Workshop on Clinical Trials Capacity in Low- and Middle-Income Countries

MEETING REPORT

Workshop on Clinical Trials Capacity in Low- and Middle-Income Countries: Experiences, Lessons Learned and Priorities for Strengthening

Initiative on
Public-Private
Partnerships
for Health

ALLEVIATING THE HEALTH CONSEQUENCES OF
POVERTY BY ENHANCING PUBLIC-PRIVATE COLLABORATION

Workshop on Clinical Trials Capacity in Low- and Middle-Income Countries: Experiences, Lessons Learned and Priorities for Strengthening

Report of a Meeting Organized by the Initiative on Public-Private Partnerships for Health

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The Initiative on Public-Private Partnerships for Health

ICC (Block G, 3rd Floor)
Route de Pré-Bois 20
P.O. Box 1826
1215 Geneva 15
Switzerland

E-mail: info@ippph.org
Website: www.ippph.org

IPPPH SECRETARIAT

Roy Widdus, Project Manager
Armelle Armstrong, Communications Officer
Pamela Atiase, Administrative Assistant
Alessandra Botta, Information Research Specialist
Karin Holm, Senior Programme Officer

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Acronyms and Abbreviations

AFHR	African Forum for Health Research
AMANET	African Malaria Network Trust
AMVTN	African Malaria Vaccine Testing Network
ARV	Antiretrovirals
CRO	Contract Research Organization
EDCTP	European and Developing Countries Clinical Trials Partnership (European Union)
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration (USA)
FIC	Fogarty International Center, NIH (USA)
GATBDD	Global Alliance for Tuberculosis Drug Development
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HIV/AVTN	HIV/AIDS Vaccine Trial Network
HRP	Special Programme of Research, Development and Research Training in Human Reproduction (WHO)
IAVI	International AIDS Vaccine Initiative
ICAR	International Centers for AIDS Research
ICDDR	International Centre for Diarrhoeal Disease Research (Bangladesh)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Institutional Ethics Committee
INCLEN	International Clinical Epidemiology Network
INDEPTH	International Network of Field Sites with Continuous Demographic Evaluation of Populations and Their Health in Developing Countries
IPM	International Partnership for Microbicides
IPPPH	Initiative on Public-Private Partnerships for Health
IRB	Institutional Review Board
IUATLD	International Union Against Tuberculosis and Lung Diseases (France)
IVI	International Vaccine Institute
JCRC	Joint Clinical Research Center (Uganda)
KEMRI	Kenya Medical Research Institute
LMICs	Low- and middle-income countries
MTCT	Mother-to-child transmission
MMV	Medicines for Malaria Venture
MVI	Malaria Vaccine Initiative
NGOs	Nongovernmental organizations
NIAID	National Institute of Allergy and Infectious Diseases (USA)
NIH	National Institutes of Health (USA)
NIMR	National Institute for Medical Research (Tanzania)
NIPRD	National Institute for Pharmaceutical Research (Nigeria)
PATH	Program for Appropriate Technology
PAVE	Preparation for AIDS/HIV Vaccine Evaluations
R&D	Research and development
SIDA/SAREC	Swedish International Development Agency/Research Branch
SOP	Standard Operating Procedure
STI	Sexually transmitted infection
TB	Tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases (WHO)
USAID	United States Agency for International Development
WHO	World Health Organization

1. Thematic Summary

1.1 Background

In November 2002, the Global Forum for Health Research held its sixth annual meeting, Forum 6, in Arusha, Tanzania. During that meeting and in association with the Global Forum, the Initiative on Public-Private Partnerships for Health (IPPPH) organized a workshop entitled **Clinical trials capacity in low- and middle-income countries: Experiences, lessons learned and priorities for strengthening**[1] on 15–16 November 2002. IPPPH decided to hold the workshop because of concern that the current capacity to conduct clinical trials of products for health problems in low- and middle-income countries (LMICs) would be insufficient over the next 10 to 20 years. Clinical trials for products to deal with the so-called neglected diseases cause particular concern, given the increased attention and new funds directed at them, and the advent of a number of public-private partnerships to develop them.

The meeting brought together 77 individuals from 24 countries. The participants reflected the wide range of groups that associate to implement and support clinical trials: researchers from both developing and developed countries who are implementing trials in LMICs; public health policy-makers; community relations specialists; national health research institutes in industrialized and developing countries; disease-oriented trials networks; pharmaceutical industry representatives; foundations; public-private partnerships for product development; and bilateral agencies.

The meeting sought to identify and concentrate on cross-cutting needs and themes relevant to all clinical research and trials, whether for products needed in health interventions (drugs, vaccines, contraceptives, diagnostics, etc.) or for the disease or health problems addressed.

[1] Such as IAVI, Medicines for Malaria Venture (MMV), Global Alliance for Tuberculosis Drug Development (GATBDD), Malaria Vaccine Initiative (MVI), International Partnership for Microbicides (IPM) and others.

This summary presents an overview of discussions and conclusions, organized by theme. A more detailed record of discussions can be found in the meeting record, which is organized by agenda session.

1.2 Overall 'global' planning to strengthen clinical trials capacity

Participants first considered what is known about the current capacity of certain LMICs to conduct clinical trials and how this related to planning for future needs, with special emphasis on sub-Saharan Africa. It emerged that while isolated efforts have been made to assess capacity and future demand (for example, by national health institutes (NIH) in the United States and the International AIDS Vaccine Initiative (IAVI) on HIV/AIDS; the European and Developing Countries Clinical Trials Partnership (EDCTP) on HIV/AIDS, tuberculosis and malaria; and the African Malaria Network Trust (AMANET), formerly known as the African Malaria Vaccine Testing Network), there were no consistent criteria for assessing current trials capacity or future needs and no organization that maintained an overview on which to base coordinated efforts to strengthen capacities to match future needs. Participants cautioned that attempting to predict future needs was always subject to scientific uncertainty but that it could and should be attempted.

Given that strengthening sites for clinical trials is expensive, it was suggested that investments should focus on a limited number of sites, which would hopefully be 'multifunctional', across diseases and product categories. This means, however, that not all aspiring institutions could expect major support.

1.3 Perspectives on clinical trials in East Africa

Dr Ebi Kimanani reported on a survey of attitudes towards, and capacities for involvement

in, clinical trials in East Africa. A number of factors constrained capacity, including access to equipment, understanding of Good Clinical Practice (GCP), absence of ethical review capacity, and communications, especially in rural areas. However, the 'good news' was that despite some negative experiences, there is still a strong desire to engage in clinical trials on locally relevant products, even where these had been developed outside the region.

1.4 Clinical trials as a 'gateway'

The concept of clinical trials (for efficacy) as a 'gateway' between research and use of products in public health was widely recognized among meeting participants.

Clinical trials may be viewed as an exercise around which organizations from many different 'constituencies' collaborate but to which they bring different motivations, contributions and levels of resources (hence greater or less 'power') and have different aspirations and expectations. These constituencies include: researchers, clinicians and institutions in developing and developed countries; public health 'practitioners'; various funders, including national health research agencies and foundations; development assistance agencies; commercial pharmaceutical companies; members or representatives of the community in which the trial is undertaken; and the participants in the trial themselves. Each constituency brings its own 'culture' and expectations to the collaboration. Problems arise, however, as often not enough care has been taken to reach agreement on widely acceptable outcomes. This, according to the meeting participants, may help to explain difficulties, frustrations and disappointments that often accompany clinical trials and strengthening of the capacity to conduct them.

1.5 Concerns regarding historical experience with clinical trials

Problems that may occur in conducting clinical trials in LMICs can be grouped in three categories although these may overlap and compound:

- **Difficulties arising from inadequate planning**, including insufficient input from LMIC investigators into products or interventions to be studied or into trial design; inadequate resources for pre-trial site characterization; and inadequate engagement of local communities during preparations for trials.
- **Frustrations in executing trials**, including underestimation of the time needed to instal equipment and train staff; lack of clarity about essential GCP norms; absence of local or national ethical review committees and/or the need for multiple Institutional Review Board (IRB) ethical clearances; defining the purpose and nature of informed consent; and inadequate training and involvement of LMIC investigators in data management and statistical analysis.
- **Disappointments in post-trial outcomes**, including lack of access to products successfully tested; inadequate preparation for retaining site capacities, e.g., through preparing 'local' investigators to compete for research funds on projects relating to regional or national health problems; lack of career structures for LMIC clinical trials specialists, necessitating part-time private practice or emigration.

1.6 Communications

The need for careful attention to the multiple aspects of communications around clinical trials was a theme that arose repeatedly in the workshop.

- For clinical trials to succeed, partners from the different constituencies need to trust each other, understand the use of terminology and have clear expectations. Building this trust and understanding may take considerable time, and longer that some investigators from developed countries anticipate.
- Discussing post-trial expectations (by different constituencies) was generally felt to be a useful component of trial planning.
- Implementation of the trial itself may be facilitated by explicit written agreement on roles, responsibilities, milestones and deadlines for all major players.
- Early and frequent communication with all relevant regulatory authorities is essential.
- Frequent communications between implementers and sponsor(s) of trials

(especially if the latter is a commercial pharmaceutical company) are also very important.

- Investigators in rural areas need to be able to communicate both with inward transmission of trial and patient information and feedback to the rest of the trial team. New technologies offered possibilities in some of these areas.

1.7 Major needs in strengthening clinical trials capacity

Major needs highlighted by the working groups included:

- **Overall management:**
  - Leadership and management training.
  - Training local researchers for principal investigator positions.
  - Strengthening financial accounting in institutions in LMICs.
  - Possible creation of specialized training courses in academic institutions on clinical trials design and execution.
- **Good Clinical Practice and quality control**:
  - Define and create a broad understanding of the GCP components that are essential for regulatory approval of products subject to trials in LMICs.
  - More training in GCP adherence.
  - Creation of *functioning* national and institutional ethical review committees and training for their members.
- **Community relations and engagement**:
  - Wider understanding that strategies to engage the community are an integral part of the research and development (R&D) process.
  - Development of strategies that better define the 'community', which will differ according to the phases of trials being carried out.
  - Implementing 'social contracts' with communities, to define expectations and 'deliverables'.
  - Define and differentiate informed consent and informed decision-making.
  - Inclusion of community 'preparation' strategies as part of essential expenditures.

1.8 Responsibilities of national governments

LMIC national governments can create an environment conducive to strengthening clinical trials capacity by:

- Ensuring that national bioethical review committees are actually functioning in a timely fashion.
- Ensuring that national regulatory functions for pharmaceuticals are strengthened.
- Establishing national policies encouraging health research and contributing to them financially, even in modest amounts.
- Identifying national health research priorities.

