International trials in middle-income countries: different local scenarios require different ethical approaches

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The conduct of international trials, most of which are initiated by a commercial sponsor based in a high-income country but include participants from relatively poor settings and communities, has been debated for more than two decades. The ethical guidelines on how to conduct such trials have constantly evolved.^{1–3} Since these trials may include vulnerable individuals and groups, all efforts should be implemented to protect them from exploitation when participating in a trial. The Declaration of Helsinki³ states that a clinical trial in a vulnerable population (poor with limited or no access to health-care – as opposed to those lacking capacity to make their own decisions)⁴ is only justified if: (a) it is responsive to a health need of the vulnerable group; (b) cannot be carried out in non-vulnerable individuals; and (c) the group should stand to benefit from the knowledge, practices or interventions resulting from the trial. Furthermore, post-trial access for those participants who still need the intervention should be prospectively agreed.³ However, recently it has been highlighted that these provisions might fall short in many trials and that the ethical conduct of international trials should ensure that, to prevent exploitation, fair benefits should be provided to both vulnerable participants and communities, even in trials yielding negative results.⁵

The two main issues of serious ethical concern regarding international trials refer to the improper conduct of trials (e.g. lack of adequate provision of informed consent by all participants, of appropriate ethics review, and of operational and/or regulatory

oversight) or trials that assess interventions, notably new drugs and biologics, that most likely will not be available for the community once the trial is successfully concluded.⁶ Trials can have a range of sponsors, including academic institutions, non-governmental and governmental agencies, and industry, but the evaluation of new medicines that are unlikely to be available to the participating individuals or community are usually industry-sponsored projects. Although all trials – irrespective of the sponsor/funder – should be subject to appropriate and rigorous review, industry-sponsored international trials may require particular scrutiny, since they may be at particular risk of insufficiently addressing ethical concerns due to the financial imperatives involved: they could be used to gain marketing approval in wealthy countries – and thus obtain substantial profits – whereas the new drug may never be marketed at an affordable price in some or all of the countries where trials were conducted. This is particularly complex when trials are conducted in middle-income countries⁷ with heterogeneous populations.

The huge and growing economic and social disparities between groups of people within a middle-income country have highlighted a particular issue when conducting trials with investigational medicines: the potential for variable access within countries. This issue requires in-depth consideration by all stakeholders involved in international trials – but especially those in host countries – as to what actions should be taken to prevent exploitation of vulnerable

groups who might participate in trials where there is a potential benefit for other non-vulnerable citizens of those countries.

The conduct of trials in middle-income countries: two scenarios, two approaches

China and India are very different countries from a political, economic, social and cultural perspective, but currently share a common characteristic relevant to the conduct of international trials: income disparities are growing in both countries.^{8,9} This is highlighting an important issue relevant to the ethical conduct of trials in many middle-income countries: the heterogeneity of the population leads to the possibility of stratification into at least two defined ‘communities’ with different and potentially competing interests in having trials conducted within their country. In China and India, there is one growing ‘community’ of hundreds of millions of people with an economic and social status that is broadly similar to that of high-income countries (in terms of education, income, access to and expectations of healthcare services, etc. – although with significant differences within them in terms of social and economic factors). There is another ‘community’ of hundreds of millions of vulnerable poor people with no or very limited access to healthcare and social services,^{10,11} sharing many characteristics of people in low-income countries. This latter situation is much more common in India¹⁰ than in China, where a remarkable change towards more equitable health coverage has been observed in recent years, but where a large gap persists for poor rural groups.¹¹

The ethical conduct of trials in these two ‘communities’ deserve different approaches. Prevention of exploitation in trials conducted in vulnerable communities, whether in a low-income country or in disadvantaged communities in China and India (and other middle-income countries), should have a similar approach: since the investigational medicine if proven efficacious will not be available for these groups, fair benefits for both participants and communities should be agreed before commencement of the trial between the external sponsor and host investigators, research ethics committees, local health authorities and community representatives.^{5,12,13} On the other hand, when the trial is conducted in non-vulnerable groups, where potential participants have access to healthcare services through health insurance (or other means), the external sponsor should behave in a similar fashion as in developed countries: ad hoc agreements are not needed with host stakeholders. The discussion and final decision on which of the

two types of approach is appropriate for a trial and specific community should be held within the relevant research ethics committee.

