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, TMIH 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

Nuffield Council on Bioethics - NOCB 2005

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

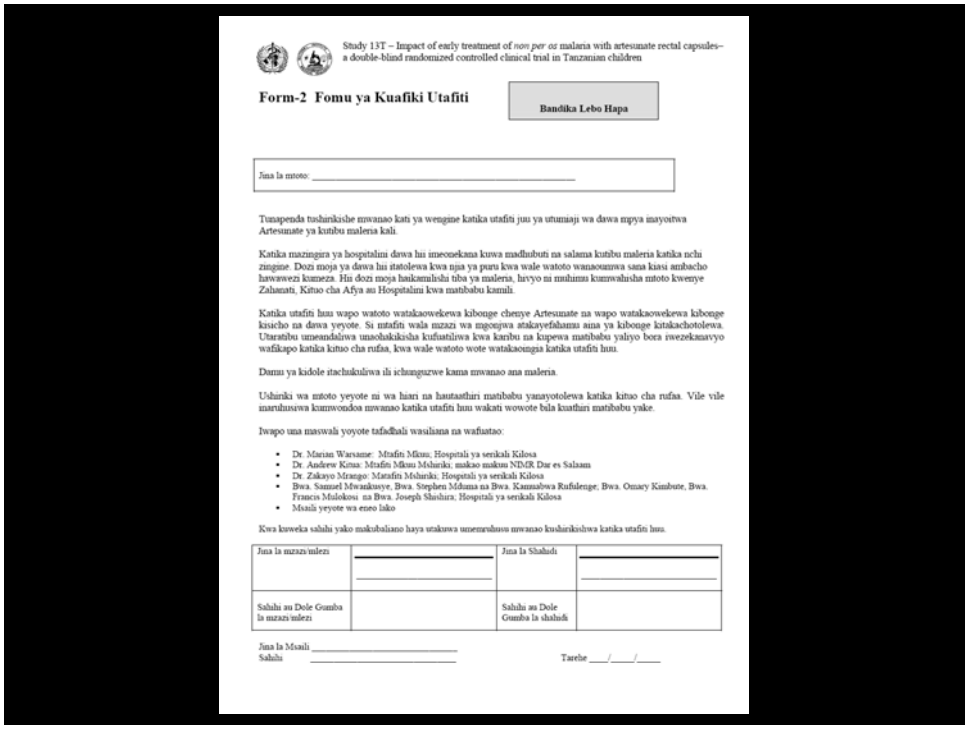
Rectal Artesunate – Community-based Clinical trial Information and Consent Process

- 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



Study 13T – Impact of early treatment of *non per os* malaria with artesunate rectal capsules– a double-blind randomized controlled clinical trial in Tanzanian children

Form-2 Fomu ya Kuafiki Utafiti

Bandika Lebo Hapa

Jina la mtoto: _____

Tunapenda tushirikishe mwanao kati ya wengine katika utafiti juu ya utumiaji wa dawa mpya inayoitwa Artesunate ya kutibu malena kali.

Katika mazingira ya hospitalini dawa hii imeonekana kuwa madhubuti na salama kutibu malaria katika nchi zingine. Dozi moja ya dawa hii itatolewa kwa njia ya puru kwa wale watoto wanaoonzwa sana kiasi ambacho hawawezi kumeza. Hii dozi moja haikamilishi tiba ya malaria, hivyo ni muhimu kumwahisha mtoto kwenye Zahanati, Kituo cha Afya au Hospitalini kwa matibabu kamili.

Katika utafiti huu wapo watoto watakaowekewa kibonge chenye Artesunate na wapo watakaowekewa kibonge kisicho na dawa yeyote. Si mtafiti wala mzazi wa mgonjwa atakayefahamu ana ya kibonge kitakachotolewa. Utaratibu umeandaliwa unaohakikisha kufuatiliwa kwa karibu na kupewa matibabu yaliyo bora zwezekanavyo wafikapo katika kituo cha rufaa, kwa wale watoto wote watakaongia katika utafiti huu.

Damu ya kidole itachukuliwa ili ichunguzwe kama mwanao ana malaria.

Ushiriki wa mtoto yeyote ni wa hiari na hautaathiri matibabu yanayotolewa katika kituo cha rufaa. Vile vile maruhusiwa kumwondoa mwanao katika utafiti huu wakati wowote bila kuathiri matibabu yake.

Iwapo una maswali yoyote tafadhali wasiliana na wafuatao:

- Dr. Marian Warsame: Mtafiti Mkuu; Hospitali ya serikali Kilosa
- Dr. Andrew Kitua: Mtafiti Mkuu Mshariki; makao makuu NIMR Dar es Salaam
- Dr. Zakayo Mrango: Matafiti Mshariki; Hospitali ya serikali Kilosa
- Bwa. Samuel Mwankusye, Bwa. Stephen Mduma na Bwa. Kamuabwa Rufilenge; Bwa. Omary Kimbute, Bwa. Francis Mulokosi na Bwa. Joseph Shishira; Hospitali ya serikali Kilosa
- Msaili yeyote wa eneo lako

Kwa kuweka sahihi yako makubaliano haya utakuwa umemruhusu mwanao kushirikishwa katika utafiti huu.

