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.
of peer review remains unclear (2, 3). Nevertheless, references to trial results should thus continue to indicate their data source to distinguish peer-reviewed and non-peer-reviewed results.

What is clear, however, is that critical appraisal of trial methodology remains vital for placing a set of results into its appropriate context. Sufficient methodological information must therefore accompany all trial results, whether in a results database or journal.

Full results disclosure will improve the status quo of subjective, selective reporting and data suppression. Being fully transparent with numerical data is the only solution free of subjective judgment. As the global, neutral body with legitimacy and international support, the World Health Organization International Clinical Trial Registry Platform (www.who.int/ictrp) will continue its leadership role in consulting all constituencies to define global norms and standards for trial registers and results databases (4).

Response

I AM PLEASED THAT MY POLICY FORUM HAS prompted discussion on the value of clinical trials databases and ways to ensure that, whether created by industry, government, or international organizations, they benefit all who have a stake in the development of safe and effective health products.

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 generate scientifically valid conclusions?

Timely and transparent reporting of clinical trials results is essential to public health and public confidence. To fulfill this mission, those who are lobbying for or creating clinical trials databases must ensure that such sites are of equal benefit to the multiple stakeholders in the development of health products worldwide.

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Ethics Issues in Stem Cell Research

THE INTERNATIONAL STEM CELL FORUM (ISCF) supports research on all stem cell types, including adult stem cells, embryonic stem cells, and stem cells from umbilical cord blood (1). The Ethics Working Party (EWP) of the ISCF has 19 participants from 17 (2) countries. In 2004, the EWP defined its mission as (i) clarification of ethical issues and, where possible, the international harmonization of ethical standards; (ii) the sharing of stem cell lines; and (iii) an agreement on standards for the characterization and registration of lines. As it pursued this mission, by conducting ongoing study of regulatory approaches to human embryonic stem cell research in 50 countries, the EWP identified certain international trends, effective practices, and emerging issues that require further discussion and clarification.

International trends include the following. A small number of countries prohibit all embryonic stem cell research (3). Most other countries either permit in vitro research with embryos with no mention of stem cells, limit the creation of stem cell lines to surplus in vitro fertilization (IVF) embryos under certain conditions (such as governance, accreditation, ethics review, and restrictions on research objectives), or limit research to imported cell lines. Seven countries (4) explicitly permit the creation of embryos for research purposes, but it must be shown that the research cannot be achieved with the use of other stem cell lines (such as IVF embryos or adult cell lines). All 50 countries studied prohibit or strongly discourage human reproductive cloning (through laws or guidelines). In most countries that allow human embryonic stem cell derivation from human embryos, there are shared principles as well as professional norms and substantive and procedural conditions that further constrain this work. Currently, common principles and procedures include respect for human dignity (5); respect for life (limiting growth to 14 days, at which time the primitive streak forms); autonomy (requirement for informed donor consent); donor and/or patient privacy and confidentiality; noncommercialization (prohibiting the buying and selling of embryos); avoidance and declaration of conflicts of interest; limitation to therapeutic purposes (in contrast to reproductive cloning); ethics review before commencement of study; and the traceability of cell lines with respect to their sources.

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 participants. 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 country. 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
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.

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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.