This proposal is based on two main principles when sponsors are setting up an international trial in one or more middle-income countries – irrespective of whether high-income countries are also involved. First, if the investigational drug will (most likely) not be available – due to an unaffordable price – to the vulnerable population, the trial should be conducted in non-vulnerable communities that eventually will have access to the drug if proven efficacious and safe. Implementing an approach like this will not be straightforward, and much effort will be required to develop workable models.

Second, if a vulnerable population is engaged in a trial, and where the likelihood of obtaining ongoing benefit from the intervention after the trial is completed is negligible, all stakeholders should agree on how and when participants and the community will obtain fair benefits from the external sponsor,⁵ following the same approach as if the trial was conducted in a low-income country. Benefits could include provision of life-long therapy to participants, primary care education, development of research (upskilling investigators and research ethics committees) or medical care capacity, or monetary compensation (to buy food or drugs).^{12,13}

When a site provides care to both vulnerable and non-vulnerable groups, local stakeholders should agree a common approach to be discussed with the sponsor on what would be the most (ethically) appropriate approach to combine the interests of both communities. These could include any benefit mentioned above for low-income countries that could be considered appropriate to no additional benefits as happens in high-income countries.

Why the two approaches are ethically appropriate

Provided the ethical requirements mentioned above^{3,5} are followed, this strategy will have two main positive effects when international trials are conducted in middle-income countries: it will prevent vulnerable communities from exploitation and will facilitate the conduct of trials with investigational medicines that eventually will be available to the population in which they were run. The fact that, following this proposal, many new products could be marketed only for the benefit of part of the population of a middle-income country – the non-vulnerable – should not be regarded as an unethical byproduct of the trial. First, because the vulnerable group involved received

Table 1. Pivotal clinical trials from 677 marketing authorisation applications submitted to the European Medicines Agency in 2005–2011, comprising 898,000 trial participants.

	China	India	Brazil	South Africa
No. of participants	8,053	16,793	21,171	18,712
No. of pivotal trials conducted	39	148	153	157
Participants/site	206	113	138	119
No. of inspections in third countries*	6 [†]	16 [‡]	4	6

Middle East/Asia/Pacific contributed with 84,000 participants. Data from China and India; Brazil and South Africa data are provided as benchmark of other middle-income countries.¹⁶ The rate of inspections per 1000 participants in China and India was 2.3–5 times higher than in Brazil or South Africa.

*From a total of 191 conducted outside the European Union/European Economic Area/The European Free Trade Association.

[†]Worldwide, China was No. 6 (with Philippines and South Africa).

[‡]Worldwide, India (with Canada) was No. 2 after the United States ($n = 77$).

appropriate benefits for its participation.⁵ Second, when dealing with the conduct of ethical clinical research, national boundaries should not be more important than ‘vulnerability’ boundaries within a country.^{10,11} Indeed, in high-income countries like the United States – with no universal public healthcare service – many new drugs and biologics that are tested in trials and marketed, are not accessible for millions of poor people with no healthcare insurance. Provided host stakeholders – including community representatives if vulnerable groups are involved – are appropriately engaged, international trials could (and should) be more frequently run in middle-income countries.

China and India: differences and commonalities in the clinical trial enterprise

Clinical trials should be only one part of the health research that national authorities should promote in middle-income countries. From a whole population perspective, research aiming to generate data on prevalence, risk factors, validation of screening interventions, burden of diseases and conditions, validation of prevention strategies, etc., could potentially be more important than the conduct of drug trials. Yet the importance of clinical trials, and the potential opportunity they offer, should not be neglected. Considering that high-income countries and middle-income countries share many of the 10 projected leading causes of death and disability in 2030¹⁴ (Supplemental Information 1), it is reasonable to expect that sponsors based in high-income countries will continue to have growing interest in running trials in middle-income countries. Furthermore, there is an increasing interest in multi-regional trials

with the participation of sites located in several high-income countries and middle-income countries.¹⁵ Finally, there is great value in running trials that include all the settings where the treatment will eventually be provided, to ensure generalisability can be maximised, and any local differences potentially identified.

