

EDITORIAL OVERVIEW

Challenges in the evaluation, consent, ethics and history of early clinical trials – Implications of the Tuskegee 'trial' for safer and more ethical clinical trials

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The ethical and scientific challenges of early-phase clinical trials

Currently, the earliest-phase clinical trials are designed to test drug safety. Although everyone agrees that this is a lofty aim, doctors and scientists face the challenge of explaining to patients and their families why it is worth participating in such early trials. After all, these are strictly toxicity trials, and are not aimed at determining the efficacy of new treatments. Nevertheless, despite increasing doubts, the process of limiting early-phase clinical trials only to the identification of safe drug doses appears to be engraved in stone [1].

The issue is not in pursuing a toxicity trial per se, as most clinical trials collect toxicity data as part of their protocol. The point of contention is that early-phase clinical trials are restricted exclusively to assessing the safety of a new treatment [2-4]. Why is efficacy not considered during phase I clinical trials? During phase I trials, little is known about the effective drug dose and, therefore, dose escalation of a new drug is used to identify the safe dosing range. The challenge, of course, is to determine what constitutes a safe dose, which is usually the dose that does not exert any toxic side effects.

The problem with this approach is that it begs the following question: how do we know that the dose that will have no toxic effects will be effective? The answer is that we do not know and, further, that we have no information demonstrating that a safe dose will indeed be effective. We first need a safe dose to determine if a drug is effective, and therefore, a safe dose is identified before we try to determine if this dose is indeed effective.

Patients could ask why they should volunteer for phase I trials from which they are not supposed to benefit, especially when suffering from incurable diseases. On the other hand, there is much experience in many fields, particularly cancer, where drugs have indeed moved from being safe drugs to being effective drugs, and this historical record is what maintains the current approach as a suitable one to continue pursuing.

Nevertheless, an important question that needs to be addressed is why early-phase clinical trials do not assess toxicity and effectiveness simultaneously. The standard answer is that this would be impossible, as it would compromise the quality of early phase I clinical trials. The safe dose needs to be identified first, and whether this dose is actually effective needs to be determined at a later stage. The rationale is to first identify a safe dose in a smaller number of patients, and then to determine the efficacy of the dose in a later trial; as efficacy trials are usually statistically powered to detect small differences, large numbers of patients (usually in the hundreds or thousands) are used in phase III trials. In this way, when patients are asked to participate in an early-phase trial, they are contributing to finding the safe dose, but are potentially also helping to identify the effective dose for a new treatment and, thus, they may eventually benefit therapeutically from such trials.

The fact that this ethical rationale of the two-tiered approach has been accepted by the medical community has hampered the continued search for alternative early-phase clinical trials that assess toxicity and efficacy simultaneously. However, unless such an initiative is more strongly supported by patients, doctors, scientists, statisticians and, eventually, the pharmaceutical industry, the status quo is unlikely to change [1-8].

An historical inquiry into the evolution of clinical ethics

Can history help to address the challenge of not only what to tell patients and what we ask them to sign, but also what patients believe and what they understand about patients' rights when participating in clinical trials? In the early 1930s, a study began in Tuskegee, Macon County, AL, USA. The purpose was to document the progression of untreated syphilis in black males [9,10]. The study was funded by the US Public Health Service and involved almost 600 men, approximately two-thirds of which suffered from syphilis, and one-third of which represented healthy controls. The researchers decided that as most black men in the area would go through life untreated, they would simply document the progression of the disease. The objective of the study was to understand the natural progression of untreated syphilis in black males. Although the objective of the study was not to develop new treatments, the proponents of this 'trial' possibly thought that a better understanding of the natural history of the disease would aid in its future treatment.

Although the patients were not directly paid for the study, they were offered alternative benefits that, given the conditions under which these men lived, were in effect indirect inducements to participate. In addition, the patients were led to believe that they were part of a joint federal and local medical program to provide them with healthcare, and thought they were receiving treatment for an ill-defined 'bad blood'. The participants were not told specifically that they would not be treated, but were told that if they were to be treated elsewhere, they would then be excluded from the benefits associated with this study.

Although early treatments for syphilis were not considered particularly successful, mercurials, arsenates (such as salvarsan) or pyrotherapy were never offered to the men who participated in the Tuskegee study. Even after penicillin became available as the treatment of choice for syphilis in the late 1940s, it was never prescribed to any of the infected men. And, although a meeting of the CDC in 1969 determined that the study would neither limit disease progression, nor cure any patients, the study was surprisingly allowed to continue. It was only a few years later when the press reported on the Tuskegee study that the Department of Health, Education and Welfare acted to stop it. It was at that time that the Tuskegee Syphilis Study Ad Hoc Advisory panel was formed to investigate the study. The panel concluded that the study was ethically unjustified because of lack of informed consent from the patients, and because of the lack of treatment with penicillin after the drug had become available [1,11].

