EDITORIAL

The past, present and future of clinical research

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Clinical trials have been fundamental in fostering the development of novel treatments in medicine and for understanding disease mechanisms. One important issue in this field is how they continue to change over time. For example, a recent study analyzing clinical trials in psychiatry over the past 60 years showed substantial changes in the use of statistical methods in the reporting of abstracts and results, as well as increased use in recent trials of informed consent, washout periods, the intention-to-treat approach and parametric tests.[1]

Many of these changes have been shaped by historical events. For example, the development of ethical guidelines has been marked by three milestones: the Nuremberg Code[2] made voluntary consent mandatory for clinical research; the Declaration of Helsinki[3] codified the ethical principles for human experimental research and the infamous Tuskegee Syphilis Study[2] led to the Belmont Report, which increased protection for human research subjects and defined informed consent in different research settings.

Another important historical event that has shaped clinical research is the issue of adverse effects associated with novel interventions. One of the landmark examples is the use of thalidomide, which resulted in unexpected harm to the fetus. Here, the development of study phases (phases I, II, III and IV) and additional pre-clinical studies has greatly increased the safety of new drugs and devices.

Regulatory changes have also been important in increasing the safety of clinical trials. A heated debate is currently taking place on the use of placebos and the further development of non-inferiority trials. At the same time, some scientists claim that ethics committees are becoming overly bureaucratic and not fulfilling their mission well.[4] Options for balancing the prevention of unethical behavior with the promotion of research include decreasing the length of research proposals and informed consent forms, and giving different review processes according to the risk of the intervention and the benefits to patients.

Clinical trial reporting has also been constantly developing to increase transparency in clinical research. One example is the database registry clinicaltrials.gov,[5] which has had a significant impact on clinical research. This is also the case for the Consolidated Standards of Reporting Trials (CONSORT),[6] an important effort to improve transparency in reporting randomized controlled trials so that readers can better understand a study's design, methodology and the validity of its results.[7]

Globalization is also having important effects on the conduct of clinical research. Brunoni and Fregni[1] found that more multicenter trials are being conducted. Glickman et al.,[8] who discuss the economic benefits of globalization, found that clinical trials increasingly occur on a global scale and claim that one-third of trials are now being conducted in developing countries,[9] as pharmaceutical and medical device companies have embraced globalization.[8] This clearly raises numerous ethical concerns, including the testing of drugs for wealthy populations in human subjects of developing countries, the exacerbation of economic disparities and exploitation of low-income workers in developing countries, and their exposure to potentially dangerous drugs that could not be approved for testing in developed countries.

With this rapidly changing environment and increasingly complex system, the training of clinical researchers becomes ever more critical. One of the topics in clinical research that needs to be addressed is the increasing number of studies that use complex statistical analyses which can be difficult for readers to interpret.[10] Standard clinical research training requires students to be present on site, but this prevents some from participating owing to limited time and funds. One of the more innovative models of training programs for clinical researchers uses the principle of collaborative learning,[11] in which participants build and learn by discussing the concepts and ethics of clinical research in a course forum that blends live lectures (via video-conference) with online discussion and small-group work with highly trained teaching assistants.

One final issue is that with the increasing complexity of biomedical research, translational research has also become more complex. The immediate consequence is that discoveries at the laboratory bench may not be translated into full clinical trials to validate them.[12] The U.S. National Institutes of Health (NIH) is aware of this problem and has created ''the Clinical and Translational Science Awards (CTSA) Consortium'' to link institutions in an attempt to catalyze translational research.[13] However, researchers need to be engaged in order for the program to succeed.

In conclusion, the often painful lessons from the past have made clinical trials safer and contributed to development of

Azeka E, Fregni F, Auler Junior JOC. The past, present and future of clinical research. Clinics. 2011;66(6):PAGES

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novel treatments. However, in the era of globalization, new ethical challenges arise as does the need for training programs to promote the development of discoveries in medicine.

ACKNOWLEDGMENTS

The authors are grateful to Kayleen Weaver for copyediting this manuscript and to the reviewers of this manuscript for their helpful comments.

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