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ETHICAL TRADEOFFS IN TRIAL DESIGN: CASE STUDY OF AN HPV VACCINE TRIAL IN HIV-INFECTED ADOLESCENT GIRLS IN LOWER INCOME SETTINGS

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Abstract

The Declaration of Helsinki and the Council of the International Organization of Medical Sciences provide guidance on standards of care and prevention in clinical trials. In the current and increasingly challenging research environment, the ethical status of a trial design depends not only on protection of participants, but also on social value, feasibility, and scientific validity. Using the example of a study assessing efficacy of a vaccine to prevent human papilloma virus in HIV-1 infected adolescent girls in low resource countries without access to the vaccine, we compare several trial designs which rank lower on some criteria and higher on others, giving rise to difficult trade-offs. This case demonstrates the need for developing more nuanced guidance documents to help researchers balance these often conflicting criteria.

Keywords

standard of care; research ethics; public health; vaccines; clinical trials

INTRODUCTION

Two controversies have dominated ethical debate over standards of care in clinical trials. The first arose after a landmark placebo-controlled trial showed that an intensive regimen of azidothymidine (AZT) could reduce mother-to-child transmission of the human immunodeficiency virus (HIV) by 70%[1]. Given the high cost and complexity of the study regimen, it was not clear that it could be implemented in lower income countries. Follow-up studies were conducted using shorter, cheaper, and easier-to-administer regimens, which were ultimately found to significantly reduce HIV transmission to non-breastfed infants using an endpoint assessed six weeks after birth. All but one of these sixteen trials compared short course AZT to a placebo[2]. The second controversy involved a proposal for a placebo-controlled trial of a new surfactant (Surfaxin) administered to premature infants with underdeveloped lungs in Bolivia[3]. Surfactants were not available to infants in lower income countries and were unlikely to be made available in Bolivia after the study. Both cases were criticized as unethical for using placebo controls rather than providing a higher standard of care. The ensuing vigorous ethical debate helped shape current international guidelines on standards of care in clinical research[4]. Though the issue of standard of care remains controversial,[5] current ethical guidelines outline when use of a placebo is justifiable. However, they provide limited help to a researcher having to choose among study designs with complex trade-offs among multiple criteria, including scientific validity, social value, protection of participants, and feasibility[6]. A study design that satisfies one criterion may

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fall short on another, and there is little guidance on how to balance these sometimes conflicting criteria.

These trade-offs are illustrated by considering how to design a trial to determine the efficacy of a licensed vaccine to prevent human papilloma virus (HPV) infection in HIV-infected adolescent girls living in lower income countries without current access to the vaccine. Vaccination against HPV is recommended by the World Health Organization (WHO)[7] for all female adolescents (but not males), including those who are HIV-infected. Despite this recommendation, governments with limited health care dollars may be reluctant to add the costly (currently $130/dose[8]) vaccine to their national program. The choice is especially complicated for countries with high HIV prevalence, as efficacy of the HPV vaccine has not been studied in HIV-infected people and there are numerous examples of vaccines that are safe but less immunogenic or efficacious in HIV-infected individuals[9]. Adoption of a vaccine that might be less effective for a substantial proportion of recipients would waste money and divert resources that should be spent on more effective prevention strategies.

After providing some additional information on HPV and HPV vaccines, we describe alternative study designs which vary in how well they achieve balance in satisfying the criteria of scientific validity, social value, participant protection, and feasibility. We then show how existing ethical guidance (The Declaration of Helsinki[10] and The Council of the International Organization of Medical Sciences (CIOMS[11]) is largely insensitive to these trade-offs. This case illustrates the need for improved ethical guidance that is better calibrated for research and public health decision-making.

BACKGROUND

HPV is the most common sexually transmitted disease in the world. Persistent HPV infection with certain high-risk strains is the most important risk factor for development of cervical and other anogenital dysplasias (pre-cancerous cells) and subsequent cancers in women[12]. High-risk HPVs and cervical cancer are common among women in lower income countries[13]. HIV-infected women are less able to clear HPV infection and more likely to develop cervical cancer than HIV-uninfected women[14]. Although there are some data on antibody levels in HIV-infected individuals, it is unclear whether a protective effect can be extrapolated from these data, and HPV vaccines do not have proven efficacy in HIV-infected individuals.

