THE CASE FOR DOING FIRST-IN-HUMAN (PHASE 0 and PHASE 1) CLINICAL TRIALS IN DEVELOPING COUNTRIES

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Abstract

Despite the increase in the number of clinical trials in developing countries, there has been little serious discussion of whether First in Human (FIH; phase 0 and phase 1) clinical trials should be conducted in developing countries, and if so, under what conditions. This paper aims to stimulate debate on our contention that for products meant primarily for conditions most prevalent in developing countries, FIH trials should preferably be done first in developing countries. We provide reasons for doing so, sketch the changing product-development and regulatory landscape that provide further justification for our arguments, and point to the likelihood of secondary benefits such as capacity building for innovation and for research ethics. Our arguments take into account the critical importance of protecting human subjects of research while developing capacity to undertake FIH trials.
Introduction

Despite the sustained proliferation of clinical trials in developing countries, [1] there has been little examination of whether First in Human (FIH; phase 0 and phase 1) clinical trials should be conducted in developing countries, and if so, under what conditions. Most of the discussion has focused on later phases of clinical trials. The purpose of this paper is to stimulate debate on the merits of FIH trials in developing countries: we argue that for products meant primarily for conditions that are most prevalent in developing countries, FIH trials should preferably be done first in developing countries and not in remote locations in North America or Western Europe, where most such trails have been undertaken until now.

Interest in FIH clinical trials has grown recently, in part because of the disastrous experience of the TGN1412 drug trial in the United Kingdom where six healthy volunteers developed a cytokine release syndrome with multi-organ failure and required intensive care [2, 3]. There were mistakes made in that case, and some of the key lessons have been translated into more stringent rules and new guidelines [3]. FIH trials are studies where an investigational medical product (drug, vaccine or medical device), previously developed and assessed through in vitro or animal testing, or through mathematical modeling, is tested on human subjects for the first time [4, 5]. In drug development, such trials involve administering single low, sub-therapeutic doses to a small number of healthy volunteers (10 to 15) to gather preliminary data on the product’s pharmacokinetics and pharmacodynamics. These trials help researchers identify the drug candidate with the best pharmacological parameters to take forward for further development. Traditionally, these early phase trials have been conducted in developed countries. Until recently they were very rarely, if ever, performed in developing countries even for conditions that are most prevalent in the latter countries. Why haven't FIH trials been more common in developing countries?

The main historical reasons have been the lack of research and clinical infrastructure, inadequate institutional capacity, and weak regulatory agencies in many developing countries. This has made it difficult for product developers, usually large multinational pharmaceutical companies, and regulatory agencies in developed countries, to be assured of the necessary conditions to evaluate the safety, efficacy and quality of
new products in ways that satisfy the most stringent international standards [6]. Developing countries themselves have often relied on product registration processes by regulatory authorities in developed countries [16]. At the same time, stringent regulatory authorities in developed countries often lack knowledge of the diseases, including many of the so-called Neglected Tropical Diseases (NTDs), and the local conditions most prevalent in developing countries, making it possible that they will make judgments based on inappropriate risk-benefit assessments [7], sometimes to the detriment of populations in developing countries. Another reason is that Western companies, which currently develop most new and innovative products, have considered it reputationally risky to conduct FIH trials in developing countries for various reasons, including the inability to discriminate adverse events (AEs) caused by the investigational product from the generally much higher frequency of all types of AEs, and cultural obstacles to undertaking autopsies [14]. The fact that so few companies do FIH trials in developing countries [10], leads to a chicken-and-egg situation where others are reluctant to start. Finally, in a recent review of the globalization of clinical research Glickman et al [8], highlight a number of issues related to equity and argue that clinical trials do not always contribute to improving equity or even quality of healthcare in developing countries.

**We now argue that it is time the situation changed.** There are compelling scientific and pragmatic reasons to so argue: developing countries are where the diseases are most prevalent, and where the epidemiology, health services, social determinants of health, compliance patterns, co-morbidities and the genetic make-up of the population accurately reflect the way in which the health products will ultimately be used and hopefully achieve the desired outcomes [9]. There is evidence that; based on mutations in genes coding for drug-metabolizing enzymes, drugs may be metabolized differently in different populations [10], affecting the response and AEs to drugs and vaccines [11]. Apart from possible pharmacogenetic differences, the gastrointestinal micro biome may make a difference: individuals with gastrointestinal infections have been found to respond differently to medical products, for example the live polio vaccine [12]. Thus testing drugs and vaccines in developed countries may give misleading results.
It just does not make much sense to be testing malaria vaccines, for example, in the United States today, as has recently happened with the live attenuated sporozoite vaccine developed by Sanaria [13,14]. Malaria transmission stopped in the US after World War II [15], but it continues to kill about 1 million children a year in sub-Saharan Africa [16]. Or consider the harm that came of testing the original rotavirus vaccine in the US when a few adverse events stopped that trial at a time when there was no alternate vaccine that would have saved thousands of lives in the developing world, where the risk-benefit calculus is dramatically different [17]. In such cases there is a compelling rationale for FIH trials to be conducted in developing countries to meet the urgent needs of their populations [18].

