ACV Guide to Participants

ETHICAL CONSIDERATIONS IN MALARIA VACCINE TRIALS

Dear Participant,

We will be examining a case about a malaria vaccine trial that is designed to debate the responsibilities that sponsors/ investigators have to respond to the healthcare problems of participants; to pay participants appropriately and to avoid "undue inducement" as well as various other issues.

Objectives of the exercise

1. To consider complex ethical concerns in vaccine trials, with reference to theory and/or data, and ethical guidance. These concerns include "ancillary care", "undue inducement" and payment of trial participants; and
2. To develop and defend ethical arguments, and to analyze the arguments advanced by others.

Your assignment is to read the case study below; read the assigned articles, then participate in a debate, where notes will be taken. Your groups' outputs will be presented briefly to the full group.

You can find the articles on the course website at www.advac.org

Name: ?

Password: ?

Have a good time with this exercise!

CASE STUDY

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Note: all case studies have missing information. You may need to make some assumptions. Make these assumptions explicit.

PLASMOVAX, a France-based company, has developed a vaccine against malaria that appears promising. Animal studies have been successful. Phase I and II studies in Europe and Africa in both adults and children aged 6 weeks up to 5 years have demonstrated that the vaccine is safe and produces significant immune responses in the majority of participants. These studies have also demonstrated no interference of immune responses to co-administered routine infant vaccines; and efficacy of about 50% against clinical malaria. Furthermore Phase I studies with clinical challenge of volunteers showed that about 50% of those vaccinated are protected.

PLASMOVAX now wishes to begin a Phase III vaccine trial in The Congo. Epidemiological studies have identified Congolese sites with high incidence of malaria in young children. The target population has been identified as young infants (from 6 to 14 weeks) in co-administration with DTP1-3. Half of the enrolled infants will be randomized to receive the experimental malaria vaccine and half will receive a placebo injection, because the company has not been able to identify a suitable comparator vaccine likely to be beneficial that is licensed for the infant population. The trial vaccinations (3 doses in total) will occur in co-administration with the routine EPI vaccines, i.e. pentavalent DTP/HIb/Hep B vaccine at 6, 10 and 14 weeks of age. The background HIV prevalence varies from <5% to >15% in the mothers, with lower prevalence in infants.

The Congolese government agrees that PLASMOVAX may conduct the trial in their country. As a result of negotiations between the government and the sponsor, PLASMOVAX agrees to provide the vaccine at no cost for the trial, as well as provide laboratory and computer equipment for the conduct of the study, and training for GCP clinical trial conduct. PLASMOVAX also agrees that if the vaccine proves effective it will be given free of charge through EPI vaccination in the country for an unspecified time-period.

The trial will be carried out by the Medical Research Institute of The Congo (MRIC). The study is a randomized double-blind placebo-controlled trial. It aims to enroll 8000 young children in 4 sites in The Congo with different levels of malaria transmission intensity.

The trial will end when **800 clinical malaria disease episodes** have accumulated – which is sufficient to assess the primary endpoint of the trial, namely whether the malaria vaccine can reduce the incidence of <u>all episodes</u> of malaria disease by 50% (with a 95% lower limit of the confidence interval of 30%). The trial also aims to assess if the vaccine will reduce <u>severe disease</u> and to assess clinical malaria efficacy at each of the 4 sites.

The overall costs of the study are approximately 50 million USD including infrastructure support.

Community engagement
Prior to study start, the MRIC will meet with community leaders at all trial sites to ensure their understanding of the consent form and seek their feedback on the trial. The sponsor has undertaken to take into account feedback received from community leaders. The MRIC will organize community education classes where mothers and other interested community members may attend to learn more about the study before enrolment starts. Mothers will be encouraged to ask questions, as well as to discuss the issue with their husbands or significant others.

Recruitment and consent:
Mothers bringing their infants to EPI clinics for their first vaccinations will be approached and invited to enroll their children in the study. Prior to the mother's enrolling their infants into the trial, the relevant trial information will be presented in a 12 page consent form, translated into the local language. Trial staff do not plan to formally assess the comprehension of key trial concepts in the consent form.

Standard of prevention*:*
In The Congo, donor agencies, notably the Global Fund to Fight AIDS, Tuberculosis and Malaria and the US President's Malaria Initiative have awarded funds to make Insecticide-treated bednets (ITNs) available to all Congolese residents. However, uptake and use of ITNs remains low at the start of the planned trial in the communities surrounding trial sites. WHO has recommended that ITNs be used by the population in malaria-endemic countries, because they have been shown to reduce malaria disease and all-cause mortality in several settings in Africa. In addition, there is a plan to introduce indoor residual spraying in some parts of the Congo. This spraying may reduce the incidence of malaria substantially. PLASMOVAX says they will work with the MRIC to supply ITNs to the health facilities co-located with trial sites, and that mothers of enrolled infants will be regularly counseled by the trial site staff to use ITNs, however they do not plan to monitor 'defaulters'.

Access to treatment*:*
Infants being screened for enrollment in the trial will have a general medical exam and tests to identify pre-existing conditions. There will be pre-defined exclusion criteria including severe anemia and severe malnutrition, but in order to have a reasonably representative Phase III study population, mild anemia and non-severe malnutrition will not exclude children. Those acutely unwell with, for example, respiratory infections or clinical malaria will have enrolment deferred and may be re-screened a few days later. Treatment can be provided for most of these conditions by health facilities co-located with sites.