Gardasil, the Merck quadrivalent HPV vaccine (qHPV), administered as a three-dose series over six months[15], is safe, immunogenic, and in HIV-uninfected women, prevents more than 98% of middle and high-grade cervical dysplasia caused by the HPV serotypes included in the vaccine[16]. Persistence of protection has been documented for at least five years[17]. Typically once a vaccine is proven efficacious in individuals without HIV infection, extension of its use to HIV-infected people depends only on demonstrating safety and immunogenicity. This, however, ignores the potential for wide variation in the extent or duration of protection in immune compromised individuals. A further complication is that for some vaccines, including qHPV, the level of immune response required to provide protection against disease (the correlate of protection) is not known. Without knowing this immune correlate, researchers cannot definitively infer that a vaccine will be efficacious in HIV-infected persons without recourse to a study using the efficacy endpoint of HPV infection[18].

Safety and immunogenicity of qHPV have been established in HIV-infected girls and boys 7–12 years of age in the United States (US) who were either receiving highly active antiretroviral therapy (HAART) or were immunologically robust (CD4% ≥25%) and did not require HAART[19]. Importantly, immunogenicity was 30% to 50% lower than in HIV-

uninfected girls and boys for two of the four serotypes, raising the possibility that the vaccine might be less effective or offer protection for a shorter time in HIV-infected vaccinees and establishing a need for efficacy data.

POSSIBLE STUDY DESIGNS

Given the importance of establishing the efficacy of qHPV in HIV-infected girls for public health decision-making, we consider alternative study designs. We assume the studies would be conducted only in countries with high HIV prevalence, where the vaccine is not available, and where local Institutional Review Boards deem the study to be acceptable and of sufficient value to the country. Studies would counsel participants in safe sex and offer condoms. It should be noted that even if the vaccine was shown to be insufficiently efficacious to justify adoption as standard of care, a properly designed study might provide enough information to determine the correlate of protection for qHPV. This in turn would facilitate design of future studies addressing new vaccine formulations and strategies for lower income settings. Negative evidence would also allow governments to reallocate resources planned for the HPV vaccine and could lead to additional research to enhance efficacy in this population.

All proposed study designs discussed below would follow participants for three years with a study endpoint of a new persistent HPV infection with any of the four serotypes present in qHPV which was not present at study entry, an endpoint which has been used in multiple previous studies[20] (the gold standard of using PAP smears is not feasible in resource-poor settings). The age range reflects the Advisory Committee on Immunization Practices (ACIP)[21] recommendation to vaccinate in early adolescence before sexual debut. Both perinatally and horizontally HIV-infected girls would be enrolled just before or soon after they become sexually active.

It is likely that there would be sufficient numbers of HPV-negative individuals in the target population. Very few perinatally HIV-infected girls would be HPV-infected before sexual initiation. Horizontally HIV-infected girls would likely have become HIV-infected through sex, but it is unlikely they would be HPV-positive at enrollment for all four HPV types in the qHPV vaccine.

Each design is discussed in terms of the following criteria: scientific validity, social value, protection of participants, feasibility (represented by sample size) and compliance with existing ethical guidance (summarized in Table 1). It is important to note that only the design described in Option 1 would allow direct measurement of vaccine efficacy[22] in the target population.

Option 1 - Superiority, Placebo Controlled, Crossover Design

The first option is to randomize HIV-infected adolescent girls to either three doses of qHPV or placebo. At the end of follow-up, participants would be unblinded and the placebo group would receive the vaccine, so that ultimately all participants would receive qHPV.

Scientific validity—Randomization would help ensure that placebo and vaccine groups were similar not only with respect to HIV clinical status, but also for sexual behavior and exposure to HPV during the study, allowing unbiased estimates of vaccine efficacy. Because the HIV-infected girls in the study would likely have other co-morbidities, having a placebo group would also be the best way to determine whether adverse events might be attributable to the vaccine.

Feasibility—Because of the relatively large anticipated vaccine efficacy, sample sizes are not overly large relative to competing study designs (see Table 1).

Social value—This design will provide definitive in-country safety, immunogenicity and efficacy information, giving governments in areas of high HIV prevalence the most easily interpretable data for making a decision about adopting qHPV vaccination.

Protection of participants—The major concern with this design is use of a placebo when the efficacy of qHPV has been established in immune competent populations. Each participant would have a 50/50 chance of receiving qHPV immediately and those in the placebo group would receive the vaccine after three years of follow-up. The ethical cost of this approach is that during the initial three years of the study, placebo recipients would not have whatever protection against HPV infection would be afforded by qHPV, which could be considered a harm. It is widely accepted in the medical ethics literature that researchers have a duty to provide the standard of care, meaning that it is not sufficient to simply ensure that participants are made better off than they would be otherwise with study participation[23]. One reason for this is that all of us, including researchers, have a duty to perform easy rescues. The classic example is an adult walking by a child drowning in a shallow pool of water, who could easily be pulled to safety. Just as the adult has the duty to pull the child out of the water even if there is a slight cost to him/her, it seems clear that we all have duties to help the people we interact with when we can help them greatly at minimal cost to ourselves[24].

