Ethical Considerations in Community–Engaged Research in International Studies

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Disclaimer
Community engaged research

Framework for community involvement in:

- Research question
- Study design
- Recruitment and retention strategies
- Methods
- Data collection
- Interpretation
- Results dissemination
Community

• Group of people with common social ties, perspectives, and joint action in geographical locations or settings
• Not necessarily homogeneous and don’t speak with one voice
• Risks and benefits of research affect not only individual participants but also the community
Potential consequences of lack of community engagement

- Failure to address complexity of health needs
- Failure to assess true impact of interventions
- Failure to initiate a project
- Failure to recruit and retain subjects
- Shutdown of entire research program

Suspicious mount against U.S. laboratory

Abdul Khaik, The Jakarta Post, Jakarta | Sat, 04/26/2008 12:02 PM

The U.S. Namru-2 research lab has increasingly been accused of providing little benefit to Indonesia, with officials, lawmakers and experts voicing suspicion the lab is used for intelligence activities.

The criticism mounted following the United States’ demand that Indonesia grant diplomatic status to all of its 19 citizens working at the Naval Medical Research Unit No. 2 (Namru-2) in Jakarta.

University of Indonesia international law professor Hikmahanto Juwana said diplomatic immunity given to the U.S. researchers violated international law.

He cited the Vienna Convention that says only diplomats are entitled to immunity.

"We are wondering what the use of diplomatic immunity is for a researcher. Are they so in danger of being arrested or prosecuted in their work that they need protection?"

"Is Indonesia so weak that they can protect foreigners working here?" he told The Jakarta Post on Friday.
Laboratory of Malaria Immunology and Vaccinology

- Antigen & Biomarker discovery
- Immunopathogenesis
- Immunity

Discovery

- Protein production
- Conjugation
- Formulation
- QA/QC

Vaccine production

- Animal studies
- GLP tox

Preclinical studies

Clinical development

- Phase 1 & 2, US & Mali
- Proof of concept
Clinical Development of Malaria Vaccines

• First in human studies in malaria naïve adults (typically US, Europe, or Australia) to establish initial safety and immune responses (Phase 1a, Phase 2 if challenge component)

• Immediately followed by studies in malaria exposed adults, usually in Africa (Phase 1b)

• If safe and immunogenic age de-escalate to children and infants (Phase 1b and Phase 2)

• Children are defined as vulnerable populations: must have likely benefit

➢ Risk is reduced by careful preclinical evaluation but not eliminated
Phase 1 Trial of Malaria Transmission Blocking Vaccine Candidates Pfs25 and Pvs25 Formulated with Montanide ISA 51

Yimin Wu¹, Ruth D. Ellis¹, Donna Shaffer², Erica Fontes², Elissa M. Malkin¹ᵃ, Siddhartha Mahanty¹ᵇ, Michael P. Fay³, David Narum¹, Kelly Rausch¹, Aaron P. Miles¹ᶜ, Joan Aebig¹, Andrew Orcutt¹, Olga Muratova¹, Guanhong Song¹, Lynn Lambert¹, Daming Zhu¹, Kazutoyo Miura¹, Carole Long¹ᵈ, Allan Saul¹ᵉ, Louis H. Miller¹, Anna P. Durbin²

¹Malaria Vaccine Development Branch, National Institute of Allergy and Infectious Diseases, Rockville, Maryland, United States of America, ²Center for Immunization Research, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, ³Biosciences Research Branch, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, United States of America
Anaemia in a phase 2 study of a blood stage falciparum malaria vaccine

Ruth D Ellis¹, Michael P Fay², Issaka Sagara³, Alassane Dicko³, Kazutoyo Miura¹, Mempen A Guindo³, Aldiouma Guindo³, Mahamadou S Sissoko³, Ogobara K Doumbo³, Dapa Diallo³
"Cytokine Storm" in the Phase I Trial of Monoclonal Antibody TGN1412: Better Understanding the Causes to Improve PreClinical Testing of Immunotherapeutics

Richard Stebbings, Lucy Findlay, Cherry Edwards, David Eastwood, Chris Bird, David North, Yogesh Mistry, Paula Dilger, Emily Liefooghe, Isabelle Cludts, Bernard Fox, Gill Tarrant, Jane Robinson, Tony Meager, Carl Dolman, Susan J. Thorpe, Adrian Bristow, Meenu Wadhwa, Robin Thorpe and Stephen Poole

