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Pharmaceuticals & Healthcare Programme

# CLINICAL TRIAL TRANSPARENCY

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A GUIDE FOR POLICY MAKERS



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**The Collaboration for Research Integrity and Transparency (CRIT)** is an inter-disciplinary initiative launched in 2016 at Yale to enhance the quality and transparency of the research base for medical products. Through research, advocacy, and litigation, CRIT is focused on ensuring that the clinical evidence that supports and informs our understanding of the safety and effectiveness of pharmaceuticals, medical devices, and other medical products is accurate, comprehensive, accessible, and reliable.

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**TranspariMED** is an initiative that works to end evidence distortion in medicine by developing and promoting policy solutions to improve clinical trial transparency.

This study was written by Till Bruckner, founder of TranspariMED, in close consultation with team members at Cochrane, CRIT and Transparency International's Pharmaceuticals and Healthcare Programme.

While the content of this study is the sole responsibility of Cochrane, CRIT, Transparency International Pharmaceuticals and Healthcare Programme and TranspariMED, many external experts generously volunteered their time to review and comment on earlier drafts of the document. We would like to thank the following individuals for their valued input:

Erick Turner (Oregon Health and Science University), Simon Kolstoe (University of Portsmouth), Vaseeharan Sathiyamoorthy (World Health Organization), Fahmy Aboulenein-Djamshidian (Medical University of Vienna, TI-Austria), Yannis Natsis (European Public Health Alliance), Stuart Buck (Laura and John Arnold Foundation), Al Weigel (International Society for Medical Publication Professionals), and three additional expert reviewers who asked to remain anonymous.

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Published December 2017.

ISBN: 978-1-910778-75-3

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Printed on 50% recycled paper.

Transparency International UK's registered charity number is 1112842.

# Clinical Trial Transparency:

A guide for policy makers



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# Executive summary

## The problem

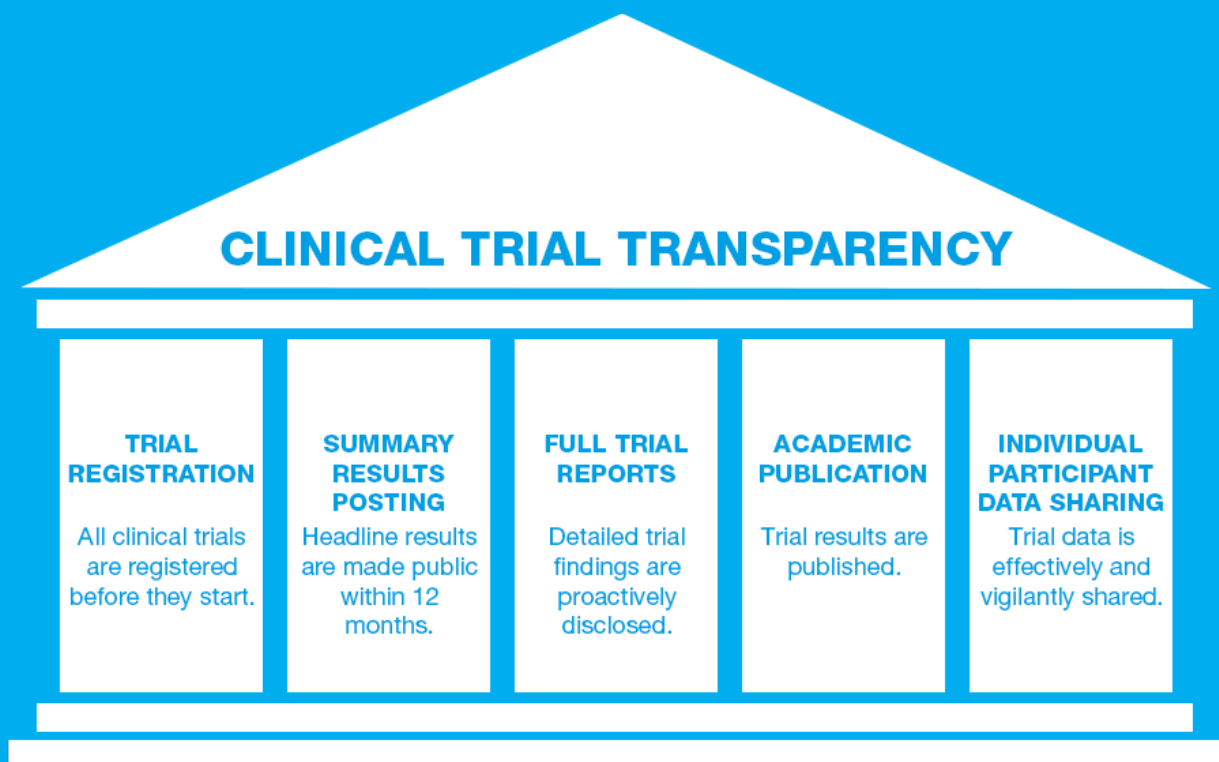
Clinical trials are a key driver of medical innovation and progress, but scientists have known for decades that the existing evidence base on drugs and medical devices is incomplete and biased due to the opacity of clinical trials. The medical community, the private sector and public bodies all lack access to reliable information on the benefits and harms of drugs, devices and treatments. The negative consequences of this lack of transparency are severe:

- Patients are harmed
- Public health agencies cannot make informed decisions
- Public health funds are wasted
- Medical progress is slowed down
- Shareholders are exposed to substantial risks

This lack of transparency in clinical trials can increase the risk for undue influence, manipulation of data and evidence distortion. It is a symptom of limited regulatory authority over the reporting process. It opens the door to fraud and corruption and undermines both medical advances and public health objectives.

## The solution

Strengthening clinical trial transparency would positively and directly benefit patient outcomes, improve the allocation of scarce medical research and healthcare resources, and facilitate and accelerate the development of new treatments and cures. Clinical trial transparency rests on five distinct pillars:



# Implementation

The United Nations have recently called on governments to take action to resolve this pressing public health issue. Making clinical trials more transparent would be both low-cost and highly cost-effective. Indeed, many significant transparency gains can be achieved within current legal frameworks through administrative action alone.

## Concrete steps

Decision-makers should take the following three steps to increase clinical trial transparency and make the sector more accountable to citizens, patients, taxpayers, and investors:

### **Step 1: Ensure that publicly funded clinical trials are transparently reported**

As a first step, political decision-makers should require all public research funding bodies within their jurisdiction to adopt and expand on World Health Organization transparency standards for disclosure of clinical trial findings, and ensure that they are fully implemented. Taking this simple first step would deliver significant gains at minimal cost.

### **Step 2: Enforce existing rules for clinical trials reporting**

Second, decision-makers should provide government agencies with the resources, powers and political support they need to enforce existing laws, rules and regulations, which at present are often not consistently implemented. Decision-makers should support government agencies in setting up effective monitoring and sanctions mechanisms to bring greater accountability into the sector.

### **Step 3: Strengthen legal and regulatory frameworks**

Third, decision-makers should bring existing laws, rules and regulations into line with global best practice standards and ensure that they cover all clinical trials, past and present, across all five pillars of clinical trial transparency.

# Background

## What are clinical trials?

Clinical trials are a key driver of medical innovation and progress. Medical researchers enlist human volunteers into trials to investigate whether drugs, medical devices and treatments<sup>1</sup> are safe and effective for use. Clinical trials typically seek to determine the effectiveness of a drug, device or treatment by giving it to a number of patients, and comparing the outcomes against a control group that gets another drug or a placebo. Scientists then monitor trial participants in both groups for changes in their health status, as well as any negative side effects they may experience. By analysing the data and comparing the two groups, researchers learn whether a drug, device or treatment is safe and effective.

The process of medical research and development is complex, time consuming and costly. Every year, pharmaceutical companies, universities and other research groups conduct around 20,000 clinical trials involving over two million patients worldwide, at an estimated cost of over US\$60 billion.<sup>2</sup> Larger trials can involve multiple funders, numerous research institutions and thousands of patients in several different countries, presenting formidable regulatory challenges.

The design, conduct and outcomes of clinical trials, and how they are reported, have significant commercial and public health implications. Government agencies use the results of clinical trials to decide whether to allow a new drug or device onto the market, and whether to fund their provision. Clinical trials also inform the decision-making of individual doctors seeking to determine the best treatment options for their patients.

## Why are clinical trials so important?

Clinical trials are the foundation of evidence based medicine. Government regulators, public health agencies, insurers and family doctors rely on the results of clinical trials to make potentially life-saving decisions regarding healthcare. By searching clinical trial registries and reviewing trial outcomes, they can see what researchers around the world have discovered to inform their decisions on the best treatment options.

Trial registries also provide an overview of the current state of medical knowledge and of research projects currently underway, enabling funders and scientists to avoid wasteful duplication and build on each other's work (Zarin et al., 2008).

## Untrustworthy trials: reporting bias and evidence distortion

Scientists have known for decades that the existing evidence base on drugs and medical devices can be biased. Numerous studies have shown that published evidence on drugs and medical devices systematically overstates benefits and downplays harms (Bekelman et al., 2003; Goldacre, 2012; Golder et al., 2016; Sani, 2014; Song et al., 2010).

Two important factors contributing to this problem are reporting bias and evidence distortion.

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1 This paper adopts the following definition of clinical trials set out by the World Health Organization (WHO): "For the purposes of registration, a clinical trial is 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. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc." [http://www.who.int/topics/clinical\\_trials/en/](http://www.who.int/topics/clinical_trials/en/) The text of this paper at times only refers to drugs and/or medical devices; this is purely to make the document more readable, and should not in any way be read as a narrowing of the WHO definition.

