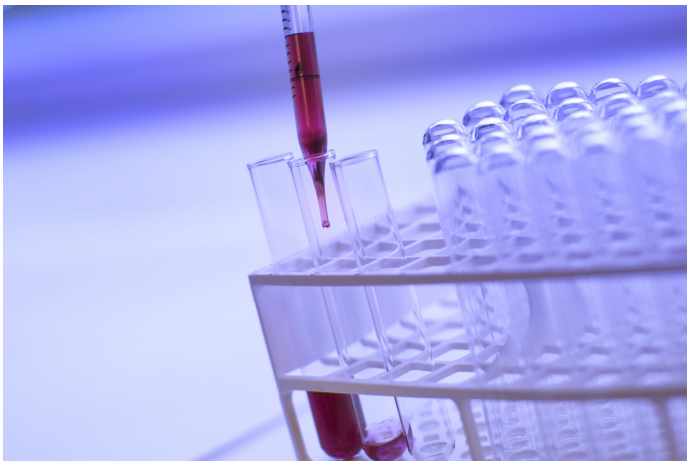

Promoting Transparency in Clinical Research

Why and How

A Policy Paper

By the

Yale Collaboration for Research Integrity and Transparency

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C R I T

collaboration for research integrity and transparency

This policy paper was developed and written by the faculty and staff of the Collaboration for Research Integrity & Transparency (CRIT) at Yale University. It was edited by Margaret E. McCarthy (Executive Director, CRIT), Jeanie Kim (Research Fellow, CRIT) and Joseph S. Ross (Associate Professor, Yale School of Medicine).

About the CRIT Program

The Collaboration for Research Integrity and Transparency (CRIT) is an interdisciplinary 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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The Issue

Clinical research generates information that is critical to our understanding of medical products. Researchers and pharmaceutical companies conduct clinical studies to see if a promising biomedical discovery can lead to a safe and effective medicine for patients. Investigators start with laboratory testing and preclinical studies that provide basic answers about a treatment's mechanism. Then, studies involving human participants provide a clearer picture of how the drug, biologic, or device will interact with the human body.

Human studies occur in phases, with each phase intended to address specific questions: Is the drug toxic or safe to use? What is the appropriate dosage? What are the side effects? How does the drug interact with other substances? Does the drug have the intended clinical effect? Do the benefits of the treatment outweigh harms? Roughly 90% of drugs that enter the first phase of clinical testing do not reach the market because they are unsafe or ineffective.[1]

Despite the public health significance of the information gathered through clinical research, much of the data is withheld, missing, or inadequately disclosed. This lack of transparency has sweeping negative consequences for medical research, regulation, clinical care, and the healthcare system.

Study Phases	
Phase 1	Trial in a small number of healthy volunteers to determine whether the drug is safe to use, and the minimum and maximum safe dose.
Phase 2	Trial in a larger number of patients to gather information about side effects, dosage, and some information about whether the drug might work for the proposed use.
Phase 3	Larger trial to determine whether the drug works for the proposed use, and to get more information about side effects.
Phase 4/ Postmarket	Trial to study longer term safety and effectiveness.

What Is Clinical Research Transparency?

Clinical research transparency exists when decisions and data from a clinical study are shared with other researchers, clinicians, and the public.[2] Transparency throughout the research process helps to ensure that the answers derived from clinical trials are complete and scientifically sound.

At each stage of a clinical study, investigators create and collect different types of data. Before the first participant is enrolled, investigators design the study and make an analysis plan to use with data they will collect. The study protocol describes all the outcomes that the researchers intend to measure, and the statistical tests they will use. During the study, investigators collect raw data from individual participants according to the protocol. After the study is completed, investigators clean and organize the raw data into analyzable datasets. Investigators then carry out analyses, summarize results, and prepare findings for scientific publication or regulatory review.

Regulatory Review: In the US, the Food and Drug Administration (FDA) is responsible for regulatory review of medical products. Drugs, biologics and the highest risk devices can only be sold in the US after they are approved by the FDA. In the European Union (EU), the European Medicines Agency conducts reviews of new medical project, and each member country then decides if a new product can be sold within its borders.

