



Ethics of Clinical Trials in Low-Resource Settings: Lessons From Recent Trials in Cancer Medicine

Randomized clinical trials in cancer medicine are increasingly conducted in low- and middle-income countries (LMICs). The proper way to conduct such studies is complex and the subject of much debate.¹ Two key questions outline the debate. First, what is the appropriate control arm for such studies? For example, when can trials use placebo or some control less than global best practice? Second, what obligations do trial sponsors have toward host nations and communities?

These key questions were first debated more than a decade ago in the context of clinical trials in Africa, which tested shorter, cheaper courses of zidovudine against placebo to prevent perinatal transmission of AIDS. Critics argued that these placebo-controlled trials were unethical and that control participants should have access to the longer, full course of zidovudine used elsewhere in the world. Proponents countered that only placebo-controlled trials could answer the relevant question: whether an affordable course of therapy is better than the actual practice of doing nothing, and not the ideal, but unrealistic question: whether a shorter course is noninferior to a longer course. In recent months, these questions have regained relevance as recent trials recapitulate these tensions.

Citing recent examples in cancer medicine, we argue that placebo-controlled trials may be ethical but only if the intervention being tested has a reasonable chance of being implemented in the host community.

WHAT IS THE APPROPRIATE CONTROL ARM FOR TRIALS IN LOW-RESOURCE SETTINGS?

Advanced cervical cancer, now infrequently encountered in developed nations, carries a substantial global burden.² Unfortunately, universal screening programs that use cytology-

based techniques that have been credited with transforming outcomes have been deemed impractical or unaffordable in low-resource settings.³ For this reason, several randomized controlled trials have tested whether a low-cost cervical cancer screening program can improve outcomes. In a recent large, randomized trial conducted in India, Shastri et al³ tested whether four successive biennial visual inspections with acetic acid (VIAs) performed by public health workers could reduce cervical cancer mortality. VIAs involve a process in which a trained health care worker uses a speculum and applies dilute acetic acid (vinegar) to the cervix and is able to directly visualize abnormal preneoplastic tissue that turns white. The results of the Shastri study were positive and showed 31% relative risk reduction in cause-specific death. As a result, this intervention has been hailed as a realistic, affordable cervical cancer screening program with the potential of saving 22,000 lives per year. But because the study used a control arm that received the local standard of care (no screening), it has been criticized as unethical.^{4,5} However, India had already deemed a screening program with cytology impractical and, in practice, it is seldom performed. We believe the study is ethical and meets the standard for such trials in low-resource settings. We support this because in India, there is no universal cervical cancer screening, and the burden of disease is high. Furthermore, the study by Shastri et al was reviewed by the US National Cancer Institute before funding, was approved by a local institutional review board, and was reviewed annually by the institutional review board and a data safety and monitoring committee.

Discouraging studies like that of Shastri et al³ would limit the ability of individual nations to set

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their own research agenda and conduct trials they deem important. Furthermore, diffuse criticism of screening studies in LMICs diverts attention from truly unethical trials, which explore questions that will not benefit the country in which the trials are conducted. The study by Shastri et al provided the highest level of evidence that VIAs save lives and can be reasonably expected to benefit the host population in India and other LMICs with high burdens of cervical cancer and no cytology-based universal screening programs.

IS THERE A REASONABLE EXPECTATION OF BENEFIT FOR THE HOST POPULATION FROM CLINICAL TRIALS?

Some have argued that sponsors must not only provide benefit to the individual patients on trials but must also provide health-related resources to the host community and help with infrastructure development. Others submit that sponsors and investigators should ensure that participation in such trials is voluntary, that individual participants are provided fair benefits for their participation, and that this is the sole requirement for ethical research.¹

We take a middle position. Sponsors and investigators should not be expected to provide health-related resources and infrastructure to the host community in which they conduct clinical trials. Conducting clinical trials is expensive, and in today's economic environment, an expectation to provide additional, post-trial services could be prohibitive and discourage sponsors from supporting rational trials. We do believe, however, that when trials in low-resource settings reach positive conclusions regarding an intervention's benefit, that intervention should be reasonably likely to be implemented by the community in which the trials are conducted.

