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Offshoring Clinical Trials

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Abstract

As more and more American companies offshore large randomized clinical trials—a cornerstone of evidence-based medicine—considerable debate has occurred over this practice. Hosting clinical studies in certain foreign countries can be more cost-effective and allow for easier, more rapid enrollment than studies in the U.S. However, concerns about potential exploitation of vulnerable populations as well as the integrity of data and processes have come to light. Many of these concerns apply to clinical trials in general, regardless of where they take place. Our overview considers the reasons for the trend to offshoring, potential benefits of offshored trials, and concerns as well as drawbacks to this practice. Offshoring trials has the potential of increasing the speed of completion of clinical trials, which may benefit patients if this can translate into the more rapid market clearance of important treatments.

Keywords: Clinical Trials; Offshoring Clinical Trials; International Clinical Trials

Introduction

Historically, pharmaceutical companies relied on a very simple albeit expensive business model: new drugs were discovered, developed, and launched to market, where patent protection afforded them monopolistic pricing for a specific window of time until lower-priced generics entered. Big Pharma was a viable business model as long as the pipeline was primed—that plenty of new drugs entered the market as the older name-brands were retired and replaced by less expensive generic versions[1]. A similar paradigm is in place for medical devices. This model is expensive: in 2008, it was estimated that it took about 12 years to go from drawing board to market for a new drug and the average cost was over $1 billion[1]. A substantial amount of that money goes to the clinical trials required by regulatory agencies to support the application for a new drug or device. For the past two decades, a clear trend has been evident in the offshoring of clinical trials since the Food and Drug Administration (FDA) accepts data from studies without regard to their location, providing those data are obtained ethically and meet FDA requirements and scientific standards[2]. The migration of clinical trials to support U.S. products to overseas investigational sites raises some important issues about globalization and health. Controversies about offshoring clinical trials require us to take a balanced look at the advantages and drawbacks of this trend. The aim of this review was to look at the current situation and offer an assessment of the main viewpoints.

Methods

We searched PubMed, Embase, Google Scholar, and Google for articles about offshoring clinical trials using keywords such as "international clinical trials," "offshoring clinical trials," and "international clinical trial data." We also pulled relevant FDA documents and we reviewed the bibliographies of some of the important articles we found.

The Cost of Clinical Trials

Cost may be a primary driver in the decision to offshore a clinical trial or to add multinational sites to a domestic trial. The costs of conducting a clinical trial in the US are exorbitant and increase by about 10% annually[3]. Delays add substantially to the costs of a clinical trial and 86% of U.S. clinical studies suffer a delay of a mean of over one year (366 days) because Ameri-

cans by and large are difficult to recruit into clinical studies[4]. Only about 5% of Americans said they would have any interest in participating in medical research[4]. The cost differential can be substantial; one patient in a large randomized clinical study in the U.S. costs an estimated $20,000 but only $1,000 to $2,000 in India[1,5]. Not only are clinical trials being offshored, but there is a trend to migrate biostatistical support overseas as well, such as to China[6]. In some cases, migrating a clinical trial from the U.S. to an international location can save up to 50% of costs[3], but international studies also add their own costs (travel, running a remote location, translation) and not all locations are bargains. Thus, cost savings can be substantial but must be considered on a case-by-case basis.

Recruitment, Participant Compensation, and Ethical Concerns

A successful clinical trial requires the study to identify, recruit, enroll, and then follow a fairly large population of patients, sometimes over an extended period of time. Recruitment into clinical trials in the U.S. can be burdensome, while overseas trials may allow for the recruitment of large numbers of patients quickly, which, in turn, allows for speedier study completion[5]. Despite the barriers to setting up overseas sites (travel, time zones, language barriers, unfamiliar local laws and customs, cultural sensitivities, etc.), international sites may offer certain significant advantages. The main appeal of the offshored trial after cost reduction is rapid high enrollment per site. In an FDA study of new drug and biologic marketing applications in 2008, U.S. sites enrolled an average of 75 subjects each, while international sites enrolled an average of 505 subjects [7]. In some locations and for certain types of trials, enrollments may be even higher.

