

Compensation for research-related injury in South Africa: A critique of the good clinical practice (GCP) guidelines

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This article examines the current South African Department of Health Good Clinical Practice (2006) guideline recommendations regarding compensation for harm incurred in clinical trials. It applies the case of a phase IIb HIV vaccine trial in South Africa, for which enrolments and vaccinations were suspended early, based on data from an international companion study that indicated no evidence of efficacy and greater susceptibility to HIV infection in a subgroup of vaccinees. The case application indicates certain substantive and procedural limitations within the South African Department of Health Good Clinical Practice (2006) guideline recommendations on compensation for harm, which should be re-considered in order to improve protections for trial participants.

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In October 2007, enrolments into and vaccinations for a South African phase IIb HIV vaccine trial (HVTN 503, or Phambili) were suspended, based on negative results from a companion study in the Americas (HVTN 502 or STEP). STEP results showed that the vaccine did not prevent HIV acquisition or ameliorate disease, and in fact indicated a trend towards increased infection in a subgroup of vaccinees.

Although, as far as the authors are aware, no claim for compensation was made by participants in the South African Phambili trial, this article explores the complexities that would have faced participants had they attempted such a claim in terms of the Department of Health (DoH) Good Clinical Practice (GCP) guidelines of 2006.¹ Using the Phambili trial as a case study, we are able to identify certain limitations of DoH GCP (2006) that might apply across a range of clinical trials.

The South African ethical-legal framework

South Africa has a comprehensive ethical-legal framework for regulating clinical trials.² The framework creates a system of regulation through:

- a number of institutions that set the policy agenda, establish norms and standards and review individual studies
- ethical guidelines and, to a lesser extent, laws, which establish substantive and procedural norms for conducting research
- monitoring and enforcement mechanisms administered by statutory institutions such as the Medicines Control Council (MCC), research ethics committees (RECs), the National Health Research Ethics Council (NHREC), professional councils and the courts.

The framework deals with research-related injuries expressly through the DoH GCP (2006) guidelines. These guidelines set out the circumstances and requirements that must be met for participants to claim financial compensation for such injuries.

Delictual claims in South Africa are not the subject of this article, but harm from a research-related injury could also be classified as a delict. Participants are not precluded from claiming damages in terms of the civil law, though such claims would require plaintiffs to demonstrate negligence.

The STEP and Phambili HIV vaccine trials

Both the STEP and Phambili trials were phase IIb, randomised, double-blind, placebo-controlled HIV vaccine trials of the Merck adenovirus serotype 5 (Ad5) vector-based vaccine. Ad5 is a strain of the common cold used to deliver HIV genes made in a laboratory.

The STEP HIV vaccine trial was designed to evaluate the safety and efficacy of the Merck Ad5 vaccine. It enrolled 3 000 HIV-negative volunteers from different geographical areas in the Americas, Australia and the Caribbean who each received three doses of either the vaccine or a placebo. The vaccine contained a mix of Ad5 vectors carrying one of three different HIV genes – gag, pol, or nef. The inserts were from HIV clade B, matching the predominant clade circulating in the areas where the trials took place.³ The trial was co-sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), and the pharmaceutical company Merck & Co., Inc., which developed and supplied the candidate vaccine.⁴

Immunisations were stopped on 21 September 2007, after an interim analysis by the data safety monitoring board (DSMB) determined that the vaccine would not meet its efficacy endpoints. Subsequent analysis indicated a trend toward more HIV infections among a subset of vaccinees than among placebo recipients.

The HVTN 503 (Phambili) trial of the same candidate vaccine was conducted in South Africa and funded by grants from the NIAID to

the HIV Vaccine Trials Network, as well as by Merck & Co., Inc. The South African AIDS Vaccine Initiative (SAVI) provided support to the clinical trial sites.⁵ This companion study aimed to evaluate the safety and efficacy of the Merck vaccine and enrolled 801 participants prior to the suspension of enrolments.⁴ The Phambili study tested the vaccine in high-risk men and women in South Africa, and was intended as a test of the vaccine's potential for cross-clade protection.

Following the interim findings from the STEP study, immunisations and enrolments in the Phambili study were paused to allow for further analysis of the STEP data. Based on the additional review of this data, a separate, independent DSMB for the Phambili trial concluded that there was no basis for anticipating more favourable results in the South African clinical trial. Therefore, the Phambili oversight committee permanently suspended immunisations and enrolment in the study.⁴ This DSMB also noticed a trend towards increased HIV susceptibility in volunteers who had received the vaccine, although this was not statistically significant.

