A critique of phase IV seeding studies on the basis of a non-paternalistic justification for subject protections in human research

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Abstract

English

Phase IV and other post-marketing studies have come under scrutiny and are often viewed as ethically dubious. These criticisms generally take the form that benefits of studies aimed at marketing do not redeem the risks and burdens phase IV impose on volunteers. This view of phase IV studies, while well intended, errs in grounding a critique in what are, in the end, paternalistic appeals to the welfare of human subjects. Instead, appeals to the integrity of the scientific enterprise provide a more cogent framework for the moral evaluation of such studies. This approach provides a clearer picture of why, who, and how the ethics of phase IV studies should be approached. I will indicate the ways in which the current formalised practice of human research ethics is paternalistic and indicate how the integrity of the human research enterprise is another legitimate moral concern that should limit what research is permissible. Finally, I will apply this framework to the case of phase IV drug trials.

French

La phase IV et les autres études, traitant de l'après-commercialisation, ont été examinées minutieusement et sont souvent perçues comme étant éthiquement douteuses. Les critiques de ces études marketing déplorent que les avantages des celles-ci ne contrebalancent pas sur les risques et les ennuis subis par les volontaires. Cette manière de percevoir les études de la phase IV, même si elle est bien intentionnée, fait erreur dans sa critique qui devient une approche paternaliste envers le bien-être des humains. Par contre, les approches de l'intégrité des entreprises scientifiques amènent un cadre plus convaincant lors de l'évaluation morale de ces études. Cette approche donne une image plus claire sur la façon dont l'éthique des études phase IV devrait être traitée. J'indiquerai comment la pratique actuelle de l'éthique sur les études sur les humains est paternaliste et comment

l'intégrité des études sur les humains est une préoccupation morale qui devrait aider à établir des limites sur ce que la recherche peut faire. Finalement, je mettrai en pratique ce cadre dans le cas des études sur les médicaments de la phase IV.

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Chapter 1 : The problem of paternalism

Introduction

In 2003, Dan Markingson was enrolled in CAFE,[1] a phase IV study sponsored by AstraZeneca on the atypical antipsychotic Risperdal. During the course of this study, Dan Markingson committed suicide, which brought about intense scrutiny of the study itself. Carl Elliot criticises the CAFE study[2] largely on the basis of the risk that was imposed on Dan Markingson as a result of participation, but the drug had already been approved for use in humans. There was relatively low risk to participation in the study, which makes it difficult to criticise it on the basis of the risk to Dan Markingson.

Phase IV trials are studies of drugs that occur after the drug in question has already been approved for use in humans. They are an important and necessary part of the development of drugs, because they provide information regarding safety and efficacy, as well as helping to identify adverse drug reactions.

Many phase IV and other post-marketing studies have come under scrutiny generally and are widely considered to be morally questionable. However, it is difficult to criticise phase IV studies on the paternalistic grounds of protecting the human subjects of medical research, since the risk to these human subjects is so low. Paternalistic appeals to the welfare of human subjects have largely been the justification for criticising phase IV "seeding" studies, but I will argue that a more

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[1] Comparison of Atypicals in First Episode

[2] (Elliott, 2010)

relevant reason for criticising such studies would be that phase IV "seeding" studies have a negative impact on human research as a collaborative project. Viewing the problem under the light of protecting the human research enterprise will help us to identify who should address the problem of phase IV seeding studies and through what means. There are many stakeholders in human research, all of whom will be impacted by policies that do not protect the human research enterprise, and all of whom will be able to play a part in ensuring the integrity of human research.

In the first chapter, I will address the problem of paternalism, and argue that human research ethics is largely paternalistic, but that there may be non-paternalistic reasons that justify restrictions on human research. In the second chapter, I will outline and defend one such candidate justification for human subject protections—the integrity of the human research project. I will make an analogy to other forms of market regulation and indicate how this could be used to justify restrictions on human research. In the final chapter, I will provide a critique of phase IV seeding studies on the basis of the integrity of the human research project, and conclude with recommendations regarding which of the many stakeholders in human research should be involved in ensuring the integrity of the human research project.

Outline

In this chapter, I will address the problem of how we ought to think about subject protections in human research. I will define paternalism, indicate what parts of our evaluation of human research are based on paternalism, and try to clarify what it is about paternalism that is morally problematic. I will evaluate some considerations that might be relevant when trying to determine what restrictions on human research are legitimate.

The current formalised practice in the ethical evaluation of research protocols involving human subjects is paternalistic. By this, I mean that the major criteria on which a research protocol might be approved or rejected by an REB would be ones that make reference to a concern for the patient's good or protecting the patient

from harm, without reference to the subject's personal goals, interests or desires. A concern for the subject's good that could be characterised as paternalistic exists explicitly in modern codes of human research ethics, and even as background assumptions in many of the concepts that are appealed to in human research ethics.

I will take as a starting point Beauchamp and Childress' definition from *Principles of Biomedical Ethics*. They define paternalism to be "the intentional overriding of one person's preferences or actions by another person, where the person who overrides justifies this action by appeal to the goal of benefiting or of preventing or mitigating harm to the person whose preferences or actions are overridden."[3] I will be using the term "paternalism" in a somewhat more broad sense than the one given by Beauchamp and Childress, though—after all, policies, institutions, practices, etc. can be paternalistic, not only people.

I will address the ethical problem with paternalism by reference to our moral intuitions and by analogy with example cases where paternalistic influences are obviously unacceptable. Then I will consider more problematic cases where regulatory bodies and rules that constrain freely chosen risk actions are generally considered legitimate. I will pose the question as to whether consent trumps all other moral concerns, and ultimately argue that informed consent is neither a necessary nor a sufficient condition for ethical human research.

I will consider the motivation behind subject protections in human research, and give reasons that there must be a limit to the practices of human research even in cases where there is valid informed consent. I will consider possible candidates for criteria to use in establishing exactly where the line should be drawn between human research practices that are acceptable and ones that are not, even given ideal consent.

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[3] (Beauchamp & Childress, 2009, p. 208)

What makes clinical research ethical?[4] is a high-level analysis of a number of primary sources on medical ethics, including the Nuremburg Code, the Declaration of Helsinki, the Belmont Report, the International Ethical Guidelines for Biomedical Research Involving Human Subjects, and other similar documents. In this paper, Emanuel et al. conclude that there are seven conditions that must be met for research on human subjects to be ethical. They are, (1) social or scientific value, (2) scientific validity, (3) fair subject selection, (4) favourable risk-benefit ratio, (5) independent review, (6) informed consent and (7) respect for enrolled subjects. In *Rethinking the Ethics of Clinical Research*,[5] Wertheimer examines these seven requirements and argues that each of them is paternalistic.

I will begin by going over Wertheimer's analysis and give reasons why I agree with Wertheimer and take five of the requirements given by Emanuel et al. to be paternalistic. Namely, I will discuss the balancing of risk-benefit ratios, informed consent, independent review, fair subject selection and respect for enrolled subjects.

I will argue that the remaining two requirements from *What makes clinical research ethical?*, scientific value and validity, indicate that there are other moral considerations that bear on what human research is permissible, which I will explore in greater detail in the next chapter.

What makes clinical research ethical?

Let us turn our attention to the current formalised practice of the ethics of medical research. Wertheimer examines the seven conditions that Emanuel et al. give as requirements for ethical human research, and argues that each of them is paternalistic. I will agree with Wertheimer with regard to fair subject selection, favourable risk-benefit ratios, independent review and informed consent, that there

[4] (Emanuel, Wendler, & Grady, 2000)

[5] (Wertheimer, 2011)

could be a paternalistic rationale for each of these requirements for ethical human research.

However, it is much more difficult to make the case that value and validity are paternalistic. I will discuss how they may point to another justification for subject protections in human research.

Fair subject selection

Fair subject selection is a criterion of ethical human research identified by Emanuel et al. which requires that subjects of human research not be drawn from "stigmatized and vulnerable individuals," in the case of risky research and that the "rich and socially powerful" not be targeted for potentially beneficial research.[6] The main thrust of the section on fair subject selection in the article by Emanuel et al. is a concern that subjects of human research not be exploited by the financial or medical inducements offered to subjects of human research. It could be argued that this criterion is paternalistic because it may override a subject-patient's preferences (namely, a preference to participate in human research) out of a concern for the well-being of the patient-subject. In many of such cases, it is arguably not morally problematic to provide inducements for participation that may attract participants who are not financially well-off.

Let us consider the example of a person offering an unfavourable job for a low wage—for example, cleaning and maintaining washroom facilities at a factory. Out of a dire need that was not produced by the person offering the job, (for example, a need to pay university tuition) a worker accepts her offer of employment. There may be a sense in which the worker is "exploited," but not a morally problematic one. While it is lamentable that anyone would find herself in great financial need to begin with, financial or medical inducements are not exploitative in a morally problematic way. This "exploitation" is mutually advantageous and beneficial to both parties.

[6] (Emanuel, et al., 2000, p. 2703)

In the same way that we think that a person offering an unfavourable job for a very low wage does not act immorally when he "exploits" workers who accept such jobs out of dire need, likewise, we should think that a researcher who provides financial inducements for participation is not acting immorally. Considerations of fair subject selection are paternalistic in the sense that they prevent investigators and subjects from being able to enter into a mutually advantageous research arrangement.

Favourable risk-benefit ratio

When evaluating a human research procedure, a research ethics board must consider the risk-benefit ratio for the subject of the research. It is not difficult to see how this criterion can be shown to be paternalistic. A committee that decides which procedures will provide benefit to a human research subject, and how likely that will be to occur in relation to the probability of harm will be acting paternalistically, because they will do so without reference to the desires or goals of the research subject. A research subject may have desires that do not line up with the ones that are taken for granted by a committee who is appealing to a risk-benefit ratio to justify or condemn a study, and so in this way, this criterion is paternalistic in nature.

Clinical equipoise is one criterion often cited by ethicists when determining whether a research protocol is ethical. Equipoise, defined broadly, exists when there is genuine uncertainty in the medical community between the effectiveness of one arm of a study as compared to the current medical standard of care. If a research protocol is said to be one that will disturb clinical equipoise between a proposed new treatment and the standard of care, it is taken to be a point in its favour, ethically speaking.

The concept of equipoise, however, is one that is essentially embedded in the paternalism of medical practice. The question of whether a study is in clinical equipoise or not takes as a background assumption that the research subject would only be interested in participating in research that was equally likely to produce

good therapeutic results for the subject in the opinion of the physician or the medical community. It allows no space for subjects who are interested in participating in very risky research.

In *The Irrelevance of Equipoise*, Veatch argues it is not equipoise that is "morally critical" in evaluating a research protocol.[7] He argues for this firstly because equipoise is fleeting. Under certain circumstances, an entire clinical community may move in and out of equipoise even during the course of the study, making it difficult or impossible to conduct an ethical study, if equipoise is a necessary condition for ethical human research.

Further, Veatch argues against equipoise as a condition for ethical research by appealing to paternalism. Potential subjects will bring "subjective, idiosyncratic preference functions to bear, and based in part on those functions, may see it appropriate to consent to being randomised after being adequately informed," even in cases where there is no equipoise.[8]

For example, a drug whose side-effects include weight gain or drowsiness may be considered by the clinical community to be inferior to a drug that has no such side-effects, but a human subject of research with an "idiosyncratic preference function" may even consider weight gain or drowsiness to be a point in the drug's favour. For this reason, she may agree to be randomised even though there is no state of equipoise.

Independent review

Investigators in human research have many goals besides ensuring the welfare of the subjects of their research. Independent review of human research is meant to be a safeguard against possible harms that human subjects may incur.

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[7] (Veatch, 2007)

[8] (Veatch, 2007, p. 182)

Wertheimer compares the process of independent review to a parent-child relationship.[9] In this analogy, the review of a research protocol by an REB is likened to a parent giving informed consent for a child in paediatric research, and informed consent of the research participant is the equivalent of the child giving assent to the research procedure.

The way that we currently evaluate human research by requiring the permission of a "higher" decision-maker before subjects are allowed to consider participation, we are treating human subjects like children—there is a need for a higher body to grant approval to the research. In the case of a child, it is the parent, and in the case of a human research, it is the REB.

