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Pierik, R.H.M.

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Human Rights and the Regulation of Transnational Clinical Trials

Roland Pierik

University of Amsterdam

One of the more worrying trends in globalization today is the growing practice of Western companies relocating clinical trials to impoverished countries. This article begins by providing a comprehensive description of the practice and its current regulatory oversight. It is argued that this regulatory scheme is insufficient for protecting the interests of test subjects in such relocated trials. The article then suggests an alternative scheme, embedded in the general framework of human rights protections, and develops the contours of such a human-rights-based regulatory scheme. It concludes by arguing why this alternative regulatory framework does a better job of protecting the interests of test subjects than those regulatory schemes currently available: the Declaration of Helsinki and the statement of Good Clinical Practice.

Keywords: globalization; human rights; FDA; clinical trials; Declaration of Helsinki; Statement of Good Clinical Practice

In 2001, the American corporation Discovery Laboratories sought the approval of the United States Food and Drugs Administration (FDA) for a study of Surfaxin. This is a surfactant – a drug intended to prevent and treat IRDS, which is a lung-related disorder and a common cause of death in infants born prematurely.¹ The experiment was controversial for two reasons: first, although the purpose of the trial was to gain approval for the American market, it was planned to take place in Mexico, Bolivia, Peru and Ecuador; and second, it was designed as a placebo trial in that all of the infants in the trial would undergo an uncomfortable intubation procedure, while only half of them would receive the experimental drug and the rest would receive ‘sham air’.

This is an example of an increasingly important practice in which Western commercial corporations relocate clinical trials of medical drugs to impoverished countries in Latin America, Eastern Europe, Asia and Africa.² A recent survey shows that 31 per cent of the trials submitted to the FDA are conducted entirely outside of the United States and that 55 per cent of all registered study sites are outside of the US (Glickman *et al.*, 2009, p. 816). Many such trials concern medicines that are developed by Western companies and are targeted primarily at Western markets since they will be prohibitively expensive for the average patient in impoverished countries, especially those in the countries in which such trials are conducted. These trials are primarily relocated for reasons of convenience: they can be carried out faster, at a lower cost, under less governmental scrutiny and with a more abundant population of eligible subjects.

This relocating of clinical trials is an iconic example of globalization in that it takes advantage of a globalized market that matches supply and demand. There is an abundant supply of trial participants – i.e. poor patients facing acute medical crises and living in societies without a properly functioning medical infrastructure. On the demand side, we

find multinational pharmaceuticals with abundant financial resources, only hampered by the limited availability of test subjects to produce the statistical data necessary to get medicines approved for sale to Western markets.

Many observers will have ambiguous feelings about the practice of relocating clinical trials. Some might argue that participation in such a trial provides a unique opportunity for the global poor to gain access to essential medicines that would otherwise be unavailable to them. Others might argue, however, that such trials harm individuals, exploit them and/or violate their human rights. The fact that a trial can be life-saving and exploitative at the same time only makes it harder to evaluate it on ethical grounds.

This article starts from the assumption that there is no *ipso facto* reason why Western governments should prohibit the offshoring of clinical trials altogether. For persons in dire need, participating in clinical trials might provide a life-saving form of health care where none is otherwise available (Petryna, 2009, pp. 19 and 31; Pogge, 2008). However, to what extent can the parlance of medical crises in impoverished countries be employed to create legitimacy for medical experiments that would otherwise be considered to be patently unethical? It is argued in this article that current regulatory oversight is insufficient for curtailing potentially exploitative effects of relocated trials. An alternative regulatory scheme, embedded in the general framework of human rights protection, is suggested here. Furthermore, it is argued that this alternative might do a better job of protecting the interests of test subjects than those currently available – i.e. the Declaration of Helsinki (DoH) and the statement of Good Clinical Practice (GCP).

The article is organized as follows. It begins by analyzing why the practice of relocating has emerged over the last two decades, and shows why the current regulatory oversight on relocated trials is insufficient, especially since the FDA discarded the DoH as its main ethical guideline in October 2008. The argument of why the regulation of relocated clinical trials should be embedded in the more general framework of human rights protection and how this can be done are then explored. Since the term ‘internationally accepted human rights’ remains too vague and underdetermined to provide practical guidance, the article sketches the contours of how the idea of respect for human rights can be translated into specific regulations for relocated clinical trials. The final section of the article discusses two possible objections and draws some conclusions.

Three caveats are in order. First, the analysis primarily focuses on the ‘standard of care’ debate – i.e. the discussion about which treatment researchers should provide to the control group in a randomized trial of an investigative medicine. The article will not delve into other subjects that have also figured in recent discussions of the ethics of relocated clinical trials, including informed consent, trial registries or the role of institutional review boards. Second, the article is primarily concerned with the United States because, as Daniel Carpenter (2010, p. 1) argues, ‘admission to the US market is the pre-eminent site of profit for the world’s drug companies’. Since the United States is by far the largest market for medicines, other countries generally follow American regulations in order to qualify for selling their products there. It would be irrational for pharmaceutical companies to circumvent American regulations. Finally, a human rights framework is applied to transnational clinical trials. This does not imply that such a framework might not also be relevant domestically – e.g. for trials conducted on uninsured patients within the United States.

