

## FDA abandons the Declaration of Helsinki: The effect on the ethics of clinical trial conduct in South Africa and other developing countries

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Four years ago, the US Food and Drug Administration (FDA) ceased compliance with the Declaration of Helsinki (DoH) (2000 revision and all subsequent revisions) for conduct of clinical trials outside its borders. It instead ruled that compliance with the Good Clinical Practices (GCP) of the International Conference of Harmonization (ICH) is sufficient. However, the ICH-GCP guidelines do not address certain ethical requirements stipulated in the DoH, such as the use of placebos v. standard therapy, post-trial access to treatment and other benefits for participants; public disclosure of trial design; publication of trial results; and disclosure of conflicts of interest.

The FDA's adoption of less morally stringent guidelines could encourage pharmaceutical companies to take ethical short cuts. It could also have practical consequences for trial ethics in developing countries, especially where research ethics committees may not be promoting high standards of protection for participants in clinical trials, due to lack of financial and human resources.

Pharmaceutical companies may also pressurise research ethics committees to relax guidelines and legislation, in order to facilitate future clinical trials in developing and emerging countries that lack the resources to conduct their own clinical research on epidemics such as HIV/AIDS, which have devastating effects on their populations.

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In April 2008, the US Food and Drug Administration (FDA) published its controversial decision to abandon the Declaration of Helsinki (DoH) as an ethical guideline when conducting, and reviewing data from, clinical trials performed outside the USA. As early as 2006, the FDA declared it would eliminate all reference to the 2000 and subsequent revisions of the DoH. While it stipulated that it would continue to recognise the 1989 revision, this revision is considered invalid by the World Medical Association (WMA), the authors of the DoH.<sup>1</sup>

Accordingly, the FDA now considers it sufficient that a trial performed outside USA soil adhere to the Good Clinical Practices of the International Conference of Harmonization (ICH-GCP). The reasons for this decision include the need to protect human subjects and to assure the quality and integrity of foreign data obtained from studies performed outside the USA.<sup>2</sup>

### Discussion

The DoH has been considered the benchmark of ethical and medical standards in clinical trials worldwide, even though it is not a legally binding document in international law. It has its origins in the Nuremberg Code (1947), and was developed in 1964. Its author, the WMA, includes 85 national medical societies from around the world, compared with the ICH which consists only of voting members from the USA, the European Union, and Japan.<sup>3</sup> In October 2008, the WMA General Assembly, meeting in Seoul, South Korea, voted to adopt the latest revision of the DoH after an 18-month revision process.<sup>4</sup> The WMA considers the 2008

DoH the only official revision, and regards it not just as an internal policy but as a universal statement of medical research ethics.<sup>4</sup>

The 2008 revision of the DoH<sup>5</sup> is more ethically demanding than the ICH-GCP, and addresses moral issues that the ICH-GCP guidelines do not.<sup>6</sup> These include the restriction of placebo controls in clinical trials in developing countries; the disclosure of the trial design to the public; a requirement that the population in which the research is conducted should benefit from it, particularly in developing countries, and that participants should have post-trial access to treatment; the need to publish results; and the disclosure of conflicts of interest.<sup>3</sup> There are concerns that the FDA's abandonment of the DoH may cause other regulators to follow suit, with serious implications for ethical standards and participant safety in Third-world countries.

### Research ethics in South Africa

In 2001, the World Health Organization Regional Committee for Africa expressed its concern that some health-related trials undertaken in developing African countries were not subjected to any form of ethics review.<sup>7</sup> Some of the reasons quoted for conducting research in Africa, rather than in developed countries such as the USA or Europe, include lower costs, lower risk of litigation and less stringent ethical review.<sup>7</sup> Concerns have also been raised that research ethics committees (RECs) in developing countries may not promote high standards of protection for research participants, due to a lack of financial and adequately trained human resources.<sup>7</sup>

However, a 2010 comparison between the US Common Rule and South African research ethics requirements by Cleaton-Jones and Wassenaar<sup>8</sup> revealed that, at a structural level, the research ethics review process in South Africa is in many cases equivalent to the US institutional review board (IRB) and Office of Human Research Protections (OHRP) oversight system. In fact, it would appear to be stricter as it makes no exclusions, compared with the many exemptions allowed in ethics review and waivers of participant-informed consent in the USA system.<sup>8</sup>

Although strict guidelines and regulations *per se* will not prevent sub-standard ethical review, the FDA's renouncement of the DoH may have long-term practical implications, and could encourage pharmaceutical companies to take ethical short cuts in developing and emerging countries.