There are three types of clinical trial data:[2]

Types of Clinical Trial Data	
Individual participant data (IPD)	Include raw data collected from trial participants;
Summary data	Include scientific publications, summaries for the public, summary-level results, and clinical study reports (CSRs);
Metadata	Include protocols, statistical analysis plans, and analytic code.

Trial funders and researchers can promote transparency at three key points in the clinical research process:

Promoting Transparency Through Data Sharing	
Data to Be Shared	**When Data Should Be Shared**
Metadata: Prospective registration of trial protocols and statistical analysis plans	Before enrolling participants;
Reporting of results and other summary data	At trial completion;
Sharing of IPD and all supportive metadata	Six months after scientific publication, or 30 days after regulatory approval.

Why Researchers Should Care About Transparency

The free flow of information between original researchers and secondary researchers is crucial to advancing medical science.

When clinical studies are not registered, investigators can conduct research in the dark and deviate from good research practices.

Registration of clinical trials in a publicly accessible database like ClinicalTrials.gov allows other investigators to learn about the existence of trials and keep track of ongoing and completed trials.[3] Transparency at the beginning of a study makes it harder for researchers to hide unfavorable or negative findings. One problem that has plagued clinical research is outcome switching. Outcome switching occurs when researchers fail to report the original outcomes that they had planned to measure and instead report different outcomes that are more favorable.[4]

GlaxoSmithKline's Study 329 is a well-known example of how physicians and patients were misled by outcome switching.[5] From 1998 to 2003, GlaxoSmithKline marketed its antidepressant paroxetine (Paxil) for pediatric use, although it was never approved for children and adolescents. Employees distributed copies of a 2001 medical journal article on Study 329 that claimed that Paxil was "generally well tolerated and effective"[6] for young patients.[7] The marketing campaign was successful, and in 2002, over two millions prescriptions were written for children and adolescents in the U.S. for Paxil.[7]

The FDA conducted a study, and reviewed original data from multiple studies of selective serotonin re-uptake inhibitor (SSRI) antidepressants in children, adolescents and young adults, including Study 329. The analysis showed an increased risk of suicidal thinking and behavior in those taking some SSRIs. In 2004, the FDA required that Paxil carry a black box warning for this risk.[8,9]

The results of the Study 329 had been questioned initially by an FDA scientist, and by other researchers.[10-12] In 2015, a group of independent researchers reanalyzed the *same data* used for Study 329 and published their results. They found that Paxil was not effective for treating adolescents and increased the risks of self-injury and suicide.[5] The original article on Study 329, which was never retracted,[6] did not report the results of the original planned tests – all of which had negative results – but reported different outcomes with better results, creating a distorted picture of the drug. Researchers had also under-reported the drug-related side effects for Paxil. Switching the outcomes that were reported, and under-reporting the drug-related side effects, meant that Paxil's safety risks and lack of efficacy were hidden. In 2012, the company was convicted criminally, in part for its misleading conduct in marketing Paxil for pediatric use.[13]

Requiring prospective sharing of study protocols, including planned outcome measurements, means that researchers can be held accountable for selectively reporting outcomes that bias the literature.

When clinical study results are neither published nor reported, research is wasted and unnecessarily repeated.

Researchers typically learn about new studies by reading journal articles in peer-reviewed journals. These articles are accepted for publication only after review by at least one expert researcher.

Researchers fail to publish their results for about half of clinical trials.[14,15] When the results of trials are not shared, scientists' ability to learn from one another is hindered. Research results that are negative or not statistically significant, for example, results showing that a drug is ineffective, are less likely to be submitted and accepted for publication.[16] There is a risk that unsuccessful studies will be repeated. This not only

wastes resources, but also exposes additional participants to unnecessary risks and experimentation.

When trial results and analyzable data are available to independent researchers, the research findings can be scrutinized, which improves credibility.

Access to trial results and underlying data ensures accountability. It allows independent investigators to verify claims and expose biases or questionable research conduct. Some questionable conduct can be discovered without access to the original data. For example, in 1999, researchers examined the published results from multiple studies that had compared fluconazole with other antifungal medications in cancer patients.[17] In the course of their research, they found that most of the individual studies were skewed to favor fluconazole. A large multisite study was supposed to compare 3 medications: amphotericin b; nystatin; and fluconazole. Yet published articles combined the group treated with nystatin—known to be ineffective against systemic fungal infection—with the group treated with amphotericin b, thus distorting the results. In addition, some published studies compared fluconazole with oral amphotericin b, even though amphotericin b only works against systemic infection when given intravenously.[17] The company, Pfizer, that sponsored most of the trials, refused to provide data to the researchers. Even without the underlying data, the independent researchers were able to determine that the trials were biased.

