Conduct of human participant research in low and middle income countries with limited infrastructure to meet international standards

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Vaccination context and low middle income countries

1. After water, vaccination has the most significant impact on global health and/or further improvement in health in the low middle income countries of the world

2. Safety threshold
   - Healthy population (prevention)
   - Young children & infants

3. Very large studies (x1000) to assess Safety, reactogenicity/Immunogenicity, Vaccine efficacy, Vaccine effectiveness, Community-based

4. Millennium Development Goals, **Ensure healthy lives and promote well-being for all at all ages,** provided a strong mandate for a new approach to the development of vaccines for low-income countries and answer the health needs in those regions

Ethical considerations

Scientific and social value

…All research is carried out in ways that uphold human rights, and respect, protect, and are fair to study participants and the communities in which the research is conducted.,, [CIOMS 2016]

- GSK principles
  - Sponsored clinical trials are only conducted in countries where the medicines are likely to be suitable for the country's wider community.
  - Clinical trials of investigational medicines are not conducted in countries when it is known at the outset that there is no intent to pursue registration and make the medicine available for use in that country.

Low middle income countries : what are the challenges for conduct of research ?

Culture

Family or community taking care or the child

Prominent role of the community leaders

Geographical dispersion of population

Experience

Understanding' of medical & scientific concepts

Conduct of human subject research in international setting

Subject illiteracy

Resources

Medical infrastructure & material

Pharmacovigilance system

Prevalence of 'poverty' related diseases malaria, TB and HIV Control measures and access to medicines in general

Regulation

Clarity in regulation for conduct of Human subject research conduct

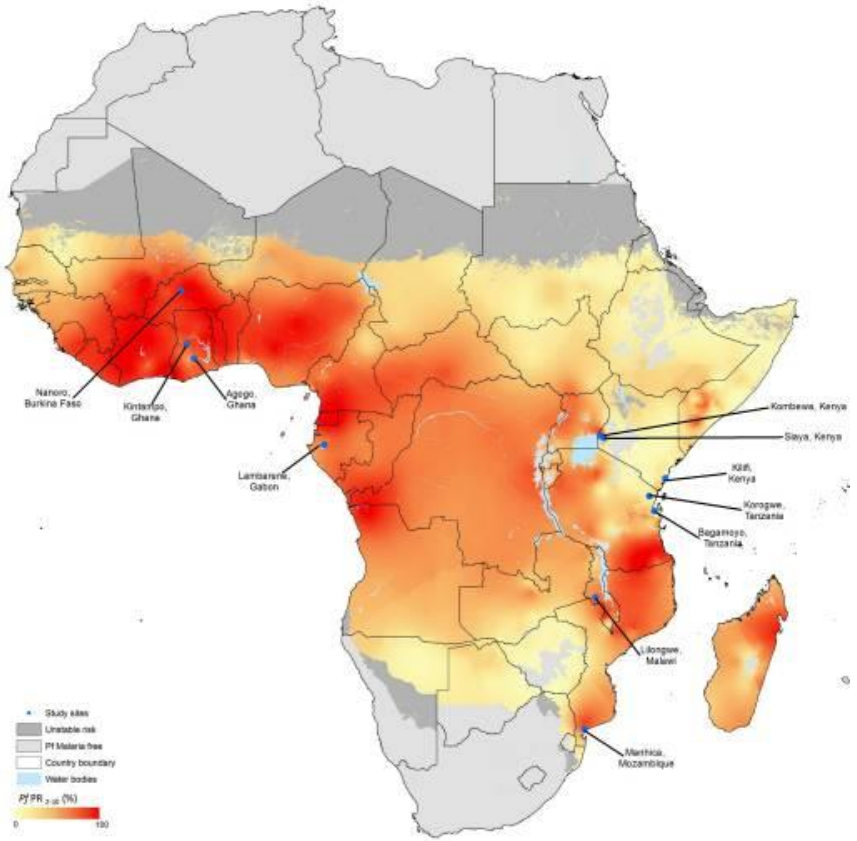
Expertise from independent ethical committees

Official attestation of the LAR (legal acceptable representative)

Case study- example - Malaria Vaccine study

www.ClinicalTrials.gov NCT00866619

- large-scale phase 3 clinical trial involving 15,460 children recruited at 11 sites in seven countries across Africa
- Countries : Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, Tanzania
- Type of subjects :
  - Heathy volunteers
  - Children and Young Infants - 6 Weeks to 17 Months
- Study duration 18 months



Way to overcome challenges: Local engagement

Local authorities

- Engagement prior to study design initiated
  - Alignment on the responsiveness of research to health needs and priorities for the country/community
  - Usually done by the sponsor with local authorities, supranational organisations such as PATH, WHO, GAVI etc.

