

Ethical issues in international research and multicentre studies

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Udo Schüklenk

University of Queen,
Kingston, Ontario, Canada
udo.schuklenk@gmail.com



Darragh Hare

University of Caledonia,
Glasgow, United Kingdom

Abstract

This article provides an overview of the key issues pertaining to international research and multicentre studies, with particular emphasis to international biomedical research in the developing world. The article begins with a brief explanation of the regulations governing international biomedical research and an exposition of the debate surrounding the standards of care that should be provided by research conducted in the developing and developed countries. The article describes the issues involved in the participation of vulnerable groups in research, with specific reference to developing countries. Eventually, the article considers matters related to emergency and post-trial care, exploitation, reward and undue inducement, voluntariness and benefits to local communities.

Keywords

standard of care; clinical research; post-trial care; emergency care; vulnerable research participants

Introduction

International biomedical research is an issue affecting international research ethics and multicentre studies, and it has been the focus of widespread and often controversial discussion for the last ten years. Whenever and wherever biomedical research takes place, a raft of ethical questions arises. It is not the purpose of this article to consider all of the ethical issues that relate to biomedical ethics, but it will consider some of those that apply to international multicentre research.

Biomedical research must be carried out in accordance with a large number of national and international laws, regulations and guidelines. Most countries' ethical guidelines include the same basic principles, since many nations have devised and amended their guidelines to reflect the most up-to-date international agreements. However, the content of international guidelines – and therefore often of countries' own guidelines – is evolving over time. This evolution is driven by cultural and societal changes as well as changing research patterns.

In light of the details of Nazi experimentation on human subjects which emerged during the Nuremberg Trials, the international community devised The Nuremberg Code, a set of principles for ethical human experimentation. This was replaced in 1964 by the World Medical Association's Declaration of Helsinki, which remains the most influential set of principles governing medical research involving human participants. In 1993, the Council for International Organizations of Medical Sciences (CIOMS), a small Geneva-based organisation, published its International Ethical Guidelines for Biomedical Research Involving Human Subjects. Like the Declaration of Helsinki, these guidelines attempt to offer a robust set of instructions and principles for ethical biomedical research.

However, none of these sets of guidelines is universally accepted. There exists widespread debate over their content, and indeed over how they should be incorporated into national research guidelines, if at all. It is this disagreement which gives rise to the most important ethical questions relating to international biomedical research.

This article provides an overview of the key issues pertaining to international research and multicentre studies, with particular emphasis to international biomedical research in the developing world. The article begins with a brief explanation of the regulations governing international biomedical research and an exposition of the debate surrounding the standards of care that should be provided by research conducted in the developing and developed countries. The article describes the issues involved in the participation of vulnerable groups in research, with specific reference to developing countries. Eventually, the article considers matters related to emergency and post-trial care, exploitation, reward and undue inducement, voluntariness, and benefits to local communities.

Standards of care

The standard of care debate

Perhaps the most contentious ethical issue affecting international biomedical research is that of the standard of care that should be provided to human participants in clinical trials. Essentially the question here is what constitutes an appropriate control arm in a biomedical trial. The scientific method requires that the experimental drug is tested against a placebo whenever there is no gold standard of care, that is, a successful treatment or vaccine. The idea is that, in the absence of a gold standard of care or prevention, it should first be found out whether the experimental agent is any better or worse than, or equal to, whatever would be in place otherwise. If there is nothing otherwise, that is, if there is no treatment or vaccine, one may legitimately use a placebo.

The ethical reason for this is hidden away under the concept of "clinical equipoise". Clinical equipoise has a few slightly different interpretations, but essentially it means that a clinical trial is only ethical if all of the par-

ticipants in any of the trial arms have an even chance of getting a successful or failing experimental agent. By this means risks are evenly distributed among trial participants. This is one of the key methodological ingredients that make clinical trials ethical. Of course, once there is a gold standard, one would not normally test an experimental drug or procedure against a placebo, because we would really want to know whether the new concoction is better, worse or equal to what exists already.

This consensus was recently challenged with regard to trial participants based in the developing world. This issue is neatly summed up by Michael Selgelid (2005: 55):

High-profile and often heated debate has largely focused on the question of *what should count as an ethically acceptable control arm* in medical experiments involving human participants and (accordingly) the question of whether or not the clause of *the Declaration of Helsinki* that addresses this issue should be revised.

This debate began with an article published in *The New England Journal of Medicine* by medical doctors Peter Lurie and Sydney Wolfe (1997). Lurie and Wolfe raised questions about the appropriate level of care for control group participants in biomedical trials, and were highly critical of some existing practices based on observations they had made on trials designed to develop drugs that would combat mother-to-child transmission of HIV (MTCT) in developing countries.