Testing and Approving Medicines

Developing new medicines and having them approved for the market is an expensive, time-consuming and perilous process. Most candidate drugs will never hit the shelves; some of those that do will become 'blockbusters' – drug industry parlance for drugs that generate revenue of at least US\$1 billion per year. Clinical trials, in which these drugs are tested on humans, are pivotal in this process. They are generally divided into four phases. Most relevant to the argument here is the phase III trial in which the experimental drug is administered to large groups of patients (i.e. 1,000–3,000 people) to confirm the drug's effectiveness and scrutinize its side effects with statistical certainty. Phase III trials usually concern randomized controlled clinical trials. The recruitment of participants for phase III trials is expensive and time-consuming, and has become the bottleneck in the process of getting new drugs approved.³ In order to speed things up, the enterprise of drugs testing has moved from academic medical settings to specialized contract research organizations (Fisher, 2009). Moreover, in the last two decades, many of these trials have been relocated abroad (Petryna, 2009). There are several reasons why this relocation is advantageous to pharmaceutical companies (Angell, 2005; Macklin, 2004; Petryna, 2009): production costs are reduced considerably by working in impoverished countries; trials can be completed more rapidly; and relocating trials enables pharmaceutical companies to conduct placebo-controlled tests in cases where they would be prohibited domestically.

This brief taxonomy enables us to stipulate that relocated phase III trials, in which the proposed subjects are not healthy volunteers but persons with a serious medical condition, are most relevant to the argument in this article. Participation in such a trial provides access to effective medicines that are generally not available.

Regulating Clinical Trials at Home and Abroad

Clinical trials within the United States can start only after the trial sponsor has submitted an application to the FDA that includes a detailed description of the test protocol. The application is evaluated by the reviewers on scientific and ethical criteria. The *scientific* requirements determine how a trial should be designed to generate reliable results to ensure that medicines are safe and effective before they are authorized. The *ethical* requirements determine how a test should be designed to minimize as far as possible the risks to participants.

From a *scientific* point of view, the FDA generally has a preference for placebo-controlled trials in which the effectiveness of the experimental drug is compared with an inactive substance, over active-controlled trials in which the effectiveness is compared with an established treatment that has proven to be effective, because the former are easier to interpret and provide more robust results than the latter. However, *ethical* considerations determine that placebo-designs are only allowed in two situations domestically: in cases in which no effective therapy exists (i.e. when active-controlled trials are simply impossible) and in trials of medicines that only fight symptoms, such as heartburn or hay fever, since the use of placebos will merely cause inconvenience but no (irreversible) harm. Ethical requirements oblige researchers to use active-controlled trials of medicines that potentially save lives, improve health or prevent harm to make sure that all participants receive some

medication – be it the experimental drug or a conventional drug. In such trials, ethical considerations trump scientific considerations because the FDA deems it unethical to deprive subjects in the control group of potentially beneficial treatment.⁴

Which requirements does the FDA impose when it reviews applications for relocated trials? The *scientific requirements* apply equally for domestic and relocated trials. Regardless of where the trial is conducted, the results must be reliable. Yet most *ethical requirements* that are enforced domestically are not enforced on relocated trials. The FDA assumes that the ethical merits of a relocated trial will be evaluated by a sister agency in the host country. *Ipso facto*, such an approach makes sense. From the perspective of the FDA, a relocated trial is an interaction outside one's jurisdiction and it makes sense to assume that the host country should determine its own ethical requirements.

The transnational relocation of trials raises specific issues of regulation, especially since it involves different levels of access to health care in the sponsoring and host country and different legal regimes concerning medical bioethics. In such a context, an institution like the FDA finds itself stuck between a rock and a hard place. On the one hand, they run the risk of being accused of paternalistically imposing Western values when they impose their nationally endorsed ethical standards on trials performed outside one's jurisdiction. However, it is a harsh but undeniable fact that impoverished countries usually lack the institutional means to protect the interests of participants that are taken for granted in affluent countries, such as a substantive standard of care, a robust practice of informed consent and well-established institutional review boards. On the other hand, a lenient approach, imposing no ethical standard whatsoever, might be criticized because it paves the way to a race to the (ethical) bottom. The Surfaxin trial described at the beginning of this article is a vivid example of this phenomenon.

The Trench Warfare over a Standard of Care for Transnational Research

One way for Western governments to steer a middle course between too intrusive regulation and no regulatory oversight whatsoever is by employing an ethical guideline for relocated clinical trials that is more widely endorsed, for instance, in international alliances or treaties. A good example is given by the Declaration of Helsinki (DoH), which has been recognized for decades as the leading ethical international standard for medical research. It specifies the minimum rights of individuals participating in experimental research, and describes the duties and responsibilities of physicians engaged in experimental research involving humans. The DoH was approved in 1964 by the World Medical Assembly, the main decision-making body of the World Medical Association (WMA), consisting of delegations from 85 national medical societies from all over the globe.

By requiring sponsors to comply with such an internationally endorsed guideline, Western governments regulate relocated clinical trials without enforcing their domestic ethical requirements outside their jurisdiction upon contracts between Western companies and researchers and participants abroad. The United States actually followed the middle course from 1975 by taking the DoH as the authoritative formulation of the FDA's position on relocated clinical trials. That position entailed that while foreign research does not need to conform to all American norms, it should at least be 'conducted in accordance

with ethical principles acceptable to the world community' (FDA, 1993). Since the beginning of the current century, however, the FDA has become more and more reluctant to accept subsequent revisions of the DoH as the 'voice of the world community' on border-crossing medical ethics.