When trial results and analyzable data are shared with other researchers, additional knowledge can be generated from existing data.

Access to trial results allows independent researchers to conduct systematic reviews and meta-analyses that pool together multiple studies, creating higher standards of evidence. Access to underlying data also allows independent investigators

to explore new research questions, and to conduct secondary analyses that may not be possible using summary data.[18]

In the field of genetics research and disease-specific research, researchers embraced transparency and data sharing to promote collaboration and to accelerate scientific discoveries. For example, since 2004, the Alzheimer's Disease Neuroimaging Initiative (ADNI) has been collecting clinical, imaging, and genetic data from 58 sites across the US, where the datasets are made immediately available to other researchers.[19] By 2011, the datasets were downloaded thousands of times, and 160 papers were published using the data.[20] During 2014 and 2015, there were approximately 400 publications that used ADNI data.[21]

Why Regulators Should Care About Transparency

Pharmaceutical companies submit summary data and IPD to the US Food and Drug Administration, and the agency analyzes the data to assess whether the harms of a treatment are outweighed by the benefits. However, once medical products are approved, the results and data from clinical studies that support regulatory approval are often not shared with independent researchers. This creates missed opportunities for further study of the safety and efficacy of medical products.

Results from clinical studies that support regulatory approval are often not published.

For many approved medical products, information in the scientific literature about clinical trials is missing or incomplete. Trial results submitted to regulatory agencies can differ significantly from published results.[22] One study found that 14% of key trials that led to approval of a new drug or biologic were not published in peer-reviewed journals.[23] An analysis of 15 drugs from 10 large manufacturers that were approved by the FDA in 2012 found that a median of 35% of clinical trials were either unregistered or unpublished.[24]

When clinical research is available for scientific scrutiny, independent investigators can help regulators identify safety and effectiveness issues.

Independent reanalysis of clinical study reports and patient-level data can inform regulatory efforts to ensure that medical products on the market are safe and effective. For example, in 2007, independent researchers conducted a meta-analysis of clinical trials for GlaxoSmithKline's diabetes drug rosiglitazone (Avandia). The researchers published a study that revealed that Avandia was linked to an increased risk of strokes, heart attacks, and heart related deaths.[25,26] This independent study signaled critical safety concerns to regulators. A few months after the study was published, the FDA issued a black box warning and for several years, imposed restrictions on its use.

[9,27] In 2010, the European Medicines Agency (EMA) – the FDA's European counterpart – recommended that Avandia be taken off the market.[28] The UK's Medicines and Healthcare Products Regulatory Agency (MHRA) suspended use of the drug.[29] Avandia and related products are no longer sold in the European Union. In the US, Avandia remains on the market with a black box warning, although the restrictions on its use were lifted in 2015.[30,31]

The 2007 independent reanalysis of Avandia data was possible as a result of a high-profile litigation settlement. In 2004, GlaxoSmithKline was required to make clinical study reports for all its sponsored studies available to other researchers.[32]

Similarly, data made available during litigation also led to a more thorough review of the extent of cardiovascular risk apparent during clinical trials of Vioxx (rofecoxib). By the time that Vioxx was withdrawn from the US market, it had caused an estimated 88, 000 to140, 000 additional serious cardiac events, of which 44 were likely fatal.[33] Using data made available during litigation, independent researchers, who had served as expert witnesses in litigation, conducted a cumulative pooled analysis of all known placebo-controlled studies of the drug. Their evaluation showed that the increased cardiovascular risk became more apparent over time, as more studies were completed by the manufacturer, although these studies were not consistently published, nor were safety results made available to the scientific community.[34]

Yet most medical product litigation settlements and final orders do not allow for external access to the clinical research data supporting the efficacy and safety of the product involved. Broader access to clinical study reports and patient-level data from pharmaceutical companies could allow for more robust independent studies of drugs approved by the FDA.

Why Clinicians Should Care About Transparency

When clinical research is available to researchers and clinicians, it can inform and improve medical care and patient outcomes.

