From research to control: Translating research findings into health policies, operational guidelines and health products

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A B S T R A C T

Although Africa’s health research capacity is still weak, African R&D institutions are contributing immensely to the development of health policies, guidelines and products essential for diagnosis, treatment, prevention and control of Africa’s leading health problems.

In order to increase Africa’s contributions, all health research stakeholders should participate in setting health research priorities and agenda, followed by establishing health research networks and consortia, holistic capacity strengthening, and gathering of baseline data.

The evaluation of candidate tools, and the research preceding it, must abide by international scientific and ethical standards, and must involve institutional and national regulatory authorities.

The funding of product development and product availability in Africa benefits from national govern-ments, bilateral, multilateral, and philanthropic agencies. When a trial is over poses many social and ethical issues, and not infrequently existing guidelines may not be adequate. Mechanisms for making products available in resource constrained countries are presented, as are problems relating to manufacturing, markets and procurement. So are obligations to trial and research communities.

The paper concludes by outlining the obligations of each stakeholder, in order to make research products readily available in resource constrained settings.

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1. Introduction

The translation of research findings has made tremendous contributions to Africa’s overall socioeconomic development, mainly in guiding policies, making decisions but also through application of research results to develop and apply new clinical and public health products. Africa has for example witnessed the eradication of smallpox, the ugly telltale signs of the disease which was so common several decades ago have been relegated to history books, thanks to the global smallpox eradication programme of the late 1960s. Similarly in much of Africa it is extremely rare to encounter childhood victims of paralytic polio, whose causative agent has succumbed to the efforts of an all out polio eradication programme. Childhood immunization programmes have in many instances led to closure of measles wards in public clinics. Indeed in many parts of Africa there is obvious decrease in the prevalence of many of the childhood immunizable diseases. Current gains over respiratory and diarrhoeal diseases in childhood are to a great extent due to the improved availability of appropriate interventions. Research results in the form of health products are also lessening the effects of some of Africa’s major public health threats including HIV/AIDS and malaria. With the introduction of combination antiretroviral drugs it is no longer common to encounter obviously ill AIDS patients on African streets. Furthermore with HIV/AIDS there are decreased estimates of prevalence in several African countries, which are attributable to changes in risky behaviours, whereas declines in deaths “in the past two years are partly attributable to the scaling up of antiretroviral treatment services” (UNAIDS, 2007). Research results are even denting Africa’s malaria burden in a number of countries, which can already look forward to its elimination (Fig. 1). Increased efforts in providing vitamin A and deworming, to name a few, are also contributing substantially to improved child health in Africa.

The contributions of health research to overall human development are immense. In the examples presented above, the power of health research to improve public health is made abundantly clear. What is not always clear are the tribulations inherent in the process; quite often it takes ages to arrive at a tool and a strategy suitable for application in public health. Although the research process often seems to start from basic research whose aim is to advance basic understanding and contribute to the frontiers of knowledge, there must concurrently be undertaken epidemiological research whose role it is to identify and set priorities among health problems; without good epidemiological understanding, it would not be clear which health problems should be prioritized in finding solutions, and indeed without epidemiology there would
be no baseline data to determine progress in disease control. In these examples new tools and fresh strategies had to be developed by researchers through translational research to address each of the target diseases. Moreover through implementation research the knowledge previously gained was applied in order to accelerate the perceptible impact of the developed interventions.

But Africa is beset with other major public health problems that are nutritional, cardiovascular, psychiatric, and many other life style diseases. Road traffic accidents are becoming a leading cause of morbidity and mortality. Moreover there are such new and rising threats as occupational and environmental hazards, substance abuse, and the like. Although these health problems were previously much more common in industrialized countries than in Africa, the latter which is undergoing epidemiological transition is quickly catching up, and in some cases (e.g. cardiovascular and other noncommunicable diseases, road traffic accidents and injuries) surpassing them. Developed countries have utilized research results to for example change lifestyles, which has resulted in the slowing down of these health problems. They have also relied on research results to improve their health systems. Although these are major impediments to human health in Africa, they will not be presented further; since they are shared with developed countries, Africa is encouraged to adopt and utilize their research experiences. This paper will therefore concentrate on research aimed at the development of health products intended at addressing health problems that are predominantly African.

From the health research ethics perspective, undertaking research to correct the health anomalies listed above, must take cognizance of the realities in Africa that include:

- The great burden of diseases, which are likely to attract researchers who wish to quickly attain the required sample size;
- The scarce and poor health facilities, which readily accept hosting research projects, that would bring in badly needed funds, facilities, and personnel;
- Poor research systems, with poor management, weak science and ethical review processes;
- Rampant poverty coupled with ignorance;
- Abundant human right abuses, e.g. common disregard of children’s and women’s rights;
- Rich biodiversity subject to exploitation through bioprospecting and biopiracy;
- The need to test new tools being churned out by the ongoing biomedical and genomic revolutions.

These African realities expose African research participants and even African research institutions to exploitation, coercion, enticement, and inducement; which would compromise overall voluntariness.

The research to be undertaken in order to adequately address the above outlined health problems must foremost ensure that there are competent research personnel, and that they have the requisite experience. In this regard the International Conference on Harmonization of Good Clinical Practice (ICH-GCP, 1996) in several paragraphs clearly stipulates that “The investigator(s) should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s) . . .” Moreover “the investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely” (ICH-GCP para 4.2.3). Furthermore the methods used must be appropriate for the planned study.