2 The figures quoted here are all conservative estimates. Data sources: Between January and November 2017, over 25,000 new studies were registered on the largest trial registry, Clinicaltrials.gov, alone. Around 80% of trials registered on Clinicaltrials.gov are interventional trials, hence the estimate of around 20,000 clinical trials worldwide as defined by this study. See: <https://clinicaltrials.gov/ct2/resources/trends#RegisteredStudiesOverTime> [accessed 04 December 2017] It has been estimated that between 1,950,000 and 11,400,000 people join drug trials alone every year. See: <http://blogs.plos.org/absolutely-maybe/2017/05/25/the-case-of-the-missing-neuro-drug-trials/#Proportion> [accessed 04 December 2017]

The figure of over US\$60 billion per annum is conservative as it is based on three separate estimates of the value of industry-run trials alone (thus excluding trials sponsored by universities, government agencies, and nonprofits). See: [http://www.pharmsource.com/market/how-big-is-the-market-for/#Clinical\\_Research\\_Total](http://www.pharmsource.com/market/how-big-is-the-market-for/#Clinical_Research_Total) [accessed 04 December 2017]

**Reporting bias** occurs when the results of successful trials are more likely to be reported than those of unsuccessful trials. Reporting bias has multiple causes. Commercial players tend to prioritise publishing evidence that makes their products appear in a positive light,<sup>3</sup> and sometimes use contractual mechanisms or informal pressure to prevent scientists from publishing trial results that run contrary to commercial interests (Angell, 2005; Bass, 2008; Lexchin, 2003; Steinbrook, 2005).

Even when no commercial interests are at stake, bias can occur (McGauran et al., 2010). Editors of academic journals generally prefer to publish positive trial results that might herald new medical breakthroughs. Scientists know this and may not attempt to publish the outcomes of trials with zero or negative results, and if they do try, they may not find a high profile journal willing to publish their paper (Song et al., 2014).

Trials that have neither been registered nor reported remain completely invisible. This is a serious problem for scientists, including those working at national regulatory agencies,<sup>4</sup> who need to see all trials conducted to date to be able to determine whether a drug or device is safe and effective.<sup>5</sup> Invisible trials also lead to significant research waste: valuable discoveries are not shared, and scientists may repeatedly explore the same dead ends.

## How an important clinical trial nearly became research waste

In 2015, Dr. Aus Alzaid, a practicing physician working in Saudi Arabia, set out to discover whether a widely used diabetes drug that was being taken by millions of patients worldwide – including some of his own – might affect memory or cause dementia. He found that the publicly available evidence on the drug's possible link to dementia was contradictory, and limited to laboratory data and observational surveys.

Only a single relevant clinical trial existed. According to its registry entry, it had been completed three years earlier, but had not publicly shared its results in any form, potentially exposing millions of patients to unrecognized harms. Its results were only published after repeated prompting by Dr Alzaid and others.

If the trial had not been registered in the first place, it would have remained completely invisible, and its results would have been lost forever.

Dr. Alzaid later commented that “it should not be left to a random physician or a private individual to chase after the results of clinical trials or personally plead with investigators to publish their finished work. Publication of registered clinical trials is a professional responsibility, not a personal prerogative of the main investigator. This fact is clearly stated in all professional codes of conduct” (Alzaid, 2016).

Evidence distortion in the reporting of trial results is the second reason why published evidence on drugs and medical devices overstates benefits and downplays harms. It takes a many forms, including spin, statistical manipulation, selective reporting of partial results, and (far less frequently) outright data manipulation.<sup>6</sup> Although all forms of evidence distortion are considered unethical, and many are classified as scientific misconduct, very few constitute blatant corruption or criminal offenses. While some forms of evidence distortion are widespread, perpetrators are rarely detected and are unlikely to face consequences.

Evidence distortion is driven by a range of factors, from confirmation bias<sup>7</sup> to individual scientists' career ambitions to vested financial interests. In some instances, scientists with limited statistical understanding may distort evidence unintentionally, not realising that they are generating misleading data, violating scientific and ethical norms, and potentially causing harm to patients.

3 This simple online game further illustrates the dynamics at work:

<https://www.economist.com/blogs/graphicdetail/2015/07/daily-chart-other-placebo-effect>

4 Note that some government agencies have better access to information on clinical trials than others. Notably, regulatory agencies such as the US Food & Drug Administration and European Medicines Agency can routinely access some types of information related to clinical trials that other government agencies have no access to.

5 Some regulators now require prospective trial registration to prevent companies from cherry picking only those trials with positive results to present for regulatory review. However, many of the most widely used drugs and devices on the market today were approved by regulators before these rules came into force, and hence the full evidence base on many of them remains inaccessible today, even to regulators.

6 Providing an exhaustive list of all forms of evidence distortion and explaining the underlying statistical principles and fallacies is beyond the scope of this study. Notable examples include outcome switching, post hoc subgroup analysis, p-hacking, HARKing, and non-reporting of protocol deviations. An overview of the topic is provided in: Goldacre, Ben. 2012 *Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients* (Fourth Estate)

7 Confirmation bias is the tendency to interpret new evidence as confirmation of one's existing beliefs or theories.

## 4 Clinical Trial Transparency



## Quantifying publication bias and evidence distortion

A team of researchers examined the reporting of clinical trials of 12 antidepressant drugs approved by the US Food & Drug Administration (FDA). The team located 74 FDA-registered trials involving 12,564 patients and compared reviews made by FDA experts with the available academic literature.

All but one of the 38 clinical trials that the FDA had deemed to have had a positive outcome had been published. Of the remaining 36 trials with negative results, only 3 were published. The other 33 trials had either not been published at all (publication bias, 22 trials), or had been published in a way that suggested that the results had been positive (evidence distortion, 11 trials).

Thus, while FDA experts had concluded that nearly half of 74 trials had not had a positive outcome, doctors and researchers relying on the academic literature alone would have gained the impression that the vast majority (49 out of 52) of all relevant antidepressant trials had resulted in a positive outcome (Turner et al., 2008).

A separate 2015 analysis of 15 drugs approved by the FDA found that, per drug, around 35% of results from all clinical trials conducted to gain FDA approval were unavailable to doctors and external researchers (Miller, 2015).

## The cost of clinical trial opacity

Reporting bias and evidence distortion in medicine have continued unchecked for decades due to the selective opacity of clinical trials. Patients, doctors and public health agencies must rely on pre-packaged research findings presented by players with a vested interest in overstating the benefits of drugs and medical devices and downplaying their harms, without being able to examine how these findings were generated.

The negative consequences of this lack of transparency include direct harm to patients, a slowdown in scientific progress, and heightened financial risk for investors.

### Patients are harmed

Lack of transparency in clinical trials harms patients. The benefits and risks of drugs and medical devices cannot be fully understood and assessed if information generated about them through research is missing, biased, distorted or incomplete. There are numerous well-documented instances in which large numbers of patients have been harmed due to weak clinical trial transparency.

### Public health agencies cannot make informed decisions

When pharmaceutical companies apply for a license to market a new drug or medical device, they provide regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) with a large amount of information generated during clinical trials. However, both companies and regulators typically refuse to share such information with third parties. As a result, independent researchers and other government agencies<sup>8</sup> cannot review or re-analyse the data presented by commercial players. Several drugs and devices approved by regulators have subsequently been removed from the market over safety concerns after patients experienced unexpected harmful side effects (Onakpoya, 2016). Consequently, scientists working at regulatory agencies and other public health bodies are often strong advocates for greater clinical trial transparency.

### Public health funds are wasted

Due to rapidly increasing global healthcare costs, public health systems and private insurers face difficult decisions on which treatments to fund. To determine whether a drug's effectiveness justifies its cost, decision-makers need access to the full results of all clinical trials. However, this data is usually not accessible. In the past, this has led to the waste of substantial public funds.

<sup>8</sup> This includes health technology assessment bodies tasked with assessing the comparative effectiveness and cost-effectiveness of drugs in order to inform the allocation of limited public health resources. Please see the section on "Full trial reports" for more details.

## Medical progress is slowed down

Weak clinical trial transparency prevents research funders and scientists from effectively coordinating their efforts. An estimated US\$85 billion in medical research funding is being wasted every year as trials that cost millions to run fail to contribute to medical progress because their results are not reported.<sup>9</sup> Scientists may needlessly repeat trials of drugs that others have already found to be harmful, ineffective, or both. Promising new approaches as well as potential harms may go unnoticed for a long time, and scientists cannot build on each other's discoveries. All this delays the development of new treatments and cures, and undermines efforts to prepare for public health emergencies, such as epidemics.

## Shareholders are exposed to substantial risks

Investors in pharmaceutical companies have joined the call for greater clinical trial transparency because the lack of transparency exposes them to substantial market, legal and regulatory risks (AllTrials, 2015; The Economist, 2015). The information asymmetry between companies and investors undermines capital market efficiency. Investors cannot reliably assess the market potential of new drugs under development, or ascertain whether there is hidden data whose emergence could threaten existing revenue streams or lead to legal action (Feuerstein, 2016).

## Moving from opacity to transparency in clinical trials

At present, clinical trials are characterized by a high level of opacity (CRIT, 2017). The medical community, the private sector and public bodies all lack access to reliable information on the benefits and harms of drugs, devices and treatments. This is unethical, and the resulting information asymmetry negatively impacts individuals' health, public health, public finances, and the effective functioning of markets.