The FDA's emerging reluctance can be traced back to the regulation concerning relocated clinical trials, especially those rules concerning the proper formulation of the standard of care – i.e. the minimal level of care that researchers and sponsors of clinical trials should provide to the control group. As described in the last section, domestically the FDA enforces a quite substantive standard of care and allows placebo designs for only a limited set of trials. Since the FDA relied on the DoH for standards related to relocated trials, the latter's formulation of the standard of care was highly relevant. The DoH became a subject for discussion after it included a new Section 29 in the 2000 revision that dramatically limited the possibility to conduct placebo-controlled tests:

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention. ...⁵

The reason why this discussion arose was that the wording turned out to be confusing. Characteristic of relocated trials is the fact that the sponsoring country is different from the host country. In such a context, the reference in Section 29 to 'the best current proven intervention' is ambiguous because it does not say *where* it should be available. Should it be in the host country, in the sponsoring country or anywhere else in the world (see Levine, 1998, p. 6)? A strict interpretation would imply that the DoH prohibits placebo trials when a proven intervention is available anywhere in the world. A more lenient interpretation requires only that the control group receives the best-proven intervention available in the community that hosts the trial. The lenient interpretation would allow placebo-controlled trials in impoverished countries without a properly functioning health care system. A 50:50 chance of treatment in a placebo trial is still better for the patient than no treatment at all, which indeed is the actual level of care in most parts of impoverished societies. As a result, this lenient interpretation would generate a strong incentive for Western pharmaceutical companies to relocate their clinical trials. The move from a resource-rich context, with a wide array of approved medicines generally available to the public, to a context in which even the most basic provisions for health care are lacking, lowers the default standard almost to zero and opens the door to placebo-controlled trials that would be prohibited domestically.

Addressing this ambiguity, the WMA unequivocally endorsed the strict, anywhere-in-the-world interpretation in the 2002 as well as later revisions to the DoH. The FDA, on the other hand, fiercely fought this strict interpretation and campaigned for a more lax one. It started by simply ignoring the various revisions of the DoH, stubbornly holding on to the defunct 1989 revision. In 2008, the FDA abandoned the DoH altogether and replaced it with the Statement of Good Clinical Practice (GCP) as formulated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH for short). The GCP is a self-regulatory procedural manual aimed at harmonizing the regulations governing clinical trials in the United States, Japan and

Europe. The relevant passage in the GCP on standards of care is the ICH GCP E-10 Guidance:

Whether a particular placebo-controlled trial of a new agent will be acceptable to subjects and investigators when there is known effective therapy is a matter of investigator, patient, and Institutional Review Board judgment. ... Acceptability could depend on the specific trial design and *population chosen* [emphasis added].

In one fell swoop, this replacement made redundant the discussion about identifying the relevant benchmark society in defining the standard of care. The GCP simply postulates that the acceptability of placebo-controlled trials depends on the population chosen. The FDA justifies replacing the DoH with the GCP in policy-driven arguments concerning coherence and jurisdiction. It argues, for example, that American legal instruments are incompatible with dynamic referencing – i.e. embedding external documents such as the DoH that are subject to change beyond the FDA's control.

However, editorials in several authoritative medical journals such as *The Lancet*, *British Medical Journal*, *Hastings Center Report* and *New England Journal of Medicine* have assessed this policy change as nothing more than a backdoor tactic for reducing safeguards for test subjects abroad. Jonathan Kimmelman *et al.* (2009) enumerate several important ethical protections that are guaranteed in the DoH, but are lacking in the GCP. Michael Goodyear *et al.* (2009, p. 1158) argue that the FDA 'is creating an impression that it is more interested in facilitating research than in respecting the rights of people who are the subjects of research'. For one thing, the DoH is first and foremost a substantive code of research ethics, whereas the GCP is merely a self-regulatory procedural manual designed to harmonize the scientific regulations of clinical trials in the United States, Japan and Europe. Moreover, unlike the DoH, the GCP cannot appeal to general endorsement since it is merely the outcome of negotiations among just six parties: the regulatory authorities and the drug industries of the United States, the European Union and Japan, respectively. The FDA seems to (intentionally?) have made a category mistake, introducing the GCP – a *scientific* standard – as the predominant *ethical* standard (see Petryna, 2009, p. 24). It appears to be a deliberate attempt to undermine the substantial ethical regulation of relocated trials:

The FDA has apparently adopted the GCP to provide guidance for research in developing countries while steering clear of sticky questions about justice and inequity. But if you remove those issues, what kind of ethics guidance is left? Or rather, whose interests are served? (Rennie, 2009, p. 3)

The answer to John Rennie's rhetorical question is clear: adopting the GCP serves the interests of pharmaceutical companies because it paves the way for placebo-controlled studies abroad that can be performed more cheaply and more rapidly. Peter Lurie argues that the fierce battle the FDA initiated against the more substantive standard of care in the DoH was fought on behalf of major drug companies 'who stayed in the background, allowing the FDA to carry the torch for them. The change thus appears to have come from a government agency, rather than companies that have an economic interest in the issue.'⁶