1.9 Responsibilities of research institutions

Research institutions can create an environment that encourages the strengthening of clinical trials capacity by:

- Ensuring functioning institutional bioethical review committees.
- Establishing adequate, audited financial management capacities.

1.10 Sustainability of clinical trials capacity

Participants repeatedly noted the waste of resources and frustration caused by inadequate planning for sustaining capacities developed during trials. However, they recognized that funders would not support maintenance of capacity that was not being put to productive ends.

A number of approaches to sustaining capacity were proposed:

- Support for trials could incorporate components to train junior/LMIC investigators in trial design and proposal writing (including budget preparation and management). This would help them to compete for funds offered by external sources such as the World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases (TDR) and its Special Programme of Research, Development and Research Training in Human Reproduction (HRP). This was widely supported as a means to

strengthen local clinical research and clinical trials capacity and to encourage testing of interventions identified as relevant to local health problems.

- Exploring the possibility of establishing pharmaco-vigilance studies and systems, subsequent to efficacy trials. (Some participants stressed that such efforts were ethically necessary before wide application of successful products.)
- Encouraging even modest support from LMIC governments for maintaining capacity, possibly in the form of small competitive grants on local health problems.

1.11 Perspective of different 'constituencies'

Participants from various 'constituencies' represented at the meeting provided the general perspectives of their institutions:

- Although participants recognized that much needs to be done to strengthen clinical trials capacity in LMICs, the major funders have particular missions, mandates or business goals. Therefore, while a generalized strengthening effort might be desirable and efficient, in practice it might be achievable in some areas, but would be difficult across the whole array of needs.
- Planning and capacity strengthening appeared to be most effective when built around discrete projects. Particular products passing through the clinical research and clinical trials pipeline provided the best opportunity for the design of targeted activities.
- The challenge is how to match general contributions to strengthening clinical trials capacity (e.g., general training in GCP, bioethics, management, data management, etc.) to the efforts needed on specific products or diseases. Some overarching planning seems feasible and desirable, but no institution appears at present to have the full information (or inclination) needed to do this.

It was agreed that input should be sought from a representative sample of francophone countries, since their representation in the meeting was numerically low.

1.12 Follow-up to the meeting

In a brainstorming session at the close of the meeting, two principal suggestions emerged:

- In the course of the discussions, many relevant (but relatively unknown) information sources or discrete assessments relating to clinical trials capacity in LMICs had been identified. An attempt should be made to produce and disseminate a compendium of these sources with contact information.
- Preparation of a consensus document on 'Good Practices in the Sponsorship and Implementation of Clinical Trials in Low- and Middle-Income Countries' should be discussed among relevant, interested parties.

2. Meeting Report

2.1 Plenary session I

Chair: Dr Wenceslas Kilama
Co-chair: Dr Roy Widdus

Drs Wenceslas Kilama and Roy Widdus welcomed the participants and explained that the meeting aimed to identify areas of need and potential collaboration for clinical trial infrastructure in low- and middle-income countries.

In order to assess capacity, Dr Widdus proposed to use a matrix approach based on three dimensions:

- The 'product pipeline' and what trials will be needed in the near future.
- The geographical locations and potential sites.
- What strengthening is needed based on current capacity?

The areas to focus on should also be clarified, by identifying common needs among all clinical trials.

Dr Ebi Kimanani presented an assessment of existing clinical trial capacity, particularly in Africa, based on a survey she conducted in 28 sites in 16 African countries, including university training centres, medical practitioners and some researchers. The most common specialists involved in trials were public health and prevention professionals and paediatricians. The most common subjects were HIV, tuberculosis (TB), malaria, paediatric diseases and nutrition. Some 38% of personnel have experience with Phases I to IV studies, and only 9% mentioned having preclinical experience.

The survey identified the following issues:

- Medical professionals from rural areas are often isolated.
- Investigation selection criteria are not transparent.
- Facilities and transportation are inadequate.
- There is a lack of political will and lack of funding.

Dr Kimanani concluded that guidelines and review boards need to be put in place and that regulatory and ethics procedures need to be agreed upon and more widely understood.

Dr Rodney Hoff presented an overview of international health programmes organized by the United States' National Institute of Allergy and Infectious Diseases (NIAID) focusing on tropical diseases and HIV/AIDS (available on request, see annex 9). The assessment of needs and clinical trial sites is disease burden-oriented. The approach used is testing interventions in a individual site or using an existing disease network. A competitive peer review drives the site selection based on trials requirements.

Dr Hoff provided an example of how this was achieved in the past with HIV prevention: the United States' National Institutes of Health (NIH) and International Centers for AIDS Research (ICAR) began seroprevalence studies in 1988; PAVE (Preparation for AIDS/HIV Vaccine Evaluations) conducted cohort studies (1991); HIVNET (an NIH/NIAID trials network) carried out population-based laboratory studies (1993); and two networks for clinical trials were set up in 1999. The network was established, investigators were requested to propose studies (sexually transmitted infections (STIs), antiretrovirals, microbicides, etc.) and second sites were asked to demonstrate capacity to enrol and submit credentials.

Also presented was the concept of the European and Developing Countries Clinical Trials Partnership (EDCTP) as a platform for funding trials in sub-Saharan Africa (available on request, see annex 9). The programme aims at investing in the long-term sustainability and rational use of trial sites and anticipates ten trials in the next five

years. The programme has classified four categories of trial sites:

- Those that are already capable of conducting major studies and that comply with the regulatory requirements of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).
- Those that could rapidly reach ICH requirements.
- Those that need significant capacity building to reach ICH requirements.
- Those that are unlikely to meet regulatory standards in the foreseeable future.

EDCTP also plans to implement a programme on leadership training, to begin in 2003.

Discussion

Participants noted that trials should be categorized according to the nature of their intervention, for example:

- Epidemiology and behaviour (intervention of education, advocacy, questionnaires).
- Clinical epidemiology (intervention based on readouts from biological samples (blood) taken from participants).
- Vaccine trials (invasive administration of a candidate product to the participants and long follow-up).
- Drug trials where more or less invasive treatments are administered to the patients and in general need relatively limited follow-up for efficacy, safety and adverse events.

During the discussion a number of issues and questions were raised:

- Many researchers working part-time on clinical trials seem to be less effective than full-time staff. What can be done?
- Is the research agenda driven by external donors or by the indigenous national research community? Products developed in the 'North' are usually tested in the 'South'.
- How to raise standards?
- What could be the role of industry?
- Would larger investments in fewer projects be more effective?

2.2 Plenary session II: Lessons learned

Chair: Dr Wenceslas Kilama
Co-chair: Dr Roy Widdus

Dr Lise Riopel presented the results of a survey of lessons that participants had learned from their experience with clinical trials in LMICs (see also annex 4).
The issues identified were summarized as follows:

- Training in GCP and study management.
- Improving local communication with sponsors, particularly pharmaceutical companies.
- Sustaining resources beyond the trial period.
- Underestimation of funding required for clinical trials.
- Improving ethics review which is often not understood.
- Improving communication among all parties in results analysis and publication.

Dr Osman Sankoh (INDEPTH) reported on a capacity-building meeting (May 2002). The meeting discussed the EDCTP assessment document which aimed at creating an enabling environment for clinical trials in developing countries, e.g., strong rationale for trials, solid infrastructure, qualified skilled personnel.
However, the meeting concluded that there was:

- Insufficient medical research and equipment.
- Deficient clinical design.
- Low national interest and support.
- Lack of clear applicable guidelines.
- Lack of control and regulatory harmonization.
- Little interaction with industry.

To improve capacity, activities should focus on collaboration procedures, the assessment of trial sites and a greater participation of local scientists.
Other issues discussed included:

- How to improve facilities, training (who and how) and management.
- How to halt the 'brain drain'.
- Factors influencing costs (number of trials, requirements, complementarity, etc.).

- Supporting local review systems and follow-up in order to develop good, locally-originated studies.

Discussion

Participants agreed that, before beginning trials in a certain locality, the availability of products to that community once the trials have finished must be ensured. Also, local manufacturing capacity or at least supply and cost issues need to be considered when discussing long-term sustainability of drugs and vaccine supply. Participants asked whether some sponsors held product trials in countries where they did not plan to register them, and pointed out that, ethically, the products should be made available wherever successfully tested.

Participants also brought up the following issues during the discussion:

- In low-income countries, trials are usually public-private partnerships. Negotiations for trials take account of local interests. Many neglected diseases have been addressed in this way.
- Although quality standards are universal, future product supply should be addressed on a case-by-case basis.
- Documentation, audits and issues concerning placebos should be taken into account.
- Before each trial, the risk/benefit ratio for the trial population has to be considered.
- Some investigators are overwhelmed and confused by the multitude and variety of guidelines. One solution would be to build on existing guidelines to compile all relevant major guidance. Simplification is preferable to creating regional, local or specific guidelines, which would be time-consuming and complex.

Dr Giorgio Roscigno added that it is very important to have standard operating procedures (SOP) that are fully understood locally. GCP has been implemented successfully in Africa in different trials (microbicides, HIV vaccines, etc.). However, few sites currently meet GCP standards. A continuous flow of resources is key to keeping trial sites up to good standards but resources may lapse after trials are completed. Technology transfer is a critical issue, and a challenge. Site maintenance needs to be considered. Mary Newton (Roche) mentioned that clinical trial capacity compatible with international standards needs government involvement, and that there is now good support in South Africa.

Dr Luis Jodar (IVI) mentioned that the product profile should be considered together with local scientists and government, taking into account local epidemiological, logistical and programmatic issues. So-called 'learning by doing' was challenged in the discussion, as credibility needs to exist before funding is given. However, establishing credibility without prior experience of actual trials is a challenge.

Working group sessions

Working groups were set up to enable participants to feed maximum information into the development of priorities. The topics addressed by each of the working groups were:

- Overall management
- Good Clinical Practice and quality control
- Community relations and engagement.

Participants to each working group and the topics assigned to them are shown in annexes 5 and 6 respectively.

Reports from the working groups are taken into account in the thematic summary and are included as annexes 7a, 7b and 7c.

2.3 Plenary session III: Sustaining capacity

Chair: Dr Wenceslas Kilama
Co-chair: Dr Uford Inyang

Dr Wenceslas Kilama introduced the general concerns over sustaining capacity based on observations in Africa, particularly in East African malaria interventions. Personnel are assembled for a trial (particularly Phase III), investments in training have been made, the community's interest is mobilized, but often there is no thought as to what will happen once a trial is over. An issue is long-term efficiency, i.e., not losing the value of investments already made, rather than sustaining capacity as an end in itself.

