinical trials ever conducted. Nor is there a precise date for the first trial worth counting. Clinical trials, as we would recognise them,

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<sup>1</sup> <http://www.consort-statement.org/>

have been run since at least the 1960s, so should we start counting from here? Should we start in the 1980s, when the US Food and Drug Administration regulations on clinical trials were formalised? Or from 1995, when the World Health Organization published guidelines on good clinical practice for running trials? Or from 2005 when the International Committee of Medical Journal Editors (ICMJE) brought in requirements for trial registration?

We could try using all trials that have been publicly registered as the number for trials that have happened, but this would be far from accurate. It is impossible to know for sure how many trials have never been registered. Researchers have explored this, for example in 2012 Van de Wetering *et al*<sup>2</sup> found that 61% of trials that had been reported in journals had been registered so the percentage of *all* trials that have been registered is probably lower than this. It is difficult to know how many unreported trials are unregistered. How do we count trials we don't know anything about?

What we do know from research is that registration rates have improved dramatically in the last decade as more attention has been focused on the issue and as journal editors agreed not to publish the results of trials that were never registered<sup>34</sup>. What does this say about the recent past before 2005? Are we looking into a dark age of buried trials? This table, produced by Liz Wager in 2013, shows the state of research on registration of trials:

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<sup>2</sup> <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0049599>

<sup>3</sup> ICMJE evaluation [http://www.icmje.org/news-and-editorials/clincial\\_trial\\_reg\\_jun2007.html](http://www.icmje.org/news-and-editorials/clincial_trial_reg_jun2007.html)

<sup>4</sup> Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013 *BMJ Open* 2015;5:e008932 doi:10.1136/bmjopen-2015-008932  
<http://bmjopen.bmj.com/content/5/9/e008932.full>

Author	Pub date	Survey start date	Survey end date	Source	Type of studies	N	% NOT reg	% registered	% properly registered	% inadequately reg
Huser	2013	2010	2011	5 ICMJE jnls	clinical trials	698	<i>4</i>	<i>96</i>		
Jones	2012	2008	2011	emerg med jnls	RCTs emergency med	123	<i>54</i>	<i>46</i>	<i>4</i>	
Freshwater	2013	2007	2011	Medline	plastic surgery studies	155	<i>94</i>	<i>6</i>	<i>1</i>	
van de Wetering	2012	2010	2010	Medline	RCTs	302	<i>39</i>	<i>61</i>		
Shane	2013	2009	2010	top 10 journals	surgery RCTs	246	<i>35</i>	<i>65</i>	<i>44</i>	<i>21</i>
McGee	2011	2005	2010	?	RCTs kidney transplant	307	<i>76</i>	<i>24</i>		
Scherer	2012	2009	2009	ARVO abstracts	RCTs ophthalmol	171	<i>26</i>	<i>74</i>		
van de Wetering	2012	2010	2008	Dutch Register	RCTs	312	<i>40</i>	<i>60</i>		
Mathieu	2009	2008	2008	Medline	RCTs cardio, rheum, gastro	323	<i>28</i>	<i>72</i>	<i>46</i>	<i>26</i>
Scherer	2012	2008	2008	ARVO abstracts	RCTs ophthalmol	153	<i>33</i>	<i>67</i>		
Rasmussen	2009	1996	2008	FDA new cancer drugs	published 2007-8	35	<i>20</i>	<i>80</i>		
Scherer	2012	2007	2007	ARVO abstracts	RCTs ophthalmol	172	<i>38</i>	<i>62</i>		
Rasmussen	2009	1996	2006	FDA new cancer drugs	published 2005-6	33	<i>58</i>	<i>42</i>		
Rasmussen	2009	1996	2004	FDA new cancer drugs	published 2003-4	40	<i>70</i>	<i>30</i>		

Numbers in *italics* are calculated, others are taken directly from articles

Adding to the complexity, there are 15 primary clinical trial registers and three partner registries in the WHO national register platform representing dozens of countries. Trials can appear on more than one register so adding up the number of trials on these registers won't be accurate. And register entries also don't always make it clear whether any particular trial is completed, abandoned or still active. Companies, charities, research institutes, governments and funders sometimes have their own separate registers, which contain trials that may or may not be registered on a national register, and research ethics committees and institutional review boards in hospitals and universities have databases of trials carried out at their locations. There is no easy way to search through or combine information from all of these sources.