Aggressive recruitment, however, may pose bioethical concerns. Global income disparities provide the backdrop for accusations that clinical research studies exploit vulnerable poor populations. While it is easy to divide nations into the categories of "rich" and "poor," substantial disparities in wealth distribution within nations further fuels the wealth gap, so that there are vulnerable, impoverished people in otherwise wealthy parts of the world, like the United States, Canada, and the European Union, even as there are wealthy individuals in otherwise poor countries, such as Cuba, Ethiopia, Nigeria, Laos, and so on. Wealth is a major determinant of health[8], and poor nations carry 80% of the global burden of disease in disability-adjusted life years (DALYS) with substantially lower life expectancies[9]. As scientific breakthroughs and technological advances define Western healthcare, healthcare costs per capita have increased in the U.S. to $10,000[10] while in 2014, poorer nations such as Mexico spent $1,122[11], Kenya $169[12], Afghanistan $167[13], and Haiti $131[14]. At the heart of this issue is how we manage these disparities. On the one hand, offshoring clinical trials may exploit vulnerable populations who see in these studies the only way to access the medical care and treatment they need. Such patients may be so eager to get medical care that they overlook the risks that clinical studies may represent. On the other hand, conducting clinical trials in certain locations may allow for these populations to get otherwise inaccessible treatments. Thus, clinical trials in low-income countries can be perceived as a social good, in that they bring state-of-the-art medical care and new treatments to populations who can benefit from them. For some clinical trials, offshoring allows the investigators to reach patient populations that might be unavailable in the U.S. For example, the use of cyanoacrylate for the treatment of venous insufficiency was tested in the Dominican Republic in part because that nation has a relatively large number of untreated individuals with the disease[15]. Certain population-dense countries offer a very concentrated number of people with a specific disorder, such as the 34 million diabetics in India[4].

Fundamental to the sound ethics of any clinical trial is informed consent. Lack of consent and nonconsensual experiments in foreign countries represent a serious ethical issue that is not thoroughly addressed in the literature[16]. Informed consent requires that patients be fully apprised and appreciate the potential benefits of a therapeutic intervention and associated risks, even rare risks, and that they freely volunteer to participate and meet the terms of the protocol. Nonconsensual participation has many variations: the patient may be informed and consent but not be fully informed. Patients may wrongly believe or be led to believe that the therapeutic intervention is good for them or that participation in the study is the only way they can get important treatment. In some cases, patients may be deceived outright by being told they are receiving standard treatment and not participating in an experimental study at all[16]. Furthermore, some international patients may not have a clear idea about how clinical trials work and may assume that the drug or device company sponsor has the same goals as their local physicians. In some foreign countries, literacy rates are low and not all prospective patients can read informed consent forms or other reports. It has been posited that true informed consent only occurs when there is no "therapeutic misconception" between patient and clinician(s) [17]. However, in many poor parts of the world, there can be linguistic, social, cultural, and even conceptual barriers that may preclude a truly informed consent[18]. For example, the investigators may not be able to provide adequate information in the patient's first language[19]. However, it can be argued that many prospective patients are not that interested in reading the official forms presented to them, even if they have the reading skills and are comfortable in the language; it has been suggested that most people decide whether or not they want to participate in a clinical trial when it is first explained to them and they have already made the decision when they receive the paperwork[19]. Furthermore, the issue of true informed consent has no geographical boundaries; vulnerable patients in the U.S. and other developed nations are susceptible to such inducements as well.

Individuals may be vulnerable to the inducements of clinical

trial participation when they come to view their enrollment in a study as the only means of obtaining an expensive or otherwise inaccessible treatment. This occurs in all nations, including the United States with its large population of uninsured individuals or individuals whose insurance would not cover state-of-the-art treatment. For people with advanced disease or conditions difficult to treat with conventional medicine, cutting-edge therapy or drugs may only be available from clinical trials[19]. Vulnerable populations may be exploited when the research team (whether the drug sponsors or local investigators) leverages its power differential over prospective patients in order to persuade them to participate in the study without considering and openly disclosing the risks to that patient[20]. However, vulnerable populations can exist anywhere. Drug companies in the United States have been exposed for recruiting study participants among the homeless[21] and clinical research organizations (CROs) may become aggressive in offering payment for participation in studies[22].

