
In the Patient's Interest: Improving Access to Clinical Trial Data

August 2014

-
Prepared by:

Brenda J. Huneycutt, PhD, JD, MPH;
Judith Illes, MS;
Chris Boone, MHA, PhD;
Kathryn Jackson, PhD;
Gillian Woollett, MA, DPhil
Avalere Health LLC



EXECUTIVE SUMMARY

Recent European initiatives, including the European Medicines Agency (EMA)'s publication and access to clinical trial data draft policy, have brought the issue of data transparency to the forefront of policy discourse. Such initiatives aim to increase access to data and benefit the public through accelerating research, enhancing patient outcomes, and increasing public trust in the research enterprise. However, these intended outcomes are not guaranteed and must be considered in the context of the risks and rewards that come with increased transparency of clinical trial data. This paper explores clinical trials transparency and potential consequences to the public's health, including: (1) obligations to clinical trial study participants, (2) privacy, and (3) data quality. These key issues were identified through discussions with key opinion leaders and reviewing the EMA's publication and access to clinical trial data draft policy, as well as other enhanced transparency proposals and commentary surrounding these issues.

Our research found that these three issues warrant immediate consideration because, if mismanaged, they could sabotage the ability of enhanced transparency to benefit the public. Policymakers should thoroughly vet how investigators' obligations to clinical trial study participants (and others) will be met after increased transparency, including how the policy can respect informed consent documents and safeguard participant privacy. How these obligations are met (or not) will impact whether clinical studies continue to be conducted or whether people lose trust in the research enterprise and decrease participation in clinical trials.

Data quality determines the validity of subsequent research conclusions. Good quality data can contribute to increased and better research; but, poor quality data could be destructive and lead to inappropriate conclusions. We include case studies to show the potential harm that poor quality data can cause, including increasing the probability of faulty conclusions, which can ultimately produce public fear and negatively impact the health decisions of regulatory agencies, physicians, clinical practice guideline developers, health authorities, and patients. Therefore, policymakers should consider mechanisms to ensure an agreed-upon level of quality of the data. Further, lack of clarity in research protocols can limit the expected gains from enhanced transparency by restricting the secondary use of data—e.g., replicating and/or critiquing the original study, and conducting subsequent studies with different study designs. Also, stakeholders may need to consider articulating the responsibilities of those releasing the data prior to disclosure of the data.



Finally, we outline tools and strategies to help implement enhanced transparency policies to ensure patients benefit, including: accountability for the release of data, educational campaigns, training for researchers, tools to facilitate informed consent, organized consensus meetings around clinical data standards, mechanisms to validate secondary research and outcomes assessments. As for any comprehensive policy decision, broad stakeholder involvement will likely enable the best outcome.

TABLE OF CONTENTS

Introduction	5
The Relationship of Science to Medicine is Evolving	6
Key Issue 1: Respecting Informed Consent and Other Agreements Supports the Health Gains Envisioned by Clinical Trial Data Sharing	9
Key Issue 2: Safeguarding Study Participant Privacy	10
Key Issue 3: Maintaining Appropriate Quality of the Data and Its Potential To Be Useful And Contribute to Public Health Gains	11
Data Standardization and Accessibility May Limit the Ability of Subsequent Research to Draw Meaningful Conclusions	14
Poor Data Reliability Hinders Meaningful Use of All Data	16
Lack of Clarity in Research Protocols May Limit Expected Gains from Increased Clinical Trial Data Sharing	17
Enhanced Patient Outcomes Can Be Achieved Through Increased Clinical Trial Data Sharing	19
Increased Transparency Allows Confirmation of Current Results and the Generation of New Scientific Findings and Hypotheses, all Benefiting Patients	19
Flawed Studies and the Publication of Misleading Reports About Existing Medicines Present Real Dangers	20
Considerations	25
Conclusion	28
Acronyms	29

This analysis was funded by PhRMA.
Avalere maintained editorial control over the content of the analysis and release.

INTRODUCTION

An essential debate is emerging around data transparency and broader access to clinical trial information submitted as part of registration dossiers in Europe.¹ While the recent European initiatives, including the European Medicines Agency (EMA)'s publication and access to clinical trial data draft policy² precipitated this paper, the consequences of data sharing are much broader. Indeed, data release in Europe can have global ramifications given that data shared anywhere is data shared everywhere. And, such instant distribution of data will only increase in a world of split-second global communications and growing use of electronic medical records. This paper aims to be a resource to stakeholders grappling with the complicated issues surrounding policies to increase the public release of clinical trial data.

This paper explores issues policymakers should consider when designing policies related to increased clinical trial transparency. We identified three key issues through discussions with key opinion leaders and review of enhanced transparency proposals, including the European Medicines Agency (EMA)'s publication and access to clinical trial data draft policy. They are:

1. Respecting promises made by trial investigators to study participants, including individuals' informed consent, as well as contracts and agreements with institutions and research facilities
2. Safeguarding study participant privacy
3. Ensuring the quality of data, including the appropriateness of the availability, use and reliability of the data such that conclusions from subsequent research are valid, and will not undermine current and future therapies and their appropriate use

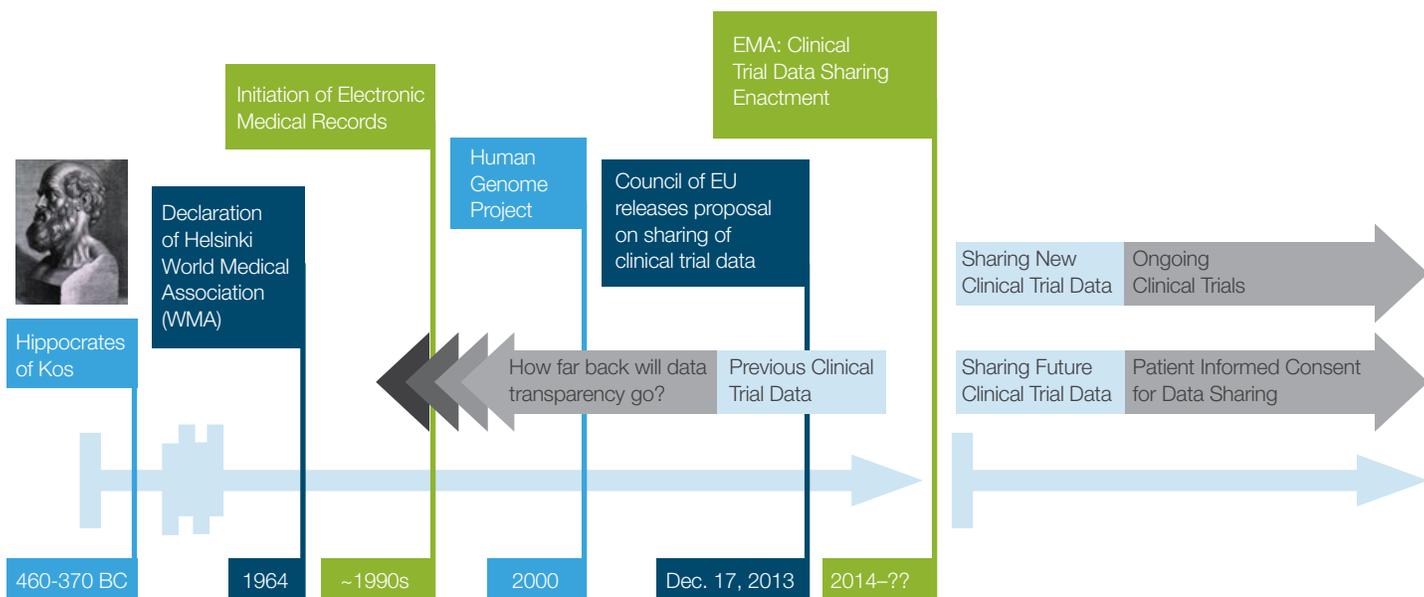
We also explore how increased data transparency can benefit the public and the potential harm that poor quality data can cause. Avalere conducted this research through a targeted review of primary sources (e.g., peer-reviewed scientific journal articles, EU directives and proposed regulations) and grey literature (e.g., published reports, presentations) related to the implications of data transparency for the regulatory and policy environment. Avalere used the following search engines to initially identify primary sources: PubMed, Google Scholar, NICE Evidence Search, and Europa.eu. Searches were generally limited to literature available in English and published within the last 5 years (2008–February 2014). Finally, although European policymakers may be further along than their global counterparts, the points raised in this paper go beyond specific country policies given that medicines are developed for concurrent registration in multiple jurisdictions and data disclosure can impact patients worldwide.

