Commentary

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Commentary: Data monitoring confidentiality and FDA transparency

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Clinical trials provide the data on which patients, clinicians, policy makers, and others rely to make decisions that impact the health, welfare, and resources of individuals and communities. Producing these data requires the cooperation of stakeholders whose interests can dovetail or conflict with one another, or with the requirements of sound science. The delicate task of effective regulation and oversight is to create structures and policies that align the interests of these stakeholders with the production of high-quality medical evidence and prevent any one stakeholder from co-opting the system for purely personal gain.[1] Rules that determine flow and control of information play a critical role in this process.

In 2008, the US Food and Drug Administration (FDA) issued guidance that alters the way that two oversight bodies—Data Monitoring Committees (DMCs) and the FDA—handle information during the development of drugs for type 2 diabetes mellitus.[2] In "Protecting the Confidentiality of Interim Data: Addressing Current Challenges," Thomas R. Fleming[3] describes procedures intended to permit DMCs to comply with this guidance while "preserving the essence of confidentiality." Out of a concern for the integrity of ongoing trials, he defends what I will call "moderated asymmetric" confidentiality, the view that DMCs should be permitted to disclose detailed interim trial data to the FDA but must not disclose it to other stakeholders, such as patients and their care givers. In what follows, I suggest that even if asymmetric confidentiality poses fewer risks to study integrity than symmetric disclosure of interim results, a broader defense of the regulatory innovations that make asymmetric confidentiality necessary is needed to justify the practice.

Altering regulatory practice

A fundamental challenge of research ethics is to mitigate the potential for conflict between the interests of the stakeholders whose efforts make the research enterprise possible. DMCs play an important role in mitigating the potential for conflict between the welfare of study participants and the interests of sponsors and the larger community in generating rigorous data from clinical trials. A DMC is an independent group of experts who have access to interim data from ongoing clinical trials with the fundamental mandate to protect the interests of study participants. They help to assure study participants that the risks to which they are exposed have been minimized to those necessary to answer the study question and that remaining risks are in some sense proportional to the value of the information the study is designed to generate. Under this mandate, DMCs can recommend that studies be terminated if there are clear concerns about the safety of interventions, clear evidence of efficacy, or for futility.

However, DMCs are also responsible for preserving the integrity of the studies they review. For this reason, it is widely accepted that DMCs must practice what I will call "symmetric confidentiality": they may review interim trial data but they may not disclose that information to any other stakeholder to the research enterprise.[4]

In contrast, the FDA plays a fundamental role in mitigating the tension between the profit motive of research sponsors, the interest of patients in timely access to medical interventions, and the public interest in ensuring the safety and efficacy of new drugs, devices, and biologics. To carry out its mission, FDA mandates that a wide range of data be submitted in support of a new drug application (NDA)/biologics license application (BLA), and when approval decisions are made, the FDA makes public the information on the basis of which licenses are granted. The comprehensive and transparent sharing of data from across the lifecycle of research is critical to the integrity of the research enterprise and to the public's trust in the independence and competence of this oversight agency.[5]

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In 2007, controversy erupted over the prospect that the popular diabetes drug rosiglitazone was responsible for an increase in cardiovascular (CV) morbidity and mortality.[6] CV disease is the leading cause of death and a significant cause of morbidity in people with type 2 diabetes and similar concerns surfaced for other drugs in this area. In response, the FDA released regulatory guidance in 2008 raising the bar for data required to approve a new diabetes drug. In addition to demonstrating efficacy for glycemic control, data must be submitted that rule out an unacceptable increase in CV risk as well. FDA will grant marketing approval if the sponsor can submit data indicating that the upper bound of the two-sided 95% confidence interval for the estimated risk ratio of the new intervention to control is less than 1.8. However, study sponsors must provide additional post-marketing data that rule out a relative risk ratio greater than 1.3.