Informed consent

While the criterion of informed consent largely does contribute to protecting a patient-subject's autonomy, there are a few situations in which even giving informed consent could be conceived of as paternalistic. If informed consent is only a process by which the good of the research subject is protected, that is, if the giving of informed consent is nothing more than the endorsement on the part of the subject of a protocol that has been pre-conceived to bring about some good, where the good is decided up by the researchers, and it is one that does not conform to the subject's own desires or aims, then in that case, the giving of informed consent is itself a paternalistic practice.

Usually, what a person wants and what would promote that person's welfare are the same thing. In some cases, such as that of altruism, these two diverge. It may, on the last analysis, be justifiable to only allow research participants to consent to studies that are favourable to their welfare, but there is some paternalism in making such a requirement.

[9] (Wertheimer, 2011, pp. 33–34)

Also, Wertheimer remarks that "the very principle of *informed* consent is at least somewhat paternalistic," because there many areas of life where it is the responsibility of the decision-maker to obtain the necessary information in order to make a decision.[10] For example, people are allowed to engage in sex, gambling or the use of bicycles, sometimes in complete ignorance of the risks in doing so. While it may be justified to require such disclosure of risks in human research, there is at least some paternalistic element to it. In some cases, there is insistence on an elaborate informed consent process, including constant documentation that many patients are indifferent about. If a patient has a desire not to be burdened by the details of a research protocol, it is paternalistic to impose a requirement of understanding out of concern for her well-being.

Informed consent is generally taken to consist of three elements: capacity, voluntariness and understanding. It is the requirement that a research subject understand the protocol that is possibly paternalistic.

In medical research, there is an imposition of a standard of comprehension and voluntariness that is not expected in other situations where consent is required. Consider the example of buying a financial investment product. A consumer can say, "If this investment is being offered by my bank, then that's all I need to know." She may not be wise to act in this way, but we wouldn't say that the banker acts unethically by accepting this as a valid token of consent. In fact, it would be problematic for a banker to insist that the prospective investor go through all the details of the investment product and understand it to the banker's satisfaction before consent could be given.

On the other hand, a human research subject cannot say, "If this research is being conducted by McGill University, then that's all I need to know." There are requirements on her dictating that she must come to her decision to participate in

[10] (Wertheimer, 2011, p. 35)

the research on the basis of the right sorts of reasons, as determined by the research ethics board.

Flory and Emanuel argue that in order for informed consent to be valid, investigators must do more than simply disclose the details of a research protocol—"Research participants should also understand the essential disclosed information."[11]

This is what makes informed consent paternalistic: the imposition of external standards of reasoning and mental processes on the human subjects of research.

Respect for enrolled subjects

Many of the requirements for ethical research that are considered under respect for enrolled subjects (such as monitoring the welfare of the subjects) are also justified by paternalism. Wertheimer cites the example of the right of human subjects to withdraw from research at any time, without penalty. He argues that there are many contexts in which it is permissible to make commitments from which it is difficult to withdraw, such as marriage, or for which there would be penalties for non-compliance, such as in the use of legal contracts.[12]

Consider the case of a patient-subject who is morally committed to the cause of research into a particular illness, but who suffers from a lack of will-power, of which she is very well aware. By its nature, the research into this illness is very difficult and painful for a patient-subject to endure. In our example, the patient-subject wants to make a strong commitment to completing the research protocol, and she wants to be bound to that protocol under pain of some penalty because she fears that her resolve will break during the course of the protocol. It would be

[11] (Flory & Emanuel, 2005)

[12] (Wertheimer, 2011, p. 35)

paternalistic to override the patient-subject's preferences and take away an incentive that the patient-subject wants, in order to preserve her well-being.

There are other facets to this requirement that are not so easily captured under paternalism. For example, it is often considered to be a requirement of ethical research that at the conclusion of the study, the results be communicated to the human subjects that participated in the study. This does not fall under protecting the subject from harm.

Value and validity

It is much more difficult to make a case that social value and scientific validity are paternalistic. In fact, I will argue that our concern for value and validity as moral requirements for ethical research indicate that it is not just paternalistic concern for human subjects that is the grounding for human subject protections.

Wertheimer admits in the first sentence of his analysis of value and validity, that these are "not the best examples of [his] thesis," that human research regulation is paternalistic.[13]

The best argument that Wertheimer gives in support of his claim that even social value and scientific validity are paternalistic is that altruistically-minded subjects may not be able to discern whether the risks imposed on them in a study are compensated by the potential benefits that may accrue to others. Hence, when a research ethics board reviews a protocol and finds that it will produce valid and valuable data, Wertheimer claims that it "protects subjects from harm or burdens that do not serve their altruistic ends" in the judgement of others with advanced knowledge.[14]

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[13] (Wertheimer, 2011, p. 31)

[14] (Wertheimer, 2011, p. 32)

This is not a very strong claim of paternalism against value and validity, and it's even hard to see why this is paternalistic at all.

In the practice of human research, value and validity are relevant only in that they can be traded off against personal risk to the patient-subjects of human research. This is an example of paternalism in that it deprives patients of the choice to trade off something else against their own risk, but it also imposes one party's views of value and validity on another. So a patient cannot choose to enter a study on the basis of her personal relationship with the investigating physician, without regard for the value and validity of the study, for example.

Or a self-experimenting physician-investigator may not be able to engage in research on herself because an REB views her study as not sufficiently valuable, despite the fact that she fervently believes in the study's value.

Wertheimer admits that there may be other considerations at work in the justification of value and validity as moral constraints on what human research is permitted:

> Evaluating protocols for "social value and scientific validity" is no doubt partly justified by the goal of making good use of scare resources devoted to biomedical research and ensuring that the study design will generate findings that will advance the standard of care for future patients.[15]

This is an enlightening comment. Wertheimer is saying that the sorts of research that is permissible may be limited by the concerns of other stakeholders and by the availability of resources for the human research project. It is much easier to see these principles, value and validity as justifiable on the basis of something other than the welfare of the subjects of research.

[15] (Wertheimer, 2011, p. 31)

Before I discuss other candidate non-paternalistic justifications for subject protections in human research, I will look into what is morally problematic about paternalism.

What is problematic about paternalism?

The problem with paternalism, put simply, is that there is an implicit or explicit disregard for the desires and aims of the research subject. I argued earlier through a number of cases, that paternalism exists in research ethics as a result of external values being imposed on or constraining the choices of research subjects. It is problematic that our ethical frameworks and conceptual tools for human research are so rife with paternalism.

The problem with this situation is that there is a very strong moral intuition which most of us have in which, if a person wants to engage in risky kinds of human research as a subject, then that person should be free to do so. Most of us would generally agree that there is no moral problem with allowing someone to pursue the ends she sets for herself, and that, in fact, there should be some very strong reason for constraining someone from pursuing her own plans. To illustrate the problem of paternalism, I will start by giving a non-medical example of paternalism that is obviously morally wrong.

Let us imagine the case of a person who visits his bank to withdraw a very large sum of money. While completing the paperwork for the withdrawal of such a large sum, the banker asks his client what it is that he will be spending the money on.

“A bicycle,” the client replies. “A very nice one.”

Now imagine the client’s frustration and shock if the banker were to tell him that he would love to release to the client his funds, he could not do so because buying a bicycle was an unwise investment, and it was the bank’s policy to refuse to release the funds in situations of very unwise investment. It would be outrageous for the banker to refuse to produce the client’s money because of a bank policy against

releasing funds to a client if they are to be spent frivolously. This is the sort of problem that we run into in human research. Assuming that subjects are not rendered incapable of choice by their illness, at first glance it is unclear why it is that there should be any restrictions at all on what sorts of human research is allowed, assuming that there are both researchers and subjects who value it and are willing to participate in it, and all of our thinking about research ethics seems to be very strongly paternalistic.

A person may choose to engage in high-risk medical research of her own accord, and while we may urge her to be cautious, and we may question how well-informed she is regarding the probability of harm or the severity of the harm, or we might even question her capacity to consent to a very risky protocol, yet still, if these concerns were answered to our satisfaction, we would seem to have no grounds on which to condemn the proposed research.

The case of the banker was clearly and non-controversially paternalistic in an ethically problematic way. Let us consider some other cases which are arguably paternalistic, but are generally regarded as legitimate.

High-risk sports and recreational activities such as skydiving are generally considered to be morally acceptable. Even high-risk jobs such as deep-sea oil drilling, where there is financial compensation, are not regarded to be unethical. That said, there are restrictions placed on such activities by law. On high-risk job sites, there are safety precautions that, by law, must be observed by all workers. This could come in the form of safety training or equipment mandated by law. The equipment used in high-risk sports and recreational activities are also similarly regulated, so that the harnesses used in rock climbing are all of a certain quality, for example.

These restrictions may indeed be paternalistic, but they are not problematic in the same way as the case of the banker because there may be other legitimate reasons to require them.

Reification

Let us examine whether there are other concerns besides a patient's autonomous decision-making which may place restrictions on what practices can be allowed in human research. One candidate for something that has been considered by some to take precedence in certain cases over even informed consent is the problem of reification. Reification is the morally problematic issue that human research subjects are turned into "things" by fact that they are acted upon, and are not actors themselves in human research.

Jonas addresses this problem and concludes that "... the 'wrong' of reification can only be made 'right' by such authentic identification with the cause that it is the subject's as well as the researcher's cause—whereby his role in its service is not just permitted by him, but *willed*."[16] Jonas' solution to the problem of reification is that medical research on human subjects is permissible if the subjects themselves take up and identify with the goals of the research being performed.

So, on examination, this concern cannot be used to trump informed consent. The solution of the problem of reification that Jonas offers is just a higher standard of respect for the autonomy of the research subject. Not only must the patient's consent be respected, but the patient must indeed identify herself with the goals of the research.

It is tempting to say that many of the restrictions on our autonomy that we experience are justifiable because there are so few cases where the desires and goals of the person engaging in a high-risk activity or job are incompatible with accepting the external restriction on the activity. By this I mean, the goal of rock-climbing (presumably, physical exercise and enjoyment) is compatible with the restriction of wearing a safety harness. Similarly, the goal of a worker on a deep-sea oil rig (making money, most likely) is compatible with certain safety precautions. In a case

[16] (Jonas, 1974, p. 122)

like the banker and the would-be cyclist described above, the problem was that the goal of withdrawing the money (buying a bicycle) was incompatible with the restriction that the banker placed on him, that he would not allow the withdrawal for the purposes of buying a bicycle. The outrageous nature of the banker's actions were felt so strongly because the banker prevented the client from performing an action that was essential to her desires and goals.

In contrast, we do not feel the same sense of moral shock at the case of a driver being required to wear a seatbelt, because the driver's goals and desires (reaching her destination, enjoying a ride in the country, etc.) are not hampered by the restriction placed upon her by the requirement to wear a seatbelt.

Unfortunately, this line of argument cannot be used to justify many of the protections that are in place even in non-medical contexts. For example, someone may enjoy risky rock-climbing without a safety harness or a net, and she may enjoy it just because it is risky. Because it is the riskiness of the activity that is essential to her enjoyment, and indeed that is the object of her enjoyment, it would be impossible to establish protections for the subject that do not interfere with her goal of enjoying the risk of rock-climbing.

If this line of thought does not hold in a simple non-medical case, it is doubtful that this principle could be used as a principle to establish whether subject protections in human research are permissible or not.

Subject protections

There is a very commonly held moral intuition that there should be some external restrictions on human research, beyond just what a researcher and subject will agree to. Imagine a case in which legitimate informed consent is given. There is a subject who is fully and vividly informed about the consequences of her decision to participate in a very harmful medical procedure, who is aligned with the goals of the study and who gives a legitimate informed consent to a brain extraction, for

example. Also imagine that there is a researcher who is willing to perform this operation that would certainly end the subject's life. It is not unreasonable to think that even in this case, there is some legitimate moral reason why this research would not be acceptable.

There must be a line drawn between what is a morally acceptable human research practice, and what is not. The question is not whether there is such a line, but where that line lies, and what criteria are legitimate considerations when trying to determine where to draw it.