Most importantly, “the sponsor and the investigator must make every effort to ensure that the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out.” Where these are not in place, steps must be taken to strengthen the available capacity (CIOMS, 2002 para 1, 10 and 20).

In order to ensure that studies undertaken in African communities are ethical, researchers and sponsors in African settings should make all out efforts to meet the above ethical requirements. This paper tries to abide by these requirements, and therefore takes a holistic approach to developing interventions within the above African contexts. The procedures recommended are starting from undertaking a needs assessment, filling the gaps identified, followed by research to characterize study areas, and then undertaking research leading to products needed for disease diagnosis, treatment, prevention, and control. The information obtained during this long process would be utilized appropriately to make the
research product available, and also to advise decision and policy makers, operational health workers, different communities, and other research stakeholders.

2. Before a study starts

2.1. Needs assessment

Foremost a needs assessment exercise should be undertaken of all institutions intending to participate in the planned research. It should also include national regulatory authorities and other pertinent stakeholders especially those involved in the relevant management, treatment, prevention and control of the particular disease or health problem. This exercise would at least cover personnel and infrastructure needs, so as to identify gaps to be filled.

2.2. Capacity building

The needs assessment exercise should be followed by capacity building, which should be holistic and not limited to human resources (http://www.un.org/esa/coordination/Capacity_Building_for_Poverty_Eradication.pdf): it should in this regard extend to institutional development so as to include for example the provision of equipment and refurbishment of infrastructure essential for participation in product development. Older models whereby highly trained national experts returned to empty laboratories failed. Indeed according to the United Nations capacity building (vide supra) is “meant helping recipient countries to invent, develop and maintain institutions and organizations, which are capable of learning and bringing about their own transformation, so that they could play a dynamic role in supporting national development processes.” In order to overcome the many weaknesses characterizing prospective study participants and research institutions, it is absolutely essential that capacity building be given utmost priority. A number of ethical guidance documents prioritize capacity building, and examples of such set ups are provided in the papers by W.L. Kilama in this issue.

The development of the essential human resources is central to product development undertakings in Africa. The paper on the 10/90 gap by W.L. Kilama in this issue lists leading human resource needs for such undertakings, which includes both long and short-term training needs. Investigators involved in product development in Africa, should be required to receive mandatory training and gain experience in health research ethics, good clinical practice, and good laboratory practice. There should also be short-term training in data management, financial accounting, and institutional management as appropriate. Institutions involved in product development should have well established and appropriately functioning Ethics Committees, making sure that their members are already trained in health research ethics, or they get trained soon after joining. Similarly members of Data Safety Monitoring Boards should also be appropriately trained and experienced. Furthermore sponsors should ensure that their trials abide by the trial protocol, by having a trial monitor working on their behalf; similarly the host institution should have an internal monitor. Given the likely shortage of appropriately trained personnel, as training proceeds consideration should be given to outsourcing Clinical Research Organizations, Clinical Research Associates, and consultants as deemed necessary.

2.3. Setting research priorities and agenda

Given the innumerable health problems listed above, it would not be possible for a country, particularly a resource constrained country, to address all of them adequately. It is advisable therefore to start by setting research priorities, a process that should involve all research stakeholders, especially policy and decision makers, health workers, health researchers, and community representatives. According to COHRED (Council on Health Research for Development, http://www.cohred.org/main/prioritysetting.php) priority setting is a cycle of continuous consultation, learning and improvement, that:

- Involves a growing number of health research actors over time
- Develops increasingly accurate data as it progresses
- Sets a foundation for action.

Such consultations should among other things study available disease statistics and literature, giving priority to diseases that are leading causes of morbidity and mortality. Focused group discussions involving key stakeholders are likely to make valuable inputs. Priority should also be given to areas where there is available expertise, and there is likely feasibility of arriving at utilisable results. These considerations would then factor into the setting of research agenda. Research undertaken in resource poor settings that is outside the set research agenda is not likely to produce utilisable research results, and would have subjected research participants or other resources for no good purpose, and is in this regard unethical.

2.4. Networking and consortia

Given the fact that most African health research institutions are weak, there is pressing need for them to harness their available human and other resources, so that they tackle the addressed problems together. Research collaboration would aim at overcoming current isolation, where researchers even within the same department or institution, are unaware of what research each is undertaking. Efforts should be invested in creating consortia, at institutional and national level, whereby problems addressed would be tackled more holistically, bringing diverse talents and expertise into action, and providing for wider national coverage, where disease epidemiology and endemicity levels may differ considerably. The networking and collaboration would be indispensable in product development, whereby multicentre trials in different epidemiological settings are essential. There are very many thriving health research networks and networked institutions in Africa; they are for example collaborating in trials of various products against targeted diseases. The GMZ2 Consortium is presented as an example:

The European Developing Countries Clinical Trials Partnership (EDCTP) starting in 2008 funded the establishment of the GMZ2 Consortium coordinated by the African Malaria Network Trust (AMANET) and involving study centres in Burkina Faso, Gabon, Gambia, and Uganda, with two European partners. In this consortium the European Malaria Vaccine Initiative (EMVI) owns the vaccine candidate, the University of Tubingen had undertaken the “first in humans” Phase Ia trial, while the Medical Research Unit at Lambarene, Gabon had already undertaken a Phase Ib trial in adults. The MRC in the Gambia had considerable prior trial experience, while the CNRFB of Burkina Faso had limited trial experience, and Makerere University of Uganda had none. The consortium would carry out phase 2b trials in all the African sites, and promote capacity strengthening whereby weaker sites would gain trial experience within the consortium. AMANET is the sponsor of both trial phases and capacity strengthening in Africa.