One way of assessing whether trial conduct in China and India follows international standards is by observing if pharmaceutical companies are conducting pivotal trials in these countries (Table 1). Another is to observe the percentage of industry-sponsored trials in which enrolment resulted in local investigators’ authorship: in the range of China (Chinese investigators authoring papers in 47% of trials) and India (30%) are high-income countries like Italy (43%), the Netherlands (41%), or Australia and Switzerland (36%).¹⁷

The number of ‘open’ (i.e. recruiting or not yet recruiting) phase 1–3 trials with drugs and biologics run in China and/or India and registered on ClinicalTrials.gov has dramatically increased in the last six years: 52, 310 and 1158 in 2008, 2011 and 2014, respectively. As of 18 May 2014, 62% ($n = 722$) were sponsored by Universities/Hospitals, 36% ($n = 422$) by Industry and 1% ($n = 15$) by the U.S. National Institutes of Health and other U.S. Federal Agencies (Table 2). Using a random sample of 10% of those 422 industry-sponsored trials, 50% and 29% were sponsored by foreign and local (Indian or mostly Chinese) companies, respectively, whereas the rest were sponsored by Universities/Hospitals having as a collaborator a local or foreign pharmaceutical company.

As far as sponsorship is concern, China and India show a remarkable difference: 68% of trials

Table 2. Number (%) of 'open' trials conducted in China and/or India on drugs or biologics per sponsorship, and registered on ClinicalTrials.gov as of 18 May 2014.

Phase 1 to 3*	China	India	Total
Sponsor			
Universities, Hospitals, etc. [†]	637 (67.7)	87 (36.1)	722 (62.3)
Industry	298 (31.7)	145 (60.2)	422 (36.4) ^{††}
NIH and U.S. Federal Agencies	7 (0.7)	9 (3.7)	15 (1.3) [#]
Total	941 [‡]	241	1158 ^{**}
Phase 4			
Universities, Hospitals, etc. [†]	258 (77.9)	28 (59.6)	284 (75.5)
Industry	72 (21.8)	17 (36.2)	89 (23.7)
NIH and U.S. Federal Agencies	1 (0.3)	2 (4.3)	3 (0.8)
Total	331	47	376
Grand Total (Phases 1 to 4)	1272 [§]	288 [§]	1534

'open': trial in a 'recruiting' or 'not yet recruiting' phase. NIH: U.S. National Institutes of Health.

*Phase 1 to 3 trials comprise not only trials with investigational products but other innovative research such as, for instance, new dosage regimens with marketed products.

[†]Individual investigators, research institutions, etc., are also included.

[‡]One co-sponsored trial between Universities/Hospitals and Industry.

[§]See Supplemental Information for trial registration on Chinese and Indian registries.

^{||}Two trials run in both countries.

^{††}Twenty-one trials run in both countries.

[#]One trial run in both countries.

^{**}Twenty-four trials are conducted in both countries.

conducted in China are sponsored by Universities/Hospitals, whereas in India 60% of trials are industry-sponsored (Table 2). It is remarkable that among the projected leading causes of death in 2030, respiratory, gastric and liver cancers plus diabetes are the diseases of 80% of phase 1–3 trials sponsored by both Universities/Hospitals and industry (Supplemental Information 2 and 3). So, data from ClinicalTrials.gov strongly suggest that most phase 1–3 trials with drugs and biologics in China and India are neither conducted by industry, nor by foreign pharmaceutical companies.

Looking forward

There is no doubt that the conduct of clinical trials in middle-income countries, particularly in China and India, will increase in the future.¹⁸ Although a persistent risk of unethical relationships between foreign pharmaceutical firms and local physicians could disturb the scenario,¹⁹ these companies are in a privileged situation to lead the ethical conduct of trials in

middle-income countries. They are bound to follow the international regulatory and ethical guidelines all over the world regardless of the countries where trials are conducted. Their collaboration with many Chinese and Indian Universities/Hospitals, a fairly common situation, must translate into better trained physicians, scientists and technicians, and specific efforts to support these activities are crucial. For instance, there is an urgent need for investigators in these countries to be developed in protocol development, data analysis and interpretation. Ethics should always be on the training agenda. Thus, special attention should be made to investigators' appropriate training on informed consent process and accreditation of both research centers and research ethics committees.²⁰ These benefits for the host country should be pursued in all trials, but especially in those run in resource poor settings. In the long run, this approach will be beneficial to both parties involved and will create an atmosphere of mutual respect and collaboration. In any case, the scientific community in middle-income countries should be

vigilant to denounce any deviation from the correct ethical conduct of any clinical trial.