*J Immunol* 2007;179;3325-3331
LMIV Vaccine Research

- 10 Investigational New Drug (IND) applications initiated
- 10 Phase 1 trials in malaria naïve adults (US, Australia)
- Challenge study in malaria naïve adults (UK)
- 3 Phase 1 trials in Malian adults
- Phase 1,2 trial in 336 Malian children
- 3 epidemiologic studies in Malian villages to provide baseline data to support clinical trials

➢ Malian studies are by far the most successful in terms of community engagement
Mali

- Landlocked, mostly desert
- 4th highest infant mortality rate
- 205th in life expectancy
- ~50% of population < 15 y/o
- One of the 25 poorest countries in the world
- Stable democracy
- Relatively high % of GDP spent on health (7%)
- 90% Muslim
- Traditional health providers play a large role

Malaria Research and Training Center, Bamako, Mali

- 20 year history of collaboration with NIAID
- International Center for Excellence in Research (ICER)
- Established teams of vector biologists, epidemiologists, parasitologists, immunologists, and clinical trialists
- Located at University of Bamako, under Faculty of Medicine, Pharmacy, and Odonto-Stomatology (FMPOS)
- Researchers come from the villages impacted by the diseases under study
Strong local collaborators: international leaders in setting malaria research agenda
Regulatory Structure

- Protocols reviewed internally at NIAID for scientific validity
- Ethical review by both NIAID and University of Bamako/ FMPOS IRBs/ECs
- Reviewed by NIAID intramural regulatory group
- Reviewed by FDA and Mali Ministry of Health if investigational product
- Safety overseen by local medical monitor, NIAID Data Safety and Monitoring Board
- Study site monitored by NIAID for compliance with good clinical practice
- Study insurance required by FMPOS EC and Mali MOH
- Additional site monitoring by WHO
Dual Ethical Review of Protocols: Value Added

- **NIAID IRB**
  - Scientific elements
  - Assessment of risk/benefit
  - Regulatory issues (FDA requirements)

- **FMPOS Ethics Committee**
  - Community standards
  - Compensation
  - Family issues
  - Consent/assent
  - Benefit to community
Ethics review in Mali

- 3 ethics committees review human subjects research in Mali; FMPOS typically reviews more complex/risky studies. ~50 new submissions annually
- Staff: 2 part time support
- Protocols and consents translated into French prior to review (not Investigators Brochures)
- Strong support from NIH: ethics training for researchers and committee members conducted in collaboration with Department of Bioethics in 2003 and 2007

(NIAID IRB: 32 initial reviews annually, 4 full time staff)
Study design/protocol development

- Vaccine trial objectives pre-defined (safety and immunogenicity), not much flexibility
- Blood draws limited due to community sensitivity
- Use of comparator vaccines (active, not placebo) in Mali increases benefit to participants
- Standard of care, free medicines, follow up, and referrals
- Frequent screening leads to earlier diagnosis and treatment, improved health outcomes

Problem: research activities reduce frequency of outcomes of interest (malaria), more so if active intervention to find and treat malaria cases. How to preserve data integrity and usefulness of field site while maintaining benefit to community?
Study community and identify leaders

Introductory meetings, formal and informal

Meet with traditional health providers

Obtain permission as part of a dynamic consultative process, including meetings to discuss important changes in study design
Recruitment and Retention

• Enhanced by getting early “buy in” and making community leaders part of the study team
• Announcement of study recruitment at community meeting
• Community as a whole understands benefits of research and importance of follow up in achieving study outcomes
• Problems with loss to follow up brought to community for help with solutions
Data Collection

• Principal and sub-investigators come from the community
• Sub-investigators often live in the village during the course of the study
• Local “guides” are responsible for facilitating community consent, recruitment, follow up reminders, clerical procedures, and in some cases conduct follow up visits
Benefits to community

- Presence of medical personnel in the village as part of research team
- Construction and/or renovation of clinics and health infrastructure (water, electricity)
- Provision of medications
- Referrals and transportation
Individual consent: a basic principle of ethical research

Individual consent is complicated by:

• Language issues: consent written in English, translated to French, and administered in local language (which does not have a written form)
• Illiteracy and lack of basic scientific knowledge
• Gender issues
• Guardianship issues (who can give consent)
Some data suggests that research participants in developing countries are not likely to understand research and thus may often fail to provide valid informed consent:

- 90% of respondents did not understand withdrawal criteria
- 93% did not understand the existence of study side effects
- 74% did not understand that they were enrolled in an investigation as opposed to receiving therapy.