Recent breakthroughs had demonstrated that the use of zidovudine (AZT) could reduce the risk of MTCT by around one third. This meant that the chances of an HIV-positive mother's newborn inheriting the disease from his or her mother reduced from around 25 to 8% with the use of AZT. In wealthy nations, therefore, the use of AZT became the gold standard treatment for HIV-positive pregnant women. Importantly, when further trials of medication and techniques to reduce MTCT took place in the developed world, trial participants in the control arm were treated with AZT, as it was by this time the accepted standard of care. Clinical equipoise existed so the trial met this crucial criterion designed to determine whether the scientific method underlying the research was ethical. This was in line with the relevant section of the Declaration of Helsinki, which stated: "In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method". (Selgelid 2005: 65)

This requirement of the declaration is designed to prevent research participants from being harmed as a result of their participation in a study, by not receiving whatever constitutes the international gold standard at the time a given study is undertaken. One example of this type of harm would be if a participant is assigned to a placebo-controlled arm of a study when an acknowledged gold standard exists, and he or she is therefore given poorer treatment than if she had not participated in the study at all. The premise of this argument is obviously *if he or she had access*. The aim of this requirement, it would seem, is to ensure that when people participate

in medical experiments they are guaranteed to receive care that is at least as good as that which they would have received if they had not participated in the trial. If this requirement is not met, a trial would be unethical according to the Declaration of Helsinki, and therefore considered unacceptable by many countries' ethical review committees.

It is useful to view this requirement alongside the principle of clinical equipoise, which has been a feature of bioethics for decades. Remember, the principle of clinical equipoise states that when participants are randomly assigned to an arm of a study, there should be no clinical reason to prefer one arm of the study over another. In other words, before the trial takes place, there should be no clinical reason to believe that any given method of treatment is superior to another. The principle of equipoise and the standard of care requirement of the Declaration of Helsinki, when taken together, should ensure that trial participants are not being treated unjustly – in this case, exploited by investigators.

In the developed world, pregnant women who were assigned to the control arm in experiments pertaining to MTCT would have received AZT, as it was the accepted standard of care in their medical circumstances. However, AZT was then quite expensive and constituted state of the art, cutting-edge medication. At the time it was not considered economically viable for developing world countries to use it as freely and frequently as countries in the developed world. Therefore, while AZT was the accepted standard of care in the developed world, it was not the accepted standard of care in the developing world. This disparity gave rise to the debate that was instigated by Lurie and Wolfe and has persisted since.

The MTCT trials referred to by Lurie and Wolfe took place in the developing world, primarily in sub-Saharan Africa, but were funded and carried out by organisations from the developed world. They aimed to respond to the medical need and economic context – that is, a context in which the gold standard was unaffordable due to the price tag multinational pharmaceuticals put on AZT – that existed in the host countries and throughout the developing world. In effect, they were placebo controlled trials in which participants in the treatment arm received the trial drug (a lower, and therefore cheaper, dosage than the gold standard) and participants in the control arm received a placebo with no therapeutic benefit.

It is important to note that the trials were intended to find a cheaper alternative to AZT that would be affordable in the developing world. However, given that AZT was unaffordable in the countries in which the trials took place, the women who were assigned to the control group were not given AZT – in fact, they were given a placebo, with no therapeutic value whatsoever. But if the same trial had taken place in the USA, for example, the women in the control group would have received AZT, as it was the accepted standard of care in the USA. Are these double-standards ethically acceptable conditions under which biomedical research should be carried out?

The problem can be summed up like this: what standard of care should apply to international clinical trials, the standard in the local area where the trial is taking place, or the highest international standard? Were the organisations that were responsible for the trials referred to in Lurie and Wolfe's *New England Journal of Medicine* article acting unethically? If so, what made their research unethical? These questions have constituted much of the debate that has followed since Lurie and Wolfe. Roughly speaking, those who have written or spoken out on this issue can be divided into two main groups: the critics, who hold that the participants in the control group in such trials have been treated unethically; and the defenders, who deny that the participants in the control group in such trials have been treated unethically. These positions will be examined in turn.

The critics

The critics believe that it is not ethically defensible to conduct clinical trials in the manner outlined above. In fact, the first critics would be Lurie and Wolfe, whose original article condemned the trials as unethical. The critics point out that any trial carried out under such conditions is in direct conflict with the above requirement of the Declaration of Helsinki. It is in direct conflict because the placebo control, at the time when the trial took place, did not constitute "the best proven diagnostic and therapeutic method" (Selgelid 2005: 65).

The critics also maintain that such trials are unjust because they involve double standards: in such a trial the standard of care for participants in the developing world is vastly inferior to that of participants in the developing world. This procedure, the critics hold, cannot be deemed ethical in international research. For example, if there was a worldwide study involving groups of participants in the developed world and other groups in the developing world, the difference in the standard of care for participants in the control arms is enormous and, the critics say, indefensible. It also seems to be the case that the gold standard was rejected in the control arm not for scientific reasons but for economic reasons. The question arises: why should someone in a control group in Paris, for instance, be provided with far superior care to a fellow participant who happens to be participating in Botswana?

Furthermore, some of the critics argue, if we allowed standards of care to slip according to economic considerations, the developing world could well be used to stage such trials *because* of this disparity. That is, it is easier and more cost-effective for the organisations responsible for these trials to stage them in countries where the accepted standard of care is minimal, or even nil. It could be argued that the efficacy of a new drug can be better judged in comparison to no treatment in the control arm than in comparison to an advanced alternative treatment. However, it is far from clear that this reason can serve as justification for carrying out placebo controlled trials of the sort highlighted by Lurie and Wolfe.