As Africa strengthens its science and technology base, it has moved from adaptive R&D whereby African research institutions merely tested licensed products so as to establish their suitability to African needs. More recently, Africa is participating in product
development. Eventually and hopefully soon, through networking Africa’s participation would extend beyond testing inventions from industrialized countries, to African inventions; this would have to bring together capacities and activities in biomedical and other sciences, and other branches of human health, to study and develop new products for the treatment and prevention of disease in Africa.

2.5. Site characterization

The testing of new tools should follow site characterization, so as to adequately address the situation at hand. In malaria research for example the need to determine the vector species, their feeding and resting behaviour, the entomological inoculation rate, susceptibility to insecticides, are paramount, otherwise the wrong mosquito species or stage would be blamed and targeted for malaria control using wrong tools and strategies. There will in this regard be need to determine the parasite species, their prevalence, and above all their susceptibility to different antimalarial drugs. Other epidemiological studies should also be undertaken, to for example determine the disease rate by age, location, gender, and the like. Demographical studies and vital statistics including data on birth rates, age and sex stratified mortality, case morbidity and mortality should also be carried out in prospective trial communities; this would provide opportunity for community engagement. Data management and data sharing should be given the attention they rightly deserve. Such work “must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and where appropriate, animal experimentation” (WMA, 2000 para 11). CIOMS guidelines (CIOMS, 2002, 2008 para 1) are more emphatic in this respect. Such early field data if properly handled could already contribute not only to epidemiology but also to public health by advising policy and decision makers.

2.6. Ethical and regulatory considerations

Ethics review committees in Africa are generally weak as was recently reported by Nyika and his associates (Nyika et al., 2009). All health research, more so clinical and even epidemiological research, must abide by the basic ethical principals of respect for the autonomy of research participants, beneficence/nomaleficence and justice. As much as these principles are usually regarded to have equal force, the principle of respect of autonomy is usually given much greater attention in product development and indeed in all guidance documents. Given the rampant ignorance, poverty, vulnerability to exploitation, scarcity of health facilities, the research participants in African settings, deserve great protection, as will be presented later. Furthermore some new intervention tools, as is presented by Kilama elsewhere in this series, call for their population wide application, which introduces much wider ethical demands, surpassing individual ethical considerations in clinical trials. Since in many situations the test products, the sponsors, and the lead researchers come from foreign cultures, the resulting relations deserve attention especially with respect to issues of justice.

The review of protocols may differ from one institution to another. It however seems many African institutions start with scientific review, so that ethical review is only undertaken on protocols that are scientifically sound. Appendix 1 of the 2002 CIOMS guidelines and appendix 2 of the 2008 guidelines contain required contents of a protocol. Since it may be necessary, especially during Phase III, to undertake multicenter trials which use the same study methodologies, it would also be necessary to harmonize the operations of their institutional ethics review committees.

There are very heavy demands for documentation in clinical trials; these are outlined in ICH-GCP Guidelines, section 8. To these should be added:

- Standard Operating Procedures (e.g. for ethics committee, biosafety committee, laboratory procedures, etc.),
- Conflict of Interest Declaration Form, and
- Contracts or memoranda of understanding with various parties.

A number of developing country institutions now demand full involvement in study protocol preparation. Furthermore loopholes in some sections of ICH-GCP Guidelines especially those relating to insurance, subject compensation, memoranda of understanding with host and regulatory institutions are likely to be overlooked. Not infrequently sponsors and many guest researchers give too much attention to legal aspects, rather than the inherent ethical basis of the studies.

Since the preparation of all the above documents is not included in traditional academic curricular, the know how has to be acquired on the job. In some cases legal opinion has to be sought, and are likely to favour northern partners besides consuming excessive energy and being distractive. The challenge is overwhelming when developing products for poverty related diseases, as there may be no interest from the pharmaceutical industry which possesses the requisite experience.

The development of intervention tools relies on considerable review, regulation and oversight, which are vested in:

- Peer reviewers of trial protocols and plans,
- Sites Development Committees,
- Clinical Development Teams,
- Regulatory Authorities,
- Data Safety and Monitoring Boards,
- Ethics Committees.

Almost invariably African academic and research institutions intending to participate in product development lack prior pertinent experience essential for membership on the above bodies, and consequently necessitating their de novo establishment, although the members often lack the required long experience.

The complexities inherent in the responsibilities of the above bodies are exemplified by the roles of a Data Safety Monitoring Board (DSMB), which is a body of highly qualified and experienced researchers, established by the sponsor of a trial, to mainly undertake interim analysis of safety and efficacy data, particularly in randomized control clinical trials, where the design or data gathering and analysis are complex. The DSMB may recommend to the sponsor continuation, modification, or stoppage of a trial (Lang et al., 2008). Many major clinical trials undertaken in Africa rely on foreign DSMB members.

3. Trials of candidate intervention tools

The undertaking of trials, particularly in Africa, is underpinned by the preceding activities involving needs assessment, site characterization, capacity strengthening and ethical considerations. Although it is desirable that the listed requirements are in place before a study starts, their accumulation would demand considerable investment of financial and other resources, they would therefore have to be phased, so that eventually essential capacity is built.

