

The Duty to Disclose Adverse Clinical Trial Results

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Abstract

Participants in some clinical trials are at risk of being harmed and sometimes are seriously harmed as a result of not being provided with available, relevant risk information. We argue that this situation is unacceptable and that there is a moral duty to disclose all adverse clinical trial results to participants in clinical trials. This duty is grounded in the human right not to be placed at risk of harm without informed consent. We consider objections to disclosure grounded in considerations of commercial interest, and we argue that these concerns are insufficient to override the moral duty to disclose adverse clinical trial results. However, we also develop a proposal that enables commercial interests to be protected, while promoting the duty to disclose adverse clinical trial results.

The Duty to Disclose Adverse Clinical Trial Results

I. Introduction

Participants in some clinical trials are at risk of being harmed and sometimes are seriously harmed as a result of not being provided with available, relevant risk information. In particular, participants are often not provided with *adverse clinical trial results*, that is, results obtained from previous clinical trials that provide evidence of harms caused to participants and animals in those trials.¹

There are many recent examples of serious harms occurring that look to involve issues of non-disclosure. Arguably this has led to a culture of distrust in the system, prompting moves to reform and restructure. Merck's market withdrawal of their arthritis drug, Vioxx, in 2004 and Eli Lilly's out of court settlement of lawsuits involving its drug Zyprexa both involve general claims of non-disclosure (Matthews and Martinez 2004). In the former case, Merck's former chief scientist testified that in 2001, some key people in Merck already knew from the results of two studies that Alzheimer's patients taking Vioxx had higher death rates than those who took a placebo.² In the latter, the New York Times reported the existence of

¹ We are concerned here with a narrower category of harms than those most commonly referred to as adverse events. That is, we are concerned only with those adverse events that are the result of the properly conducted trial. See for example the Medicines and Healthcare products Regulatory Agency website:

http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2030709&RevisionSelectionMethod=LatestReleased

² Doherty v. Merck, Case Number 2005M00638, Court of New Jersey, Atlantic County Civil Division.

internal documents showing that Eli Lilly was well aware of Zyprexa's tendencies to cause obesity and raise blood sugar — both known risk factors for diabetes.

Our concern in this paper is not with these more general worries about non-disclosure but, specifically, with the non-disclosure of adverse clinical trial results to potential trial participants. The Jesse Gelsinger case provides an example of just this kind.³ In 1999 at the University of Pennsylvania, Jesse Gelsinger died during an experiment after being injected with viruses designed to carry healthy copies of a gene into his body. The Food and Drug Administration and the National Institutes of Health found afterwards that Gelsinger was not informed that two other patients had experienced serious side effects from the same procedure; and that monkeys had died when given a similar treatment (Thomson 2000, Walters 2000).

In this paper, we argue that there is a moral duty to disclose all adverse clinical trial results to participants in clinical trials. We first argue that this duty is grounded in the human right not to be placed at risk of harm without informed consent. We then consider a countervailing argument that appeals to the health benefits delivered by the pharmaceutical industry and the consequent value associated with its protection. A key element of this protection is the ability of the pharmaceutical company to keep commercially sensitive information from its competitors. We argue that although the protection of the pharmaceutical industry is important, it is not sufficient to outweigh the duty to ensure that informed consent is provided in the face of risk of harms. However, we also demonstrate that an important form of industry protection is actually compatible with the duty to disclose clinical trial results. A key concern in this paper is to balance, appropriately, the competing moral claims presented

³ The more recent TGN1412 trial at Northwick Park is another, more complex and controversial example of involving this kind of non-disclosure (Kenter and Cohen 2006, Schneider et al. 2006).

by the risk of harm to trial participants and the benefits delivered by a productive pharmaceutical industry. Thus, we critically evaluate current and proposed regulatory practices. We then propose a set of institutional arrangements that we believe to be significantly superior to existing policies and other proposals, and finally, we consider some possible objections to our proposal.

II. A Case for the Moral Duty to Disclose Adverse Clinical Trial Results

A case for a moral duty to disclose all relevant adverse clinical trial results that involve harms to prospective participants in clinical trials can be put as follows:⁴

- 1) Human beings have a human right not to be placed at risk of harm without their informed consent *first being obtained* (To save words, we shall henceforth say ‘informed consent’ when we mean ‘informed consent first being obtained’).
- 2) Therefore, there is a moral duty not to place others at risk of harm without their informed consent.
- 3) If adverse clinical trial results are not disclosed to prospective participants then they are placed at risk of harm without their informed consent.
- 4) Therefore, there is a moral duty to disclose adverse clinical trial results to prospective participants in clinical trials.