Possible justifications for protecting human subjects

As I have argued earlier, paternalistic concern for the subject's well-being has largely been the justification for subject protections in human research thus far, which may be justifiable to a greater or lesser extent, depending on the situation. Another possible candidate for a principle that places limits on human research practices would be a concern for Jonas-style reification. This would certainly limit the kinds of research that would be acceptable even given informed consent, but as we saw, it would still leave open the possibility that a patient who identifies with the research project could find a researcher who would be willing to engage in very risky procedures, and an appeal to this principle would have nothing to say on the matter.

There is still an intuition that there is something wrong with allowing just any high-risk human research to go on, but this wrong can't be a violation of the interests of the human research subject—by hypothesis, this person consents and even identifies herself with the research project. Further, the wrong can't be a violation of the interests of the researcher. In our thought experiment, this person is also willing to engage in this very risky or harmful research.

Wertheimer's comments on value and validity point us toward another, more promising justification for protecting human subjects—protection of the human research project as a collaborative enterprise.

The Tri-Council Policy Statement

Appeals to the protection of the human research project can also be found in other places. The Tri-Council Policy Statement governs research on humans in Canada, and it acknowledges three core principles: respect for persons, concern for welfare and justice,[17] none of which make any reference to stewardship of resources or the human research enterprise. In fact, these three principles are arguably paternalistic for reasons that I give above under "What makes clinical research ethical?" And yet, where the TCPS discusses phase IV studies, there is an indication that there are other concerns that go beyond its three core principles that should constrain phase IV studies.

When considering phase IV studies, the TCPS encourages REBs to keep in mind "utilisation of public resources (e.g. diagnostic services and medical imaging)," and concludes that "phase IV trials designed with the primary goal of increasing sales do not constitute legitimate research."[18]

The TCPS does not explicitly endorse the protection of the human research enterprise, but it certainly does mention a couple issues that are directly related—public resources for research and keeping science separate from marketing exercises.

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[17] (Canadian Institutes of Health Research, December 2010, p. 8)

[18] (Canadian Institutes of Health Research, December 2010, p. 152)

Analogy to minimum wage

A good, non-paternalistic argument in favour of the protections in place for workers in cases such as minimum wage (where many may be willing to work for less), would be one in which it is argued that a minimum wage is required to protect all workers from having to accept the lower wages that some workers may be willing to accept. In this argument, it is not out of a concern for the individual's well-being that a minimum wage is enforced, but rather it is out of concern for maintaining the job market for everyone. Not having a minimum wage would make it more difficult to recruit workers. There would be liabilities that all the stakeholders—employers, workers, etc. would incur if there were no restrictions on the sorts of wages that could be agreed to.

Webb argues that a minimum wage is justified economically because "… as compared with no regulation of wages, or with leaving the employer free to deal individually with each operative, it must tend actually to increase the productivity of the industry."[19] Webb argues that a labour market that had no minimum wage would be one where preference is given to lower-quality workers, since they would be willing to work for less. Further, there would be more stability in the job market due to a lower rate of turn-over. Thus, out of concern for the productivity of the market itself and not necessarily out of concern for the welfare of the workers, there should be restrictions on the minimum wage.

These theoretical concerns are borne out empirically. In 1996 and 1997, American federal legislation increased the minimum wage, and as a result, there were "strong wage gains and no negative impact on job opportunities."[20] This is in sharp contrast to the expectations of some economic theorists who argue that a rise in the minimum wage must cost jobs.

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[19] (Webb, 1912, p. 977)

[20] (Bernstein & Schmitt, 2000, p. 1)

The case of medical research is analogous to that of minimum wage. Both cases can be conceived of as a market in which there are players that must work together on a common project. Rather than hindering the effectiveness of the market to bring together employers and employees (or by analogy, investigators and patient-subjects), regulations serve to protect the market from certain inefficiencies.

I will argue in the next chapter by analogy that it is the integrity of the human research enterprise as a whole that is being violated when very risky human research is allowed. Put simply, if human research were allowed to engage in any practice that a human subject and a researcher would consent to perform, the human research project would quickly gain a reputation for being the sort of activity where "anything goes." Participants in research might become more cautious, since they can no longer assume that the research process is designed to secure their "best interests"—the fact of the matter will be, they don't—and this would have deleterious effects on human research as a whole.

This is not just an attempt to recapture paternalistic concern using the language of the integrity of the human research enterprise. A person committed to upholding the integrity of human research may have no commitments at all regarding whether research subjects cause harm to themselves, insofar as they are making judgements regarding the ethics of human research. They would, of course, take issue with using the machinery of human research to do so, because this would impact the integrity of the human research project as a whole.

The integrity of the human research enterprise

In this chapter, I argued that while the current practice in evaluating human research protocols is largely paternalistic, there are still at least two considerations that appear to have a non-paternalistic grounding: scientific validity and value. In the next chapter, I will outline what I take to be a viable candidate for a non-paternalistic justification for these conditions for ethical research and other

restrictions on human research protocols, namely, the protection of the human research project.

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Chapter 2 : The integrity of the human research project

Introduction

In the first chapter, I made an argument that the current formalised practice in human research ethics is paternalistic, and described why that may be problematic. Even though human research ethics is largely paternalistic, some parts of the practice of human research ethics seem to point toward non-paternalistic values that may be used to justify human subject protections. Wertheimer indicated that concerns regarding confidence may be used to justify restrictions on human research. Also, the concepts of value and validity seem to be very difficult to capture under a paternalistic framework.

One candidate for a non-paternalistic justification for human subject protections is a concern for the protection of human research as a collaborative project.

In this chapter, I will consider the integrity of the human research project as a non-paternalistic justification for human subject protections.

I will begin this chapter by addressing a concern raised by Wertheimer in *Rethinking the Ethics of Clinical Research*, that a loss of integrity cannot be cause for moral concern because a loss of integrity must be the result of a pre-existing moral commitment that is compromised, and a mere transgression of "integrity" in this way cannot itself be the source of a moral wrong. I will respond to this argument directly, respond to the objection that this is just a disguised form of paternalism, and clarify the issue by defining two kinds of integrity—the integrity of internal moral consistency and the integrity of a border.

I will outline an argument that could be legitimately made in favour of protecting human research subjects on the non-paternalistic grounds of protecting the integrity of the human research project. Then, I will compare this to other forms of

regulation, and argue that in the same way that market regulations help to establish healthy markets, subject protections in human research help to maintain and protect the broader human research project.

I will bring out some of the consequences that would result in the case that human research was totally unregulated with regard to human subject protections. I will specifically consider a loss in public confidence, the problem of recruiting other stakeholders beyond the research subjects themselves, and impacts on the quality of the research. I will also outline other important repercussions such as the cascading effects that research in one area may have on other research projects and human research as a whole, as well as the consumption of scarce resources for human research.

Wertheimer's worry

In *Rethinking the Ethics of Clinical Research*, Wertheimer grants that non-paternalistic concerns may legitimately justify constraints on human research.[21] He considers the possibility that high-risk research be "ruled out for the sake of protecting the research enterprise from loss of public confidence."[22] Before we address this concern, it is worth looking into what he could mean by this claim. Wertheimer rightly notes that "it can't be wrong to perform an act *because* doing so will compromise one's integrity."[23] Someone can only incur a loss in integrity if it is the case that the action that compromises her integrity was wrong in the first place.

[21] (Wertheimer, 2011, p. 21)

[22] (Wertheimer, 2011, pp. 40–41)

[23] (Wertheimer, 2011, p. 40)

For example, if a doctor were to release some confidential medical information about a patient, we would call that a breach of integrity. It would be a breach of integrity because the doctor did something that she herself would have taken to be wrong. It is the violation of one's own principles that constitutes a compromise in integrity. Wertheimer's point is that the breach of integrity is wrong because it was a violation of the doctor's principles. If there was no principle compromised, then there would be no breach in integrity. In this example then, if it was not the case that the doctor was bound by confidentiality in the first place, then releasing the medical information would not have been a compromise in integrity.

So such an argument will not work on a simple appeal to "integrity" alone. Wertheimer argues that if it is not the case that we have a pre-existing moral commitment that high-risk research is wrong, then it cannot possibly be the case that it could be the source of a breach of integrity. Our task must be to describe what it is exactly that will make it immoral to allow very risky forms of human research.

In the same way that research with little or no scientific, social or medical value is morally problematic, in that the harm or risk of such research cannot be justified by the value it produces (since, by hypothesis, it produces none), we can also think about research that is unregulated with regard to risks for human subjects.

This may seem worrisome, because such a move in justifying an appeal to integrity seems to make the justification of the appeal into one that depends on an unfavourable risk-benefit ratio for the research subject. Fortunately, this argument does not need to rely on considerations of the research subject's benefit at all.

I will argue in the sections that follow that research that involves a high degree of risk would be the sort of research that would undermine the collaborative project of human research as a whole. Because the human research enterprise would be compromised, it would be unable to fulfil its goal of producing valuable, scientifically valid knowledge, and so it would be unethical to allow such research to proceed.

Two kinds of integrity

The problem raised by Wertheimer only exists because of a particular conception of integrity. The integrity of the human research enterprise can be conceived of in two related, but distinct ways: Integrity can be thought of as the quality of adhering faithfully to one's own moral commitments—this is the sense of integrity that was addressed in the previous section, and the sense that generates Wertheimer's objection. One loses this first sort of integrity by holding some sort of moral commitment and acting in a way that is inconsistent with that moral commitment.

For example, if one held that the autonomous decision-making of research subjects was something that one took to be morally valuable, and at the same time endorsed a research protocol that obviously undermined a research subject's autonomy, then that would constitute a breach of the first sort of integrity.

The second sort of integrity is more like the integrity of a border. Policies or practices that compromise the integrity of the research project on this conception of integrity would be ones that undermine the ability of machinery of the human research enterprise to function. So, policies that would produce difficult or unfavourable conditions for collaboration for one or more of the many stakeholders in human research would be policies that compromise the integrity of the human research project.

An appeal to the second conception of integrity that I have outlined side-steps the objection raised by Wertheimer. While the first kind of integrity cannot be the source of new moral commitments, the second kind of integrity certainly can. Social value and scientific validity, two of the conditions identified by Emanuel et al. as requirements for ethical human research, seem to be in part grounded by a concern for the integrity of the human research project, in this second sense of integrity.

It is clear that a concern that developed along the lines of this second conception of integrity would not be one that depends on considerations of the welfare of the

human subjects of research at all. That is to say, this is a non-paternalistic justification for human subject protections, since the concerns are grounded on the impact on the human research project, and not on any particular human subject.

The empirical question

After Wertheimer raises the issue of what it would mean for something to constitute a breach of integrity, he goes on to say that concerns of a public loss of confidence in human research may give a good reason for constraining the sorts of human research that should be allowed. Ultimately, though, Wertheimer indicates that because it is a consequentialist argument, it would come down to an empirical question regarding whether or not it would be the case that an unregulated scheme would have the negative effects that we anticipate.[24]

The task that remains, on Wertheimer's account, is to show that an unregulated scheme for human subject protections will have bad consequences for the human research enterprise. Ideally this could be the subject of extended empirical study, with experiments measuring willingness to participate of the various stakeholders in human research in cases of greater and lesser regulation.

In lieu of such an undertaking, I will rather consider by analogy the case of regulation in other areas. I will identify other institutions that share similar characteristics where the same empirical question has been addressed. Namely, I will consider market regulation in America vs. market regulation in Europe, and make the claim that as far as the analogy holds between human research and market regulation, we can anticipate the same sorts of results in regulated and unregulated schemes for human research as have been seen for market regulation.

[24] (Wertheimer, 2011, pp. 40–41)

Analogy to other forms of market regulation

I will be pursuing an analogy between market regulation in other areas, and the regulation of subject protections in human research. It is commonly believed that the American labour market has been more successful than the European one, and that this success can be attributed to the higher regulation and socialisation of the European market over the American one. On the contrary, in Fligstein's *Lessons from Europe*, he shows that a greater percentage of the European workforce is in manufacture than the American one, and that by many measures it has enjoyed greater economic success, because of its market regulation, not in spite of it. Fligstein takes the European advantage to have come from "building positive rules of integration [by which] market regulators can work to ensure that markets remain open to competition ..."[25]

It turns out to be, in fact, rules aimed at producing the optimal conditions for many stakeholders working together that, in practice, make for a good collaborative project.

