Sharing individual patient data from clinical trials

In January 2015, the Institute of Medicine (IOM)[1] issued a consensus, peer-reviewed, publicly available report that recommends how to promote responsible clinical trial data sharing while minimizing the risks and burdens of sharing. This initiative was based on the following principles: (1) Maximize the benefits while minimizing the risks of sharing clinical trial data; (2) respect individual participants whose data are shared; (3) increase public trust in clinical trials and the sharing of trial data; and (4) conduct the sharing of clinical trial data in a fair manner.[2]

The IOM had to do a balancing act. On the one hand, the privacy and consent of clinical trial participants need to be respected. On the other hand, trial investigators would want a fair opportunity to publish their analyses and receive credit for carrying out trials and collecting data. Other investigators may want to analyze data that would otherwise not be published in a timely manner and to replicate the findings of a published paper. Sponsors would want to protect their intellectual property and commercially confidential information and be allowed a quiet period to review marketing applications. All stakeholders would want to reduce the risk of invalid analyses of shared data.[2]

The guiding principle of the committee's discussions and the report is that participants put themselves at risk to participate in clinical trials. The clinical trial community, therefore, has the responsibility to reward that altruistic behavior by widely sharing the information gathered so that as much useful knowledge as possible can be gleaned from the data. Data sharing was not thought to be without risk; two major risks the committee weighed were the possibilities that individual trial participants might be identified and that persons bent on discrediting the published work would perform rogue analyses based on fallacious assumptions or approaches.[3]

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Be that as it may, the question is why should or should not clinical trial data be shared with the public at large? And rather than share the consolidated manuscript from the end of study report, why should or should we not share individual patient data? When did this journey towards being honest, open, transparent start?

The bio-pharmaceutical industry, which is the significant contributor to data generation from clinical trials, has been plagued by concerns that the data are not always shared among the medical fraternity and even less so with the public. Evidence-based medicine used to be called evidence biased medicine since it was believed that negative studies would not get published. It was said that the eye (i) makes all the difference between based and biased, and that the trained eye can sift the wheat from the chaff. However, it has been increasingly seen that "negative" studies do get published. There is a journal for negative studies. No study is negative even if the primary endpoint has not been met or if it is prematurely terminated based on an interim analysis of the futility. Science advances when the study is published, and the next research builds on the strengths and addresses the limitations of the "failed" study. The Data Steering Committee or Data and Safety Monitoring Board take such decisions, even though, the sponsor's representative(s) may be on that committee/board.

Whose study is it anyway? People tend to feel that it is the sponsor's study and hence, if the study "fails," the sponsor will not want to publish the same. Nothing could be further from the truth. More than anyone else the sponsor would want to know (and let others know) at the earliest because a "failure" at a later stage in drug development can prove very costly. Furthermore, trust once lost can never be regained fully. The sponsor's representative may design a draft protocol which is discussed with clinician researchers at a protocol development meeting and by the time the draft is finalized it is no longer the sponsor's design. The case report form designed from such a protocol has data from the investigator's patients. Investigators are privy to the statistical analysis plan, the raw data, and can challenge the sponsor at end of study meetings before the study report is finally signed by all of them, leading to the manuscript, which again needs to be reviewed and approved by all

investigators before it is submitted to a peer-reviewed journal for publication.

I come back to the same question, whose study is it anyway? Isn't it a study of the doctors, by the doctors, and for the doctors and their patients, facilitated and funded by the sponsor? Then why can't all own the study equally? Sponsors also outsource studies to academic research organizations, with no control over content or conduct, to further enhance the credibility. It is in this spirit of candor that the industry has also opened itself up to the requests from both regulators and society and agreed to make individual clinical trial data public. After all, when patients participate in clinical trials with an altruistic motive, they must know what has been the outcome of their altruism. How has it indeed helped other patients?

But can this sharing be fraught with concerns? Can it backfire? Do all doctors know how to read the data, interpret the results, and more importantly be able to extrapolate the information to their clinical practice? Will the lay public know what to make of these data? What could be the possible repercussions? Will it impinge on patient confidentiality? In Germany, there is a portal which transparently reports real-time data on a daily basis on adverse events reported by doctors on a particular non Vitamin K antagonist oral anticoagulant. From this year, the European Medicines Agency will also host data from randomized controlled clinical trials.

How far is India from being able to implement this initiative? What could be the possible challenges that we will face? Will the different languages and dialects that Indians speak introduce a unique problem? All that I can say is that clinical research (CR) in India is going through so much of the turmoil that it may not need an additional complexity to handle. I am not sure we have the maturity to be the recipient of such data. Doctors, particularly those who have never done clinical trials (CTs), will need to understand how to read evidence, how to derive the right information from data, and more importantly be able to extrapolate these data to their practice. Responsible media, an oxymoron, will also need to gear itself up not to sensationalize this sharing and respect confidentiality of individuals. Sharing of individual patient data from clinical trials has a scientific objective and meets a societal unmet medical need, and should not be trivialized by people who may not have the intelligence to understand and apply the data judiciously.

From a medical perspective, it does help to further dissect data from clinical trials, even going down to individual patient level because one rarely comes across the head to head comparative studies among drugs in a new class. In such a situation, how does a doctor decide which is the best drug for his or her patient? If companies can make their clinical trial data available for analysis to see which patients responded the best to the experimental drug, it could help doctors match the right patient to a drug. There is a difference between what happens in randomized controlled clinical trials and the real world and there are limitations in generalizability. There are also limitations of indirect comparisons, network and other meta-analyses and other ways of comparing in the absence of the head to head, well-designed and adequately powered studies. Against this back-drop, if one could correlate clinical characteristics with response to a drug (both from an efficacy and safety perspective), one could possibly help clinicians in selecting the right patient for the right drug or regimen. In the spirit of competitive collaboration, companies could facilitate investigator-initiated pragmatic clinical trials designed to answer clinically relevant questions and not only if this drug is better than another.

In this context, the sharing of individual clinical trial data is important as it may well be the tool to tailor therapy to an individual. Precision medicine is what all are aiming for though the difference between accuracy and precision is that one may be precise (reproducible) but precisely wrong, so it is always better to be accurate and precise. Number needed to treat (NNT) or harm is sometimes calculated but since the same patient may experience both benefit and harm, NNT has been further refined as NNT unqualified success and number needed to harm (NNH) as NNH unmitigated failure, but ultimately it is still difficult to be able to match the right patient to the right drug and predict response. Medicine is not mathematics. A biological experiment is beset with variability and statistics can help towards reducing the standard error of the mean. But as Max Planck has said, "science cannot solve the ultimate mystery of nature. And that is because, in the last analysis, we, ourselves, are part of nature and therefore part of the mystery we are trying to solve."

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