THE RELATIONSHIP OF SCIENCE TO MEDICINE IS EVOLVING

It is important to place clinical trial data transparency in the context of scientific capabilities that have emerged in order to properly understand the policies currently being considered.

Figure 1 illustrates that while the inception of Western medicine dates back more than two thousand years, achievements in the past half century have dramatically accelerated improvements in patient care. These achievements include the expansion of large datasets, such as the Human Genome Project, the initiation of electronic medical records, and changes in clinical research data standards and accessibility of clinical research data worldwide. The implementation of clinical trial data sharing by the EMA may represent the next major milestone in clinical data management and standards development.

Figure 1



The potential value and power of ever larger datasets is indisputable. One only needs to look at how an aspiration to sequence the human genome became a massive, and highly successful, international initiative despite that when it was originally conceived the project was not technically feasible. The success of the Human Genome Project was contingent on developments in computational power, data integration and validation, and concurrent massive improvements in the most fundamental aspects of DNA sequencing technology. Quality control at every stage was essential to its ultimate value. Similarly, for increased sharing of clinical trial data, quality control and developments in data integration and validation will be key.

The Human Genome Project illustrates the value of mechanisms to pool and analyze increasing amounts of data to drive research and enhance patient care. Sequencing the human genome has revolutionized genetic research and increasingly impacts clinical practice and drug development, as well as patient outcomes. Deciphering variations between individuals continues to be an area of considerable research. More generally, larger datasets drive science faster by allowing more hypotheses to be tested and rarer impacts, associations, and correlations to be identified. And, even as the full aspirations of precision medicine take longer to be realized, few question its current impact on patient outcomes and its potential to revolutionize clinical care. Similarly, increased sharing of clinical trial data has analogous potential, allowing for efficient study of new questions without additional burden on study participants (or recruiting new study participants). Indeed, all of the information could be electronic, and after the primary samples are collected no further patient involvement may be necessary.

Clinical trials are the primary basis for the approval of medicines because they give sponsors a way to satisfy the standards for a marketing authorisation, namely that the medicine is safe and effective. As such, all regulatory bodies, to some extent, rely on clinical trial data to determine whether medicines can enter the market they regulate. For example, in Europe, the EMA's Committee for Medicinal Products for Human Use (CHMP)³ assesses the clinical data submitted by sponsors "based on purely scientific criteria [to] determine whether or not the medicines concerned meet the necessary quality, safety and efficacy requirements."⁴ In addition, once medicines are marketed, the benefits for consumers must outweigh the risks (referred to as a "positive risk-benefit balance").⁵ Similarly, to gain marketing approval in the U.S., sponsors must demonstrate that their product is safe and effective (for drugs) or safe, pure and potent (for biologics), and have a positive benefit-risk assessment.⁶ Of course, many products are developed for multiple markets, necessitating concurrent regulatory filings, and so the same product must fulfill the cumulative requirements of all the markets they wish to enter.

Clinical trials to support the marketing authorisation of a product are conducted in a highly controlled way to minimise both bias and the potential that any effect seen is purely due to chance. In the highly regulated markets, in particular, rigorous standards

for the conduct of clinical trials must be met for their regulatory bodies to accept the resulting data. As EU regulations explain, “[i]n general, clinical trials shall be done as ‘controlled clinical trials’ if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified.”⁷ Similarly, US law dictates that sponsors must show “substantial evidence of effectiveness,” defined as “evidence consisting of adequate and well-controlled investigations, including clinical investigations.”⁸

Even though clinical trials have become the accepted gold standard in clinical research, it is noteworthy that both researchers and policymakers are now beginning to recognize the value of clinical data generated from other sources, such as observational studies. For instance, patient registries allow researchers to conduct studies impossible without these massive databases. Consistent with this shift, clinical trial data transparency as currently debated in Europe includes not just the type of trial used to support marketing approval—e.g., randomised control trials (RCTs)—but also observational studies and other trial designs. For example, the EMA’s policy on publication and access to clinical trial data defines clinical trial data as “not limited to conventional randomised control trials (RCTs), but is meant to include other types of interventional or observational clinical research methodologies, such as large simple trials, cohort studies, case control studies, or registry data.”⁹

Increased sharing of clinical trial data will undoubtedly be powerful and has the potential, when handled appropriately, to greatly enhance public health. But, the corollary is also true. Insufficient or untimely consideration of all potential consequences can jeopardize the confidence of patients, investigators and physicians, and the biomedical research enterprise as a whole will suffer. For clinical trials, trust is particularly key because if people do not trust the research system, they will not participate. Without this research, there will be no new medicines for unmet medical needs, nor better medicines for currently treatable but incurable conditions. Most simply put, without study participants there will be no clinical trial data.

Without Study Participants There Will Be No Clinical Trial Data

KEY ISSUE 1: RESPECTING INFORMED CONSENT AND OTHER AGREEMENTS SUPPORTS THE HEALTH GAINS ENVISIONED BY CLINICAL TRIAL DATA SHARING

Protecting clinical trial study participants' interests, irrespective of where the studies are conducted geographically, is widely agreed-upon as foundational to the generation of new data and the approval of new medicines. As the World Medical Association's Declaration of Helsinki explains:

*"[m]edical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects."*¹⁰

In addition to physicians' Hippocratic Oath and duties to promote and safeguard the health of their patients, many national and international statements of ethical principles for the conduct of research involving human subjects ("human subjects research") exist. These statements and regulations share requirements for (1) ensuring study participants' privacy and confidentiality of their data, (2) informed consent prior to participation, and (3) ethical review of proposed studies.¹¹

In Europe, human subject protections are well articulated in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued guideline: Guideline for Good Clinical Practice (GCP) E6.¹² As described by the guideline, "[c]ompliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical data are credible."¹³ This guideline applies to all data submitted to EMA as part of a regulatory dossier for the approval of a new medicine. Data collected in studies that do not conform to these rules are not acceptable as part of an application to EMA, irrespective of where in the world the studies were conducted.

Clinical trial investigators currently have moral and/or legal obligations to study participants and others. In addition, investigators are bound to respect the provisions included in the informed consent documents signed by study participants. Informed consent forms, signed by study participants and binding to the investigators, institution, and research sponsor, often address how clinical trial data may be shared with third party researchers or institutions seeking access to clinical trial results or re-use of these data. These obligations apply to all subsequent uses of the data, including to secondary studies not anticipated

at the time of initial consent. Therefore, transparency in data historically kept confidential may require changes in how data is handled and will need to be reconciled with study participants' expectations.

Stakeholders should consider how enhanced transparency policies comport with or depart from these global norms, and explore the effect of any enhanced transparency policy on the ability of the clinical trial investigator (and trial sponsor) to keep promises made to study participants and others. If policies do not comport with settled human subjects research protections and promises are not kept, there is a significant risk that, however inadvertently, study participants will feel harmed and disrespected, undermining the public's trust and lessening participation in the very research studies critical to bringing new treatments to market. Already study recruitment is slowing the development of new medicines due to the inherent risks for patients; the changes proposed cannot afford to compound this difficulty.

KEY ISSUE 2: SAFEGUARDING STUDY PARTICIPANT PRIVACY

In addition, stakeholders should consider the effect clinical trial transparency policies may have on protecting study participant privacy. Patients' expectations of privacy for their medical information is reflected in the numerous laws and regulations protecting patient and study participant confidentiality and privacy.¹⁴ Clinical trial investigators promise to safeguard study participants' privacy and to keep their data confidential and secure by, for example, implementing secure data retention policies.¹⁵ Participation in clinical studies is often contingent on these guarantees of privacy protection and data security.