And then we have the question of which phases of trial to count. Phase 1 trials are not mandated for public registration, so we know about fewer of those than phase 2 and 3 trials. Phase 4 trials are not generally registered either. Should we try to count those?

What if we counted all the trials a regulator had been sent in support of licensing applications for drugs? This would miss those trials that companies don't share and all those trials done for purposes other than with the intention of getting a license such as head to head comparisons of current treatments, as well as trials on surgical techniques, diets, psychological therapies etc.

Do we count trials done all around the world or do we just count trials in Europe and the US, because that's where we have the most information? If we count trials that have been registered then our numbers will be biased towards trials done in Europe and the US. Regulation and practices are very different in different parts of the world; for example, we know that compliance with ICMJE's policy is poor among Latin American and Caribbean biomedical journals. One study found that only one fifth of trials reported in these journals mentioned registration<sup>5</sup>.

### Which are the most important clinical trials to uncover?

One answer would be those trials done on the medicines we use today. The majority of medicines prescribed in the UK have been on the market for more than a decade<sup>6</sup> so they were tested in trials in the preceding decades. Researchers describe a 'golden age' of drug development in the 1990s, when medicines were discovered that may never be bettered. The trials testing those are essential for current medical practice.

Which trials on those medicines are the most useful? When it comes to information on effectiveness, perhaps phase 3. However, phase 1 and 2 trials uncover vital information about safety.

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<sup>5</sup> <http://www.ncbi.nlm.nih.gov/pubmed/23778541>

<sup>6</sup> <http://www.kingsfund.org.uk/blog/2015/07/how-much-has-generic-prescribing-and-dispensing-saved-nhs>

On past studies there is likely to be a proportion that are too old and irrelevant to be useful, and material is lost or people who ran the studies have died. In general, we'd probably prefer to decide irrelevant for ourselves than have sponsors decide it for us or second guess what other uses the information might be put to. But we do have to accept some small percentage of studies will be lost or too costly to ever recover.

What follows is a guide to the research on this missing research. We can't just combine all the results of lots of different research to produce a precise, yet spurious, number or proportion. All of the studies we're going to talk about have limitations.

### Are things improving?

It's difficult to say because there's no baseline to measure from. Each study done is looking at something slightly different than the studies before. So if a study today shows publication rate of 80%, it might always have been that way we're just looking at it differently now. However, it does seem to us that things are improving. This is good of course, but the majority of trials are not from the past couple of years, and the vast majority of trials done on treatments prescribed today certainly aren't. Hands up any doctor who prescribes only drugs that came on the market after 2010? Nobody.

If we learn that 2015's rate of publication within 2 years (very generous and more time than regulations allow) is 75% will we celebrate? That with all the regulations, guidelines and promises from 2007 on, the campaign, the investor support, and the scrutiny that now attaches itself to all this, that still 25% of trial results are hidden, will we cheer? Or will we say instead, thank goodness it is changing, but why the hell is it still okay to hide any results at all?

### Some clarity

Three big reviews that have tried to draw together much of the research done on clinical trial reporting are the NHS funded review of publication bias by Song and colleagues from 2010, a review by Dwan and colleagues in 2008, and a systematic review by Schmucker and colleagues published in 2014.

**Dwan *et al* 2008<sup>7</sup>** is a review of publication bias and outcome reporting. The authors searched for high quality research papers that examined publication bias in randomised controlled trials and found 16 pieces of research. The rate of publication found in these papers varied from 21% to 93% (have a look at table 3 here<sup>8</sup> for the range). The authors conclude that: "It is difficult to tell the current state of the literature with respect to study publication bias, as even the most recently published empirical evaluations included in the review, considered RCTs which began 10 years ago. Nevertheless, the empirical studies that were published within the last eight years show that the total amount of studies published was less than 50% on average."