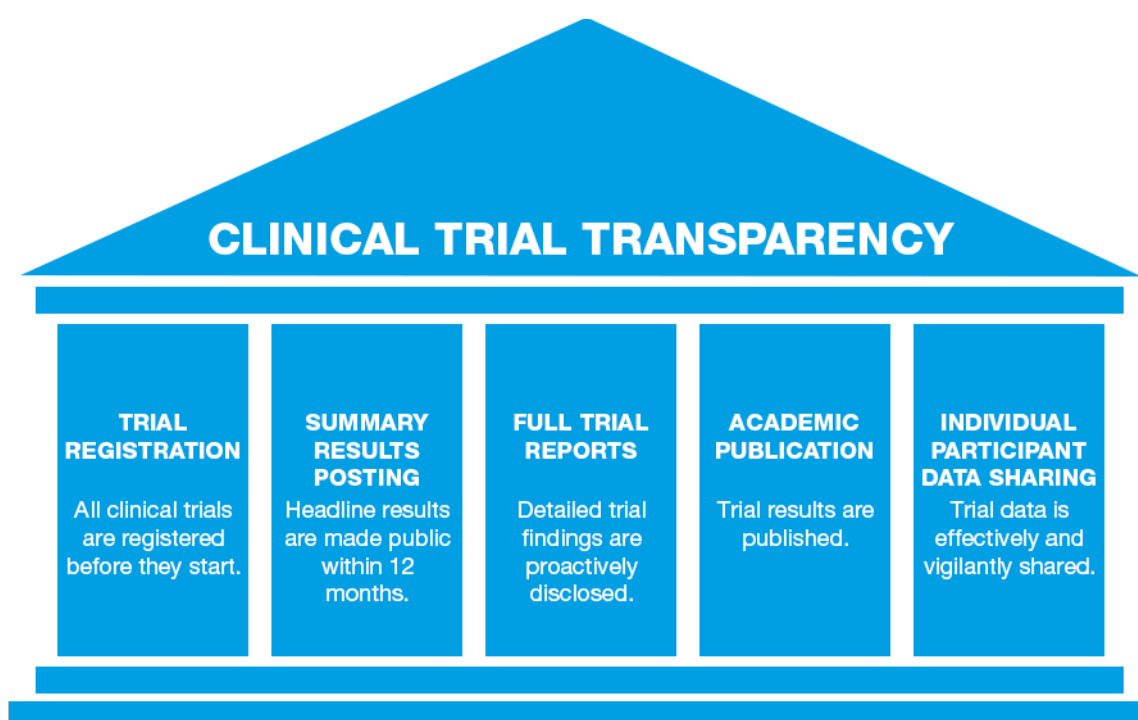
The remainder of this paper will outline the concrete steps that decision-makers can take to bring the field of clinical medical research into line with global transparency standards.

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<sup>9</sup> In total, an estimated US\$170 billion in medical research is wasted annually. Half of that waste is attributed to the failure to publish the results of completed research; hence the US\$85 billion figure.

# The five pillars of clinical trial transparency

Strengthening clinical trial transparency would positively and directly benefit patient outcomes, improve the allocation of scarce medical research and healthcare resources, and facilitate and accelerate the development of new and effective treatments and cures (Bruckner & Ellis, 2017). Clinical trial transparency rests on five distinct pillars, namely prospective trial registration, timely posting of summary results on the same registry, the publication of full trial reports, the unbiased and accurate publication of trial outcomes in academic journals, and individual participant data sharing.



## Trial registration

Prospective trial registration in a regulated online trial registry (database) is universally recognised as an ethical obligation irrespective of national legal requirements. It reduces the potential for bias and evidence distortion in the reporting of trial results.<sup>10</sup> It enables research funders to avoid duplicating previous research and identify legitimate knowledge gaps, and helps scientists to build on discoveries made by others. In many jurisdictions trial registration is already a legal or regulatory requirement, but compliance remains uneven.

<sup>10</sup> Bias is defined here as the (often unintentional) outcome of systems and processes that result in positive trial outcomes being overrepresented or more visible in the publicly available record. Evidence distortion is the result of research misconduct, which includes statistical manipulation such as the retrospective addition or suppression of outcome measures (“outcome switching”) and data dredging (e.g. p-hacking, post hoc subgroup analysis). In contrast, the fabrication or deletion of data is outright fraud and may constitute a criminal offense.

## Summary results posting.

After a clinical trial has been completed, researchers are obliged to post its summary results onto the registry (or registries) where it was originally registered.<sup>11</sup> This provides a publicly accessible snapshot of the headline results of a trial. Results posting allows scientists to quickly and systematically share new discoveries without having to wait until academic publication, which can take several years, and reduces the potential for bias and evidence distortion in the reporting of results. Some laws, rules and regulations already require research institutions to post the summary results for some trials within 6 or 12 months of trial completion,<sup>12</sup> but compliance is poor.

## Full trial reports

The core component of full trial reports are Clinical Study Reports (CSRs), lengthy documents that allow experts to determine how significant and reliable a trial's findings are, and flag additional benefits or side effects that the original research team may have overlooked. This benefits medical progress while also reducing the potential for evidence distortion and fraud in the reporting of results. Pharmaceutical companies are already required to provide regulators with CSRs when they apply for a license to market a drug, but these reports are usually not made available to third parties.

### Summary results versus Clinical Study Reports

Summary results take the form of a short table that summarizes the key features of a clinical trial: the drug or device being investigated, outcome measures used, patient characteristics, and the headline results. Summary results make a brief snapshot of a trial's findings publicly accessible, but do not contain in-depth information on the design, conduct or findings of a trial.

In contrast, Clinical Study Reports (the core component of full trial reports) are highly technical documents that are typically over a thousand pages in length and provide a very detailed picture of the design, conduct, analysis and outcomes of a trial, including details on the negative side effects experienced by patients.<sup>13</sup>

## Academic publication

Academic journals are the primary communication platform for many scientists. They are often the first port of call for doctors seeking information on how to treat their patients, and importantly are critically reviewed by other scientists or clinicians in a process called peer review. Trial results should be published in journals or made freely available to ensure that the discoveries made by clinical trials are widely shared and influence medical practice. At present the results of many trials are not published in journals.

## Individual participant data sharing

Sharing the trial-related data collected on each individual participant in the course of a clinical trial can accelerate medical progress, improve understanding of the safety and effectiveness of drugs, devices and treatments, and reduce the scope for evidence distortion and fraud. However, there are still considerable practical barriers to effective IPD sharing. While numerous initiatives are working to overcome these problems, the immense potential of IPD sharing can only be fully realized if and when the other pillars of clinical trial transparency are firmly in place.

The following explores each pillar in more depth, covering the basic features of each pillar, highlighting why transparency within the pillar matters, what progress has been made to date, relevant global standards that already exist, and policy recommendations to improve clinical trial transparency.

<sup>11</sup> The timely posting of summary results is an ethical and scientific obligation as set out by the WHO and various international standards. In some jurisdictions, notably the US and EU, the posting of summary results is also a legal or regulatory requirement for some types of trials.

<sup>12</sup> Note that legal definitions of trials and the types of trials covered by US and EU rules do not fully overlap; for example, trials of medical devices are not obliged to post results under current EU regulations. Similarly, EU rules set different time frames for different types of trials.

<sup>13</sup> For a more detailed explanation, see Wieseler, B., Kerekes, M.F., Vervoelgyi, V., McGauran, N. and Kaiser, T., 2012. Impact of document type on reporting quality of clinical drug trials: a comparison of registry reports, clinical study reports, and journal publications. *BMJ*, 344, p.d8141. <http://www.bmj.com/content/344/bmj.d8141>

# Trial registration

All clinical trials should be registered on a WHO-approved trial registry before the recruitment of the first participant.

## What is trial registration?

Trial registries were established to provide a quick and comprehensive overview of all past and ongoing clinical trials, and to reduce publication bias and evidence distortion. Currently there are 17 registries approved by the World Health Organization (WHO), all of which are managed by non-commercial entities and are freely accessible online. The largest registries are the publicly administered Clinicaltrials.gov (in the United States), EudraCT (in the European Union), and the Japan Primary Registries Network.<sup>14</sup>

Registering a trial involves filling out and uploading a brief form onto a registry<sup>15</sup> that captures basic information about a planned trial, including the drug or medical device under investigation, the expected number of participants and their medical condition, and the specific health outcomes that will be assessed at the end of the trial to determine the drug or device's effects, benefits and harms.

Once a trial has been registered, scientists everywhere can see what has been researched in the past and what their colleagues are currently working on. The permanent addition of a trial to the global map of medical research before it starts prevents unsuccessful trials from disappearing from view.

## Why does it matter?

Requiring all trials to be registered before they begin ensures that all trials conducted on a drug or device become and remain visible, irrespective of whether the results are positive or negative, and regardless of whether the results are subsequently published or not. Trial registration ensures that no trials remain hidden and is indispensable for countering the effects of reporting bias (Zarin et al., 2007). Such registries are already extensively used to gain information about medical research. Clinicaltrials.gov alone currently has approximately 170 million page views per month (Zarin, 2017).

Furthermore, because prospective registration involves specifying the outcome measures (i.e. success criteria) of a trial in advance, it significantly reduces the potential for subsequent evidence distortion in the reporting of trial results (Dechartes et al., 2016).

## Progress to date

Prospective registration of many types of clinical trials is already a legal or regulatory requirement in many jurisdictions, including in the United States (since 2007; FDA, 2016) and the UK (since 2013; HRA, 2017) but not all clinical trials are covered in every jurisdiction that has such frameworks in place, and some loopholes remain (Southworth, 2011).