For the producers of one category of medicines, this policy change turned out to be very advantageous. *Me-too* medicines are those that save lives, improve health or prevent harm,

but are not innovative. They are drugs fighting diseases for which there is already an approved treatment available. *Me-too* medicines should be distinguished from innovative medicines in that they do not treat an illness in a novel way or add any therapeutic value over existing drugs. They are copycats: minor variations of existing blockbusters sold by a competitor primarily developed with the aim of obtaining a part of the gain being earned by another drug company. Pharmaceutical companies usually give two justifications for developing these drugs: (1) competition keeps prices down, and (2) there is an advantage in having different drugs to treat a condition because if the first doesn't work, or has many side effects, the second might do a better job. Marcia Angell, however, dismisses both arguments as either far-fetched or unproven (Angell, 2005, pp. 74–93, especially 89–90). Since these *me-too* medicines are not innovative but merely copycats, it is very unlikely that they are (greatly) superior to existing alternatives. Moreover, given the availability of effective interventions, from a public health perspective there is no pressing need for another alternative (Hawkins, 2006, p. 472). Still, these *me-too* drugs are not a marginal byproduct of the pharmaceutical industry. Instead, between 1982 and 1991, they represented 53 per cent of drugs approved by the FDA and 78 per cent of the drugs that were approved in 2006 (Petryna, 2009, p. 69 and 207, note 20). Sarah Joseph (2003, pp. 434–5) considers this rise in the percentage of *me-too* medicines to be an indication of the innovation deficit in the pharmaceutical industry.

The renewed availability of relocated placebo trials has two major advantages for producers of *me-too* drugs. First, such a trial can be conducted at much lower cost. In the Surfaxin trial, discussed above, a placebo treatment – ‘sham air’ – is almost cost-free, while the best-proven alternative costs between US\$1,079 and US\$2,440 per treatment.⁷ Moreover, placebo trials are helpful in marketing *me-too* medicines in a very specific way. The FDA requires new drugs *only* to be effective, and not necessarily more effective than available medicines. Thus, a therapy can be approved even if it is less effective than one that is already on the market (Angell, 2005, p. 75). However, marketing opportunities are seriously hampered if an active-controlled trial reveals that the experimental drug is less effective than the control drug that is already on the market – an inferiority that can be kept concealed in a placebo trial.

Towards a Human Rights Approach?

From the perspective of the protection of participants in relocated trials it is very unfortunate that the FDA – *de facto* the most important and trendsetting regulator of clinical trials – deserted the DoH in 2008 and endorsed a rather weak ethical guideline. Many critics argue that this change can be traced back to the policy of ‘US exceptionalism,’ introduced under the George W. Bush administration, and considered to be on a par with other contested policies in which the human rights of foreigners were sacrificed for American interests (Lurie and Greco, 2005). There is a broad consensus in the medical-ethical literature that opting for the GCP guideline is a strategic move away from protecting the interests of participants abroad and towards the benefit of the American pharmaceutical industry. Rennie concludes that the abandonment of the DoH by the Bush administration fits ‘in a climate marked by reluctance to engage with any international regulation not suiting US interests’. Writing in 2009, at the beginning of Barack Obama’s

presidency, he encourages the new administration to 'adopt research ethics regulation that places the interests of research participants and communities, as well as concerns about social justice, back in the center of the picture, where they belong' (Rennie, 2009). An editorial in *The Lancet* also encourages the Obama administration to 'suspend' the GCP as the ethical guideline for relocated trials and to direct the FDA to 'rejoin the international community in requiring that studies be done in accordance with the DoH' (Kimmelman *et al.*, 2009, p. 14).

It remains an open question whether participants in relocated clinical trials are best served by an unqualified re-endorsement of the DoH. For one thing, the DoH was primarily developed as a general statement of ethical principles that covers all forms of medical research involving human subjects. Relocating trials is a quite specific practice, raising equally specific ethical questions, especially because of its transnational character involving different countries with large differences in medical provisions and quite different legal regimes on medical ethics. The guidelines in the DoH might be too general to provide sufficient guidance in this very specific practice. Moreover, the DoH is not a legal instrument under international law; it is merely a self-regulatory guideline for physicians and other participants in medical research written under the aegis of the WMA. As such, it might be out of place as a regulatory scheme for transnational trials: the decision to relocate a certain trial is primarily made in the headquarters of Western pharmaceutical companies, while the decision whether or how to regulate such relocation is made by national governments.

This article therefore proposes a different approach: embedding the regulation of transnational clinical trials in the framework of human rights. One advantage is that human rights have attained the status of a *lingua franca* in normative debates on the effects of globalization. Roberto Andorno argues that it makes perfect sense to embed the formulation of global bioethical standards within the context of the human rights' doctrine, in particular the 2005 Universal Declaration on Bioethics and Human Rights (UDBHR); since 'biomedical activities deal with the most basic human prerogatives such as the right to life and to physical integrity, it is perfectly sound to have recourse to the umbrella of international human rights law to ensure their protection' (Andorno, 2007, p. 153).