But: comprehension is a problem in the developed world too.
Unique Data Set

- Early phase clinical trials of malaria vaccines conducted in US (Johns Hopkins University Center for Immunization Research, Washington DC), and Mali
- True/false questionnaires used to assess understanding of essential elements: risk, voluntariness, study procedures
- Incorrect answers were reviewed with study volunteers and all final answers correct before enrollment
- The same vaccines and similar trial designs were used in the US and Mali and questionnaires were very similar: opportunity to compare responses and understanding between populations
Results/Conclusions

Questionnaires were not intended for data collection and methods were not standardized, so interpret with caution!!

But…

• Participants at both sites well informed, with high scores overall
• Mali volunteers are less informed: errors in questionnaire administration, significant effect of location seen
• Women in Mali less informed vs men in US
• Older volunteers at both sites less informed

Concern about poor understanding relative to US does not appear to be supported
Interpretation and dissemination

- Local collaborators are primary/senior authors on publications.
- Research results are communicated to villagers at meetings, which are a dialogue rather than one-way presentation of results.
- Results of one study are connected to the next (community consent for next study).
Community engaged research in LMIV/MRTC collaborations

Framework for community involvement in:
- ✓ Research question
- ✓ Study design
- ✓ Recruitment and retention strategies
- ✓ Methods
- ✓ Data collection
- ✓ Interpretation
- ✓ Results dissemination
Weaknesses of the model

• Assumes that local collaborators represent the community
• Language and cultural barriers limit ability of outside collaborators to assess impact
• Women are under-represented as scientists and study team members, under-represented at community meetings
• External partners are reliant on local partners for interpretation and guidance regarding local conditions
• Lack of transparency
• Potential for conflict of interest
• Power imbalance (US > Mali, investigators > participants)
• Cost: more expensive to maintain relationships with community
• Time: takes longer to negotiate and build consensus
• High level of community commitment and benefit may put pressure on individuals to participate or not withdraw from research
## Contrast with US/developed sites

<table>
<thead>
<tr>
<th></th>
<th>US/Developed</th>
<th>Mali</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resources</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Burden of disease</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Understanding of research</strong></td>
<td>Fair/variable</td>
<td>Fair/may be reduced in some populations</td>
</tr>
<tr>
<td><strong>Importance of research to community</strong></td>
<td>Variable</td>
<td>High</td>
</tr>
<tr>
<td><strong>Community input in study objectives and design</strong></td>
<td>Minimal; community representatives on IRB</td>
<td>High, if assume that local collaborators represent community</td>
</tr>
<tr>
<td>Variables affecting outcomes</td>
<td>US/Developed</td>
<td>Mali</td>
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<tr>
<td>------------------------------</td>
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</tr>
<tr>
<td>Community participation in research conduct</td>
<td>Low/variable</td>
<td>High</td>
</tr>
<tr>
<td>Research injury compensation</td>
<td>None in US (and often no health insurance)</td>
<td>Yes</td>
</tr>
<tr>
<td>Recruitment/retention</td>
<td>Fair/variable</td>
<td>High</td>
</tr>
<tr>
<td>Trust</td>
<td>Fair/variable</td>
<td>High</td>
</tr>
<tr>
<td>Results dissemination</td>
<td>Not required – typically by letter</td>
<td>Community meeting</td>
</tr>
<tr>
<td>“research shopping”</td>
<td>High background rates of disease</td>
<td></td>
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How to replicate Malian success?

- Partner with strong local collaborators
- Provide long term financial and scientific support: reduces brain drain and promotes stable relationships between teams and community. Endangered in current budgetary climate
- Encourage commitment from local research institutions
- Cultivate culture of connectedness
- Avoid “drop in” projects
- Avoid “drop in” PIs
- Recruit team members from community, and provide opportunities for them to give input

When bad outcomes occur, the community will be better prepared and less likely to look for villains
Further Reading

• Immortal Life of Henrietta Lacks (Rebecca Skloot)
• Do IRBs Protect Human Research Participants? [http://jama.ama-assn.org/content/304/10/1122.full?etoc#AUTHINFO](http://jama.ama-assn.org/content/304/10/1122.full?etoc#AUTHINFO)
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