Declarations

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References

- World Medical Association Declaration of Helsinki. *Ethical Principles for Medical Research Involving Human Subjects*. See [http://irb.sinica.edu.tw/doc/regulation/DECLARATION%20OF%20HELSINKI%20\(2000\).pdf](http://irb.sinica.edu.tw/doc/regulation/DECLARATION%20OF%20HELSINKI%20(2000).pdf) (last checked 11 September 2015).
- Council for International Organizations of Medical Sciences (CIOMS). 2002. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS. See http://www.cioms.ch/publications/layout_guide2002.pdf (last checked 11 September 2015).
- World Medical Association Declaration of Helsinki. *Ethical Principles for Medical Research Involving Human Subjects*. See <http://www.wma.net/en/30publications/10policies/b3/> (last checked 11 September 2015).
- Millum J, Wendler D and Emanuel EJ. The 50th anniversary of the Declaration of Helsinki. Progress but many remaining challenges. *JAMA* 2013; 310: 2143–2144.
- Dal-Ré R, Ndebele P, Higgs E, Sewankambo N and Wendler D. Protections for clinical trials in low and middle income countries need strengthening not weakening. *BMJ* 2014; 349: g4254. Erratum in: *BMJ* 2014; 349: g4516.
- MacMahon S, Perkovic V and Patel A. Industry-sponsored clinical trials in emerging markets: time to review the terms of engagement. *JAMA* 2013; 310: 907–908.
- World Bank. *Country and Leading Groups*. See <http://data.worldbank.org/about/country-classifications/country-and-leading-groups> (last checked 11 September 2015).
- Varma S. Income disparity between rich and poor growing rapidly. *The Times of India*, 28 July 2013. See <http://timesofindia.indiatimes.com/india/Income-disparity-between-rich-and-poor-growing-rapidly/articleshow/21410981.cms> (last checked 11 September 2015).
- Lelyveld M. Wealth gap worries China. Official reports may understate inequalities. *Radio Free Asia*, 18 February 2013. See http://www.rfa.org/english/commentaries/energy_watch/income-02192013110549.html (last checked 11 September 2015).
- Devadasan N, Ghosh S, Nandraj S and Sundararaman T. Monitoring and evaluating progress towards universal health coverage in India. *PLoS Med* 2014; 11: e1001697.
- Meng Q and Xu L. Monitoring and evaluating progress towards universal health coverage in China. *PLoS Med* 2014; 11: e1001694.
- Emanuel EJ. Benefits to host countries. In: Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG and Wendler D (eds) *The Oxford Textbook of Clinical Research Ethics*. New York, NY: Oxford University Press, Inc., 2008, pp.719–728.
- Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. Ethics: fair benefits for research in developing countries. *Science* 2002; 298: 2133–2134.
- Mathers CD and Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; 3: e442.
- Tsou HH, Chien TY, Liu JP and Hsiao CF. A consistency approach to evaluation of bridging studies and multi-regional trials. *Stat Med* 2011; 30: 2171–2186.
- European Medicines Agency. *Clinical Trials Submitted in Marketing-Authorisation Applications to the European Medicines Agency*. EMA/INS/GCP/676319/2012. See http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf (last checked 11 September 2015).
- Hoekman J, Frenken K, Zeeuw D and Heerspink HL. The geographical distribution of leadership in globalized clinical trials. *PLoS ONE* 2012; 7: e45984.
- Perkovic V, Patil V, Wei L, Lv J, Petersen M and Patel A. Global randomized trials: the promise of India and China. *J Bone Joint Surg Am* 2012; 94 (Suppl 1): 92–96.
- Anon. Doctors and pharma in China. *Lancet* 2013; 382: 102.
- Torjesen I. Accreditation process for clinical trials in India moves a step closer. *BMJ* 2015; 350: h1653.