Nine of the studies looked at the proportion of trials with positive and negative results that were published and found it ranged from 60% to 98% and from 19% to 85%, respectively. Four of the pieces of research looked at what percentage of studies with null results (no

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<sup>7</sup> <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0003081>

<sup>8</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2518111/table/pone-0003081-t003/>

difference observed between the two study groups,  $p > 0.10$ , inconclusive) are published and found a publication rate that ranged from 32% to 44%. The research included in this review consistently found that positive studies are more likely to be published compared to negative studies.

Dwan and colleagues' work sets out the kinds of variation there is in different pieces of research. For example, they found that the pieces of research they included in their review defined 'publication' differently: some include conference presentations and abstracts as publication, most categorised publication solely as a journal article, some didn't define it at all. The studies also allowed varying time windows for publication ranging from 3 years to 34 years. Table 4<sup>9</sup> sets out the different timelines and definitions used in research into clinical trial publication rates. These differences are the reason it's impossible to get to one, precise number for publication rate from the research done so far.

Another interesting point that Dawn *et al* draw out is that some of the research included in their review looked at whether unpublished clinical trials have been submitted to journals but rejected (one of the arguments we often hear is that journals routinely reject papers with uninteresting results) or not submitted to a journal at all. They report that "results are presented for the percentage of studies not submitted for journal publication (7% to 58%), of studies submitted but not accepted for publication (0 to 20%) by the time of analysis of the cohort and the percentage of studies not published that were not submitted (63% to 100%). This implies that studies remain unpublished due largely to failure to submit rather than rejection by journals."

**Song and colleagues in 2010**<sup>10</sup> were commissioned by the NHS to review publication bias in clinical research. The authors carried out a thorough and detailed investigation drawing together studies on publication bias conducted between 1998 and 2009. They included both "*evidence studies* that provided empirical evidence on the existence, consequences, causes and/or risk factors of dissemination bias; and *method studies* that developed or evaluated methods for preventing, reducing or detecting dissemination bias." They ended up with 300 studies which they reviewed, summarised their methods, the limitations, and what they found.

The authors found that studies with significant or positive results were more likely to be published and were published earlier than those with non-significant or negative results. The authors conclude that "the most common reason for publication bias was that investigators failed to write up or submit studies with non-significant results."

### **Schmucker *et al*, 2014**<sup>11</sup>

The researchers synthesised and analysed 39 separate research studies which looked at the proportion of clinical research studies that have been published as journal articles and the time from the research's end date to the journal publication. The researchers decided to allow a window of at least 24 months after trials were completed to follow up and check publication, to allow as many results as possible to be published. They included research

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<sup>9</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2518111/table/pone-0003081-t004/>

<sup>10</sup> [http://www.journalslibrary.nihr.ac.uk/\\_data/assets/pdf\\_file/0005/64751/FullReport-hta14080.pdf](http://www.journalslibrary.nihr.ac.uk/_data/assets/pdf_file/0005/64751/FullReport-hta14080.pdf)

<sup>11</sup> <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0114023>

studies that looked at trials captured in research ethics committees' databases and on clinical trial registers and analysed publication rates of these separately.

The authors found 17 separate research papers that followed studies after approval by ethics committees and 22 that followed studies posted on registers. They found that: "After REC [research ethics committee] approval, the proportion of studies published ranged from 26% to 76% ... the heterogeneity among individual estimates was substantial ( $I^2 = 94.4\%$ ,  $p < 0.0001$ ). If one combined the individual estimates even so the pooled estimate would be 46.2% (95% CI 40.2–52.4)." For studies on registers they found that "the proportion of studies published ranged from 23% to 76% ... again the heterogeneity among individual estimates was substantial ( $I^2 = 98.9\%$ ,  $p < 0.0001$ ). If one combined the individual estimates even so the pooled estimate would be 54.2% (95% CI 42.0–65.9)."

When they looked solely at research into publication rates of randomised controlled trials they found "a pooled proportion of published studies of 44.5% (95% CI 31.0–58.8;  $I^2 = 92.9\%$ ,  $p = 0.0002$ ; based on two MRPs [methodological research projects] following studies after REC approval) and 60.3% (95% CI 45.4–73.6;  $I^2 = 92.5\%$ ,  $p < 0.001$ ; based on seven MRPs following studies after trial registration)."