Applying this duty to the present case, we need to determine whether participants are likely to benefit significantly from receiving vaccine instead of placebo and how much it would cost researchers to do so. The cost here is not merely the monetary cost of providing the vaccine, but how critical it is to use a placebo control in order to yield scientifically valid results. As discussed in the Option 2 designs, *a priori* we know that using no control or an active control may yield biased and less interpretable results, in which case study participants could be burdened by trial participation for no good reason, and the opportunity to produce valuable data that could have saved others will have been lost.

The question then becomes - what is the minimum standard of care/prevention that investigators have a duty to provide to participants? Wendler and colleagues say that based on the duty to perform easy rescues, the answer depends on the cost of providing a higher standard and the relevance of the study question to the local population. This suggests that if the qHPV study was very relevant for the host community and the chance of yielding valid results is significantly reduced without a placebo control, then the study may be acceptable. On the other hand, some claim that investigators have to offer the best proven interventions to participants. This would mean providing qHPV to all participants, but only if certainty about the efficacy of the vaccine in HIV-infected adolescents was sufficiently high. Still others argue there is some threshold between the best proven interventions and what is locally available, though what this middle ground is in specific cases is hard to determine[25]. There is no universal agreement on the answers to these questions.

Existing ethical guidance—Several guidelines address the ethics of using a placebo in a clinical trial. The two most prominent are the World Medical Association's Declaration of Helsinki and the guidelines issued by CIOMS. The Declaration of Helsinki permits placebo controls when (1) there is no current proven intervention or (2) the use of a placebo is scientifically necessary and the placebo group will not be exposed to risk of serious or irreversible harm[26]. CIOMS guidance has a similar general rule about use of a placebo, but departs from Helsinki by providing an exception that placebo may be appropriate: '… in a country1 or community in which an established effective intervention is not available and

unlikely in the foreseeable future to become available, usually for economic or logistic reasons…' and where the intervention is responsive to local health needs[27].

The use of placebo appears to violate both conditions outlined in the Declaration of Helsinki. As mentioned earlier, although there is no current intervention that has been proven to prevent HPV in HIV-infected individuals, the question is whether we can extrapolate from the existing data in individuals who do not have HIV and from the safety and immunogenicity data in HIV-infected individuals. The WHO recommendations imply that the evidence is sufficient. There also appears to be a risk of serious and irreversible harm from the use of placebo. Any participants in the placebo arm who do not become infected with HPV would be given the vaccine at the end of the study. During the first three years of the HPV study, however, placebo recipients could be infected with HPV, increasing their likelihood of developing cervical dysplasia and even cancer.

The Declaration of Helsinki guidance, however, has been criticized as overly demanding and out of step with other guidance documents, including CIOMS[28]. Under CIOMS, use of a placebo is not permitted if an intervention is not available in a country and unlikely to be made available in the near future, since the study population would be unlikely to benefit from the data they help generate, leading to concern that the host community is being exploited[29]. It is very difficult to predict whether the HPV vaccine would become available in the near future in the host countries. Given the high cost of the vaccine, there is reason to believe it may not become widely available. However, the pharmaceutical company has raised the possibility of tiered pricing, although this is not yet in effect, and actual pricing levels would affect the ability of countries to adopt use of the vaccine.

These international ethical guidelines are influential but take different approaches and are subject to important criticisms. They raise questions without easy answers. What counts as a proven intervention? If an intervention like the HPV vaccine is proven in the general population, but there is uncertainty about extrapolating the results to a subpopulation of HIV-infected adolescent girls, can further research be accomplished under the restrictions of the existing ethical guidance? What counts as a risk of serious or irreversible harm? Is the fact that some girls who receive the placebo will likely become infected with HPV sufficiently serious? Finally, how can researchers and ethics committees predict what intervention will become available 'in the foreseeable future'? Given the high cost of the HPV vaccine, it is difficult to imagine it becoming widely available in the near future. Nevertheless, many high-cost interventions for HIV-infected patients in lower income settings were introduced because of robust placebo-controlled trials that fueled advocacy which ultimately led to their availability, e.g. combination antiretrovirals[30].