The concept of paying participants is well established and not considered unethical. Paying subjects may become controversial when the compensation can be perceived by the prospective subject as an inducement to participation in something that he or she feels might be risky, dangerous, or otherwise undesirable. On the other hand, subjects in clinical studies may have added expenditures and since they are partnering with large companies who are making a profit from the study, it seems only fair to offer subjects compensation. Some organizations navigate this difficult ethical area by offering small payments, believing they are not inducements, but inducements can be in the eye of the beholder[22]. A homeless or deeply impoverished person may find even a small payment a huge temptation. Keeping payments modest may sound like an ethical decision, but it may be a roundabout way for big pharmaceutical and medical device companies to keep study costs down.

It might be argued that this is a problem for all nations. In the U.S., CROs, drug and device manufacturers, and paid investigators have changed the landscape of medical research into a business, and in this businesslike setting, it should come as no surprise that many potential study subjects regard themselves as part of this enterprise, viewing themselves as "employees," expecting compensation and treating their study involvement as a sort of job[23]. The Internal Revenue Service (IRS) views paid study subjects as "independent contractors" and taxes payments they receive for study participation. This is not only a danger to the participants, but it may compromise research in that "professional study subjects" may falsify their medical history to get included into studies because they have a financial interest in participating in as many studies as they can. And since many CROs may conduct multiple studies, these participants may be hesitant to discuss adverse events or raise complaints, fearing it might jeopardize their chance to get paid for other future studies[23].

It could be argued that clinical trials that offer payment for participation may further benefit local peoples. Furthermore, medical manufacturers and pharmaceutical companies may profit enormously from local research and it does not seem justified to refuse to pay participants or to make payments trivial when there are major stakes for the sponsor. While it is tempting to view these foreign populations as vulnerable and poorly equipped to make decisions, clinical investigators in third-world locations often find that they are treating people who may be poor but who are also intelligent and capable of forming their own opinions[24].

The country itself may actively try to lure clinical investigators. Low-income countries may vie with one another to gain clinical trials, which can bring jobs, money, and free medical care to local communities by making their country look particularly attractive in terms of flexible patient protections and liberal regulations[16]. Further, poor citizens of these countries may be drawn to clinical trials and overlook risks when trial participation offers them the only affordable means of treatment[16]. Countries aggressively seeking clinical trials may advertise to drug companies and CROs that they offer large and "ready-to-recruit" local populations[19].

The notion of the "treatment-naïve" populations of certain foreign countries is sometimes considered an advantage to offshoring clinical trials, but this may be an exaggeration. In many low-income foreign countries, there are many drugs available over-the-counter (OTC) that would require a prescription in the U.S.[5], for example, antibiotics. Thus, assuming low-income countries are not taking drugs because they are not prescribed may not be accurate.

Finally, our growing understanding of genetics and personalized medicine has made us increasingly aware that different ethnic groups may respond differently to various treatments. For example, it is well known that certain ethnic groups may be more or less responsive to codeine or that the "angiotensin-converting-enzyme inhibitor cough" is more prevalent in Asian patients than any other group. Yet as studies are increasingly taking place overseas, there is no consistent reporting of the ethnic groups, races, or nationalities participating in these studies. When studies were conducted primarily in the U.S. by U.S. sponsors, studies typically enrolled Caucasian patients (often skewed heavily male) and reported results as if they were generalizable to both genders and all populations. Today, many but not all studies report on demographics, and offshored clinical trials should be careful to do so as well. In an analysis of clinical trial results published in 2005 in the three of the world's leading medical journals (*New England Journal of Medicine, Journal of the American Medical Association, and Lancet*), fewer than 5% of multinational clinical trials reported patient populations by country or ethnicity[25]. Pharmacokinetics and pharmacodynamics can differ among ethnic groups, owing not only to genetics but also diversity in diet, environmental factors, and lifestyle. As drug and device companies seek to sell medical products to international markets—such as India and China and Japan and others—they need to have

at least multicultural clinical trials to obtain data from more diverse patient populations[5]. Thus, there is a potential benefit in making clinical studies multinational and improving the way we report demographic data.