The roles of institutional and government policies in sustaining capacity

Dr Uford Inyang (Nigeria) identified additional issues not only in sustaining capacity once established but also in using existing capacity effectively, based on his own institution's

experience and that of others. In Nigeria, there are many specialist teaching institutions in health and specialist hospitals, plus a national drug regulatory agency. Guidelines and – in theory – an ethical review committee exist. However, the system's operations are not optimal as enforcement is weak and the ethical review committee has essentially lapsed. Variations from recommended practice are granted if sponsors insist on their own protocols or bypass usual procedures. Hence, monitoring compliance with standards is as important as the existence of policies. He emphasized the importance of national governments and implementing institutions being committed not only to create policies to guide trials but also to ensure that the mechanisms actually function.

Participants raised a number of issues:

- By 'sustaining capacity', participants from LMICs often meant creating the conditions where the personnel engaged in the trial were able to continue investigating pertinent health problems. Simply sustaining capacity to await the next 'big trial' was unrealistic and not an end in itself.
- Mid- and junior-level researchers involved in larger trials on externally developed products/interventions should be encouraged and empowered to identify and address research questions pertinent to 'local' major health problems.
- To continue to apply research capacity assembled during a large trial to local problems required building certain components, largely directed towards mid- and junior-level investigators, into the initial trial plan. These included provision for:
  - Training in study design, grant writing, and creation and management of research budgets.
  - Training in leadership and management skills, so that 'local' researchers can become the principal investigators on future new projects.
  - Giving mid- and junior-level researchers the opportunity to travel and establish their own contacts for future collaborative projects.
- Budgetary provision in the initial trial for these types of activities need not be large but should be explicit. Such provisions could be linked to information about opportunities for initial/small grants. Other sources were also available, e.g., TDR proposal writing workshops.
- It was acknowledged that, at present, funding for 'developing country driven' research is meagre; development agencies should increase its availability and broaden eligibility (from known, senior LMIC scientists to emerging ones).
- Few suggestions emerged, however, regarding creating career paths and maintaining skills among nurses and community health workers who were recruited and trained for large trials. Shortage of funds for careers in health research institutions was one of the main causes of the 'brain drain'.

Participants acknowledged that trial sites were chosen for a variety of reasons. Some were selected or deliberately established for a long-term (20 years or more) research programme, others were intended simply to test one product/intervention. However, in all cases, the sponsor could build in activities that would help strengthen and sustain 'local' capacity. Specifying desired outcomes at the outset of the collaboration would also reduce misunderstanding, unmet expectations and disappointments.

Sponsors (research funders, product developers, development agencies, health service providers, etc.) would be better able to target their support interventions if they discussed the trial's desired outcomes in early negotiations.

Participants also identified good practice in large intervention trials, which were less directly related to sustaining capacity, especially when they were held in developing countries but largely driven by sponsors from the industrialized world:

- Collaborators should agree in advance on a specific plan for analysis and dissemination of results, including publication, authorship and communication to the community.
- In long-term relationships, explicit plans should be made to correct what are likely to be initial disparities in capacity (and thus perceived power and rights of control).
- Linking research projects as far as possible to ongoing provision of health services will ultimately improve their reception and relevance.

- Capacity-building aspects of large trials were rarely documented and various different national approaches to choosing trial sites exist (e.g., China's government certifies sites which sponsors must then use). Case studies documenting and comparing approaches and experience were recommended.
- Many site assessment, technical and leadership training, and other capacity-strengthening operations exist, such as AMANET and African Forum for Health Research (AFHR). However, they are not always linked or widely known. An information resource is needed to avoid duplication of effort and to facilitate access to the extensive work already done.

2.4 Plenary session IV: Conclusions of working groups

Chair: Dr Wenceslas Kilama
Co-chair: Dr Gerald Keusch

Participants in the three working groups are listed in annex 5.

Reports from these groups are included as annexes 7a, 7b and 7c. Discussion of the working groups' conclusions was incorporated into the final plenary session (V).

Conclusions from the working groups are reflected in the thematic summary.

2.5 Plenary session V: Perspectives on coordinating support to clinical trials capacity strengthening

Chair: Dr Wenceslas Kilama
Co-chair: Dr Gerald Keusch

The IPPPH Secretariat asked the following questions:

- Is more coordination and more financial support needed?
- In what ways could more coordination be achieved?

All participants contributed to the discussion, and generally acknowledged that the strengthening of clinical trials capacity in LMICs (particularly Africa) had been a by-product of specific trials, not a primary goal at the outset.

Various participants, e.g., industry and NIAID (USA), indicated that they engaged in clinical trials mainly as a result of their commercial or scientific research mission to develop new products. Their anticipation of needs for trial sites was usually very product specific. This product orientation drove the preparation process for clinical trials, including strengthening where necessary. New engagement from NIH intramural programmes was allowing for a longer-term relationship with sites in developing countries and hence possibly more strengthening for conducting clinical trials.

Other participants indicated a broader mission related to clinical trials capacity (such as the US NIH Fogarty International Center (FIC), which conducted training in various clinical trial-related disciplines) or overall research in health problems of developing countries (e.g., Wellcome Trust, which supported research centres). The latter necessitated a substantial investment in community relations especially for population-based research projects.

Participants' comments illustrated the diverse nature of actions and actors necessary for building both clinical trial and general research capacity, particularly in Africa.

The Sequella Global Tuberculosis Vaccine Foundation (now named the Aeras Global Tuberculosis Vaccine Foundation) identified needs and ensured that sites for TB vaccine trials were prepared adequately (background information is available, see annex 9). They are working towards supporting developing groups and funding actual candidate product testing.

The Global Alliance for Tuberculosis Drug Development (GATBDD) had also identified a critical need for clinical testing (Phase III) of new drugs. It created, in collaboration with the International Union Against Tuberculosis and Lung Diseases (IUATLD), a research network in LMICs, organized from South Africa, to engage and strengthen potential clinical trials sites, especially in laboratory skills. This preparation was necessary as GATBDD aimed to have seven candidates in some phase of clinical testing by 2005. GATBDD representatives stressed the importance of parallel efforts to strengthen national regulatory capacity.

The Program for Appropriate Technology's (PATH) Malaria Vaccine Initiative was laying out expectations for clinical trials of candidate products as a preliminary step to identifying potential trial sites. A challenge was striking a balance between the desirability of general clinical

trial capacity development and the needs for their more targeted goal of product development.

Other interventions included:

- The recently-created African AIDS Vaccine Initiative is assessing trial capacity and would publish a report on its work (Dr José Esparza, WHO).
- Some sites in Africa already had considerable experience in therapeutic and preventive intervention trials. Projects such as NIAID's HIVNET/AIDS Vaccine Trial Network (AVTN) could create new capacity, train a new generation of researchers and strengthen bioethical review and community engagement approaches (Dr Danstan Bagenda).
- A number of 'donor' groups could assist with clinical trials capacity strengthening (Dr Gerald Keusch, NIH/FIC).
- Specific ventures, such as the EDCTP, might help these groups to move forward in a cohesive fashion (Dr Mike Hollingdale).
- Some bilateral aid donors, such as the research branch of the Swedish International Development Agency (SIDA/SAREC), pointed out that their support strategies were more oriented towards long-term support of institutions, not earmarked to specific projects like clinical trials.
- IAVI was committed to engaging developing country researchers in their product development 'partnerships' from the earliest stages. Nine Phase I trials were in progress including one in Uganda and Kenya and 16 potential trial sites in seven countries had been evaluated (Dr Nzeera Ketter).
- As a donor, USAID's country support was channelled through global funding (more research oriented) and local country missions. Documenting successes would help demonstrate that research supported development (Dr Ruth Frischer).
- The UK Medical Research Council Unit's experience in the Gambia showed that building capacity was a difficult and fragile process: specific individual trials would not necessarily result in sustainable capacity. The concept of 'passing the baton' between successive trials and strengthening care provision should be explored (Prof. Keith McAdam).
- Merck was moving more products into clinical trials outside industrialized countries as more products such as new HIV/AIDS drugs needed testing. The company was conducting trials in 58 countries (up from 27 countries a few years before). The increase mainly concerned countries in Eastern Europe, Asia and Latin America, although Merck felt a discussion of needs in Africa was useful, to establish contacts for a network of local expertise. In assessing trials sites, the company evaluated infrastructure and disease prevalence, but the roles of clinical monitor/study coordinator and principal investigator were considered critical among personnel needs (Dr Jacobo Sabbaj).

Participants felt site strengthening was probably best done on a case-by-case basis, but some cross-cutting needs were evident. These needs, which could be supported by governments and multilateral institutions to raise capacity and standards in general, included training, possibly with industry collaboration, to extend understanding of and capacity to implement GCP for trials, and to establish stronger capacity in regulatory structures.

In discussing this topic, a number of points were raised:

- While industry in general would welcome public sector initiatives along these lines, care should be taken to avoid bureaucratic delays. Industry, being sensitive to timelines, tended to avoid countries with cumbersome decision-making procedures (Dr Jacobo Sabbaj).
- Some companies have a large portfolio of candidate products for 'neglected' diseases and testing in disease-endemic countries was the only feasible option. GlaxoSmithKline (GSK) was collaborating with a number of not-for-profit 'partnerships' that facilitated testing and enabled the company to be more active in these less lucrative fields where the need was mostly in developing countries, e.g., malaria and rotavirus vaccines (Dr Joachim Hombach).
- At many potential sites, the capacity to conduct adequate ethical review should be strengthened. Routine health-care services also need to be strengthened and/or funded, so that existing and emerging

products could be more fully utilized (Dr Joachim Hombach).

- GSK was interested in trial sites in sub-Saharan Africa, but needed guidance on existing and prospective sites and their capabilities (Dr Opokua Ofori-Anyinam).
- Merck agreed that clinical trial capacity in Africa should be addressed – not only the range of issues mentioned by Dr Sabbaj, but also the question of availability of the products for general patient care after a successful clinical trial (Dr Henrietta Ukwu).

African participants noted some of their specific concerns:

- Africa as a whole lacked a sufficient number of centres of research excellence and funding for specific activities needed to be part of other broad-based activities (Prof. Bartholomew Akanmori).
- A longer-term dimension was needed, which AFHR might be able to provide (Dr Ebi Kimanani).
- The Central African region in particular was in need of more institutional strengthening but was often neglected in terms of targeted support from donors or programmes (Prof. Rose Leke).
- Action was needed on many fronts in Nigeria for, although it had a number of institutions with reasonable capabilities, the environment was difficult as the central government needed to fulfil certain responsibilities (in regulation and ethical oversight) (Dr Uford Inyang).
- Traditional links, often from colonial powers, dominated patterns of collaboration and support for research and institutional development. The pattern of French support for Senegal, German support for Gabon/Cameroon, British support for East Africa and the Gambia, and US engagement with South Africa supported this contention. In Africa, AMANET/AMVTN had identified 30 institutions with some research capacity; ten of them would perhaps conduct trials because of the links cited above. Hence, about 20 institutions needed support and partnering to fulfil their promise (Dr Wenceslas Kilama).
- Establishing strong national research capacity was important as it played a major role in driving national health policy generally. However, francophone institutions and networks were often not well integrated in discussions on Africa's overall needs in research and health. Dr Oumar Gaye and a number of other participants emphasized the need to incorporate francophone input in activities following the workshop.