Option 2 – Designs Without Untreated Controls

Since the vaccine is likely to be at least somewhat efficacious in HIV-infected adolescents, the designs proposed in this section are less problematic in terms of complying with existing guidelines and protecting participants, as they provide vaccine to all participants. All these designs, however, may compromise scientific validity to some degree in terms of interpretability of study results, which in turn reduces social value. Equivocal results may lead a policy-making body to not adopt an efficacious vaccine or to adopt a non-efficacious vaccine and thereby use valuable resources that might be better spent on other public health interventions. As previously discussed, this raises the concern that a study that does not violate ethical principles regarding protection of participants but is unlikely to produce readily interpretable results, may still be unethical.

The primary difficulty with scientific validity for designs under Options 2 and 3 is identifying adequate control groups. Relying on comparing the rates of HPV infection

collected in the HIV-infected subjects in the study with rates in historical HIV-uninfected controls collected at different times or in different places is problematic. If infection rates are comparable to or lower than those observed in historical controls, this might mean the vaccine was effective in the study population, or that rates of sexual activity and HPV exposure in the study population were lower than in the historical controls, or there were other unmeasured cofactors influencing persistent infection that were different in the study and control populations. If higher rates of infection are observed in the study group this could also be due to differences in exposure or other unknown factors. In addition, rates of infection with no vaccine may differ substantially between HIV-infected and HIV-uninfected adolescent females. Significantly, these designs allow no direct measurement of vaccine efficacy in the HIV-infected group.

Option 2A – Open Label Uncontrolled Trial Administering Three Vaccine Doses to HIV-Infected Girls

This simple design would enroll a cohort of HIV-infected adolescent girls, administer three doses of qHPV, collect information on safety and immunogenicity, and follow them long enough to estimate the proportion developing persistent HPV infection. This proportion would be compared to published estimates from trials in older women with the same endpoint.

Scientific validity—Although information on safety, immunogenicity, and endpoint rates would be collected, the difficulty would be in comparing each outcome to data collected in either HIV-infected (only safety and immunogenicity) or uninfected (all outcomes) historical controls. The immunogenicity information obtained would be useful when placed in the context of reference comparison groups but is likely to be of limited value in the absence of correlates of protection. Furthermore, the comparison of endpoint rates assumes similar exposure to HPV and matching for other factors between groups, which is unlikely to be achievable outside of a randomized trial.

Feasibility—The study would require a relatively small sample size.

Social value—The uncertainty of scientifically interpretable results would result in governments having less optimal information for assessing the value of the vaccine in their setting, increasing the likelihood of an incorrect decision about adopting the vaccine as standard of care.

Protection of participants—This design does not raise significant concerns about participant protection.

Current ethical guidance—This design does not appear to violate existing ethical guidance.

Option 2B – Superiority Design Randomizing HIV-Infected Girls to Four vs. Three Doses of Vaccine

The licensed and recommended dosing of qHPV is three doses. As shown in an earlier trial[31], immunogenic responses to the vaccine in HIV-infected girls and boys were lower than those in HIV-uninfected children. A follow-up study of these subjects in the US suggested that four doses yield higher immunologic responses[32]. On this basis, a potential design would randomize HIV-infected girls to receive either three or four doses of vaccine, to determine if infection rates in the four dose regimen would be lower.

Scientific validity—Immunogenicity for both dose regimens in the lower income setting could be compared to immunogenicity in the ongoing study in the US and relative efficacy of the two dose regimens within the study could be measured. Regardless of rates of HPV infection in the two arms, assessing vaccine efficacy still requires comparison with historical controls, with the associated difficulties in interpretation described previously.

Feasibility—The sample size required to detect differences in efficacy between three and four doses would probably be unfeasibly large (see Table 1), since rates of HPV infection would likely be low and differences small.

Social value—Given the higher cost of giving people four doses, this design would be less relevant to the needs of host countries facing significant resource constraints.

Protection of participants—Additional monitoring for safety of a fourth vaccine dose would be needed, but this design does not raise significant concerns about participant protection.

Current ethical guidance—This design does not appear to violate existing ethical guidance.