Whatever one’s views are about the grounds of human rights, most can agree that human beings have a human right not to be placed at risk of harm without their informed consent. Informed consent is only provided when a subject has freely and competently given their consent and only when that consent is grounded on a basis of a disclosure of sufficient

⁴ There may be other ways of explicating this duty, e.g., using Principlism or interpreting Mill’s Harm Principle in a certain way. We are open to other approaches.

relevant information. Not being placed at risk of harm without one's informed consent is a core principle of biomedical ethics. It derives its importance from both the importance of autonomy and the importance of harms (Beauchamp and Childress 2001, Gert et al. 1997). Given this, one can appeal either to the 'agency' account or the 'primary essential conditions' account of human rights to explain why there is a human right not to be placed at risk of harm without informed consent. In the former, being placed at risk of harm without informed consent undermines an individual's agency, and human beings have a right against having their agency's being undermined (Griffin 2001, Gewirth 1996). In the latter, being placed at risk of harm without informed consent undermines certain primary essential conditions for a good life, namely, the capacities to know about relevant facts, to choose an act freely in light of those facts, and to have control of the direction of one's life; and human beings have human rights to the primary essential conditions (goods, capacities and options) for a good life (Liao 2006, Tasioulas 2002).

Supposing that there is a human right not to be placed at risk of harm without informed consent, on most accounts of rights, then, this implies that there is a corresponding moral duty not to place others at risk of harm without their informed consent. For example, on a Razian 'interest' account of rights, that there is such a human right would be a reason to hold others to be under a duty not to place anyone at risk of harm without their informed consent (Raz 1986).

The reason why when adverse clinical trial results are not disclosed to trial participants, they are placed at risk of harm without their informed consent, is because without access to information about the possible consequences of participation, trial participants are unable to assess the level of the risk involved in participating in a clinical trial and are therefore placed unknowingly at risk of harm. This is a violation of their human rights, but it is also a failure to meet the duties of disclosure recognised in standard accounts

of informed consent (Faden and Beauchamp 1986, Wear 1998). On such standard views, all relevant significant risk information must be disclosed before ‘effective informed consent’ can be said to have been obtained. Although our argument is one that will have significant consequences for the pharmaceutical industry, it is not one that appeals to any particularly controversial grounds.

Since the duty to disclose adverse clinical trial results to prospective participants of these trials is based on a human right, we would argue that anyone and everyone who is in a position to provide such information is morally obligated to uphold this duty. Human rights are typically regarded as rights against all relevant individuals in appropriate circumstances. According to Maurice Cranston,

To speak of a universal right is to speak of a universal duty . . . Indeed, if this universal duty were not imposed, what sense could be made of the concept of a universal human right? (Cranston 1973, 69)

Individuals who are in a position to provide such information include policy makers, employees of pharmaceutical companies, researchers on clinical trials, previous clinical trial participants, journal editors, peer reviewers, and others. Assuming that Cranston is right, the above categories of people who are in possession of relevant information have a moral duty to disclose adverse clinical trial results to prospective participants in clinical trials.

Here it is worth pointing out that all these individuals’ having a duty to disclose adverse clinical trial results does not mean that they all have to do the same thing to fulfil this duty, that is, to perform the ‘disclosure.’ In this case, like in other cases, one person can have the same duty as another but may fulfill that duty in a different way from the other. For example, suppose Jack is drowning, and John and Kate are present and have a duty to try to save Jack. The fact that both John and Kate have the same duty does not mean that both of them are required to jump into the water and try to get Jack out. Suppose Kate is a lifeguard.

She may indeed try to fulfill the duty by swimming towards Jack and trying to bring Jack out of the water. John, on the other hand, may try to fulfill his duty by calling for additional help or just by staying nearby in case further help is needed. Similarly, in our case, it may not be necessary or desirable for all who have a duty to disclose to ‘perform’ the disclosure. Instead, as an example, the duty of previous trial participants might just be to ascertain that the proper systems that can disclose adverse clinical trial results to future trial participants are in place and are functioning effectively.