The defenders

However, the defenders argue that it is in fact ethically defensible to carry out trials of this nature. Because such research contravenes the Declaration of Helsinki, it does not follow that the research is unethical. Perhaps the declaration needs to be changed. The defenders hold that control arm participants in the developing world are no worse off than they would be if they had not participated, and therefore they are not being treated unethically. They are not any worse off, because they would have had no access to the gold standard to begin with. In fact, the defenders believe that participation in such trials can in fact be a good thing. That is, for the duration of the trial at least, participants would be entitled to the ancillary care that goes along with trial participation, such as counselling, access to medical professionals and improved knowledge of their condition.

To apply this defence to the specific MTCT trials conducted in Africa, defenders would say that participation in such a trial would be an attractive alternative to the *status quo* for those living in developing countries. Given that the *status quo* in the countries in question involves no treatment whatsoever, defenders would argue that participants would not take any additional health risks by becoming involved. On the contrary, they might actually benefit from participation: if they are in the treatment arm they likely derive some therapeutic benefits; if they are in the control arm, they could contribute to the development of an affordable alternative to AZT.

Therefore, defenders maintain that people living in the developing world would be no worse off if they participated in this type of trial; in fact, while participation carries no risk, it could yield significant benefits to the participants and their communities. Furthermore, placebo controlled trials such as those highlighted by Lurie and Wolfe show up a fundamental problem with the Declaration of Helsinki. While the declaration is intended to prevent harm to, and to promote benefits to, human participants in biomedical research, in cases like this it denies participants the possibility of benefit with no risks. In addition, ethical review committee members preventing trials like this could harm the same societies that trials such as the one we have just described were intended to benefit. The trials mentioned by Lurie and Wolfe sought to develop an affordable alternative to AZT which could be used in the developing world. By preventing this kind of trial, it is likely that the development of an affordable alternative to AZT would at least be delayed, if not prevented altogether.

The defenders' argument continues by concluding that, as the Declaration of Helsinki states that this type of research is unethical, the declaration itself is wrong. It should therefore be amended or rewritten altogether, because, as it stands, it condemns as unethical practices which are actually ethically defensible. So the standard of care argument can be expressed thus: what standard of care should be observed in international research, the best international standard, or the particular local

standard? If the answer is that the best international standard should be observed, trials such as those mentioned by Lurie and Wolfe are unethical; if the answer is that the local standard should be observed, the trials are ethical.

Discussion

The concept of local standards of care is worthy of serious consideration, and has been the subject of widespread debate itself. In particular, critics have suggested that the at first glance most persuasive aspects of the defenders' argument – that placebo controlled trials carry no risk but potential benefits, and that, in fact, some participants will definitely be better off and nobody will be any worse off – do not bear scrutiny (Schüklenk 2000).

This criticism of the defenders' position holds that there is no such thing as a fixed local standard of care. In reality, the local standards of care in the developing world are largely determined by the prices demanded by pharmaceutical companies based in the developed world. The trials referred to by Lurie and Wolfe were intended to provide a cheaper alternative to AZT because patients, and indeed governments, in the developing world could not afford to purchase it. The high prices were the only reason that the trials took place at all.

The critics' charge – that the high price that western pharmaceutical companies demand from developing world customers is the single biggest factor in bringing about the placebo controlled trials – is at the centre of the standard of care debate. Therefore, the defenders' argument that placebo controlled trials are acceptable due to the disparity between accepted standards of care in the developed world and the developing world does not stand up because those backing the trials – usually developed world pharmaceutical multinationals – are the same organisations who make the existing treatments cost-prohibitive in the first place.

An international consensus opinion?

The standard of care debate took an interesting turn in 2003, when the *Journal of Medical Ethics* accepted for publication an article by Reidar Lie et al. (2004) proposing to reject the provisions of the Declaration of Helsinki in favour of what these authors called an "international consensus opinion" on the standard of care debate. It is important to note that by this time, the World Medical Association (WMA, a worldwide umbrella organisation of national medical associations) had reworded the relevant section of the declaration to include a caveat which stated that it is permissible to provide participants in a control arm with care of a standard lower than the best available standard when there are sound scientific or methodological reasons to do so. It is noteworthy, perhaps, that while this rewording permits a number of trials with lower than the best proven diagnostic and therapeutic method in the control arm, it makes no mention of the economic reasons which arguably gave rise to the AZT trial we discussed above. In that sense, arguably

the addendum or clarification the WMA published does not resolve the conflict in the defenders' favour.

In this article, Lie et al. (2004) argue that the dispute could be resolved once and for all by referring to an international consensus on the type of care that should be provided to participants in the control arm. They firmly side with the defenders of the trial discussed earlier. Lie et al. (2004)'s analysis uses two distinct arguments.