For infants that are enrolled, a cross-sectional survey to assess anaemia and malaria parasitaemia will be undertaken at three time-points across the trial. Mothers of enrolled infants will be counseled by site staff to seek early treatment for febrile disease at trial-linked healthcare centres. WHO recommends that malaria treatment occurs with artemisinin-combination treatments (ACTs), but these are more expensive than previously used antimalarials. In the Congolese health system there is still use of older less effective drugs. ACTs are available at health facilities co-located with 2 of the sites. However, at the 2 other sites, ACTs are not available in linked healthcare centres, and there is a shortage of cold chain capacity, and nurses. The sponsor and MRIC pledges to work with donors to improve malaria care at these sites, as well as microbiology, radiology, and parasitology expertise at all health

facilities co-located with trial sites. They argue they cannot guarantee access to ACTs for all infant participants who acquire malaria during the trial.

Payment of trial participants:
Mothers will bring their infants to the trial sites 16 times over 2 years. Most of these visits will be "non-vaccination visits" where infants will undergo a brief physical exam, and the mother will answer questions about concurrent medications and adverse experiences. At some other visits, these procedures will be undertaken, plus blood draws, and/or vaccination and a reactogenicity assessment. Field workers will assess reactogenicity during home visits for 7 days after each vaccination. The researchers wish to financially compensate mothers for their time and expenses. They propose to pay 1.5 USD for non-vaccination visits (of which there are 10); 2 USD for vaccination visits (of which there are 3); and 2 USD for cross-sectional survey visits (of which there are 3). Across the two-year trial, all mothers will receive 27 USD for their time and inconvenience. In addition, the trial will re-imburse mothers their direct travel expenses which formative research in the community indicates will range from 1-2 USD per visit.

Before the study can begin, a journalist interviews the study PI about aspects of the forthcoming trial. The journalist publishes an article describing the trial's overall plans, including for prevention and treatment. This story then also runs as a BBC world service radio piece. The news of the trial is picked up by a local community group. The group (**Hands Off our Children - HOC**) is an activist group that argues that the sponsor and MRIC are providing an inferior treatment for malaria than their resources allow. They also argue that if preventive methods like ITN-counselling is left to site staff they will be biased because they need malaria infections to prove if their vaccine works. They argue that the trialists already have most of the tools needed to prevent malaria, and that the trial exploits the situation of vulnerable children. HOC condemns the trial in a series of publications and radio interviews.

The Chair of the Research Ethics Committee at the PI's home institution in The Congo (MRIC) is alerted to the crisis, and immediately arranges a consultation between the sponsors/ researchers, on the one hand, and the activists, on the other. The Chair is aware that the final protocol will be submitted to the REC in the near future.

Group work guidelines:

1. You have been divided into a number of groups.
2. Within the group assign about a third of members to be the **activists**.
3. A third of the group should be assigned the role of the **sponsor/researchers**.
4. The remaining third should be assigned the role of the **ethics committee** who will make the final decision.
5. Nominate a **chair** of the ethics committee whose role it is to call and manage the meeting between the 2 parties.
6. Then allow the activists and sponsor-researchers to have some time **on their own** to get their arguments together (about 30/45 minutes). REC reps should use this time to consider the questions they wish to ask.
7. Then both the activists and the sponsor-investigators must present and defend their points in a verbal debate which will be chaired by the REC Chair.

8. Then, after the debate is concluded, the REC should deliberate. Researchers and activists may be present at this deliberation.
9. Then the REC should make a final **recommendation in writing about the standards they would like to see in the protocol. (1-3pages)**
10. This REC memo should be given to Catherine Slack who will present an overview on the Monday morning following the ethics session.

What issues should the REC memo address?

1. What community engagement efforts should be expected for this study?
2. What standard of prevention should be ensured to enrolled participants in the trial?
3. What steps should sponsor-investigators take to address the malaria treatment needs of enrolled infants?
4. What consent measures should be undertaken?
5. What payment recommendations should be made?
6. Any other standards that need to be in the protocol?

Resources

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2. Grady, C. (2004). Ethics of vaccine research. Nature Immunology, 5, 464-467.

3. Dickert N, Grady C. (2005). What's the price of a research subject? Approaches to payment for research participation. *N Engl J Med* 1999; 341(3): 198-203.

4. Participants in the 2006 Georgetown University Workshop on the Ancillary Care obligations of medical researchers working in developing countries (2008). *The Ancillary Care obligations of medical researchers working in developing countries. PLoS Medicine, 5*, 5, 0709-0713.

5. Richardson, H.S, Belsky, L. (2004). Medical researcher's ancillary care responsibilities. BMJ, 328, 1494-6. See PDF

6. Lindegger, G., & Richter, L. (2000). HIV Vaccine Trials: Critical issues in informed consent. *South African Journal of Science, 96*, 313 – 318

7. Marsh, V. et al., Beginning community engagement at a busy biomedical research programme: Experiences from the KEMRI CGMRC-Wellcome Trust Research Programme, Kilifi, Kenya, Social Science & Medicine (2008), doi:10.1016/ j.socscimed.2008.02.007

8. *Participants (2013) Participants in the Community Engagement and Consent Workshop, Kilifi, Kenya, March 2011.* Consent and Community Engagement in diverse research

contexts: Reviewing and developing research and practice. *Journal of Empirical Research on Human Research Ethics*, Vol. 8, No. 4, 1-18.

Ethical guidelines

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