- **Community/village leader**
- Engagement through early consideration of the local constrains and feasibility
  - Investigator and community/village leader are assessing:
    - the benefit of the research for the individual and the community
    - what it mean for people in term of burden
    - if the design is acceptable/feasible in the community
- Partnership in design of the study protocol

Way to overcome challenges: Consent

Process

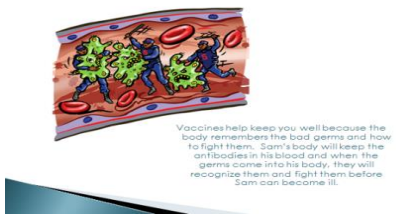
- The community leader will provide valuable insight to ensure the study participant might understand research

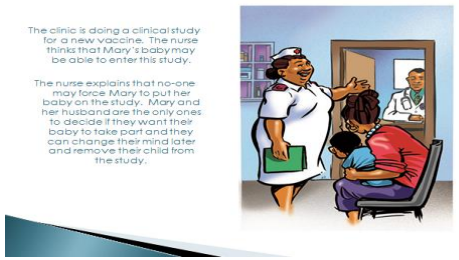
➢ Posters to create awareness of the research

➢ Use of speaking book

  ➢ What's a Vaccines

  ➢ What's a human research including subject participant right and responsibilities as well as how the safety is monitored



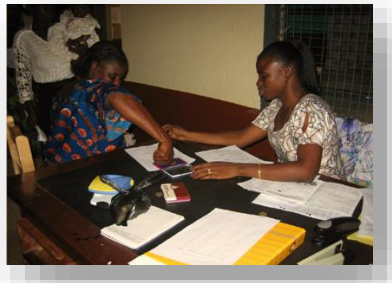


➢ Individual consent including drawing (in addition group consent could have taken place)

- **Signatory**
- Legal Acceptable representative not usually defined via legal document

➢ Village leader provide a signed statement outlining who is taking care of the child

➢ Approach approved by the independent Ethical Committee



- For illiterate subject
  - use of thumb print
    - allow to maintain subject dignity
  - independent witness to confirm the content of the document correspond to the discussion with the subject

Way to overcome challenges: Capacity Building

GSK principle

- Any capacity building provided (e.g. training or equipment) is not used as an **inducement** and if remaining after the study is sustainable by the local community
  - To develop certain skill or competence
  - Upgrade performance ability
    - To support the conduct of the research activities **AND**
    - Support the broader community
  - Supportive measures which are provided to a site at the outset of a human subject research program intended to be exclusively used for the research and returned to the sponsor at the end of the research is not capacity building

How

1. Identify needs for the study research conduct in the area
2. Define prior study start which element could remain in place after study conduct and the rational
3. Identify the ability of the community to maintain it and use it in day to day practice (e.g. cost of reagent, technical complexity, operational maintenance)
4. Define the residual cost expected at the end of the study is Fair Market Value
5. Include the component of capacity building in an agreement form (ideally prior to study start)

Way to overcome challenges: Capacity Building

- Engagement of the local authorities, local community, site and the sponsor really early in the study development

- Capacity building can be
  - strengthening local research capacity through training for PIs, nurses, study research staff
  - provision of basic clinics in remote areas where the research activity needs to take place
  - Enhancing the pharmacovigilance system
  - Facilitates refurbishment
  - Provision of equipment for the research that will remain afterward for local use

Capacity building before …

and after

Way to overcome challenges: Product management

- The vaccine vial monitor (VVM), a small label that adheres to a vaccine vial and changes color over time to indicate whether the vaccine has been exposed to too much heat.
- Provide portable temperature monitoring device
- Provide electric power generator to maintain fridge

Way to overcome challenges: Geographical spread of population

- Use of fieldworkers to perform home visit rather than ask subject to go to the study site

  - Limit transportation need for the subject and cost
  - Adequately trained staff
    - Consistency on data collection
  - Support cold chain managemnent

Summary

- Significant scientific and ethical justification
- Trial community to benefit from early access to any product of the trial, as well as to infrastructure and knowledge brought by the trial in a reasonable time
- Particular attention to populations that are vulnerable
- Engagement of the local authorities and community leader
- Access issues should form a part of negotiations among community representatives, government, health authorities and trial sponsors
- Creative solution to ensure adequate capability building and logistic to meet international standard
  - Consent
  - Cold chain
  - Filedworkers
  - Etc

Thank You