Increased susceptibility to HIV infection in the STEP and Phambili trials

There appears to be debate in the literature regarding the factors, or interaction between factors, that put STEP vaccinees at increased risk of HIV infection compared with unvaccinated volunteers.

Initial analyses of the STEP data showed a trend towards increased risk of HIV infection in Ad5-seropositive men and uncircumcised men.⁶ Further analyses only confirm that uncircumcised men who received the vaccine were at increased risk of HIV infection, but not that this risk increased for Ad5-seropositive participants who received it.⁷ Similarly it was argued that, while being an uncircumcised vaccinee was a risk factor on its own, Ad5 seropositivity is only a risk factor in conjunction with being uncircumcised and that 'pre-existing immunity to Ad5, in and of itself ... does not appear to be associated with an increased risk of HIV infection.'⁸

Multivariate analyses have shown that these risk factors are not confounded by other demographic and risk variables measured at baseline. However, this does not rule out confounding variables that have not yet been measured, such as host genetic factors.⁹ In summary, it appears that all uncircumcised vaccinees were at increased risk for HIV infection, and that Ad5-seropositive vaccinees were not at increased risk for HIV unless they were also uncircumcised.

There has also been debate about the mechanism via which enhanced susceptibility among STEP vaccinees might have occurred. One explanation is that repeated administration of the Ad5 vector in uncircumcised men, or men who were both uncircumcised and Ad5-seropositive, 'might cause an as yet undefined effect on the immune response that leads to an increase in HIV acquisition.'⁸

Another hypothesis for increased susceptibility among uncircumcised men is that vaccine-induced T-cell responses rapidly travel from the injection site to the mucosal tissue of the foreskin, creating a permissible environment for HIV infection in the early months after vaccination.⁸ Furthermore, it was speculated that 'participants with high baseline Ad5 titres may generate an altered local immune response to rAd5 vaccine administration, and this may further enhance HIV infection of target cells in the genital tract tissue.'⁸

For the Phambili trial, HIV incidence was similar in the vaccine and placebo groups (34 HIV infections in vaccinees and 28 in placebo-recipients) and 58% of participants acquiring infection were female.⁵ The authors found no evidence of increased risk of HIV infection in vaccinated participants compared with participants receiving the placebo. In addition, they found no such evidence in Ad5-seropositive participants, nor in uncircumcised men.⁵ Therefore, in this trial, antibody titres against Ad5 did not correlate with increased HIV infection.⁷ Furthermore, circumcision status did not predict infection or modify the effect of treatment.⁵ The authors stated that early cessation of vaccination and unblinding of participants made it difficult to draw conclusions about the efficacy of the vaccine.

Compensation claims under DoH GCP (2006) guidelines

The DoH GCP (2006) guidelines require researchers and sponsors of clinical trials to take out comprehensive insurance against injury and damage that participants may experience as a result of the trials. These guidelines give direction on the payment of compensation (from the insurers) for research-related injury. The guidelines also provide that participants may have a claim if it can be shown that a trial product or procedure was administered that caused serious bodily injury of an enduring character that would not have occurred but for participation in the trial.

Accordingly, 3 requirements should be satisfied:

- *conduct*, i.e. an act or omission on behalf of the researchers or sponsors leading to a harm
- *harm*, i.e. serious bodily injury of an enduring nature arising from a trial product or procedure (there is no compensation for temporary pain or discomfort or for less serious or curable complaints)
- *causation*, i.e. that the harm would not have occurred but for trial participation, and that there is an unbroken link between the conduct and the harm caused. Participants are only required to prove that such harm occurred on the balance of probabilities.

Claims for compensation should be made to the sponsor via the investigator.

The DoH GCP (2006) guidelines take a strict liability approach by providing that there is no need to prove negligence on the part of researchers or sponsors. The guidelines specify that only damages for bodily injury may be claimed. It is submitted that this means participants could only claim for damages relating to their bodily injury such as medical expenses, pain and suffering, loss of income, shortened life expectancy, and incidental costs.¹⁰

Participants may not profit from the wrongful acts of others, and therefore damages must aim at putting them in the same position they would have been in had they not suffered the wrong. Furthermore the quantum should be proportionate to the nature, severity and persistence of the injury, and should be consistent with the quantum of damages commonly awarded for similar injuries in terms of South African law on delict. Finally, the guidelines provide that where participants have contributed to their own harm, this should be taken into account (so-called 'contributory negligence').