One oft-cited issue regarding enhanced transparency is the risk that a study participant could be specifically identified from the data shared (alone or in conjunction with other publically-available information). Given the attendant harms associated with being publically identified, ranging from mild embarrassment to outright discrimination, consideration of this issue when deciding on enhanced transparency policies is critical. The risk of identification varies considerably among individuals and among clinical trials, increasing when the clinical trial only includes few participants or contains data reflecting unique characteristics of its participants, making the pool of possibilities smaller and re-identification easier. Additionally, some voice the concern that data on individuals who have participated in particular studies could inadvertently be made public along with study data itself (e.g., errors in de-identification).¹⁶

Even for large studies the possibility exists that with a few pieces of information (birth date, gender and post code, for example) study participants can be identified.¹⁷ Indeed, secondary users of shared data may try to re-identify participants, quite possibly with sound scientific reasons for doing so. The familial nature of health information, especially

for any study using genetic data, complicates considerations regarding privacy. The duties owed to study participants regarding privacy may, in some contexts and with some data, extend to their family members. Furthermore, as technologies advance, these risks will only increase. EMA recognizes this in its publication and access to clinical trial data draft policy, noting that “emerging technologies for data mining and database linkage will increase the potential for unlawful retroactive patient identification.”¹⁸

Finally, policymakers need to consider the effects of the timing of their decisions. Policymaking in anticipation of increased transparency, not concurrently with or in response to increased transparency, could prevent some unintended consequences given that data shared anywhere is data shared everywhere. In other words, once data is in the public domain it cannot be “put back” and patients’ privacy re-secured.

KEY ISSUE 3: MAINTAINING APPROPRIATE QUALITY OF THE DATA AND ITS POTENTIAL TO BE USEFUL AND CONTRIBUTE TO PUBLIC HEALTH GAINS

“Data quality” has been broadly defined as, for example, “fitness for use,”¹⁹ which in the context of clinical data can be largely context dependent and can vary by research study. High quality data has been defined as “data strong enough to support conclusions and interpretations equivalent to those derived from error-free data.”²⁰ More specifically in the context of clinical data, the following four specific dimensions are commonly used to outline data quality: reliability, validity, accuracy and completeness.²¹

When assessing data quality, three things are routinely considered:

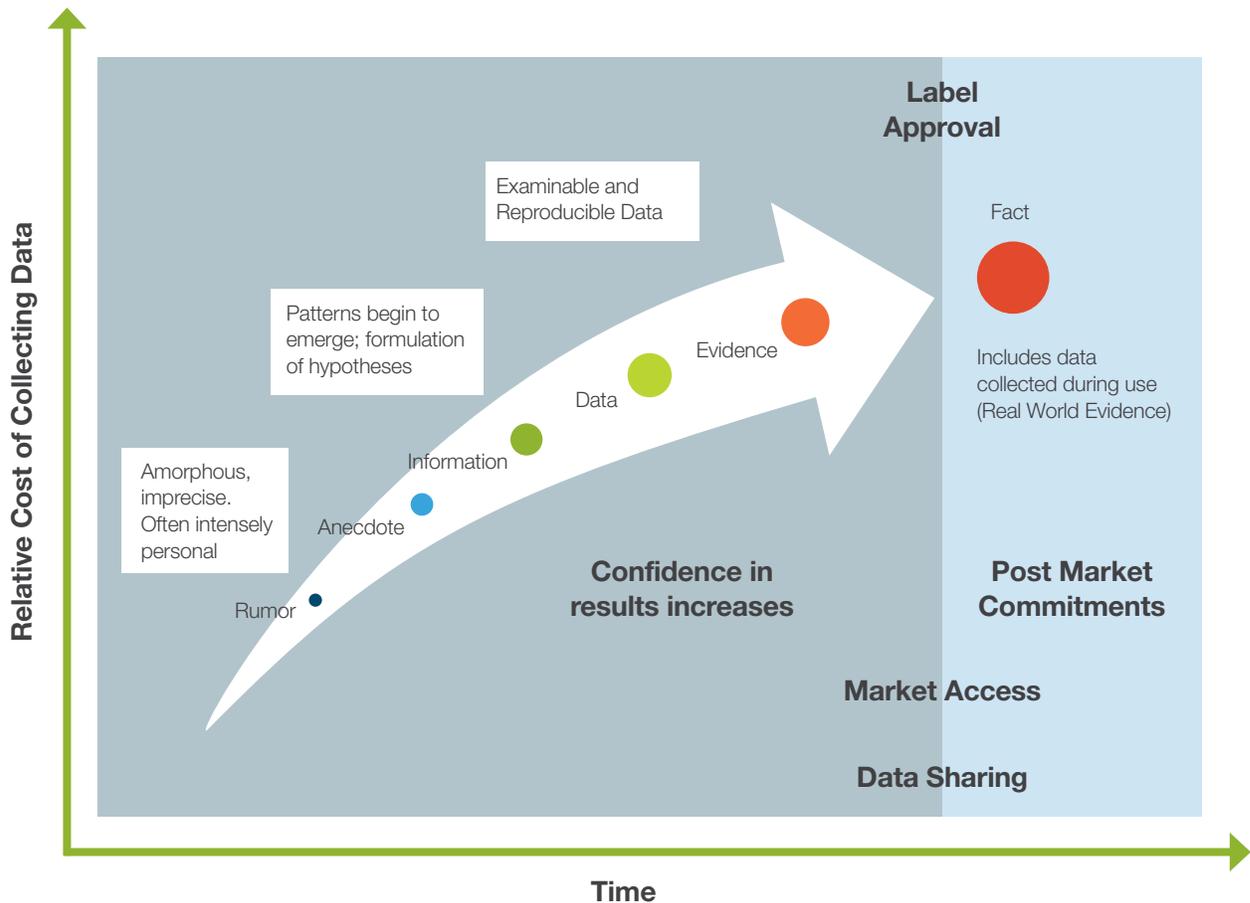
1. **Data standardization and accessibility**, or the processes through which the data is collected and reported, including how the data should be collected, entered, extracted, and transferred to avoid errors and ensure maximum usability, and what data elements should be available to researchers.
2. **Data reliability** or trustworthiness or whether the way in which data is made available and subsequently used can be trusted and relied on for future clinical research and healthcare decision making. Ensuring reliability typically involves the validation, aggregation, normalization, and/or auditing of the data sets, and assuring that even good data has not been corrupted.
3. **Data use** denotes the applied methodologies to analyze the data, and purposes that the data can be used for once it is made available.

It is important to recognize that the same considerations apply to all data—registration data or non-registration data—that may be considered, combined, or sourced, and from which clinically relevant conclusions will be made.

Poor quality data can never contribute to better decision making—at best, it will simply dilute the data pool and at worst, will distort it.

As Figure 2 below explains, the cost to collect as well as the confidence in the quality of data evolves over time as more is learned and incorporated into the data package used to support the safety and efficacy of a medicine. As one moves along the data quality continuum outlined, categories of data are more examinable, reproducible, and reliable (corresponding to greater confidence in the data).

Figure 2.



For example, at the start of drug development basic research (and occasionally rumors and/or anecdotes that reflect spontaneous observations) generates ideas used to create testable hypotheses, which form the basis for potential new therapies. These new drug candidates are assessed in preclinical experiments to generate preliminary data, and then tested in clinical trials to show evidence of safety (usually first in healthy volunteers) and then efficacy in patients. Data can come from many sources, but formal clinical trials comprise the core of the registration documents that the regulatory authority uses to approve a medicine. As illustrated by Figure 2, data must be of sufficient (high) quality to be accepted by the regulatory agency and support a marketing authorisation. After the product is approved, studies (both formal and informal) continue. Further clinical trials are conducted to add indications, and data from observational studies may suggest which populations benefit the most from the drug. The additional data, as well as spontaneous reports, submitted to the regulatory authorities contribute to changes to the product label over time.

Guaranteeing data quality is challenging even in controlled clinical trials settings. In general, the data to be shared by regulators is presumed to be of appropriate quality by definition, as otherwise the data would not have been accepted by the regulatory agency. More complicated is the situation in which an application was accepted by the regulatory agency but then the marketing application is subsequently withdrawn—this data will also be shared under the EMA's publication and access to clinical trial data draft policy. Without an explicit explanation it may be unclear whether this data is good data that simply could not or was not used to support marketing authorisation of a product, or if for some reason it was not appropriate for use. While this situation may be rare, it is important for policymakers to consider this consequence of having the regulatory agency share all clinical trial data.