The authors knew that some of the research papers might have contained trials that were not completed so they eliminated any research papers that couldn't show definitively that all trials included were ended, and found: "In the resulting sample of completed studies a pooled proportion of studies published would be similar: 46.3% (95% CI 41.0–51.6;  $I^2 = 81.1\%$ ,  $p < 0.0001$ ; based on five MRPs following studies after REC approval) and 53.5% (95% CI 40.9–65.7;  $I^2 = 98.9\%$ ,  $p = 0.0003$ ; based on 13 MRPs following studies after inclusion in trial registries)" They also found that "studies with statistically significant results were more likely to be published than those without (pooled OR 2.8; 95% CI 2.2–3.5)."

It wouldn't be surprising if some of the 39 research studies included in this analysis aren't perfect, or if there are some small problems with the analysis itself, as with everything in medicine. But it's the most current attempt to synthesis and analyse research into trial publication and it found that around half of clinical trials hadn't reported results. If someone does a better meta-analysis, or lots of them, that'd be great to see too.

There have been *a lot* of other studies investigating publication of clinical trials. Here are some of those studies which raise interesting questions about how to count trials and characterise them as reported, in chronological order:

**Easterbrook *et al* 1991<sup>12</sup>** is one of the earliest. The researchers looked at 487 research projects approved by the Central Oxford Research Ethics Committee between 1984 and 1987. As of May 1990, 285 of the studies had been analysed by the investigators, and 52% of these had been published. Studies with statistically significant results were more likely to be published than those finding no difference between the study groups (adjusted odds ratio [OR] 2.32; 95% confidence interval [CI] 1.25–4.28).

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<sup>12</sup> <http://www.ncbi.nlm.nih.gov/pubmed/1672966>

**Dickersin and Min, 1993**<sup>13</sup> spoke to the researchers who ran all 293 trials funded by the NIH in 1979 nine years later in 1988 to ask whether the trial had been published. Of the 198 clinical trials completed by 1988, 93% had been published. Trials with "significant" results were more likely to be published than those showing "nonsignificant" results (adjusted odds ratio [OR] = 12.30; 95% confidence interval [CI], 2.54 to 60.00).

**Ross et al 2009**<sup>14</sup> looked at trials registered on the world's largest clinical trial register ClinicalTrials.gov after 31<sup>st</sup> December 1999 and marked as completed by June 2007 then randomly selected 10% of the 7,515 they found to investigate publication of results. They looked for publications linked to from the register entry and searched Medline. They found that "Among the 10% subsample, less than half (311 of 677, 46%) of trials were published, among which 96 (31%) provided a citation within ClinicalTrials.gov of a publication describing trial results. Trials primarily sponsored by industry (40%, 144 of 357) were less likely to be published when compared with nonindustry/nongovernment sponsored trials (56%, 110 of 198;  $p < 0.001$ ), but there was no significant difference when compared with government sponsored trials (47%, 57 of 122;  $p = 0.22$ )."

To make sure they were allowing enough time for trial results to be published the researchers only investigated publication for those trials that ended in 2005, giving a two year window for completed studies to report. This study does suffer from problems with cross referencing and checking whether the reported results include everything they should, and it excluded phase 1 trials.

**Bourgeois et al 2010**<sup>15</sup> looked at 546 clinical trials of nticholesteremic, antidepressant, antipsychotic, proton-pump inhibitor and vasodilator drugs conducted between 2000 and 2006 and registered on ClinicalTrials.gov.

This study found that "Overall, 66.3% of trials had published results ... Trials funded by nonprofit or nonfederal organizations that did not receive industry contributions were most likely (56.2%) and industry-funded trials least likely (32.4%) to be published within 24 months of study completion ( $P < 0.005$  across groups). Trials funded by nonprofit or nonfederal organizations with industry contributions were also less likely than those without industry funding to be published within 24 months (39.0%). The proportion of trials published within 24 months of study completion increased between 2002 and 2006 after we controlled for primary funding source (increase from 9.5% to 54.4%;  $P < 0.001$  for trend). This increase was among trials in each of the funding categories (from 7.7% to 44.7% among industry-funded trials, 25.0% to 68.8% among government-funded trials, and 0% to 60.0% among nonprofit or nonfederal organization-funded trials)."