Concern was expressed by a number of participants from Africa that in both clinical trials and support for other research, the 'local' voice in setting health research priorities was weak or non-existent. One suggestion for improving this situation was to include training in proposal writing and budget development for junior and mid-level staff in trials design, so that they could propose follow-up research on local priorities. Expansion of funds for such locally-initiated research, e.g., via WHO's TDR and HRP, etc., would be essential. Some participants felt that institutions or governments should decline approval for trials that did not address local health needs.

Matching support to priority needs

Some participants supported the need for better coordinating support from different donors at particular sites and possibly doing this within a larger assessment of needs and opportunities. However, a majority of participants felt that the best course of action was an approach based on coordination of site strengthening around identified needs for testing particular products.

Common ground existed to the extent that most participants acknowledged that a wealth of information existed on different facets of the topics discussed, and that a useful and necessary first step was to inventory this and make it more readily accessible.

2.6 Plenary session VI: Next steps?

Chair: Dr Wenceslas Kilama
Co-chair: Dr Roy Widdus

The IPPPH Secretariat asked what was desirable in the aftermath of the meeting (beyond a meeting report) and who should do it. Participants noted that the discussions had covered a wide range of topics and identified many steps that would ameliorate some of the problems. In almost every area where a need had been identified, some information existed that would at least in part resolve the problem.

However, often many of those conducting trials or strengthening capacity were unaware that such resources existed and, given the lack of mechanisms or clearing houses, could not find out how to access them.

Selected examples of existing resources not widely recognized or accessible from a centralized location included:

Conduct of clinical trials

- International Conference on Harmonization Guidelines on Good Clinical Practice (GCP).
- Guides to interpretation/implementation of GCP, from UNDP/World Bank/WHO (TDR) and the SCRIP Journal.
- Training courses in clinical trials conduct and GCP implementation, e.g., TDR.

Assessment tools for clinical trials capacity

- AMANET checklist for site capacity assessment.
- EDCTP checklist for capacity assessment.
- African AIDS Vaccine Initiative assessment of site capacity (in progress).
- Covance, a contract research organization assessment tool for initial evaluation of potential trial sites (see annex 8).

Inventories of assessment sites

- AMANET assessment of sites for malaria trials in Africa.
- INDEPTH site assessments for epidemiological studies.
- IAVI site assessments for HIV vaccine trials.
- NIAID/HIVNET site assessments for HIV prevention trials.
- IUATLD trials site network.

Ethical review processes

- A number of guides, other resources or training opportunities were mentioned, including those operated by NIH/FIC and WHO programmes.
- AFHR was in the process of analysing bioethical review systems and capacity in Africa.

Participants generally acknowledged that a range of cross-cutting capacities, necessary for conducting all clinical trials, did exist. These included, for example: management and financial expertise, bioethical review and statistical analyses. However, comments revealed a wide diversity of mandates and decision-making processes that led to financial support for particular clinical trials. While participants agreed that donor support to these capacities should be better coordinated, it was clear from such comments that achieving a more cohesive approach would be neither easy to achieve nor a high priority for some funders given their mission constraints.

Participants did stress, however, the potential usefulness of some efforts:

- To identify and create a comprehensive compendium of existing resource materials.
- To consider a mechanism or centralized system where interested parties could access the existing information more easily than at present.
- To try to overcome some of the problems encountered in clinical trials, particularly dissatisfaction with outcomes on the part of developing country researchers, by preparing a general document on 'good practices' for collaboration in clinical trials in developing countries. This document should highlight certain issues that, if properly addressed, could maximize positive outcomes while avoiding negative ones. Such good practices included: building in input from local community/investigators into study design and results analysis; local capacity building through opportunities for training; and explicit discussion of introducing products locally if they proved effective in the trials. Several participants stressed the usefulness of such a document, but it was left to the IPPPH Secretariat to consider how to set in motion a process for developing consensus.

2.7 Closure of meeting

Dr Roy Widdus expressed sincere thanks to Dr Wenceslas Kilama, who chaired the meeting; the co-chairs, Dr Uford Inyang and Dr Gerald Keusch; and the working group chairs and rapporteurs for their contributions. He also thanked all participants for their input to what he felt had been a wide-ranging and frank exchange on how to better work together to build stronger clinical trials capacity in LMICs, particularly in Africa.

Annex 1: Agenda

Chair
Dr Wenceslas Kilama, African Malaria Network Trust (AMANET), Tanzania

Co-chairs
Dr Uford Inyang, National Institute for Pharmaceutical Research and Development, Nigeria
Dr Gerald Keusch, National Institute of Health, United States of America
Dr Roy Widdus, Initiative on Public-Private Partnerships for Health, Switzerland

Friday, 15 November 2002 (Day One)

Plenary session I **Chair: Dr Wenceslas Kilama ▲ Co-chair: Dr Roy Widdus**

2.30 p.m. – 2.45 p.m.	• Welcome and introductions • Aims of the meeting
2.45 p.m. – 3.00 p.m.	• Overview: Existing assessments of current resources and future demands for clinical trials in low- and middle-income countries (LMICs) – What do we know? • Dr Ebi Kimanani, Consultant, Rockefeller Foundation
3.00 p.m. – 3.30 p.m.	• Discussion: How can we better assess current resources and future demands?

3.30 p.m. – 3.45 p.m. Break

Plenary session II **Chair: Dr Wenceslas Kilama ▲ Co-chair: Dr Roy Widdus**

3.45 p.m. – 5.30 p.m.	• Key lessons from existing experience • Discussion, based upon synthesis of summaries of experience submitted by LMIC participants and selected reviews
5.30 p.m. – 6.00 p.m.	• Initial summary of key lessons

End of day one

Saturday, 16 November 2002 (Day two)

Working group sessions

8.30 a.m. – 10.30 a.m.

- Discussion (in working groups): Priority needs for clinical trials capacity strengthening within and among cross-cutting areas:
  a) Overall management
  b) Good clinical practice and quality control
  c) Community relations and engagement

- Where, within and among these areas are more financial or human resources or more coordination most needed?

10.30 a.m. – 10.45 a.m. Break

Plenary session III — **Chair: Dr Wenceslas Kilama ▲ Co-chair: Dr Uford Inyang**

10.45 a.m. – 12.00 noon

- Sustaining capacity:
  a) The roles of institutional and government policies
  b) Can pharmaco-vigilance/Phase IV studies play a role in sustaining capacity?

- *Discussion*

12.00 noon – 1.30 p.m. Lunch

Plenary session IV — **Chair: Dr Wenceslas Kilama ▲ Co-chair: Dr Gerald Keusch**

1.30 p.m. – 2.00 p.m.

- Conclusions of working groups
  (10 minutes each to report back; comments can be submitted in writing to the meeting rapporteur)

Plenary session V — **Chair: Dr Wenceslas Kilama ▲ Co-chair: Dr Gerald Keusch**

2.00 p.m. – 3.30 p.m.

- Perspectives on coordinating support to strengthening clinical trials capacity:
  (a) Selected funders, including industry and EDCTP
  (b) LMIC institutions
  (c) Product development partnerships

3.30 p.m. – 3.45 p.m. Break

Plenary session VI — **Chair: Dr Wenceslas Kilama ▲ Co-chair: Dr Roy Widdus**

3.45 p.m. – 5.30 p.m.

- Discussion: Next steps?
  (a) Beyond a meeting report, what is desirable and who should do it?

End of meeting

Annex 2: List of participants

Dr Salim Abdulla, Ifakara Health Research and Development Centre, Dar es Salaam Office – National Institute for Medical Research Compound, Sokoine/Luthuli Road, P.O. Box 78373, Dar es Salaam, Tanzania.
Tel.: 255 22 2132704; Fax: 255 22 2136687;
E-mail: abdulla.ihrdc@twiga.com

Ms Phumla Adesanya, International AIDS Vaccine Initiative (IAVI), 110 William Street, New York, N.Y. 10038, USA.
Tel.: 1 212 847 1076; Fax: 1 212 847 1112;
E-mail: padesanya@iavi.org

Prof. Bartholomew D. Akanmori, Noguchi Memorial Institute for Medical Research, University of Ghana, P.O. Box LG5681, Legon, Accra, Ghana.
Tel.: 233 21 501178; Fax: 233 21 502182;
E-mail: bakanmori@noguchi.mimcom.net

Dr Hannah Akuffo, SIDA/SAREC, Swedish International Cooperation Agency, 105 25 Stockholm, Sweden.
Tel.: 46 8 698 5263; Fax: 46 8 698 5656;
E-mail: Hannah.Akuffo@sida.se

Dr Alwyn T. Andrew-Mziray, Huron Consulting Group – Healthcare, 550 W. Van Buren, 9th Floor, Chicago, Il 60607, USA.
Tel.: 1 312 880 3158; Fax: 1 312 583 8701;
E-mail: aandrew-mziray@huronconsultinggroup.com

Dr Danstan Bagenda, University of Washington/Statistical Center for HIV/AIDS Research and Prevention (SCHARP)/Makerere University-Johns Hopkins University Research Collaboration, 6423 NE Radford Dr. No. 311, Seattle, WA 98115, USA.
Tel.: 1 206 229 9741;
Fax: 1 206 667 4812/543 3286;
E-mail: dbagenda@hivnet.fhcrc.org – dbagenda@u.washington.edu

Ms Olamide Bandele, Nigeria Chapter, African Council for Sustainable Health Development (ACOSHED), 20 Aare Avenue, New Bodija Estate, P.O. Box 21633, Ibadan, Oyo State, Nigeria.
Tel.: 234 2 810 2401; Fax: 234 2 810 2405;
E-mail: acoshed@yahoo.com

Dr Banson Barugahare, Joint Clinical Research Centre, Kampala, Plot 893 Ring Road Butikiro House – Mengo, P. O. Box 10005, Kampala, Uganda.
Tel.: 256 41 270 622/256 77 430 206;
Fax: 256 41 342 632;
E-mail: banson@medscape.com – Banson@jcrc.co.ug