Selective publication and reporting of results can bias systematic reviews and meta-analysis, which are relied upon to inform the standard of clinical care.

Systematic reviews and meta-analyses, which pool data across multiple clinical trials, often form the basis of clinical practice guidelines. However, researchers cannot easily identify and include all of the relevant trials, [35] because results from nearly half of clinical trials conducted are never published.[15]

The discrepancies between published and unpublished clinical studies can have considerable clinical implications.[31] Pfizer's antidepressant reboxetine (Edronax) has been approved in Europe since 1997, although the FDA ultimately denied it approval.[36] Published studies supported the claim that the drug was effective compared to placebo or was as effective as other medications.[36] In 2010, the German Institute for Quality and Efficiency in Health Care (IQWIG) conducted an independent systematic review and meta-analysis of both published and unpublished clinical studies. [36] The researchers found that reboxetine was ineffective and potentially harmful and that previously published data overestimated the benefits while underestimating harms.[36] The European Medicines Agency and the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) conducted their own review of the reboxetine studies, added additional studies not included in the German review, and reached a different conclusion, allowing the drug to stay on the market.[37,38]

Without access to clinical research, existing data cannot be used to improve medical care for different subpopulations.

Pooling raw patient-level data across multiple clinical studies can also provide a clearer picture of a treatment's effects for smaller subpopulations. Individual trials rarely represent the range of patient groups that a treatment is intended to benefit. Systematic reviews and meta-analyses can be used to answer questions that cannot be answered by individual clinical trials. Many of these questions have public health significance, such as variations in prescribing patterns[39] or medication dosage for understudied groups.[40]

A recent meta-analysis led to safer and more effective dosage recommendations for treatment of malaria in children. Seventy percent of deaths from malaria, which is spread by infected mosquitoes, are in children under five, primarily in sub-Saharan Africa.[41] Although the World Health Organization (WHO) recommended dihydroartemisinin-piperaquine (DP) for antimalarial treatment, the best dose for young children was unknown.[40] In 2013, members of a global antimalarial network conducted a meta-analysis of raw IPD from a wide range of age groups and settings.[40] The researchers were able to recommend increasing the dosage of piperaquine in children aged 1 to 5 years old from 48 mg/kg to 59 mg/kg. They estimated that this dosage increase would cut the risk of treatment failure in half and yet still cure at least 95% of young children – a conclusion that would have been impossible to draw from a single study.[40]

Why Payers And Policy Makers Should Care About Transparency

In the US, about 16.7% of healthcare spending is for prescription medications.[42] It is critical for clinical research to inform prescription coverage decisions and public health policies. Incomplete evidence about medicines and treatments has economic consequences for patients, payers, and the healthcare system.

Missing or incomplete clinical trial data can lead to wasteful government spending on unsafe or ineffective treatments.

Since 2002, governments around the world have been stockpiling antiviral medicines for the treatment of influenza based on information presented by manufacturers.[43] Researchers associated with the Cochrane Collaboration tried for years to obtain complete clinical study reports on influenza medication trials from government regulators and pharmaceutical companies, and eventually were successful.[31,44] In 2014, these independent researchers reviewed the clinical study reports from both published and unpublished clinical trial results, and concluded that Roche's oseltamivir (Tamiflu) and GlaxoSmithKline's zanamivir (Relenza) failed to prevent the spread of the flu, reduce admissions to the hospital, or minimize complications associated with the flu.[44] By the time the study came out, the US had spent more than $1.3 billion developing and stockpiling 65 million treatments, and the UK spent £424 million stockpiling 40 million doses of Tamiflu alone.[45] Across the globe, over $20 billion in public money has been spent on stockpiling Tamiflu and Relenza.[46]

When pharmaceutical companies fail to disclose clinical research data, payers, clinicians, and patients cannot assess the value of medicines or make informed decisions.

Outside of the medical context, consumers often comparison shop, while insurers, non-profits and government agencies in the US engage in comparative effectiveness analysis. Comparative effectiveness analysis is used to examine the risks

and benefits of treatments for the same condition. Robust comparative reviews of treatments, necessary for prescription formulary decisions and medical insurance coverage policies, and informed patient decision-making, cannot occur unless access to information from all relevant clinical trials is shared.[47,48] Pharmaceutical companies are often reluctant to reveal negative information that could hurt sales. This can lead to uninformed decisions by patients, clinicians, and payers. Patients may risk foregoing more established and/or less costly treatments that might be associated with better outcomes without full information about new therapies.