The testing of any product requires long-term investment starting from basic research, which is often undertaken in developed country laboratories, where discoveries of potential new tools are made. This is followed by patenting; some patented candidate tools may stay for years before being acquired by industry or a biotech-
nology firm. They must then go through considerable laboratory studies; in the case of chemicals that would later become drug candidates, these would for example include purification, characterization, and rigorous laboratory testing. A drug or vaccine for a disease of the poor may never get a sponsor, and when it does there are often long delays. Not infrequently new drugs for diseases of poverty are initially developed for other human diseases (e.g. a component Malaron e, a leading malaria chemoprophylactic drug was developed for cancer), or for veterinary use (e.g. ivermectin for onchocerciasis); almost invariably insecticides developed for agriculture are later adapted for public health use. The efficacy of some public health products was found through mere serendipity as was the case with DDT which was first synthesized in 1874 by O. Zeidler, but its insecticidal properties were not discovered until 1939 as part of frantic efforts to find chemicals for the World War II efforts; this discovery won Paul Muller the 1948 Nobel Prize for physiology or medicine (http://www.malariasite.com/malariamuller.htm, and http://nobelprize.org/nobel_prizes/medicine/laureates/1948/muller-bio.htm, Accessed 12/06/09). A paper in this special issue by G. Shemdoe also covers Africa’s experiences in patenting.

The evaluation of candidate tools for diagnosis, treatment, prevention or control of diseases follows standard processes, which in the case of drugs follow the International Conference on Harmonization (ICH) of Good Clinical Practice Guidelines (ICH-GCP, 1996); in the case of disease vectors the WHO Pesticide Evaluation Scheme (WHOPES) guidelines are followed (http://www.who.int/whopes/). Furthermore most countries, even in Africa, have regulatory authorities, established with the purpose of ensuring that international scientific and ethical standards are met. In Tanzania for example there is the Tanzania Food and Drugs Authority (http://www.fda.or.tz) which among other things regulates trials of medicines; the National Institute for Medical Research (http://www.nimr.or.tz) which undertakes national ethical review; and the Tropical Pesticides Research Institute (http://www.let.or.tz) which certifies pesticide use, including their testing. Table 1 lists regulatory authorities across sub-Saharan Africa.

All trials (of drugs, vaccines or pesticides) generally go through three trial phases, after which they may be registered with the relevant national authority. It is during these three phases that the safety and efficacy of a particular trial candidate is evaluated. A brief outline of the three phases in both drug and vaccine trials constitutes Appendix 3 of the CIOMS (2002) Guidelines.

In short Phase I constitute the very first stage of testing in human research participants; they are characterized by a few volunteers numbering in tens. At this stage safety and tolerability are the main concerns. There may be a Phase Ia and Phase Ib; the former being undertaken in the country of origin, while the latter is undertaken in the host (African) country. Phase I may involve some full time inpatient observations.

Phase II or III may be randomized, and may follow multicentre designs. Whereas Phase II may have a few hundred participants, Phase III may require several or even many thousands. Observations on safety still feature much in these two phases. During Phase III trials, preparations for regulatory submissions start. It is an established practice to submit trial data to the FDA (USA), or EMEA (Europe), although these may not give sufficient attention to products intended for use outside their areas of jurisdiction.

Although Phase III is often regarded as the end of any trial, that is not quite the case, the interested reader may consult the Nuffield Council on Bioethics (2005). In many trials there is quite often a Phase IV also known as a Post Marketing Surveillance Trial, which with medicines is referred to as pharmacovigilance. At this stage the product may be sold, but further studies e.g. on safety under real life conditions may still be undertaken by the pertinent regulatory authority to for example uncover rare adverse events, or the sponsor may carry out studies for competitive aspects or other reasons.

### Table 1: African Drug Regulatory Authorities.

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<thead>
<tr>
<th>Country</th>
<th>Drug Regulatory Authority</th>
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<tbody>
<tr>
<td>Angola</td>
<td>National Medicines Directorate</td>
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<tr>
<td>Benin</td>
<td>Direction Des Pharmacies</td>
</tr>
<tr>
<td>Botswana</td>
<td>Drug Advisory Board/Drug Regulatory Unit</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>Directorate of Pharmacy and Medicine</td>
</tr>
<tr>
<td>Cameroon</td>
<td>Pharmacy &amp; Medicines Department, Pharmacy &amp; Drug Directorate</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>Inspecteur des Services Pharmaceutiques</td>
</tr>
<tr>
<td>Congo</td>
<td>Direction des Service Sanitaires</td>
</tr>
<tr>
<td>Cote d'Ivoire</td>
<td>Directorate of Pharmacy and Medicine</td>
</tr>
<tr>
<td>Djibouti</td>
<td>Ministry of Health</td>
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<tr>
<td>Egypt</td>
<td>Drug Policy and Planning Centre</td>
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<tr>
<td>Equatorial Guinea</td>
<td>Aprovisionamiento de Medicamentos</td>
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<tr>
<td>Eritrea</td>
<td>Medicines Control &amp; Regulatory Services</td>
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<tr>
<td>Ethiopia</td>
<td>Drug Administration &amp; Control Authority</td>
</tr>
<tr>
<td>Gambia</td>
<td>Medicines Board</td>
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<tr>
<td>Ghana</td>
<td>Food and Drugs Board; Pharmacy Council of Ghana</td>
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<tr>
<td>Guinea</td>
<td>Direction Nationale de la Pharmacie et du Laboratoire</td>
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<tr>
<td>Kenya</td>
<td>Pharmacy Board of Kenya</td>
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<tr>
<td>Lesotho</td>
<td>Medicines Control Authority</td>
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<tr>
<td>Liberia</td>
<td>Pharmacy Board of Liberia</td>
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<tr>
<td>Libya</td>
<td>Drug Regulatory Authority</td>
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<td>Madagascar</td>
<td>Agence du Medicament</td>
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<tr>
<td>Malawi</td>
<td>Pharmacy, Medicines &amp; Poisons Board</td>
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<td>Mali</td>
<td>Direction Pharmacie et Medicament</td>
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<td>Mauritius</td>
<td>Pharmacy &amp; Drug Regulation Department, Ministry of Health</td>
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<tr>
<td>Morocco</td>
<td>National Laboratory for Drug Control</td>
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<td>Mozambique</td>
<td>Pharmacy Department, Ministry of Health</td>
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<td>National Agency for Food &amp; Drug Administration and Control</td>
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<td>Uganda</td>
<td>National Drug Authority</td>
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<tr>
<td>Zimbabwe</td>
<td>Medicines Control Authority</td>
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3.1. Length of trials

