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Timely Publication and Sharing of Trial Data: Opportunities and Challenges for Comparative Effectiveness Research in Cardiovascular Disease

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Summary

There is growing enthusiasm for the timely publication and sharing of clinical trial data. The rationale for open access includes greater transparency, reproducibility, and efficiency of the research enterprise. In cardiovascular diseases, routinely sharing clinical trial data would create opportunities for undertaking comparative effectiveness research, providing much needed evidence on how different interventions compare to each other on key outcomes. Access to individual patient-level data would strengthen the validity of such research. Novel methodological approaches like network meta-analyses using individual patient-level data could reliably compare interventions that have not been compared to each other in head-to-head trials. However, there are significant practical, methodological, financial, and legal challenges to this utopian open access that need to be continually addressed. Sharing clinical trial data openly will only occur when the previously tolerated process of clinical research involving direct ownership and secrecy is abandoned for a new culture in which medical science is open to all of its stakeholders. With this new culture, data will be accessible, reanalysis and further analysis will be considered commonplace, and comparative effectiveness research through novel synthesis approaches such as network meta-analysis can thrive—as long as measures are taken to adequately ensure the goal remains to promote public health.

Background

Currently, many trials remain unpublished and many outcomes in published trials remain unreported.[1] According to a study of government-funded clinical trials, only 46% of studies were published within 30 months of completion.[2] Moreover, publication bias is widespread, as studies with favorable or statistically significant results are more likely to be reported than are those with unfavorable or nonsignificant results.[3-5] If trials with unfavorable results are published, it is often later than those with favorable results.[6,7] Despite improvement in access to some unpublished study results through significant developments such as ClinicalTrials.gov, the results of many other studies remain unavailable.[3] Publication

alone, however, does not resolve the issue of selective reporting biases; incomplete reporting of outcomes in published study results is common, with only one third to one half of defined outcomes ever being discussed in published reports.[8] When compounded in reviews and clinical practice guidelines, these biases in publication are major threats to the validity of the medical literature.[3]

In the current landscape of medicine in which a multitude of treatments abound for several conditions, the need to determine which are the most efficacious is becoming increasingly apparent. Despite sophisticated methods of data analysis, publication and selective reporting biases greatly undermine evidence-based practice, and the knowledge contained in those unreported and partly-reported trials—successful or otherwise—leaves medical professionals and decision-makers without a full picture of a treatment's effectiveness—or in extreme cases, without full knowledge of associated risks.[9]

In this article, we discuss the rationale for publishing and making raw data from clinical trials available—which we also refer to as "open access"—the new norm, and some of the recent key developments towards achieving this goal. These recent developments are particularly relevant for cardiovascular diseases, as comparative effectiveness research is emerging as a new framework to cardiovascular disease research and delivery. As we elaborate in our article, while policies aimed at publishing clinical trial results in a timely manner are increasingly adopted, progress towards sharing individual patient-level data from clinical trials continues to face a number of practical, methodological, financial, and legal challenges, which should be carefully considered and addressed.

Rationale for publishing and sharing trial data

In the past few years, there have been numerous recent developments aimed at reporting study results in a timely manner and promoting wider access to anonymized data from clinical trials. While some of these stemmed from regulatory agencies, research funding bodies, and academic institutions, several pharmaceutical companies have also committed to publishing and sharing their clinical trial data (**Box 1**). There is emerging consensus from a range of stakeholders (international organizations, regulatory agencies, research funding bodies, academic institutions, and journals) around the need to publish all clinical trial results in a timely manner irrespective of outcome. Beyond publishing results, however, it is imperative to make raw data available for reanalysis. Progress on this front is more fragmented despite increasing enthusiasm for granting access to individual patient-level data from clinical trials.

The primary rationale for these developments is clear: publication and selective reporting biases threaten evidence-based medicine. The reasons underlying non-publication of trial results are several, and primarily include non-submission of negative results by trial investigators due to lack of time, funds, or other resources.[10,11] Irrespective of the reasons behind non-publication, there have been several cases of unpublished clinical data significantly altering the balance between benefit and harms for some drugs.[12] For example, analysis of published and unpublished randomized trials could have revealed cardiovascular risk associated with rofecoxib over 3 years before the manufacturer's voluntary market withdrawal.[13] Another key example is the systematic review performed by Whittington and colleagues, which combined both published and unpublished antidepressant drug trials to

determine their efficacy in children.[14] While all published data showed favorable risk-benefit profiles, when unpublished data were taken into account, the potential harms outweighed any benefits. A similar review of antidepressant trials showed that despite 49% of all trials under review having negative results, 94% of all published trials had positive results.[15] Doshi and colleagues (2013) suggest that "[p]lacing one's trust in the published literature implicitly assumes that what we are seeing is not distorted and is complete."[16] Greater transparency within clinical research could assuage such concerns over publication and selective reporting biases.