## The use of placebos versus standard therapy

The clinical research testing of new strategies for the prevention and treatment of epidemics, such as HIV/AIDS, has become a critical necessity.<sup>9</sup> However, developing countries, which stand to benefit the most from such research, lack the resources to conduct their own clinical trials.<sup>9</sup> Many have a limited healthcare infrastructure and citizens may not have access to basic medical services.

Article 32 of the DoH provides for the limited use of placebo arms in clinical trials. While a new test drug should be compared with the available golden standard of treatment or therapy instead of a placebo, placebo-controlled trials are allowed where no standard therapy exists, or 'where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm.'<sup>5</sup>

The debate over the application of research ethics and the use of placebo-controlled trials in developing countries surfaced in the early 1990s, in trials concerning the early prevention of mother-to-child-transmission (MTCT) of HIV.<sup>10</sup> In 1994, while there was an existing protocol from the AIDS Clinical Trial Group 076 (ACTG 076) for preventing MTCT, high antiretroviral (ARV) costs and insufficient infrastructure placed it out of reach of most of the HIV-infected population in the developing world.<sup>10</sup> Due to an almost 70% reduction in the risk of HIV transmission in the ACTG 076 trial, zidovudine became the *de facto* standard of care.<sup>11</sup> To find a more cost-effective and applicable treatment for resource-poor settings, randomised placebo-controlled trials were initiated to investigate a short-course ARV regimen.<sup>10</sup>

However, these trials sparked intense debate. On the one hand, they were viewed as exploitative as they violated the condition of equipoise, namely that placebo groups are only deemed ethical if the merit of the intervention is sufficiently uncertain. On the other hand, the responsiveness of the research was stressed. In fact, without these short placebo-based trials, countries such as South Africa would not have developed a low-cost intervention to prevent MTCT. The subsequent initiation of these trials in developing countries, funded by the US Center for Disease Control (CDC) and National Institutes of Health (NIH), raised further concern when it was learned that patients in trials in the USA had unrestricted access to the drug.<sup>11</sup>

The arguments for not providing the 'gold standard' treatment available in developed countries were founded on the low standard of care in developing countries,<sup>10</sup> and the fact that pregnant women in these countries did not access care early enough and were unlikely to cease breastfeeding. The NIH and CDC defended the trials' design and, despite early opposition, the trials began in 16 countries and included over 12 000 HIV-infected women.<sup>10</sup> These trials also appeared to be in direct conflict with guidelines for international research published by the Council for International Organizations of Medical Sciences (1993, Guideline 11), which stated that the ethical standards should be applied no less exactly than they would be in the sponsoring or initiating country.<sup>11,12</sup>

In addition to various international regulatory requirements, clinical trial investigators and pharmaceutical companies in South Africa need to adhere to the South African Good Clinical Practice (SAGCP) guideline, published by the Department of Health in 2000 and revised in 2006.<sup>13</sup> Section 1.4 states that 'Regulations established in terms of section 90(s) [health research] of the National Health Act (Act No. 61 of 2003)<sup>14</sup> enforces these guidelines. Compliance with these guidelines is compulsory under the direction of the Director-General of Health.'<sup>13</sup>

Alongside other international guidelines, the SAGCP is based on the ICH-GCP as well as DoH (2004) (Section 1.3 of the SAGCP).<sup>13</sup> Thus, the National Health Act indirectly enforces compliance with the ICH-GCP as well as the DoH for clinical trials conducted in SA.<sup>13</sup> The SAGCP states that the use of placebos should be justified, and only when there is no known effective treatment should it be considered ethical to compare a potential new treatment with a placebo.<sup>13</sup>

However, taking into account the 2004 DoH's statements on the use of placebo-controlled trials, it seems that placebo control is more flexible. Given the already flexible grounds for placebo-controlled trials based on scientific justification and compelling methodology, it would seem unlikely that the FDA's decision would significantly affect South Africa. However, other developing countries could risk having their guidelines relaxed to allow these trials. This particularly affects emerging countries which lack standard therapies and the resources to conduct their own clinical trials. Given that pharmaceutical companies can already argue that emerging countries usually lack their own standard treatments, this could put an even greater burden on the future ethical rights and safety of trial participants.