Further, to guarantee that the results of a mixed data study (one with regulatory quality data combined with other data) can be trusted, all of the combined data must meet a standard that matches that for data routinely used for regulatory decision making (e.g., subject to the same transparency and interrogability standards). Ideally, mechanisms would be in place prior to increased transparency to ensure appropriate data quality so that the outcomes of any subsequent or secondary studies are meaningful and appropriate for use in making public health decisions. Otherwise, there is a risk of “garbage in, garbage out”—where data quality is poor, resources drained, and results of the studies are meaningless, fail to extend understanding, or are wrong.

Of note, given that regulatory authorities review and approve for marketing each medical product as an independent application, there are inherent legal limits to the use of comparative data in regulatory decision making. Because of this limitation, the most robust data considered by regulators is those collected in clinical studies looking at the test medicine versus the standard of care.

In addition, some have described EMA as being significantly risk-adverse, and discussed the effect of such a stance (i.e., a bias against approving medicines, even though all stakeholders have tremendous compassion for the patients who are waiting).²² As such, policymakers should also consider increased transparency's effect on the regulatory agency—will the agency be more or less risk-adverse in an era of increased transparency, where the possibility of second-guessing regulatory decision-making is expected to be higher?

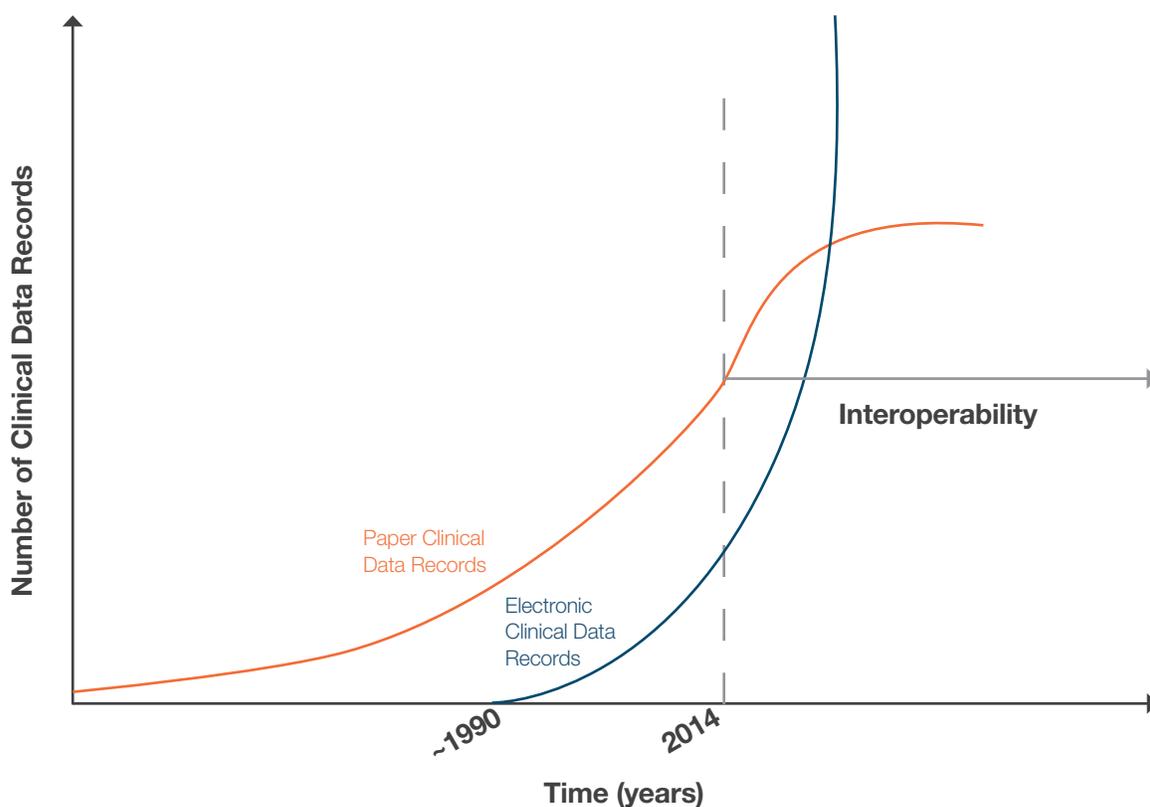
Involving regulators in how any data is to be released, and how the dangers of false positives and false negatives in current and future studies may be avoided, may be an invaluable aspect of any policy related to data transparency. Indeed, EMA having a role in preventing data judged inadequate in some way (and possibly being the basis for some withdrawn applications) from being made more broadly available would help curtail such data's confounding of other, subsequent studies. In the interests of transparency, data already judged to be unusable should not be allowed to contribute to the larger pool. If erroneous, then by definition it cannot contribute to improved healthcare decision making.

Data Standardization and Accessibility May Limit the Ability of Subsequent Research to Draw Meaningful Conclusions

One characteristic of quality data is that it is collected and reported in a standardized way such that it can be captured longitudinally across disparate systems and/or combined with other data.

As Figure 3 on the next page illustrates, it is unknown whether clinical data records from the past will be interoperable with data collected in the future. One goal of data sharing is to enable the pooling of clinical trial data across studies to improve the chances of identifying rare adverse events sooner or otherwise improve the detection of other clinically relevant findings. Prior to the initiation of systematic electronic clinical data records, any detailed medical records maintained were largely paper documents at the point of care. Although the majority of clinical data records used for European drug development and registration are now maintained electronically, the possibility for interoperability between remaining paper clinical data records and multiple electronic clinical data recording systems in different countries remains unclear. And, policymakers must anticipate a vast proliferation of electronic data sources.

Figure 3.



One component of achieving subsequently integrate-able data is defining what constitutes proper collection and reporting of data in the first place. Common terms and standards for data entry, collection, and transfer can enable standardized reporting. Furthermore, the format in which the data are entered (e.g., string, number, code, or text) impacts the data's potential usefulness. For example, when trial results are reported in text-based articles rather than properly structured datasets, it may be difficult if not impossible for researchers to run computational analyses on them.²³

Equally important is which data elements are available from a single study and whether comparable data elements are available from other studies (i.e., what is the level of consistency of the data available across multiple studies). Researchers will face challenges in using information shared with them if the right data elements are not accessible or incomplete. For example, in addition to raw data and analyzable datasets, researchers may also need access to metadata and other supporting documentation (e.g., full protocol, manual of operations, consent forms, case report forms) to allow them to analyze and use the data to obtain meaningful results.²⁴ Appropriate cross-study

analyses will likely require consistent data element accessibility across initial data sets. Blending data from heterogeneous datasets may compromise the validity of the study conclusions. Policymakers have an opportunity to address these challenges by investing in standardized ways to make data elements accessible.

Another consideration is the current heterogeneity of CDM systems, software systems that assist in the process of collecting and managing trial data, which can compromise the quality of data by hindering its exchange. A recent survey on data management procedures for clinical trials in Europe revealed variability in the kinds of clinical data management systems European clinical centres use, and that academic centres use different software from the ones used by the pharmaceutical industry.²⁵ Some expect this lack of interoperability between the various systems to hinder the exchange of trial data in Europe and recommend the use of common data standards, such as those created by the Clinical Data Interchange Standards Consortium (CDISC).²⁶ The use of CDISC standards, which the U.S. Food and Drug Administration (FDA) is already requiring for the formatting of clinical trial data,²⁷ can facilitate the transfer of data and minimise errors.

Poor Data Reliability Hinders Meaningful Use of All Data

The history of the data may be as important as the data itself. Data reliability is crucial to allow meaningful conclusions to be drawn from future research studies using that data. The processes of validation, normalization, and auditing are all necessary steps for ensuring data reliability.

Data validation typically occurs after the data is collected and imported into a data management system (database). In this process, researchers confirm the data and check for inconsistent, incomplete, or inaccurate entries. Researchers also verify that the data was collected and evaluated according to the approved study protocol, and they audit the data entered into the database by checking that it matches the source data (ultimately this must be linkable to the patient record itself). This process occurs on an ongoing basis as the trial data is collected.