The Role of the Institutional Review Boards

Institutional Review Boards (IRBs) play a crucial role in protecting subjects in clinical trials. An IRB is expected to review the design of clinical trials, evaluate the risks to patients versus the benefits, and inspect the documents relevant to the trial, most notably the informed consent forms. Thus, in an ideal world, the IRB would serve as the defender of the interests of the study participants. Much has occurred to erode confidence in the ability of international IRBs to meet this lofty goal. IRBs around the world have been implicated in scandals involving fraud, corruption, payments, conflicts of interest, and incompetence[23]. Furthermore, the emergence of the for-profit IRB has created panels that are financially dependent on study sponsors and may be hesitant to exercise the full autonomy they need to truly look out for the best interests of study subjects[23].

Many foreign nations lack sufficient experience in clinical trials or have different approaches to approvals and organizations. An evaluation of publications about clinical trials conducted in China in 2004 found that 90% did not report an IRB review of the study protocol and only 18% mentioned the informed consent in an appropriately thorough way[26]. It must be noted in this context that this deficiency referred to published articles arising from clinical trials and does not necessarily mean that there was no IRB review or informed consent, only that they were not presented appropriately in published findings from the trials. Thus, this may reflect inexperience rather than obfuscation. On the other hand, offshoring clinical trials requires the sponsor to work with reputable and diligent IRBs.

The Standard of Care

Many randomized clinical trials are set up to compare an experimental new agent, device, or therapy against a placebo which often includes the "standard of care" or conventional treatment. However, the standard of care is far from universal; it is primarily the wealth of the nation that establishes the local standard of care for medical services. It remains controversial for clinical trials whether the "standard of care" for a particular study should be that of the sponsor's country or whether it should be that of the country in which the research is being conducted[9]. In 2012, the FDA Safety and Innovation Act was signed, adding provisions regarding the use of foreign data in support of clinical trials for medical devices. While in principle, the FDA accepts all adequate, ethically obtained and scientifically sound data regardless of geography, the FDA may now consider differences between the overseas study population and the U.S. population that the device is intended to treat as well, as differences in disease characteristics and standards of care in foreign countries[2]. In some cases, pharmacological therapy must meet the standards of the sponsor's country, but medical care, hospital facilities, and nursing/follow-up care are only expected to be equivalent to local standards, which may be considerably lower than those of the sponsor's country[9]. This obstacle can be overcome by defining and then implementing an appropriate standard of care.

Research Goals

Most medical research is devoted to diseases and healthcare problems of the West rather than the problems of the developing world[9], which is why clinical trials may more likely to address, for example, overactive bladder than malaria. Thus, the therapeutic interests of the hosting foreign country may not necessarily align with those of the country organizing clinical trials[5]. In fact, about 90% of the funds spent on clinical trials around the world are devoted to diseases and conditions that are associated with 10% of the global burden of disease[20]. The Declaration of Helsinki, Article 19, states that medical research can only be ethically justified when the local population has a reasonable chance to benefit from the results of that research[27]. In practical application, the matter of determining what kind of research is relevant to a particular country becomes murky. For example, cardiovascular disease, obesity, and diabetes are increasingly prevalent in the developing world and should not be precluded from research simply because they are of keen interest to the sponsors in the developed world. Of course, there is the question as to whether it might be unethical to use local research subjects for studies which might benefit them only slightly (if at all) but benefit the sponsor country enormously[20]. It has been proposed that clinical trials be conducted in countries only when the study is relevant to the health issues of that country and that groups formed of local researchers, policy-makers, and others be involved in designing the trial[20]. However, it does not seem to be unethical to conduct a study on a treatment for, say, deep vein thrombosis in a country, even if deep vein thrombosis is not a major health risk in that country. The notion that such groups should plan clinical trials demonstrates a fundamental lack of knowledge about how clinical research is conducted; the study must meet specific regulatory standards and be affordable to the sponsor. While local authorities can certainly weigh in and approve or disapprove clinical trials, as non-scientists and non-clinicians, they should not be playing key roles in designing clinical studies.

