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# Perspectives on clinical trial data transparency and disclosure

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ABSTRACT

The increased demand for transparency and disclosure of data from clinical trials sponsored by pharmaceutical companies poses considerable challenges and opportunities from a statistical perspective. A central issue is the need to protect patient privacy and adhere to Good Clinical and Statistical Practices, while ensuring access to patient-level data from clinical trials to the wider research community. This paper offers options to navigate this dilemma and balance competing priorities, with emphasis on the role of good clinical and statistical practices as proven safeguards for scientific integrity, the importance of adopting best practices for reporting of data from secondary analyses, and the need for optimal collaboration among stakeholders to facilitate data sharing.



## 1. Introduction

Drug development is a complex and costly process that includes the collection, analysis and reporting of data from human subjects under strict protocols. Pharmaceutical companies routinely submit clinical trial results, as well as data, to regulatory agencies for licensing and other promotional activities pertaining to a new drug. In addition, pertinent information on the risks and benefits of medicinal products is communicated by publishing results of such trials in medical journals or presenting them at professional meetings. In recent years, there have been ongoing discussions among various stakeholders on the need to enhance confidence in the reliability of data reported by sponsors of clinical trials [1–6]. Accordingly, several measures have been instituted to enhance transparency through the establishment of registries for clinical trials as well as posting of basic results from such trials in publicly accessible electronic formats [7,8].

With the heightened focus on evidence-based medicine and comparative effectiveness research, there is now growing demand by third parties for enhanced transparency and disclosure of clinical trial data, with a view to advancing the field of medicine, accelerating drug development and approval, and protecting public safety. One common theme has been the importance of making widely accessible patient-level data from clinical trials, as well as other aspects of the trial, for the purpose of validating claims of sponsors or executing post-hoc analyses to address other research objectives [9–18].

In a recent draft policy statement, the European Medicines Agency (EMA) highlighted the need for access to clinical trial data and the associated issues [19]. Key elements addressed in the draft policy statement include the significance of enabling public scrutiny and secondary analysis of clinical trials for valid scientific and public health objectives, without compromising patient privacy and informed consent and stifling innovation and investment in biopharmaceutical research and drug development.

From the sponsors' perspective, data sharing presents both challenges and opportunities. Availability of patient-level data can help drug-developers to learn from the experiences of others, and use such data to inform trial design and hone their development programs. On the other hand, without proper mechanisms in place, the sharing of patient level data could have the potential to adversely impact public health, compromise patient privacy, and stifle innovation in drug development. The sponsors' views are encapsulated in a joint statement issued by

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the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) [20].

Incidentally, both EMA and EFPIA/PhRMA, while recognizing the scientific and public health value of data sharing, emphasize the importance of curtailing the risks of the potentially untoward effects of inappropriate secondary analyses and communication of results from such analyses. Viewed from a statistical standpoint, this calls for institutionalization and utilization of best practices to guard against known pitfalls of post-hoc analysis, and an effective management of operational issues associated with data sharing, including data standards, data quality and other infrastructural impediments.

In this paper we offer options to address competing priorities of diverse stakeholders, and share statistical perspectives on clinical trial data transparency and disclosure, with special emphasis on the importance of adherence to good clinical and statistical practices as sine qua non for enhancing confidence and establishing trust in evidence-based medicine, and the need for effective collaboration among all parties concerned to tackle procedural and operational issues to optimize the value of shared data to advance medical science without stifling innovation and compromising patient privacy.

The paper is organized as follows. In Section 2, we highlight the importance of Good Clinical Practice (GCP) in fostering transparency. Section 3 provided several statistical considerations that are pertinent to the issue. In Sections 4 and 5, we address the need for appropriate infrastructure to ensure optimal collaboration among stakeholders for effective clinical trial data sharing and disclosure.

## 2. Good clinical practice as a precondition for transparency

When it comes to establishing trust in the integrity of clinical trial data, there is no substitute for strict adherence to the principles of Good Clinical Practice (GCP) [21], whose central tenets require that clinical trials be conducted, analyzed and reported with the highest ethical and scientific standards, including ensuring maximum protection of the rights of human subjects, integrity and reproducibility of data, and transparency of study conduct. Key elements of these principles, as enshrined in the International Conference on Harmonization (ICH) of GCP guidelines (E6) [22,23], include:

- Adequate qualification of study personnel
- Primacy of the rights, privacy and well-being of study subjects
- Adherence to highest standards of scientific integrity and quality in the design, conduct, analysis and reporting of study
- Adherence to the Declaration of Helsinki
- State-of-the-art handling of data to ensure reproducibility.

Of particular importance are the safeguards that need to be in place for managing the data, notably the processes for collecting, cleaning and recording the data and monitoring the study. The data management plan should have detailed data handling procedures, including timelines for key activities, database design and validation, monitoring guidelines, data flow and tracking, data entry procedures, query handling, database back-up, database lock, and data archiving and security. An essential requirement for transparency is the need to have documentation for each trial activity, thereby creating a clear audit trail pertaining to actions of study personnel. The documentation effort should include data management Standard Operating Procedures (SOPs), which not only enhance transparency but also ensure consistency and proper communication in the conduct of a study that involves several staff members.

Good Statistical Practice (GSP) is an integral component of GCP that is critical to establish trust in the reporting of data by sponsors as well as in the evidence generated by third parties [24]. The hallmarks of GSP include pre-specification of hypotheses and analytical strategy, adequate rationale for study size and power, use of sound statistical tools, implementation of high quality data standards and effective quality control (QC) and quality assurance (QA) plans, and interpretation of results with fair balance. GSP presupposes a data management plan that carefully defines data handling rules, edits checks and dictionaries, as well as processes for trial monitoring, ongoing data review, database release and audit trails. In addition to an analytical approach that is grounded in the application of state-of-the-art methods and procedures, it is a vital facet of GSP to incorporate a clearly specified programming QC/QA plan which includes programming specifications, design and implementation.

## 3. Statistical considerations with data sharing

From statistical perspectives, the benefits of having access to patient-level data are inestimable, ranging from enhancing study design to assessing heterogeneity of treatment effects pooling information across various data sources. However, some of the issues that can impact effective data sharing have statistical import and require methodical approaches to mitigate the consequences. While problems of post-hoc analysis are very well known in the statistical community, other aspects of data sharing, such as de-identification of patient information to preserve patient privacy, or establishing standards and quality metrics for the data to be shared, are emerging areas that concern effective collaboration among stakeholders.

For trials intended for new drug application (NDA) or other regulatory submissions, the International Conference on Harmonization (ICH) E9 guidelines [25] provide extensive directions on steps to be taken to ensure transparency, including study design, trial conduct, analytical considerations, evaluation of safety, and reporting of results. The guidelines also address issues that are pertinent to the overall clinical development, including study population, design options to avoid bias, and definitions of study endpoints.

While ICH E9 principally focuses on the requirements for the primary analysis and reporting of data, these best practices should also be applied to secondary analyses from such trials. Indeed, the issues associated with secondary analyses tend to be even more complex and require additional measures to ensure the credibility of the findings.

When the focus of the secondary analysis is to replicate the sponsor's primary findings, it is critical that the data analyst has thorough familiarity with the original study objectives, planned analytical strategy, and other aspects of the study conduct and data quality. Deviations from the planned analysis must be justified, and may only be acceptable