A key motivation granting access to individual patient-level data from clinical trials is that of reproducibility—an issue core to the scientific method itself. The ability to fully reanalyze trial data is a crucial step for verification of results and would greatly bolster public confidence in new treatments.[16] Reproducibility goes hand-in-hand with transparency, as reanalysis of trial data will allow for the evaluation of the potential impact analytical methods may have on the trial outcomes themselves.[17] The prospect of external scrutiny may also indirectly improve the quality of clinical trial conduct, and in particular primary data collection, management, and reporting. In any trial, reproducibility will enhance the validity of any potential findings; as the goal of medical research is to help patients and doctors make informed decisions, the findings must be "reproducible, but these are qualities that current peer review processes cannot assure."[18]

Another key rationale for open access to raw data is to improve the efficiency of the research enterprise, and more specifically, and drug development.[19] Having access to full study reports and anonymized individual patient-level data serves to prevent a wasteful use of resources. In the case of false-positive outcomes, wide-adoption of the new treatment may be preempted and future studies may not be funded.[20] A prudent use of resources would be to pool resources, and generate and use publically available datasets to ask different research questions. In drug development, open access to anonymized trial data would allow scientists to use old data to answer new questions and reduce duplication of efforts.[21] And while "data-dredging" should be avoided, appropriate analyses can be performed, particularly when the scientific community is allowed critical review.[22]

Having access to individual patient-level data would advance our understanding of the nuances of treatment effectiveness, and whether a given treatment works differently for different groups of individuals. Despite important limitations such as a lack of pre-specified hypotheses, subgroups defined by patient characteristics within a trial could be analyzed to explore if some patients experience differing treatment effects, potentially generating important hypotheses for future research.[23,24] In fact, previous research has shown that what may be the best treatment overall, may cause worse outcomes in particular subgroups.[25] It remains, however, that subgroup analysis is best suited when risks of poor outcomes vary widely due to patient characteristics.[26] Although seemingly persuasive subgroup effects are often spurious, credible claims of differential treatment effects across subgroups could lead to an increase in patient-centered care by using the most relevant evidence for each patient.[27]

There is also an ethical justification for open access. Clinical research is inherently purposed with contributing to the greater body of medical knowledge for not only its benefit, but for the benefit of the patients it serves. Clinical trials would be impossible to

conduct without the expressed consent of the patients who will eventually use the treatments under investigation; therefore, there is an ethical obligation to use data from these trials to the fullest possible extent so as not to squander the philanthropy of the patients enrolled.[12]

Box 1: A selected list of recent major developments on clinical data sharing

Regulatory agencies:

- **European Medicines Agency (EMA):** EMA's landmark policy, developed with input from a range of stakeholders patients, providers, researchers, and the pharmaceutical industry in 2014, sets the stage for giving access to individual patient-level data for research use. EMA is already granting access to full clinical study reports for all pharmaceutical products reviewed[28,29]
- **The United States Food and Drug Administration (FDA):** As part of its Transparency Initiative, FDA is considering approaches to providing access to selected sets of anonymized individual patient-level data, which carry the potential to improve regulatory science and improve decision-making within the FDA.[30] However, unlike the EMA, FDA is currently not considering routine preparation and release of anonymized individual patient-level data from clinical trials[31]

Research funding bodies:

- **The United States National Institute for Health (NIH):** NIH Data Sharing Policies include polices from a number of agencies that fund clinical trials: National Heart, Lung, and Blood Institute, the National Institute of Mental Health, and the National Institute for Diabetes, Digestive, and Kidney Diseases. NIH policies require investigators of publicly funded research to submit data-sharing plans and deposit their data in an approved repository in a timely manner.[32]
- **UK Medical Research Council (MRC):** MRC Policy on Data Sharing recognizes publicly-funded research data as a public good, and expects data arising from MRC-funded research to be made available in a timely and responsible manner.[33] MRC's Clinical Trials Unit supports a controlled access approach whereby researchers make formal applications for data sharing, which are subsequently reviewed by independent reviewers.[34]
- **The Wellcome Trust** recently commissioned a study elucidating the importance of data sharing, which focused on the potential impact of data sharing on future research.[35] The Trust is also considering to establish a consortium to develop a global solution to facilitate access to trial data.[36]
- **Cancer Research UK:** Data sharing policy states that all data generated with Cancer Research UK funding should be considered for sharing whilst safeguarding intellectual property, the privacy of patients and confidential data.[37] Approach to data sharing can depend on the type, size, complexity and sensitivity of data.

Industry-academia collaboration:

- **Yale University Open Data Access Project (YODA):** In 2011, Medtronic

partnered with Yale University researchers to conduct external reviews of its clinical trial data. This collaboration established procedures for widely sharing individual patient-level data from clinical trials.[1,9,38] Recently, Johnson & Johnson also gave anonymized individual patient-level data from its pharmaceutical trials to researchers at YODA, who will give access to the data to other researchers who request it[39]

Industry:

- **GSK** was the first major pharmaceutical company in 2012 to establish a data sharing policy and give access to all anonymized individual patient-level data from its clinical trials on a secure website.[40] Data access is granted following permission from an independent review panel
- **Astellas, Bayer, Boehringer Ingelheim, Eisai, Lilly, Novartis, Roche, Sanofi, Takeda, UCB and ViiV Healthcare** joined forces with **GSK** to collectively sponsor clinicalstudydatarequest.com, an online repository for anonymized individual patient-level data from several trials conducted by the sponsoring companies. The website grants access to researchers after they submit research proposals deemed appropriate by an independent review panel[41]
- **Pharmaceutical Research and Manufacturers of America (PhRMA) and European Federation of Pharmaceutical Industries and Associations (EFPIA)** Joint Principles for Responsible Clinical Trial Data Sharing show a commitment from major pharmaceutical companies to allow qualified investigators, after review by an independent review panel, access anonymized individual patient-level data, clinical study reports, and research protocols—while calling for the publication of all trial results regardless of outcome[42,43]
- **Association of British Pharmaceutical Industry (ABPI)** report discusses both the rationale for data sharing from all stakeholder perspectives and on how best to implement data sharing policies going forward[44]

Non-governmental entities:

- **Institute of Medicine (IOM):** In its landmark report on sharing clinical trial data published in January 2015, IOM outlined key recommendations to maximize benefits and minimize risks of data sharing by developing guidelines for relevant stakeholders; establishing a timeline for when data should be shared by whom; and calling for a governance body to manage the process going forward[45]
- **The Academy of Medical Sciences** report "Clinical trials data sharing: science, privacy and ethics" discussed important issues surrounding the purpose of and optimal approaches for data sharing, as well as patient perspectives and consent[46]

International organizations:

- **World Health Organization (WHO)** statement on clinical trial results calls for disclosure of all results of trials of new medications to a clinical trial registry and publication within one year, regardless of outcome, in order to increase the transparency of drug innovation. It also encourages the collaborative sharing of data

sets when appropriate without recommending concrete steps to achieve this goal[47,81]

Journals:

- **British Medical Journal (BMJ):** Data sharing policy mandates sharing relevant anonymized individual patient-level data for all trials submitted for publication in the journal upon reasonable request[47]
- **Public Library of Science (PLOS):** PLOS journals require investigators to make all data underlying their analyses (including anonymized individual patient-level data) fully available[48]

Other:

- **The United Kingdom Parliamentary Office of Science and Technology**'s Report on data sharing a) recommends achieving greater transparency in trial data, such as registration as a condition for ethical approval, and b) outlines potential solutions to issues surrounding sharing of individual patient-level data, including a gatekeeper model to monitor access and prevent inappropriate uses of data [49]
- **Nordic Trial Alliance Working Group**'s report on transparency and registration in clinical research in the Nordic countries outlines current data transparency practices and how they can be improved, including ensuring public access to individual patient-level data after trial publication and establishing a council to oversee storage and dissemination of clinical trial data. The Group also calls for stakeholders to make "clear laws, regulations, and guidelines" establishing a lack of transparency and withholding data as a severe offense[50,82]