The need to reconsider where FIH trials are done first is becoming even more salient as the pipeline of products for conditions that occur predominantly in developing countries is improving significantly [19]. Major philanthropies such as the Bill & Melinda Gates Foundation fund discovery research directly through programs such as the Grand Challenges in Global Health initiative [20], or indirectly through many product-developing Public-Private Partnerships (PPPs) [21]. Similarly, large multinational pharmaceutical companies have begun, on their own or through PPPs, to develop more health products for NTDs and for diseases most prevalent in developing countries. Countries such as India [22], China [23, 24], and Brazil [25], now have their own strong and growing pharmaceutical and vaccine manufacturing industries- indeed half of childhood vaccines administered throughout the world by UNICEF are made by one company in India [23].

An important underlying concern in this discussion is the safety of human research volunteers. By definition, the risks in FIH trials, particularly for phase 0, are not known for sure: they could be non-existent, low or, as in the TGN1412 case, high [2,3,22, 26,27] In addition to posing risks to the participants, FIH trials that do not completely take into account the design of, and data from, preclinical trials may not provide the necessary information to adequately evaluate the results of FIH trials [5].

The necessary conditions exist

We know from the literature and from the United States Office of the Inspector General (OIG) report of June 2010 that an increasing number of clinical trials are already being carried out in the developing world
[28, 29], including a few FIH trials [10, 30]. UNAIDS also reports an increase in various HIV vaccine and microbicides trials in Kenya, South Africa, Thailand and Uganda [35]. Furthermore, the National Institutes of Health (NIH) clinical trials register also records an increasing number of phase I trials in developing countries [31], most of the increase having been registered in the most recent past 5-10 years [32].

(Table 1 here).

For those who might argue that it is too risky, in all developing countries, to conduct FIH trials [33,34], we would argue for a more nuanced approach. If the necessary conditions do exist to ensure high technical standards and the safety of research participants, there is little reason why a FIH trial should not be conducted first in developing countries. In some developing countries, the argument of lack of capacity to ensure technical standards no longer holds. The increasing number of initiatives to support clinical trials (including FIH) in some developing countries, have succeeded [33-38]. In India, China, Brazil and elsewhere Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) standards have improved dramatically. These standards often bear a close relationship to the quality of healthcare services more generally. There are new hospitals/institutions, some of them in the private sector, that are widely understood by clinical trial specialists in the West to have the same capacity as clinical trial centers in the U.S [30, 32]. This reflects a growing capacity to conduct FIH trials safely. How did these improvements come about?

Having accepted that standards must be the same for all countries, developing countries sought assistance in infrastructure and training that would facilitate implementation of a single set of internationally-harmonized GCP standards- a goal that led the World Health Organization (WHO) to develop its 2002 Handbook and to embark on a series of educational/training programs in GCP [35]. The United States Food and Drug Administration (FDA) regulations for the acceptance of non-U.S. studies are in fact linked to these internationally harmonized GCP standards. Indeed, FDA now assists developing countries to build capacity to review and inspect clinical research within their own legal jurisdictions, as a way to improve the quality of clinical trial data that might ultimately be submitted to FDA [16, 36]. Consequently, regulatory capacity is
slowly being enhanced not only in the emerging economies of India and China, where FDA itself has set up offices [37], but also in countries in sub-Saharan Africa [9, 17].

Developing countries cannot depend on others for oversight of their clinical trials. The FDA, for example, despite its good intentions, has been found to lack the capacity “to effectively oversee clinical trials conducted in developing countries” [16, 24]. Particularly for the early phase trials, the FDA has been reported to be unaware that the trials are even going on [16], making it impossible for them to provide the necessary oversight. FDA’s contribution should be in helping to build local capacity for oversight or emulating the European Medical Agency (EMEA), which has partnered with the WHO to develop detailed guidelines intended to provide a mechanism for licensing products of major public health interest for developing countries which are not expected to be licensed in the EU. Under this partnership, EMEA evaluates data on the quality, safety and efficacy of the product contained in the application in collaboration with the WHO, before issuing a scientific opinion regarding the benefit-risk ratio of the product [38].