Researchers also “normalize” the data, although the complete history of each data set is maintained. Normalization includes researchers using a standard terminology for “value sets”, and ensuring semantic consistency in the data sets so that they can be consistently queried for information on a broad scale. Furthermore, for data in regulatory submissions, the regulatory authority can audit back to the original case study form to check that all generated data was captured in a comprehensive and accurate manner. Of note, such access to the individual patient record is not expected under EMA’s publication and access to clinical trial data draft policy.

For the processes of validation, normalization, and auditing to yield high quality data that can be used in an interoperable manner among different European member states, or between other stakeholders, standardized information technology solutions need to be in place. There are a wide variety of software products available to assist European researchers in clinical trials with data management and, as mentioned above, there is considerable heterogeneity in their use.²⁸

In response to this challenge, the European Clinical Research Infrastructures Network (ECRIN) Working group on Data Centres developed and revised standard requirements through expert consensus.²⁹ While not definitive, these standards specify the criteria “for high quality GCP [Good Clinical Practice]—compliant data management in multinational clinical trials.”³⁰ A good start to ensuring data integrity (and appropriate public health conclusions are reached in secondary studies) may be requiring recipients of data shared under the EMA’s publication and access to clinical trial data draft policy to certify that they will abide by these standards.

Lack of Clarity in Research Protocols May Limit Expected Gains from Increased Clinical Trial Data Sharing

Ensuring that research protocols are public (for both the original study and any subsequent studies) helps turn increased clinical trial data transparency into public health gains. Data alone is not sufficient. The reliability of scientific findings depends on all researchers being able to:

1. Critique the soundness or rigour of the methodological approaches used by others;
2. Replicate experiments (applying the same methodology to the same dataset) in order to test study results and conclusions; and
3. Conduct subsequent studies with different study designs, and potentially additional data sources, but using the same data elements appropriately and in a consistent manner.

All of these actions are enabled by full transparency in the research protocols and methodology for all the data included. However, without access to, and a full understanding of, the comprehensive research protocol for the data, neither critique or replication can occur. Clear standards for reporting on methodology—for both those submitting clinical trial data as well as those accessing it subsequently—help researchers reach appropriate conclusions. However, sufficient public detail regarding research methods is often unavailable.³¹

The Consolidated Standards of Reporting Trials (CONSORT) statement exemplifies a guide that helps authors improve their reporting of clinical trial methodologies through the use of a checklist and flow diagram.³² CONSORT calls on researchers to detail

aspects of their methodology including trial design and changes to methods, study settings, interventions, trial outcomes and changes to trial outcomes, randomisation, and so on.³³ While the CONSORT statement has received wide endorsement from almost 450 medical journals, over 100 other reporting guidelines exist.³⁴

Ideally, this expectation would apply to all researchers, including those conducting secondary research on shared data, with protocols for secondary studies and analyses being made public and subjected to the same standards of methodological rigour as the original research, or indeed, any other clinical research. Case studies illustrate the importance of using transparent and appropriate methodologies:

Case Study: In 2010, two researcher groups independently investigated a potential link between oral bisphosphonates and esophageal cancer. Although both investigators used data from the UK General Practice Research Database to ask the same question, their research generated contradictory findings. One study found that individuals taking oral bisphosphonates did not have a higher incidence of esophageal cancer, and the other demonstrated that patients taking oral bisphosphonates did have a significantly higher risk.³⁵ In this instance, both methodologies were sound, requiring FDA to initiate its own review (which is apparently still ongoing).³⁶

Case Study: There have been instances of regulatory agencies relying on studies with flawed methodology to suspend or withdraw approved products from the market, limiting patient access. For example, the European Commission (EC) suspended marketing authorisations for aprotinin-containing medicines in the European Union based upon observational studies and a RCT reporting that patients undergoing coronary artery bypass graft surgery taking aprotinin had significantly higher 30-day mortality.³⁷ In addition, a Cochrane review of anti-fibrinolytics included data from the flawed RCT.³⁸ However, four years later EMA recommended the suspension be lifted,³⁹ after Health Canada reviewed and reanalyzed the data from the study, identifying a number of deficiencies and confirming that the benefits of aprotinin outweighed its risks in this context, and CHMP conducted a comprehensive review of the evidence on the use of anti-fibrinolytics.⁴⁰

The worst case scenario is a flawed study impacting regulatory approvals—either by allowing a truly ineffective or unsafe drug on the market or preventing a truly effective and safe drug from being made available to patients. For products already approved, flawed studies can cause extreme confusion or unnecessary public anxiety, and even result in drugs being wrongfully suspended or withdrawn from the market.

ENHANCED PATIENT OUTCOMES CAN BE ACHIEVED THROUGH INCREASED CLINICAL TRIAL DATA SHARING

So far this paper has discussed a number of crucial issues that policymakers and other stakeholders should consider to ensure that the benefits anticipated for increased transparency can be achieved. This section describes the kinds of benefits associated with data disclosure, while also acknowledging some potential concerns that policymakers must balance with these benefits.

Increased Transparency Allows Confirmation of Current Results and the Generation of New Scientific Findings and Hypotheses, all Benefiting Patients

Multiple stakeholders—including patients, research participants, the scientific community, regulators, and trial sponsors— expect to gain from increased clinical trial data sharing. These gains focus primarily on the additional opportunities that enhanced data sharing provides for research—whether it be the opportunity to review and evaluate a completed study in order to challenge or confirm it; the opportunity to ask new research questions of existing data (creating efficiencies); or the opportunity to learn more about approved medicines to enhance treatment, including using larger datasets to identify rarer events. Importantly though, these considerations also apply to secondary analyses, arguing that they themselves should also receive appropriate scrutiny.

Expanded access to data can allow for more systematic reviews across data from numerous studies, or even enable existing evidence to answer different questions. Increased transparency can be a cost-effective way to determine the risks and benefits of a therapy without investing in new research protocols or repeating entire studies (which can be ethically questionable). Using large datasets is not new, and many recent data sharing initiatives are expected to enhance the value of clinical trial research through expanded access to clinical trial data and other forms of clinical data. These include the National Heart, Lung, and Blood Institute's Biological Specimen and Data Repository Information Coordinating Center (BioLINCC) and the Yale University Open Data Access (YODA) Project.⁴¹

In addition, open access to raw data may counteract concerns of reporting bias (i.e., that only positive studies get published)—which some suggest is a significant obstacle to evidence-based decision making by and for various stakeholders.⁴² Reporting bias could occur because sponsors fail to submit manuscripts or journal editors decide not to publish uneventful studies.⁴³ Nonetheless, access to unpublished trial results, and earlier access to registration studies, may in some instances enable stakeholders, for example, clinical guideline developers, to better assess the harms and benefits of a given therapy. For example, when the UK's National Institute for Health and Care Excellence (NICE) was

developing guidelines for childhood depression, it would likely have recommended the use of all selective serotonin reuptake inhibitors had it not had access to data on unpublished trials.⁴⁴

One of the most frequently cited rationales for broad access to participant-level data is that it will allow other researchers to reanalyze data in regulatory dossiers and potentially permit them to make new findings about the safety and efficacy of treatments.⁴⁵ Furthermore, to the extent that studies can be combined, bigger data pools can enable identification of subpopulations that have different reactions, good or bad, allowing sponsors to refine labels and alerting all stakeholders to unusual events earlier. Such findings may inform more appropriate use of medicines, including screening for certain types of patients or monitoring some conditions more carefully. In addition, researchers can use aggregated participant-level data from multiple studies (perhaps in conjunction with other data) to identify class effects of therapy. Finally, secondary analyses can reveal inappropriate analytical methods, selective use of data, and/or weaknesses in the design and conduct of clinical trials.

Without a doubt, increased clinical trial data sharing holds great promise in enhancing researchers' ability to do more with the data available. Not only would it be possible to evaluate completed studies more easily, but researchers can use and combine existing data to ask new questions, gain new insights and generate new hypotheses for both understanding disease and evaluating current and future treatments. Additional quality data generated from these studies can be used to enhance healthcare decision making, leading to better patient outcomes.