Open access and comparative effectiveness research

Publishing and sharing clinical trial data create opportunities for undertaking comparative effectiveness research so that previously unexplored questions can be tackled.[25] Comparative effectiveness research aims to provide evidence on how different interventions compare to each other on harms and benefits in order to improve the delivery of care. Increasingly, it is such comparative evidence that informs clinical practice guidelines.[51] Comparative effectiveness research in cardiovascular disease has become a priority for both investigators and policy makers.[52] Gaps remain in the evidence base for treatments of common cardiovascular conditions such as atrial fibrillation, anticoagulant therapies, and ischemic heart disease.[52]

Large trials comparing all possible treatments head-to-head remain the gold standard for comparative effectiveness assessments. Such large trials have already paid dividends to the field of cardiovascular medicine. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), amiodarone was proved no better than the standard heart failure care, while implanted internal cardioverter defibrillators significantly reduced mortality.[53] Similarly, the Bypass Angioplasty Revascularization Investigation Two, Diabetes Trial (BARI 2D) indicated no significant difference in rates of death and major cardiovascular events between prompt revascularization with intensive medical therapy and medical therapy alone or between insulin sensitization and insulin provision.[54]

Traditionally, large randomized head-to-head trials take a long time to complete, require large numbers of participants, and are therefore very costly. Recent advances in randomized controlled trial design aim to improve the operational complexity and lower the corresponding economic costs of undertaking large head-to-head trials. Randomized registry trial design, for example, leverages the advantages of randomized and observational studies so that data on relevant outcomes can be captured as part of observational registries or cohorts that are already underway with established and routine data collection mechanisms. Bayesian adaptive analytic approaches allow for flexibility in the design and analysis of randomized trials, for example by adding new experimental interventions and dropping less effective ones without restarting the trial. Such approaches have the potential to reduce the sample size and cost required to collect information on relevant outcomes in a timely manner.

Despite potential efficiencies that can be obtained with such simple, practical, and adaptive trials, carrying out large randomized experiments may still be difficult in therapeutic areas with multiple treatment options. In such cases, it is not conceivable to invest in large head-to-head trials to compare all available treatment alternatives, e.g., to establish the comparative impact of all currently available statins on the incidence of type-2 diabetes. New large trials of current treatments may indeed be unnecessary when several other trials exist.[55] Systematic evidence review and synthesis methods, such as meta-analysis, offer an efficient alternative to use this existing trial evidence. In order to accomplish this task, however, access to all of the data concerning all relevant treatments is a necessity. While published summary data may be sufficient "when estimating a single pooled treatment effect or investigating study level characteristics," further investigation, such as whether treatment effects are dependent on patient characteristics, demands access to individual patient-level data.[56] Access to individual patient-level data on both outcomes and covariates can significantly strengthen the validity of relying on existing trial evidence when making inferences on the effectiveness of intervention alternatives. Meta-analyses incorporating individual patient-level data have long been established in cardiovascular research (see **Box 2**).[57-60]

Even when individual patient-level data are available for all trials of treatments for a disease, the majority are placebo-controlled and do not have active comparators. While this allows for direct, pair-wise comparison, it is often hard to determine which treatment is best from the results.[51] Interpretation only becomes more difficult and less precise when the evidence is indirectly compared through multiple successive trials.[51]

As increasing numbers of treatments become available for various conditions, the need for comparing multiple treatments becomes imperative. Relatively novel network meta-analysis methods can combine the findings of separate clinical trials to indirectly compare multiple interventions to each other, resulting in "more consistent assessment than simpler alternative approaches" and providing a ranking of treatments based on both benefits and harms.[61] Such network meta-analysis methods allow for the generation of more robust comparative-effectiveness information and "at very limited cost as compared with that of head-to-head trials."[21] This type of analysis is particularly useful when other pair-wise meta-analyses do not provide consistent estimates of effectiveness for treatment choices, as it combines both direct and indirect comparisons, thus incorporating a large share of the evidence.[55,61]

Network meta-analyses would also be a valuable tool when exploring the comparative effectiveness of interventions with different components and combinations of components.[62] As the findings of network meta-analyses have significant implications for decision makers, including coverage of certain treatments and procedures, all relevant comparators must be assessed in order to make adequately evidence-based decisions.[55] It remains, however, that network meta-analysis relies on statistical inference when using indirect comparisons. Access to individual patient-level data can significantly strengthen such analyses.[63]