Implications of history and ethics on the future of clinical trials

Nowadays, patients would find it difficult to complain of not knowing the true intent of early-phase clinical trials, as they need to sign informed consent forms in which the details associated with the trial are clearly described. Similarly, they would not be able to complain of not being

offered the best possible treatments, as they freely enter such clinical trials when the best possible treatment is truly unknown. However, in spite of the legal safety provided by the signing of informed consent forms, many studies have shown that even after being informed of the lack of efficacy of phase I trials, a large majority of patients still believes that the trial will benefit them [4,12-15]. Moreover, patients are not always informed of the potential alternatives available to them at the same, or possibly other, research centers, and are unavoidably subjected to some of the same pressures (advertently or, most likely, inadvertently) and some of the same difficult situations and choices that patients were subjected to during the Tuskegee Syphilis Study.

It is undoubtedly true that patients nowadays, in great measure as a positive outcome from the Tuskegee Syphilis Study, have many more protections compared with patients in Macon County in the 1930s. Nevertheless, there is still a quantum of uneasiness regarding early-phase clinical trials that bear a nontrivial resemblance to the situation that patients underwent in the Tuskegee study [16,17]. For example, patients likely believe that phase I clinical trials will offer treatment for their ailments, that there is sufficient evidence for the trial to go ahead, and that all potential toxicities to be encountered have already been detected in preceding animal experiments [15]. The deaths of patients in early-phase clinical trials, and the fact that most phase I clinical trials never progress to phase III trials, indicate that many such beliefs are mistaken. In addition, as was the case in the Tuskegee study [8,18,19], physicians will often still benefit from scientific publications reporting findings from trials that have no benefit to patients, and for compounds that are never fully tested for therapeutic efficacy in phase III trials.

Although most scientists will argue that there is no other way to proceed with clinical trials, the truth is that there are alternative ways to implement novel trials. Powerful alternative statistical methods are available that would allow the simultaneous recording of treatment efficacy and toxicity, and highly accomplished statisticians have been trying to implement such types of trials in practice [20-23]. However, there are issues regarding the acceptance of novel statistical analyses both by the community of statisticians and the community of regulators, and these issues continue to relegate novel clinical trial approaches to the background. Interestingly, statisticians working mainly within the field of Bayesian statistics have called for novel types of early-phase clinical trials from an ethical perspective, asking whether it is ethical to perform early-phase clinical trials that do not measure efficacy [5-7]. Additionally, these statisticians have developed methods that, if applied, could indeed simultaneously determine whether drugs tested in early-phase clinical trials are toxic and effective [5-8].

An early-phase clinical trial that would simultaneously assess efficacy and toxicity would be strongly supported

from an ethical standpoint, and would even allow an accelerated assessment of the efficacy of novel drugs [6,7]. Also, if earlier-phase trials with smaller numbers of patients could provide scientifically and statistically credible results of drug efficacy and toxicity, the need for large phase III clinical trials could be reduced [5-8,20-23].

Finally, this proposed approach is closely linked to the statistical misreading of many clinical trial results. Many trials continue to obtain very small differences between treated and control groups. Large phase III trials are regularly used to demonstrate the effectiveness of a treatment, an effectiveness that is only at that stage tested for its statistical significance and that, in many cases, is only a minor improvement [24,25]. The testing of large numbers of patients to obtain small differences poses an ethical dilemma, which has so far remained unaddressed [8].

Equally disturbing are the results of large phase III clinical trials that, because of their exceedingly long duration and complexity, arrive at statistically significant results only because data have been compared either with historical controls, or with data from control patients receiving treatments that, by the time such results are publicized, have a worse outcome than contemporaneous standard-of-care therapies; thus, there are challenges in how to analyze trials that take a long time to complete when historical controls are superseded by novel, more efficacious standards of clinical care. In such cases, when at the time of trial completion contemporaneous standard of care is known to be better than the drugs on the trial, is it ethical to say that the phase III clinical trial, which has cost millions of dollars and involved numerous patients, has worked, or should patients be diverted to be treated at those centers that can offer the best contemporaneous treatment available?

The issues discussed in this editorial are clearly complex, and cover several scientific arenas ranging from clinical practice through to statistics, mathematics, clinical trial design, regulatory affairs, governmental agencies, patient populations, the pharmaceutical industry and academia, among others. Nevertheless, it is time that a task force began to address how clinical trials can be implemented in the future to further advance the care and treatment of patients, taking into account the historical, ethical, scientific and clinical challenges imposed by a vulnerable population of patients who are desperate for novel and effective therapies for some of the most devastating diseases, such as cancer.