This tension is best illustrated in two recent examples. The first is that of afatinib (Boehringer Ingelheim, Ingelheim, Germany), a next-in-class epidermal growth factor receptor (EGFR) inhibitor in patients with lung cancer harboring *EGFR* mutations. The IPASS (First Line IRESSA Versus Carboplatin/Paclitaxel in Asia) trial published in 2009 found that patients with non-small-cell lung cancer (NSCLC) and activating mutations in *EGFR* had a marked progression-free survival benefit (9.5 v 6.3 months) and improvement in the quality of their life when treated with gefitinib (AstraZeneca, London, United Kingdom), an anti-EGFR-targeted drug, compared with standard chemotherapy.⁶ These results led the European Medicines Agency to approve gefitinib for this indication on June 24,

2009, and in turn led to an international best practice of using targeted agents as the initial therapy in patients whose tumors harbor *EGFR* mutations. Yet from August 2009 to November 2011, LUX-Lung 3 (BIBW 2992 [Afatinib] Versus Chemotherapy as First Line Treatment in NSCLC With *EGFR* Mutation) and then LUX-Lung 6 (LUX-Lung 6: A Randomized, Open-label, Phase III Study of BIBW 2992 Versus Chemotherapy as First-line Treatment for Patients With Stage IIIB or IV Adenocarcinoma of the Lung Harboring an *EGFR* Activating Mutation) randomly assigned more than 1,200 and 910 patients, respectively, with NSCLC harboring *EGFR* mutations to either afatinib or cytotoxic chemotherapy.^{7,8} Both studies were performed largely in LMICs and, in effect, addressed the question previously answered by the 2009 IPASS study: Is there value in using an EGFR-targeted agent over conventional chemotherapy? From our perspective, the ethics of these trials hinged on whether afatinib was somehow more affordable or feasible for use in the nations where the trial was conducted. But unfortunately at a cost of \$79,000 per year of treatment, afatinib could not be seen as affordable in nations that could not afford the \$25,000 cost of gefitinib (all prices are from the most recent edition of the Redbook). Instead, the results of LUX-Lung 3 and LUX-Lung 6 were used to petition the US Food and Drug Administration for an approval that was granted in 2013.

Another trial had a similar pattern. Trastuzumab (Genentech, San Francisco, CA) added to chemotherapy has been the standard of care in the initial treatment of human epidermal growth factor 2 (HER2)-positive metastatic breast cancer since 2001. A recent study sought to determine whether lapatinib (GlaxoSmithKline, London, United Kingdom), a different HER2-targeted drug, also had efficacy in this indication.⁹ From 2006 to 2009, more than 400 Chinese women were randomly assigned to lapatinib or placebo added to chemotherapy. However, because the majority of patients in China cannot afford trastuzumab (\$66,000 for 1 year of treatment), it is not clear that lapatinib (\$67,000 for 1 year of treatment) represents a realistic alternative.

It is worth noting that these trials would not have succeeded in enrolling patients in the United States, because most oncologists would not have allowed their patients to have a 50% chance of being randomly assigned to a treatment deemed inferior by previous studies.

Under what circumstances placebo-controlled research is ethical in low-resource settings is still a

contested matter. Few would criticize our position that such research is clearly unethical when the question addressed cannot realistically benefit the nation in which the trial is performed. We propose the following decision aid to help determine which clinical trials are warranted. First, in accordance with the seventh Declaration of Helsinki (2013), “Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.”¹⁰ Thus, for any proposed trial, investigators should postulate the following: If the results were positive, what changes could realistically be expected in the host nation, as well as the world? and the same question if the trial were negative. Ultimately, the decision will require weighing these potential benefits to the society against the risks to participants.

Placebo-controlled trials of anticancer drugs with prices similar to those of proven alternatives benefit only the sponsoring companies. Instead, trials seeking to identify interventions that can realistically be implemented by developing nations are justified. They are desperately needed to inform pressing policy decisions facing the leaders of these nations. Condemning these studies is a perverse form of first-world paternalism. The need for clarity regarding the ethical conduct of trials in the developing world is great, because recent criticism has been misplaced, a disservice to citizens around the world.

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