III. Commercial Interests and Confidentiality Agreements

Since we are concerned to balance the competing moral claims involved in the disclosure of adverse results in clinical trials, it is worth recalling the benefits that the pharmaceutical industry has provided and its importance.

It is easy to think of specific medical conditions that have been radically affected by a particular class of drugs: HIV/Aids and cancer stand out in this regard.⁵ Perhaps the more interesting statistical details apply to the effect of recent pharmaceutical products more generally. For example, a 2003 study argues that of the 2 years of life expectancy gained over the period from 1986-2000, 10 months can be attributed to new chemical entities (Lichtenberg 2003).⁶ In a more recent study, Lichtenberg shows that “the more medical innovation there is

⁵ (U.S. Department of Health and Human Services, 2005); (Hoyert et al., 2006).

⁶ This study used data that covered “virtually all of the diseases borne by people in 52 countries during the period 1982-2001” (Lichtenberg 2002, 2). A second earlier study showed that “that people who used newer drugs had better post-treatment health than people using older drugs for the same condition, controlling for pre-treatment health, age, sex, race, marital status, education, income, and insurance coverage: they were more likely to survive, their

related to a medical condition, the greater the improvement in the average health of people with that condition” (Lichtenberg 2006, 2).

These studies are useful reminders of the benefits that can be associated with the pharmaceutical industry. Since the industry functions more effectively as a result of market forces, society as a whole has a vested interest in ensuring that the industry remains competitive. The ability to bring a new product to market faster than one’s industry competitors is crucial to a company’s ability to maintain competitiveness. Keeping the results of early stage clinical trials from a company’s market competitors can make the difference between a company’s flourishing and failing in a competitive marketplace in which the value of a product is largely a function of the value of the ideas that lead to the creation of that product. One possible means of protecting these ideas is through confidentiality agreements with researchers and trial participants. The legal support that these agreements provide helps to discourage one form of ‘leakage’ of information. This said, it does not follow that companies have a legitimate interest in keeping adverse results of clinical trials from prospective participants in clinical trials. The argument above only supports keeping such results from prospective participants in clinical trials when there is some good reason to think that by disclosing the results to prospective participants the company will thereby be disclosing them to their commercial competitors.

Further, and more significantly, the commercial interest of pharmaceutical companies in making confidentiality agreements with their research workers and with participants in clinical trials does not override the duty to disclose risks of harm to prospective participants in clinical trials. Consider an analogous case where a health care worker has a patient who is HIV positive and who has a duty to maintain confidentiality regarding that patient’s HIV perceived health status was higher, and they experienced fewer activity, social, and physical limitations” (Lichtenberg and Virabhak 2002, 2).

status. In most circumstances we would expect the health care worker to respect the patient's confidentiality. However, in circumstances where the patient is endangering others by having unsafe sex with a partner or partners, who do not know that he is HIV positive, then we would no longer expect the health care worker to respect confidentiality. Rather, we would expect the health care worker to reveal the HIV status of patient to prospective partners (Gert et al. 1997). The threat of a serious harm to another party trumps the requirement to maintain confidentiality in this situation. The situation we are considering is straightforwardly analogous. If participation in a clinical trial would place someone in danger of serious harm, and a third party is aware of the danger of that harm occurring, then it seems to us that a prior confidentiality agreement is not a sufficient reason to justify a failure on the part of the third party to disclose that harm to the prospective participant.

Even though we have explicitly recognised the many benefits to society that come from having a flourishing pharmaceutical industry, there may be some who will suspect that we have not recognised how sufficiently important it is. These people might also think that, even if there is a moral duty to disclose harms to prospective participants in clinical trials, it is overridden by the possibility of the threat that such disclosures bring to industry competitiveness, and hence to the greater good. We do not think that such disclosures are particularly threatening to the pharmaceutical industry, if handled properly, and we will go on to show how this threat can be minimised shortly. However, if our opponent who is willing to override the duty to disclose for the sake of having a flourishing pharmaceutical industry is not convinced by this argument, then the best that we can do is to demand consistency of reasoning from her. If she is willing to override the duty to disclose for the sake of a flourishing pharmaceutical industry then it seems to us that consistency requires that she be willing to override the duty to uphold a great many other individual human rights for the sake

for the greater good.⁷ But this is the road to totalitarianism and we take it that there will not be many who will wish to follow her on it.