Option 2C – Non-Inferiority Design Randomizing HIV-Infected Girls to Two vs. Three Doses of Vaccine

This study design would randomize HIV-infected girls to either two or three doses of qHVP, based on observational data from recent large trials showing that efficacy after one or two doses of a bivalent HPV vaccine over a median follow-up of 4.2 years was similar to that of the full three-dose series[33], and immunogenicity responses were similar to those in HIV-uninfected participants receiving qHPV[34]. Showing that two doses are as effective as (or minimally less effective than) the recommended schedule could result in large savings. The two-dose regimen would be considered acceptable if the proportion of participants developing persistent HPV infection was within the non-inferiority margin of an ‘acceptable’ difference from the three-dose regimen and if the rate of infection with the three-dose regimen was deemed satisfactory relative to historical (or possibly concurrently-enrolled HIV-uninfected girls – see next section) controls.

Scientific validity—Assessment of the adequacy of the three-dose regimen using control data is vitally important to interpretation of the study results and subject to the difficulties in interpretation outlined previously.

Feasibility—Sample sizes are smaller than for the superiority design described in Option 2b (Table 1) but are sensitive to the choice of non-inferiority margin (i.e, how much less protection with two doses is acceptable). It might also be necessary to extend the length of study follow-up since short term protection might be similar in the two arms but longer-term protection might wane more quickly in the two dose regimen.

Protection of participants—Administering only two doses to half the participants could be deemed ethically problematic since it is not the recommended schedule and it could be argued that participants are being randomized to less than the best proven standard of care. Additionally, HIV-infected youth in the US study had lower humoral responses to qHPV than did HIV-uninfected youth, and it has been established for many other vaccines that HIV-infected patients need a greater number or strength of doses to achieve an optimal response[35]. These concerns could be alleviated by existing data referred to above (albeit in an HIV-uninfected population) that suggest favorable performance of a two dose regimen

and also by vaccinating those in the two-dose group at the end of follow-up, acknowledging the longer risk period of HPV acquisition (pre third dose) and that the interval between the second and third vaccinations would be longer than recommended with possible effects (beneficial or not) on immunogenicity[36]. These factors raise concern about the appropriateness of selecting an HIV-infected population for an efficacy trial of a reduced-dose regimen of HPV vaccine.

Social value—Adopting a two-dose regimen might involve a trade-off between the potential morbidities from decreased protection (a function of the non-inferiority margin chosen for trial design) and the reduction in costs incurred by administering only two vaccinations. Governments might need cost-benefit analyses to make a final decision, but if acceptable, results from this study could result in significant cost savings and would be very relevant for policy makers distributing limited health care resources.

Current ethical guidance—This design would be permissible under CIOMS. It is unclear whether the design is permissible under Helsinki because the two-dose regimen which protected women without HIV infection might offer less protection to HIV-infected girls.

Option 3 - Designs Without Untreated Controls Including Cohorts of HIV-Infected and HIV-Uninfected Girls

Study designs described in Option 2 could be expanded to include cohorts of HIV-uninfected girls.

Scientific validity—This would be increased by studying individuals in all study arms from a similar background with the same study endpoint. However, even when the HIV-uninfected subjects are drawn from the same population, they may differ from the HIV-infected participants at study entry, and their sexual behavior and exposure to HPV may differ during follow-up, biasing comparisons of HPV infection rates. Despite this limitation, they are the best reference group for comparison of incident HPV infection.

Feasibility—Including HIV-uninfected groups increases sample size, possibly to the extent that the trial will be too expensive to implement.

Protection of participants—No significant concerns are raised by including HIV-uninfected girls under designs 2a and 2b. Under a design like that presented in 2c, where half the participants would receive two rather than three doses, there would be reservations about providing HIV-infected participants with inadequate protection as discussed above, but these would be balanced by evidence of comparable efficacy for the two-dose series in HIV-uninfected girls from observational studies.

Social value—With the increased scientific value of enrolling controls drawn from the same population, governments would have better (but not ideal) information on which to base their decision about usefulness of the vaccine.

Current ethical guidance—It is unclear whether randomizing HIV-infected women to receive two doses of the qHPV vaccine would be permissible under the Declaration of Helsinki because the two-dose regimen which protected women without HIV infection might offer less protection to HIV-infected girls.

DISCUSSION

The current state of the debate over standard of care may not be helpful in illuminating situations increasingly faced by decision-makers, sponsors and clinical researchers. The qHPV vaccine example illustrates that existing ethical guidance not only fails to help them navigate amongst different trial designs that favor different ethical criteria, but in some cases, hinders research that would provide local governments with the clearest information on which to base public health decisions.

