Addressing Ethical Considerations In Undertaking Malaria Field Studies in Developing Countries

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Background

• « Few would disagree that the diseases which affect poor people in tropical countries are neglected, and more should be done to address this inequity. That means improving and deploying interventions which work, and developing new ones. (...)

Clinical trials are essential to evaluate these new interventions, and also to improve existing ones. »

– “Clinical trials in tropical diseases: a politically incorrect view”
  Nick White, TMH 2006
• «Human subjects in any part of the world should be protected by an irreducible set of ethical standards»

Marcia Angeli, 1998

Ethics and Human Health Research Reference and framework

• International guidelines or conventions
• European Union Directives
• National laws or guidelines
• Regulations and guidelines for research sponsored by the pharmaceutical industry
• Guidelines produced by funding agencies
• Institutional guidelines
• Guidelines relating to specific diseases
• Recommendations from advisory bodies.
Challenges

• Too general to provide answers to practical problems that arise in the course of research
• Too specific in that they fail to take account of differing circumstances in developing countries

➢ Applying guidance in practice is often fraught with difficulty
➢ When the different guidelines are compared, they can be markedly inconsistent in some areas

Confusion

• Principles versus Procedures
• Rules versus Guidelines

• (Ethics vs. Management of Liability)
Key Elements

- Consent
- Ethical Review
- Standard of Care
- Incentives and Reimbursement
- Insurance and Indemnity

Consent

- Informed Consent: Not a form, a process
- Local Ethical Review
  - Vulnerability of patients with no or poor access to health
  - Cultural attitudes: literacy, language (written – oral)
- Community and Individual Consent
- Community Awareness
  - Availability of information on the clinical trial before the initial contact with the recruiter
- Standardised Information
  - Simple, preferably a single page
  - Negotiated line-by-line with local ethical committee
  - Agreement on essential concepts
  - Focus: to inform the patient, not protect the researchers
- Training of study personnel
- Assessment of quality of process

Presented at ASTMH 2007
Rectal Artesunate – Community-based Clinical trial Information and Consent Process

• Sponsor: WHO/TDR
  Countries: Bangladesh, Tanzania, Ghana

• National Clearance
• Regional/District Administration
• Traditional Rulers (paramount chiefs, chiefs and sub-chiefs)

• Separate meetings with chiefs and elders
• Large community meetings

• Pre-study announcements at markets and social gatherings
• Poster Leaflets
• House-to-house visits
• Copy of consent forms made available
• Process occurred throughout the study

Community Awareness Meetings
House-to-House Visits

Development of Consent Form
Quality Assurance

- Extensive preparatory work
- Careful of selection of study team members
- Standardised training of field workers and testing
- Continuous assessment of performance
  - Consent process
  - Recruitment
- Monitoring
  - Several levels of supervision (field worker, field supervisor, research assistants, investigators, central coordination)
  - Frequent meetings
  - Communication
« Clinical researchers are being encouraged to be process rather than patient orientated. The case record form, rather than the patient, has become the focus of attention. »

– “Clinical trials in tropical diseases: a politically incorrect view”
Nick White, TMH 2006
Rectal Artesunate: A Simple Case Record Form

Intervention Trial – Brazil
Artesunate-Mefloquine FDC

- Funding from MOH and PAHO – RAVRED
- Study Steering Committee: MOH, PAHO, Farmanguinhos and DNDi
- 7 municipalities in 2 states in the Amazon Basin (Acre and Pará)
- High burden of malaria
- Total population: 219,310
- 15,959 patients with falciparum malaria (2005 data)
- Programmatic use of the drug
- MOH priority municipalities

Presented at ASTMH 2007
Intervention Trial – Brazil
Artesunate-Mefloquine FDC

Ethical Review

• Crucial safeguard for the protection of research participants

• Lack of consensus in international guidelines:
  > Separation of Scientific and Ethical Review
  > Sponsor versus Host country Review

  o Host country review:
    – Local needs, national research priorities, cultural context
    – Counterbalance to the generalized framework of international guidance

  o Sponsor country review:
    – Quality of reviews in the North vs South

  o Focus on strengthening of host country ERC
Clinical Trials in Sub-Saharan Africa and Established Standards of Care: A Systematic Review of HIV, Tuberculosis, and Malaria Trials

EVIDENCE-BASED HEALTH POLICY

Current RCTs on HIV treatment, tuberculosis treatment and malaria prevention in sub-Saharan Africa use local standards of care.

<table>
<thead>
<tr>
<th>(%)</th>
<th>Trials Providing Care Meeting Guidelines (%)</th>
<th>Ethical review reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial type</td>
<td>Total No. of trials</td>
<td>Control Group</td>
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<tr>
<td>Total</td>
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<td>19</td>
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<tr>
<td>HIV</td>
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<tr>
<td>Malaria</td>
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<tr>
<td>Tuberculosis</td>
<td>13</td>
<td>100</td>
</tr>
</tbody>
</table>
Standard of Care

- Regional or local standard of care as a comparator acceptable in some situations: CIOMS 2002, CoE 2004 and NCOB 2002.
- Not helpful to generalise
- Careful case by case assessment, which acknowledges the limitations of local and regional practicalities, may be useful
- Controversy over placebos: unrealistic requirements that might discourage valuable research

Rectal Artesunate – Community-Based Clinical Study

- Protocol developed following several scientific meetings at WHO/TDR
- No comparator in the conditions of use: placebo needed
- Discussion regarding the ethics of the conduct of this study, conclusions
  - Information needed for policy
  - Existence of "equipoise" in the conditions of use
  - Unethical to run studies that are scientifically uninformative
Rectal Artesunate – Community-Based Clinical Trial Lessons Learned

• Process driven by the priorities identified at national level

• Consistency with principles set by international guidance documents

• Procedures devised with a focus on the process for genuine consent and in responding the key scientific questions, with simplicity and common sense

• Interaction with local ethical review and national authorities

... 

• Perhaps, we should concentrate on basic principles as opposed to being more prescriptive, and therefore controversial.

• Procedures would be left for discussion and agreement with relevant stakeholders from early in the planning stage of any trial.

• Researchers, sponsors, local and national health authorities should work together to ensure acceptable solutions are developed

...
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