Given the lack of clinical areas where there is accessible data available for all comparators, network meta-analyses adopting individual patient-level data remain rare.[64-66] Fortunately, recently developed methods allow the combination of study-level findings with individual patient-level data in network meta-analyses, allowing the benefits of open access to trial data to be leveraged whenever possible.[67,68] Without access to individual patient-level trial data, network meta-analyses are confined to working with summary results in the published trials, severely limiting a powerful tool for comparative effectiveness research in both cardiovascular research and all of medicine.[66]

Box 2: Selected key examples of meta-analyses in cardiovascular medicine using individual patient-level data

- Comparison of short- and long-term dual antiplatelet therapy (DAPT) after drug-eluting stent implantation demonstrated similar rates of major adverse cardiac events but lower rates of bleeding after stent placement in short-term DAPT patients[69]
- A study of the efficacy of β blockers in patients with concomitant atrial fibrillation and heart failure showed β blockers should not be used over rate-control medication or as the standard therapy to improve prognosis in these patients[70]
- Investigation of blood pressure-lowering treatment based on cardiovascular risk revealed similar relative protection for all levels of cardiovascular risk, but greater risk reduction as baseline risk increases[71]
- A study of blood cholesterol and vascular mortality exhibited that total cholesterol was positively associated with ischaemic heart disease mortality in middle and old age patients and at all blood pressure levels[72]
- Van Walraven and colleagues[73]demonstrated in patients with nonvalvular atrial fibrillation, that when compared to aspirin, oral anticoagulant significantly decreased risk of all strokes and cardiovascular events but increased the risk of bleeding
- Amiodarone Trial Meta-Analysis Investigators showed that prophylactic amiodarone reduces the rate of sudden/arrhythmic death in high-risk patients with recent myocardial infarction or congestive heart failure, resulting in an overall decrease of mortality[74]

Challenges for sharing clinical trial data

Important research opportunities exist for using individual patient-level data from clinical trials to understand how cardiovascular interventions compare to each other. The question has changed from *whether* data should be shared to *how* it should be shared.[23] However, the road to fully open access across medicine is not without its challenges that

need to be carefully considered. A well-orchestrated policy and research agenda is needed to create meaningful financial and non-financial incentives, thereby aligning the objectives, values, and needs of several stakeholders, and in particular those of patients, research funders, pharmaceutical industry, and regulatory agencies.

Moving forward, chief among key concerns is data ownership. Does the organization or sponsor who originally funded the research own the data? Does the principal investigator who developed the hypothesis, designed the study, and executed the trial and data collection have intellectual property rights? Or do clinical research data actually constitute a public good—especially when published—as no one can be excluded from the benefits of the findings?[75]

The recent influential report from the US Institute of Medicine (IOM) offers important insights (**Box 3**). The IOM positions clinical trial data away from individual ownership and firmly into a public good, calling on everyone from funders and sponsors to scientific publications to do their part in promoting this culture of sharing. Additionally, the IOM recommends transparency for how and with whom data will be shared and proposes establishing independent review panels to review and grant data access requests, rather than data holders themselves. [45]

Indeed, this model of "controlled access" is emerging as the preferred strategy among key stakeholders including research funders, pharmaceutical industry, and regulatory agencies. For example, the MRC's Clinical Trials Unit housed at the University College London strongly favors an approach whereby researchers make formal applications for data sharing, which are subsequently reviewed by an independent review panel according to the scientific merit of the proposed analysis.[34] The Unit also highlights the feasibility challenges facing those responsible for routinely depositing individual patient-level data. Among recent major initiatives, Nordic Trial Alliance Working Group's seminal report on data sharing remains unique in its recommendation for establishing a global, public data repository to which all anonymized clinical trial data can be routinely deposited for secondary use.[82]

Box 3. IOM guiding principles of data sharing

- Stakeholders of clinical trial data should make data sharing the new norm by engaging in a number of activities including, but not limited to: ensuring the privacy of trial participants, giving appropriate credit to the original trial investigators, producing scientifically valid secondary analyses, and protecting intellectual property[45]
- Sharing of data should take place within specified times surrounding each stage of a trial: registration, completion, publication, and regulatory application when trials are for new products
- Holders of clinical trial data should implement operational strategies that include using data use agreements and designating an independent review panel for data sharing
- A multistakeholder collaborative effort should be undertaken to lead and govern the process for addressing practical challenges of making data sharing the new norm