Economists generally recognise a number of positive functions of labour market regulation. Market regulations offset market failures that result from uncertainty and asymmetrical information in labour markets. They increase efficiency, because labour standards compel firms to raise efficiency or go under. They also lower costs, "because the welfare state greatly assists in socialising the costs of labour reproduction." Market regulations also encourage mass consumption, because minimum wage legislation increases the spending ability of low skill based mass production.[26]

[25] (Fligstein, 2010, p. 163)

[26] (Esping-Andersen & Regini, 2000, p. 12)

Hence, there are good economic reasons to favour certain kinds of regulation in a job market that do not appeal to paternalism. The human research enterprise is similar to such a market in a number of ways that make this analogy useful: There is a certain degree of information asymmetry in both a labour market and in human research. Recruiting workers and other stakeholders for a sustained term depends to some extent on the confidence in the market itself. In both the labour market and in human research, there are externalities that need to be considered. Both a labour market and the human research enterprise depend on a large number of stakeholders coming together, each with their own goals, to a sustained collaborative project.

Some political scientists go further than just saying that regulation encourages market efficiency. Carpenter argues,

> Our entire political system, our society, and our economy are built upon expectations—expectations of fairness, of safe and fraud-free transactions, of known risks (but also transparent, finite and reasonable risks), of reasonable and equitable treatment … Effective regulation helps to maintain a structure of beliefs that make prosperity and liberty possible … Regulation, in other words, in some sense creates the very possibility of marketplaces.[27]

Carpenter considers the case of drug markets, which share many of the same properties as a "market" for human research protocols. They are both "credence good" markets, in that they are characterised by learning constraints and appreciable information asymmetries. Carpenter argues that markets of that type are often vulnerable to equilibrium fraud and "lemons problems"—customers (in drug markets, consumers of drugs, and in a "market" for human research protocols, patients and in some cases REBs or physician-investigators) will repeatedly

[27] (Carpenter, 2010, p. 164)

purchase and use inferior commodities and less expensive products of lower quality will drive higher quality and more expensive products out of the market.[28]

Further, in drug markets, institutions of regulation may "serve to produce more information, and higher-quality information, than would be provided in their absence. … Approval regulation actually makes new and more sophisticated markets."[29]

Public confidence in medical research

Possibly the most obvious consequence of a human research project that was attempted without any regulation on high-risk research would be a loss in public confidence in medical research. Wertheimer indicates that this is one possible concern that may ground restrictions on human research practices.[30] One reason that such a loss of confidence would be a problem because it would make it difficult to recruit human subjects, or once recruited, to ensure their adherence.

Weakening human protections might bring about a "participate at your own risk" culture in medical research. Allowing very risky research would make it necessary to have multiple informed consent procedures, to ensure that patients really do know what they are getting into, and human research would begin to look like a very shady practice indeed. Human research would share many of the characteristics of a marketplace with profound informational and bargaining asymmetries.

If it were the case that public confidence in human research were lost, it would become difficult or impossible to recruit subjects for human research, which would undermine the effectiveness of human research as a whole.

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[28] (Carpenter, 2010, pp. 165–166)

[29] (Carpenter, 2010, p. 166)

[30] (Wertheimer, 2011, p. 21)

Recruiting of other stakeholders

While a negative impact on public confidence and the recruiting of subjects of human research is one consequence of an unregulated scheme that comes to mind very quickly, there are a great many more stakeholders and participants in human research than just the research subjects. Not only that, but on a completely unregulated scheme for human research, it would also be more difficult to recruit other such stakeholders for human research.

Human research is, by its nature, a collaborative undertaking. There are a great many different stakeholders in the project of human research—doctors, scientists, nurses, pharmaceutical companies, hospital administrators, human subjects, ethicists—and each of the participants has her own personal goals desires that she wants to pursue by entering into human research, and also takes on certain liabilities by virtue of her participation.

For example, a physician researcher may come to the human research enterprise in an attempt to produce reliable knowledge about treatment for a disease. She may also have the goal of advancing her career and receiving payment for the hours spent on her research. This researcher also incurs certain liabilities—she opens herself up to the possibility of legal action in the case that something goes wrong, or risk of reputational harm. Depending on the sorts of research that she engages in, she may in fact do damage to her career. There are other goals and liabilities that she will have, of course, and a similar analysis could be given for every person who comes together to make human research possible.

Considerations for what limitations should be placed on human research must be motivated in part, at least, by what conditions would make collaboration among these essential stakeholders possible, if not perfectly ideal.

Because other stakeholders besides the investigator and the human subject are party to any research protocol, the recruitment of human research subjects and

other stakeholders is a non-paternalistic concern that may ground restrictions on what research should be allowed to take place.

Consumption of limited resources for human research

The resources that are available for human research are not infinite, and go beyond just what the sponsor, investigator and subject bring to the study.[31] Third parties, such as governments or other donors often pay for the hospitals and research centres where such research takes place. These resources also include the pool of available volunteers; time and specialised expertise; as well as any equipment necessary to pursue human research.

Because all human research consumes the limited resources available to the research project and incurs costs to other third parties, there are good reasons to impose restrictions on what research should be allowed that go beyond the concerns for the preferences or goals of the investigators and subjects. A low-quality study will be competing for many of the same resources as a high-quality study, and this would impact more than just the sponsor, the physician-investigators and the subjects in question.

Quality of research and credence goods

Let us return for a moment to the analogy with other forms of market protection. Contrary to popular belief, many markets that are better regulated perform better in a number of ways than markets that are unregulated. As we saw earlier, positive rules of integration and even market regulations help to provide good terms on which stakeholders in that market can participate in this collaborative project.[32] Fligstein demonstrates this through the example of the European market, which has

[31] (London, Kimmelman, & Emborg, 2010, p. 829)

[32] (Fligstein, 2010, p. 163)

more market regulations than the American market, but a greater percentage of its workforce in manufacturing employment.

The positive effects of market regulation can also be seen in other cases. Banking and financial services are highly regulated in order to protect the market against market failures and to protect consumer confidence.[33] These regulations also prevent adverse selection,[34] moral hazard and "grid lock."[35] Adverse selection occurs when the value of a financial product can only be known by the consumer over the long term, and so low-quality products are rewarded over higher-quality ones. Moral hazard is the situation that occurs when "good firms are induced to behave badly because they either see bad behaviour in others, or have no assurance that competitors will behave well."[36] "Grid lock" refers to competitive conditions which may induce banks to "behave in line with other banks and incur excessive risk in the process." [37]

In the cases of the European market and financial institutions, market regulation actually helped to sustain and even produced new markets. There is reason to think that, far from stifling human research and making it more difficult for researchers to engage in studies that will produce useful knowledge, regulations on human research actually make the human research project more effective and produce more and better research than would be the case on an unregulated scheme.

Making the economic analogy more specific, I will argue that medical research trials are 'credence goods.' That is to say, they are members of a set of goods that is

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[33] (Llewellyn, 1999, p. 52)

[34] (Llewellyn, 1999, p. 29)

[35] (Llewellyn, 1999, p. 48)

[36] (Llewellyn, 1999, p. 27)

[37] (Llewellyn, 1999, p. 27)

defined by the property that it is very difficult for consumers to judge their quality. In markets for credence goods, regulation is especially important, because unregulated markets for credence goods tend to produce low-quality products, since the consumers can't discern between them.

For other sorts of goods, because consumers can tell the difference between low-quality goods and higher-quality options, the market system will reward the high-quality products because they will be chosen by consumers. Conversely, low-quality products will be penalised because consumers will not choose them.

A good non-medical example would be financial investment products. There are very stringent guidelines regarding advertisement and the claims that salesmen can make regarding financial investment products. These restrictions are often justified on the basis that a completely "free market" system that did not impose such restrictions would not reward high-quality products and penalise low-quality products, since consumers do not generally have the ability to discern between them accurately. The justification for subject protections in this case is not based on a paternalistic concern for consumers, but rather it is based on a concern for protection of the market itself—if there were no market restrictions in the case of financial investment products, consumers would avoid them entirely, since they would not be to discern between a good investment and a poor one.

A report from the Harvard Kennedy School supports this conclusion:

> Consumers with cognitive limitations may use rules of thumb to guide their behavior. One such rule of thumb is to avoid the use of certain financial products altogether … This has been interpreted as a lack of trust in the financial system … there is a case for regulation to improve consumer trust through such things as restrictions on insider trading,

> suitability and fiduciary requirements, and other measures that convey a sense of strong supervisory oversight.[38]

Similarly, "clinical trial protocols are examples of what economists call 'credence goods.'"[39] The "consumers" (potential subjects of human research) are not in a position to be able to judge accurately between good and bad research protocols. A "free market" system would not reward "producers of high quality goods" (scientifically valid or valuable research protocols) and penalise "producers of low-quality goods" (studies that are less social valuable or scientifically valid). It would be very difficult, for example, for most participants in human research to be able to tell if a study is underpowered to answer the question it means to with any statistical significance. They would also be unable to tell whether a drug is likely to benefit them or not. An unregulated scheme for human research would suffer from the same pressures as an unregulated market for credence goods, so the "market for human research" (the human research enterprise) would be hurt.

Hence, for the protection of the human research enterprise, and not necessarily for the protection of the human research subject, there should be restrictions on what sorts of human research is allowed. This restriction is non-paternalistic because it is justified on the basis of preserving the collaborative project of human research, and not on the basis of protecting the welfare of the human research subjects. In the same way that restrictions on the sorts of advertising that can be done for financial investment products can be justified on the basis of protecting the financial investment market, restrictions on very risky forms of human research can be justified by appeal to protection of the human research enterprise.

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[38] (Campbell, Jackson, Madrian, & Tufano, 2010, p. 10)

[39] (London, et al., 2010, p. 830)

Cascading consequences

There may be other repercussions for allowing high-risk research that should be considered: London et al. argue that "research programmes are joined or abandoned on the basis of perceived beliefs of others."[40] That is, regardless of the harm that accrues to the subject of a human research protocol (or not), if that research is perceived in certain ways, it may cause other human subjects to be less likely to participate in human research, or it may make it harder to recruit physician-investigators, or other stakeholders to the project. This may affect not only research in related fields, but the entire human research project generally.

A scientist's reputation is important, after all. A survey was conducted of over 400 PhD students. The top prospective employers were ranked and those employers were evaluated for their reputation for publication. The researchers suggest "publication may indeed be a signalling device, thus providing a higher degree of visibility, that prospective employees consider."[41]

So it may be legitimate to impose restrictions on what research should be allowed for reasons other than the protection of the subject, because allowing such research would have a deleterious impact on the ability of the human research enterprise to undertake other research projects.

Possible objections

Human research is a collaborative project that has many characteristics that are analogous to markets, but because of its nature as an on-going cooperative enterprise, it could be argued that it is dissimilar to simple market transactions, which might weaken the support for the conclusion that regulation of human

[40] (London, et al., 2010, p. 829)

[41] (McMillan & Deeds, 1998)

research would have a positive effect on the human research enterprise in the same way it does for its market counterparts.

To resolve this question, let us consider what it is that makes cooperation work in the case of collective action problems. In *The Conditions for Successful Collective Action*, Libecap considers three empirical case studies to try to determine what conditions favour collective action and concludes that it is ultimately the private welfare of the parties involved that decides whether collective action will take place.[42]

This lines up very nicely with the integrity thesis. Conditions that best allow all the stakeholders in human research to pursue their own individual ends while producing socially valuable medical knowledge will best protect the integrity of scientific research.

Applying this framework to other cases

In this chapter, I have mainly explored the consequences to the human research project of an unregulated scheme for research protocols, and shown that beyond a paternalistic concern for the welfare of the subject, there are legitimate reasons to place limitations on human research.