Ms Sandra Botta, Initiative on Public-Private Partnerships for Health, Global Forum for Health Research, ICC Building, 20 Route de Pré-Bois, P.O. Box 1826, 1215 Geneva 15, Switzerland.
Tel.: 41 22 799 4082; Fax: 41 22 41 22 4089;
E-mail: Sandra.botta@ippph.org

Dr Sheick Oumar Coulibaly, Laboratoire National de Santé Publique, Medical Biology Department, 09 B.P. 24, Ouagadougou 09, Burkina Faso.
Tel.: 226 37 31 31/37 32 32;
Fax: 226 37 24 30;
E-mail: sheickoumar@hotmail.com

Dr J. Carl Craft, Medicines for Malaria Venture (MMV), ICC Building, Block G, Third Floor, 20 Route de Pre-Bois, P.O. Box 1826, 1215 Geneva 15, Switzerland.
Tel.: 41 22 799 4067; Fax: 41 22 799 4061;
E-mail: craftjc@mmv.org

Dr Rodolfo Dennis, INCLEN, Inc., Pontificia Universidad Javeriana, Hospital San Ingnacio, Carrera 7a No 40-62 piso 2, Bogota, D.C., Colombia.
Tel.: 57 1 340 0486; Fax: 57 1 185 6981;
E-mail: rdennis@javeriana.edu.co

Dr Jean-Pascal Ducret, Sanofi-Synthelabo/Impact Malaria, 82 Avenue Raspail, 94255 Gentilly, France.
Tel.: 33 1 41 24 65 11;
Fax: 33 1 41 24 61 24;
E-mail: jean-pascal.ducret@sanofi-synthelabo.com

Dr Jose Esparza, WHO-UNAIDS HIV Vaccine Initiative, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
Tel.: 41 22 791 4392; Fax: 41 22 791 4865;
E-mail: esparzaj@who.int

Dr Ruth Frischer, Bureau for Global Health, USAID, 1300 Pennsylvania Avenue, N.W., Ronald Reagan Building, Room 3.07-070, Third Floor, Washington, D.C. 20523, USA.
Tel.: 1 202 712 0771; Fax: 1 202 216 3702;
E-mail: rfrischer@usaid.gov

Dr Janet Ann Frohlich, Southern Africa Fogarty AIDS Training Programme, Nelson R Mandela School of Medicine, University of Natal, Private Bag 7, Congella 4013, South Africa
Tel.: 27 31 2604277; Fax: 27 31 2604307;
E-mail: jafrohlich@netactive.co.za

Prof. Oumar Gaye, Faculty of Medicine, Université Cheik Anta DIOP de Dakar (UCAD), Dakar, Senegal.
Tel.: 221 825 1998/637 5055;
Fax: 221 825 36 68;
E-mail: ogaye@refer.sn

Dr Lawrence J. Geiter, Aeras Global Tuberculosis Vaccine Foundation, 9610 Medical Center Drive, Suite 220, Rockville, MD 20850, USA.
Tel.: 1 301 762 3100; Fax: 1 301 762 2122;
E-mail: lgeiter@aeras.org

Dr Sam Gobin, Aids Fonds, Keizersgracht 390, 1016 GH Amsterdam, The Netherlands.
Tel.: 31 20 6262669; Fax: 31 20 6275221;
E-mail: sgobin@aidsfonds.nl

Dr Marian Griffiths, Medical, Safety and Therapeutics, Covance Inc., Clinical Development Services, 210 Carnegie Center, Princeton, NJ 08540-6233, USA.
Tel.: 1 609 452 4706; Fax: 609 734 9208;
E-mail: marian.griffiths@covance.com

Dr Tony Hawkridge, Sequella/UCT BCG Trial, Child Health Unit, Department of Paediatrics and Child Health, University of Cape Town, 46 Sawkins Road, Rondebosch 7700, Cape Town, South Africa.
Tel.: 27 21 685 4103; Fax: 27 21 689 5403;
E-mail: tony@rmh.uct.ac.za

Ms Christina Heiler, INCLEN, Inc., 1420 Walnut Street, Suite 411, Philadelphia, PA 19102-4003, USA.
Tel.: 1 215 222 7700; Fax: 1 215 222 7741;
E-mail: heiler@inclen.org

Dr Carole A. Heilman, National Institutes for Health, NIAID/DMID, 6700B Rockledge Drive, Room 3142, MSC 7630, Bethesda, MD 20892-7630, USA.
Tel.: 1 301 496 1884; Fax: 1 301 480 4528;
E-mail: gn4d@nih.gov

Dr Rodney Hoff, National Institute of Allergy and Infectious Disease, National Institute for Health, Bethesda, MD 20892-7628, USA
Tel.: 1 301 496 6179; Fax: 1 301 402 3684;
E-mail: rh25v@nih.gov

Prof. Michael Hollingdale, London School of Hygiene and Tropical Medicine, Gates Malaria Program, 50 Bedford Square, London WC1B 3DP, United Kingdom.
Tel.: 44 207 299 4714; Fax: 44 207 299 4720;
E-mail: Michael.Hollingdale@lshtm.ac.uk

Dr Andreas Holtel, European Commission, Office SDNE 7/36, Rue de la Loi 200, 1049 Brussels, Belgium.
Tel.: 32 2 295 3716; Fax: 32 2 295 5365;
E-mail: andreas.holtel@cec.eu.int

Dr Joachim Hombach, Government Affairs, GlaxoSmithKline Biologicals, 89 Rue de l'Institut, 1330 Rixensart, Belgium.
Tel.: 32 2 656 70 80; Fax: 32 2 656 81 45;
E-mail: Joachim.hombach@gskbio.com

Dr Akira Homma, Bio-Manguinhos, Fundacao Oswaldo Cruz, Av. Brasil 4365, Manguinhos 21045-900, Rio de Janeiro, RJ, Brazil.
Tel.: 55 21 3882 9305; Fax: 55 21 2260 4727;
E-mail: akira@bio.fiocruz.br

Dr Uford Inyang, National Institute for Pharmaceutical Research and Development (NIPRD), Idu Industrial Area, P.M.B. 21, Garki, Abuja, Nigeria.
Tel.: 234 9 5239089/234 9 6700834; Fax: 234 9 5231043/0804 418 0278;
E-mail: ufordi@yahoo.com

Dr Rajiv Kumar Jain, Infectious Diseases Chapter, Indian Academy of Pediatrics, 480 Sector 37, Faridabad–121003, Haryana, India.
Tel.: 91 11 3002256; Fax: 91 11 3387556;
E-mail: rajivkjain@vsnl.net

Dr Soren Jepsen, European Malaria Vaccine Initiative (EMVI), c/o Statens Serum Institut, 5 Artillerivg, 2300 S Copenhagen, Denmark.
Tel.: 45 3268 3188; Fax: 45 3268 3228;
E-mail: sje@ssi.dk

Dr Amina Jindani, International Union Against Tuberculosis and Lung Disease, 68 Boulevard Saint-Michel, 75006 Paris, France.
Tel.: 33 1 44 32 03 66; Fax: 33 1 43 29 90 87;
E-mail: Ajindani@iuatld.org

Dr Luis Jodar, International Vaccine Institute, Shillim-dong, San 56-1, Kawnak-ku, Seoul National University Campus, Seoul, Republic of Korea.
Tel.: 82 2 872 2801; Fax: 82 2 872 2803;
E-mail: ljodar@ivi.int

Dr Saidi H. Kapiga, Harvard School of Public Health, 665 Huntington Avenue, Bldg 1 Room 1105, Boston, MA 02115, USA.
Tel.: 1 617 432 1237; Fax: 1 617 566 0365;
E-mail: skapiga@hsph.harvard.edu

Mr Andrew Kennedy, Department of Research Policy and Cooperation, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
E-mail: kennedya@who.int

Dr Nzeera Ketter, International AIDS Vaccine Initiative (IAVI), 110 William Street, New York, N.Y. 10038, USA.
Tel.: 1 650 854 9806; Fax: 1 650 854 1076;
E-mail: nzeera@pacbell.net

Dr Gerald Keusch, Fogarty International Center, National Institutes of Health, 31 Center Drive, Bethesda, MD 20892-2220, USA.
Tel.: 1 301 496 1415; Fax: 1 301 402 2056;
E-mail: keuschg@mail.nih.gov

Dr Marie-Paule Kieny, Initiative for Vaccine Research, Vaccines and Biologicals, Health Technology and Pharmaceuticals, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
Tel.: 41 22 791 3591; Fax: 41 22 791 4860;
E-mail: kienym@who.int

Dr Wenceslas L. Kilama, African Malaria Network Trust (AMANET), C26/27 Tanzania Commission for Science and Technology Building, P. O. Box 33207, Dar es Salaam, Tanzania.
Tel.: 255 22 270 0018; Fax: 255 22 270 0380;
E-mail: wkilama@africaonline.co.tz
(Chair)

Dr Ebi Kimanani, Ebitendo Statistics Inc., Beaconsfield, QC H9W 5B6, Canada.
Tel.: 1 514 697 5902; Fax: 1 514 697 6597;
E-mail: ebi@ebitendo.com

Dr Ivana Knezevic, Quality Assurance and Safety Biologicals, Vaccines and Biologicals Department, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
Tel.: 41 22 791 31 36; Fax: 41 22 791 49 71;
E-mail: knezevici@who.int

Mr Gunnar Kvale, Centre for International Health, Armauer Hansen Building, University of Bergen, 5021 Bergen, Norway.
E-mail: Gunnar.kvale@cih.uib.no

Dr Richard Lane, The Wellcome Trust, 183 Euston Road, London NW1 2BE, United Kingdom.
Tel.: 44 207 611 7230; Fax: 44 207 611 0681;
E-mail: r.lane@wellcome.ac.uk

Dr Valerie Lameyre, Sanofi-Synthelabo/Impact Malaria, 82 Avenue Raspail, 94255 Gentilly, France.
Tel.: 33 1 41 24 63 64; Fax: 33 1 41 24 61 24;
E-mail: valérie.lameyre@sanofi-synthelabo.com

Dr Juntra Laothavorn, Product Research and Development, Special Programme for Research and Training in Tropical Diseases, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
Tel.: 41 22 791 3867; Fax: 41 22 791 4854;
E-mail: karbwangj@who.int

Dr Janis K. Lazdins-Helds, Product Research and Development, Special Programme for Research and Training in Tropical Diseases, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
Tel.: 41 22 791 3818/3817;
E-mail: lazdinsj@who.int

