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# New strategies in research ethics: guidance for a global approach

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## Key points

- Clinical research is needed in Africa to improve contraceptive methods and develop new ways to prevent and treat HIV.
- The international research community is working to harmonise its guidelines for the development of new drugs, including contraceptives.
- Whatever ethical guidelines clinical researchers follow, they must observe these principles: respect for others, beneficence, and justice.

The need for clinical research that tests strategies for preventing unintended pregnancies, as well as interventions for preventing and treating HIV/AIDS, is widely recognised. However, countries that stand to benefit most from the results of such research lack the resources to conduct their own clinical studies. International partnerships among scientists, governments, pharmaceutical companies, and non-profit organisations make research on reproductive health and family planning possible.

Necessary as they are, these partnerships also raise concerns. Bioethicists wonder how the scientific community can ensure that *all* clinical trials conform to rigorous ethical standards – no matter where they are conducted or who supports them.

## Pursuing new leads

Conducting contraceptive research in sub-Saharan Africa is important, because this region has some of the world's highest rates of unmet need for contraception. Research on microbicides to prevent HIV (as well as pregnancy, depending on the product) is also crucial in Africa, where the HIV epidemic is concentrated.

Collaborations between organisations are one way to ensure that externally sponsored research is rooted in local concerns and conducted with local expertise. For example, Family Health International (FHI) and CONRAD – two US-based non-profit organisations – are working with the Centre for the AIDS Programme of Research in South Africa (CAPRISA) at the University of KwaZulu-Natal, in Durban, on a study assessing the safety and effectiveness of a tenofovir gel to prevent HIV infection in women.

Only a small share of clinical trials related to HIV are being conducted in Africa. Most of the trials are supported by funders outside of Africa, and few of the principal investigators are African.<sup>1</sup> Given these circumstances, making

sure that the research is both ethical and appropriate to African societies and cultures is a challenge.

The urgency of the HIV crisis has directed many of the resources for reproductive health research to the development of microbicides and barrier methods of contraception. As a result, alternative ways to prevent unplanned pregnancy have received less attention.<sup>2</sup> Research that seeks to improve contraceptive technologies – such as contraceptive implants that are easier to insert and remove – is necessary, but many funding agencies do not regard it as a high priority. Efforts to integrate HIV and family planning services have attracted new interest, however, and some advocates have characterised family planning as 'the best-kept secret in HIV prevention.'<sup>3</sup>

## Addressing ethical concerns

When researchers from developed countries conduct international clinical trials, economic disparities between regions inevitably come into sharp focus. These inequalities highlight specific ethical concerns.

For example, it is often less expensive to conduct a large clinical trial in a developing country (where the



*International health professionals take part in a research ethics training facilitated by Family Health International in Kenya. During the training, participants learn how to incorporate fundamental ethical principles into the design and implementation of human clinical trials.*



*At a research ethics training in Kenya, a participant from the Democratic Republic of Congo writes the contents of informed consent on a flip chart. Informed consent is one of many concepts addressed in the Declaration of Helsinki.*

comparatively low salaries of physicians, nurses, and study coordinators keep overhead costs down) than in a developed country. Pharmaceutical companies may also prefer to do clinical testing in developing countries, because there they have access to a larger number of potential participants. Finally, doing research in these countries may establish relationships that can help companies overcome regulatory barriers for drug approval there later on. Such an advantage is compelling for companies hoping to do business in developing countries, whose large populations promise expanding markets for new drugs.<sup>4</sup>

Some critics worry that people in high-resource settings benefit disproportionately from research conducted in low-resource settings. This fear has some merit, says Kate MacQueen, a research scientist with FHI who has collaborated on HIV-prevention trials around the world.

‘Whenever someone’s expecting a profit based on the results of the research, there is the potential for people to be blinded by that bottom line,’ says MacQueen. She believes that trials funded by pharmaceutical companies are more vulnerable to the profit motive than those conducted by non-profit public health organisations.

For example, conducting a clinical trial in India to test a new allergy medication could raise ethical concerns. Such a trial would be questionable, because if the medication proved effective, the pharmaceutical company could make a lot of money selling it in developed countries but never market it in India, because of its doubtful profitability there. The trial would have put people in India at risk with no compensating national benefit. In contrast, conducting a contraceptive trial – such as research on injectable contraceptives – in India would be

less likely to elicit this concern, because the research would address a need in the country, and the Indian people would stand to benefit from the research.