Patients with cancer, in particular, are facing rising costs for therapies that are either not supported by evidence of clinical benefit or that only provide marginal therapeutic benefit.[49,50] Lack of transparency can allow companies to hide information about survival rates. For example, Genentech misrepresented survival data for its $7,800 per month cancer drug erlotinib (Tarceva).[51,52] When the FDA approved Tarceva for severely ill non-small cell lung cancer patients in 2004, Genentech researchers had data indicating that the drug only worked for patients who had a particular gene mutation or who had never smoked. However, Genentech downplayed the mutation's importance and discouraged patients from testing for the mutation. In 2010, the FDA requested that a postmarket study examining the genetic mutation and drug effectiveness be completed by 2015.[53,54] Once Genentech released the post-market study results in 2016, the FDA restricted the drug to use in the small number of lung cancer patients who have the mutation.[51] Before the label change, Tarceva was prescribed to thousands of patients, of whom at least 90% did not have the genetic mutation.[51] Between 2011 and 2015, the Medicare program spent over $1.8 billion on Tarceva for 66,105 beneficiaries.[55] In 2016, Genentech agreed to a $67 million civil settlement to reimburse the federal and state governments for improper prescription costs.[13]

Realizing The Benefits of Transparency in Clinical Research: Where Are We Now, and What More Can Be Done?

Clinical research transparency has the potential to improve health. Data sharing can advance medical knowledge, strengthen regulatory oversight, enhance clinical care, and help to manage healthcare costs. This requires transparency at different stages of the clinical research process:

(1) prospective registration of trials, including protocols and statistical analysis plans;

(2) reporting of results and summary data, including clinical study reports; and

(3) sharing of IPD and metadata, including complete clinical study reports and appendices.

Registration and Reporting: Where Are We Now?

Registration and Reporting as a Prerequisite for Scientific Publication

Since 2005, the International Committee of Journal Editors (ICMJE) has required prospective trial registration as a condition of consideration for publication.[56] This policy change, announced in 2004, has been a major catalyst for the move to transparency.[57]

Creation of Clinical Trial Registries

The ICMJE policy was quickly followed by the development of publicly accessible registries and registration and reporting standards. The World Health Organization developed an International Clinical Trials Registry Platform and established the Trial Registration Data Set standard, which is an attempt to standardize registration and reporting elements across international registries, and to provide unique identifiers so that trials registered in more than one registry can be linked.[58]

Including ClinicalTrials.gov, there are now seventeen international clinical trials registries, the first of which were operational in 2005.[57]

US Legal Requirements for Registration and Reporting

In the US, there are several requirements for registration and reporting on ClinicalTrials.gov. a publicly accessible registry and database managed by the National Institute of Health (NIH). For Phase II and subsequent trials of drugs, biologics and devices, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires sponsors and investigators to register trials, including protocols and statistical analysis plans, within 21 days of the first participant's enrollment, and to report results within 12 months of study completion. However, the FDAA requirements do not apply to Phase I trials, and trials done outside the US where there is no US manufacturing involved.

New US regulations, effective January 2017, also require registration and reporting of all studies involving human subjects funded by the National Institutes of Health.[59] The requirements for registration and reporting have now been extended to US Department of Veterans Affairs (VA)-funded studies.[60]

Failure to comply with FDAAA and the additional registration and reporting policies could result in civil monetary penalties or withholding of research funding by HHS agencies.[61]

Major Private Funders Also Require Registration and Reporting

In May 2017, in coordination with the AllTrials campaign to have all trials registered and reported, nine major global funders of medical and clinical research, including the Bill & Melinda Gates Foundation, released a joint statement to commit to

a policy requiring grantees to meet the WHO standards for prospectively registering and timely reporting clinical trial results.[62]

Clinical Trial Data Sharing: Where Are We Now?