IV. Current Practices: An Analysis

In the following, we analyze current and proposed regulatory practices and we argue that they fail to promote the duty to disclose adverse clinical trial results and they fail to ensure that sensitive information are not passed on to commercial competitors. Our analysis focuses particularly on the situation in the US largely because of the number of trials conducted but also because a large part of the regulatory attention is similarly focused.

Since November 1997, as a result of the Food and Drug Administration Modernization Act, the Department of Health and Human Services has been required to establish a registry of clinical trials for both federally and privately funded trials “of experimental treatments for serious or life-threatening diseases or conditions.”⁸ According to this Act, clinical trials with efficacy endpoints from Phase II (generally considered to be Phase III trials), and Phase III and Phase IV trials must be registered.⁹

⁷ For instance, consider a variant of the HIV example discussed previously. Suppose the patient is a multi-billionaire, and suppose he will donate billions of dollars if you do not inform his partner that he has HIV. Those who would be willing to override the duty to disclose for the sake of a flourishing pharmaceutical industry should also be willing to override the partner’s right to know about the other partner’s HIV status for the sake of a greater good.

⁸ <http://www.fda.gov/cder/guidance/4856fnl.htm> (Accessed 08/03/07)

⁹ Section 113 of the Modernization Act. A clinical trial is often preceded by animal trials. When a clinical trial is ready for human beings, it is typically divided into four phases. Phase I is conducted in a small group to evaluate safety; determine a safe dosage range; and identify

Moreover, since 1997, several hundred clinical trial registries around the world have been set up, including the World Health Organization (WHO)'s International Clinical Trials Registry Platform.¹⁰ Also, pharmaceutical companies, including Eli Lilly, Merck, GlaxoSmithKline (GSK) and so on, have voluntarily set up their own websites reporting clinical trial results.¹¹ Some of these companies have gone beyond what is mandated by the federal regulation. For example, Merck is registering *all* Phase II, Phase III, and Phase IV trials.¹² GSK have reportedly decide to include all Phase I trials in the public registry as well (Bouchie 2006).

In May 2006, the WHO extended their guidance to suggest that all phases of clinical trials involving human beings be registered (Sim et al. 2006). In September 2006, the U.S. Institute of Medicine published *The Future of Drug Safety: Action Steps for Congress*.¹³ This report recommends that, at the minimum, all Phase II, III and IV trials be registered. It also encourages the public disclosure of results in addition to registration of trials, and it urges that

side effects. Phase II is to determine a drug's effectiveness and safety. Phase III is to confirm a drug's effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely. Phase IV is a follow-up study to evaluate risks, benefits, and optimal uses after a treatment is already available for general use. See ClinicalTrials.gov website:

<http://clinicaltrials.gov/ct/info/whatis:#phases> (Accessed 08/03/07).

¹⁰ <http://www.clinicalstudyresults.org/>; <http://www.centerwatch.com/>;

<http://www.who.int/ictpr/en/>

¹¹ <http://www.lillytrials.com/>; http://www.merck.com/mrl/clinical_trials/;

<http://clinicaltrials.gsk.com/>

¹² http://www.merck.com/mrl/swf/Merck_Position_on_Clinical_Trials_Registries.swf

¹³ (Institute of Medicine, 2006)

both industry and researchers be held accountable for making drug safety study results public. In February 2007, U. S. Senators Mike Enzi and Ted Kennedy re-introduced a bill to congress,¹⁴ called The Enhancing Drug Safety and Innovation Act, which would enact many of the findings of the Institute of Medicine report. In September 2007, a version of this bill was passed as the US Food and Drug Administration Amendments Act.

All of these policies fall short of ensuring that adverse clinical trial results are disclosed to prospective participants in clinical trials. First, while laws requiring the disclosure of clinical trial results may vary internationally, in the US, where a significant number of clinical trials take place, the Modernization Act's requirement is only that some of Phase II, and all of Phase III and Phase IV clinical trials, are registered; and there is no requirement to disclose *any* adverse trial results to trial participants. The US Food and Drug Administration Amendments Act of 2007 requires the disclosure of some clinical trial results, but they do not require the disclosure of safety tests, which are typically done during Phase I and Phase II trials. So far, there has been no call to disclose adverse results from animal trials.