Prof. Rose Leke, Faculty of Medicine and Biomedical Sciences, University of Yaounde 1, Yaounde, Cameroon.
Tel.: 237 223 7429/237 222 5955; Fax: 237 223 7429; E-mail: rl23@georgetown.edu – rose.leke@camnet.cm

Dr William Macharia, INCLEN, Inc., University of Nairobi, Clinical Epidemiology, P.O. Box 19676, Nairobi, Kenya.
Tel.: 254 2 713 462; Fax: 254 2 710 164;
E-mail: africlen@net2000ke.com

Dr Isaac Malonza, Department of Reproductive Health and Research, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
Tel.: 41 22 791 3641; Fax: 41 22 791 4171;
E-mail: malonzai@who.int

Prof. Keith P.W.J. McAdam, Medical Research Council Laboratories, P. O. Box 273, Banjul, Gambia.
Tel.: 220 496 715; Fax: 220 496 513;
E-mail: kmcadam@mrc.gm

Dr Martin Meremikwu, Department of Paediatrics, University of Calabar, G.P.O. Box 1211, Calabar, Nigeria.
Tel.: 234 8777 6512; Fax: 234 8721 0403;
E-mail: meremikwu@skannet.com – meremikwum@yahoo.com – ehcapnigeria@infoweb.abs.net

Dr Mark Miller, Division of International Epidemiology & Population Studies, National Institutes of Health, Fogarty International Center, 16 Center Drive MSC 6705, Bethesda, MD 20892-6705, USA.
Tel.: 301 496 0815; Fax: 301 496 8496,
E-mail: millermark@nih.gov

Ms Jessica B. Milman, Malaria Vaccine Initiative, PATH, 6290 Montrose Road, Suite 1000, Rockville, MD 20852, USA.
Tel.: 301 770 5377; Fax: 301 770 5322;
E-mail: jmilman@malariavaccine.org

Dr Declan Mulkeen, Medical Research Council, 20 Park Crescent, London W1B 1AL, United Kingdom.
Tel.: 44 207 636 5422; Fax: 44 207 7436 5229; E-mail: Declan.mulkeen@headoffice.mrc.ac.uk

Dr Mary Newton, Medical Pharmaceutical Division, Roche Products (Pty) Ltd., P.O. Box 129 Isando 1600, 4 Brewery Street, Isando, South Africa.
Tel.: 27 11 928 8870; Fax: 27 11 392 4144;
E-mail: mary.newton@roche.com

Dr Andrew Nunn, Clinical Trials Unit, Medical Research Council, 222 Euston Road, London NW1 2DA, United Kingdom.
Tel.: 44 207 670 4703; Fax: 44 207 670 4815;
E-mail: a.nunn@ctu.mrc.ac.uk

Dr Opokua Ofori-Anyinam, GlaxoSmithKline Biologicals, Rue de l'Institut 89, 1330 Rixensart, Belgium.
Tel.: 32 2 656 9863; Fax: 32 2 656 6160;
E-mail: opokua.ofori-anyinam@gskbio.com

Dr Sonia R. Pagliusi, Vaccines and Biologicials, Health Technology and Pharmaceuticals, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
Tel.: 41 22 791 4265; Fax: 41 22 791 4860;
E-mail: pagliusis@who.int

Prof. K. J. Pallangyo, Faculty of Medicine, Muhimbili University College of Health Sciences, P.O. Box 65001, Dar es Salaam, Tanzania.
Tel.: 255 22 2151680; E-mail: kpallangyo@nzcgs.ac.tz

Dr Bernard Pecoul, Médecins sans Frontières Campaign for Access to Essential Medicines, 12 Rue du Lac, 1207 Geneva, Switzerland
Tel.: 41 22 849 8405; Fax: 41 22 849 8404;
E-mail: bernard.pecoul@geneva.msf.org – nathalie.bergeret@geneva.msf.org

Ms Beth Peterman, Bill and Melinda Gates Foundation, P.O. Box 23350, Seattle, WA 98102, USA.
Tel.: 1 206 709 3293; Fax: 1 206 709 3170;
E-mail: katherineg@gatesfoundation.org – elizabethp@gatesfoundation.org

Dr Regina Rabinovich, Malaria Vaccine Initiative, PATH, 6290 Montrose Road, Suite 1000, Rockville, MD 20852, USA.
Tel.: 1 301 770 5377; Fax: 1 301 770 5322;
E-mail: rrabinovich@malariavaccine.org

Dr Rolf Reed, University of Bergen, Harald Harfagresgate 1, 5009 Bergen, Norway.
Tel.: 47 5558 6389; Fax: 47 5558 6230;
E-mail: rolf.reed@fys.uib.no

Dr Rob Ridley, Product Research and Development, Special Programme for Research and Training in Tropical Diseases, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
Tel.: 41 22 791 3767; E-mail: ridleyr@who.int

Dr Lise Riopel, Medicines for Malaria Venture (MMV), ICC Building, Block G, Third Floor, 20 Route de Pre-Bois, P.O. Box 1826, 1215 Geneva 15, Switzerland.
Tel.: 41 22 799 4070; Fax: 41 22 799 4061;
E-mail: riopell@mmv.org

Dr Anita Rønn, Department of International Health/University of Copenhagen, Blegdamsvej 3B, The Panum Institute, 2200-Copenhagen N, Denmark.
Tel.: 45 35 32 78 35; Fax: 45 35 32 78 35;
E-mail: ronn@dadlnet.dk

Dr Giorgio Roscigno, Strategic Development, The Global Alliance for TB Drug Development, 27 Boulevard Bischoffsheim, 1000 Brussels, Belgium.
Tel.: 32 2 210 0220; Fax: 32 2 223 6928;
E-mail: Giorgio.roscigno@tballiance.org

Dr Jacobo Sabbaj, Merck & Company, Inc., 126 East Lincoln Avenue, Maildrop: RY 34-A100, Rahway, NJ 07065, USA.
Tel.: 1 732 594 5520; 1 732 594 6580;
E-mail: jacobo_sabbaj@merck.com

Dr Osman A. Sankoh, Indepth Network, 9 Adenkum Loop, P.O. Box KD 213, Kanda, Accra, Ghana.
Tel.: 233 21 254752; Fax: 233 21 254752;
E-mail: Osman.sankoh@indepth-network.org

Dr Abha Saxena, Department of Research Policy and Cooperation, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
Tel.: 41 22 791 2406; Fax: 41 22 791 4169;
E-mail: abhas@who.int

Dr Sally Stansfield, Bill and Melinda Gates Foundation, P.O. Box 23350, Seattle, WA 98102, USA.
Tel.: 1 206 709 3293; 1 206 709 3170;
E-mail: katherineg@gatesfoundation.org – sally@gatesfoundation.org

Dr Coumba Toure Kane, Laboratoire de Bacteriologie-Virologie, CHU Aristide Le Dantec, B.P. 7325, Dakar, Senegal.
Tel.: 221 8216420/8225919/6372266;
Fax: 221 8216442;
E-mail: kane@eci.harvard.edu

Prof. Thorkild Tylleskar, Centre for International Health, Armauer Hansen Building, University of Bergen, 5021 Bergen, Norway.
Tel.: 47 55 97 49 75; Fax: 47 55 97 49 79;
E-mail: Thorkild.Tylleskar@cih.uib.no

Dr Henrietta Ukwu, Merck Research Laboratories, P.O. Box 4, BLB-22, West Point, PA, USA.
Tel.: 1 484 344 7176; Fax: 1 484 344 3602;
E-mail: Henrietta_ukwu@merck.com

Dr Lut Van Damme, Contraceptive Research and Development Program (CONRAD), 1611 North Kent Street, Suite 806, Arlington, VA 22209, USA.
Tel.: 1 703 276 4020; Fax: 1 703 524 4770;
E-mail: lvandamme@conrad.org

Dr Remko Van Leeuwen, Business Development, International Antiviral Therapy Evaluation Centre (IATEC), University of Amsterdam, Academic Medical Centre, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands.
Tel.: 31 20 566 7158; Fax: 1 240 757 7091;
E-mail: r.leeuwen@amc.uva.nl

Dr Roy Widdus, Initiative on Public-Private Partnerships for Health, Global Forum for Health Research, ICC Building, 20 Route de Pré-Bois, P.O. Box 1826, 1215 Geneva 15, Switzerland.
Tel.: 41 22 799 4088/4086;
Fax: 41 22 41 22 4089;
E-mail: roy.widdus@ippph.org

Annex 3: Building a platform for clinical trials in Africa

Summary

Assessment of clinical trials capacities in Africa

A major hindrance to clinical trials in Africa is a general lack of knowledge of its scope and potential including the existence of trained investigators and the level of government regulations in the continent. This issue was the purpose of a baseline survey conducted in East Africa by Ebitendo Statistics and funded by the Rockefeller Foundation in 2001 to map the current status of clinical research with special emphasis on clinical trials in the region.

The survey's results were (or will be) published in:

- Kimanani, E. (2002) "Current status of clinical trials in Kenya", *Drug Information Journal*, 36.1: 1–39 (http://www.dia.org).
- Kimanani, E. (2001) "Good Clinical Practice: A call for regional harmonization of the GCP guideline", *East African Medical Journal*, Nov.
- Kimanani, E. "A database of investigators and clinical trials in East Africa", *Drug Information Journal* (under preparation).

They are also presented in the form of a database of investigators and investigative sites, available on the Internet (http:www.ebitendo.com/members) for easy access by potential sponsors. The database is only a first component to a site management organization that is being built by Ebitendo Statistics.

Based on this survey, the following observations, results and recommendations are made:

- **The potential for clinical trials exists**. This is evidenced by a critical mass of individuals with solid academic training in the clinical sciences. A framework for performing academic types of research also exists. However, there is still much regulatory work to do to build a framework for clinical trials that meets global standards. At present, much of the conduct of clinical trials is sporadic and left to the discretion of the principal investigator and/or the sponsor.
- **Political will towards clinical trials exists but is distracted**. Governments in the region have shown some initiative in promoting clinical research by setting up research institutions with the general mandate to carry out medical research for innovation and especially to influence public policy. Examples of these institutions are the National Institute for Medical Research (NIMR), in Tanzania, the Joint Clinical Research Center (JCRC) in Uganda, the Kenya Medical Research Institute (KEMRI) in Kenya, and the National Institute for Pharmaceutical Research (NIPRD) in Nigeria. These institutions have been responsible for raising the general public's awareness of the advantages of clinical research, providing venues for local scientists to pursue clinical research investigations and, to some extent, influencing public policy.
- **Medical practitioners in remote areas who have the potential to be clinical investigators feel isolated from the core of clinical research, facilities, funding and decision-making.** According to these people, almost all clinical studies in their countries take place in one or two institutions usually located close to the capital city. This is unfortunate given that remote areas tend to have patient populations with little or no access to care and attention. In addition, the patients would be suitable for clinical studies because they are drug-free. In some sites just 30 km from the cities, the survey was the first time that anyone had shown an interest in them.