As hinted above the length of trials varies considerably. From discovery through preclinical testing takes a number of years, usually up to a decade. Atrocious delays are the norm for candidates against diseases of poverty, mainly because product development is generally driven by market forces. As a result the testing of such products may not receive priority, and may take a decade or more. For the sponsor the delay has negative implications on the life of the patent; similarly for the disease endemic communities it delays the availability of new products for diagnosis, treatment, or disease control. In practice however these delays may be offset by the high disease rates likely to be encountered in African settings. All in all however, delays have negative implications for all stakeholders.

Poverty may delay the availability of a product after a trial. Indeed it is not uncommon that medicines may be available in rich countries immediately after licensure, while it may take over a
decade to be available in developing country markets, often waiting for the patent to expire.

3.2. Funding

Due to the need for prior capacity strengthening which involves erecting essential infrastructure, training needed staff, and site characterization, undertaking initial trials in Africa becomes costly, although this may be compensated by the low remuneration packages. Furthermore, the high disease rates enable early attainment of the target sample size. As implied earlier, because of lack of a lucrative market, the pharmaceutical industry is least interested in developing products for diseases of poverty. Indeed, up to several years ago, all antimalarial drugs on the market were developed by the US Department of Defense (Ockenhouse et al., 2005); some few former ones by the British Army, and ACTs which are leading the war against malaria across Africa are a product of the Chinese during the Vietnam War. Until now, the leading malaria vaccine candidate, RTSS is a product of the US Department of Defense. Estimated costs for developing a single drug range from US$ 800 million to US$ 2000 million (DiMasi et al., 2003; Adams and Brantner, 2006).

Given the exorbitant costs of drug development and the deteriorating health situation in sub-Saharan Africa, quite a number of bilateral, multilateral, and philanthropic agencies have contributed immensely to product development, as shown for malaria, in Figs. 2–3.

Fig. 2. 2004 malaria research investment by sector. Source: Malaria R&D Alliance 2005. Malaria Research and Development, an Assessment of Global Investment. Program for Appropriate Technology in Health (PATH).

Contrary to common belief, for-profit institutions were not the leading investors in malaria research; they contributed only 12%. On the other hand, public funding contributed 56%, and not-for-profit institutions contributed 32%.

But how was that money spent? Note that most of the funding was spent on drug research (37%) and on vaccines (24%), areas that are crucially important to endemic countries, but which would also benefit greatly the pharmaceutical companies in the donor countries. Also note the sparse funding allocated to vector (<1%) and diagnostic research, two areas of current major concern to Africa.

4. When research is over

Most guideline documents do not address the question of what to do when research is completed. Many argue that research is over after licensure, although some maintain that research is not over at this stage. Those guidelines that do, mainly outline the obligations of the investigator to the sponsor, which is the case with the ICH-GCP Guidelines. Most of the documents that do, are based on distributive justice, i.e., rich countries have an obligation to transfer resources to poorer countries.

Besides distributive justice, other reasons for continuing the relationship between the researcher and the participant after the study is over, include:

• the therapeutic misconception,
• the fear of a rebound effect following the termination of the availability of a treatment or preventive product,
• the feeling by the participants that they are abandoned by the trusted researchers,
• the often encountered deterioration of health services after the project is over,
• the end of ancillary care and support associated with the research project,
• researchers may need to return to the abandoned community for future research projects.

To complicate matters, trials go through phases, some of which are repetitive (e.g., with age de-escalation, dose finding) and to conclude a trial usually takes a decade or more, whereby different study communities and cohorts would have participated in the trial. Furthermore, research cohorts may have changed their status as happens for example in vaccine trials in children. The dilemma then is how to compensate participants in early phase trials. Several guidelines have recommended prior agreements to be entered between the study communities on one hand and researchers and sponsors on the other hand, as a way of overcoming this and similar difficulties. Ancillary care may also contribute in addressing this issue.