The current US regulation requires only trials “of experimental treatments for serious or life-threatening diseases or conditions” to be registered. But it seems to be a mistake to focus on the *kind* of trial rather than the *results* of a trial, whatever kind of trial it may be. For example, harm can result from a clinical trial of hair products. Even though hair product clinical trials are not “experimental treatments for serious or life-threatening diseases or conditions,” such harm is relevant information for prospective participants and should therefore be reported and disclosed.

It should also be clear that most recent policies, including the US Food and Drug Administration Amendments Act of 2007, do not ensure that commercial interests are protected. Requiring that the registration and disclosure process be *public* makes it impossible

¹⁴ The original bill was introduced in August 2006.

for pharmaceutical companies to keep sensitive information about the details of their clinical trials from their commercial competitors. Current and proposed regulatory frameworks fail to ensure that adverse clinical trial results are disclosed to prospective trial participants and fail to do enough to protect commercially sensitive information.

V. A Proposal

To safeguard participants in clinical trials while making sure that sensitive information is not passed on to the commercial competitors of pharmaceutical companies, we propose the following institutional arrangements. As we shall explain, we do not claim that the proposal is perfect or fail-safe. However, we believe that the proposal is significantly better than existing policies.

To start, we propose that a database be set up and administered by an oversight body. All adverse clinical trial results at any stage, that is, clinical trial results that involve, or indicate a risk of, harm to any participants or animals are to be disclosed to this oversight body. By harm, we mean core cases of harms, primarily, measurable, physical harms.¹⁵

¹⁵ In addition to run of the mill measurable physical harms, some people might consider a variety of actions and events as harmful. There are, for example, sometimes said to be spiritual harms. We do not expect that either pharmaceutical companies or the oversight body will be able to anticipate every possible action or event that prospective participants in clinical trials might consider to be harmful. We are concerned to ensure that core cases of harms are disclosed to prospective participants in clinical trials. These are instances where there exists widespread inter-subjective agreement that harm has taken place. We take it that it is uncontroversial that measurable physical harms fall into this category. If prospective participants are concerned with the possibility of more subjective sorts of harm occurring, within the context of a clinical trial, then they should think carefully about their participation.

This oversight body is then charged with the task of ensuring that appropriate adverse clinical trial results are passed on only to appropriate prospective participants in clinical trials. By appropriate prospective participants, we mean individuals who have been recruited by a particular company to participate in trials and who are likely to have undergone at least an initial informed consent process. Our proposal involves all relevant adverse clinical trial results of a particular company's being disclosed to participants. If the oversight body has reason to believe that adverse clinical trial results from other companies are relevant to this trial, then the oversight body will also inform the participants of these other results.

The disclosure of results by the oversight body will take two forms: *raw results*, which are all the adverse clinical trial results from a company unabridged and uncommented; and *summary results*, which are the oversight body's summary of these results and explanation of their relevance as they pertain to a particular trial. We propose that prospective participants be given the summary as a supplement to the participant information sheet provided through the informed consent process. This summary is an independent account of the overall adverse results, suitably contextualized, and of their relevance to the trial in question. At the time that prospective participants are presented with the summary, they should also be given an opportunity to examine it alongside the raw results, that is, to cross-reference the summary with the raw results and to examine the raw results themselves, if they so choose. In cases where the oversight body has reasons to disclose results from other companies, these results

They are also welcome to discuss their concerns with the pharmaceutical company in question, which is subject to existing legal requirements concerning the way it represents itself to prospective participants. The proposal that we have developed is intended to improve the conduct of clinical trials, but it is not a panacea for all possible problems that may occur within clinical trials.

will be presented to the participants only as summary results.¹⁶ The rationale for disclosing the results to the participants in these forms is that giving the participants the raw results has the advantage of ensuring that the oversight body is acting impartially. However, the raw results alone may not be of much use to most participants as these may be difficult for non-specialists to interpret. Although giving the participants a summary of the results relevant to a trial may make these results more usable and understandable for participants, doing so may also raise worries of partiality, corruption, and so on. In the case of disclosing adverse results of a particular company to prospective participants, to balance impartiality and usability, it seems that a workable solution would be to recommend that participants are given a summary by the oversight body, but that they also have access to the raw results.