Jina la mzazi/mlezi	_____ _____	Jina la Shahidi	_____ _____
Sahihi au Dole Gumba la mzazi/mlezi		Sahihi au Dole Gumba la shahidi	

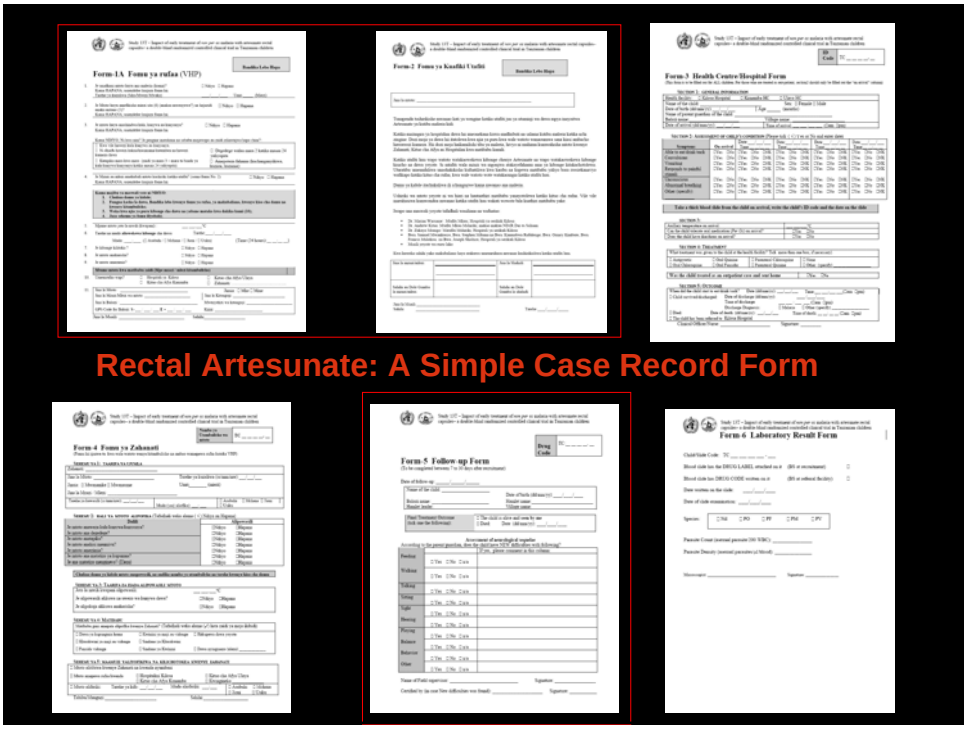
Jina la Msaili _____
Sahihi _____ Tarehe ___/____/____

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, TMIH 2006

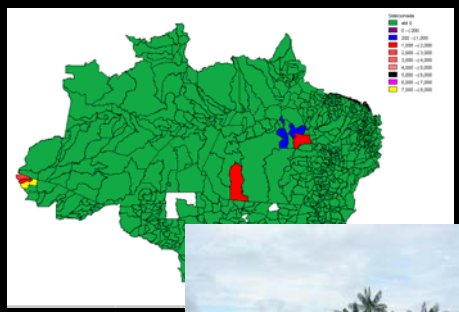


Rectal Artesunate: A Simple Case Record Form

Intervention Trial – Brazil
Artesunate-Mefloquine FDC

- Funding from MOH and PAHO – RAVREDA
- 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



Intervention Trial – Brazil
Artesunate-Mefloquine FDC


SUS-MS-FNS-CCDTV
DATASUS

PROGRAMA DE CONTROLE DA MALÁRIA

MALÁRIA

FICHA DE EXAME PARASITOSCÓPICO/NOTIFICAÇÃO DE CASOS

DADOS DO PACIENTE

RESIDEN

DADOS COMPLEMENTARES / RESULTADO EXAME / TRATAMENTO

LOCAL PROVÁVEL DE INFECÇÃO

MENOR QUE 1/2

RESPONSÁVEIS

Ethical Review

- Crucial safeguard for the the protection of research participants
- Lack of consensus in international guidelines:
  - Separation of Scientific and Ethical Review
  - Sponsor versus Host country Review
    - Host country review:
      - Local needs, national research priorities, cultural context
      - Counterbalance to the generalized framework of international guidance
    - Sponsor country review:
      - Quality of reviews in the North vs South
    - Focus on strengthening of host country ERC

Standard of Care

Evidence-Based Healthcare & Public Health (2005) 9, 54–55

Clinical Trials in Sub-Saharan Africa and Established Standards of Care
A Systematic Review of HIV, Tuberculosis, and Malaria Trials

Evidence Based healthcare & public health
www.elsevier.com/locate/ebhph

EVIDENCE-BASED HEALTH POLICY

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

(%)		Trials Providing Care Meeting Guidelines (%)		Ethical review reported		
Trial type	**Total No. of trials**	**Control group**	**Intervention Group**	**Trials reporting ethical review (%)**	**Host country reviewed (%)**	**Sponsoring country reviewed (%)**
Total	73	19	44	81	100	64
HIV	34	3	3	85	100	72
Malaria	29	10	72	86	100	72
Tuberculosis	13	100	100	62	100	25

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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