Our analysis suggests that to assess the efficacy of an HPV vaccine in HIV-infected girls, Option 2c—randomizing HIV-infected girls to two versus three doses of qHPV—does the best across the various criteria. This design has the best scientific validity among the designs with no untreated controls, clear social value for the host countries, is feasible, and provides some degree of protection to all participants. Although it is not clear whether this design would satisfy the Declaration of Helsinki criteria, Helsinki has been widely criticized for treating participant protection as trumping all other considerations, and failing to recognize other ethical criteria sufficiently. It is possible, however, that Option 2c will be unable to produce scientifically valid results. The least problematic design in terms of scientific validity is Option 1 - the placebo-controlled crossover trial randomizing HIV-infected girls to three doses of the vaccine or placebo, but this is also the most problematic approach on the criterion of participant protection.

Stepping back from existing ethical guidance and criteria, there are other ways to evaluate this research. One way would be to take a utilitarian approach and assume that whatever study design serves the greater good should be adopted[37]. However, almost everyone would agree that there must be some limits to utilitarianism in research. Some of the research scandals of the past may have been justifiable on utilitarian grounds, but are almost universally seen as unethical today. On the other end of the spectrum, guidance documents like the Declaration of Helsinki value participant protection above all else. Yet this approach simply does not fit with the primary goal behind the conduct of research—the goal of developing generalizable knowledge for future patients.

Neither utilitarianism nor relying on absolute participant protection is sufficiently nuanced to capture the complex ethical trade-offs involved in the conduct of research, and existing ethical guidance has significant limitations. We argue that, to be useful to those involved in the conduct of research, ethical guidance should recommend that determining how to design a research study amongst competing options, researchers and sponsors should choose the design that achieves the best balance regarding scientific validity, social value, feasibility, and protection of participants.

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22. Vaccine efficacy is defined as:

$$VE = \frac{Rp - Rv}{Rp} * 100\ \%$$

where R_p is the proportion or incidence rate of participants developing persistent HPV infection with no vaccination and R_v is the corresponding rate in the group receiving the vaccination.

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Biographies

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Table 1

Summary of ethical principles for alternative study designs for assessing efficacy of an HPV vaccine in HIV-infected adolescent girls in resource-limited settings

Design	Scientific validity	Local social value of the data	Protection of participants	Feasibility			Compliance with ethical guidance under Helsinki and CIOMS
				Estimated HPV infection rate		N/arm (evaluable)[4]	
1. Superiority: 3 doses vs placebo +crossover	Cleanest data	Highest	Participants in active arm protected from start, placebo arm will receive benefit of vaccine in 3 years	3 dose rate	Placebo rate		Not permissible under Helsinki; unclear whether allowed under CIOMS
				2%	10% (80% VE[3])	162 [1]	
				2%	20% (90% VE)	57	
				4%	14% (70% VE)	147	
				4%	40% (90% VE)	25	
2a. Open label of 3 doses vs historical controls	Depends on interpretable comparison of efficacy to historical controls	Limited	All participants equally protected	3 dose rate	Width 95% CI		Permissible under both
				2%	± 3%	200	
				4%	± 4%	200	
2b. Superiority of 4 vs 3 doses (historical controls)	Depends on interpretable comparison of efficacy to historical controls	Limited—4 doses even less affordable	Both arms receive same or greater protection as developed countries	4 dose rate	3 dose rate		Permissible under both
				2%	4%	1239 [1]	
				2%	6%	524	
				4%	6%	1962	
				4%	8%	602	
2c. Non-inferiority: 3 vs 2 doses (historical controls)	Depends on interpretable comparison of efficacy in 3 dose arm to historical controls	Arguably highest, depending on whether 2 or 3 doses plausibly offer protection	Both arms receive some protection	3 dose rate	2 dose rate		Unclear whether permissible under Helsinki, clearly permissible under CIOMS
				2%	4%	862[2]	
				2%	6%	255	
				4%	6%	1547	
				4%	8%	411	
3. Adding HIV uninfected controls to 2a–2c	Better comparison arm	More relevant controls which improves decision-making	All participants equally protected				Permissible under both for 2a and 2b, unclear whether permissible under Helsinki for 2c

[1]Difference in event rates between standard 3-dose regimen and comparator arm interpreted as ‘clinically meaningful difference’ between arms that study designed to detect. Sample size assumes a 2-sided Type I error of 0.05

[2] Difference in event rates interpreted as 'acceptable decrease' in efficacy of 2-dose regimen relative to 3-dose regimen. Sample size assumes a 1-sided Type I error 0.025.

[3] Vaccine efficacy (VE)

[4] Needs to be inflated to account for loss-to-follow-up, interim analyses, exposure to HPV by age etc