CONTROVERSY

AIDS vaccine trials for India: "unanswered questions" remain unanswered

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We are glad that the International AIDS Vaccine Initiative (IAVI) has, through Ms Anjali Nayyar, vice president, country and regional programmes of IAVI, responded (1) to our editorial (2). We hope that IAVI will continue to engage with health professionals and readers of IJME about ethical concerns related to AIDS vaccine trials in India and elsewhere. As emphasised in the editorial, the IAVI-sponsored AIDS vaccine trials in India have established some high ethical standards and benchmarks in the conduct of vaccine trials in particular and clinical trials in general. We need to collectively continue advocacy to ensure that all research institutions and sponsors adopt these standards in all clinical trials conducted in India. IAVI's partners in India, the various departments and institutions of the government of India, have a mandate, responsibility and authority to achieve such standards for all clinical trials.

However, achieving better standards does not rule out the scope and need for further engagement on contentious issues. Hence we must express our disappointment that Ms Nayyar's article does not directly engage with the substantive issues of the editorial. The "unanswered questions" remain unanswered.

We discussed three major issues: (a) ethical concerns related to the collaborative relationship between IAVI as sponsor and Targeted Genetics, the producer of the candidate vaccine on one hand, and IAVI and its Indian collaborators on the other; (b) the issue of the patent of the candidate vaccine and whether there has been any specific agreement and institutional mechanism established for making the successful vaccine accessible to Indian people; and (c) the systematic indifference to investment in the development of a therapeutic vaccine for HIV/AIDS.

Of these, we understand that IAVI cannot provide any specific clarification on the last issue as its mandate is for the development of a preventive vaccine alone. On the issue of patents and access to vaccines, apart from a brief comment on IAVI's commitment to ensuring access (by referring to the 2004 WHO document in the first paragraph of her article), Ms Nayyar's response provides no specific information on agreements with the government of India and present manufacturers for ensuring access to a successful vaccine. We believe that people in India have a right to know about the post-trial benefits of the vaccine, particularly pertaining to patents and intellectual property rights for the manufacture, sale and use of the vaccine in India. The lessons from recent experiences related to access to second-line AIDS drugs and legal contentions between AIDS activists and manufacturers must inform agreements between sponsors and government in India.

Why are these agreements not placed in the public domain? When can we expect to see these documents?

Ethics of collaborative research

Since Ms Nayyar's response primarily discusses the first point, the ethics of international collaborative research, we will focus on this part of her response. We had mentioned that while the IAVI-sponsored trial commenced at the National AIDS Research Institute (NARI) on February 7, 2005, on February 22, 2005, Targeted Genetics, the company producing the candidate vaccine tgAAC09, publicly announced the results of the multi-centric double-blind trial of the same candidate vaccine, using the same protocol, in Belgium and Germany. We thought this was very unusual. Ms Nayyar has provided no explanation for why the results of two centres were unblinded/decoded, analysed and publicly announced when the third centre, NARI, which was ostensibly a part of the multi-centric trial, had begun the trial only 15 days earlier. What is the scientific explanation for announcing results of two centres when the third centre was just about beginning the trial?

In our editorial we had assumed, and said, that the IAVI and Targeted Genetics were co-sponsors of the trial. But in a personal communication to one of us IAVI corrected us, stating that Targeted Genetics did not have the status of co-sponsor; and that it is only a producer and supplier of the candidate vaccine.

This leads us to ask how a company which is not even a co-sponsor of the multi-centric trial had access to the results of the trial in two centres and was the first to announce the trial results. The company could have received results only from the sponsor. Can results of a clinical trial be put in the public domain before the data are fully analysed and peer reviewed? Even after this process is completed, surely time would be needed to communicate results to the company which in turn would take some time to decide whether to make the findings public. And this entire process would definitely take more than 15 days. Thus it is logical to assume that before the trial commenced in India, IAVI as the chief and sole sponsor had in its possession the unblinded/decoded raw data and their findings from the centres in Belgium and Germany. Following the publication of our editorial, one of us was informed in a

personal communication by IAVI that the Indian researchers were informed of the results only after the company published them. However, Ms Nayyar's response does not provide any specific information in this regard.

Did the scientists of ICMR and NARI - also partners in this trial as per the tgAAC09 protocol - have similar access to the raw data and results of the two other centres linked to the trial being conducted by them? If data were shared, it is important to know when these data were made available and to which partners and authorities in India.

We may speculate that a private company would be eager to let its shareholders know, as early as possible, the results of one of its candidate vaccines. While this may be understandable, can a sponsor privilege the interests of a company over the interests of developing country researchers and trial participants?

Harm and wrong

Ms Nayyar makes a strong point that "the vaccine was safe and well tolerated amongst the European population". We agree that as per available evidence she is absolutely right. Surely then, she and readers of this journal have a right to ask us: "what is all this fuss about?" if no harm has been demonstrated. But the bioethics literature provides sufficient evidence that the absence of data showing harm is not sufficient justification for scientists to expose participants to potential risks. Also, even if one does not cause harm doing wrong is also unethical.

In this case, the Belgium-Germany trial showed that not only was the vaccine being tested at NARI safe for the "European population", but as per the press release of the Targeted Genetics on its website, it "did not elicit significant immune responses" in that population. Ms Nayyar interprets this result as: "while the vaccine candidate was not disappointing, the European results had fewer responses than expected". Perhaps she is correct in her interpretation.

But the problem remains that this information was with IAVI before the first person was recruited in the trial at NARI. And all those recruited up until the information was made available to the Indian researchers (and the protocol amended to incorporate that information) had the right to know of these results, as such information has significant bearing on people's readiness to participate in an experiment.

Evidently, none of those recruited was harmed. But is it possible to say that they were not wronged since the information was available to the sponsor but not made available to them when informed consent was first sought?

There is a factual point on which Ms Nayyar contradicts us in her article. After making a general assertion that there was no failure to share information with Indian researchers, she says that the early availability of the data from Belgium-Germany trial "did not mandate the need to alter the protocol in India as it had no implication for the trial design". This directly contradicts our statement in the editorial that sponsors were "compelled to make amendments - including amending the informed consent form to give information on the results of the Belgium-Germany trial to participants - a few months after the trial started". We must stress that our information that more than one amendment was made in the original protocol is absolutely correct. One of the amendments was in the informed consent form, which is an integral part of the protocol, but we do not know the precise content of the change. No information is available from the public domain about this or other amendments made in the protocol.

Besides, it would have been unethical for ICMR/NARI to commence the trial of Feb 7, 2005 in India without amending the protocol if they had prior knowledge of the results of the Belgium-Germany trial. As per information available to us, ICMR/NARI amended the protocol on receipt of results and approached the scientific and ethics committees for review of those amendments "a few months after the trial started". By taking this action ICMR/NARI followed standard ethical procedure.

The fact is that the new information was already available with IAVI much before the trial commenced on February 7, 2005. Had IAVI given its collaboration with Indian researchers and the participants of the trial at least as much importance as it gave to its collaboration with the company (we believe that collaboration with researchers and concerns of participants should be given more importance), it would have spared itself from doing wrong.

References

1. Nayyar A. AIDS vaccine trials for India: getting the facts right. *Indian J Med Ethics* 2007; 4: 109-10.
2. Jesani A, Coutinho L. AIDS vaccine trials in India: ethical benchmarks and unanswered questions. *Indian J Med Ethics* 2007; 4: 2-3.