Furthermore, recent developments have made the human rights framework even more relevant. In June 2011, the United Nations Human Rights Council adopted by consensus a resolution on human rights and transnational corporation, endorsing the conclusions of the Ruggie report, including the following 'foundational principle' on the state's duty to protect human rights: 'States should set out clearly the expectation that all business enterprises domiciled in their territory and/or jurisdiction respect human rights throughout their operations.'⁸ Moreover, the American government acted as a co-sponsor for this resolution. United States Deputy Assistant Secretary of State Daniel Baer stated at the Council that 'the United States believes that the Guiding Principles provide a valuable, important and complete framework for working through a wide range of challenges' and that the country 'seek[s] to implement the Guiding Principles' (HumanRights.Gov, 2011). Only the future can tell whether the principles and the American endorsement will be more than merely aspirational declarations, but Ruggie's formulation provides a promising point of departure for embedding the discussion of relocated clinical trials in the human

rights' framework. After all, such 'soft law' can over time be endorsed by national governments and be implemented as 'black letter law' in national legislation (Andorno, 2007, p. 151).

Ruggie's principle can guide the discussion of transnational clinical trials because it explicitly addresses the extraterritorial activities of businesses, such as pharmaceutical companies, domiciled in the United States but conducting clinical trials abroad. The United States, Europe and Japan can still hold onto the GCP as the predominant scientific guideline. However, if these parties would also take their commitment to the Ruggie principles seriously, the GCP would be complemented with an *ethical* guideline that is embedded in human rights law. This would then result in a *de facto* global regulatory scheme. After all, the United States, the European Union and Japan dominate more than 80 per cent of the global drugs market. It would be irrational for pharmaceutical corporations to produce medicines that are not allowed on their markets.

Developing a Human-rights-based Standard of Care

If we conceive human rights to be those rights that protect the fundamental interests of all human beings on account of their humanity, they seem to provide a good framework with which to analyze the ethical aspects of transnational clinical trials. Unfortunately, a clearly demarcated set of human rights that can be employed seamlessly and directly in the context of relocated clinical trials is currently not available. This does not imply that a new set must be developed from scratch; instead, the formulation of such a human-rights-based guideline should start from current human rights doctrine and practice as we find it in international political and legal practice, including the relevant conventions, treaties and similar guidelines (Beitz, 2009, pp. 42–4 and 102). For example, the DoH does not refer explicitly to human rights; however, it has its roots in the Nuremberg Code of 1947, which was formulated more or less simultaneously with the 1948 Universal Declaration of Human Rights and for roughly similar reasons: abhorrence over the atrocities committed during the Second World War and the wish to prevent similar atrocities in the future. In addition, in 2005 the United Nations Educational, Scientific and Cultural Organization (UNESCO) adopted the UDBHR.

A formulation of a human-rights-based guideline for relocated clinical trials needs to build upon relevant sources of human rights doctrine and practice. Such an approach should reflectively adopt relevant elements and ignore the irrelevant ones. A complete formulation of a guideline for relocated clinical trials should cover all relevant ethical issues, including informed consent, trial registries and the role of institutional review boards. The formulation of a complete guideline falls outside the scope of this article. The remainder of the article only focuses on the issue that is central here: the standard of care in transnational clinical trials. Is it possible to translate relevant sources of human rights doctrine into a standard of care? *In concreto*, this boils down to the question of which conditions in placebo-controlled designs are acceptable for relocated clinical trials.

Two sections in human rights' documents are especially relevant for this analysis of relocated clinical trials. Section 21–2 of the UDBHR states:

Transnational health research should be responsive to the needs of host countries, and the importance of research contributing to the alleviation of urgent global health problems should be recognized.

This argues that a relocated trial cannot merely be a means for the development of (expensive) drugs for the affluent world. It should also, in one way or another, take into account the needs of participants in a trial, their communities or other persons in similar situations. Call this the *requirement of responsiveness to local needs*.

Section 6 of the Nuremberg Code states that:

The degree of risk to be taken [in a trial] should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

This argues that the humanitarian importance of a trial should determine the amount of risk that is acceptable during such a trial. In the case of clinical trials, we can interpret 'humanitarian importance' to be the extent to which a trial aims to provide an important and innovative contribution to the body of medical knowledge.⁹ Call this the *humanitarian importance requirement*, which is relevant for both domestic and relocated trials. Since placebo-controlled trials are the more risky option compared to active-controlled trials, they are only acceptable when the problem dealt with in a specific trial exceeds a certain threshold of humanitarian importance.

Later in this section, these requirements will be used to formulate a human-rights-based standard of care for relocated trials. Yet they can also be employed in a critical assessment of the formulation of the standard of care in the DoH. Consider the following example. A Western humanitarian non-governmental organization (NGO) has obtained the rights to an older version of life-saving medicine *X* to treat a certain condition.¹⁰ It seeks to revamp it to make it withstand tropical heat and humidity so that it can be stored unrefrigerated. Or imagine that the original version is difficult to deliver in impoverished countries because it must be administered intravenously, whereas researchers have found a way to administer the drug orally. In short, the NGO has found ways to turn the older version into a medicine that can be administered in the less than ideal circumstances of impoverished countries.

For the more affluent market, a new treatment *X*^{*} already exists that is more effective and/or has fewer side effects, but is prohibitively expensive for most impoverished countries. Under the current DoH regulations, the tropical-resistant version *X* must be tested against *X*^{*} since the latter is the best proven intervention currently available anywhere in the world.¹¹ This seems to be an unnecessarily stringent and even counter-productive requirement. In fact, it makes it impossible to test *X* in a meaningful way. '[A] placebo-controlled trial may be the only way to obtain an answer that is ultimately useful to people in similar circumstances' (Varmus and Satcher, 1997, p. 1005). The fact that *X* is less effective and has more side effects than *X*^{*} is already factored in. Moreover, one can even argue that *X*^{*} is *de facto* not 'available' for the average citizen in the host society because it cannot be stored properly in impoverished circumstances, nor can it be administered safely. Finally, an active-controlled trial would put the NGO to huge expense because it would be forced to stock up on a large supply of the topnotch *X*^{*} version of the medicine to function as the control.