Pharmaceutical industry's leadership in the timely publication and sharing of clinical trial data is imperative. Despite industry enthusiasm for transparency and open access, full

information from clinical trials may still be inaccessible as the quality and completeness of study protocols and clinical reports can vary, complicating efforts aimed at reproducibility and validation of trial findings. Approximately two thirds of clinical trials are sponsored by the industry, and large investments from pharmaceutical companies are needed to develop standards for content of the accessible reports.[76] To incentivize pharmaceutical companies to participate in collaborative initiatives to improve data harmonization, future policy efforts should be aimed at assuaging pharmaceutical industry's legal concerns for more widespread data sharing. Indeed, pharmaceutical companies may face legal challenges if re-analyses find unexpected results. It is therefore important to devise and implement necessary statutory safeguards such as legally binding data sharing agreements to protect the trial sponsors from potential future litigation on the basis of *post-hoc* analyses. Important exceptions to any legally binding agreement should include identification of fraud and deliberate misinterpretation of data.

With increasing access to individual-patient data comes potential threats to the privacy of participants in the trials. While informed consent is required before enrollment in any trial, few (if any) consent forms include the potentiality of disclosure of individual patient-level data to parties other than trial investigators and regulators, let alone the Internet through open access.[34] Similarly, there are instances where consent is given through a parent for a child's participation or through a guardian where the patient has dementia. There is additional concern where trials investigate rare or chronic diseases, as patient-level datasets will likely include potentially identifiable variables such as age, sex and geographic location.[34] This issue is compounded when data can only be anonymized at the risk of making the dataset unusable for further research. Emerging models for seeking consent from research participants could resolve these tensions.[77]

Even with the benefits of having the totality of the evidence available through open access to clinical trial data, there are methodological challenges with using the individual patient-level data gained for comparative effectiveness research. Advanced statistical knowledge and expertise may be required to combine data from multiple trials conducted at different time points, by different sponsors, and measuring different outcomes in potentially diverse patient populations. Of key concern is the extent to which patient-level data may be missing in different randomized trials and how original trial investigators have dealt with missing data. New approaches are needed to quantify and validate the contribution of different trials into a combined dataset. Additional methodological issues reside with how to appropriately use all of the data once they are accessible.

Network meta-analyses are particularly vulnerable to bias when the trials used are not comparable due to effect modifying or confounding variables, specifically when direct and indirect comparisons are used.[78] If an imbalance in effect modifiers exist between the direct and indirect comparisons, the results will not be justifiable.[55] Differences in the included trials' populations or differences in the relevant treatment details for each trial can also impact the results.[61] In addition, investigators performing network meta-analyses will face challenges when they encounter discrepancies in outcome definitions and measurement methods in different randomized trials. Whether widespread access to individual patient-level data can alleviate these methodological concerns remains to be seen. As more data become available, there will be particular concern with combining historical and

contemporary trials, as patients in the historical trials may be more severely ill due to the advancement of medicine.[51] Study populations may also have different underlying risks for a particular illness or trials may differ in their randomization or blinding procedures.[79] Additionally, meta-analyses are only as robust as the trials that comprise the evidence network. If one trial lacks internal or external validity the analysis will suffer.[55,80]

Researchers must be discerning so as to avoid poor trial data—whether in general or just for the specific analysis—so that results will be valid, robust, and generalizable. The financial implications of addressing key methodological challenges of data sharing should not be underestimated. A new methodological research agenda is needed to develop and evaluate new methods for combining and analyzing new datasets. In the immediate term, large and sustained investments from governments and research funding bodies will be required to train the next generation of statisticians, investigators, and applied researchers who will increasingly encounter combined datasets with individual patient-level data obtained from different randomized controlled trials.

Conclusion

In the age of comparative effectiveness research, summary data from only published trials are inadequate to fully utilize the extensive investments sponsors and funders have made to medical research. Early believers in open access data have already brought us to the precipice of having truly open science in which researchers will have exciting opportunities for comparative research and the public will have renewed trust in scientific investigation. However, we must continue to build on the foundation provided by early adopters and work to establish the new "expected norm" of clinical trial data sharing. Comparative effectiveness research has already become the "bedrock" for creating clinical practice guidelines and in an age where spending on healthcare has only increased, access to the entirety of clinical trial data can propel comparative effectiveness research forward to improve clinical decision making.[51]

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