The Speed of Innovation

Speed-to-market is an important consideration in any business, but speed in pharmaceuticals and medical devices involves navigating the requirements set forth by the various regulatory bodies, over which manufacturers can exercise very little control. It is not unusual for drugs and devices developed in the U.S. to be approved and marketed abroad before the FDA grants market clearance there. There have been many calls to reform the systems that regulate therapies. For example, advocates are calling for progress-centered regulation for lethal

diseases which essentially streamlines approval so that new therapies can be deployed more rapidly and potentially save lives[28]. High drug and device costs can be linked back to the costs of complying with clinical research—not just FDA regulations but regulations imposed by IRBs, sponsors, clinical research organizations, the Health Insurance Portability and Accountability Act (HIPAA), hospital administrations, the legal system, and others. It may be argued that intensified regulation is in the best interest of the healthcare system, but for example, tighter regulations have reduced deaths in phase I trial participants from 0.8% to 0.5% and has now reached a point where further improvement are unlikely although the regulatory burden continues to increase[29].

The delays imposed add more than just cost, in that a slow-to-market effective treatment can cost lives[30,31]. Regulatory challenges are not unique to the U.S. or the developed world. As healthcare and other industries become more global, multinational approaches to regulation must be achieved. Yet as more nations approach medical research and the regulations grow more tangled, the emphasis has shifted from medical progress to regulatory compliance. Stewart and colleagues talk about situations in which very valuable clinical data had to be discarded because of issues surrounding informed consent or other paperwork[28]. While no one supports egregious violations or nonconsensual medical research, the point of medical research is to save lives, a vision that is sometimes lost.

As a result, it is imperative to focus attention back on advancing science, collecting useful data, and finding effective treatments particularly for potentially life-threatening diseases. There have been many suggestions made in the literature: smaller and faster studies, unifying regulatory bodies, standardizing contracts and other paperwork, relaxing privacy restrictions, simplifying documentation requirements, and maintaining the focus on medical research rather than bureaucratic compliance[28].

In 1992, the Prescription Drug User Fee Act (PDUFA) required the FDA to reach a specified number of regulatory decisions within a set timeframe (for example, within six months for priority reviews of new drug applications [NDAs])[32]. This raised concern that shortened approval times might compromise drug safety. Indeed, studies in the U.S. have found that for products approved from 1993 to 2005, those in which decisions were reached close to the deadline expiration were more likely to have post-marketing safety events[33,34]. A similar study of products approved close to the 210-day deadline by the European Medicines Association (EMA) (n=161 medicines) found no association with post-marketing safety events[35].

There are no geographical restrictions on where clinical data are obtained in support of a new product, providing the study meets both FDA requirements and local regulations. Work is being done to clarify the roles of various entities and harmonizes their activities, of which the activities of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) is likely the most prominent. Thus, a clinical study may be conducted entirely or in part outside of the U.S., and the FDA has the right to conduct site inspections and issue inspectional observations (Form 483 notices). The FDA cannot send "warning letters" to overseas clinical research sites, but it retains its right to reject data from any site that does not meet its requirements. Thus, data collected from a study center in Thailand or Peru or Germany or India are all subject to the same standards as they would be in the U.S. While sponsors may feel there is little they can do to overcome regulatory speedbumps that delay their product's entrance to the market, they may find that offshoring trials shortens the clinical trial phase—and that may represent a considerable time savings.