In addition, many important medical research stakeholders, including research funders, pharmaceutical companies and universities, have adopted policies promoting the registration of trials.<sup>16</sup> Notably, a policy

<sup>14</sup> In an attempt to consolidate the multiple existing registries, the World Health Organization (WHO) has created the International Clinical Trials Registry Platform (ICTRP). The WHO currently recognizes and pools data from 17 data providers (see <http://www.who.int/ictrp/network/primary/en/>) that meet internationally defined criteria (see [http://www.who.int/ictrp/network/criteria\\_summary/en/](http://www.who.int/ictrp/network/criteria_summary/en/)) including public or non-profit status, free public accessibility, and the ability to capture comparable information about key trial parameters (see <http://www.who.int/ictrp/network/trds/en/>) [Links accessed 20 September 2017].

In total, ICTRP registries contain over 300,000 unique entries. The US registry, Clinicaltrials.gov, is by far the largest with over 200,000 entries, although not all of these entries are interventional clinical trials; the EU registry is second in size with 27,000 entries (all of which are drug trials); some of the other registries contain only a few hundred trials.

See Table 1 in: Zarin, D, et al. "Update on Trial Registration 11 Years after the ICMJE Policy Was Established" *N Engl J Med* 2017; 376:383-391 <http://www.nejm.org/doi/full/10.1056/NEJMs1601330#t=article>

<sup>15</sup> This is an example of a trial registration made on Clinicaltrials.gov: <https://clinicaltrials.gov/ct2/show/NCT02662556> [Accessed 20 September 2017].

<sup>16</sup> Numerous medical research stakeholders have adopted policies that support clinical trial transparency. For examples and suggested best practices, see: <http://www.alltrials.net/wp-content/uploads/2017/02/AllTrials-Roadmap.pdf> [Accessed 20 September 2017].



adopted by the International Committee of Medical Journal Editors resulted in a steep increase in the number of trials being registered (Laine et al., 2007).

As a result of these developments, trial registration rates have increased over the past decade, but research shows that many trials are still not being registered even today, including in jurisdictions where registration has long been mandatory.<sup>17</sup> Around a third of those trials that do get registered are only registered retrospectively in violation of ethical norms and World Health Organization standards, leaving the door open to outcome switching and other forms of evidence distortion (Zarin et al., 2017). In other cases, the data provided is of poor quality (Zarin et al, 2011). All of the above indicates that existing laws, rules and regulations are being insufficiently enforced.

## Many trials still remain unregistered

Prospective trial registration has been a universal ethical obligation for medical researchers worldwide since 2008 (WMA, 2013). However, a 2017 study of 860 clinical trials found that 556 trials had not been registered at all, and a further 157 had only been retrospectively registered. Less than 19% of the clinical trials assessed had been prospectively registered (Jones et al., 2017).

## Numerous trials in the UK not registered, no penalties imposed

Every trial conducted in the United Kingdom has to secure approval by one of the country's 68 regional Research Ethics Committees. Since 2013, ethics approval is only granted to researchers who commit to register a trial.

In 2015, the UK's Health Research Authority (HRA), which oversees all Research Ethics Committees, conducted an audit to discover how many trials had not been registered. The government agency found that 23% of Phase 1 trials, 40% of trials for medical devices, and 40% of 'other' trials had not been registered in a timely fashion. The HRA announced that it would follow up by emailing the sponsors of the trials that remained unregistered, but it also noted that "[t]here are no HRA sanctions in place at this time" (HRA, 2017). A senior HRA official subsequently explained that the agency lacks the resources and legal framework to effectively enforce existing regulations (Kolstoe et al., 2017).

## Global standards

- The 2016 United Nations High-Level Panel on Innovation and Access to Health Technologies called on governments worldwide to ensure that all clinical trials are registered.
- World Health Organization standards adopted in 2012 and 2015 require trial sponsors to:
  - register all clinical trials on a WHO-approved registry "before the first subject receives the first medical intervention"
  - regularly update all registry entries
  - retrospectively register all clinical trials conducted in the past
- Prospective trial registration has been a universal ethical obligation for individual medical researchers worldwide since the World Medical Association's 2008 revision of the Declaration of Helsinki (WMA, 2013).

## Policy recommendations

There already exist a number of robust international guidelines, as well as legislation and policy applicable to national jurisdictions. The main barrier to achieving universal proactive and retroactive trial registration, however, is lack of monitoring and effective sanctions for non-compliance to these instruments. In many jurisdictions, effective enforcement of the existing laws, rules and regulations would ensure that in future, all trials are registered before they begin.

<sup>17</sup> The exact number of trials that still fail to register worldwide is impossible to quantify, as unregistered trials that subsequently also fail to publish results are – almost by definition – invisible.

Where no legislation or policy exist, the World Health Organization can serve as the standard upon which robust instruments can and should be based upon.

Furthermore, Regulatory Authorities for Ethics Committees, which give approval to conduct a clinical trial, can act as a bottleneck for ensuring trial registration. Mandating registration as part of the ethics approval process, would necessitate that trials are registered before the trial can begin .

# Summary results posting

Summary results for all clinical trials should be posted on the registries where they were originally registered within 12 months of study completion.<sup>18</sup>

## What are summary results?

After a clinical trial has been completed, its summary results are posted onto the registry (or registries) where it was originally registered to make basic information on the trial's conduct and outcomes publicly accessible. The initial registration of a trial records what researchers were looking for and their proposed methodology; the summary results later complement this information by summarizing key features and outcomes of the trial in a short table.<sup>19</sup> Summary results can be posted rapidly and at a negligible cost.<sup>20</sup>

## Why does it matter?

Access to summary results allows scientists to quickly and systematically locate, access and share new discoveries. In addition, research funders can draw on summary results to improve their decision-making on whether to fund additional research into a new drug or device. Summary results also reduce the potential for reporting bias and evidence distortion because the trial's pre-specified outcomes, actual results, and outcomes reported in academic publications can be cross-checked for consistency (Rosati et al., 2016; Wieseler et al., 2012). Importantly, summary results often provide a more robust and accurate picture of trial outcomes, including serious adverse events,<sup>21</sup> than journal articles do (Riveros et al., 2013; Tang et al., 2015).

### Serious adverse events are better documented in summary results

Under United States law, all serious adverse events experienced by trial participants (such as death, conditions requiring hospitalization, and permanent damage or disability) must be included in the summary results posted on the Clinicaltrials.gov registry (FDA, 2016).

A 2015 study found that these summary results provided a more complete picture of serious adverse events than papers published in academic journals. A research team examined 300 clinical trials that had reported serious adverse events (SAEs) in their summary results and compared them to corresponding journal articles. Only 33 journal publications (11%) provided a complete and consistent account of all the SAEs experienced by trial participants.

Without the availability of summary results, none of the SAEs recorded in 41% of all trials would have become public knowledge as their results had not been academically published at all, or the publications omitted to mention any SAEs. In the remaining cases, journal articles provided an imperfect account of the SAEs experienced. In addition, the study found that posted summary results communicated SAEs far more rapidly than journal articles did because of lengthy academic publication timelines.

The authors concluded that: "For policymakers, our results advocate an extension to all countries of the mandatory posting of trial [summary] results... Consulting safety results posted at ClinicalTrials.gov [...] is crucial for more information on serious harms" (Tang et al., 2015).

18 "Study completion" here refers to primary study completion, as defined by the WHO: "primary study completion [is] the last visit of the last subject for collection of data on the primary outcome". <http://www.who.int/ictpr/results/jointstatement/en/index1.html>

19 This is an example of a summary result posted on Clinicaltrials.gov: <https://clinicaltrials.gov/ct2/show/results/NCT02662556>

20 The estimated cost of compiling and uploading summary results is only US\$2,000 per trial, which is negligible compared to the overall cost of conducting a clinical trial. See: Hoffmann, Tammy et al. "Focus on sharing individual patient data distracts from other ways of improving trial transparency" *BMJ* 2017;357:j2782 <http://www.bmj.com/content/357/bmj.j2782> Estimates for the time required to post summary results range from 25-60 working hours. <http://www.tandfonline.com/doi/full/10.1185/03007995.2012.739152>

21 Note that medical terminology distinguishes between adverse events and side effects. Recorded adverse events can be in the comparator or placebo arm as well the active treatment arm, and, even in the active treatment arm, may not have been related to the treatment given.

Importantly, researchers can upload the summary results to registries as soon as the trial data has been analysed, thereby speeding up the pace of scientific progress. Both global standards and existing laws and regulations usually require summary results to be posted within a maximum of 12 months. In the case of paediatric trials and public health emergencies, a tighter time frame is sometimes applied (EU, 2009; WHO, 2015). In contrast, getting a paper published in an academic journal can take several years (Tang et al., 2015).

## Accelerating the pace of medical discovery

In 2016, two employees of a pharmaceutical company published a study showing that 67 out of 69 clinical trials successfully completed by the pharmaceutical company during 2010 had been submitted to academic journals for publication. However, three years after trial completion, only 54% of the studies had been published. The main reason for this was the slow academic publication process. Even in cases where the first journal approached accepted a paper, the median time to publication was 28 months (Mooney & Fay, 2016).

In contrast, clinical trial registries typically only take a few weeks to review and publish the summary results of clinical trials. Summary results posting thus makes it possible for scientists to share research findings far more rapidly.

Posting results also saves medical discoveries from being lost forever in case a trial's results never get published in a journal, for example when researchers move to a different institution or retire shortly after a trial has been completed. A research team led by the director of Clinicaltrials.gov recently estimated that results are published in the literature for only half of all trials registered there (Zarin et al., 2017).

## Progress to date

The timely posting of summary results is an ethical and scientific obligation as set out by the WHO and various international standards. In addition, in some jurisdictions, laws, rules and regulations already require the timely posting of summary results of some – but not all – clinical trials onto trial registries.