Secondary benefits

Doing FIH trials in developing countries and the required rigorous regulatory requirements will also drive capacity building for local ethical review capacity, facilitate health care infrastructure development, increase economic activity by encouraging research into more innovative products, and reduce the culture of dependency on developed countries [16, 39,40]. As noted, there are many late-phase clinical trials taking place in developing countries, helped by initiatives to strengthen clinical trial sites [41]. These include initiatives associated with the European and Developing Country Clinical Trial Partnership (EDCTP) [42], the Malaria Clinical Trials Alliance, and the African Malaria Intervention Network (AMANET) [43], the African Vaccine Regulatory Forum (AVAREF), as well as initiatives to strengthen local training institutions such as Uganda’s Mulago Hospital HIV research centre of excellence, which helps provide research training for the African region [44]. These initiatives responded to the proliferation of clinical trials in developing
countries. Many researchers from developing countries believe the only way their countries will improve their capacity to conduct and regulate FIH trials is by doing so within their home contexts [38].

We recognize the challenges of regulatory and other deficiencies in those countries that have not already caught up. We neither wish to trivialize the importance of protecting human subjects, nor to argue that all countries are now ready to do FIH trials, but we do argue that many are, and that improving the necessary conditions everywhere is good for research and good for health. We acknowledge that clinical research in developing countries has a mixed history and in many instances has not enhanced equity, but we believe, on balance, that transitioning to doing FIH trials in developing countries, while also calling attention to health systems and regulatory deficiencies, could help to improve standards, particularly if taking more ownership of trials and product development allows for less reliance on developed countries.

**The way forward: a role for both the developed and developing worlds**

We believe that cooperative policy mechanisms can and should be developed to allow for systematic progress in the ability of developing countries to conduct FIH trials, including building the necessary regulatory infrastructure. Since increasing FIH trials in developing countries benefits both developing and developed countries, a concerted effort needs to be made by both to build the necessary health infrastructure, scientific, ethics and regulatory capacity to facilitate such trials, and indeed all clinical trials.

In the developing world, regulators and policymakers should internalize the reality that there will increasingly be products meant specifically for the developing world, manufactured in the developing world, that are of immense value locally, and that will unlikely ever to be used in the developed world. A change in mind-set is needed. Developing world regulatory agencies must prioritize improvements of their own regulatory regimes for these circumstances and begin to reduce their reliance on the FDA or EMEA for prior approval of products before they have the courage to approve them locally. In order to benefit from local experience and be able to benefit more from capacity-building offers from the donor communities, and to negotiate more effectively, it would be wise to coordinate and harmonize local regulatory approaches at a
regional level. In East Africa, for example, this could be through the East African Community that links Tanzania, Kenya, Uganda, Rwanda and Burundi. Indeed, there is already a move to establish an East African Medicines and Food Safety Commission [45].

Current thinking about research ethics review and oversight in developing countries is shifting from an emphasis on training and ethical principles to a deeper account of the systems requirements to sustain effective review and oversight. This thinking might offer some direction about what types of capacity-building will be required to enhance FIH trials in developing countries [46]. The capacity for training ethicists and establishing ethics review boards [46], which have increased significantly in the past decade, could be strengthened even further through creative programs such as the one developed by the NIH Fogarty International Centre [47], which has spawned dozens of local training programs around the world such as those in India [48], Pakistan [49] and South Africa [50]. Such initiatives could add FIH trial oversight to their curricula.

Summary

We argue that for products primarily addressing the needs of developing countries, more FIH trials should be performed in developing countries, provided the safety of human research subjects is not compromised. While some countries in the developing world already have the capacity to conduct FIH trials, to make this happen on a larger scale will require enhanced capacity in regulatory oversight, health care infrastructure, clinical research infrastructure, and ethics review in those countries where these have not yet reached the necessary standards. Since the advantages extend to both the developing and developed worlds, we argue that all should work cooperatively to address those impediments that currently discourage FIH trials from being done in the developing world.
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Table 1: Number of Phase 1 trials in developing countries as registered by the NIH (2010)\textsuperscript{37}

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of Phase I trials registered</th>
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<tbody>
<tr>
<td>Africa</td>
<td>103 (0 registered between 1995/2000)</td>
</tr>
<tr>
<td>Central America</td>
<td>84</td>
</tr>
<tr>
<td>East Asia (including Japan)</td>
<td>659</td>
</tr>
<tr>
<td>Middle East</td>
<td>267</td>
</tr>
<tr>
<td>South America</td>
<td>128 (0 registered between 1995/2000)</td>
</tr>
<tr>
<td>South Asia</td>
<td>94 (81 registered in India)</td>
</tr>
<tr>
<td>South East Asia</td>
<td>120</td>
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