In cases where the oversight body has reasons to believe that other adverse clinical trial results from other companies are relevant to this trial, we recommend that the participants be given only summary results. This is so, first, because giving them raw results from other companies seems vastly impractical, not to mention that it would undermine commercial interests. Secondly, especially if the oversight body has deemed that certain information are relevant information, not giving the participants this information would also be a failure to fulfill ordinary informed consent process.¹⁷ Thirdly, our rationale for giving raw results of a particular company to participants in the case is not wholly arbitrary. When trial participants

¹⁶ These results could be anonymized so that they would not reveal which companies had obtained the results.

¹⁷ Indeed, in the case of TeGenero and Northwick Park Hospital, where six healthy young clinical trial volunteers became violently ill minutes after having been injected with a drug, apparently side effects had been observed in similar drug trials of which TeGenero was not aware and which could have been relevant for both TeGenero and for the trial participants.

<http://news.bbc.co.uk/1/hi/health/5377866.stm> (Accessed 12/03/07)

are trying to determine whether it is safe to participate in a particular trial, similar trials are only one set of relevant information for them; another set is the past record of the particular company running the trial, which may indicate their behaviour towards their trial participants. Are they reckless? Are they particularly safe? Since the raw results of the company running the trial can be indicators for the attitudes and behaviour of the company, they are relevant information for the trial participant. In contrast, the raw results of other companies do not seem as relevant given that the participant is not participating in trials run by those companies.¹⁸

To continue our proposal, the oversight body is further charged with the task of ensuring that the prospective participants are not to transmit the information to third parties without the explicit permission of the company that is conducting the clinical trial in which they are contemplating participating. We also recommend that previous trial participants who wish to ensure that pharmaceutical companies have made an appropriate disclosure regarding clinical trials in which they had experienced harm have a legal right to contact the oversight body to see to it that this is the case.¹⁹

¹⁸ Consider an analogy: When one is ill, there is justification for a doctor to inquire about one's past health history. A doctor may be able to glean even more information if the doctor also has access to the exhaustive set of one's family health history. But for practical and ethical reasons, doctors typically do not seek this much information. Similarly, for practical reasons, it may be sufficient if the prospective participants have access to the raw results of a particular company.

¹⁹ As we have argued previously, the moral duty to disclose evidence of harms applies also to previous participants in clinical trials. While it is not necessary to set up legal and institutional arrangements to compel previous participants to make such disclosures, given especially, that these are, after all, people who have been harmed or placed at risk of harm, giving them a

In order to make our proposal work, legal and institutional arrangements would need to be put in place. It is beyond the scope of this paper to stipulate exactly what these arrangements are, but we imagine that they would be founded on the basis of two sorts of legally binding agreement. Pharmaceutical companies would face appropriate penalties for failure to make disclosure of adverse clinical trial results. Prospective participants would be required to sign a confidentiality agreement regarding the information that has been disclosed to them by the oversight body and would face appropriate penalties for any breaches of this agreement.

Other measures that we advocate to complement these arrangements are the following. We recommend holding lead researchers accountable for the disclosure of these adverse clinical trial results. To achieve this, legal arrangements could be instituted requiring that lead researchers ensure that such disclosures are made by their employing companies or that these disclosures are made by the lead researchers themselves. In the latter, the lead researchers would be required to sign an ethical statement certifying that to the best of their knowledge, all adverse clinical trial results of the company have been reported. Researchers who fail to ensure that such disclosures were made by their employers or who fail to make these themselves would be subject to appropriate penalties. These might be financial penalties, but they might also be ‘career penalties’. A step in this direction has already been taken by the International Committee of Medical Journal Editors, a group representing 11 prestigious medical journals, who instituted a policy in 2005, whereby a scientific paper on clinical trial results cannot be published unless the trial had been recorded in a publicly accessible registry at its outset (DeAngelis et al. 2004). Another possibility is that researchers who have been shown to have failed in a duty to make relevant disclosures be subject to personal publication legal right to ensure that harms that they had experienced have been disclosed seems appropriate.

bans for a period commensurate with the severity of the wrong. To provide an incentive to the researchers to report these results, we also recommend that journals publish adverse clinical trial results, which can promote public health and knowledge. The oversight body could also be charged with the task of providing protection for researchers who wish to report misconduct with respect to disclosure. As a body that is out of the direct public eye, it can provide the kind of confidentiality that may enable researchers to be more confident of coming forward to report wrongdoing. This feature of the oversight body also helps pharmaceutical companies by ensuring that false or misleading claims can be detected before any consequences are felt.