One way that countries have responded to ethical concerns about inequitable risks and benefits of clinical trials is to require or strongly encourage researchers to register all trials in a publicly accessible database, thus making medical research more transparent (see ‘Advances in trial registration’).

### Harmonising regulations

In 1964, the World Medical Association adopted the Declaration of Helsinki as the international standard on medical research ethics. The declaration grew out of principles established by the Nuremberg Code, which sought to prevent the abusive medical experimentation practiced by Nazi physicians. It emphasises the importance of obtaining informed consent from participants, having a scientifically qualified research team, and ensuring that the risks to participants do not outweigh the benefits.

Since 1964, the declaration has undergone six revisions. Organisations from the countries that fund the most clinical research – the United States, Japan, and members of the European Union – have adhered to the requirements outlined in the original document. However, some countries (including the United States) have been hesitant to adopt recent revisions that limit the use of placebos and require scientists to provide treatment for research participants, if needed, after a study has ended. Although not an issue for most contraceptive research, the revised requirements present new challenges for scientists studying microbicides and other HIV-prevention strategies (see ‘Debating the declaration’).

In addition to having differing views on the current version of the Declaration of Helsinki, many countries maintain a second set of regulations to govern domestic clinical trials.

Inefficiencies created by these different regulations can impede the progress of research conducted on a global scale. Thus, a unifying document was needed to provide detailed guidance on research ethics, especially given the Declaration of Helsinki’s lack of specific directives to help study teams implement the recommendations.

To address this gap, representatives of international regulatory agencies and the pharmaceutical industry formed the International Conference on Harmonisation to develop a unified regulatory framework for registration of pharmaceuticals for human use. The resulting guideline, known as Good Clinical Practice (GCP), was published in 1996.<sup>5</sup>

The European Union, Japan, and the United States immediately endorsed the GCP as their main national

regulatory guideline. Canada, Australia, the Nordic countries, and the World Health Organization soon followed. More recently, in October 2008, the US Food and Drug Administration (FDA) adopted the GCP as its regulatory guideline for scientists seeking approval of new drugs – including contraceptives – based on data collected in foreign countries.

### Questioning policies

In the mid-1990s, the number of international clinical trials being conducted increased notably, in part owing to worldwide concern about HIV. Between 1995 and 2005, the number of trials with sponsors within the United States but conducted elsewhere doubled. By 2007, almost 20% of clinical trials that were actively recruiting participants were in developing countries.<sup>6</sup> Given this rise in US-sponsored trials overseas, some bioethicists are concerned about the FDA's new regulatory guideline.

'At a time when the volume of overseas trials is increasing, the FDA's new policy is troubling,' writes a group of bioethicists in a recent editorial in the British medical journal *The Lancet*.<sup>7</sup> The group fears that the GCP, which is not as stringent as the Declaration of Helsinki on the use of placebos and post-trial treatment for research participants, will make it easier for US pharmaceutical companies to test drugs overseas and get them approved quickly for use at home.

David Borasky, the director of regulatory affairs and quality assurance at FHI, does not share these concerns. 'I don't want to say these worries are irrelevant, but I think too many checks and balances are in place for the new guidelines to compromise the ethics of clinical trials,' he says.

Furthermore, Borasky points out, the GCP is consistent with principles that have their origin in the Declaration of Helsinki. 'Given that all clinical trials still have to be vetted by ethics committees and local institutional review boards, I think rigorous ethical standards will continue to be applied,' he says.

### Showing respect

Whatever specific regulations govern a clinical trial, the basic principles of ethical research are the same.

'The three main principles are respect, beneficence, and justice,' says Michele Commins, an expert in GCP and an associate director of regulatory affairs and quality assurance at FHI. 'The biggest concern research participants have is that they don't want someone from another country telling them what to do. They want respect for where they live and for their way of doing things,' she says.

Commins says she emphasises these principles during GCP trainings, which she conducts around the world for health professionals who are involved in or could become involved in clinical research during their careers.

The three principles are considered universal and so have no national, cultural, legal, or economic boundaries.

'Everyone involved in clinical research needs to understand these principles and follow them,' she says.