This non-paternalistic framework for thinking about limiting human research protocols would also apply in cases where there is minimal harm to the human subject. That is to say, even in a case where the human subject was at very minimal risk of harm, rather than in the high-risk cases that I have mostly been considering so far, there might be reasons for restricting the sorts of research that are permissible, that go beyond just the largely paternalistic concerns that I outlined in my first chapter.

[42] (Libecap, 1994, pp. 589–590)

In my next chapter, I will discuss the case of phase IV seeding studies, which are generally very low-risk studies, and show that there may be non-paternalistic reasons to criticise them.

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Chapter 3 : Phase IV seeding studies

Introduction

Let us return to the case of Dan Markingson, who committed suicide while enrolled in a phase IV trial of an atypical antipsychotic Risperdal. In this chapter, I will describe how such phase IV studies can be criticised without appealing to paternalistic foundations. In my previous chapter, I outlined a justification for subject protections on the basis of ensuring the integrity of human research.

Phase IV studies make an excellent case for the integrity thesis because by definition, a phase IV study is one where the drug or other treatment has already been approved for regular medical use in humans. There are of course, some cases of phase IV studies where the risk to patient-subjects is greater than that of standard care, but provided appropriate conduct and oversight, the risk to patient-subjects in a phase IV study will generally be very low.

I will begin this chapter by describing what a phase IV drug study is and distinguishing what separates a "good" one from a "bad" one. I will introduce and use examples like the ADVANTAGE seeding study to illustrate a number of the criticisms and objections to phase IV studies. I will consider four common types of arguments against phase IV seeding studies: the hidden intentions behind seeding studies, financial incentives for physician investigators, concerns regarding patient privacy, and unnecessary harm to patients in phase IV studies. I will indicate that all of these kinds of objections are rooted in concerns for risk vs. benefit and that none of these objections are very satisfying. Further, many of these risk vs. benefit arguments hint at a commitment to a grounds for objection to seeding studies that goes beyond just concerns for subject welfare.

I will conclude by outlining what it would mean to criticise a phase IV seeding study on the basis of the integrity of human research, and then I will show how this is different from the other risk-benefit criticisms. I will end this chapter by responding

to objections to a criticism of phase IV seeding studies on the basis of the integrity of the human research project, and discuss who bears the responsibility for ensuring the integrity of human research.

What is a phase IV study?

Phase IV studies are studies of drugs that have already been approved for regular medical use in humans. A phase IV study should be designed to provide data concerning "effectiveness and safety for the target population or important subgroups of patients."[43] Further, phase IV studies include assessments for "quality of life, functional capacity, satisfaction with treatment and health economics."[44] The drug being studied is provided free of charge by the sponsor of the phase IV study—often the company that produces the drug.[45] Phase IV studies are conducted according to a protocol that is based on what the investigators wish to study, and the treatment is not necessarily catered to respond to a particular patient's medical needs. For example, participation in a phase IV study may be conditional on the subject taking a particular dosage of the drug in question, when a physician might have otherwise changed the dosage to respond to the subject's particular reaction to it. This may make participation in some phase IV studies slightly more risky than standard treatment, however in some phase IV studies, patient compliance with the prescription of the drug is not controlled for at all, and there is no particular protocol being followed, aside from the "actual routine practice of the treating physician."[46]

[43] (Sampalis, 2007, p. 14)

[44] (Sampalis, 2007, p. 14)

[45] (Sampalis, 2007, p. 14)

[46] (Sampalis, 2007, p. 14)

Phase IV studies are meant to be research that fills an important gap in our knowledge of the effects of drugs on humans—namely, they should be designed to give us information regarding the safety and effectiveness of drugs that have already been approved and that are now being sold for use in humans.

"Good" and "bad" phase IV studies

There are some "good" phase IV studies and some "bad" ones. By this, I mean that while some phase IV studies are a useful and necessary part of the machinery of human research, many are legitimately the subjects of intense criticism.

One criterion for identifying a good phase IV study would be that it should provide reliable information regarding comparative effectiveness and safety of drugs that have been already approved for use in humans. A good phase IV study should be designed to answer a question that has medical, social or scientific value. It should also be statistically powerful enough to provide scientifically valuable information.

Many phase IV studies are designed in a relatively inefficient way, when evaluated from the perspective of their officially stated goals. Many phase IV studies recruit hundreds of physicians, with only a few patients each.[47] The reason for this inefficient design is because the actual purpose behind many phase IV studies is to market the drugs under study to the physicians who are acting as "investigators" in the phase IV trial.

In fact, phase IV studies are often funded directly by the marketing departments of large pharmaceutical companies.[48] They are sometimes referred to as "seeding" studies, because the drug company uses studies like these to market the drugs to physicians, in an attempt to influence what drugs they prescribe through a combination of professional flattery, financial incentives and habituation. Physicians

[47] (Sox & Rennie, 2008, p. 279)

[48] (Privitera, 2003, p. 741)

are flattered by recruiters for phase IV studies—they are often told they are being recruited to be an investigator for the study because of their professional influence. For their work in the study, physicians may also be given very large financial compensation, disproportionate to the work done.[49]

> These studies are usually intended to increase use of a manufacturer's product and sometimes lack scientific integrity. There is usually a marketing component to these studies, and by doing them the pharmaceutical companies get to speak with the doctors about a product and ultimately get them used to prescribing it. The intent is to influence physician and patient behaviour.[50]

This is done because, from the perspective of the drug company, it works. Seeding trials are one of the "main techniques used by drug companies to promote 'me too' drugs in a crowded therapeutic class."[51] ("Me too" drugs are drugs that are "chemically related to the prototype, or other chemical compounds which have an identical mechanism of action."[52]) Because this marketing is done under the guise of research, it allows drug companies to circumvent rules against directly inducing physicians to prescribe their drug.[53]

The publication of the seeding studies also act as an inducement for physician-investigators who are looking to advance their careers by adding more publication

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[49] (Sox & Rennie, 2008, p. 279)

[50] (Pena, 2003, p. 3)

[51] (Psaty & Rennie, 2006, p. 2787)

[52] (Garattini, 1997, p. 283)

[53] (Psaty & Rennie, 2006, p. 2787)

credits to their CV's.[54] At the same time, a publication is an advertisement for the drug under study.

There are some obvious signs that a phase IV study is a "bad" one. One common mark is the lack of a control group. In *The European Journal of Clinical Pharmacology*, a review of thirty-five post-marketing studies identified by "hand-searching through medical journals, writing to pharmaceutical manufacturers and using MEDLINE," not a single post-marketing study included a control group.[55] Others include incomplete follow-up, unduly high compensation for physicians, unpublished results,[56] or an unimportant question asked and answered (or failed to have been answered) by the trial.[57] Conducting studies with a duration that is too short to give accurate data regarding chronic conditions and adverse drug reactions is also very common. The median observation time for the previously mentioned review of thirty-five post-marketing studies found there to be a duration of only eight weeks. None was more than 48 weeks long.[58] This is not a long enough time to observe new adverse drug reactions (or ADR). Only one new ADR was discovered among the thirty-five studies reviewed.[59] Phase IV studies also very commonly overemphasise efficacy data.[60] Some studies with unfavourable results are never published, and in cases where the results are more in favour of the interests of the

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[54] (Sox & Rennie, 2008, p. 279)

[55] (Hasford & Lamprecht, 1998, p. 369)

[56] (Psaty & Rennie, 2006, p. 2787); (Privitera, 2003, p. 742)

[57] (Psaty & Rennie, 2006, pp. 2787–2788)

[58] (Hasford & Lamprecht, 1998, p. 369)

[59] (Hasford & Lamprecht, 1998, p. 370)

[60] (Privitera, 2003, p. 742)

marketers, some other studies are published repeatedly, sometimes under different authors' names.[61]

"Good" phase IV studies are harder to discern. The presence of a randomised design of a phase IV study is not a sufficient condition that a study is of high quality. There are standards of scientific rigour that must be followed, and there must, of course, be a favourable risk-benefit ratio, but I will be arguing later in this chapter that for a phase IV study to be a good one, the integrity of human research must be maintained, and the collaborative project of human research in general—and post-marketing research in particular—must not be undermined.

Having looked at phase IV studies and what makes them good or bad, let us turn to a few examples of phase IV studies and how they have been criticised.

The HOPE clinic

The HOPE clinic, funded by Eli Lilly and Company, was a post-marketing study done on Zyprexia, an antipsychotic drug. Participants were randomly assigned to receive either the drug or a placebo for a year, in order to study the effects of the drug on teenagers showing early signs of schizophrenia.[62]

Jonathan Fast, a social worker, criticised this study mainly on the harmful effects of the study toward its participants. He cited an extensive list of side effects of the drug under study[63] and argues that the study is unethical, since "Prescribing a powerful antipsychotic to a teenager who may not be headed down the path to schizophrenia cannot possibly contribute to his or her well-being."[64] He concluded his commentary

[61] (Psaty & Rennie, 2006, p. 2788)

[62] (Fast, 2003, p. 425)

[63] (Fast, 2003, p. 426)

[64] (Fast, 2003, p. 426)

by remarking that "it is not just a question of [financial] fraud, but also the risk of endangering patients' lives and well-being" that gives moral force to his critique of the HOPE clinic and other studies like it.

Fast's criticism of the HOPE clinic takes us down the well-trodden path of paternalism that I outline in my first chapter. The force of Fast's argument comes from an appeal to the well-being of the subject of the study—despite the fact that the study has been independently reviewed for scientific merit and a favourable risk-benefit ratio, and subjects have consented to participate in the study, he would condemn the study on the grounds that the risks to the subjects are too great.

The STEPS Neurontin study

STEPS (Study of Neurontin: Titration to Effectiveness and Profile of Safety) was a phase IV trial of Neurontin. Neurontin is a drug that was approved by the FDA for adjunctive treatment of partial complex seizures in 1993, but by the mid- to late 1990's it was being "widely used for the off-label treatment of pain syndromes and psychiatric conditions."[65]

Neurontin first came under scrutiny when David Franklin, an employee at Parke-Davis, grew concerned that he was participating in illegal marketing. Franklin was told by a Parke-Davis executive,

> I want you out there every day selling Neurontin. … We all know Neurontin's not growing for adjunctive therapy, [what Neurontin was approved for] besides that's not where the money is. Pain management, now that's money. Monotherapy, that's money. … We can't wait for [physicians] to ask, we need [to] get out there and tell them up front. … Neurontin for pain, Neurontin for monotherapy, Neurontin for bipolar, Neurontin for everything. I don't want to see a

[65] (Steinman, Bero, Chren, & Landefeld, 2006, p. 284)

> single patient coming off Neurontin before they've been up to at least 4800 mg/day.[66]

Franklin left Parke-Davis and filed a "whistle-blower" lawsuit for off-label marketing of Neurontin. This case brought more than 8000 pages of corporate documentation regarding Neurontin's marketing into the public domain. [67]

STEPS was an un-controlled open-label study in which more than 700 physicians (with an average of 3 patients) were instructed to use Neurontin in patient-subjects with epilepsy until they were seizure-free or until they reached a dosage twice that of the maximum FDA-approved limit.[68]

"Research and publications on gabapentin [Neurontin] served as key elements in the marketing strategy for the drug."[69] In some cases, such as monotherapy for epilepsy, research was conducted in an attempt to obtain another on-label indication for Neurontin from the FDA, but in other cases, Parke-Davis' research into Neurontin was aimed at another goal entirely: Phase IV research into Neurontin was being used to encourage off-label use of the drug through research and publishing articles in medical literature.[70]

Parke-Davis published its own trials, and hired medical education companies to develop articles on the drug for "$13,375 to $18,000 per article, including a $1000 honorarium for the physician or pharmacist author."[71] Parke-Davis documents

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[66] (Landefeld & Steinman, 2009, p. 104)

[67] (Landefeld & Steinman, 2009, p. 104)

[68] (Steinman, et al., 2006, pp. 289–290)

[69] (Steinman, et al., 2006, p. 288)

[70] (Steinman, et al., 2006, p. 288)

[71] (Steinman, et al., 2006, p. 288)

revealed that, on instruction from the "core marketing team," unfavourable trials were not published,[72] and that these medical education companies were instructed to take "particular interest in proper dosing and titration as well as emerging [off-label] uses."[73] Internal documents indicate that the purpose of one of the large seeding trials for Neurontin was to "teach physicians to titrate Neurontin to clinical effect" and "to give neurologists the opportunity to titrate to higher doses [up to twice the FDA-approved limit] when needed."[74]

Ultimately, the drug manufacturer pled guilty and paid more than $430 million for illegal promotion of unapproved uses of Neurontin.[75] The marketing practices used by Parke-Davis to promote off-label uses of Neurontin have come under scrutiny by critics who say that such off-label marketing affects safety.[76] Specifically, critics worry about increased risk of suicide among those who take the drug.[77] This is a clear appeal to the welfare of the subjects of the phase IV study in critiquing the study itself.