It is moreover to be recalled that without research participants, who in the research process were exposed to lost time, inconveniences and risks, researchers and sponsors would never be able to gain the knowledge and develop new tools. Furthermore, without research participants, researchers would never attain the highly valuable knowledge, publications, promotions, peer recognition, and other academic accolades. As much as research participants are owed gratitude by the successful researchers, and there is a moral obligation to reciprocate, the question may however arise, as to whether the researcher should continue reciprocating, and for how long.

4.1. Availability of successful product and related questions

The question of availability is not crucially important when research is concluded in most developed countries, mainly because
the successful product can be adopted onto the state medical insurance or the product can be accessed through market forces, after effective advertising. Furthermore in industrialized countries an effective drug is quite often already available, so there may not be pressuring need to make it immediately available. Increasingly however Ethics Committees and regulatory bodies in developing countries are raising such questions as what should be provided to research participants, by whom, for how long, how soon and how far, after the research is over. These are legitimate questions given the reasons provided above, and the mere fact that many of the research participants are usually poor, as are their governments, and cannot afford the intervention which they helped to develop. It is not uncommon that the developed product may be used almost exclusively in developed countries as is the case with Malarone (see infra), or initially in the better off segment of developing countries as with Insecticide Treated Nets, which were extensively tested in rural areas, but became available widely in urban areas, before mechanisms were developed for their wide distribution and availability in rural areas.

The question of providing benefits at the end of a study is very complex. It for example raises such questions as: what benefit should be provided to participants, to the control group, and to the study community? Should neighbouring communities, who probably accepted to participate in the study, but were not selected due to the randomization process, also receive the product? A follow up dilemma is how far, an entire district, province or country? One may also ask how soon and how long? For wide scale availability, a purpose made factory or several of them, meeting Good Manufacturing Practice (GMP) standards, may have to be built. Another important question is who will bear the cost of providing the product after the study: the investigator, the sponsor, the local or national government, an NGO? Will any of them agree to an open ended commitment? Will the new product be integrated into the local or national health plan, health policies, or pharmacopeia? There are indeed almost endless social, economic and practical questions relating to the availability of products at the end of a study.

4.2 Guidelines on product availability

Indeed guidance on what happens after the research is over is rather recent, and sometimes contentious. The World Medical Association (i.e. Helsinki Declaration) did not address this issue until its 2000 edition (para 30), and it raised considerable debate. Nevertheless WMA (WMA, 2008, para 33) is still quiet on whether should provide the successful product. On the other hand CIOMS (2002, 2008) under guideline 10 requires the sponsor and the investigator to make the intervention or product developed or knowledge generated, made reasonably available. Unexpectedly the Council of Europe (CoE, 2004) did not address the issue at all. The European Group on Ethics in Science and New Technologies on the other hand requires provision of successful treatment to all participants after the trial. Unexpectedly the National Bioethics Advisory Commission (NBAC, 2001) which is American stand out as leading advocates on behalf of the poor:

“Researchers and sponsors in clinical trials should make reasonable good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have been proven effective for the participants...” NBAC Recommendation 4.1.

“Research proposals submitted to ethics review committees should include an explanation of how new interventions that are proven to be effective from the research will become available to some or all of the host country population beyond the research participants themselves...” NBAC Recommendation 4.2.

The Nuffield Council on Bioethics (2002) endorsed the 2001 NBAC guidelines on this aspect, but begged for certain clarifications. Many developed country guidelines are rather modest, whereas those of developing countries, when they exist, differ much. Kenya (2004) guidelines for example stipulate that

“The sponsoring agency should agree in advance of the research that any product developed through this research will be made reasonably available to the inhabitants of the community in which research has been conducted or to the whole country at the completion of successful testing. ... Consideration should be given to the sponsoring agency agreeing to maintain health services and facilities established for purposes of the study in Kenya after the research has been completed. ... Such collaborative research should help to develop capacity for similar research in Kenya.”

South African (2004) guidelines (Medical Research Council of South Africa, 2004) are more forthcoming with regard to availability of treatment to research participants after a trial is done. The Ugandan (2007) guidelines (8.1d) (Uganda National Council for Science and Technology, 2007) impose more affirmative obligations, in that “If the investigational product is found to be beneficial, the investigator should assist to secure its provision, without charge, to participants in the research project following the conclusion of the research project.” In this regard the Tanzanian (2004) guidelines (para 8.2.4) are in comparison different if not shy, they only state that “arrangements regarding post-study treatment are included in the proposal and informed consent form to the extent that available resources allow”.

At the international scene, it was the 2000 UNAIDS (Guidance Point 2) document Ethical Considerations in HIV Preventive Vaccine Research that the question of planning the availability of successful products before the study starts, and who should be involved, and what issues must be addressed was clearly advocated:

“any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.”

4.3. Mechanisms to ensure product availability to the needy

Since affordability of health products is a very major concern, particularly with diseases of poverty, a number of mechanisms have been proposed or established, that make the product readily available to study and similar communities. Among those mechanisms are for example tiered pricing also called differential pricing, under which different groups are charged different prices for the same product; this is the case for example with vaccines, whereby low income countries are charged less than rich countries. Affordability may also be achieved through bulk purchasing. Novartis developed Coartem, the first fixed dose antimalaria combined therapy, and in cooperation with WHO developed a mechanism for providing the drug to developing countries at cost only. As a result Coartem is readily available in public clinics in poor countries, sometimes free of charge, whereas prices in private pharmacies are many times more. In 2006 Novartis claims to have delivered 62 million treatment courses of Coartem (Artemether Lumefetrin) to more than 30 countries across Africa, claiming to have saved an estimated 200,000 lives (http://www.novartis.com/newsroom/news/2007-04-17/coartem-africa.shtml, Accessed 04/06/08). Outwardly the companies involved in these donation programmes may claim performing acts of mercy; they however gain considerable publicity
from such social corporate responsibility activities, besides hefty tax write-offs as the products are donated to charitable organizations. Table 2 summarizes information on some recent drug donation programmes.