For example, in the United States, a 2007 law<sup>22</sup> requires the “responsible party” – typically trial sponsors<sup>23</sup> – to post the summary results of certain clinical trials<sup>24</sup> to Clinicaltrials.gov, a publicly administered trial registry, within 12 months of trial completion. The law states that those who fail to comply must pay a fine of up to US\$10,000 each day until overdue results are posted. In reality, however, this law has never been enforced. Several years after it was passed, a study of a cohort of trials subject to mandatory reporting found that 78% had not complied with the legal requirement to post summary results (Prayle, Hurley & Smyth, 2012).<sup>25</sup> To date, commercial trial sponsors alone have run up over US\$25 billion in fines for failing to post summary results, but no fines have been collected (Piller, 2015; Piller, 2016).

Overall summary results posting rates on Clinicaltrials.gov (i.e. including trials not covered by the law) are even lower. A 2013 study of a cohort of cancer drug trials found that only 9% had posted summary results within 12 months; two thirds of trials still had not posted results three years after completion (Nguyen et al., 2013). As of October 2016, ClinicalTrials.gov contained more than 227,000 entries, but 90% lacked summary results (Anderson et al., 2015; Riveros et al., 2013; Zarin et al., 2017).

22 Section 801 of the 2007 Food and Drug Administration Amendments Act, see: <https://clinicaltrials.gov/ct2/manage-recs/fdaaa> [Accessed 20 September 2017]

The final rule for this law (42 CFR Part 11) was formally adopted in September 2016, see:

<http://www.nejm.org/doi/full/10.1056/NEJMSr1611785#t=article> [Accessed 20 September 2017]

Looking forward, transparency advocates have expressed concerns about whether the new rule would be implemented:

<http://www.alltrials.net/news/new-us-rules-fail-to-impose-full-transparency-on-clinical-trials/> [Accessed 20 September 2017]

23 Technically, the law refers to the “Responsible Party”, which is usually the institution sponsoring the trial. Under some circumstances, the sponsor can delegate that responsibility. The procedures for determining which individual or entity meets the definition of “responsible party” are specified in § 11.4(c) and described in Section IV.A.2 of this document: <https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission#sectno-reference-11.66%20>

24 Current U.S. legal requirements for summary results posting only cover a small minority of trials registered on Clinicaltrials.gov. In addition to leaving many types of trials uncovered, the law also only applies prospectively, and hence fails to cover many drugs widely prescribed today: <http://science.sciencemag.org/content/322/5898/44.3>

**Note that WHO standards call for all trials to post summary results within 12 months of completion.**

25 An analysis conducted in 2014 using a different methodology suggested a legal non-compliance rate of 33%.

<http://journals.sagepub.com/doi/abs/10.1177/2168479014529115>

A 2017 industry-funded analysis of a small sample of trials found higher (but still suboptimal) compliance rates:

<http://bmjopen.bmj.com/content/7/9/e015110>

## Results of 96 clinical trials involving children remain unknown

In 2016, researchers at Harvard Medical School published a study examining all paediatric trials registered with Clinicaltrials.gov from 2008-2010. Out of 455 completed trials, 136 had not published results in academic journals.

Thanks to summary results posted on ClinicalTrials.gov, scientists can access the headline findings of 42 of those trials even though they have not been reported in the academic literature.

However, the results of the remaining 96 unpublished trials, which involved tens of thousands of children, remain completely unknown and may be lost forever unless their summary results are posted (Pica & Bourgeois, 2016).<sup>26</sup>

Similarly, a European Union regulation that came into force in 2014 requires sponsors to post the results of certain trials<sup>27</sup> within 12 months (six months for paediatric trials) at the latest (EMA, 2014). However, even though all trials registered on the EU-administered registry, EudraCT, are subject to this law, around one third of trials listed there are currently missing results.<sup>28</sup> This strongly suggests that the national agencies<sup>29</sup> in individual European Union countries that are responsible for enforcing the EU regulation are failing to effectively enforce it.

## Global standards

- The 2016 United Nations High-Level Panel on Innovation and Access to Health Technologies called on governments worldwide to ensure that the summary results of all clinical trials are posted on registries in a “timely” fashion.
- World Health Organization standards adopted in 2015 and a commitment made in 2017 require trial sponsors to:
  - post the summary results of all clinical trials onto a WHO-approved registry within 12 months at the latest following study completion,<sup>30</sup>
  - retrospectively post the summary results of all clinical trials conducted in the past onto a WHO-approved registry.

## Policy recommendations

While relevant laws, rules and regulations already exist in some jurisdictions, compliance is weak due to a lack of monitoring and enforcement by those government agencies responsible for doing so.<sup>31</sup> In addition, existing frameworks only cover some types of clinical trials. For example, trials of medical devices are not obliged to post results under current EU regulations. Also, at present, some trial registries do not have a function allowing summary results to be posted.<sup>32</sup>

26 Note: The authors calculated that over 69,000 children took part in the 136 medical trials not reported in academic journals, but did not provide a figure for the number of participants in the 96 trials that remained completely unreported.

27 The types of trials covered by US and EU rules do not fully overlap. For example, EU regulations on summary results posting only apply to certain trials of drugs; trials of medical devices are not covered. Note that WHO standards call for all trials to post summary results within 12 months of completion.

28 Based on a search of EudraCT (<https://www.clinicaltrialsregister.eu/ctr-search/search>) conducted on 28 September 2017. Note that some of the trials missing results are not yet due results as they are still ongoing or have only recently been completed. A University of Oxford research team is expected to release more precise data on non-compliant trials in late 2017 or early 2018.

29 A list of the responsible national agencies can be found here: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general\\_content\\_000155.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp) [Accessed 20 September 2017]

30 The WHO has subsequently clarified that in the case of public health emergencies, such as outbreaks of epidemics, the 12 month timeline should be “greatly shortened”. See: Developing Global Norms or Sharing Data and Results during Public Health Emergencies [http://www.who.int/medicines/ebola-treatment/data-sharing\\_phe/en/](http://www.who.int/medicines/ebola-treatment/data-sharing_phe/en/) [Accessed 20 September 2017]

31 In addition, existing laws, rules and regulations are sometimes poorly communicated to trial sponsors and individual researchers, resulting in a lack of clarity.

32 WHO should consider encouraging all WHO-recognised ‘Primary Registries’ (<http://www.who.int/ictrp/network/primary/en/>) to include this function.



Expanding the scope of existing laws, rules and regulations and effectively enforcing them would ensure that in future, the summary results of all clinical trials are posted to registries within a maximum of 12 months following trial completion, and that summary results are retrospectively posted for all trials conducted in the years since the relevant laws came into force. To effectively enforce the law, the responsible government agencies<sup>33</sup> will require strong and sustained political support, clear and adequate legal powers, appropriate technical infrastructure, and adequate human resources (Kolstoe et al., 2017).

Securing the summary results of older trials is equally important but will require a different approach. Many of the medicines in common use today were developed in the 1990s or earlier, so the results of older clinical trials are highly relevant to current medical practice. Retrospectively registering these older trials and posting their summary results would improve healthcare delivery and government agencies' decision-making on resource allocations, as well as saving billions of dollars' worth of medical research from being lost forever. Pharmaceutical companies could be required to register and post the results of trials they have sponsored in the past as a condition of continued market access.<sup>34</sup> The results of many past trials sponsored by non-commercial institutions, such as academic institutions, could be secured through a combination of financial incentives and technical assistance.

The investments required to ensure that the results of clinical trials past and present are reported are miniscule compared to the costs of conducting the research in the first place, and are dwarfed by the wider resource allocation, public health and scientific benefits of making this data accessible.<sup>35</sup>

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33 Within the European Union, Member States' national agencies are responsible for enforcement. Article 94 of the new EU Clinical Trials Regulation, which was adopted in 2014 and will come into application in 2019, states that: "Member States shall lay down rules on penalties applicable to infringements of this Regulation and shall take all measures necessary to ensure that they are implemented. The penalties provided for shall be effective, proportionate and dissuasive."

[https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg\\_2014\\_536/reg\\_2014\\_536\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf)

A list of the responsible national agencies can be found here:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general\\_content\\_000155.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp) [Accessed 20 September 2017]

34 In 2013, GlaxoSmithKline voluntarily committed to making available the CSRs of all approved medicines dating back to the formation of the company in 2000, illustrating the practical feasibility of releasing archived CSRs.

"UPDATE 1-GSK promises to publish detailed drug trial data". Reuters, 5 February 2013.

<http://www.reuters.com/article/gsk-data/update-1-gsk-promises-to-publish-detailed-drug-trial-data-idUSL5N0B5CV920130205>

35 The entire annual budget of the FDA could be covered several times over through collection of the fines outstanding for overdue summary results. <http://www.who.int/ictrp/results/jointstatement/en/> [Accessed 20 September 2017]

"Failure to report: A STAT investigation of clinical trials reporting". Stat News, 13 December 2015.

<https://www.statnews.com/2015/12/13/clinical-trials-investigation/>

# Full trial reports

All information relevant to interpreting a trial's findings should be proactively disclosed and made available to the scientific community. This information includes the original trial protocol, a pre-specified statistical analysis plan, Case Report Forms, and Clinical Study Reports.

## What are full trial reports?

Full trial reports contain the information that researchers need to fully understand a trial's conduct and outcomes.<sup>36</sup> The core component of full trial reports in commercial settings are Clinical Study Reports (CSRs), highly technical documents that are typically over 1000 pages in length and provide a very detailed picture of the design, conduct, analysis and findings of a trial, including details on the negative side effects experienced by individual patients. CSRs thus allow far deeper insight into a trial's methodology and findings than do summary results or articles published in academic journals (Doshi et al., 2012).