The authors found that trials sponsored by industry were more likely to show positive findings, across all phases of trials, than government, nonprofit or nonfederal funded trials.

The authors also looked at registration of trials and found that "Government-funded trials were more likely to be appropriately registered before the start date of the trial (25.7%),

<sup>13</sup> <http://www.ncbi.nlm.nih.gov/pubmed/8306005>

<sup>14</sup> <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000144>

<sup>15</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3374868/>

before study completion (75.3%), and before publication of the study (95.1%) ( $P < 0.001$  across groups for all 3 variables).”

The authors wanted to look at the impact of the ICMJE policy on trial registration and found that: “Among ongoing trials as of 1 July 2005, 70.1% of industry-funded trials were compliant with the ICMJE policy, compared with 80.5% of government-sponsored trials and 60.0% of nonprofit or nonfederal organization–funded trials ( $P = 0.068$  across groups). Also, the number of trials registered before study completion increased, with an overall increase from 22.0% among trials completed before the policy began to 72.9% of trials completed after the policy took effect ( $P < 0.001$ , Cochran–Mantel–Haenszel test controlling for primary funding source). This improvement in timely registration occurred among trials in all funding categories, increasing from 18.9% to 73.6% among industry-funded trials, 68.8% to 80.5% among government-sponsored trials, and 1.9% to 67.1% among nonprofit or nonfederal source–funded trials.

They had a look at links between trial results and register entries and found that “government-funded trials had the lowest proportion of reported primary outcomes (30.9%;  $P < 0.001$  across groups). Provision of links to online abstracts of published results did not differ across funding sources, but industry-sponsored trials were most likely to provide links to unpublished results posted in study result registries or company Web sites. During the period studied, very few trials had begun including actual study results in the record.”

This paper is interesting because it draws out registration versus results publication and found lots of *published* trials were not registered at all. Trials are routinely not registered, even those that have been published in journals. This is another reason estimates of how many trials have been conducted derived from trial registers are likely to be underestimates.

**Chang *et al* 2010**<sup>16</sup> looked at clinical trials on recently approved high risk cardiovascular devices that were cited in FDA approval summary reports and compared the characteristics of these trials with the trial characteristics and results as reported in journal publication on the same trials.

They selected devices approved by FDA between 2000 and 2010. That end date was selected to allow at least two years from approval of the device to publication of the clinical trial. For every trial identified in an FDA approval summary they searched Medline on 15 January 2013 for a corresponding publication with a publication date from 1 January 1990 to 1 January 2013 and emailed the manufacturers asking for publication if they couldn't find one. The authors “identified 177 studies (mean 1.7 per device) in these summaries, of which 86 (49%) were published.”

The authors included publications where data from a number of trials was pooled as a mark that each of those trials was reported, so it is unclear whether publication here meets the standards of results reporting set down by CONSORT or the global registers.

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<sup>16</sup> <http://www.bmj.com/content/350/bmj.h2613>

**Ross et al 2012**<sup>17</sup> looked at NIH funded clinical trials registered on ClinicalTrials.gov on or after 13<sup>th</sup> September 2005 and which were marked on the register as completed by 31<sup>st</sup> December 2008 and found 635. They chose 2008 as a completion date to give a window of 30 months for publication of results, which they then searched for by following links in each trial's registration entry and searching journals indexed by Medline.

They found that "6% of trials were published within six months of study completion, 15% (n=98) within 12 months, 35% (n=223) within 24 months, and 46% (n=294) within 30 months" and "overall, 68% (n=432) of trials were published in peer reviewed biomedical journals indexed by Medline and 32% (n=203) remained unpublished. Among published trials, the median time to publication was 23 months (14-36 months). Unpublished trials had a cumulative target (or actual) enrolment of about 60,000 participants."

They summarise their findings as "we found that fewer than half of trials were published in a peer reviewed biomedical journal indexed in Medline within 30 months of trial completion, although there were more recent improvements in timely publication. Furthermore, after a median of 51 months after study completion, we found that about a third of NIH funded trials remained unpublished."