### Reference

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## Debating the declaration

### Use of a placebo

The revisions to the Declaration of Helsinki brought up some ethical questions surrounding the use of placebos. Some ethicists argue that a placebo should not be used to test a drug if a better treatment is available, even if that treatment is not available in the country where the research is being conducted. This is a contentious issue – one that has not been resolved by ethicists, regulators, and researchers.

### Context of care

Many developing countries have a limited healthcare infrastructure, and citizens may not have access to basic medical services. The revised Declaration of Helsinki states that all trial participants are entitled to the worldwide best standard of care. This requirement has been rejected by every national and international committee that has examined this issue. The consensus now holds that it is ethically permissible, in some circumstances, to provide research participants with the best possible care available in the country where the research is conducted (which may or may not be the worldwide best standard of care).<sup>1</sup>

### Access to treatment

The revisions to the declaration require that all research participants have post-trial access to any prophylactic, diagnostic, or therapeutic methods tested in a trial and found to be effective. Although this revision is not necessarily an issue for contraceptive trials, it has provoked considerable disagreement among HIV activists and prevention researchers. Some pharmaceutical companies have addressed the issue by pledging to allow local pharmaceutical companies to produce an HIV-prevention drug if it is shown to be effective in a trial. Investigators and sponsors of other trials have written entire proposals planning for the dissemination of effective products in the research community. To date, however, none of these plans has been tested, because an effective product has not yet been developed.

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## Advances in trial registration

The Declaration of Helsinki requires clinical researchers to register all trials in a publicly accessible database. Likewise, the World Health Organization (WHO) considers trial registration a scientific, ethical, and moral responsibility.

To register a trial, researchers provide their national registry with a summary of the study's design and goals, a description of the intervention being studied, the criteria for patient participation, and the location of the trial. Researchers must provide this information before the trial begins.

Not all countries require trial registration, but efforts to increase voluntary registration are under way. In early 2009, the HIV/AIDS, Tuberculosis and Malaria (ATM) Clinical Trials Registry became the principal registry for all clinical trials conducted in Africa. Recently renamed the Pan African Clinical Trials Registry (PACTR), this registry is part of a growing trend to comply with the Declaration of Helsinki and to increase local oversight of international medical research.

In an effort to increase the number of trials included in the registry, the PACTR helps African researchers overcome some of the challenges they face in registering trials. For example, for researchers who do not have reliable access to the Internet, the PACTR provides manual registration by email, postal mail, or facsimile.

In the past several years, some countries – including the United States – have established mandatory clinical trial registries. Many other countries have national guidance on voluntary registration. In June 2009, India became the latest country to require trial registration.<sup>1</sup>

The WHO's International Clinical Trials Registry Platform (ICTRP) recognises 13 national registries. Not a registry itself, the ICTRP provides centralised access to these 13 databases, with the goal of improving research transparency and strengthening the validity and value of the scientific evidence base.

A significant proportion of medical research remains unpublished, and even when it is published, some results may be left out. Selective reporting leads to an incomplete and potentially biased view of a trial and its results. Trial registries require that all results are made public, thus mitigating the negative effects of publication bias.

Being able to easily access information about the thousands of clinical trials conducted throughout the world may also help researchers and funding agencies avoid unnecessary duplication of trials, and could even lead to better scientific collaboration.

### Reference

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## Provider tools and resources

<http://www.fhi.org/en/rh/training/trainmat/ethicscurr/index.htm>

The *Research Ethics Training Curriculum*, developed by Family Health International, is used to train international scientists and community representatives on the ethics of human clinical trials.

<http://www.who.int/ethics/research/en/EthicalStandardsandProceduresforResearchwithHumanBeings> provides an overview of the ethical requirements for clinical trials, as mandated by the World Health Organization, as well as information on accessing national registries of clinical trials.

<http://www.wma.net/e/policy/b3.htm>  
The most up-to-date version of the *Declaration of Helsinki* is available from the World Medical Association.

<http://www.ich.org/LOB/media/MEDIA482.pdf>  
The official website for the *International Conference on Harmonisation* provides many guidelines on quality, safety, efficacy, and multidisciplinary research, including the Good Clinical Practice guideline.

<http://www.atmregistry.org>  
The *Pan African Clinical Trials Registry* is the principle registry for all clinical trials conducted in Africa.

<http://www.who.int/ictrp/en>  
The World Health Organization's *International Clinical Trials Registry Platform* provides access to 13 national registries.



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