Risks to Patients

Clinical trials involve risk to their subjects, and many patients are injured in the course of clinical trials. Sponsors, both in the U.S. and overseas, do not always provide free medical treatment or care for patients injured in their studies. In the U.S., only 16% of academic health centers compensated Phase I participants for injuries and they only did so in the form of offering free care; there were no payments for lost wages, pain, or suffering[36]. Typically, private sponsors for drug studies explain in their informed consent forms that subjects are responsible for their own medical expenses in the event that they are harmed in the study[22]. However, it is not clear that study subjects fully understand or appreciate what this means if they even read it at all. The fundamental difference in domestic versus international clinical trials is that an American participating in a clinical trial and suffering injury may be more able to litigate successfully for damages and compensation much more readily than an international study participant.

Injuries to patients occurring in clinical trials is not a thoroughly researched or often discussed topic. No agency is tracking injuries in Phase I clinical trials, domestically or internationally. This problem affects both U.S. and international clinical trials, although it is incumbent on study organizers to impress on overseas participants in clinical trials through informed consent and patient education that they may be exposing themselves to risk in the course of the study and that injury may not be compensated—or even treated without the patient's making payment.

After the Study Is Over: The Reach of Medical Progress

Once the clinical trial is over, there is considerable debate about the responsibilities of the sponsor. In some cases, the clinical trial can be concluded with no after-care and no harm to the patient, for example, in the case of a surgical repair or a treatment that has come to a conclusion. But in some cases, patients may have chronic conditions that necessitate long-term care or at least reasonable follow-up. It has been debated whether

it is ethical to conduct a clinical trial in a location which may not gain benefits from that research, either because the drug or treatment is too expensive or will not be locally accessible through the healthcare system[20]. In some cases, the damage is more acute in that following the trial, patients may no longer have access to the drug or therapy even if it is shown to have benefited them during the course of the study[20].

The Role of U.S. Oversight, Regulations, and the Globalization of Healthcare

Clinical trials for drugs or devices manufactured by U.S. companies historically took place exclusively in the U.S. until the 1980s or 1990s, when a dramatic shift occurred during which more and more foreign countries hosted the studies and fewer U.S. sites were involved[25]. Several factors are driving this migration away from the U.S. The healthcare industry has come under and continues to withstand tremendous financial pressures to contain costs; and even factoring in travel, translation, managing differences in laws and customs, and related expenses, it is often much cheaper to conduct clinical trials outside the U.S. Globalization is a trend in many other American industries and the pharmaceutical industry is no exception. An important factor in offshoring clinical trials is the shortening of study times. Overseas trials can recruit and complete studies more rapidly than those conducted in the U.S. owing to a number of factors: a large pool of potential research participants, eager researchers willing to actively recruit patients into studies, and patients willing to join studies[37].

The FDA allows for clinical trials to be conducted outside of the U.S. providing that the trial meets the standards set by the FDA. Technically, the FDA has the right to inspect international study sites as it might inspect a domestic research site, but in fact, site inspections are rare in the U.S. and virtually nonexistent overseas[23]. Indeed, the FDA is neither funded nor properly equipped to monitor worldwide clinical trials. The number of active FDA-regulated investigators working outside the U.S. has grown by 15% while FDA-regulated investigators in the U.S. declined by 5.5% in the same period[38]. A search of ClinicalTrials.gov reveals that the majority of clinical trials are being conducted outside of the U.S., roughly paralleling trends seen in other fields[25]. Since all studies must meet the FDA's standards for the FDA to accept their data, it is at least theoretically of little concern whether that data is collected in the U.S. or other countries or a group of countries.

Clinical research in foreign countries may also be a necessity for companies wishing to market their drugs and devices around the world. The perception is that nations may view new drugs and devices more favorably if there is research conducted in that country on the product; thus, manufacturers may find that it helps them meet overseas regulatory requirements to have overseas clinical trials[25]. This may not be an issue in small nations, but many developing countries, such as India and China, represent very large potential markets in sheer numbers of patients and the European Union and Japan are large markets that are willing to pay higher-tier prices for pharmaceutical products and medical devices. The globalization of research is recognized in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice (ICH-GCP) guidelines, which have been accepted by many nations around the world.