Some clinical trials on ClinicalTrials.gov are subject to mandatory reporting requirements under the FDA Amendment Act 2007 (FDAAA) and others are not. This makes the situation even more complicated. **Prayle et al 2012**<sup>18</sup> looked at trials that were subject to mandatory reporting and found "Of the 738 trials that were classified as subject to mandatory reporting, 163 (22%) had reported results. In comparison, 76/727 (10%) trials covered by the FDAAA but not subject to mandatory reporting had reported results (95% confidence interval for the difference in proportions 7.8% to 15.5%;  $\chi^2$  test,  $P=2.6 \times 10^{-9}$ ).

This study was criticised by the FDA for failing to include situations where an extension had been given, and including some studies where it was not possible to determine whether the legislation was applicable or not. The authors of the study noted these limitations but were not able to quantify them because the information is not available. The NIH's own informal review, following the scandal caused by the Prayle study, reportedly found: "The NIH's unofficial analysis does agree with the *BMJ* study in one important respect: companies are outperforming their governmental and academic counterparts. On-time reporting rates were 52% for industry, 21% for NIH-based sponsors and 14% for NIH-funded academic sponsors."

**Jones et al 2013**<sup>19</sup> investigated large randomised controlled trials registered on ClinicalTrials.gov and completed or still active at January 2013. They identified 585 trials, the earliest of which was registered in November 1999. Most of the trials (67%) were phase 3. They looked at the register entry for a link to a publication of results and searched Medline and other databases for any papers that contained some data from the trial. They found that 414 of the 585 included trials (71%) had a peer reviewed paper associated with them, and that: "Eleven percent (n=64) of studies received funding from the National Institutes of

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<sup>17</sup> <http://www.bmj.com/content/344/bmj.d7292>

<sup>18</sup> <http://www.bmj.com/content/344/bmj.d7373>

<sup>19</sup> <http://www.bmj.com/content/347/bmj.f6104>

Health or other federal sources; 80% (n=468) of studies were supported by industry. Non-publication was less common among trials supported by the National Institutes of Health or other federal sources compared with those without federal funding (17% v 31%, P=0.025). Non-publication was more common among trials that did than did not receive industry funding (32% v 18%, P=0.003)."

The authors say that "We identified an estimated 250 000 trial participants for whom we were unable to find results either in the published literature or in the result database of the registry, which was approximately 26% of the total participants in the included trials."

The authors' decided to look only at large trials with more than 500 participants as these are more likely to be reported because they appeal to journal editors and represent significant investments by the trial sponsors. So they already have that intentional bias in their study. The authors here note that they count a trial as reported if a peer reviewed paper containing *some* of the reportable data, i.e. not necessarily what would be considered complete reporting by international standards.

**Munch *et al* 2014<sup>20</sup>** The authors here are part of a group that want to develop a repository of registered clinical trials on treatments for pain so they investigated registration and results reporting from trials on three chronic pain conditions on all 15 WHO partner registers as of June 2013. They looked for results associated with each unique trial that was not still in active recruitment. They found that "Overall, 46% of the 391 trials analyzed that are not actively recruiting have available results. Trials registered on ClinicalTrials.gov are significantly more likely to have results publicly available than trials exclusive to other registries (52% vs 18%, Fisher's exact test P < 0.001)."

The authors speculate that because ClinicalTrials.gov allows researchers to post results directly on it, this makes it easier to report, and to find, results from trials on this register. Other registers do not allow results to be posted which means that researchers need to search separate databases and these are not always linked to from register entries. However, most (91%) of the trials they found peer reviewed publications for (118 of the 391 trials) were also registered on ClinicalTrials.gov. Of 325 trials registered on ClinicalTrials.gov, 33% have results in peer-reviewed journals, compared to 17% of 66 trials exclusive to other registries (overall P = 0.008 Fisher's exact test).

This is a very interesting paper with regards to cross-referencing. The authors identified that 86 of the trials were registered on more than one global register, and they found that searching each register individually gave different results to searching through all the WHO registers in one go through the ICTRP portal.

Cross-referencing is a problem when it comes to counting and monitoring trials as a trial can be registered on one register and its results reported on another. Some assumptions have to be made. In the same vein there are thousands of medical journals, but no central place to search all of them. Though doctors would use the online database Medline to find published clinical trials, it is also not a complete record.

