LETTERS

edited by Etta Kavanagh

Assessing Clinical Trial Results

IN HER POLICY FORUM “CLINICAL TRIALS RESULTS DATABASES: UNANSWERED questions” (13 Jan., p. 180), C. B. Fisher warns of several undesirable effects that might result from open access to raw data from clinical trials. Referring to the editorial policy of a new journal, Fisher suggests that “lack of emphasis on the direction of results or size ... risks diluting scientific standards for peer review.”

In fact, neither the size of a trial nor the direction of its results in itself determines the trial’s scientific validity. Certainly, it is vital that trials based on small numbers of participants and trials delivering negative results should not be overinterpreted. But, if properly conducted and controlled, small trials and trials with negative results can both make important contributions to medical knowledge.

For example, the sample size of a certain trial may be large enough to allow general conclusions to be drawn but may not have sufficient power to distinguish effects on a particular age group. By taking the raw data of several such small trials together, though, it may be possible to safely extend the conclusions beyond those of the original trials. The inclusion of results from trials with both positive and negative results is vital to such meta-analyses to ensure they are not statistically skewed.

Fisher also wonders whether “the availability of large bodies of data from studies that may or may not have scientific merit will improve or distract from the peer-review process.” Recent events in South Korea and elsewhere strongly suggest that making additional raw data available to peer reviewers whenever possible would be desirable. While not eliminating the possibility of fraud, it would at least make it less straightforward and so, arguably, less tempting.

Finally, Fisher worries that, by making available early data from clinical trials, drug companies may fall afoul of regulations relating to “forward-looking statements.” However, the data from trials are not forward-looking statements, they are reports of concrete past events. It is difficult to see how making these records available in a transparent fashion could be seen as misleading. Of course, some investors may overinterpret promising early results, just as they may overinterpret a profitable first quarter, but if companies clearly warn against overinterpretation, they should not be held accountable for it.

Any science, including published peer-reviewed research, may be abused by misinterpretation. This should not be used as a justification for hiding important data behind closed doors.

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References and Notes

3. A set of guidelines that take an evidence-based approach to improving the quality of reports of randomized trials.

THE INTERESTING POLICY FORUM BY C. B. FISHER “Clinical trials results databases: unanswered questions” (13 Jan., p. 180) contains some misconceptions that warrant comment.

First, the overarching rationale for full disclosure of trial information has been to fulfill ethical obligations to trial participants, who are subjected to potential risks in exchange for the creation of public knowledge. Although potentially important, other competing concerns raised by Fisher must be subsidiary to this fundamental ethical responsibility.

Second, Fisher confounds trial results with trial methods when discussing the validity of peer-reviewed, open-access publications. An appropriately designed study is scientifically valid regardless of its findings or size alone. Small studies may provide less precise yet valid results; precision can be increased by pooling data across studies through meta-analysis. Thus, the publication of all properly conducted trials regardless of the nature or magnitude of their results will help to address the biases associated with selective reporting of research.

Third, an unjustified assumption underlying much of the paper is that peer-reviewed results are inherently better—an unresolved issue that is neither new nor specific to results databases (1). On the basis of empiric evidence, the scientific value

IN HER POLICY FORUM “CLINICAL TRIALS RESULTS DATABASES: UNANSWERED questions” (13 Jan., p. 180), C. B. Fisher equates negative trial results with poorly conducted trials. There is no evidence that this is the case. Rather, the existence of a bias toward the publication of positive outcomes is not only well known (1), but documented examples underscore its effects: Inclusion of unpublished data can sometimes abuse by misinterpretation. This should not be used as a justification for hiding important data behind closed doors.

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Cockerill and Norton and Chan et al. emphasize the value of clinical trials for specific types of stakeholders. I agree that medical science benefits when other scientists can evaluate raw data from published studies and that one advantage of transparency is that trial participants can learn how their efforts contributed to public knowledge. However, the range of individuals who will be affected by the quality of clinical trials databases goes beyond these two segments and includes the general public, patients, practitioners, health management organizations and other third party payors, and federal and private sponsors of research. For example, although investigators and sponsors may recognize that reporting of early data is not meant to be “forward-looking statements,” various proposals for databases that include public summaries or implications of early results may inadvertently push sponsors in that direction or create a loophole in current regulations meant to protect the public.

In response to Veitch’s Letter, it is good to see more detail on the steps that PLoS Clinical Trials will take to increase transparency of research reporting. However, the additional information she provides does not change the value of the question posed in my Policy Forum. What will be the effect on established scientific standards of peer review and public confidence in these standards when investigators and the public are inundated with trial results that fail to confirm or disconfirm hypotheses, yield small effect sizes, or use sample sizes insufficiently powered to disprove that results are true? We have not yet seen peer-reviewed results in clinical trials databases.

In the absence of a more formal international ethics framework specific to stem cell research, some countries have added more stringent and effective practices. Licensing requirements ensure the competence of personnel and the quality and safety of stem lines and verify the informed consent of patients. Equivalence requirements ensure that the importation or exportation of stem cell lines is limited to countries that meet the ethical requirements of the host country and are lawful in the importing countries. Sunset clauses (6) in guidelines or laws ensure continual review of changing scientific and socioeconomic norms. Additional requirements include monitoring the research using the established lines in stem cell banks.

Recent evidence of scientific fraud and unacceptable egg donor procurement practices in South Korea (7) highlights the importance of regulation as an emerging issue in this field. Scientific responsibility and integrity must be promoted with attention to possible economic and political influences that might negatively affect researchers. Incentives for open exchange, registration, and validation of results need to be controlled carefully.
identified. The conditions (such as financial gain, informed consent, protections of confidentiality, and privacy of the donor) for egg donation for IVF treatment should be distinguished from the conditions surrounding egg donation for research purposes, and potential egg donors should be informed clearly as to the intended uses of their eggs. The failure to follow good ethical practices in egg donation could result in a loss of trust and reluctance to donate among prospective donors. The scarcity of human ova available for research makes human-animal chimeras more attractive, but the application of chimeras to stem cell research requires conceptual clarification and attention to its ethical dimensions. Finally, transparency on the powers and the composition of the necessary oversight bodies is a sine qua non for all stem cell research irrespective of a country’s position.

INTERNATIONAL STEM CELL FORUM ETHICS WORKING PARTY

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References and Notes
2. Australia, Canada, China, Czech Republic, Denmark, Finland, France, Germany, Italy, Israel, Japan, Netherlands, Singapore, Switzerland, Sweden, United States, and United Kingdom.
3. Austria, Cyprus, Costa Rica, Italy, Ireland, Lithuania, Norway, and Poland.
4. Belgium, Japan, Singapore, South Korea (not an ISCF member), Sweden, United Kingdom, and several U.S. states (MA, CA, and NJ).
6. A sunset clause is a provision in a statute or regulation that terminates or mandates review of all or portions of the law after a specific date.

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