Beyond the paternalistic criticisms of the STEPS trial, there have been a number of integrity-like critiques of Neurontin by other commentators. An article by Mitka argues that the main problem with the conduct of Parke-Davis in STEPS was that it allows "industry [to] use research to advance marketing goals."[78]

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[72] (Mitka, 2008, p. 1760)

[73] (Steinman, et al., 2006, p. 288)

[74] (Landefeld & Steinman, 2009, p. 105)

[75] (Mitka, 2008, p. 1760)

[76] (Jablow, 2004)

[77] (Rosack, 2005)

[78] (Mitka, 2008, p. 1759)

Landefeld and Steinman also argue that "'drastic action is essential' to preserve the integrity of medical science and to justify public trust."[79]

The ENHANCE Vytorin trial

Vytorin is a combination of ezetimibe and simvastatin, which was approved by the FDA in July 2004 for reducing levels of low-density lipoproteins.[80] The ENHANCE study was an active comparator trial where participants were randomised between receiving Vytorin and simvastatin alone. This trial used a surrogate end point, vascular ultrasound, rather than a clinical endpoint such as heart attack or stroke.[81]

ENHANCE came under scrutiny because of a two-year delay in publishing results, and changing the primary endpoint before the study was published.[82]

Silverman criticised ENHANCE by appealing directly to the benefit of the patients in the study. He wrote, "The trial, of course, ended in failure … raising questions about whether patients received sufficient benefit …"[83]

Greenland and Lloyd-Jones criticise ENHANCE on a number of grounds, including the design of the study itself. ENHANCE had some of the most problematic characteristics identified in the section on "bad" phase IV studies—it was not designed to answer a valuable question. Greenland and Lloyd-Jones argue that "a negative outcome most likely would not lead to a different clinical conclusion than a positive outcome, and it is unlikely that the ENHANCE results could have affected

[79] (Landefeld & Steinman, 2009, p. 105)

[80] (Greenland & Lloyd-Jones, 2008)

[81] (Greenland & Lloyd-Jones, 2008, p. 953)

[82] (Silverman, 2008)

[83] (Silverman, 2010)

approval of ezetimibe by the FDA for any indication."[84] Further, they argue that ENHANCE was not conducted for the purpose of seeking a new drug indication, since it was statistically underpowered for clinical endpoints.

Finally, these commentators infer from their analysis of the study design, "Given these facts, one reasonable conclusion is that ENHANCE may have been undertaken primarily or exclusively as a marketing tool."[85]

The criticism that Greenland and Lloyd-Jones offer is worth noting because they sum up their argument by appealing both to the integrity of scientific research, and to the welfare of patient-subjects enrolled in the ENHANCE study.

> Trials designed for marketing purposes should not be conducted. Such trials divert attention and resources away from the critically important information needed from clinical end point studies, pose a serious risk to the integrity of the scientific process in clinical research, and may place patients at unnecessary risk.[86]

In the other example cases provided, there are clear cases where patients were harmed during the course of the study: The criticism of HOPE is entirely on the basis of the risk to the patient-subjects and in the STEPS trial, Neurontin was administered to hundreds of patient-subjects at doses up to twice the maximum FDA-approved amount.

This is not the case with ENHANCE, and yet the paternalistic language of benefit vs. harm for patient-subjects is still invoked in these critiques.

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[84] (Greenland & Lloyd-Jones, 2008, p. 954)

[85] (Greenland & Lloyd-Jones, 2008, p. 954)

[86] (Greenland & Lloyd-Jones, 2008, p. 954)

The CAFE antipsychotic study

The CAFE study was also a post-marketing study of an antipsychotic drug, Risperdal. This drug is often prescribed for patients with schizophrenia or bipolar disorder. The CAFE antipsychotic study has been widely criticised because during the course of the study, Dan Markingson committed suicide.

Carl Elliott's main criticism of the 2003 CAFE[87] antipsychotic study is that the study was one where risk was imposed on the subjects for the benefit of AstraZeneca's marketing. In his words,

> The ethical breach was built into the study from the start. It is one thing to ask people to take risks for science, or the common good, or to help other people. It is another thing to ask them to risk their lives for the marketing goals of AstraZeneca.[88]

The study was randomised and double-blinded, meaning that a computer assigned Markingson to his treatment, one of three antipsychotic drugs, olanzapine, quetiapine and risperidone.[89] Markingson was recruited to CAFE as a condition of an involuntary commitment order, but even Elliot, a critic of the study, remarks that Markingson "was a legitimate target for recruitment,"[90] since he was known to be at risk of homicide, not suicide.

By the end of CAFE, there was no significant difference found among the three drugs in terms of the all-cause discontinuation rate. "However, the analysis of the

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[87] Comparison of Atypicals in First Episode

[88] (Elliott, 2010)

[89] (AstraZeneca, 2010)

[90] (Elliott, 2010)

improvement of positive symptoms showed that patients on olanzapine improved more than those on quetiapine."[91]

Markingson's suicide brought considerable criticism of the study, the university and the institution of human research generally, which I will discuss in more detail in the section on "cascading effects."

Elliott criticises CAFE on the grounds that the research was too risky, considering that the study was a seeding study, run mainly for the benefit of AstraZeneca's marketing. This criticism has a paternalistic basis. It is because the study was risky that Elliott has a problem with the CAFE study.

The ADVANTAGE seeding study

The ADVANTAGE[92] study is an example of a phase IV study that was originally published by the *Annals of Internal Medicine* as a "large, community-based, randomized comparison of a cyclooxygenase-2 inhibitor (Vioxx [refcoxib]) and a nonselective cyclooxygenase inhibitor (naproxen)."[93] Three years later, through the use of publicly accessible trial documents, including emails sent by Merck employees, Dr. David Egilman was able to disclose the true intent of the ADVANTAGE trial in a letter to the editor, as quoted here:

> Internal Merck documents reveal that the ADVANTAGE trial did not have a medical purpose. Instead it was a "seeding trial," meant to seed the medical community with Merck's new drug before it was approved for the market. … The real participants in the trial were the physician

[91] (Moyer, 2005)

[92] Assessment of Differences between Vioxx And Naproxen To Ascertain Gastrointestinal tolerability and Effectiveness

[93] (Sox & Rennie, 2008, p. 279)

> "investigators" (nonparticipants served as controls) who were chosen to participate by Merck sales representatives.[94]

This study is unique in that there is direct evidence in the form of internal communications among Merck employees that indicate clearly the intent of the drug company in this study—namely, the marketing of drugs to physicians.

In *Seeding Trials: Just Say "No,"* Sox criticises Merck for the clandestine nature of the ADVANTAGE study. He writes,

> The documents do tell us that deception is the key to a successful seeding trial. That information—once it becomes general knowledge—could be the fatal blow for seeding trials. Institutional review boards, whose purpose is to protect humans who participate in research, would probably not likely approve an action that places patients in harms' way in order to influence physicians' prescribing habits.[95]

Sox's criticism rests on the assumption that human subjects in the ADVANTAGE study were placed "in harms' way" by participation. This is a clear appeal to paternalism in his critique of the ADVANTAGE phase IV seeding study.

I have argued that in each of the examples of seeding studies, the main criticism is one that is paternalistic. In the following sections, I will outline some of the common objections to seeding studies. I will show how each one is an appeal to the risk vs. benefit for the subjects of the research, and indicate why argumentation along the lines of a risk-benefit analysis are difficult to maintain and do not provide a legitimate reason for criticising phase IV seeding studies.

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[94] (Egilman & Presler, 2006, p. 781)

[95] (Sox & Rennie, 2008, p. 279)

The hidden intentions behind seeding studies

In an analysis of Merck's internal documents relating to the ADVANTAGE study, Hill et al. make an argument against bad phase IV studies from the hidden nature of such studies, as I quote here:

> [T]he primary marketing objectives of seeding trials are hidden from the public, the medical profession, and institutional review board members, preventing them from making a fully informed decision about the balance of benefits and harms to themselves and society.[96]

The main objection here is that a fully informed decision regarding the balance of benefits and harms is impossible, if the true intention of a research protocol is hidden. Implied is the conclusion that this is unethical because people may enrol in such a study and may incur a greater risk than they would have otherwise, had they known.

Responding to the criticism that the hidden intention of seeding studies makes it impossible to accurately judge the risks of a study, this is a difficult position to maintain. Not knowing some of the details of the protocol would certainly impair one's judgement of the risks and benefits involved, but it is hard to see how not knowing the intentions behind a study would make an evaluation of the risks of the study more difficult, especially if the study was reviewed by a research ethics board and found to have an acceptable risk-benefit ratio.

Financial incentives for physician investigators may cause harm to patients

One common criticism against phase IV studies that is difficult to maintain under close scrutiny is that patients may be harmed by the fact that their physicians are

[96] (Hill, Ross, Egilman, & Krumholz, 2008, p. 256)

being motivated through financial incentives.[97] Arguably, doctors cannot be trusted to place the patient's interests above his or her personal gain. Rao and Cassia (Fast, 2003; Rao & Saint Cassia, 2002) make the argument that financial incentives for physician investigators will "corrupt the ideal" of a physician being in equipoise between two treatments, placing the subjects at risk. They also argue that by withholding information from patients regarding such incentives, we treat them as less than "equal partners" in the process of human research.[98]

In some cases, far from being active in shaping the direction of the research, patients are not aware that they are participating in a clinical study.[99] It is also difficult to maintain the position that physicians' judgement would be impaired to the detriment of patients by financial incentives that would make equipoise difficult to establish. It is easy to see how financial inducement for prescription of a drug in a non-research clinical setting would be problematic, but if phase IV research is prospectively reviewed by a research ethics board and shown to meet conditions of clinical equipoise and all participants meet the study's eligibility requirements, it is hard to see how a financial motivation for a physician to recruit subjects could be harmful. First, the physicians who are recipients of the financial inducements for acting as investigators are not solely responsible for evaluating the protocol for clinical equipoise. This responsibility is shared with the research ethics board. Second, often patients are randomised between arms of the trial. Physician judgement is not used for deciding whether a patient receives one treatment or another in the first place. It could be argued that because physicians are given financial incentives to enrol patients, that some subjects who should not be in the study at all might be enrolled. It would be a large oversight indeed on a doctor's part, for her to admit a patient to a study for a drug that she didn't need in the first place,

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[97] (Rao & Saint Cassia, 2002, p. 36)

[98] (Rao & Saint Cassia, 2002, pp. 36–37)

[99] (La Puma, Stocking, Rhoades, & Darling, 1995, p. 1660)

and it is not likely that the financial incentive for enrolling patients would cause a physician to make such a bad decision.

These same inducements for physician-investigators exist for drug trials in phases I-III, which carry a much higher risk than a phase IV study, and yet there are few criticisms of such studies on these grounds.

Concerns regarding patient privacy

One possible objection to phase IV and other post-marketing research is that patients' privacy may be violated. It can be argued that a patient could be harmed by post-marketing research because her private health information is released without her consent. This could occur by bad anonymisation of data, or by the risk that a patient-subject's chart would be read by someone who doesn't need to see it, in the course of the research protocol.