Flawed Studies and the Publication of Misleading Reports About Existing Medicines Present Real Dangers

While stakeholders are optimistic that the benefits outlined above (as well as others) will materialize, policymakers must acknowledge that this is not the only possible outcome. Inherent in the discussion on benefits is the assumption that findings generated from subsequent studies are valid and not misleading in and of themselves. However, the potential exists that increased clinical trial data sharing will result in the conduct of flawed studies and the publication of misleading reports about existing medicines. These can be extremely harmful to the reputations of the original investigators, product sponsors, and regulatory agencies, and more importantly to patients and the public as a whole.

Specifically, there are significant and dangerous risks to public health associated with the use of incomplete or inaccurate clinical data, inappropriate data pooling, naive secondary analyses, poor study design and inadequate quality control. A study that the regulatory authorities would not accept as part of a primary registration file, by definition, does not meet the same standards as a study that would be (or was) accepted by

regulators. As such, conclusions from each of these types of studies do not compare, and should not be regarded as equally valid. As we enter an era interested in greater use of observational data, patient-reported outcomes, and various forms of data grouped together as real world evidence, particular care must be taken. This data can be important, but it is not controlled for statistical bias, representativeness, or accuracy in the manner of a randomised controlled trial. Unfortunately, publication in peer-reviewed journals cannot compensate for poor studies, and journals will likely be unable to screen out the most dangerous studies given their tendency to publish only the most dramatic results.⁴⁶ That is not to say that all contributions to the broader understanding of clinical data are not welcome, just that they are not all created equal.

The regulatory authorities have extensive experience in the management and appropriate derivation of conclusions from clinical data. Their experience has a role in how the results of secondary analyses are used to impact the labeling and use of marketed medicines. While even amongst regulatory authorities opinions can vary, it is generally accepted that the highly regulated markets are particularly careful in the data requirements they impose on sponsors to substantiate the safety and efficacy of the medicines they approve. Generally, products approved in Europe will be acceptable in most markets around the world, even though each jurisdiction requires separate applications.

As Figure 4 on the next page explains, not all clinical data are created equal; quality, quantity and clinical study design differ based on regulatory stringency. Highly regulated markets, such as the E.U., U.S., Canada, Japan and Australia impose similar clinical data standards on the regulatory submissions that they consider suitable for review and approval. Emerging markets, such as India, China, Russia and Brazil, as well as the remaining world markets, do not maintain the same stringent clinical data standards for regulatory approval as those of the highly regulated markets. Accordingly, while clinical data from highly regulated markets can serve as a basis for regulatory approval in emerging markets, clinical data from emerging markets and the remainder of the world are generally not sufficient for approval in highly regulated markets. In Figure 4, the relationships between varying standards and regulatory approvals are illustrated by the arrows and the (size of the) green deltas between the three categories of markets.

Figure 4



To the extent that the results of secondary analyses are not managed carefully, nor subject to the usual constraints imposed on the sponsors of human drug applications, the consequences for public health should be considered. The source of data and the methodologies used to reach a given clinical conclusion may not be immediately apparent when a headline is published or story tweeted. Consequently, competent authorities may need to create mechanisms to rapidly respond to health scares—inappropriate as well as appropriate. Of primary concern is that mis-information would negatively impact clinical decision making, either by:

1. Affecting patients' beliefs in the medicines they are taking and altering their decisions about their own care—such as stopping to take a critical medicine based on a press story;
2. Changing physician decisions for their patients, and appropriate medicines being denied to a patient as a result;

3. Impacting the development of clinical practice guidelines in a manner that denies choice to health care providers and their patients;
4. Influencing health authorities to make patient access decisions that limit options for patients; or
5. Causing regulatory authorities to pull medicines from the market or restrict their use inappropriately.

Flawed conclusions based on studies of data sets that include any elements of poor quality, or even good data that is inappropriately analyzed, or melded with unsuitable additional data, can ultimately result in patients receiving suboptimal care or avoiding care at all.

Case Study: This was the consequence, for example, when in 1998, the publication in the *Lancet* of a report on 12 children that suggested a potential association between getting vaccinated for measles-mumps-rubella (MMR) and autism⁴⁷ resulted in MMR reemerging after individuals refused to get vaccinated.⁴⁸ Not only does this put the individuals at risk and lead to an increase in the actual incidence of the diseases that the vaccines would have otherwise prevented, but it harms the public at large by putting individuals at risk who cannot receive the vaccine and would otherwise be protected by so-called herd immunity. The consequences are still being felt today. Vaccines as a whole continue to be prejudiced even as they represent one of the most critical public health tools available worldwide, and the only basis ever of a human disease being eradicated.

Given such examples, it is imperative that stakeholders and policymakers carefully explore the implications of potential enhanced transparency policies.

Moreover, publication of misleading or inaccurate information about any marketed product can create unwarranted public anxiety and confusion as to the efficacy and safety of specific products individually or even medicines more broadly, and even undermine confidence in the regulatory authorities themselves. Policymakers should not underestimate the effects of negative publicity, whether completely unsubstantiated, or based on faulty secondary analyses, because researchers will not have the wherewithal to rebut all misconceived analyses in a post-enhanced data transparency world.

News based on poor use of data can cause patients to worry about the safety and efficacy of their medications which may, in turn, have negative health consequences for those who stop adhering to their treatment regimens. It is often the most vulnerable and least well-informed patients that become alarmed by the dramatic headlines. Ideally, the authorities with the greatest understanding of the safety and efficacy of medicines should be included in the decision making regarding the significance of secondary analyses for currently approved products, and be available to advise patients accurately and in a timely manner.

By definition in Europe, this is the EMA. Only EMA has seen the full regulatory dossier and on that basis made the decision that the medicines given market authorisation are indeed of appropriate quality, safety and efficacy.

In addition, flawed studies can compromise the development of clinical practice guidelines, which uses peer-reviewed publications based on secondary analyses of clinical trial data and the use of these data to examine other treatments or outcomes in longitudinal studies. It is difficult to identify deficiencies in the methods used in conducting longitudinal studies.⁴⁹ For example, a 2008 review of the application of specific methods in cardiovascular longitudinal studies concluded that over 95% of the studies were poorly conducted, despite having been published in prestigious cardiovascular journals.⁵⁰ The level of rigour in guideline development processes varies,⁵¹ and a risk exists that the treatment guidelines and associated health care recommendations could be based in part on flawed data and misinterpreted evidence.

Weak data or flawed secondary analyses can also influence decisions made by health authorities regarding patient access. Outcomes are becoming increasingly important in health authority decision making as EU member states strive to manage national healthcare expenditures.⁵² However, different health services in Europe vary with regard to their organization and the kind of evidence they require,⁵³ even though EU member states are now more often working with the same data. The UK's NICE, which produces clinical guidance documents that assess both the efficacy and cost-effectiveness of therapies, has come to be regarded as a model for centralized health authority decision making. In countries like Spain and Italy, which have decentralized health authority decision making, local decision makers apply their own processes for assessing and vetting evidence. Variation among the different national and local health authorities and a lack of standardized approaches to vetting data make it less likely that flawed data or inappropriate analyses will be filtered out of data disseminated across Europe.

One of the most worrisome outcomes of the use of flawed data is a product being inappropriately pulled or suspended from the market, limiting access for patients who have previously benefited from the product in question (see the aprotinin example described above).

Additional clinical data cannot add value unless it is high quality and well understood. Bad data is not just noise, it dilutes meaningful results, misleads, and compromises health systems' ability to create sound norms and healthcare

Bad data is not just noise, it dilutes meaningful results, misleads, and compromises health systems' ability to create sound norms and healthcare practices

practices. It is a mistake to ignore the possibility and associated harms of flawed studies being conducted and misleading information being published about currently-approved products. Ideally, before an increase in clinical trial data sharing, these risks and potential harms must be considered and addressed.

Considerations

A smooth transition to enhanced clinical trial data sharing requires consideration of the roles and responsibilities of the various players in the system, ideally articulating them fully before increased transparency. Without this, it would be exceedingly difficult if not impossible to ensure that all of the concerns discussed throughout this paper—from protecting patients' privacy and respecting study participants' intent and informed consent, to ensuring appropriate data quality, to minimizing potential harms from flawed studies or misleading information—are addressed. In addition, whether and how to clearly articulate the responsibilities of those releasing the information, for example EMA, and to whom and for what, as well as the investigator that uses the shared data, needs to be explored.