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<sup>20</sup> <http://www.ncbi.nlm.nih.gov/pubmed/24726925>

**Rawal & Deane** produced two papers, in **2014**<sup>21</sup> and **2015**<sup>22</sup>, commissioned by the Association of the British Pharmaceutical Industry to look at reporting rates of industry sponsored trials. They looked at the publication of trials on new medicines approved by the European regulator after 2009. In the 2014 paper they found that “Rates of results disclosure within 12 months were 71%, 81% and 86% for new medicines approved in 2009, 2010 and 2011 respectively. Disclosure increased to 86%, 93% and 91% respectively by 31 January 2013.”

And the 2015 paper found “Of the completed trials associated with 23 new medicines licensed to 17 different companies in 2012, results of 90% (307/340) had been disclosed within 12 months, and results of 92% (312/340) had been disclosed by 31 July 2014.”

The researchers characterised trials as having reported results if any data from the trial was included in a European public assessment report (documents on new medicines held by the European Medicines Agency) or in conference abstracts. This raises a question: of the trials Rawal and Deane included as reported how many are actually compliant either with the time frame or with the completeness set out as standard by CONSORT and by US and new EU laws?

**Anderson et al 2015**<sup>23</sup> looked at trials that are likely to be subject to the US’s FDA Amendment Act 2007 (ie that have to be registered before they begin and publish results on ClinicalTrials.gov within a year of the trial’s end) that had been completed between January 2008 and August 2012. They allowed a window of at least a year and then searched ClinicalTrials.gov to see if the trials had reported results. This study focused on investigating whether the trials were compliant with the law so the researchers did not search the peer reviewed literature for any trial results as this is not mandated by the FDAAA.

The researchers looked at a sample of 205 of the trials they identified as being subject to the law and found “On the basis of this review, we estimated that during the 5-year period, approximately 79 to 80% of industry-funded trials reported summary results or had a legally acceptable reason for delay. In contrast, only 49 to 50% of NIH-funded trials and 42 to 45% of those funded by other government or academic institutions reported results or had legally acceptable reasons for delay.”

The fact that the peer reviewed literature has not been considered is a fair decision for the researchers to have made. Other studies of course have looked just at the peer reviewed literature. It is difficult to know the extent to which this is additive to rates ClinicalTrials.gov or whether the overlap is large. **Shamliyan’s 2012** study<sup>24</sup> in *Paediatrics* on trials involving children, for example, did look at both ClinicalTrials.gov and the peer reviewed literature and seems to have found very low reporting rates for studies in both cases.

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<sup>21</sup> <http://informahealthcare.com/doi/abs/10.1185/03007995.2013.860371>

<sup>22</sup> <http://informahealthcare.com/doi/abs/10.1185/03007995.2015.1047749>

<sup>23</sup> <http://www.nejm.org/doi/full/10.1056/NEJMsa1409364>

<sup>24</sup> <http://pediatrics.aappublications.org/content/129/5/e1291.full>

So that is what we know about publication rates of clinical trials. It is regrettable that more isn't known. We would love to see more work on specific parts of trial publication. AllTrials is encouraging researchers to take responsibility for illuminating the situation in their particular area. We have been looking at commitments from trial sponsors and working with investors to get companies to make broad commitments to uncover old information. If it was as simple as monitoring specific hidden trials we would do that, but we don't have a clear enough picture of the scene. We probably never will. There are far too many factors and variables and caveats and limitations and too much missing information.

We are campaigning hard on retrospective trials. We should prioritise finding all the clinical trials on the treatments we use today. Fixes for the future were touted and promised before (see the pharmaceutical industry group PhRMA's 2009 promise<sup>25</sup> "to provide results summaries for all interventional clinical trials involving patients – regardless of whether the medicines are approved or the particular research programs have been discontinued" for example) and were never implemented. The longer it takes to get commitments to publish these past studies, the more will be lost or costly to recover. Unless there is an active programme to uncover old trials information will be lost forever.

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<sup>25</sup> <http://www.phrma.org/media/releases/revised-clinical-trial-principles-reinforce-phrma%E2%80%99s-commitment-transparency-strengthe>