While I am inclined to agree with the conclusions of these criticisms—that there is something morally suspect about phase IV studies—the sense in which a patient is *harmed* seems small or avoidable. It is hard to take a case of violating a patient's privacy as a compelling reason to criticise phase IV research generally—all other human research is vulnerable to the same criticism. Also, objections regarding a patient's privacy can be addressed by tightening up restrictions on the use of patient data. If such measures were successfully taken though, and to everyone's satisfaction, there were no concerns regarding patient privacy, I think we would still have the same uneasiness regarding phase IV and other post-marketing studies.

Patients incur harm unnecessarily in seeding studies

In Egilman's letter to the editor, he levels one main criticism against such phase IV studies. He writes, "The deaths of trial patients receiving Vioxx were deaths in an unnecessary trial."[100] That is to say, his main criticism is that there was harm to

[100] (Egilman & Presler, 2006, p. 781)

participants in the study, and because the study was not one where the harm was outweighed by the value of the study, there is a moral problem with this kind of phase IV study.

In his editorial, Sox mentions twice that the problem with the ADVANTAGE study was the harm toward human subjects in such research protocols. He writes,

> Institutional review boards, whose purpose is to protect humans who participate in research, would probably not likely approve an action that places patients *in harms' way* in order to influence physicians' prescribing habits. … Few physicians would knowingly enrol their patients in a study that placed them *at risk* in order to provide a company with a marketing advantage, and few patients would agree to participate.[101]

At their heart, these common arguments against the current practice in phase IV studies are based on concerns for the research subject's welfare.

One major problem with trying to criticise a phase IV study on the basis of an unfavourable risk-benefit analysis is that phase IV studies don't carry much risk at all to human subjects. By definition, a phase IV study is one that occurs *after* the drug has been approved for regular medical use in humans.

The risk in taking the drug under study for the subject consuming the drug is no greater than the risk to a patient in a clinical non-research setting who has been prescribed the drug.

Phase IV studies are often comparisons between two already-approved drugs. This is why drug companies use these studies for marketing purposes—they think (and often they can) influence physicians to prescribe the drug being tested more. For this reason, human research subjects in phase IV studies are often allocated to one

[101] (Sox & Rennie, 2008, p. 279, emphasis added)

treatment or another based on a principle called “clinical equipoise”—that is to say, if two drugs are in equipoise, there should be no prior preference within the community of experts between the arm of the study where the subjects are given the drug under study, and the arm of the study where subjects are given the drug that is the current market leader.[102] It's hard to see how there could be harm in randomising patients between two drugs for which there is genuine medical uncertainty as to which is better. Phase IV studies are usually equivalence or non-inferiority trials.[103] As such, risk-based arguments against phase IV studies devolve into a criticism of either an REB’s ability to determine clinical equipoise or a criticism of a physician to exercise sound medical judgement regarding the eligibility of certain patient-subjects.

Unless the research ethics board and the physician-investigators have missed a crucial part in a protocol, like admitting a subject who is ineligible for the study, the fact is, there isn't much risk to a human subject who participates in a phase IV study, and it's very difficult to make a good argument against phase IV studies on the basis of the welfare of the subjects of the study. Many postmarketing studies involve patient-subjects who are already taking the drug, or who decided to start taking the drug before being invited to the study. Some participants in a phase IV study might be subject to research risks, such as blood draws for non-clinical purposes or a chart review, but these risks are minimal. Even if reforms were made such that all the criticisms regarding the risk vs. benefit for patient-subjects were adequately addressed to everyone's satisfaction, that would not change what we find to be morally questionable about these studies. If the main criticism of Egilman’s is that “the deaths of trial patients receiving Vioxx were deaths in an unnecessary trial,”[104]

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[102] (Freedman, 1987, p. 141), (Corrigan, 2002, p. 503)

[103] (Glasser, Salas, & Delzell, 2007, p. 1078)

[104] (Egilman & Presler, 2006, p. 781)

then one possible solution to the problem would be to try to decrease the amount of risk to the subjects of such a trial.

This is not a solution because even if it were found to be the case that no human subjects actually were being harmed, or if the practice of phase IV studies were changed such that there actually was no harm to its subjects, I think we would still find there to be something morally problematic about the practice of phase IV studies. It is not really the harm to the patients *per se* that is giving us misgivings about these studies.

Criticising on the basis of the integrity of human research

Even though an appeal to the welfare of the human subjects will be of little avail, there have been a few hints at another commitment that might ground a legitimate objection to phase IV seeding studies. When Egilman writes, "The deaths of trial patients receiving Vioxx were deaths in an unnecessary trial,"[105] the emphasis is of course on the fact that harm has occurred, but it is the unnecessary nature of the trial that makes it so morally egregious. That is, most people would be all right with medical research causing some harm, even deaths. It is when it is for something *unnecessary* that occurs under the banner of research, that there is a major moral problem.

Sox et al., in their editorial on the ADVANTAGE seeding study, while they are primarily arguing on the basis of the harm or risk to which a subject in such a research protocol would be subject, they still hint at another reason why we would want to reject such research practices as unethical—the recruitment of different stakeholders into the collaborative research project would be threatened. He writes, "Few physicians would knowingly enrol their patients … in order to provide a company with a marketing advantage, and few patients would agree to

[105] (Egilman & Presler, 2006, p. 781)

participate."[106] It is likely that Sox takes the fact that physicians and patients would not participate in seeding trials only as evidence that there is something wrong. I am not suggesting that he would take the position that their reluctance to join in the collaborative project of human research would be the reason that seeding trials are unethical. That said, many of us seem to share a moral intuition that there is something wrong, beyond the harm that may occur to subjects, and this seems to be a very clear indication of what that might be.

The integrity of the human research project is a moral concern that should constrain what kinds of research is and is not allowed to occur and one that I think best explains our moral intuition that there is something wrong with phase IV seeding studies. By this, I mean that the human research enterprise is a collaborative project that requires the cooperation of a great number of stakeholders. These stakeholders include physician investigators, patient-subjects, nurses, pharmaceutical companies, REB's, hospital administrators, etc. All of these come to human research with different motivations and with different goals that they mean to pursue through the means of human research.

By violating the integrity of human research, we undermine the terms under which these stakeholders in human research are able to pursue their own ends within the human research project. If it were the case that studies solely aimed at marketing were allowed, human research would not be completely destroyed. Rather, a new collaborative enterprise would emerge—one with different stakeholders and different goals. The problem would be that the new collaborative project would not meet the socially valuable goal of producing scientifically valid medical knowledge, and this is the goal toward which scientific research is publicly subsidised either directly, by funding research institutions or through the subsidisation of the education of medical professionals who participate.

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[106] (Sox & Rennie, 2008, p. 279)

By “the integrity of human research,” I do not mean the integrity that comes from closely adhering to one’s stated values. To violate that sort of integrity would mean doing some action that has been deemed to be wrong by the human research establishment, and so violating the integrity of one's principles. If that were the case, as Wertheimer notes,[107] an appeal to “integrity” of this sort could not be the basis for saying that something is wrong (since, in order for something to violate one's integrity, it would have to have a prior reason for being immoral).

Rather, in this context, “the integrity of human research” should be conceived of more like the integrity of a border. In order to allow for the cooperative work of all the stakeholders in human research, there are certain things that should be allowed to be considered scientific human research, and certain things that should not be allowed to be considered scientific human research. The way to distinguish between these two is what best allows all the different players in the collaborative project to best work together to pursue their own ends while also producing the socially valuable good of scientifically valid medical knowledge. If something undermines the institution of human research in its ability to allow all the stakeholders to come together and achieve the goals that they mean to, then it can be said to have “violated the integrity of human research.”

This sort of argumentation does not rely on an appeal to the risk vs. benefit for the patient-subject. Because it is non-paternalistic in this way, it is not vulnerable to the criticisms that I brought to bear on the risk-benefit objections to phase IV seeding studies. That is, as far as this principle is concerned, it doesn't matter whether harm occurs to the subjects of human research *per se* or not—what is important is whether or not such research would have a deleterious effect on the kinds of activities necessary for legitimate phase IV studies as a part of the functioning of the cooperative enterprise that is human research.

[107] (Wertheimer, 2011, p. 40)

It now remains to be shown that this is the sort of thing that would threaten the proper functioning of the human research project. Intuitively, this seems to be true. The clandestine nature of seeding studies makes it clear that the drug industry believes that there is good reason to think that if its true intentions were known in seeding studies, it would be difficult to recruit physician investigators or patients, and that they would be sharply criticised by the bodies that control what research is allowed to occur. The very fact that the ADVANTAGE study was so remarkable in that it was one of the few phase IV seeding studies for which the true intention of the study is known should tell us that pharmaceutical companies have good reason to hide the nature of seeding studies.

The question of intention

Let us return for a moment to the question of intention: Is the intent of a pharmaceutical company to use scientific research for marketing purposes sufficient to render a study unethical, according to the integrity argument?

Imagine a phase IV drug study that is designed to answer a socially valuable question. It is statistically powered enough to accomplish this goal and it has been designed in a way that is an efficient use of resources such as research centres, doctors, nurses, etc. The study is otherwise ethically acceptable—the comparator arms are in equipoise and there is a favourable risk-benefit ratio.

If it were discovered after the fact that internal company documents referred to this study as a "seeding study," (a study whose purpose is to market the drug through exposure to physicians) would this be an example of a study that compromises the integrity of the human research enterprise?

Every stakeholder comes to human research with their own individual self-interested goals, including pharmaceutical companies. It is ultimately an empirical question as to whether or not such a revelation would have the consequences of hindering human research. That said, it is not a controversial claim that clinical

investigators, research centres and patient-subjects all know already that a drug company is ultimately trying to profit by researching drugs. They agree to participate because they see the scientific value in the research as being worthy of their cooperation, and because they trust that some actors are present in human research in order to check the self-interested motives of other stakeholders. The intention on the part of the pharmaceutical company to make profit through research would not undermine the integrity of the human research enterprise any more than the self-interested motives of the other participants would.

However, if a pharmaceutical company's intentions with regard to a drug study were kept secret, that might be reason to be suspicious. Also, if there was "bad" intent with regard to a particular study, a company would be less likely to be concerned about the right things, and so they would not be likely to produce a valuable phase IV study. So ultimately, intention to use a study for marketing purposes is neither sufficient to render it unethical nor is it irrelevant.

Next, let us consider some ways in which the integrity of human research can be compromised.

Confidence, cascading consequences, consumption, and credence goods

There are three main ways in which phase IV seeding studies can threaten the integrity of the human research project.

First, phase IV studies that are poorly designed or executed undermine the confidence of various stakeholders in phase IV studies and, more broadly, would have cascading effects on the institution of human research itself. Phase IV studies play a crucial function in pharmacovigilence, but these important studies fall under a cloud of suspicion as a result of seeding studies. This suspicion may make it difficult to recruit physicians for phase IV research, publish results of phase IV studies in journals and may attract undue and intrusive REB oversight, or for others to make decisions on the basis of this knowledge.

These "cascading effects" of phase IV seeding studies threaten support both for phase IV studies that produce scientifically and medically useful knowledge and for human research generally. By this, I mean that because "research programmes are joined or abandoned on the basis of perceived beliefs of others,"[108] a phase IV study that is statistically under-powered or one that asks a question that is not scientifically valuable because it was designed to serve primarily a marketing, rather than a scientific purpose, might have deleterious effects for phase IV research, generally. "[P]oorly conceived trials can dampen interest in promising therapies. Repeated failures can diminish the standing of a research programme, interrupting recruitment of talent, investment and institutional support."[109] In this way, a "bad" phase IV study could be criticised for the sake of protecting other, "good" phase IV studies, and the human research project in general.

The CAFE study is an example of a phase IV study that came under intense ethical scrutiny in which there were clear cascading effects. In the aftermath of the study, many faculty members from the University of Minnesota penned an open letter in which they called for further investigation not just into Markingson's case, but into "any larger structural or financial conditions that might have played a role in his death and which may still be putting patients at risk."[110]

The Minnesota Daily newspaper printed an editorial criticising the university for "a willfully ignorant attempt to sweep the Markingson case under the rug." The editorial claimed that this conduct "damages the integrity of the entire University."[111]

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[108] (London, Kimmelman, & Emborg, 2010, p. 829)

[109] (London, et al., 2010, pp. 829–830)

[110] (Elliott et al., 2010), (Smirnitskaya, 2010)

[111] (Board, 2011)

Not only was the CAFE study criticised for what happened in Markingson's case, but the structural and financial conditions under which human research takes place and even the University of Minnesota's integrity were both called into question as a result.