In 2016, the Institute of Medicine (IOM) released a report that calls for responsible sharing of clinical trial data and provides recommendations for sharing summary data, metadata, and individual participant level data. Their report provides a comprehensive examination of the issues involved with data sharing in the clinical trial context.[2]

Regulators

In addition to policies and litigation that encourage trial sponsors and researchers to share data, there have been efforts by regulators to proactively share research data. Since 2012, the FDA has published the action packages leading to approval of medical products on their website. The action packages contain summary data and analyses created by FDA employees after review of company data. The FDA also publishes transcripts of advisory committee meetings, along with complete documents presented to the advisory committees, although this is primarily summary data created by companies and FDA analyses of company data.

A 2013 FDA proposal to share masked and de-identified IPD submitted by pharmaceutical companies was never implemented after public comment was received.[63,64] Notably, objections raised to the lack of informed consent for sharing IPD with secondary researchers will soon not be a barrier to data sharing. New US Human Subjects regulations, effective in January in 2018, contain new provisions allowing routine sharing of identifiable patient data with secondary researchers.[65]

In 2014, the European Medicines Agency finalized a policy on proactively sharing clinical study reports and other materials submitted for approval.[66] Material submitted for approval commencing in January 2015 will be shared on its website. The EMA is exploring ways to share de-identified patient level data accessible. In 2014, Canada enacted a law allowing the Minister of Health authority to disclose pharmaceutical information upon specific request.[67] The Canadian government recently began a public consultation process and solicited comments on a white paper recommending that the law and regulations be amended to allow for proactive sharing of medical product applications.[68]

Industry

In 2013, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA), two major trade organizations, announced a data sharing policy. Once a medical product is approved, the policy recommends that companies share synopses of CSRs with the public, and consider requests from researchers for IPD, summary-level data and metadata. The policy became effective January 1, 2014.[69]

Some pharmaceutical companies now share data proactively. GlaxoSmithKline established ClinicalStudyDataRequest.com (CSDR), a consortium for pharmaceutical data sharing joined by other major pharmaceutical companies.[70] Two other academic initiatives share pharmaceutical data with researchers, the Yale University Open Data Access (YODA) Project at the Center for Outcomes Research and Evaluation[71], and the SOAR (Supporting Open Access for Researchers) at the Duke Clinical Research Institute.[72] Each of these data sharing organizations shares clinical trial data with academic and scientific researchers whose research proposals are accepted after review.

Funders

US government funders have taken a large role in supporting data sharing by implementing standards and creating mechanisms to ease the challenges of sharing research data. The NIH requires that applications for $500,000 or more in direct funding in any given year contain a data sharing plan.[73] As a pioneer in promoting data sharing, the NIH's National Heart, Lung, and Blood Institute (NHLBI) requires data sharing for studies that meet certain criteria and provides the option of sharing data through its formal data repository.[74] NHLBI established a data repository to collect datasets from NHLBI-supported studies, including clinical trials, and to facilitate data sharing with qualified researchers. This repository, now managed by Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), includes individual-level data from over 110 NHLBI-supported clinical trials and observational studies.[75] Secondary investigators can make use of collected datasets for new research.[76] BioLINCC provides extensive guidance on best practices for sharing clinical research data, a critical component to making data sharing more feasible.[77] Other Institutes of the NIH have engaged in similar efforts to share research data.

Private funders have also established guidelines for requiring grantees to share research data. Since January 2015, the Bill & Melinda Gates Foundation has required grantees to make data underlying published research immediately accessible.[78]

Journals

Journal editors have attempted to increase data sharing to maximize the value of research. At least one prominent general medical journal – *PLOS Medicine* – requires data sharing as a condition of publication.[79] In 2016, the ICMJE proposed a policy requiring authors to share IPD six months after publication.[80] After receiving comments, the ICMJE announced a policy in June 2017 that requires authors to submit a data

sharing plan as a condition for consideration for publication and to include the data sharing plan in the trial registration and in all submitted manuscripts that report on the results of clinical trials.[81] While the ICMJE's 2017 policy requiring a data sharing statement falls short of ensuring that data are shared, ICMJE cited legal and practical challenges to data sharing that have yet to be resolved and expressed commitment to moving closer to responsible data sharing.