Very recently the Affordable Medicines Facility for malaria was launched in Oslo, with the aim of expanding access to the most effective treatment for malaria, viz artemisinin combination therapies, through both public and private sectors. The fund started off with a pledge of US$ 225 million (http://www.theglobalfund.org/en/amfm, Accessed 04/06/09).

In order to further address the needs of trial communities, when negotiating research collaboration with sponsors and funders, some developing country researchers, and their research institutions, now demand inclusion of a statement on tiered pricing and shared ownership of the final product.

Donation programmes may sometimes be abused, as illustrated by the Malarone Donation Programme, which was accepted under considerable international political pressure (Shretta et al., 2001) by Kenya; the drug was donated to Kenya and Uganda, where considerable data on its wide scale use was collected, then the company withdrew the donation. The drug is now only available as prophylaxis for short-term travelers visiting affordable by communities where it was tested, and is generable at very high cost (around US$ 60 per dose) which is not company withdrew the donation. The drug is now only available.

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<thead>
<tr>
<th>Disease</th>
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<tr>
<td>Schistosomiasis</td>
<td>Praziquantel</td>
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<td>Soil Transmitted helminthes</td>
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4.4. Manufacturing, market and procurement

Ethical guidance documents do not generally address local manufacturing, transfer of technology, markets and procurement, despite their central importance in making the trial product readily available, when the trial ends.

Manufacturing of pharmaceutical products is extremely weak across sub-Saharan Africa, with the exception of a few countries (e.g. South Africa and Kenya). As a result African institutions participating in clinical and field trials inadvertently create markets for finished products manufactured by northern industries. Furthermore links between African R&D institutions and the national or international private sector are often nonexistent, so much so that with very few exceptions there is very limited experience with technology transfer when trials are over (Chataway et al., 2008). The seeming lack of local markets may be responsible.

On a global scale the African market for pharmaceuticals and related products may be regarded as insignificant, mainly because the profit motive drives the market, which invariably favours the development of products for affluent communities. Attempts to make such products available have been made by national governments, and NGOs (see infra) which therefore constitute target markets for the developed products. Anecdotal comments on procurement of finished products through donations claim that they stifle local manufacturing and importation of generics.

4.5. Obligation by researchers to provide post-trial benefits to trial communities

Although researchers usually think they are not in a position to provide post-trial benefits to research participants or host communities, they can play major roles in ensuring the availability of products when the trial is done. Researchers and their institutions should make all out efforts as early as the planning stage to alert sponsors, multilateral and bilateral donor agencies, and foundations, to the need of making successful products available. Researchers can do this as recommendations in their interactions with sponsors and donors, in their publications, and in their consultations. The research promoting bilateral agencies should be put in the picture and involved; they can bring on board the development arms of their national bilateral development agencies, who have considerable finances at their disposal. Eventually the development arms of bilateral and multilateral donor agencies, which quite often have the development mandate, philanthropic organizations, and the private sector, would be brought together in public–private partnerships, in order to make products available at the conclusion of a study.

4.6. Obligations to host research communities

Almost invariably, after large trials the mood among the researchers, their research assistants, auxiliary staff, laborers and even the study communities may be described as filled with great anxiety, but for different reasons. Foreign researchers want to break the code, analyze the results usually at a foreign location, and publish the findings hopefully in a very prestigious international journal, address seminars and workshops based on their experiences abroad, hold interviews with the international press and media, prepare and make presentations at international conferences, and in the process gain international recognition and accolades. Quite often, international researchers relocate to more prestigious academic institutions, they may join bilateral or multilateral donor agencies or even get employment with pharmaceutical companies. They may publish more papers; earn consultancies with development cooperation ministries or the pharmaceutical enterprise.

Meanwhile the national co-principal investigator is weighed down by solitude and concern for the forthcoming study aftermath, which may include:

- Developing and disseminating pertinent information from the research experience, targeting each of the various stakeholders including the national ministry of health, national researchers, national health operational staff, health educators, district health management teams, relevant NGOs, local health personnel, opinion leaders, and above all the communities studied;
• Developing country research institutions

Carrying out essential national health research;
Participating in setting national research priorities and agenda;
Promoting participatory research including community consultation and engagement;
Working closely with relevant government institutions particularly the ministries of health and regulatory agencies;
Training and developing health research and regulatory personnel;
Networking and collaborating with health and other research institutions in the country;
Networking with research institutions and researchers outside the country;
Rapprochement with bilateral, multilateral and philanthropic research funding agencies;
Advocating for product availability;
Ensuring establishment and proper functioning of institutional ethics and scientific review committees;

The study community would also be anxious for the results, and fulfilment of the agreement in the memorandum of understanding. Moreover the end of a trial sees the departure of the research team, who not infrequently provided health services, local employment, rented accommodation, bought provisions and much more. So indeed the end of a trial is a moment of anguished uncertainty and even tribulation.