Their first argument is a procedural argument relying on the fact that some organisations in different countries and jurisdictions have reached their favoured conclusion. Despite some concerns about the relevance of this fact – as exemplified in their correct statement that “moral questions are not decided simply by which view gets the most votes” –, the authors use this fact as evidence of an emerging international consensus opinion, as implied by the heading of their article. Confusingly, also within their article, they concede that “it is also patently obvious that there presently is no worldwide consensus”, which makes it unclear why they aim to give in their heading and for much of the article the impression that there is in fact an international consensus opinion on this matter (Schüklenk 2004). The second argument advanced by Lie et al. (2004) aims to demonstrate that the purported international consensus opinion is one that we should adopt, and it provides three distinct reasons for this conclusion. However, this paper has been heavily criticised; critics are adamant that the international consensus they refer to does not in fact exist and that the authors' paper is question begging (Schüklenk 2004).

The first argument advanced by Lie et al. (2004) is that the traditional stance taken by the WMA on the standard of care issue has become the odd voice out, given that the Joint United Nations programme on HIV/AIDS (UNAIDS), the US National Bioethics Advisory Commission (NBAC), the Council for International Organizations of Medical Sciences (CIOMS), the European Group on Ethics in Science and New Technologies (EGE), and the UK-based Nuffield Council on Bioethics (NC) have come independently to the same different conclusion on the matter – namely, that lower than best current standards of care are ethically acceptable, provided certain conditions are met. However, one could be forgiven for being suspicious of claims that these organisations, institutions, and groups have reached these similar conclusions independently of each other, given that their various documents were published not at all independently of each other. Rather, these documents undoubtedly informed each other.

Why would this matter? It matters because none of the organisations mentioned by Lie et al. (2004) is actually anywhere near as large by way of representing real world membership as is the WMA. The obvious danger is that a few key individuals were chosen by whoever had the power in each of these smaller organisations to choose the members of the drafting committee. This would have allowed democratically unaccountable players to utilise their positions to manipulate outcomes. This is a seri-

ous concern about smallish groupings such as CIOMS, NBAC and NC, and their committee-based response to bioethical policy development.

It is argued by the critics that the consultations referred to by Lie et al. (2004) cannot be accepted as legitimate policy documents. A policy document of this sort should be based on a transparent method of working as far as the discussions (including selection of participants) and the utilisation of the input provided by professionals and the interested public are concerned. Also, seeing that in this particular instance the ramifications would be most severe for participants in developing countries, it could be argued that substantially greater efforts should be put into ensuring that the developing world-based delegates at consultative meetings are truly representative of their constituents. This would require that members of the same socioeconomic groups of patients affected by a given guideline be consulted in a meaningful way. Not all, but some ethical guidelines lack rational justifications for the substantive guidance provided. Justification of the policy guidance proposed should be mandatory for any document wanting to be taken seriously.

It is therefore not clear that the procedural case that Lie et al. (2004) set out for the recognition of an international consensus is a sound one. That is, although there does in fact exist a procedure whereby what might seem to be an international consensus has been brought about, the procedure itself is questionable and, as a result, so is the consensus that it purports to demonstrate. However, Lie et al. (2004) do not only rely on this procedural argument for an international consensus. Their second argument is that experimentation should be ethical if there is a sound scientific reason for conducting it in such a manner. This would mean that, for example, if the only way in which a certain drug could be properly tested would be to test it against a placebo with no therapeutic benefit, then this trial is ethically acceptable. At first glance, this might appear to many to be an appealing argument, but critics have pointed out in response that even if one accepts this principle, it does not follow that the type of placebo controlled trial they intend to defend can be ethically justified.

Lie et al. (2004) suggest that the need for access to cheaper drugs in the developing world is a scientific reason sufficient to allow placebo controlled trials. However, it is not clear that this reason is sufficient, or indeed that it is scientific at all. Critics of Lie et al. (2004) might argue that this is in fact an economic reason, and not a scientific one. That is, the reason for such trials taking place at all is that western drug companies refuse to provide affordable access to their products. Critics might, eventually, argue that anyone who regards this reason as “scientific” in the same way as, say, a clinical or biological matter is “scientific” is guilty of equivocation.

Post-trial and emergency care

Two further important aspects of international biomedical research, and ones which are of particular

relevance to multicentre studies, are the standards of post-trial and emergency care that are afforded to trial participants. After a drug trial is over, it is sometimes necessary for people who have participated to require some treatment that is linked to their participation. Sometimes this treatment is for obvious direct side-effects of the trial drug, but in other instances it can be more subtle treatment, for example for a side effect that does not manifest itself until long after the trial, or counselling for trauma during a trial.

There are many different types of post-trial care, but they have one very important thing in common: it is far easier and far more likely for trial participants in the developed world to receive the requisite post-trial care than it is for trial participants in the developing world. In the developed world, trial participants have easy access to a whole range of advanced public and private health care. However, in the developing world, participants generally have very limited access to health care at all, and when they do, the technology is very often far less advanced than that which is standard in the developed world.

Many drug trials that take place in the developing world involve temporary screening and treatment facilities that are set up within very impoverished, isolated communities for the duration of the trial. During the trial, therefore, participants have reasonable access to good quality health care. However, when the trial is over and the temporary facilities are removed, the participants are often left to deal with the aftermath of the trial on their own.