Author contributions

Pedro R Lowenstein conceived the idea for this editorial and wrote the first draft of the text, Elijah D Lowenstein researched the Tuskegee trial, and provided the corresponding text and references, and Maria G Castro participated in discussions concerning the ideas presented in the editorial, reviewed the manuscript and oversaw its timely completion. All authors reviewed and approved the final text.

Suggested reading

1. Emanuel EJ, Crouch RA, Arras JD, Moreno JD, Grady C (Eds): *Ethical and Regulatory Aspects of Clinical Research*. The Johns Hopkins University Press, Baltimore, MD, USA (2003).
2. Lowenstein PR: **Clinical trials in gene therapy: Ethics of informed consent and the future of experimental medicine.** *Curr Opin Mol Ther* (2008) **10**(5):428-430.
3. Lowenstein PR: **A call for physiopathological ethics.** *Mol Ther* (2008) **16**(11):1771-1772.
4. Kimmelman J: **The ethics of human gene transfer.** *Nat Rev Genet* (2008) **9**(3):239-244.
5. Berry DA: **Bayesian clinical trials.** *Nat Rev Drug Discov* (2006) **5**(1):27-36.
6. Kadane JB: **Progress toward a more ethical method for clinical trials.** *J Med Philos* (1986) **11**(4):385-404.
7. Kadane JB (Ed): *Bayesian Methods and Ethics in a Clinical Trial Design*. John Wiley & Sons, Chichester, UK (1996).
8. Ziliak ST, McCloskey DN (Eds): *The Cult of Statistical Significance*. The University of Michigan Press, Ann Arbor, MI, USA (2009).
9. Lederer SE (Ed): *Subjected to Science: Human Experimentation in America Before the Second World War*. The Johns Hopkins University Press, Baltimore, MD, USA (1995).
10. Jones JH (Ed): *Bad Blood: The Tuskegee Syphilis Experiment*. Free Press, New York, NY, USA (1993).
11. **Final Report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel.** US Department of Health, Education, and Welfare. Public Health Service, Washington DC: Government Printing Office (1972) HE 20.2:T 87.
12. Piantadosi S: **Rigor in monitoring clinical trials is ethical.** *J Clin Oncol* (2008) **26**(4):683-685.
13. Fetting JH, Siminoff LA, Piantadosi S, Abeloff MD, Damron DJ, Sarsfield AM: **Effect of patients' expectations of benefit with standard breast cancer adjuvant chemotherapy on participation in a randomized clinical trial: A clinical vignette study.** *J Clin Oncol* (1990) **8**(9):1476-1482.
14. Piantadosi S: **Hazards of small clinical trials.** *J Clin Oncol* (1990) **8**(1):1-3.
15. Kim SY: **Assessing and communicating the risks and benefits of gene transfer clinical trials.** *Curr Opin Mol Ther* (2006) **8**(5):384-389.
16. Frank SA, Wilson R, Holloway RG, Zimmerman C, Peterson DR, Kiebertz K, Kim SY: **Ethics of sham surgery: Perspective of patients.** *Mov Disord* (2008) **23**(1):63-68.
17. Kim SY, Frank S, Holloway R, Zimmerman C, Wilson R, Kiebertz K: **Science and ethics of sham surgery: A survey of Parkinson disease clinical researchers.** *Arch Neurol* (2005) **62**(9):1357-1360.
18. Schuman SH, Olansky S, Rivers E, Smith CA, Rambo DS: **Untreated syphilis in the male negro; background and current status of patients in the Tuskegee study.** *J Chronic Dis* (1955) **2**(5):543-558.
19. Rivers E, Schuman SH, Simpson L, Olansky S: **Twenty years of followup experience in a long-range medical study.** *Public Health Rep* (1953) **68**(4):391-395.
20. Houede N, Thall PF, Nguyen H, Paoletti X, Kramar A: **Utility-based optimization of combination therapy using ordinal toxicity and efficacy in phase I/II trials.** *Biometrics* (2009):doi:10.1111/j.1541-0420.2009.01302.
21. Thall PF: **A review of phase 2-3 clinical trial designs.** *Lifetime Data Anal* (2008) **14**(1):37-53.
22. Thall PF, Wathen JK: **Practical Bayesian adaptive randomisation in clinical trials.** *Eur J Cancer* (2007) **43**(5):859-866.

23. Wathen JK, Thall PF: **Bayesian adaptive model selection for optimizing group sequential clinical trials.** *Stat Med* (2008) **27**(27):5586-5604.
24. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D *et al*; National Cancer Institute of Canada Clinical Trials Group: **Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group.** *J Clin Oncol* (2007) **25**(15):1960-1966.
25. Miksad RA, Schnipper L, Goldstein M: **Does a statistically significant survival benefit of erlotinib plus gemcitabine for advanced pancreatic cancer translate into clinical significance and value?** *J Clin Oncol* (2007) **25**(28):4506-4507.