The regulatory environment for clinical studies is a two-edged sword. On the one hand, extensive and complex regulations may be good tools to help provide effective, safe research that protects patients and achieves its desired scientific goals, but, on the other hand, increasingly complex regulations can become burdensome, expensive, and create bureaucratic obstacles to drug and device development. Clinical investigators in the U.S. face substantial (at times overwhelming) compliance burdens, particularly in terms of documentation[39]. The costs for conducting clinical research in the U.S. have become so prohibitively high that some potential sponsors might not be able to participate if there were not overseas alternatives for large clinical trials. Furthermore, the influx of new regulations has not been coordinated or subjected to evidence-based evaluation; in other words, some of these extra regulations may add expenses and time to the study without affording extra protection to patients or benefits to research[40].

Despite the criticisms of international clinical study in the literature, there are important benefits to offshoring studies. Such studies help to foster positive, helpful relationships between investigators from different countries around the world. Many physicians and scientists in developing nations gain access to their peers in more developed countries, some of whom might be key opinion leaders. This sort of networking can advance individual careers in the developing nations but also helps build a better, more globalized research community. The World Health Organization advocates that international research involves partnerships with local scientists[41].

Conclusion

International clinical trials will be a mainstay of medical research in the coming years. Ethical concerns about these studies and protecting vulnerable populations are not misplaced, but these trials may also benefit local populations and certainly benefit medical research. Shortening the length of clinical trials has the potential to reduce costs and increase speed to market which can translate into the most rapid approval of effective treatments at lower prices. Furthermore, international clinical research provides opportunities to network and build a more harmonized global research community.

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References

1. Garnier JP. Rebuilding the R&D engine in big pharma. Harv Bus Rev. 2008, 86(5): 68-70, 72-76, 128.

2. FDA. Acceptance of medical device clinical data from studies conducted outside the United States: Draft guidance for industry and Food and Drug Administration Staff. Rockville, MD: Food and Drug Administration; 2015.

3. Belforti RK, Wall MS, Lindenauer PK, Pekow PS, Rothberg MB. International outsourcing of medical research by high-income countries: changes from 1995 to 2005. J Investig Med. 2010, 58(2): 287-294.

4. Maiti R. Clinical trials in India. Pharmacological research communications. 2007, 56(1): 1-10.

5. Kamat VR. Fast, cheap, and out of control? Speculations and ethical concerns in the conduct of outsourced clinical trials in India. Soc Sci Med. 2014, 104: 48-55.

6. Quan H, Chen X, Zhang J, Zhao PL. New paradigm for drug developments--from emerging market statistical perspective. Contemporary clinical trials. 2013, 36(2): 697-703.

7. Levinson D. Challenges to the FDA's ability to monitor and inspect foreign clinical trials. Office of the Inspector General, Department of Health and Human Services; 2010.

8. World Health Organisation The determinants of health Health Impact Assessment (HIA), 2016.

9. Benatar SR. Reflections and recommendations on research ethics in developing countries. Soci Sci Med. 2002, 54(7): 1131-1141.

10. Munro D. U.S. Healthcare Spending on Track to Hit $10,000 Per Person This Year. Pharma & Healthcare, 2015.

11. Organisation WH. Mexico. Countries, 2016.

12. Organisation WH. Kenya.Countries, 2016.

13. Organisation WH. Afghanistan.Countries, 2016.

14. Organisation WH.Haiti Countries, 2016.

15. Almeida JI, Min RJ, Raabe R, McLean DJ, Madsen M. Cyanoacrylate adhesive for the closure of truncal veins: 60-day swine model results. Vasc Endovascular Surg. 2011, 45(7): 631-635.

16. Spielman B. Nonconsensual clinical trials: a foreseeable risk of offshoring under global corporatism. Journal of bioethical Inquiry. 2015, 12(1): 101-106.

17. Sankar P. Communication and miscommunication in informed consent to research. Med Anthrop Quarterly. 2004, 18(4): 429-446.

18. Molyneux S, Geissler PW. Ethics and the ethnography of medical research in Africa. Social science & Medicine. 2008, 67(5): 685-695.