So far most African institutions are still weak and so cannot negotiate favourable terms for research collaboration; they often accept sometimes grudgingly, whatever is available from their research collaboration. The Swiss Commission for Research Partnership (1998) which developed eleven basic principles for research collaboration between developed and developing countries, lists sharing of profits equitably as one of the principles. The Commission argued that “research results have intellectual worth, and may also have a commercial value . . . partners from industrialized countries have published results under their own names that were the results of collaborative work (and have then held the copyright), or have even benefited financially . . . .” Such unethical practices still continue. Quite often African research institutions and researchers are blinded by the enticing fees, allowances, some equipment, and motor vehicles that are provided as part of research collaboration, in a way mimicking the early colonial trade practice of exchanging trinkets for ivory. Surely the intellectual and legal rights of all researchers and their institutions should be shared equitably.

Costello and Zumla (2000) advocate for avoidance of what they labeled as a “semicolonial model” of research collaboration. Before outcries arise for equitable sharing of research benefits, sponsors, product developers, and lead researchers, should already consider upfront the inclusion of southern institutions in sharing benefits through such mechanisms as capacity strengthening, and technology transfer.

4.7. Partnerships, shared responsibilities to ensure access to research products

The development of a health product involves many actors, each playing a crucially important role, although traditionally researchers and sponsors claim to have made larger contributions; but the other stakeholders play their respective roles, which contribute to the success of the research system, in which product development is a mere component. Consequently making health research products available is a very complex issue particularly for diseases of the poor. It is hereby suggested that the responsibility be shared among different institutions as follows.

4.7.1. Developing country research institutions

Carrying out essential national health research;
Participating in setting national research priorities and agenda;
Promoting participatory research including community consultation and engagement;
Working closely with relevant government institutions particularly the ministries of health and regulatory agencies;
Training and developing health research and regulatory personnel;
Networking and collaborating with health and other research institutions in the country;
Networking with research institutions and researchers outside the country;
Rapprochement with bilateral, multilateral and philanthropic research funding agencies;
Advocating for product availability;
Ensuring establishment and proper functioning of institutional ethics and scientific review committees;
Involving NGOs, CBOs and similar bodies in research endeavours as appropriate;
Developing research funding programmes, projects, and proposals;
Communicating targeted research information to the media, and research stakeholders at all levels.

4.7.2. Developing country governments

Setting national health policies;
Defining health care delivery priorities;
Leading in setting national research priorities and agenda;
Establishing and funding national health research system including regulatory bodies;
Advocating to international agencies and forums for research support to essential national health research (ENHR) agenda and capacity strengthening;
Promoting collaboration of national research institutions in s-s and n-s dialogues;
Promoting linkages with non-health sector and other stakeholders;
Participating in health systems and demand driven research;
Spearheading adoption and utilization of research results;
Preparing policies, laws, and guidelines from research results, and ensuring their implementation;
Channeling and supporting young professionals into health research careers;
Providing political will;
Providing, maintaining and sustaining health care infrastructure;
Creating and disseminating education, information and communication (IEC) strategies;
Participate in the formation and in the activities of PPPs.

4.7.3. Communities participating in research

Participate in the research process as appropriate (e.g. providing community assent and permission, identifying locally appropriate models of community engagement such as Community Owned Resource Persons (CORPS) and Community Advisory Boards, CABS),
Participating in planning local components of the research;
Participating in local ethics review activities;
Acting as research participants.

Providing locally available research inputs (e.g. labour, accommodation, water, storage facilities).

4.7.4. Developed country governments

Political will, including advocacy for developing country research support;
Linking their country research arm with their country development assistance arm;
Contributing to sustainable development of African R&D institutions

4.7.5. Multilateral agencies (e.g. WHO, UNICEF, UNDP, World Bank)

Assisting developing countries in identifying research priorities, setting, and implementing research agenda;
Contributing to funding of ENHR and capacity strengthening, including national participation in product development;
Coordinating international networking and responses;
Providing technical assistance in e.g. national drug policies;
Advise on intellectual property rights, technology transfer, material transfer agreements, bioprospecting, etc.;
Support health research policy development.

4.7.6. Philanthropic agencies

Provide sustained funding for holistic R&D capacity strengthening and research undertaking;
Fund accessibility of research products through PPP.

4.7.7. Nongovernmental organizations

Network with like-minded international and national NGOs;
Participating in local ethics review activities when invited;
Advocate for access to successful new interventions and ancillary care;
Advocate for research;
Participate in planning and undertaking research as appropriate;
Assist in targeting research results at relevant communities;
Promote formation of local partnerships.

4.7.8. Media

Raise public awareness;
Educate all research stakeholders;
Play advocacy role for research.

4.7.9. Industry (e.g. pharmaceutical)

Sponsor or fund research and product development;
Preferential pricing for poor participating countries or communities;
Initiate product donations as appropriate;
Technology transfer, Participate in forming PPPs.

5. Concluding remarks

Health research has contributed greatly to the improvement of Africa’s health, but a lot still needs to be done through the development of new tools, guidelines and policies to address the huge persisting diseases burdens.

Africa’s vulnerabilities however expose research participants to possible exploitation by researchers and sponsors, thus calling for thorough preparations of researchers, trial and regulatory institutions before trials start, and making sure trials meet international scientific and ethical requirements, so that all stakeholders participate and benefit from the research process.

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