Application to the Phambili case

While we argue that conduct exists that leads to potential harm, in the form of the act of administering the experimental vaccine to participants, demonstrating other elements in this case is a complex exercise. Some might argue that Phambili vaccine recipients experienced serious bodily injury in that they were at risk of enhanced susceptibility to HIV. However, it might be counter-argued that the trial data do not support this view as there are no statistically significant differences in HIV infections between vaccine recipients and placebo recipients. Even if this view was supported by data, enhancement may not endure (G Gray, personal communication) and therefore the injury may not be of an enduring nature as required by GCP (2006). It could also be argued that vaccine-recipients who experienced enhancement, and subsequently acquired HIV infection, suffered serious bodily harm of an enduring nature, satisfying the requirements in GCP (2006), and furthermore that a causal link existed between the conduct and the serious bodily injury, because 'but for' vaccination the enhancement would not have occurred

However, it might be counter-argued that trial data do not support this conclusion, as the difference in HIV infections between vaccine and placebo groups was not statistically significant (in other words, there are no reasons to believe that the results observed are not due to chance). Damages would be calculated according to costs incurred for participants' actual 'bodily injury' in the categories described above. It is possible that sponsors might argue for a reduction in damages based on 'contributory negligence', i.e., that trial participants who became HIV-infected contributed to their own harm by not implementing risk-reduction measures provided in the trial.

It is important to note that the issue of financial compensation for research-related injury should be viewed as distinct from two other ethical responsibilities in such trials. First, it is distinct from researchers' responsibility to provide a high standard of preventative measures to prevent participants contracting HIV.¹¹ In the Phambili trial, these measures included the provision of counselling, condom promotion, treatment for sexually transmitted infections, the option of free medical male circumcision, and post-exposure prophylaxis for both sexual assault and high-risk sexual encounters.⁵ Second, the issue of compensation is also distinct from researchers' responsibility to ensure that HIV-related care needs identified in trials are addressed.¹²⁻¹⁴ In the Phambili trial these steps included intensive counselling, monitoring of CD4 and viral loads, and assisted referrals for care and treatment including anti-retroviral treatment (ART).⁵

Critique of the DoH GCP (2006) guidelines

Using the Phambili trial as a case study reveals a number of shortcomings of the DoH GCP (2006) guidelines. Key concerns that emerge include:

- The DoH GCP (2006) guidelines limit claims for harm to those of an 'enduring' nature. This is a narrow approach insofar as many harms that are serious might not endure, but this does not detract from their status as harms. The best time to take durability of harm into account may be when determining quantum of damages.
- The guidelines exclude claims that are not for 'bodily' injury, which is out of step with modern approaches to providing damages for both physical and psychological harm.¹⁰ Our courts have consistently held that claims for psychological damages may be made (*RAF v Sauls* 2002 (2) SA 55(SCA)). Furthermore, they have dismissed arguments

that such an approach opens the floodgates to thousands of claims by holding that the normal standards of delictual liability and onus of proof will ensure the parameters of liability are carefully drawn.¹⁵ In the Phambili trial, knowledge of enhanced susceptibility to HIV infection may have caused participants anxiety or stress, especially for participants with knowledge of increased risk who were unable to implement risk-mitigation steps because they were unable to negotiate safer sex with their partners.

The guidelines state that claims should be made to the sponsor via the investigator. We argue that this requires participants to make their first approach to parties who may not be neutral in relation to the pursuit of a claim. It also provides no institutional support to such claimants, e.g. by involving RECs whose mandate is to protect participants' rights and welfare. In addition, this stipulation provides no process for appeal or review, thus forcing unsuccessful applicants to rely on administrative or civil law if their claims fail.

Conclusion

Compensation for research-related harm is an important protection for trial participants,¹⁶ and it is commendable that South African authorities require investigators to obtain insurance to cover the cost of research-related injury.¹⁷ We submit that the South African DoH (GCP) 2006 guidelines could be strengthened by addressing certain substantive and procedural limitations. We recommend that these guidelines be amended to ensure:

- the term 'harm' is more broadly defined
- more detail is provided on a range of possible damages that may be claimed
- RECs are recommended as a party more appropriately placed to assist participants who have queries about compensation for research-related injury.

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