19. Fisher J. Medical research for hire: The political economy of pharmaceutical clinical trials. New Brunswick, NJ: Rutgers University Press; 2009.

20. Benatar SR, Fleischer TE. Ethical issues in research in low-income countries. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2007, 11(6): 617-623.

21. Cohen LP. To screen new drugs for safety, Lilly pays homeless alcoholics. Wall St J. 1996: A1-A10.

22. Elliott CG. Guinea-pigging. The New Yorker. 2008, 7: 36-41.

23. Elliott CG, Abadie R. Exploiting a research underclass in Phase 1 clinical trials. N Eng J Med. 2008, 358: 2316-2317.

24. Sariola S, Simpson B. Theorising the "human subject" in biomedical research. International clinical trials and bioeththetics discourses in contemporary Sri Lanka. Social science & medicine. 2011, 73(4): 515-521.

25. Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA et al. Ethical and scientific implications of the globalization of clinical research. The New England journal of medicine. 2009, 360: 816-823.

26. Zhang D, Yin P, Freemantle N, Jordan R, Zhong N et al. An assessment of the quality of randomized controlled trials conducted in China. Trials. 2008, 9:22.

27. World Medical Association. Declaration of Helsinki. Bull World Health Organ. 1964, 79(4): 373-374.

28. Stewart DJ, Batist G, Kantarjian HM, Bradford JP, Schiller JH et al. The Urgent Need for Clinical Research Reform to Permit Faster, Less Expensive Access to New Therapies for Lethal Diseases. Clinical cancer research : an official journal of the American Association for Cancer Research. 2015, 21(20): 4561-4568.

29. Stewart D, Whitney S, Kurzrock R. Equipose lost: ethics, costs, and the regulation of cancer clinical research. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010, 28: 2925-2935.

30. Stewart D, Batist G. Redefining cancer: a new paradigm for better and faster treatment innovation. Journal of population therapeutics and clinical pharmacology = Journal de la ther-

apeuticque des populations et de la pharamcologie clinique. 2014, 21:e56-e65.

31. Stewart DJ, Kurzrock R. Fool's gold, lost treasures, and the randomized clinical trial. BMC Cancer. 2013, 13:193.

32. Sherman R, Li J, Shapley S, Robb M, Woodcock J. Expediting drug development-the FDA's new "breakthrough therapy" designation. The New England journal of medicine. 2013, 369: 1877-1880.

33. Carpenter D, Zucker E, Avorn J. Drug-review deadlines and safety problems. N Eng J Med. 2008, 358: 1354-1361.

34. Carpenter D, Chattopadhyay J, Moffitt S, Nall C. The complications of controlling agency time discretion: FDA reviews deadlines and postmarket drug safety. Am J Pol Sci. 2012, 56: 98-114.

35. Zeitoun JD, Lefevre JH, Downing NS, Bergeron H, Ross JS. Regulatory review time and post-market safety events for novel medicines approved by the EMA between 2001 and 2010: a cross-sectional study. Br J Clin Pharmacol. 2015, 80(4): 716-726.

36. Steinbrook R. Compensation for injured research subjects. The New England journal of medicine. 2006, 354: 1871-1873.

37. Stough WG, Zannad F, Pitt B, Goldstein S. Globalization of cardiovascular clinical research: the balance between meeting medical needs and maintaining scientific standards. Am Heart J. 2007, 154(2): 232-238.

38. Global clinical trials activity in the details. Applied Clinical Trials, 2007.

39. Yusuf S. Randomized clinical trials: slow death by a thousand unnecessary policies? CMAJ. 2004, 171(8): 889-892.

40. Dilts DM, Sandler AB. Invisible barriers to clinical trials: the impact of structural, infrastructural, and procedural barriers to opening oncology clinical trials. J Clin Oncol. 2006, 24(28): 4545-4552.

41. Shuchman M, Wondimagegn D, Pain C, Alem A. Partnering with local scientists should be mandatory. Nat Med. 2014, 20(1): 12.