Legal Settlements

In at least one case, data sharing has been made a condition of settlement in a case brought by the government against a pharmaceutical company. In 2004, the New York State Attorney General sued GlaxoSmithKline for misrepresenting the safety and efficacy of its antidepressant Paxil for children and adolescents. As part of the settlement agreement, GlaxoSmithKline agreed to create an internet site where all clinical study reports related to Paxil and summaries of clinical study reports for all company-sponsored clinical studies were made public. The company was required to maintain a clinical trial registry.[32,82,83] A second manufacturer, Forest Laboratories, now known as Allergan, entered into a similar agreement in 2004 with the New York State Attorney General to resolve an investigation.[84,85]

Registration and Reporting: What More Can Be Done?

First, the FDA should begin to enforce requirements for registration and results reporting on ClinicalTrials.gov. The new regulations are now in effect, and the grace period has passed. In addition to imposing civil monetary penalties and withholding of funding, the FDA could also publish a list of responsible parties who are not in compliance. The NIH and VA could also publish a list of funded researchers who are not in compliance. This would alert researchers and the public to studies where the methods and results are not available for scrutiny.

Second, the research community should embrace registration and results reporting across all types of research, including public health research, health services and outcomes research, and all clinical studies. One of the major limitations of FDAAA is that the statutory requirements apply only to clinical trials of FDA-regulated products. While the NIH and VA recently implemented policies requiring that all research funded by these agencies be registered and report results, many other studies not of FDA-regulated products are carried out. To this end, all research funders should develop policies to ensure that all research is registered and that results are reported. Furthermore, journals, funders, and academic institutions should implement standards with effective enforcement mechanisms for both registering and reporting.

Academic institutions can also exert greater oversight by promoting registration and results reporting as a factor in evaluating research credibility and quality. Institutional Review Boards (IRBs), which review and approve studies before they begin, can require principal investigators to submit documentation that they have complied with registration and reporting requirements. As organizations with educational and public health missions, academic institutions should adopt a goal of 100% compliance—with all completed research reported to the wider scientific community.

Clinical Research Data Sharing: What More Can Be Done?

Six months after publication[80] or 30 days after regulatory approval,[2] trial sponsors and researchers should be ready to share analyzable IPD and all relevant metadata, such as case-report form templates and data dictionaries.[2]

As a commitment to responsible data sharing, investigators should include data sharing plans when they register trials. Although FDAAA and associated federal regulations do not require sharing of IPD, ClinicalTrials.gov allows researchers to

include a data sharing plan when registering trials.[86] HHS, trial funders, journals, and academic institutions should require submission of data sharing statements when researchers register studies, so that investigators can specify how they plan to share IPD and how other researchers can access underlying data.

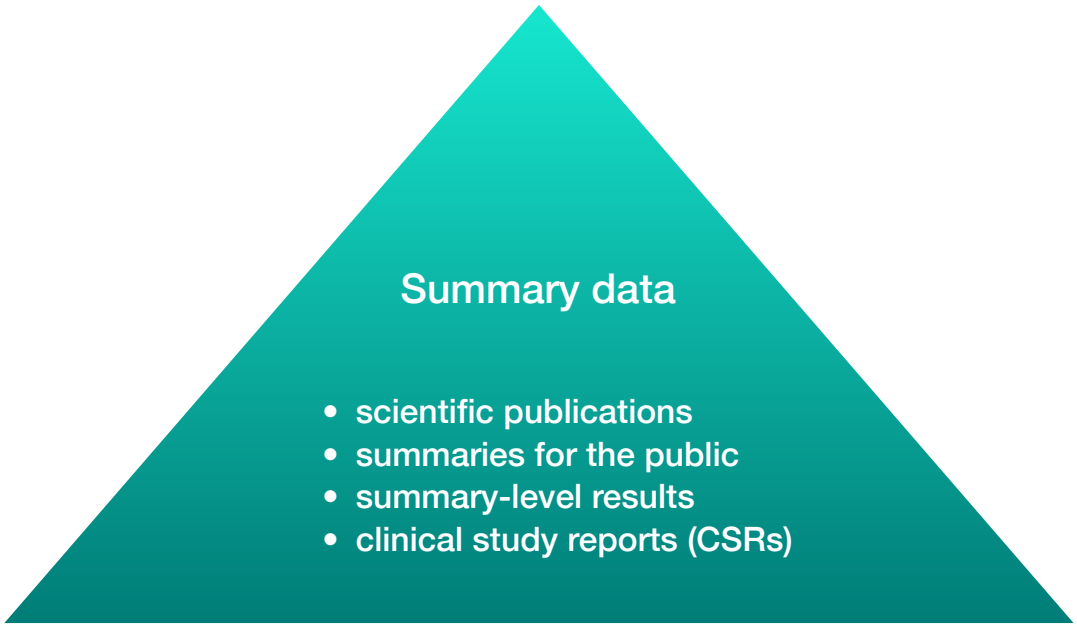
Trial sponsors and investigators should voluntarily share analyzable datasets with qualified researchers using established data repositories. Furthermore, research funders should continue to prioritize data sharing as a condition of funding receipt.