A problem with the formulation of the standard of care in the DoH is that it does not distinguish between trials of the tropical-resistant drug as developed by the humanitarian NGO and trials of the *nth me-too* version of that same drug for the Western market. This distinction is central, however, to the contextualized assessment of the two requirements of *humanitarian importance* and *responsiveness to local needs*, as formulated above. One way of taking these two requirements into account is by attuning the standard of care in a trial to the level of prosperity of the population at which the investigative new drug is aimed. Consider the following formulation:

The control-group in a randomized controlled clinical trial shall not be denied the most effective treatment for the specific condition under study that is *de facto* available to the population that the control-group represents, regardless of the standard of care actually available to the control-group.¹²

The phrase ‘shall not be denied’ explicitly says that members of the control group have a right to certain minimal treatment. The phrase ‘*de facto* available’ requires that the medicine is not only available to the wealthiest citizens of that society, but to the population in general – i.e. it is included in health insurance schemes provided regularly as part of the public health system. The phrase ‘most effective treatment’ refers to the most effective treatment among those available in a specific society for a certain condition, as determined by medical experts.

This formulation provides a contextual standard of care that must be provided to the control group subject to the population at which the prospective medicine is targeted. An investigative drug for the affluent Western market must be tested against a drug that is already *de facto* available in the Western world, which in fact boils down to an active-controlled trial. On the other hand, it allows for placebo-controlled trials of an investigative drug that is targeted at impoverished communities in which a medicine for this disease is *de facto* unavailable. Before pharmaceutical companies start investigating a medicine, they have to determine the market for which they want to produce it. This is not a prohibitive condition: by phase III of the development process, companies know very well which market they seek to target.

Both the requirement of humanitarian importance and the requirement of responsiveness to local needs provide independent support for this contextual standard of care. First, the *responsiveness requirement* demands that transnational research is responsive to the needs of participants, their communities or other communities in similar situations. Relocated trials of expensive (*me-too*) medicines will not have any long-term beneficial effects for the community in which they are tested because the prospective products of the research will be too expensive. The contextual standard of care formulated above will make such trials optimally responsive to needs in the host country – after all, requiring an active-controlled design guarantees that all participants, including those in the control group, will benefit from participating. Given the fact that this concerns a phase III trial, it is safe to assume that the investigative drug is at least partially beneficial, and that negative side effects are not worse than the disease being treated. Trials of easily administered or cheap investigative medicines against malaria, sleeping sickness or tuberculosis, on the other hand, will *ipso facto* score high on the *responsiveness requirement*. Such

trials will have huge long-term benefits for the community in which they are conducted and will contribute to the alleviation of health problems in poverty-stricken areas in general.

Second, the requirement of *humanitarian importance* implies that the amount of risk that is acceptable during such a trial should be determined by its relevance. The problem tackled in trials of *me-too* medicines is rather mundane since their only aim is to grease the path of a copycat into a marketable medicine for the affluent world. This requires that the risks in these trials must be minimized through an active-controlled design. So for example, the Surfaxin trial previously mentioned could, under this regulatory scheme, only be conducted in an active-controlled design. On the other hand, research on medicines that fight diseases that are prevalent in impoverished countries, such as malaria, sleeping sickness and tuberculosis, is of utmost humanitarian importance. However, only a relatively small amount of the research and development budget of pharmaceutical companies is spent on these medicines. Research should not be hampered by the counter-productive requirements and excessive development costs found in an active-controlled design as enforced under the current DoH. The long-term benefits of such trials justify the more risky placebo-controlled design.

This human-rights-based formulation of the contextual standard of care strikes the most optimal balance between the interests of test subjects in relocated trials in two different senses: as participants in clinical trials, and as persons in need of affordable and essential medicines. Moreover, it protects these participants, even at the expense of foregoing benefits for others, including the sponsors of trials.

Two Objections

The previous section presented a contextual standard of care for relocated clinical trials. However, a number of objections could be formulated. One might be that the idea of a *contextual* standard of care fits only uncomfortably into a context in which human rights are considered *universal*. Would that not also require a universal standard of care that applies equally to clinical trials all over the world? Indeed, Ruth Macklin, among others, would consider it a ‘double standard’, as opposed to a ‘universal standard’ as presented in the DoH (Macklin, 2004, p. 218). Of course, the underlying intuition of these critics is correct: equal treatment should be the norm, while the burden of proof lies with those who seek to deviate from this norm. However, equal treatment fails as a standard of justice in grossly unequal situations. Transnational medical trials occur against a background of huge global inequality, which usually implies that the participants will never have regular access to the medicines under investigation. Arguing for such a universal standard, while ignoring the background condition of global inequality, might result in an unproductive ‘form of sloganism’ (see Van der Graaf and Van Delden 2009, p. 39). The rigid adherence to a single standard might imply that people in impoverished countries lose access to the benefits of participating in clinical trials. Indeed, this context of global inequality is precisely the reason why this article does not endorse one single standard of care for all possible clinical trials, but instead develops one especially geared towards transnational clinical trials. It is *universal* in that it protects all participants in such transnational tests. It is *contextual* in the sense that the standard of

care in a certain transnational trial is determined by two requirements as derived from the human rights doctrine: the extent to which a trial is responsive to local needs, and its humanitarian importance.