- **Facilities for handling and managing clinical trial data are minimal at best, especially compared to global standards**. Subject-screening tools and facilities and biological sample-handling laboratories are limited to the research institutions (~1 per country), medical training institutions hospitals (~1–3 per country) and national hospitals (~1 per country). Data processing and reporting are largely left to individuals.
- **Logistics involved in conducting clinical trials in several sites in the region are challenging but can be overcome.** Transportation and communication issues remain challenging in this region as in most developing areas. Air travel between the major cities generally exists, although air links within each country is not assured. Most of the remote areas can be reached by road with a reliable vehicle. Communication in most areas is possible by cell phones.
- **Cultural factors are significant issues to be taken into consideration when planning and conducting clinical trials in this region and in Africa in general.** As long as a study is seen to be from the 'outside', acceptance and cooperation may not be as forthcoming as they may seem.
- **Current methods of sponsoring studies do not deliberately foster self-sufficiency and capacity building.** The reasons are multi-factorial but may be largely due to the lack of indigenous drug development, lack of financial resources, insufficient political support and questionable motives of the sponsors.

Annex 4: Summary of survey of lessons learned

Dr Lise Riopel, Medicines for Malaria Venture (MMV), Geneva, Switzerland

A survey questionnaire on lessons from prior experiences of conducting clinical trials in LMICs was sent to invitees who had either worked in or were from these countries.

Reponses were received from the following:

Name	Affiliation
Dr Osman Sankoh	INDEPTH Network, Ghana
Prof. Dicky Akanmori	Noguchi Memorial Institute for Medical Research, Ghana
Prof. Oumar Gaye	Faculty of Medicine, Université Cheik Anta DIOP de Dakar (UCAD), Senegal
Dr Coumba Toure Kane	Laboratoire de Bactériologie-Virologie, Dakar, Senegal
Dr Roberto Badaro	Federal University of Bahia, Brazil
Dr Harriet Mayanja-Kizza	Department of Medicine, Makerere University Medical School, Uganda
Dr Danstan Bagenda (Uganda)	University of Washington/Statistical Center for HIV/AIDS Research and Prevention (SCHARP)/Makerere University-Johns Hopkins University Research Collaboration
Dr Demissie Habte	Former Director, International Centre for Diarrhoeal Disease Research (ICDDR), Bangladesh
Dr Tony Hawkridge	Child Health Unit, University of Cape Town, South Africa
Dr Wenceslas L. Kilama	Managing Trustee, African Malaria Network Trust (AMANET)
Dr John Clemens	International Vaccine Institute, Seoul, Republic of Korea
Prof. Keith McAdam	Director, Medical Research Council Laboratories, Gambia
Ms Christina Heiler	INCLEN, Inc., Philadelphia, USA

The issues most often raised in responses to the survey included:

- The need for more training in GCP and study management, including the possible addition of clinical research to academic curricula.
- The role of the trial sponsor in GCP training.
- The need for experienced study coordinators, how to increase their availability and ensure the sustainability of this resource.
- Ethical review: the need for further definition; at present, understanding of procedures and processes often takes too long.
- Communication difficulties, particularly in rural settings.

Annex 5: List of participants in working groups

1. Overall management

Dr Mary Newton
Mr Andrew Kennedy
Dr Andreas Holtel
Dr Nzeera Ketter
Dr Alwyn Andrew-Mziray
Dr Ruth Frischer
Ms Christina Heiler
Dr Salim Abdulla
Dr Regina Rabinovich
Dr Carole Heilman
Dr Luis Jordar
Dr Uford Inyang
Dr Remko Van Leeuwen
Dr Sam Gobin
Prof. Bartholomew Akanmori
Dr Lise Riopel
Dr Rajiv Kumar Jain
Ms Jessica Milman
Dr Opokua Ofori-Anyinam
Dr Jacobo Sabbaj

2. Good clinical practice (GCP) and quality control

Dr Danstan Bagenda
Dr Isaac Malonza
Dr Andrew Nunn
Dr Martin Meremikwu
Dr Joachim Hombach
Ms Phumla Adesanya
Dr Tony Hawkridge
Dr Rob Ridley
Dr Ivana Knezevic
Dr Hannah Akuffo
Dr Marian Griffiths
Dr Henrietta Ukwu
Dr Banson Barugahare
Dr Giorgio Roscigno
Dr Rodolfo Dennis
Prof. Michael Hollingdale
Dr Lut Van Damme
Dr Anita Rønn
Prof. Oumar Gaye
Dr Larry Geiter

3. Community relations and engagement

Prof. Keith McAdam
Dr Coumba Touré-Kane
Prof. Rose Leke
Dr Amina Jindani
Dr Richard Lane
Dr José Esparza
Dr Janet Frohlich
Dr Gerard Keusch
Dr Rod Hoff
Dr Ebi Kimanani
Ms Olamide Bandele
Dr Osman Sankoh
Ms Sandra Botta

Annex 6: Topics assigned to working groups

1. Overall management	2. Good Clinical Practice (GCP) and quality control	3. Community relations and engagement
• Site characterization and baseline studies • Projects start-up/operations • Financial management • Management community relations • Data records management • Coordination with partners • Training • Staffing • Communication • Ethical review committee management • Unexpected problems	• Ethical review • Training • Project start-up/operation • GCP adherence • Regulatory requirements • Data records management • Statistical and data analysis • Unexpected problems	• Ethical review • Social and behavioural aspects of clinical research/clinical trial • Size characterization • Informed consent • Unexpected problems
Co-chairs: Prof. Bartholomew Akanmori Dr Lise Riopel	Co-chair: Prof. Oumar Gaye	Co-chairs: Dr José Esparza Dr Osman Sankoh
Rapporteur: Dr. Gina Rabinovich	Rapporteur: Dr Lawrence Geiter	Rapporteur: Dr Janet Frohlich

Annex 7a: Report of the working group on overall management

Major issues identified

Trial-specific issues

- Characterization: certain core characteristics need to be identified, such as political will; in addition, a baseline surveillance system that will define demographics and baseline incidence of disease is needed. How are patient or volunteer populations identified?
  - Disease-specific issues: it could be important to involve groups that access programmes for retroviral care.
- It is useful to do observational studies that enable a new site to develop training and capacities.
- Good laboratory practice (GLP) and training for staff: these usually come after epidemiology and surveillance as investigators know less about what the requirements are. This is balanced by the increased need for central laboratories.
  - Everything needs to be done – but it is important to prioritize. WHO's TDR talks about 'GCP laboratory'. GLP is very expensive and is something that laboratories should aspire to.
- The standard of medical care in the population needs to be raised.
- A long timescale: it takes years to set the infrastructure up and then prepare for the studies.

Cross-disease, cross-site management issues

- Management of expectations as to when a site is ready (and for what?).
- There should be a body/organization charged with continuous education on aspects of GLP and GCP.
- What is a site? It can vary enormously: is it an institution that has already started work? Hospitals? Given existing infrastructure, what needs to be added to make a site? What is the relationship between a 'site' and an institution?
  - The European Union's EDCTP can be useful in classifying sites. But it should not be forgotten that in order to enhance capacity, it first needs to be assessed.
- Accreditation for laboratories is required. But should accreditation be under the auspices of the government or the private sector? In most African countries, the reference laboratory system is part of government. Should this be independent to avoid potential corruption?
- Key management issues include the fact that, in a few sites, multiple sponsors are funding the trial and each has their own standard for financial reporting. There is a need for adequate control measures and transparency. It would be useful to have a set of broad principles for use in different sites. How to charge some costs across different trials? Procedures should be acceptable both in a given country and to donors, and should be audited. Corruption can be organized , widespread and 'subtle'. A clear understanding of what is culturally expected and acceptable to funders is therefore necessary.
- Data management:
  - Issues of varying standards also affect different standards to which data management needs to be held – is it for a pivotal trial for granting a license? To whose regulatory standard?
  - South Africa has developed data management capacity, which is locally driven when it is a local priority.
- It is important to establish trials that undertake several types of studies, i.e.,

vaccines and microbicides. However, the management of multi-site and multi-disease sites needs to be discussed further.

- Sustainability of clinical trial sites: historical experience already exists and gives an idea of what may happen after a key trial has ended. What would increase the likelihood of extension and growth of sites? How to prevent languishing of sites that have already been established?
- Communication between funders and sites: it is important to designate leaders/lead organization, not just with donor(s), but also with the community. Coordination requires not only access to e-mail or fax, but an awareness that everyone can bring up issues.
  - A study coordinator and study monitor are needed. Face-to-face communication is best for many issues, but there needs to be a commmitment from all players to make this happen.
- Ethical review management: Many donors, etc., are coming into countries and trying to help with workshops, etc. How to get the various groups together? While standards are the same, SOPs in many countries may vary. There is little thought of age and gender balance in many countries. The International Clinical Epidemiology Network (INCLEN) in India has set up its own review board.

In general, the group suggested that many problems arose from what it terms a 'hit-and-run' historical approach to trials in Africa.

Annex 7b: Report of the working group on Good Clinical Practice (GCP) and quality control

Major issues identified

Ethical review

- Institutional Review Boards (IRBs) do exist. They approve or disapprove new trials.
- IRB review of ongoing trials is, however, weak.
- Data and safety monitoring committees:
  - Their capacity is weak to non-existent.
  - Their roles are poorly understood.
  - Independent experts are lacking.

Ethical review/Regulatory authority

- Very weak and underfunded.
- Some countries have national GCP guidelines.
- "The FDA [Food and Drug Administration] is your friend." Consult early and often to avoid problems

General training

- Start early, in academic and pre-trial programmes.
- Create a baseline understanding and culture of clinical research, e.g., P>.05 is a failed/negative trial.

Training

- "Knowledge is power".
- Trial-specific training starts with protocol development.
- Early training at all levels is important.
- Training should be continuous, and flows from monitoring.
- Multiple courses already exist.
- Regional networks could catalogue and identify gaps.
- Some trainees should fail.
- Certification/compensation/profession.

Trials and monitoring

- Strict adherence needed for registration.
- Could it be relaxed for Phase IV trials?
- Early involvement of local investigators helps avoid problems (e.g., lab results in 24 hours).
- Protocol and SOP are the basis for audits.
- Monitor early and often, and train on the basis of audit results.

Guidelines of best practices of clinical trial sponsorship

- Industry.
- Governmental and international organizations.
- Alliances, forums, foundations.