A further issue pertaining to post-trial care is that of availability of a successful trial drug to trial participants. In developed world countries, if a trial drug is successful, it is likely that it will be made available via the country's publicly-funded health service or equivalent. If the trial is not successful, it is likely that the health service will continue to provide the best available treatment – for example AZT in the case of MTCT. However, in a developing world country, it is not guaranteed that a successful trial drug will be provided by the health service. That is, it may not be affordable enough to be provided universally within that country, or in fact at all.

This leads to some very interesting ethical questions. Should trial participants be provided with a successful trial drug after the trial has finished? If a trial does not yield a successful drug, should trial participants have access to the best available alternative? If participants in the control arm receive a treatment that helps to manage their condition, should they receive that treatment after the trial, regardless of the success of the trial drug? Here is the position of the WMA (2004) on this matter:

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

Would the promise of at least some post-trial treatment represent an undue inducement and therefore be unethical? Many international research ethics guideline argue that post-trial care should be provided in therapeutic drug trials, and, of course, when trial related injuries occur. Interestingly, there has been some argument about the question of whether or not an HIV infection that occurs during an HIV vaccine trial constitutes a trial related injury that should be subject to compensation.

Some bioethicists have argued that due to what is known as the “therapeutic misconception” some trial participants in HIV vaccine trials are likely to engage in AIDS risk behaviour that they would not engage in if they were not trial participants. A therapeutic misconception occurs when a trial participant believes he or she is receiving a drug that works, fully or even just a bit, when really he or she is participating in a randomised double-blind trial where the participant might get an *experimental* drug or a placebo. This therapeutic misconception could well result in a trial participant taking unreasonable risks in the HIV vaccine trials we just mentioned.

This is so, despite best efforts to educate them about the nature of clinical research and the uncertainties that go with experimental drugs. So some have argued that for this reason an HIV infection acquired during the trial (even by means of engaging in unsafe sexual activity) should be considered a trial related injury. Others have held against this that a review of actual risk behaviour in such trials suggests that on average the risk behaviour of trial participants is lower than that of comparable non-participants.

The prevalent view amongst many with a professional interest in HIV prevention trials is that people who contract HIV whilst participating in an HIV prevention trial should receive post-trial treatment on the basis that their contraction of the virus is a trial related injury. In fact, UNAIDS (2004) stated that “(t)here is now broad, though not unanimous, agreement among sponsors of HIV vaccine trials that antiretroviral therapy (ART) and a clinical care package should be provided to those who become infected during the conduct of a trial”.

However, Charles Weijer and Guy LeBlanc (2006) argue that, in the majority of cases, people who become HIV-positive during the course of an HIV prevention trial do so not as a result of their participation, but because they belong to a high-risk group in the first place. The problem with this approach is that the factual claim might be correct, but not sufficient to invalidate the moral argument from the therapeutic misconception. The reason for this is that those who undertook high-risk behaviour *might* have been the victims of the therapeutic misconception. In terms of the overall cohort of trial participants, this might have been counterbalanced by many others who did not engage in risk behaviours they otherwise might have engaged in. The moral obligation of the ethical review committee is to prevent harm incurred by *individual* trial participants. If there are some who have become infected during such a trial it is no good for them to know that others might not have

been infected due to their trial participation. They have still been harmed as a direct consequence of their trial participation and so deserve compensation, probably by means of providing them with access to life-preserving anti-retroviral medication.

Interestingly, Weijer and LeBlanc reach the same conclusion via a different avenue. They believe that it is desirable to give the appropriate treatment to anyone who is HIV-positive, regardless of how they contracted the condition. Therefore people who become HIV-positive during participation in an HIV prevention trial should indeed receive treatment. This should be a consequence of reasonable negotiations between the researchers and the host community prior to the trial. This would provide an ethical basis for post-trial care for participants who contract HIV during a trial without incurring some of the problems associated with viewing the contraction of HIV as a trial related injury.

The difference between developed and developing world care is also important when emergency care is required during a trial. To take a recent example, on March 13, 2006, six men suffered immediate and catastrophic side effects during a Phase I clinical trial of a drug named TGN1412. In Phase I clinical trials, which usually involve only a small number of human participants, the toxicity of an experimental agent is investigated. Only minutes after having been injected with the drug, the men became seriously ill, unconscious and suffering multiple organ failure. Their condition was afterwards diagnosed as a cytokine storm, a potentially fatal reaction within the immune system. Fortunately for these men, the trial took place in hospitals in London, UK, and they were rushed immediately to high dependency units and received intensive care treatment. All of the men were released from hospital, although it is uncertain that their immune systems will ever fully recover. If this trial had taken place in the developing world, especially in a temporary facility in a remote community, it is uncertain whether any participant who suffered such a reaction would have survived.

In multicentre studies, therefore, the standard of care provided to participants in the control arm is not the only issue that can separate the benefits of participating in a centre in the developed world as opposed to one in the developing world. The more advanced health care systems in the developed world mean that participants in the developed world have access to far better emergency and long-term care when necessary. This is something that trial organisers should perhaps take into account when they are embarking upon complex multicentre studies: even when the conditions under which the trial itself is taking place can be standardised, the ancillary care in the developed world is considerably better. Members of ethical review committees have a quasi-fiduciary duty toward the prospective trial participants to investigate this matter.