A second objection can be formulated in the terms of Thomas Pogge, who has argued that imposing such substantive requirements on pharmaceutical companies might have severe counter-productive effects (Pogge, 2008, pp. 115–23). After all, the aim is to shut the door to trials in which the human test subjects in the control arm are deprived of beneficial treatment (relocated placebo-controlled trials) and to enforce a design in which all participants receive working medication (relocated active-controlled trials). Pogge is worried, however, that pharmaceutical companies could reply as follows: *If we must comply with this contextual standard of care for relocated trials, they will simply become too expensive. In that case we will be forced to conduct them domestically, which will have the unfortunate effect that many patients in impoverished societies will be cut off from participation in possibly life-saving trials.* Pogge concludes that such ethical requirements might indeed turn out to be counter-productive: ‘There is a real danger, then, that the very people in whose behalf morality imposes such constraints end up worse off than they would otherwise have been without’ (Pogge, 2008, pp. 122–3).

Pogge’s objection only concerns relocated trials of those drugs that are primarily targeted at the affluent Western market, which under the proposed contextual standard would fall under an active-control regime. It is understandable that pharmaceutical companies would come up with such a threat. The standard of care as proposed here will make relocated trials of medicines targeted at Western markets much more expensive and hence in all likelihood have a negative impact on the profits of these companies. Under Pogge’s proposal, placebo-control trials of such drugs would be allowed, which implies that participants have a 50 per cent chance of receiving a treatment. Under the regime of the proposed contextual standard, 100 per cent of participants in a test would receive some form of medication – either the experimental drug or a conventional drug – unless the more demanding standard of care has such a deterrent effect that trials will be conducted domestically. So the question is which of the proposals will result in better access to medicines through relocated tests.

Unpacking the set of relocated trials and separating the *me-too* drugs from more novel treatments might diminish our fear of the possible counter-productive character of morality. Remember that it is predominantly the category of trials of *me-too* drugs that is relocated – i.e. medicines that save lives, improve health or prevent harm, but are not innovative because there is already an approved treatment available. And this is precisely the category of drugs for which it is so hard to find trial participants in affluent societies. Relocating tests is not only cheaper, but also a necessity for completing trials. Consider the trial of a medicine against a disease like meningitis that only occurs sporadically in developed countries due to prosperity, good health care provisions and routine vaccinations. It will be very hard, if not impossible, for sponsors to conduct trials of *me-too* drugs in the affluent world because it will be impossible to gather the 1,000–3,000 participants in the relatively short time span of such a trial. Relocating such trials, on the other hand, provides a large pool of trial subjects because such diseases are still widespread in poor regions. Moreover, even if patients were available in affluent societies, it is highly unlikely

that they would volunteer themselves or their children for participation in such a perilous trial when established drugs are readily available and often reimbursable through health insurance. A final advantage of relocating trials is that it provides access to patients who are ‘medicine-naïve’ – i.e. patients who have not yet been exposed to existing treatments for their condition. The best way to prove whether a new drug is safe and effective is to test it on patients with no other diseases and who are indeed medicine-naïve. Even if Western citizens were willing to participate, they take so many medications that they are ‘poor lab rats’ anyway. Most people in impoverished countries have not yet used other medicines, thereby avoiding the chance of drug-to-drug interaction and making the data less ambiguous and thus more valuable.

In short, the more redundant a trial is – in the sense that it concerns a less novel treatment for a disease which has less humanitarian importance – the harder it will be to conduct the trial in the affluent world, and the more the sponsors will be critically dependent on relocated trials to get their *me-too* drugs approved for the lucrative American market. Yes, introducing the contextual standard of care might deter some sponsors from relocating trials; yet, all the participants in those relocated trials will receive medication. I think that Pogge’s fear is unwarranted because, on balance, the contextual standard will ensure that the beneficial effects of participating in clinical trials are made available to more participants in impoverished countries.

Conclusion

The growing practice of relocating clinical trials by Western pharmaceutical companies to impoverished countries is one of the more worrying trends in globalization. Moreover, there is no reason to assume that this practice will disappear anytime soon. It raises specific ethical questions, especially because of the transnational character, involving different countries with different levels of prosperity, different levels of medical care, and different political and legal regimes. Ultimately, the primary aim of most relocated trials is to generate the statistical data necessary to get the medicine approved for profitable Western markets, and *not* to provide care to patients. In the words of one researcher: ‘We don’t see patients, we see data’ (Petryna, 2009, p. 140).

For persons in dire need, however, participating in medical trials might provide a life-saving form of health care where none is otherwise available. Therefore, there is no *ipso facto* reason why Western governments should prohibit the relocating of clinical trials altogether. On the other hand, the parlance of medical crises in impoverished countries should not be employed to legitimize medical experiments that otherwise would be considered to be patently unethical. The relevant question, then, is what obligations researchers and sponsors of clinical trials owe to participants, and how these obligations can be anchored in regulatory schemes.