When pharmaceutical companies apply for a license to market a new drug, they must submit CSRs of relevant clinical trials to regulators, such as the US Food and Drug Administration or the European Medicines Agency, for review. In order to facilitate the process, the International Conference on Harmonization sets out a globally standardised format and structure that all CSRs must follow (ICH, 2015). In contrast, full trial reports that are produced in non-commercial settings may not follow a standardised format.

## Why does it matter?

The wealth of detail contained in full trial reports allows scientists to 'look under the hood' and understand exactly how a clinical trial was conducted, gauge the accuracy, reliability and validity of trial findings, and get far information on the benefits and side effects of drugs than can be found in summary results or journal articles (Jefferson et al., 2014).

Without access to full CSRs, including all appendices, the scientific community cannot fully verify the accuracy, reliability and validity of trial findings, or detect many kinds of omissions, mistakes, misinterpretations, evidence distortion and misrepresentations in other forms of trial reporting (Doshi & Jefferson, 2013).<sup>37</sup>

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36 For reasons of brevity, this section focuses on the discussion of CSRs, which have the advantage of being documents that are already widely in use and follow a standardised format. However, full trial reports should be understood to encompass all information relevant to interpreting a trial's findings, including (but not necessarily limited to) the original trial protocol, a pre-specified statistical analysis plan, Case Report Forms (CRFs), reproducible descriptions of measurements and interventions, study manuals, code and codebooks, and audit reports. For an overview, see:

Hoffmann, Tammy et al. "Focus on sharing individual patient data distracts from other ways of improving trial transparency" *BMJ* 2017;357:j2782 <http://www.bmj.com/content/357/bmj.j2782>

On the importance of access to CRFs in particular, see:

<https://law.yale.edu/centers-workshops/collaboration-research-integrity-and-transparency-crit/critical-thinking/what-state-evidence-base-medical-products-we-use-currently> [Accessed 20 September 2017]

Also note that access to full CSRs is required to interpret trial results; this includes access to all appendices of CSRs.

37 Citing multiple studies, the German health technology assessment agency IQWiG has stated that:

"There is overwhelming evidence, that so far publicly available trial data are insufficient to provide a complete and unbiased picture of a given health care intervention [...] clinical trial documentation (i.e., CSRs) held by regulatory agencies provides substantial additional information compared to publicly available trial reports".

<https://www.iqwig.de/de/projekte-ergebnisse/publikationen/iqwig-stellungnahmen/submission-of-comments-on-policy-0070-on-publication-and-access-to-clinical-trial-data.6423.html> [Accessed 20 September 2017]

## Deadly side effects often remain hidden

A 2016 meta-analysis of 28 separate studies into the underreporting of harms found that over 60% of negative side effects detected during clinical trials and recorded in unpublished documents are not reported in academic journals. All 28 studies of the topic, without exception, had identified a higher number of all (or all serious) adverse events in the unpublished versions.

In one example, 198 deaths were recorded in clinical trials of four new drugs, but in the subsequent published papers, only 29 deaths were fully reported. In another example, an unpublished report documented 15 suicides, but only seven were revealed in published papers.

The meta-analysis concluded that “[t]he extent of ‘hidden’ or ‘missing’ data prevents researchers, clinicians, and patients from gaining a full understanding of harm, and this may lead to incomplete or erroneous judgements” (Wieseler et al., 2010).

Notably, public health technology assessment bodies, responsible for the evaluation of properties, effects and impacts of health technologies, need to be able to review CSRs to improve their decision-making on the clinical effectiveness, safety and cost-effectiveness of different treatment options (Wieseler et al., 2010; Wieseler et al., 2012).

## CSRs “essential” for informed decision-making on health policy

The German health technology assessment agency IQWiG routinely requests CSRs from manufacturers for its drug assessments, which inform policy decision-making in the German health care system. In 2013, an IQWiG team reviewed 101 clinical trials whose full CSRs had been voluntarily supplied by pharmaceutical companies. They found that CSRs provided over twice as much information on patient-relevant outcomes than all publicly available sources combined.

The IQWiG scientists concluded that CSRs were “essential sources to inform meaningful indirect comparisons [between different drugs]”. Noting that drug companies are currently not obliged to provide CSRs to health technology assessment agencies or other third parties, they recommended that “CSRs should be made publicly available” (Wieseler et al., 2013).

In addition, independent researchers need CSRs to independently verify the presented summary evidence from trials and how it was generated, and to re-evaluate the conclusions arrived at by pharmaceutical companies and regulatory agencies.

## How CSR transparency improved regulatory decision-making

In 2007, independent researchers analyzed the CSRs of clinical trials for a widely used diabetes drug and concluded that the drug was linked to an increase risk of strokes, heart attacks, and heart related deaths. The company marketing the drugs had made the CSRs available to external researchers in the course of a litigation settlement.

Regulators in both the US and in Europe promptly reacted by revising their previous assessments of the drug’s safety; at least one regulator recommended that it should be taken off the market altogether (CRIT, 2017).

Making full trial reports – including but not limited to CSRs – publicly accessible reduces the potential for mistakes, misinterpretations, bias, evidence distortion, corruption or fraud in other forms of trial reporting (Doshi & Jefferson, 2013). In addition, access to full trial reports can help independent experts flag benefits or harms that the original team conducting the trial may have overlooked or incompletely reported, thus improving patient safety<sup>38</sup> and speeding up the discovery of new treatments and cures (Association of Medical Research Charities, 2016).

38 For example, independent evaluations were important in raising concerns about the heart-attack risks associated with Vioxx, a painkiller that was recalled in 2004, and in flagging harms of the drugs Tamiflu and Orlistat that regulators seem not to have detected.

## Using CSRs to unearth unrecognized drug harms

An independent team of researchers examined seven previously undisclosed CSRs from the European Medicines Agency (EMA) and unearthed data on adverse effects that had neither been thoroughly gathered nor fully reported. All CSRs related to orlistat, a drug designed to treat obesity that can be bought without prescription in the US and many European countries.

In their 2016 study, the researchers concluded that harms had been “systematically understated” not only in academic papers, but also in the summarised results submitted to the EMA during the drug’s approval process.

Because the CSRs were submitted long before the EMA’s proactive disclosure policy came into effect, the researchers had to use Freedom of Information requests to gain access to them, a process that took nearly four years.

After reviewing the data, the lead author concluded that “[i]t is very unlikely that the EMA discovered the difference in duration of adverse events in the orlistat and the placebo arm. The EMA relies on the analysis conducted by the sponsor and typically does not do their own statistical analysis” (Schroll, Penninga & Gøtzsche, 2016).

## Progress to date

Pharmaceutical companies have long been obliged to share relevant Clinical Study Reports with regulators when applying for licenses to market new drugs. However, in the majority of cases, only the pharmaceutical company marketing a drug and officials working for regulatory agencies can access CSRs. By contrast, scientists working for other government agencies such as health technology agencies and public health bodies have often been unable to access these important documents, as have independent researchers (Gøtzsche & Jørgensen, 2011; Wieseler et al., 2013).

In 2016, the EMA broke fresh ground by proactively releasing some CSRs. Unfortunately, the new policy only covers some CSRs received by the regulator since 2015.<sup>39</sup> Older CSRs in particular are not covered by the policy and thus remain in the agency’s archives, so the vast majority of CSRs held by the EMA are still inaccessible, leaving open questions about many drugs commonly used today (AllTrials, 2016). Furthermore, the EMA does not release CSRs into the public realm as documents that can be freely downloaded and shared by anyone. CSRs can currently only be viewed on screen, and only by scientists who have been granted access upon request, which limits their utility. Despite these caveats, the EMA’s move constitutes a bold and significant step in the right direction.

Some pharmaceutical companies have taken the EMA to court to prevent the release of further information (Wieseler et al., 2013). The pharmaceutical industry often argues that publishing CSRs could breach patient confidentiality or reveal commercial secrets, but the EMA found that these concerns could be managed by making a very limited number of redactions.<sup>40</sup>

In the United States, the US Food and Drug Administration has no comparable transparency policy, precluding third parties from accessing CSRs submitted to the American regulator except through Freedom of Information requests.

Full trial reports not compiled for consumption by regulators, including many produced by researchers working at universities and non-profit research institutions, are usually also not publicly available. Scientists working in these contexts typically lack incentives to publish full trial reports, and there are no well-established mechanisms for enabling public access. For example, the most frequently used trial registries have no dedicated function that would allow full trial reports to be uploaded.

39 The forthcoming EU Clinical Trial Regulation, which contains transparency provisions, will only come into effect in 2019. In 2016, the EMA adopted “Policy 0070” to bring forward some transparency provisions: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2016/03/WC500202621.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202621.pdf)

40 In December 2016, the EMA announced some changes to its approach to redactions: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2016/12/WC500218566.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/12/WC500218566.pdf) [Accessed 16 October 2017]

## Global standards

- The AllTrials Campaign calls for all CSRs to be made publicly accessible.<sup>41</sup> Over 730 groups worldwide, including leading medical associations and many pivotal medical research stakeholders, have explicitly endorsed the AllTrials principles, giving them the weight of global standards.<sup>42</sup>

## Policy recommendations

Regulators worldwide should follow and extend the positive example recently set by the EMA. Specifically, they should make all CSRs (including all appendices) currently held in their archives publicly accessible after making limited redactions to safeguard commercial and patient confidentiality. Going forward, regulators should make newly received CSRs publicly accessible at the time of regulatory approval, or within 24 months latest of receiving the CSR if not approved.