It is important to be sensitive to this issue as it affects not only clinical research but also much of social science, humanities and psychological research. Ques-

tionnaires on sensitive issues, for instance, rape, ageing, euthanasia, sexuality and such matters can easily trigger serious emotional problems in research participants, as well as investigators, interpreters, research assistants and so on and so forth. This is particularly so in cross-cultural research settings. Members of ethical review committees must satisfy themselves that investigators are sufficiently prepared for such consequences.

Many of the ethical considerations associated with biomedical research also apply to social science, humanities and psychological research. As explained, much of this type of research can also carry with it the potential of harm to research participants. However, whereas all biomedical research carries with it some procedural risk of harm, some social science or humanities research might not. In the case of multicentre studies, the process of ethical review must by necessity be longer and more complicated than the process for research that is taking place in one location only. That is, multicentre studies require collaboration between a number of local or national ethical review committees.

This can be frustrating for the investigators in research that obviously carries no (or a negligible) risk of harm to participants – for example, a survey of readership of international press publications in a number of different countries –, and can delay or even hinder the research. However, the determination as to whether a piece of research carries with it the potential for harm to participants must be made by someone; presuming that the investigator cannot make this determination, by necessity ethical review committees must make this determination. Perhaps the problem of risk-free research becoming stuck in ethical review for inordinate periods of time could be resolved by ethical review committees subjecting all research which claims to be risk-free to an early screening process which would prevent obviously risk-free research from being subject to full review.

Vulnerable groups

The issue of the participation of people belonging to vulnerable social groups has attracted much attention over the past few decades, given the special ethical considerations that apply to involving them in research. It is important to note that “vulnerable groups” does not simply mean people from impoverished, developing world communities. In fact, many people who could be said to belong to a vulnerable group might very well live an affluent lifestyle, perhaps in the developed world (think of people suffering from anorexia nervosa for instance); pregnant women, children, prisoners and mentally disabled people are all generally considered as vulnerable groups.

The use of vulnerable groups in biomedical research carries with it some special ethical considerations. Because of their vulnerability, individuals from vulnerable groups can be more open to exploitation than individuals who do not belong to vulnerable groups. For example, impoverished people may be offered financial inducements, prisoners may feel like they have no real choice,

and mentally disabled people may not be able to provide proper informed consent. The pregnant African women who took part in the MTCT trials that were condemned by Lurie and Wolfe did so because of their vulnerability: given that AZT was unaffordable, these women saw participation in the trial as the only possible way to reduce the chances of transmitting HIV to their unborn children, so they took part in a placebo controlled trial that would not have been ethically defensible in the developed world. Desperation, in other words, rather than a genuine free, informed choice, forced them into enrolling in these trials.

In fact, many of the scandals in biomedical research centre around the voluntary or enforced participation of people from vulnerable groups, for example, Nazi experimentation on Jews, gypsies and the mentally disabled, research involving refugees or prisoners as trial participants and the infamous Tuskegee syphilis study. When deciding on whether to approve a multicentre study, ethics committees must be careful that they take into account those participants who belong to vulnerable groups. When all of the participants come from similar vulnerable groups, for example, the pregnant African women in the AZT trials, the special ethical considerations may be quite clear-cut. However, when research involves a number of participants from various vulnerable groups, the ethical considerations become far more complicated. Furthermore, when one or more participants belong to more than one vulnerable group (a prisoner in the developing world, or a child with a mental disability), the ethical considerations become more complicated still.

It is easy to suggest that involving people who are particularly vulnerable in research trials should be avoided, but this is not a feasible solution to the problem. Leaving aside issues pertaining to civil liberties, sometimes research participants must by necessity be drawn from vulnerable groups. Consider a trial of a new treatment that is designed to reduce the effects of cerebral palsy if given to children prior to their fifth birthday. The only way to test such a treatment would be to organise a trial involving children with cerebral palsy. So an absolute prohibition of people from vulnerable groups participating in biomedical research is not viable; in fact their participation is sometimes necessary. However, a golden, and often repeated rule that is found in research ethics regulations the world over, is that if the same research question can be investigated without enrolling people belonging to vulnerable groups, that is what should be done.

Incentives, exploitation, and undue inducements

Most of the discussion surrounding vulnerable groups is centred on protecting groups or their constituent individuals from harm. In the majority of circumstances, the harm referred to is a form of exploitation. It is generally accepted that studies or trials that involve vulnerable persons are unethical if they involve exploitation. However,

there exist various forms of exploitation, some of which are very obvious and others that are more subtle.

It is unusual to offer any kind of substantial personal or material incentive for people to participate in research. Sometimes compensation provided to trial participants for inconvenience, time spent, lost earnings, transport etc. can take the form of what is called in the literature an “undue inducement”, or a “perverse incentive”. As a rule of thumb, compensation reaching levels that may impact on a prospective participant’s choice to participate, that is, an offer a prospective participant could not reasonably decline, should be rejected by ethical review committees.

At the same time, in multicentre trials spanning different countries, one would want to ensure that there is a reasonable equity in terms of how participants in the different trial sites are being compensated. However, the fact that some compensation might be considered ethically justifiable does not mean that a participant in São Paulo should necessarily receive the same amount as a trial participant in Tokyo, because what might be a trifle amount in Tokyo could become an undue inducement in São Paulo. It is notoriously difficult to establish just what level of incentive is appropriate in any given trial.