This article has argued that the current regulatory oversight of transnational trials through the GCP is insufficient as an ethical guideline. An alternative approach – a regulatory scheme that is firmly embedded in the more general framework of human rights protection – has been formulated. One central element of such a regulatory scheme has been focused on in particular – namely the *standard of care* that researchers must provide to the control group. From relevant human rights documents two requirements for relocated

clinical trials were inferred: the requirement of *humanitarian importance* and the requirement of *responsiveness to local needs*. A *contextual* standard of care was developed, based on these two requirements, which concludes that the level of care that researchers must provide to the control group is determined by the extent to which participants in a trial and their community receive long-term benefits from the specific trial. In other words, the fewer the long-term benefits participants and their community will receive from participating, the higher the standard of care researchers must provide to members of the control group.

This proposal has a number of advantages over the GCP, which is the current regulatory scheme in the United States, and the DoH, which many critics see as the most preferable alternative to the GCP. First, it is explicitly embedded in the framework of human rights that is widely acknowledged to be the most relevant regulatory framework of border-crossing activities of business enterprises currently available. Moreover, focusing on the more general framework of human rights might provide a way out of the deadlock between the FDA and the WMA that has dominated this debate for over a decade. The final advantage of this approach is that the contextual character of the standard of care enables policy makers to distinguish trials of relatively redundant *me-too* copycat medicines for the Western world from trials of innovative medicines that are essential for the host countries. It enforces a higher level of care upon the former trials and in this way the proposed contextual standard of care is sensitive to the degree in which a relocated trial is responsive to the needs of host communities.

An ethically defensible regulatory scheme of relocated clinical trials should find a good way of protecting the rights of those who participate in such a trial. The GCP fails in this respect because it too strongly favors the interests of the sponsors of a trial over the interests of the participants. On the other hand, the DoH fails because it thwarts the interests of people in impoverished countries in need of affordable and essential medicines. The proposal outlined in this article strikes a much better balance between the interests of people as participants in clinical trials and as those living in communities in need of affordable and essential medicines.

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About the Author

Roland Pierik is Associate Professor of Legal Philosophy at the Paul Scholten Centre for Jurisprudence, University of Amsterdam. His research interests concern the intersections of legal philosophy, political theory, law and public policy. His recent work focuses on contemporary liberal theories of justice, human rights, the rule of law, religious diversity and cosmopolitanism. His work has been published in the *Journal of Social Philosophy*, *Ethics and International Affairs*, *Ethnicities*, *Critical Review of International Social and Political Philosophy* and *Ratio Juris*. He is the co-editor of *Cosmopolitanism in Context* (Cambridge University Press, 2010). Roland Pierik, Faculty of Law, University of Amsterdam, PO Box 1030, 1000 BA Amsterdam, The Netherlands; email: r.pierik@uva.nl

Notes

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1 IRDS stands for 'idiopathic respiratory distress syndrome'. Surfactants are drugs that make it easier to inflate the poorly functioning lungs of newborn infants.

- 2 Admittedly, this is a rather extreme example. Not surprisingly, the intended design of the trial encountered so much resistance that it was not actually carried out. Eventually, an actively controlled version of the trial was conducted in medical facilities in the United States and Europe.
- 3 Pharmaceutical companies spent approximately 40 per cent of their research and development budget on clinical trials (Petryna, 2009, p. 206, note 5).
- 4 There is an important medical-ethical discussion on whether there are weighty enough arguments to prefer placebo-designed randomized controlled trials since they generate more unequivocal results. But this debate does not affect our argument on whether different designs are allowed for trials at home and abroad. After all, if there are good scientific arguments to prefer placebo-controlled trials to actively controlled trials, then these arguments apply for both domestic and relocated trials.
- 5 The quoted text is the formulation in the most recent 2008 revision (now Section 32), which is not different in any relevant sense for this argument.
- 6 As quoted in Edelson (2005). See, for similar arguments, Greco (2004, p. 21); Lurie and Greco (2005, p. 1119).
- 7 See the calculation as made by Public Citizen, a non-profit consumer advocacy group (Public Citizen, 2001).
- 8 John Ruggie (2010, p. 7) wrote the report as the Special Representative of the UN Secretary-General on the issue of human rights and transnational corporations and other business enterprises.
- 9 This concept of 'humanitarian importance' closely resembles Jennifer Hawkin's concept of 'moral weightiness' (Hawkins, 2006, p. 491).
- 10 This fictional example is based on the case that originally sparked the standard of care debate in the 1990s. It concerned the use of placebo controls in trials of affordable substitutes for the expensive '076 regimen' for preventing mother-to-child transmission of HIV using zidovudine (AZT).
- 11 In the discussion of the trials of an affordable alternative for the 076 regimen for impoverished countries, this 'best-proven' criterion is defended by Angell (1997) and Lurie and Wolfe (1997), among others. This article would justify a placebo-design for this trial because it argues that their long-term benefits justify the more risky placebo-controlled design. As such, it sides against the positions taken in this historical debate by Marcia Angell and Peter Lurie, authors whom I quote approvingly above. The argument as defended here is more in line with those presented by others, including Varmus and Satcher (1997), Hawkins (2006) and Abdool Karim (1998).
- 12 For similar formulations, see Van der Graaf and Van Delden (2009, p. 40); London (2001).

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