Regulators already hold these and other documents on file, so placing them online poses no logistical challenges and can be done at minimal cost (Turner, 2007).<sup>43</sup> From a legal perspective, such transparency provisions could be enforced by making continued market access of any drug contingent on the public release of all relevant CSRs.<sup>44</sup>

Due to some industry players' active resistance to increased transparency in this area, regulatory agencies – which are generally supportive of transparency measures – will require strong and sustained political support throughout this process (EMA, 2016).

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41 “All trial reports (Clinical Study Reports or their equivalent in non-commercial settings) should be posted online in full, with only minimal redactions.” See:

<http://www.alltrials.net/wp-content/uploads/2017/02/AllTrials-Roadmap.pdf> [Accessed 20 September 2017]

42 As of 26 September 2017, 734 organisations had formally lent their support to the AllTrials campaign. The full list is available here: <http://www.alltrials.net/supporters/supporters-organisation-list/> [Accessed 26 September 2017]

43 There is software that can automatically redact confidential information in CSRs. See: <https://www.outsourcing-pharma.com/Article/2016/03/30/AI-solution-redacts-hundreds-of-studies-per-day>

44 Note that sharing of CSRs for generic products or withdrawn/discontinued products cannot be incentivized through market access measures.



# Academic publication

The results of all clinical trials should be published in an academic journal or made freely available in appropriate trials registries or databases (preferably both).

## What is academic publication?

Researchers traditionally share discoveries made during a clinical trial by submitting a paper that summarises the trial's design and outcomes to a scientific journal for publication. If the journal is interested in publishing the paper, it will send the article to other scientists and experts in the field for peer review and ask the author to make necessary amendments to the article based on feedback received and then resubmit it. This process can be time consuming, but is regarded by many scientists as an essential quality assurance mechanism.

## Why does it matter?

Scientific journals are the primary communication platform for many researchers around the world and are often the first port of call for doctors seeking information on how best to treat their patients. Therefore, to ensure that the discoveries made by clinical trials are widely shared and improve medical practice, the results of all clinical trials should be published in an academic journal or made freely available in appropriate trials registries or databases (preferably both). However, many trials fail to publish their findings; a 2012 study of a cohort of publicly funded trials in the United States found that around 60,000 people had participated in trials that subsequently remained unpublished (Asiimwe & Dickson, 2016; Hwang, et al., 2016; Pica & Bourgeois, 2016; Ross et al., 2012).

Many other trials are published in subscriber-only or pay-per-article journals, limiting access to the results of important and often publicly funded research. In some cases, it can take several years for an article to be published in a journal. Additionally, academic papers often omit important data points (Duff et al., 2010). And sadly, multiple studies show that the academic literature paints a systematically biased and frequently inaccurate picture of the safety and effectiveness of drugs (Golder et al., 2016).

## Progress to date

The medical research community has come up with multiple ways to overcome non-reporting, bias and research misconduct in academic publication, but implementation has proven difficult in practice due to the large number of individuals and institutions involved, the fragmented publication landscape, and perverse incentives. There are now journals committed to publishing trials with zero or negative results, fast-moving pre-publication journals, journals providing open access to articles free of charge, and journals that accept 'registered reports', but current career incentives in academia often discourage scientists from publishing in them (Goldacre et al., 2016). Also, scientists who fail to publish their results currently face no sanctions, and those who distort evidence are unlikely to get caught and even less likely to face effective sanctions; even fraudulent data falsification often goes unpunished (Doshi, 2015).

## Evidence distortion: outcome switching, the exception or the norm?

‘Outcome switching’ is a form of evidence distortion that involves moving the goal posts of a trial after it has been completed. To use an analogy, researchers shoot their arrows first and then draw bull’s eyes around wherever the arrows have landed, making their archery look far more impressive than it really is. In essence, reporting successes in treating patients based on trial data using switched outcomes makes drugs and devices appear far more effective than they really are.

In 2015-2016, a team of researchers at the University of Oxford reviewed papers published in the world’s top five medical journals to find out how widespread outcome switching is. Many doctors rely on these journals for guidance on how to treat their patients. The Oxford team found that of 67 trials, publications for 58 contained altered outcomes. In total, 354 pre-specified outcomes had not been reported, while 357 new outcomes had been silently added. Only nine trials out of the 67 had been accurately reported.

The Oxford researchers discovered multiple instances of evidence distortion by comparing the outcomes reported in medical journals with those previously recorded in clinical trial registries. If these trials had not been registered, misleading information on some drugs and devices would have been impossible to detect in practice (Goldacre, Drysdale & Powell-Smith, 2016).

## Global standards

- The World Medical Association’s Declaration of Helsinki states that researchers “are accountable for the completeness and accuracy of their reports” (WMA, 2013).
- A 2016 United Nations report states that “[t]hose undertaking clinical trials must not prevent researchers from publishing their findings”.
- The EQUATOR Centre has developed best practice guidelines for clinical trials.<sup>45</sup>

## Policy recommendations

National governments have the ability to shape the medical research landscape. At the same time, most have been hesitant to take steps that could be perceived as encroaching on academic freedom.<sup>46</sup> However, governments could decrease bias and evidence distortion in the medical literature without direct intervention in the academic sphere.

In some jurisdictions, the public bodies overseeing research ethics committees are well positioned to monitor non-publication of trial results and some forms of evidence distortion within publications based on records they already hold on file (Chan et al., 2017).<sup>47</sup>

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45 The UK EQUATOR Centre, based at the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, focuses on national activities aimed at raising awareness and supporting adoption of good research reporting practices. Their best practice guidelines include those for trial protocols (SPIRIT), trial reporting (CONSORT), and making interventions more replicable (TIDieR). See the EQUATOR website: <http://www.equator-network.org/reporting-guidelines/> [Accessed 26 September 2017]

46 Note that China recently proposed harsh criminal penalties for research fraud, see: “Chinese courts call for death penalty for researchers who commit fraud”. Stat News, 23 June 2017. <https://www.statnews.com/2017/06/23/china-death-penalty-research-fraud/> [Accessed 26 September 2017]

47 The feasibility of creating a national system for monitoring academic publication and detecting ‘outcome switching’ has been proven by recent pilot projects in the UK and Finland. HealthwatchUK et al. 2017. “A National Clinical Trial Audit System to Improve Clinical Trials Reporting” Submission to the UK House of Commons Science and Technology Committee’s inquiry into research integrity, 05 October 2017

Furthermore, as many clinical trials are funded using taxpayers' money, political decision-makers could instruct public funding bodies to actively monitor grantees' subsequent publications performance, and sanction institutions whose publications fail to meet best practices. Some funders have already begun to put such monitoring systems in place.<sup>48</sup>

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48 Many public funding bodies, including the U.S. National Institutes of Health, have already adopted trial transparency policies that go beyond minimum legal requirements. The WHO recently brokered the "Joint statement on public disclosure of results from clinical trials", which by the end of September 2017 had been signed by 20 organisations, including the Indian Council of Medical Research, the Research Council of Norway, UK National Institute of Health Research, and major foundations. <http://www.who.int/ictrp/results/jointstatement/en/>

Note that signatories to the statement commit to tracking whether, when and where a trial is academically published, but not to monitor for evidence distortion (such as 'outcome switching' or misreporting of benefits or harms) within journal articles.

# Individual participant data sharing

Frameworks, standards, policy and legislation that enable effective, vigilant individual participant data sharing should be established.

## What is IPD sharing?

Individual participant data (IPD), or individual patient data, is the data collected on each participant in the course of a clinical trial. IPD sharing means that researchers make this individual-level data available to other scientists after a trial has been concluded.

## Why does it matter?

Clinical trials data sharing has great potential to accelerate scientific progress (Zarin & Tse, 2016). By aggregating data from multiple trials, researchers can generate better evidence on the safety and effectiveness of drugs, devices and treatments (Debray et al., 2016). Scientists can also disaggregate the data from multiple trials and recombine it, for example to explore variances in treatment effects in different sub-groups of the population. Data sharing can also create additional opportunities for exploratory research, which could lead to new scientific discoveries, more effective treatments, or alternative uses of existing treatments (Tierney et al., 2015).

In addition, independent researchers can use IPD to conduct further analyses of data generated by one trial. Independent re-analysis of patient data reduces the potential for mistakes, misinterpretations, evidence distortion and fraud in other forms of trial reporting (Ross, 2016).

### How IPD sharing helped more small children to survive malaria

Malaria kills an estimated half a million people every year, many of them children. However, doctors were long unsure about the optimal dose of a commonly used treatment in young children. A 2013 analysis pooling the IPD from 26 separate clinical trials showed that children aged 1-5 years were more likely to recover if they were given higher doses of the treatment. This discovery would have been impossible to make looking at any single study (CRIT, 2017).

## Progress to date

While this pillar of clinical trial transparency is considered sensitive, as it requires particular consideration for robust data protection, numerous research funders and pharmaceutical companies have put into place IPD sharing policies, and many researchers running clinical trials have shown a commitment to voluntarily share IPD (Bergeris et al., 2017; Smith et al., 2017; Storm, 2014; Wellcome Trust, 2015). The U.S. Food and Drug Administration already requires pharmaceutical companies to submit IPD, which the agency then analyses to better assess the benefits and harms of medicines (CRIT, 2017).

However, concerted efforts to make IPD sharing the norm are relatively recent, and considerable barriers to effective IPD sharing remain. Practical barriers include the significant input required to turn raw data into formats that other investigators can use, the current lack of universally agreed standards, challenges related to safeguarding patient confidentiality, legal and regulatory issues, and methodological challenges.

Due to these concerns, the International Committee of Medical Journal Editors (ICMJE) in 2017 abandoned a proposal to make IDP sharing compulsory in the short term, while at the same time reaffirming its hope and belief that IPD sharing would become the norm in future (Taichman et al., 2016).