As discussed above, policymakers should consider a multitude of issues, potential implications, and avoidable risks when deciding on the contours of a specific enhanced data transparency policy and balancing competing interests. We have outlined and explored many of these considerations, including recognizing that no data disclosure policy can change a clinical trial sponsor's prior or current commitments or absolve it from complying with contract provisions already entered into or other legal duties. Clinical trial sponsors are still liable for breaking previously-made promises, violating agreed-upon contract provisions, or failing to meet ethical and legal duties. It will be important for policymakers to resolve these tensions before any clinical trial data is shared because sponsors are put in an impossible position if they cannot share data that supports a product's registration.

Enhanced clinical trial data sharing offers opportunities but also presents the challenge of translating the legitimate aspiration for better outcomes into actual advancements in medical research and ultimately, improved public health. All these steps, including how those outcomes will be fostered and measured, are important components to consider and ideally have in place before any data are released.

With appropriate thought and planning, the public health benefits of enhanced clinical trial transparency that all stakeholders anticipate can be achieved. It is possible for data transparency to have the support of all stakeholders—patients, researchers, industry, and governments. A transparency policy developed through multi-stakeholder involvement creates better prospects for improvements in public health than a process that polarizes the debate into those currently possessing data—researchers in academia and industry, and those wanting access—patients and the public more broadly. Importantly, the involvement of all stakeholders, including patients, is key to identifying the best ways to accomplish enhanced transparency while balancing competing interests. In particular, the patient voice is critical to understanding study participants' needs and expectations.

Some noteworthy tools and strategies that can help implement the EMA's draft policy on publication and access to clinical trial data and ensure it achieves its objectives, while maintaining the public's trust in the global biomedical research enterprise, include:

- **Accountability for the release of the data:** Mechanisms in place to maintain data integrity regardless of how the data is released, and include the necessary patient information (within the terms of informed consent). The responsibility for ensuring this, and the liability for the release, lies with the individual and their organization releasing the data.
- **Educational campaigns to support consumers and the general public:** The primary goal of clinical data sharing is to enhance public health, but how this occurs is generally not well understood. There is the need, within each European country, to ensure that the public understands the implications of clinical trial transparency for themselves, and their families, within their local health systems. Clear communication and responsible discussions about topics such as individuals' rights to control their personal data as well as any special obligations owed to study participants are important, especially for those individuals who have already contributed to studies under a previous set of expectations.
- **Training for researchers:** Individual investigators, like their sponsoring institutions, have legal and ethical obligations that they must uphold vis à vis trial participants. Researchers will benefit from additional training to ensure that they are able to continue to comply with these duties, and understand their own responsibilities and liabilities, as clinical trial data sharing becomes the new status quo.
- **Tools to facilitate informed consent:** To ensure that the interests of human subjects continue to be adequately protected in an environment of broad clinical data sharing, local regulators and research sponsors (such as the European Commission, government research councils, and companies) should consider providing investigators and institutions with a process, or even a template, for modified study participant consent forms. This could include those to be used in future trials, as well as templates for addendums to existing consent forms in the case of ongoing trials that began before the enactment of a data sharing policy, if necessary.

- **Organized research/ consensus meetings around clinical data standards:** As data sharing policies envision integrating data sources that may be of variable quality and originate from a variety of different sources, assuring data quality before data is pooled becomes a precondition for the ability of that data to optimally enhance decision making and benefit public health. Lack of standards around the interoperability of data as well as for the use of data from sources other than clinical trials, such as observational studies in real world settings, calls for uniting stakeholders to exchange best practices and reach consensus on standards needed to ensure quality.
- **Mechanisms to validate secondary research:** In addition to concerns about the quality of the original data that will be shared through a data sharing policy, there are equally serious concerns about the use of these data by external investigators. Good data are only as good as the methodology applied to them, so the transparent use of data is as important as making the data available to the public. Requiring proactive publication of the methodology used in secondary analyses and their results can be one effective way to ensure that these studies receive appropriate scrutiny.
- **Outcomes assessments:** Policymakers may wish to commission independent evaluations of the outcomes and consequences of data sharing policies and measure success by factors like publication of new studies, improved clinical outcomes, and impact on the availability and access to medicines.

CONCLUSION

All stakeholders, including the public and patients waiting for new and better medicines, anticipate that enhanced data transparency will lead to public health benefits. This paper highlighted key issues including patient privacy, respect of study participants' informed consent, and data quality. Consideration of these issues is critical to ensuring that the expected benefits of increased transparency and sharing of clinical trial data—in particular better patient outcomes—are enabled while minimising any unintended negative consequences to the research enterprise and regulatory authorities as a whole. Furthermore, multi-stakeholder involvement in policy development is crucial to gaining support and addressing the myriad of issues important to different stakeholders, including patients.

Ideally, the risk of unintended consequences would be addressed prior to any data being released because once released, data cannot be recaptured. Even if data is shared with good intentions, without adequate safeguards in place, it can result in harm to the public. As in all medicine, the axiom “first, do no harm” is worth bearing in mind.

Importantly, with access comes the responsibility to protect the research enterprise, which includes competent authorities—the regulators—being charged with making quality, safe, and effective medicines available to the patients who need them, as well as researchers. As such, additional data analyses or combining of data from multiple sources comes with a corresponding accountability to advance public health. While science is an iterative process, medicine can be fraught with issues of confidence and trust. It is critical to remember that the availability of a medicine is based on the overall risk-benefit assessment for a population as a whole, but all use is individual and acutely personal.

ACRONYMS

BioLINCC	Biological Specimen and Data Repository Information Coordinating Center
CDISC	Clinical Data Interchange Standards Consortium
CDM	Clinical Data Management
CHMP	Committee for Medicinal Products for Human Use
CONSORT	Consolidated Standards of Reporting Trials
DNA	Deoxyribonucleic Acid
EC	European Commission
ECRIN	European Clinical Research Infrastructures Network
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference for Harmonisation for Technical Requirements for Registration of Pharmaceuticals for Human Use
MMR	Measles-Mumps-Rubella
NICE	National Institute for Health and Care Excellence
RCT	Randomised Control Trial
US	United States
WMA	World Medical Association
YODA	Yale University Open Data Access Project

NOTES

1. European Medicines Agency, "Publication and access to clinical-trial data: an inclusive development process," available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000556.jsp (last accessed August 20, 2014).
2. European Medicines Agency, "Publication and access to clinical-trial data," EMA/240810/2013, June 24, 2013, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf (last accessed August 20, 2014).
3. CHMP assesses specific products for an EU-wide approval. There are other pathways to marketing approval in individual European countries as well as other avenues for multi-country approval.
4. European Medicines Agency, "CHMP: overview," available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&mid=WC0b01ac0580028c7a (last accessed August 20, 2014).
5. Id.
6. Federal Food, Drug and Cosmetic Act (FD&C Act) § 505, 21 U.S.C. § 355; Public Health Services Act (PHSA) § 351, 42 U.S.C. § 262.
7. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, Sec. 5.2.5.1, available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20070126:en:PDF> (last accessed August 20, 2014).
8. FD&C Act § 505(d), 21 U.S.C. § 355(d); see also FDA guidance Providing evidence of effectiveness for human drug and biological products, May 1998, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf> (last accessed August 20, 2014).
9. European Medicines Agency, "Publication and access to clinical-trial data," EMA/240810/2013, June 24, 2013, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf (last accessed August 20, 2014).
10. The World Medical Association, Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, available at: <http://www.wma.net/en/30publications/10policies/b3/> (last accessed August 20, 2014).
11. Id.; see also e.g., Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, Sec. 5.2.5.1, available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20070126:en:PDF> (last accessed August 20, 2014); U.S. Federal Policy for the Protection of Human Subjects ("Common Rule"), available at: <http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html> (last accessed August 20, 2014).
12. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1), June 1996, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf (last accessed August 20, 2014).
13. Id.
14. Any transparency policy aimed at benefiting public health must comport with key principles and rules of European data protection law, e.g., Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data, available at: https://secure.edps.europa.eu/EDPSWEB/webdav/site/mySite/shared/Documents/EDPS/DataProt/Legislation/Reg_45-2001_EN.pdf (last accessed August 20, 2014), and Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, available at: http://ec.europa.eu/justice/policies/privacy/docs/95-46-ce/dir1995-46_part1_en.pdf (last accessed August 20, 2014).
15. These promises are represented by Principle Investigator signatures on the individual informed consent forms, which they are authorised to sign by their institutions and employers creating an obligation, and a liability if the terms are not honoured.
16. Eichler et al., Open Clinical Trial Data for All? A View from Regulators, *PLoS Medicine* (April 2012) 9(4): 1-2.
17. Melissa Gymrek et al., Identifying Personal Genomes by Surname Inference, 339 *Science* 6117 (2013) 321-324.
18. European Medicines Agency, "Publication and access to clinical-trial data," EMA/240810/2013, June 24, 2013, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf (last accessed August 20, 2014).
19. Juran JM, Gryna FM. Juran's quality control handbook. 4th ed. New York: McGraw-Hill 1988.
20. Institute of Medicine, Assuring data quality and validity in clinical trials for regulatory decision making, Workshop Report (1999), available at: <http://www.ncbi.nlm.nih.gov/books/NBK224577/pdf/TOC.pdf> (last accessed August 20, 2014).
21. R.L. Richesson, J.E. Andrews (eds.), *Clinical Research Informatics*, Health Informatics, Springer-Verlag London Limited 2012 ("Reliability and validity address the underlying concept being measured. . . . Accuracy is important with respect to and intrinsic to the data value itself. . . . And completeness is a property of a set of data values.").
22. Eichler HG, et al. The risks of risk aversion in drug regulation. (Opinion) *Nature Reviews Drug Discovery* (Perspectives). 12(12):907-16 (2013).