We believe that this framework is superior to existing policies in achieving the aims of safeguarding participants in clinical trials while making sure that sensitive information are not passed on to commercial competitors, for the following reasons.

1. As the oversight body will pass on all the adverse clinical trials of a particular company to prospective participants, prospective participants will receive relevant risk information.

2. Since only the prospective participants recruited by a particular company will have access to these adverse clinical trial results, and since the oversight body will ensure that no one else will have access to these results, commercial interests are in this respect protected.

3. Our proposal does not require that any trial result be disclosed publicly. This is another way in which commercial interests are protected.

4. In the event that there are adverse clinical trial results from other companies that are relevant information for the trial participants, our proposal explains why there is a duty to disclose these results to the trial participants and why this duty takes precedence over commercial interests.

5. This proposal promotes researcher responsibility. As we have seen researchers too have a duty to disclose but are currently not encouraged to ensure disclosure.

6. The proposal encourages and provides a non-public forum for previous participants who suffered or were privy to harm to come forward or to check that the duty to disclose is being fulfilled through the process of the oversight body.

VI. Objections

Even though our proposal is only presented here in outline form, we anticipate that objections will be raised. One possible objection is that there may be cases where the causation of harms is unclear. For example, it may be unclear whether or not the results of an early-stage clinical trial on a particular animal is or is not indicative of potential harms to human participants in future trials. In such unclear cases we envisage that pharmaceutical companies should be persuaded to ‘err on the side of caution’ and disclose results to the oversight body. Since pharmaceutical companies will be pre-selecting trial participants, they will have an opportunity to explain to these participants whether or not they believe that such ambiguous information should be interpreted as indicative of harm. Also, the oversight body will decide whether it was or was not indicative of harm when they draft their summary of the results.

A second objection is that the risks that have been found in other trials are (or can be) already covered in the standard informed consent forms and process that pharmaceutical companies currently use. If so, it might be asked, how is anything added when a potential trial participant is given the raw results of the other trials, as we are proposing? Most pharmaceutical companies act in good faith vis-à-vis the current informed consent process. However, as we have mentioned at the outset, there are potential cases of non-disclosure, which can lead to a culture of distrust in the clinical trial participant recruitment system. Indeed, arguably, the Food and Drug Administration Modernization Act, the WHO’s

International Clinical Trial Registry Platform, the voluntary reporting of clinical trial results by major pharmaceutical companies, the US Food and Drug Administration Amendments Act of 2007, and so on, are all efforts intended to instil trust and allay trial participants' potential distrust in this important system. Our proposal has the potential to demonstrate to potential trial participants that there can be impartiality in this system and that this system does aim to safeguard their interests, while at the same time, our proposal also protects vital commercial interests.

A third objection is that the oversight body we envisage is a fallible organization. It may fail to collect relevant information, it may fail to protect relevant information and it may fail to pass relevant information on to prospective participants in clinical trials. A further concern is that it may be corruptible. There are some circumstances under which the independence of the oversight body would be undermined if it was unduly influenced by special interest groups. We acknowledge that these are indeed possibilities, and part of the rationale for allowing participants to have access to raw adverse clinical trial results is to minimize such possibilities. In any case, we do not see these possibilities as ones that are peculiar to our proposal. Rather, they are possibilities that have to be addressed whenever bureaucratic structures are put in place to administer relations between different groups within a society. Most societies contain mechanisms to address the possibility of the corruption and incompetence of government agencies. One can seek recourse through the legal system for wrongs done and alert others of such dangers via the media. What we have proposed is an administrative structure, and administrative structures have their shortcomings. Our claim is not that it is a perfect structure, only that it is superior to existing arrangements and superior to any other proposals to rectify existing arrangements that we are aware of.