Fleming describes a mechanism by which a single CV safety study could be conducted to meet these requirements sequentially. In 2011, this mechanism was used to support the approval of alogliptin. Interim data ruling out an increased risk of 1.8 from an ongoing CV safety study were submitted to FDA and used to support the drug's approval. However, neither the DMC nor the FDA disclosed these data to other stakeholders, such as study participants and their clinicians, until the study was completed and all available data were submitted to the FDA.[7] This sequential design empowers DMCs to share detailed interim study data with the FDA and requires regulators at the FDA to grant regulatory approval on the basis of data that they will keep confidential until the completion of the ongoing CV safety study.

Asymmetric confidentiality

Fleming argues persuasively that strict confidentiality of interim data is critical to maintaining the integrity of ongoing studies. Although this position is not without its critics,[8,9] this concern is widely regarded as sufficient justification for what I have called symmetric confidentiality, and I will not dispute this position here. If our fundamental concern in this area is with study integrity, however, then it is unclear why asymmetric confidentiality should be preferred to an alternative policy that preserves the symmetric confidentiality of interim findings. In other words, if concerns about CV risks in this domain are sufficiently credible to warrant the provision of additional data, then why not simply require a definitive CV safety study to rule out a specified upper bound on such risks (e.g. a 30% increase in risk) without a mechanism for interim approval? This preserves symmetric confidentiality of DMCs, ensures trial integrity by eliminating any possibility of prejudgment, preserves FDA transparency, prevents some unsafe drugs from entering the market and then having to be removed, and ensures that safety data are generated in a timely manner.

Presumably one concern with such an approach is that it further delays patient access to new medicines. But the clinical merit of an intervention involves a compendious evaluation of multiple dimensions, including side effects. Given the concerns about CV risk that motivated the 2008 change in guidance, an argument is needed demonstrating that the benefits and risks of early access in this domain outweigh the risks and benefits of delays from higher regulatory standards.

A different concern is that requiring a definitive trial with no provision for early approval will add to the time and expense of drug development, potentially discouraging new investment in favor of disease targets with lower regulatory hurdles.[10] Allowing approval when the more modest 1.8 increase can be ruled out increases the sponsor's time "on patent" while facilitating the timely provision of additional safety information. If we take the FDA's 2008 guidance as a compromise along these lines, then we can see Fleming's proposal as a way of trying to mitigate the degree to which early disclosure endangers the integrity of ongoing studies. Moreover, I call his view "moderated" asymmetric confidentiality because if interim data are used to grant regulatory approval of a new drug, then study participants will know that the investigational agent is probably not 80% worse than the comparator. In this case, some disclosure is made to all parties; the main difference lies in the detail of the information disclosed.

Nevertheless, even moderated asymmetric disclosure of information raises questions of fairness since the financial interests of funders are being accommodated at some risk to study integrity (efficacy data regarding glycemic control will be disclosed at approval and this may alter the behavior of some patients/clinicians), at some risk to the public (if interventions approved on strong interim results ultimately fail to rule out the 1.3 threshold), at some cost to the public's interest in transparent regulatory disclosure, and at some cost to trust in regulatory bodies (who have to explain why newly approved interventions are being black-boxed or withdrawn from the market).

The claim that interim findings used for regulatory approval should not be disclosed to patients because of the need to gather rigorous data about safety of an already approved drug is in deep tension with the decision to approve the investigational agent for clinical use while such concerns remain outstanding. Moreover, this argument is easily generalized, and Fleming[3] seems to countenance extending the blanket of confidentiality to whole studies, if separate studies are used to establish the different risk thresholds. What, then, are the limits on this new discretion to keep participants and the public in the dark about study results that are used to grant market approval if future studies are planned?

Conclusion

Fleming's recommendations seek to preserve the essence of confidentiality of interim results given the FDA's 2008 guidance. However, many of the concerns used to argue against symmetric disclosure of interim results also speak against the policy of asymmetric disclosure, and the legitimate concern to preserve study integrity cannot justify the background policy that motivates these recommendations. The legitimacy of asymmetric disclosure of interim results requires a broader defense, one that surveys the impact of this innovation on the interests of the various stakeholders to the research process and defends the merits of this proposal in comparison to the alternatives.

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