## Post-trial access to treatment and other trial benefits

Articles 14 and 33 of the DoH state that the clinical trial protocol should contain a statement of the ethical considerations involved, and should indicate how the DoH's principles have been addressed.<sup>5</sup> It should also describe arrangement for participants' post-trial access to appropriate care or benefits resulting from the trial.<sup>5</sup>

However, this requirement is absent from the ICH-GCP. SAGCP stipulates that specific recommendations should be made for the continuation of treatments beyond after the trial, especially in research requiring additional attention, such as HIV research involving vulnerable communities.<sup>13</sup> In developing countries without such an additional guarantee, this issue could become problematic.

Since the FDA renounced the DoH, some pharmaceutical companies are choosing to omit any reference to the DoH when drafting protocols for trial conduct in South Africa or any other developing country. These companies can also test their new drugs in developing or emerging countries without planning to register them there, and with no obligation to provide participants with post-trial access to any treatment or other benefits.

## Trial registration and publication of results

Article 19 of the DoH requires that all clinical trials be registered in a publicly accessible database before the first participant is recruited.<sup>5</sup> Likewise, the WHO considers trial registration a scientific, ethical and moral responsibility.<sup>9</sup>

In early 2009, the HIV/AIDS, Tuberculosis and Malaria (ATM) Clinical Trials Registry became the principal registry for all clinical trials conducted in Africa.<sup>9</sup> Recently renamed the Pan African Clinical Trials Registry (PACTR), it is part of a growing trend of compliance with the DoH and increasing local oversight of international medical research.<sup>9</sup> In the past several years some countries, including the USA, have established mandatory clinical trial registries.<sup>9</sup>

As well as revealing the trial design, Article 30 of the 2008 DoH states that authors and sponsors have an ethical obligation to the public to publish research conducted on human participants,<sup>5</sup> including negative, inconclusive and positive outcomes. A significant proportion of medical research remains unpublished, or may be published with some results omitted.<sup>9</sup> Selective reporting leads to an incomplete and potentially biased view of a trial and its results.<sup>9</sup>

A lot of money, time and resources have been spent on compliance with the DoH. For countries such as SA, which already have guidelines for trial registration and results publication, the FDA's decision might not be as significant. Yet for developing countries without these guidelines, this could hamper the current and future efforts of trial registries, and have financial implications for efforts already invested.

## Conflicts of interest

Article 14 of the 2008 DoH states that the clinical trial protocol should contain a statement of the ethical considerations involved and indicate how the DoH's principles have been addressed. It should also provide information on funding, sponsors, institutional affiliations, and other potential conflicts of interest to both RECs and trial participants.<sup>5</sup> However, this principle is not specified in ICH-GCP. This raises another ongoing ethical issue, since in 2012 the FDA announced that it might relax certain conflict-of-interest restrictions that prevent scientists with financial ties to the drug industry from becoming members of its advisory panels<sup>15</sup> (the FDA appears to be holding back on its decision for the time being).<sup>16</sup>

In January 2012, a conflict-of-interest scandal rocked the FDA when a pharmaceutical giant was allowed to keep its oral birth-control product on the US market, despite the FDA's own reports of dozens of deaths caused by blood clots in women using the product.<sup>17</sup> The FDA had appointed at least three scientists with financial ties to the pharmaceutical company to the product's advisory committee, who voted in favour of the product. The FDA neglected to disclose their

connections with the pharmaceutical company.<sup>17</sup> Once again, the inclusion of a conflict-of-interest clause in the SAGCP is instrumental in dealing with this issue in South Africa.

## Conclusion

The FDA's reliance on the ethically less stringent ICH-GCP rather than the DoH may weaken the protection of research participants in many developing countries. This will depend on how well drug developers and clinical trial investigators will be able to abide by moral ethics, and how well they regulate themselves in terms of ethical conduct when conducting research in Third-world countries, especially where RECs are unable to uphold participant protection.

In South Africa, research participants should be informed about these areas of concern in order to maintain awareness and emphasise the importance of a strong bio-ethical system. This could be done through public conferences, published articles, training methodologies for investigators and other research personnel, and discussion forums with leading and representative organisations and committees in the industry.

Fortunately, in South Africa, the SAGCP goes a long way towards protecting research participants. It is imperative, however, that researchers in other developing countries are also made aware of these issues and advocate for stronger national ethico-guidelines.

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