Annex 7c: Report of the working group on community relations and engagement

Major issues identified

Emerging issues

- Community participation and preparation.
- Establish social contract with community.
- Ethics at a community level.
- Social and behavioural aspects of clinical research.
- 'Informed consent'.

Overriding principles

- Community preparation and participation benefit both community and science, and define the outcome of the research.
- Ethics and community preparation are integral to scientifically sound research.

Community participation and preparation

- Define 'community':
  - Two levels:
    - Higher/macro
    - Community/micro
  - Pool of people from which the study population is drawn.
  - Popular-opinion leaders and decision-makers including health service providers.
- Define community in context of research:
  - Phase I and II trials versus Phase III and IV trials.
  - Type of research impacts of stigma and discrimination at both individual and community level.
- Mechanisms to engage community:
  - Need for a clear strategy:
    - Integral part of R&D process.
    - Investment begins prior to trial.
    - Not a process for damage control.
  - First need national-level support for research agenda.
  - Parallel process of negotiation and consultation at levels of:
    - Authority and government.
    - Civil society/local government/nongovernmental organizations (NGOs).
    - Community.
- Community concerns:
  - Strengthen and build on existing community structures and development.
  - Transparent communication, interactive decision-making and regular information dissemination help build trust.
  - Identify community understanding and expectations.
  - Financial investment – who pays for community preparation strategies?

Establish social contract with community

- Empowerment and enablement training; build knowledge and understanding of research process.
- Research relevant to community.
- Communities face multiple choices in the merging international research agenda: mother-to-child transmission (MTCT); microbicides; vaccines, tuberculosis (TB) and antiretrovirals (ARV).
- Understanding of benefits during and after trials.
- Recognition of community and individual altruistic responses. Communities desire and choose to contribute to their own benefit.
- Shift from conducting research *on* people to *with* people from research subjects to research participants/volunteers.
- Explore immediate benefits versus long-term benefits with community.
- Gain community support.

Ethics at community level

- Issues to be addressed:
  - What does 'equivalent protection' mean?
  - Do the available guidelines adequately address the notion of 'community confidentiality'?
  - Avoid ethical imperialism: How to establish a mechanism to hear the voice of vulnerable populations?
- Good guidelines are available. Help communities to be able to interpret these guidelines. Need for virtual guidelines.
- Need for external advisory body to guide ethical decision-making:
  - Local needs to be supported through training and resources.
  - Expand existing case books to capture local context.
- Critical issue in international research:
  - Multiple trial sites need a mechanism to establish communications between the IRBs that set up common assurance processes.
- Who should provide support and build capacity of ethical review committees and IRBs? Should funding be a direct cost for doing research?

Social/behavioural/ethnographic aspects of clinical research

- Should be part of community preparation strategy.
- Explore understanding, perceptions and experiences of research.
- Determine decision-making mechanisms.
- Understanding of autonomy.

'Informed consent' versus 'informed decision-making' versus 'genuine consent'

- Consent cannot be 'informed' as participants do not have access to all information pertaining to the study to make a truly 'informed choice'.
- Seek consent when assured person has been provided with adequate information to understand critical aspects of the study.
- 'Informed decision-making' is a process and includes involving the community, opinion leaders and individuals in development of 'genuine consent' tool.
- Do not assume that illiterate and vulnerable populations cannot make a choice and provide 'genuine' consent.

Where, within and among these areas, are more financial or human resources or more coordination most needed?

The working group emphasized the need for financial investment in a clearly defined community education and preparatory programme that addresses the five key emerging issues and that is an integral part of the scientific agenda.

Annex 8: Criteria for assessing sites for clinical trials

Assessment tool of Covance Inc.

Provided by Dr. Marian Griffiths, Covance Inc., Princeton, NJ, USA.

Investigator

- Therapeutic area/specialty training and experience (with respect to both the therapeutic area and participating in clinical trials).
- Appropriate medical (or dental, if relevant) qualifications, current registration to practise, specialist training if applicable, and experience in conducting studies. A recent CV (within the past two years) is checked, and licensing is verified with the applicable licensing board. The investigator must show affiliation with the investigator site being considered (e.g., hospital admitting privileges or affiliation with a clinic).
- Preference is generally given to investigators who have assisted with feasibility or protocol development, or who have worked successfully with Covance or the sponsor in the past, or who are considered experts in their field.
- Restricted and/or debarred investigators are excluded (this is checked with applicable regulatory authorities).
- Review of any previous regulatory audit findings to see if any findings would lead to exclusion.
- Interest in participating in the study; competing studies (which might siphon off otherwise eligible patients).
- Appropriate and available patient population for the required recruitment rate.

Other staff at investigator site

- Degree of delegation to other staff and how other staff will be supervised. Qualifications; licensing and/or specialty training of staff (as applicable), including sub-investigators.
- Experience of study coordinator(s).
- Experience and qualifications of administrative support staff.
- Degree of staff turnover especially for crucial positions such as co-investigators and site coordinator(s).
- Flexibility of coverage (e.g., for a hospital-based emergency type indication, will staff be available 24 hours a day?).

Source documentation practices

- Adequacy of source documentation practices; assurance that monitors, auditors and regulatory authorities will have direct access to source documents.
- Suitable storage facilities which can assure long-term storage of trial documents in a secure environment, protecting patient confidentiality.

Laboratory and specialized diagnostic equipment

- Availability of any required special diagnostic tools and/or laboratory facilities.
- Laboratory appropriately licensed or accredited; lab equipment should be calibrated regularly – good laboratory practices followed.
- Familiarity with specific questionnaires (e.g., psychometric testing) that may be required by the protocol (this is not usually necessary as training on testing instruments is conducted prior to study start-up).
- Availability of suitable ancillary personnel (for example, independent psychometric assessor if required, etc.).

The facility

- Suitable facility (exam rooms or wards, etc.).
- Suitable storage for study medication (e.g., freezer or refrigerator if required; controlled-temperature room with thermometer and temperature log).
- Available space for storage of records, archiving records (for two to five years) – adequate space; secure; restricted access; respects patient confidentiality.
- Suitable space for monitor to review source documentation.

Ethics requirements

- IRB or IEC including list of members and their qualifications, the meeting schedule and the timelines for meeting, review and response.
- Adequacy of Informed Consent procedures and documentation of informed consent. The subject must be given information on all reasonably foreseeable potential risks and inconveniences and potential benefits associated with the study, alternate available treatments and the purpose(s) of the study, and must be given an adequate opportunity to ask questions. Consent must be fully voluntary with no coercion; the consent procedure must be conducted in the subject's language; and the adequacy of the consent procedure must be documented by an impartial witness.
- A Standard Operating Procedure should document the process of giving and receiving informed consent.

Requirements based on GCP and/or past experience

- Familiarity of site staff with Good Clinical Practice (GCP), Declaration of Helsinki and other applicable regulations.
- Familiarity with requirements and procedures for maintaining blinding.
- Familiarity with protocol deviation procedures (requirement for documentation of approval and for keeping deviations to an absolute minimum).
- Understanding of the particular protocol and its requirements.
- Agreement to ongoing training of study personnel on study protocol and GCP (this will be provided by sponsor or contract research organization (CRO)).
- Agreement to provide access for periodic monitoring and auditing of study sites to assure compliance and adequate record keeping.
- Familiarity with adverse event reporting, including serious adverse event documentation and reporting to sponsor/CRO within 24 hours; also familiarity with endpoint reporting if applicable.

Study drug requirements

- Reliable method of receiving and storing lab kits; reliable means of processing, labelling, storing and sending samples (e.g., blood samples).
- Who will maintain drug? Storage and control of study drug; maintenance of records for administering drug; control of drug in secure environmentally-controlled facility, with monitoring of temperature and/or humidity if required; tracked method of controlling temperature, etc. Is the storage capacity adequate? Is it secure (drug cannot be removed for other purposes)?
- Method of tracking receipt, preparation, dispensation, inventory and return of study drug (and other supplies).
- Awareness that study drug may not be used for any other purposes and must be represented as investigational only.

Annex 9: Presentations and other documents

These materials are available on request from the Initiative on Public-Private Partnerships for Health
E-mail: info@ippph.org

Presentations

Clinical Trials in Low-Income Countries (Powerpoint slides)
Clinical Trial Capacity in Low- and Middle-Income Countries (LMIC): Current, Potential and Future Needs (Word document)
Dr Ebi Kimanani, Ebitendo Statistics Inc., Beaconsfield, Canada.

Good Clinical Practice (GCP): Why So Critical to Industry? (Powerpoint slides)
Dr Henrietta Ukwu, Merck Research Laboratories, West Point, PA, USA.

European and Developing Countries Clinical Trials Partnership (Powerpoint slides)
Professor Michael Hollingdale, London School of Hygiene and Tropical Medicine, Gates Malaria Program, London, United Kingdom.

Major NIAID Programs in International Health (Powerpoint slides)
Dr Rodney Hoff, National Institute of Allergy and Infectious Disease, National Institute for Health, Bethesda, MD, USA.

Issues Most Often Raised in The Questionnaire of Experiences and Lessons Learned (Powerpoint slides); responses available.
Dr Lise Riopel, Medicines for Malaria Venture (MMV), Geneva, Switzerland.

Workshop on Clinical Trials Capacity in Low- and Middle-Income Countries: Experiences, Lessons Learned and Priorities for Strengthening (Powerpoint slides)
Dr Roy Widdus, Initiative on Public-Private Partnerships for Health, Global Forum for Health Research, Geneva, Switzerland.

Other documents

Clinical Research Training Project Description (Word document)
Sequella Global TB Foundation Projects in the Western Cape Province of South Africa (Word document)
Dr Lewellys Barker, Sequella Global Tuberculosis Foundation (now Areas Global TB Vaccine Foundation), Rockville, MD, USA.

The aim of the Initiative on Public-Private Partnerships for Health is to increase the effectiveness of public-private collaboration, particularly by helping those seeking to develop health products, or to improve access to such products needed to fight neglected diseases and other health problems in developing countries.

Created in 2000 in Geneva, Switzerland, the Initiative on Public-Private Partnerships for Health is sponsored by the Bill and Melinda Gates Foundation, the Rockefeller Foundation and the World Bank. It operates under the aegis of the Global Forum for Health Research, an independent international foundation helping to correct the 10/90 gap in health research, from which it also receives support (www.globalforumhealth.org).

www.ippph.org

Initiative on Public-Private Partnerships for Health
International Center Cointrin · Block G
3rd Floor · 20, route de Pré-Bois
Case Postale 1826
1215 Geneva · Switzerland

Tel: (+41 22) 799 4086 / 4088
Fax: (+41 22) 799 4089
E-mail: info@ippph.org