A fourth objection is that prospective participants may misinterpret some of the information presented to them. If such misunderstanding is liable to lead to poor decision

making, then it is better that this information is not presented to prospective participants, or so an objector may argue. An example of information that could be presented and that is liable to be misunderstood is information about animal deaths in clinical trials. In some early stage trials involving animals, animals are given successively higher doses of a particular experimental drug until death or a serious adverse event occurs. However, the actual doses of the drug that a prospective human participant may be asked to take in a clinical trial will typically be much lower than the dosage that resulted in the death of, or serious adverse event for, the animal in the relevant trial. In such circumstances, the disclosure of information about animal deaths has the potential to mislead prospective participants who may become overly concerned about the possibility of their own death if they participate in a clinical trial.²⁰ The possibility of misunderstanding of information is a matter of concern, but we do not think that the appropriate way to deal with it is by withholding data from prospective participants. Rather, the appropriate way to address this concern is to take steps to ensure that potential participants understand the significance of such information. Our proposal allows for two ways in which this may occur. First, the oversight body is to present a summary of results which explains their relevance to the trial in question. Where there is a significant concern regarding the likelihood of misinterpretation, this will involve explaining their relevance in such a way as to avert misinterpretation. Second, companies also have the opportunity to avert misinterpretation of data when they are recruiting research participants by explaining the significance of that data within the ordinary informed consent process.

A fifth objection, closely related to the fourth objection, is that there are a host of well known biases that infect ordinary interpretation of information. Prospective participants are liable to overestimate the importance of low probability events and small differences between probabilities; and their interpretations of information are likely to be subject to ‘framing

²⁰ Thanks to an anonymous reviewer for suggesting this example.

effects'.²¹ For example, if information about previous deaths is presented in terms of mortality rates then participants will likely to respond to it very differently than if the very same information is presented in terms of survival rates (Kahneman and Tversky, 1984). Our answer to this line of objection is in keeping with our answer to the fourth objection. The possibility of biases of interpretation can be addressed by the oversight body in their explanation of the summary of data released. It can also be addressed by companies within the ordinary informed consent process. A point worth making here is that interpretive biases bedevil all attempts to present statistical data to the public. In other contexts in which statistical information is made available to the public to inform decision making, appropriate efforts are made to reduce the possibility of biased interpretation by the careful presentation of statistical information, and there is no reason to believe that similar efforts will not be effective in this context.²²

A final objection, also related to the fourth and fifth objections, is that if we deluge prospective participants with information, much of which will be of very low relevance to their actual decision making, then they may have trouble identifying the information that is genuinely significant and may become overly worried about disclosed information that someone who understood the clinical trial in question would find to be of extremely low relevance. Our answer to this concern is that the summary document prepared by the oversight body will only refer to sufficiently relevant past trials. If a result is judged by the oversight body to be of very low relevance then its (low level of) significance will not be

²¹ The literature on biases of interpretation of events under uncertainty is vast. For a relatively recent summary see Gilovich and Griffin (2002).

²² One of the authors of this paper has discussed issues of interpretation of statistical information in the context of the disclosure to patients of surgeons' performance information (Clarke 2007).

directly discussed in the summary at all. However, we appreciate that there are some individuals who will find particular aspects of a past study to be more relevant to their decision making than these would ordinarily be found. For this reason, we do not propose to exclude any results of past trials from access in the raw results. Furthermore, the existence of material that is of low relevance should be mentioned in the summary so that prospective participant who may be concerned about it can identify the raw results that they find relevant to their decision about whether or not to participate in a particular clinical trial.

VII. Conclusion

Harms are taking place because participants of clinical trials are not being provided with available, relevant information regarding the clinical trial. In this paper, we argue that there is a moral duty on the part of all relevant individuals including policy makers, workers in pharmaceutical companies, researchers of clinical trials, clinical trial participants, journal editors, peer reviewers, and so on, to disclose adverse clinical trial results to participants of clinical trials. We further argue that this duty takes priority over the duty to maintain confidentiality, and we proposed some ways by which this duty can be promoted without endangering industry competitiveness.

We realise that our proposal will not guarantee that those involved in clinical trials will act ethically. Such guarantees would require that the individuals themselves become moral, something that cannot be forced. However, by explicitly defending the moral duty to disclose all adverse clinical trial results in terms of human rights, by showing how this duty takes priority over the duty to maintain confidentiality, by arguing that researchers, participants in clinical trials, and others also have this moral duty, we hope to have provided a

system that will encourage ethical behaviour and so as to have created a context in which such ethical behaviour becomes the norm.²³

²³ We would like to thank Jeremy Sugarman, LeRoy Walters, and participants of the James Martin 21st Century Advanced Research Seminar Series at Oxford University for their helpful advice and comments on earlier versions of this paper.

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