For example, consider a study that is designed to test a new treatment for prostate cancer, and there are good reasons for testing the treatment on men who have lived their entire lives in an inner-city environment as well as on men who have lived their entire lives in an isolated rural environment. If this trial took place in Canada, for instance, it would be difficult to agree a payment that was acceptable to both the urban and the rural participants. For example, if a fee of 200 Canadian dollars per participant was proposed, it would represent a larger proportion of the average annual income for the rural Canadians than that of their urban counterparts. The problem becomes exacerbated when if the study includes participants in different countries: 400 American dollars in Vancouver is worth considerably more in real terms than 400 American dollars in London, UK.

Because of the problems associated with financial incentives, some trial sponsors or coordinators prefer to offer non-financial incentives, especially when dealing with participants from impoverished nations. Non-financial incentives might include food, clothing, medications, local facilities and such like. However, this solution is not always appropriate, because the relative values of each of these non-financial incentives is just as susceptible to fluctuation as a financial incentive. For the trial coordinators, sponsors or organisers, who by and large come from affluent backgrounds, it can be very difficult to assess what kind and what degree of incentive is appropriate. They must make sure that whatever incentive is offered to trial participants is not disproportionately large, otherwise they could be seen to be offering a coercive or undue inducement, a practice that is condemned by ethics committees around the world.

A coercive offer is an offer that a prospective participant is likely to be unable to decline because of the

magnitude of what is on offer, or because of a lack of alternative courses of action. Coordinators, sponsors or organisers of multicentre trials, therefore, must do some delicate and precise calculations regarding the structure of the incentives that will be offered in the different geographical locations of the trial. Once again, this problem is exacerbated if the trial involves participants from areas or countries that are of vastly different socio-economic status. As with many bioethical issues, the problems associated with coercion, exploitation and undue inducement are brought sharply into focus when applied to the developing world.

The question is simple: what benefits should be given to research participants in the developing world? There is no straightforward answer to this question. Local ethical review committees, whose members have a good understanding of the local communities, have an important role to play in answering this kind of question. The type of research that best illustrates the problem of appropriate benefits and incentives is known as “international externally-sponsored research”. This is research that is carried out in a host country, but is organised and funded by an organisation from another country with the support of the appropriate authorities in the host country. This type of research usually brings with it some kind of reward or incentive for the individuals who are trial participants. There is almost universal agreement that it is right that these rewards should be provided, and that the rewards should not be so large that they constitute undue inducement.

The problem of undue inducement is particularly related to international externally-sponsored research. Very often the organisations that are responsible for the research have no real understanding of the level of poverty in the host nation, and they compare it to standards of poverty in their own nation. This is a mistake, because it is not unusual to find that the trial participants are far more impoverished than anyone in the organisation’s home country, and that the social-economic status of the two nations is very different. It is very easy, therefore, for the trial coordinators, sponsors or organisers to offer what they think is a reasonable reward which in actual fact is worth far more in real terms to prospective participants than is appropriate. That is, the incentive is heightened by a disproportionately high reward, meaning that potential participants are far more likely to sign up for the trial.

Sometimes undue inducements may be offered deliberately, and sometimes they may be the result of a genuine miscalculation or misunderstanding of the economic status of the host country. In any case, though, an unfair inducement can be seen as an exploitation of trial participants because the disproportionately high reward interferes with the voluntariness of their decision to participate: the reward is desirable, regardless of the inconvenience or risks that come with participation. However, the very existence of rewards and incentives is an attempt to prevent another form of exploitation, namely taking on participants without anything

to offset the inconvenience and risks associated with participation.

There is therefore a paradox concerning rewards and incentives. As Ruth Macklin (1989: 1) points out,

The paradox can be stated as follows: The higher the monetary payment, the greater is the benefit; the greater the benefit, the more acceptable is the research. However, the greater the monetary payment, the more potential subjects are unduly influenced to participate; the more coercive the recruitment, the more unacceptable is the research. Thus, the more acceptable the research protocol is, the less acceptable it is. Herein lies the paradox.

Macklin’s paradox highlights a real ethical problem in the case of international externally-sponsored research. The organisations in charge of the research must strike a balance between two undesirable outcomes, namely exploiting participants by providing too little by means of reward and unduly inducing their participation by means of a reward that is disproportionately high.

Earlier in this article, some issues relating to post-trial care were considered. One school of thought regarding post-trial care was that research participants should be entitled to some treatment after the trial is over. That is, whether or not a trial yields a successful drug, perhaps participants should be entitled to some treatment, be it the trial drug, a less-effective or more expensive alternative, or even a control drug that helped to manage their condition. The rationale is presumably that participants should receive treatment after a trial has finished as a reward for participation.

The people who believe that participants should be furnished with this type of post-trial care do so because they do not want the participants to be exploited. It is not clear, though, whether the promise of treatment after a trial is not objectionable on the grounds that it could be an undue inducement. That is, the promise of any kind post-trial treatment could disproportionately influence a potential participant’s decision to become involved in a trial in the same way as a financial reward. Once again, this problem would be exaggerated in parts of the developing world where the potential participants would receive no treatment whatsoever if they did not become involved.