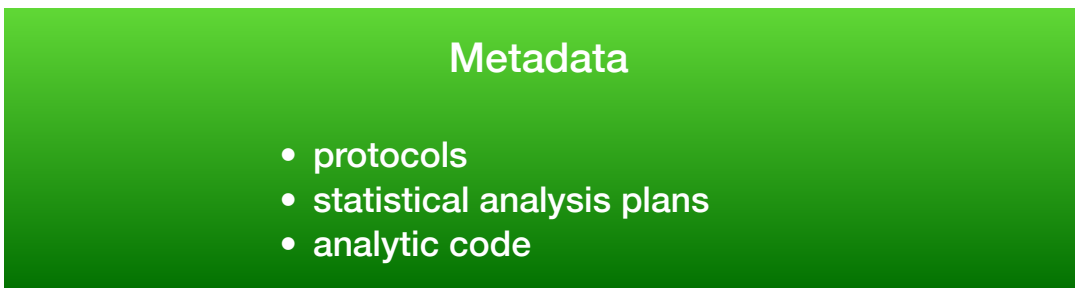
More trial funders, particularly government agencies, should develop funding mechanisms that support the time and effort of investigators to make use of shared research data. Currently, investigators who use shared data typically self-fund these efforts, or rely on the time and support of the original data generation team to prepare the data for sharing. If a culture of using shared data is to be developed, resources are needed to support the effort.

Academic institutions and journals should ensure that credit for data authorship is given for publications by secondary researchers.[87] Journal editors can also require that authors put their data in escrow once the paper is accepted for publication.[88] This would ensure that data that are later disclosed for use by secondary analysts are the same data used in the published paper.

State attorneys general and the Department of Justice should continue to include data sharing provisions in settlements with medical product companies.


Register Clinical Trial
Report Results and Share Summary Data
Share IPD and Metadata
Before enrolling participants
At trial completion
6 months after scientific publication, or 30 days after regulatory approval


Summary data
• scientific publications
• summaries for the public
• summary-level results
• clinical study reports (CSRs)


Metadata
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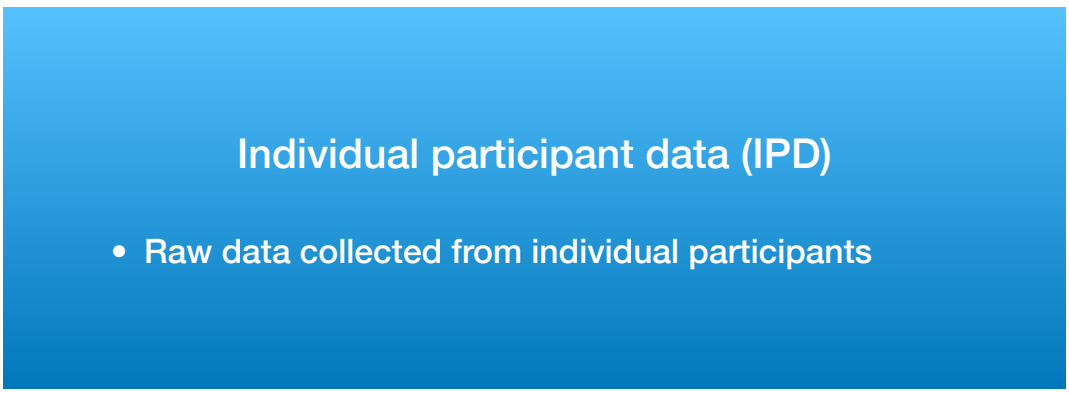
• statistical analysis plans
• analytic code


Individual participant data (IPD)
• Raw data collected from individual participants

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