23. Van Valkenhoef G et al. Deficiencies in the transfer and availability of clinical trials evidence: a review of existing systems and standards, *Medical Informatics & Decision Making* (2012) 12:95, 1-11.
24. Institute of Medicine, Discussion framework for clinical trial data sharing: Guiding principles, elements and activities (2014), available at: http://books.nap.edu/openbook.php?record_id=18610 (last accessed August 20, 2014).
25. Kuchinke et al., Heterogeneity prevails: the state of clinical trial data management in Europe – results of a survey of ECRIN centres, *Trials* (2010) 11:79.
26. Id.
27. US Food and Drug Administration, “Study Data Standards for Submission to CDER,” available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm> (last accessed on August 20, 2014).
28. Kuchinke et al., Heterogeneity prevails: the state of clinical trial data management in Europe – results of a survey of ECRIN centres, *Trials* (2010) 11:79.
29. Ohmann et al., Standard requirements for CGP-compliant data management in multinational clinical trials, *Trials* (2011) 12:85 (“In summary, there is no standard for GCP-compliant data management and the underlying IT infrastructure available, which is both generally applicable and practical, as well as being open and available free of charge.”); Ohmann et al., Revising the ECRIN standard requirements for information technology and data management in clinical trials, *Trials* (2013) 14:97.
30. Ohmann et al., Standard requirements for CGP-compliant data management in multinational clinical trials, *Trials* (2011) 12:85.
31. Siegel V., Reproducibility in research (editorial), *Dis Model Mech.* (2011) 4(3):279-280.
32. The Consolidated Standards of Reporting Trials, The CONSORT Statement (2010), available at: <http://www.consort-statement.org/> (last accessed August 20, 2014).
33. Id.
34. Anderson JA et al., Ethical reproducibility: towards transparent reporting in biomedical research (Commentary), *Nature Methods* (2013) 10(9):843-845.
35. Cardwell, CC et al., Exposure to oral bisphosphonates and esophageal cancer risk: A UK General Practice Research Database cohort study, *JAMA* (Aug. 2010) 304(6): 657-663; Green J et al., Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort, *BMJ* (2010) 341cc4444.
36. U.S. Food and Drug Administration, FDA Drug Safety Communication: Ongoing safety review of oral osteoporosis drugs (bisphosphonates) and potential increased risk of esophageal cancer (July 21, 2011), available at: <http://www.fda.gov/Drugs/DrugSafety/ucm263320.htm> (last accessed August 20, 2014).
37. McMullan V and Alston RP, Aprotinin and cardiac surgery: a sorry tale of evidence misused, *BJA Editorial III.* 110(5):675-678 (2013).
38. Henry D et al., Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion (review). *Cochrane Database Syst Rev* 2011: CD001886180.
39. European Medicines Agency, European Medicines Agency recommends lifting suspension of aprotinin (Feb. 17, 2012), available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/02/news_detail_001447.jsp&mid=WC0b01ac058004d5c1 (last accessed August 20, 2014).
40. Health Canada, Final report- Expert Advisory Panel on Trasylol® (aprotinin) (Sept. 15, 2011), available at: http://hc-sc.gc.ca/dhp-mps/medeff/advise-consult/eap-gce_trasylol/final_rep-rap-eng.php (last accessed August 20, 2014); European Medicines Agency, European Medicines Agency recommends lifting suspension of aprotinin (Feb. 17, 2012), available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/02/news_detail_001447.jsp&mid=WC0b01ac058004d5c1 (last accessed August 20, 2014).
41. National Institutes for Health, National Heart, Lung and Blood Institute, Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), available at: <https://biolincc.nhlbi.nih.gov/home/> (last accessed August 20, 2014); Yale School of Medicine, Yale University Open Data Access (YODA) Project, available at: <http://medicine.yale.edu/core/projects/yodap/index.aspx> (last accessed August 20, 2014).
42. Gotzsche PC, Why we need easy access to all data from all clinical trials and how to accomplish it, *Trials* (2011) 12:249.
43. Hopewell S et al., Publication bias in clinical trials due to statistical significance or direction of trial results (Review), *The Cochrane Library* (2009) Issue 1; Turner EH et al., Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy, *N Eng J Med* (2008) 358(3):252-260.
44. Kendall T et al., If NICE was in the USA, *Lancet* (2009) 374:272-273.
45. Mello M et al., Preparing for Responsible Sharing of Clinical Trial Data, *N Engl J Med* (2013) 369(17):1651-1658.
46. *The Economist*, Unreliable research: Trouble at the Lab, Oct 19, 2013, 26-30.
47. Wakefield AJ et al, Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children, *Lancet* (1998) 351:657-641 (now retracted).

48. Thomas D Rh et al., Rates of first measles-mumps-rubella immunisation in Wales (UK), *Lancet* (1998) 351: 1927; McBrien J et al., Measles outbreak in Dublin, 2000, *Pediatr Infect Dis J* (2003) 22(7):580-584; Ratzan SC, Setting the Record Straight: Vaccines, Autism, and the *Lancet* (Editorial), *Journal of Health Communication*, (2010) 15: 237-239.
49. Spertus JA, The Double-Edged Sword of Open Access to Research Data, *Circ Cardiovasc Qual Outcomes* (March 2012) 5:143-144.
50. Austin PC, Primer on statistical interpretation or methods report card on propensity-score matching in the cardiology literature from 2004 to 2006: a systematic review, *Circ Cardiovasc Qual Outcomes* (Sept. 2008) 1(1):62-67.
51. Qaseem A et al., Guidelines International Network: Toward International Standards for Clinical Practice Guidelines, *Annals of Internal Medicine* (2012) 156(7):525-531.
52. Carlson JJ et al., Linking payment to health outcomes: A taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers, *Health Policy* (2010) 96:179-190.
53. Fantoni M., Outcomes shape the new European payer networks. PMLive, Aug. 19, 2013, available at: http://www.pmlive.com/pharma_intelligence/outcomes_shape_the_new_european_payer_networks_493615 (last accessed August 20, 2014).

About Us

Avalere is a vibrant community of innovative thinkers dedicated to solving the challenges of the healthcare system. We deliver a comprehensive perspective, compelling substance, and creative solutions to help you make better business decisions. We partner with stakeholders from across healthcare to help improve care delivery through better data, insights, and strategies.

Contact Us

Avalere Health

1350 Connecticut Ave, NW Suite 900

Washington, DC 20036

202.207.1300 | Fax 202.467.4455

www.avalere.com