Questions of rewards, incentives and undue inducements become even more complicated when the host community in a given trial is one whose culture relies more on reciprocity than on market principles. The most common way to think about any exchange of goods and services – at least in the developed world – is as a financial agreement. However, this type of agreement is not the norm in some developing world cultures; in these cultures the merits of a given transaction are judged on the respect and esteem that each party has for the other rather than any material transfer of possessions. That is, although a transaction with a community with this type of culture may involve the transfer of money or material goods (food, clothes, shelter), the important

aspect of the transaction would not be the material worth of the goods received but the respect and esteem that underpin the deal.

To the typical pharmaceutical company or western government, this kind of transaction may prove particularly difficult, and may deter them from involving such communities in research. However, like in the hypothetical case of the children with cerebral palsy, it may be necessary or desirable to involve such a community in some research. For example, it may be believed that a drug might combat a condition that is specific to members of one such community. Once again, this type of vulnerable group should not be prohibited from biomedical research, but, if they are to be involved, careful scrutiny should be applied to the terms of their participation.

A contrarian point of view

A minority of authors, mostly from the USA, have suggested that we should discard the notion of undue inducements altogether (Emanuel 2005). They argue that as long as trial participants are aware of the consequences of participation, and as long as they are competent in their decision-making and as long as they are true volunteers. Emanuel points out that it would never be possible to induce people into unethical (excessively risky) research because such research would be rejected by ethical review committees due to the risk involved, regardless of the inducement matter.

If, on the other hand, trial participants opt to join a particular trial that is not excessively risky because they get paid handsomely, why should ethical review committees wring their collective hands about this matter, seeing that everyone else involved in the trial (the investigator, nurse, research assistant, secretary, etc.) get paid? This is certainly an argument ethical review committees should have in mind when they review research proposals. It would be in nobody's interest if a proposal of an otherwise ethical trial – with a reasonable risk-benefit ratio, sensible research question, sound methodology – was rejected because the investigators decided to offer generous compensation to the participants.

Societal utility of proposed research

Any kind of research that you can possibly think of is not a cost neutral activity. It requires money, people, time, infrastructure and other components to undertake research. Partly in recognition of this it has been suggested by some ethicists that research, particularly research that involves a degree of risk, should have the potential to be useful for the populations in which it is carried out. Say, a researcher proposing to investigate the utility of satellite-transmitted on-line classes in the USA, Brazil, Japan, Germany, and Sudan would have to explain to a review committee for social science type research involving human participants how the potential findings of such research could likely benefit the Sudanese people. Or someone trying to investigate how effective an experimental, laser based brain surgery technology is would need to explain how this could be beneficial to

Zimbabwean patients if he or she proposes to investigate the matter in that country. Here is what the WMA has to say on this issue in paragraph 19 of the Declaration of Helsinki (2004): “Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research”.

This is a very important recent development in research ethics. Why? It is very significant because, until this requirement was added, research proposals would have been evaluated *internally*, that is, the informed consent document would have been checked, and the risk-benefit ratio would have been established. Nobody would have asked whether there was any likelihood that societal utility could be derived. This means that, until fairly recently, research would have been approved that would, predictably so, have yielded no utility for the populations in which it was carried out.

For members of ethical review committees throughout the world, the question they have to address, in addition to all of the traditional basic issues that have been mentioned above, is that of societal utility. Is there much point in doing this research here? What would be the benefit for our people if we permitted this to go ahead? Or, in the words of CIOMS (2004), “committees in the host country have a special responsibility to determine whether the objectives of the research are responsive to the health needs and priorities of that country”.

For the first time in the history of ethical review of research involving human participants, members of ethical review committees find themselves in a situation where they are called upon to make what are partially policy decisions about the societal desirability of proposed research.

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About the authors

Udo Schüklenk

Udo Schüklenk is a professor of philosophy at Queen’s University, Kingston, Ontario, Canada. He holds the Ontario Research Chair in Bioethics. He is author of editor of 6 books and more than one hundred publications in peer reviewed journals and books. He is a Joint-Editor-in-Chief of the journals *BIOETHICS* and *DEVELOPING WORLD BIOETHICS*. He is currently co-editing a volume on humanist thought (*50 Voices of Disbelief* - Wiley-Blackwell 2009), and he is working with Soren Holm on a book on Global Health Ethics (Wiley-Blackwell). He held appointments in Germany, Australia, South Africa, the UK before coming to Canada and still is an Honorary Professor of Bioethics at Witwatersrand University in South Africa.

Darragh Hare

Darragh Hare é is a Researcher in the Centre for Applied Ethics and Legal Philosophy in the University of Glasgow, Scotland. Darragh graduated from the University of Glasgow with a Master’s in Philosophy in 2001 and has held a number of research, policy and communications posts in universities, media and in the Scottish Parliament. Darragh has published on ethics in biomedical and social science research and on ethical obligations to humans and nonhuman animals. He is particularly interested in end of life choices. He teaches medical ethics, research ethics and ethical theory at undergraduate and postgraduate level at Glasgow Caledonian University.