Meanwhile, transparency advocates have noted that companies tend only to offer controlled access to approved requestors, rather than sharing IPD as open data that can be downloaded and freely shared, and that industry continues to view IPD as the property of trial sponsors and not as part of a global scientific commons.

## Global standards

- The WHO supports the development of frameworks, norms and standards to enable effective IDP sharing. A WHO consultation in September 2015 affirmed that timely and transparent sharing of data and results during public health emergencies must become regular practice (Modjarrad et al., 2016).

## Policy recommendations

There is broad consensus in the medical research community that IPD sharing, if done well, can contribute significantly to medical progress. The field is evolving rapidly and a number of promising initiatives are currently underway, which policy-makers should encourage and support. To ensure that these efforts are able to realise their full potential, legislation for robust clinical trial data protection must be put into place.

Finally, it is important to emphasize that the immense potential of effective IPD sharing can only be fully realized if and when the other pillars of clinical trial transparency are firmly in place (Hoffmann et al., 2017; Zarin & Tse, 2016).



# Principles and practical steps for policy-makers

## Opacity carries a steep price

Opacity in clinical research has already cost countless human lives and wasted substantial public health funds. As a parliamentary committee in the United Kingdom has pointed out:

“Important information about clinical trials is routinely and legally withheld from doctors and researchers by manufacturers. This longstanding regulatory and cultural failure impacts on all of medicine and undermines the ability of clinicians, researchers and patients to make informed decisions about which treatment is best.”

Public Accounts Committee, 2013

## Transparency measures are feasible and highly cost-effective

On the positive side, clinical trial transparency can be significantly strengthened using existing systems, processes and tools. In many jurisdictions, appropriate laws, rules, and regulations are already in place, and the public agencies tasked with implementation tend to be strongly supportive of transparency measures. Many significant transparency gains can be achieved within current legal frameworks through administrative action alone (US FDA, 2017). In many cases, costs could be fully recovered by imposing fines for violations.<sup>49</sup> In other cases, making clinical trials more transparent would be both low-cost and highly cost-effective, as a WHO-convened coalition of major medical research funders recently pointed out:

“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.”

WHO, 2017<sup>50</sup>

## Imperative for political action

Political decision-makers worldwide need to assume responsibility for resolving this pressing public health issue; it is an issue that impacts on the lives of all people across the globe. In 2016, the United Nations demanded that:

“Governments should require that the unidentified data on all completed and discontinued clinical trials be made publicly available in an easily searchable public register [...] To facilitate open collaboration, reconstruction and reinvestigation of failures, governments should require that study designs and protocols, data sets, test results and anonymity-protected patient data be available to the public in a timely and accessible fashion [...] For the public to reap the full benefit of the public investment in research, public funding agencies must ensure that, when feasible, data, results and knowledge generated from such public investment be made broadly available [...] Increased transparency of clinical trial information is an important contributor to improved public health outcomes.”

2016 UN High Level Panel<sup>51</sup>

49 According to one widely cited calculation, clinical trial sponsors have accumulated over US\$25 billion in outstanding fines for violating U.S. legal requirements on summary results posting. Due to lack of enforcement, these fines remain uncollected.

<https://www.statnews.com/2015/12/13/clinical-trials-investigation/> [Accessed 20 September 2017]

In contrast, the 2016 budget for the entire U.S. Food and Drug Administration (FDA) was less than US\$5 billion.

<https://www.hhs.gov/about/budget/budget-in-brief/fda/index.html> [Accessed 29 September 2017]

50 <http://www.who.int/ictrp/results/jointstatement/en/>

51 <http://www.politico.eu/wp-content/uploads/2016/09/HLP-Report-FINAL-Sept-2016.pdf>

# Three steps towards making clinical trials more transparent

Decision-makers should take the following three steps to increase clinical trial transparency and make the sector more accountable to citizens, patients, taxpayers, and investors:

1. Ensure that publicly funded clinical trials are transparent
2. Effectively enforce existing rules
3. Strengthen legal and regulatory frameworks

## Step 1: Ensure that publicly funded clinical trials are transparent

As a first step, political decision-makers should require all public research funding bodies within their jurisdiction to adopt and expand on the provisions of the recent WHO-brokered 'Joint statement' by research funders, and ensure that they are fully implemented. In future, to help ensure that public funding for medical research actually benefits the public, government funders should only give taxpayers' money to institutions and individuals that verifiably comply with best practices in clinical research. Taking this simple first step would deliver significant transparency gains at minimal cost.

## Step 2: Enforce existing rules

Second, decision-makers should provide government agencies with the resources, powers and political support they need to enforce existing laws, rules and regulations, which at present are often not consistently implemented. Decision-makers should support government agencies in setting up effective monitoring and sanctions mechanisms to bring accountability into the sector. One promising monitoring model is to use existing Research Ethics Committee records to monitor the registration, summary results posting, and academic publication of all trials conducted within a jurisdiction.<sup>52</sup>

## Step 3: Strengthen legal and regulatory frameworks

Third, decision-makers should bring existing laws, rules and regulations<sup>53</sup> into line with global best practice standards and ensure that they cover all clinical trials, past and present, as defined by the WHO. For example, in the European Union, current guidelines on results reporting should be extended beyond their current focus on certain drug trials, and disclosure policies for Clinical Study Reports should be extended to cover older trials. To ensure that clinical trials are transparent, legal and regulatory frameworks should incorporate the following five elements:

1. **Trial registration:** All clinical trials should be registered on a WHO-approved trial registry before the recruitment of the first participant.
2. **Summary results posting:** Summary results for all clinical trials should be posted on the registries where they were originally registered within 12 months of study completion.

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52 For more details, see: HealthWatch UK et al. 2017. "A National Clinical Trial Audit System to Improve Clinical Trials Reporting" Submission to the UK House of Commons Science and Technology Committee's inquiry into research integrity, 05 October 2017

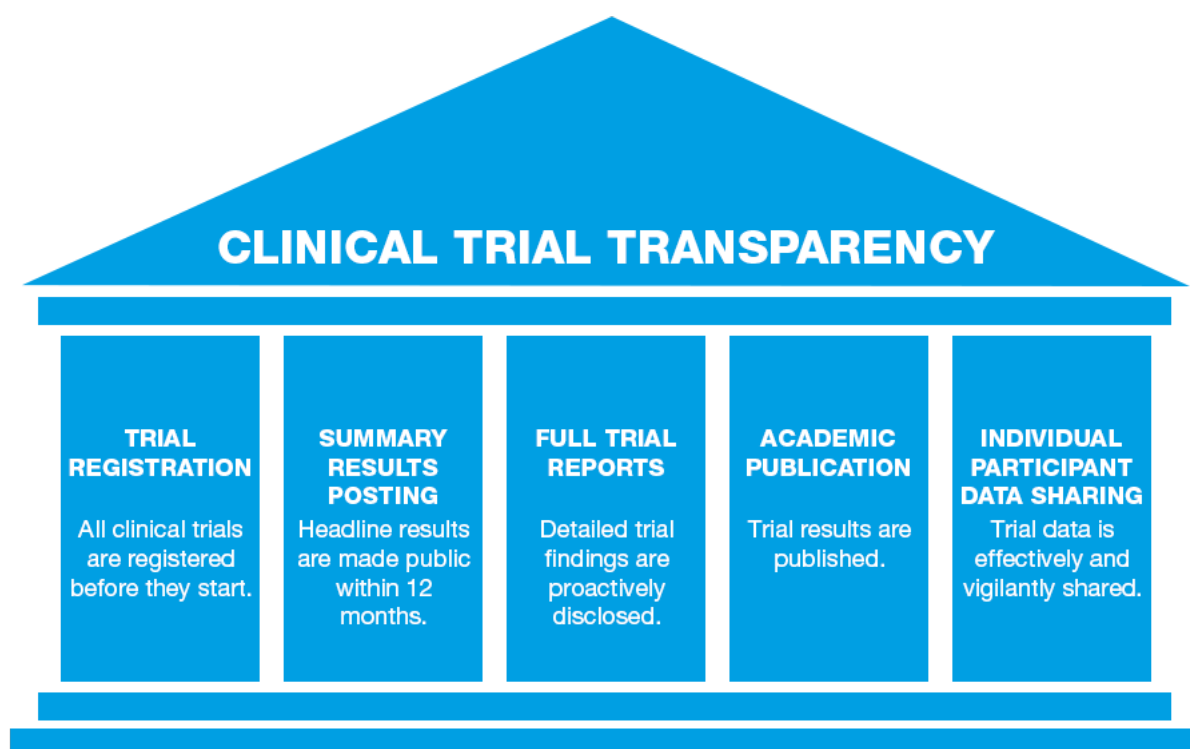
<http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/70815.pdf> [Accessed 24 November 2017]

Schmucker, C. et al. "Extent of Non-Publication in Cohorts of Studies Approved by Research Ethics Committees or Included in Trial Registries" PLoS ONE 9(12): e114023.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0114023> [Accessed 04 October 2017]

53 Note that medical research ecosystems as well as legal and regulatory frameworks may vary considerably between different jurisdictions. Thus, decision-makers will need to tailor concrete implementation measures to their own regional and national contexts.

3. **Full trial reports:** All information relevant to interpreting a trial's findings should be proactively disclosed and made available to the scientific community. This information includes the original trial protocol, a pre-specified statistical analysis plan, Case Report Forms, and Clinical Study Reports.
4. **Academic publication:** The results of all clinical trials should be published in an academic journal or made freely available in appropriate trials registries or databases (preferably both).
5. **Individual participant data sharing:** Frameworks, standards, policy and legislation that enable effective, vigilant individual participant data sharing should be established.



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