Badly-done phase IV studies have undermined the confidence of some stakeholders in human research. Egilman and Presler conclude their letter to the Annals of Internal Medicine by saying, "If anything, ADVANTAGE teaches us that we cannot rely on drug companies to honestly report all of the important data."[112] For Egilman and Presler, this is the take-home message from their analysis of the ADVANTAGE study—that drug companies cannot be trusted where research into their drugs is concerned. This is an excellent example of a threat to the integrity of human research. The conduct of the ADVANTAGE seeding trial has caused two members of the scientific establishment to lose confidence in at least one part of the proper functioning of human research.

Hill et al. criticise the ADVANTAGE study and argue that "the undisclosed use of research by corporate marketing divisions threatens the integrity of the relationship of industry, academia, patients and society."[113] That is to say, because of studies like ADVANTAGE, the relationship among all these partners is damaged, and not just for the study in question, but generally.

Landefeld and Steinman's criticisms of the Neurontin scandal focussed on "the integrity of medical science and practice and … public trust."[114] For them, the "Neurontin legacy" was one of distrust in the institution of human research. They

[112] (Egilman & Presler, 2006, p. 781)

[113] (Hill, et al., 2008, p. 256)

[114] (Landefeld & Steinman, 2009, p. 105)

recommend "drastic action," harsh penalties, and higher standards of independent review of phase IV trials.[115]

Because of the STEPS trial, commentators want it to be more difficult to conduct a phase IV trial, in order to reduce the number of "bad" phase IV studies. Unfortunately, this has effects for "good" phase IV studies as well—this will discourage the valuable studies as well as the studies that are purely marketing exercises without scientific merit.

In the wake of the ENHANCE trial, there was an investigation by the House Energy and Commerce Committee into the trial itself, to try to explain the confusing and often contradictory nature of the data, as well as the changing endpoints during the course of the study and any potential conflicts of interest between the American College of Cardiology, the American Heart Association and Merck/Shering-Plough, the sponsor of the study.[116] This is an example of another way in which poorly designed studies like ENHANCE can have cascading consequences for other drug trials. The increased government and regulatory scrutiny that results from studies like ENHANCE make it difficult for legitimate phase IV drug studies to be conducted.

Second, phase IV seeding studies may threaten longer-term collaboration toward socially useful medical knowledge by consuming resources. "Practically every clinical trial makes demands on social and material resources beyond those provided by study sponsors, investigators and human subjects."[117] These resources include the administrative resources of research centres, the pool of available volunteers for human research, specialised expertise and equipment, and the

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[115] (Landefeld & Steinman, 2009, p. 105)

[116] (Greenland & Lloyd-Jones, 2008, p. 955)

[117] (London, et al., 2010, p. 829)

financial resources of third parties who have to share the burden in the case of trial-related injury.[118]

The time of physician-investigators is limited and phase IV studies (good or bad) compete for their attention along with other clinical investigations. This is even more problematic in cases where the expertise that licenses clinical investigation has been publicly subsidised on the expectation that such expertise will be directed toward socially valuable ends.

The consumption of resources by inefficient phase IV studies has drawn criticism to the whole class of phase IV studies. Hasford and Lamprecht argue that the conduct of these phase IV studies may "indicate a need to reconsider the organisation and funding of phase IV research."[119] This is of particular concern to phase IV studies because the resources for doing phase IV studies are so limited.

> The current system of postmarketing safety monitoring is falling short. According to the FDA, of all 1259 open postmarketing commitments for new drugs, 71% was classified as 'pending,' which means that the study has not been initiated.[120]

There are very limited resources allocated for phase IV studies, and so it is crucial to prioritise studies that have greater scientific value.

Third, a procedure that only considers the interests and preferences of investigators and subjects in evaluating the design and execution of phase IV studies may reward low-quality trials and penalise high-quality trials. In chapter 2, I outlined an analogy between market regulation in other areas, and the regulation of subject protections in human research. "[C]linical trial protocols are examples of what economists call

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[118] (London, et al., 2010, p. 829)

[119] (Hasford & Lamprecht, 1998, p. 371)

[120] (Thiel & Delden, 2008, p. 415)

'credence goods': Products whose quality is difficult to judge by consumers."[121] In some cases, even medical professionals are not able to discern good from bad studies. The ADVANTAGE study was not revealed to be a seeding study until after it was published. Like other markets for credence goods, human research protocols will tend to be of low quality unless they are well regulated, since the "consumers"—the human subjects of research—will be unable to discern between good ones and bad ones.

Consider the case of free product samples given at medical clinics. These do not violate the autonomy of those who accept them, but by building customer loyalty apart from any appraisal of quality, they cause customers to reward inferior products. Similarly, allowing patients to consent to bad phase IV trials would not violate the patient-subject's autonomy, but because patient-subjects are unable to gauge the quality of the research, some bad phase IV trials would be rewarded rather than more worthwhile ones.

Sox considers recommending that patients ask investigators about the intent of the trial:

> If the answer was "It's a seeding trial," most would say no, and seeding trials would soon fade away; but this scenario is a fairy tale, because sponsors would probably ascribe a scientific purpose to the trial and proving otherwise would be difficult.[122]

If it is the case that sponsors can ascribe a legitimate scientific purpose to the trial, even though there is a marketing purpose to the trial as well, this may be acceptable.

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[121] (London, et al., 2010, p. 830)

[122] (Sox & Rennie, 2008, p. 280)

Unfortunately, in phase IV studies, patients are not well-positioned to be able to judge between good and bad studies, and so low-quality studies may be rewarded while higher-quality ones are passed over.

Possible objections

The integrity thesis is only paternalism disguised

One might object that this is just a disguised appeal to a risk-benefit argument, and if so, then this criticism of phase IV seeding studies is subject to all the objections covered in the previous sections dealing with risk-benefit arguments.

This objection does not carry very much weight. A person who had no concern at all for the welfare of the subjects of human research would still be constrained by considerations regarding the integrity of the human research project. The optimal conditions for collaboration on human research are not dependent on a favourable risk-benefit ratio for its subjects.

Integrity as an empirical problem

It could also be argued that this line of argumentation turns the issue into an empirical problem. The optimal conditions for working together, given the sorts of creatures that we are and the way that our society has set up the institutions of medicine and research will determine what sorts of things are and are not ethical, according to this criterion. If it happens to turn out, on measurement, that cooperation is impaired by something, then it is immoral in the context of human research. If this is the case, then it may turn out that we have to condemn something that we otherwise would consider permissible or praiseworthy. Also, because it is an empirical problem, there may be different standards of what is right and wrong, depending on the location where the optimal conditions for cooperation are measured. For example, in Canada, a particular research practice may turn out to have no effect on the ability of different stakeholders to participate in human research, but in Europe, the medical community might find that particular practice

objectionable. Because the morality depends on the actual impact on the collaboration of different stakeholders in human research, we would have to be committed to the position that the research practice is wrong in one context and right in the other.

First, the integrity of the human research project is only one of a number of moral principles that should be brought to bear on considering whether a practice in human research is permissible or not. Second, this sort of sensitivity to the actual conditions under which research flourishes might be something that we want a good theory regarding what is permissible to have. We do, in fact, want to be able to condemn things that we would otherwise have to consider permissible (like phase IV seeding studies), and having a theory that allows for variability across contexts and times can be seen a strength of the theory, and not a weakness.

Where to draw the line

Another objection is that because it is an empirical problem, there will be some things that hurt the collaborative project only a little, and some things that hurt it a great deal. This principle doesn't give us guidance as to how much something must affect the human research project before it should be deemed immoral.

This is a common problem for all consequentialist moral theories, including those that underwrite paternalistic protections like the appeal to risk vs. knowledge value. How much knowledge value will be gained is an empirical question, and it is often difficult to weigh the value of knowledge against the risk toward patient-subjects.

Further, most moral theories do not give exact prescriptions on particular issues. Those are (rightly) the subject of moral debate, even if the underlying theory is generally accepted. For example, two utilitarians may agree on the general principle of utility, and yet disagree about the extent to which something impacts human happiness, and so come to different conclusions about whether a particular practice is permissible. This is not taken to be an argument against the principle of utility,

and there will be a great deal of clear-cut cases where both will agree on the conclusion, given their common commitment to the principle of utility.

Similarly, two people may disagree about the extent to which something harms the integrity of the human research project, however they may both agree that it is a relevant moral concern. This also should not be taken as an argument against appealing to the integrity of human research as something that constrains what practices are permissible. The case of phase IV seeding studies are clear enough that few would argue that they do anything but harm the integrity of the human research project, and for that reason, they are not permissible.

Integrity might include paternalism

I have presented integrity as standing in opposition to paternalism, but it is entirely possible to conceive of the human research enterprise as delegating a paternalistic role to certain actors, namely physicians or REB's, and doing so in the name of integrity. In such a case, the integrity thesis would encompass the "old paternalistic" research ethics, rather than offering an alternative. REB's, for example, would act in a paternalistic way in order to protect the integrity of the human research project.

I concede the claim that a concern for the integrity of human research may indeed delegate what could be described as a "paternalistic" role to certain actors, but deny that this is a problem for the thesis I have been advocating.

There are certainly some protections for patient-subjects that could be characterised as paternalistic, if we take "paternalism" to be just overriding a patient-subject's desires or preferences in order to protect her well-being. The ultimate grounds for such paternalism would not be the patient's well-being, but the integrity of human research.

If it was the case that protection of the integrity of human research required certain stakeholders to act in a paternalistic way, this would be distinct from old paternalistic research ethics in that the ultimate grounds of justification for the

"paternalistic" actions of such stakeholders would be the protection of the integrity of human research, and not the well-being of the patient-subjects themselves.

The well-being and the autonomy of the patient-subject are certainly relevant moral concerns when evaluating a research protocol. I am suggesting that the integrity thesis provides new moral concerns that must be considered along with all the other relevant considerations.

Dividing the moral labour

The question remains, *What responsibilities do each of the stakeholders in human research have with regard to ensuring the integrity of the human research enterprise in the context of phase IV?* Whose job is it to make sure that research practices that jeopardise the human research project are not allowed, and who bears the responsibility for ensuring the integrity of human research?

The standard model

The standard model for medical research ethics puts three players (namely, the investigator, the research subject and the research ethics board) in a privileged position, where they are often considered to be the main, if not the only, morally relevant actors in human research ethics.

Certainly, each of these three stakeholders should take some responsibility in maintaining the integrity of human research, since they are three of the major players, ethically speaking, in any human research situation. One criterion that research ethics boards should adopt when evaluating a protocol for research involving human subjects should be an evaluation of the potential effects that the pursuit of such research would have on the integrity of the human research project.

A research ethics board should look out for protocols like the phase IV seeding studies I criticised earlier, that will have a deleterious effect on human research. In cases where there are obvious financial conflicts, or the study is statistically

underpowered, or designed in a manner that is an inefficient use of resources, the research ethics board should be able to criticise the study on the grounds that such a trial would impact the integrity of human research itself, rather than trying to frame the ethical problem with such a study in terms of harm or benefit to the human subjects. REBs should also require prospective registration of all phase IV studies, regardless of whether they fall under FDAAA or TCPS. The FDAAA requires only prospective registration for phase IV studies where there are active interventions.[123] The TCPS charges researchers and REBs to "ensure that trials are undertaken for a bona fide scientific purpose … Phase IV trials designed with the primary goal of increasing sales do not constitute legitimate research."[124] The publication of all results of phase IV should be required as well as the publication of protocols.

Physician-investigators for human research protocols are often well positioned to be able to discern between a good phase IV study and a bad one. They have access to the protocol, experience in human research, and they are trained to be able to prepare a good drug trial for research on humans.

It is in the best interest of physician-investigators themselves to refuse to participate in, and to critique bad phase IV studies. By participating in a bad phase IV study, a physician-investigator opens herself up to the risk of a loss of reputation, the influence of a pharmaceutical company, and a waste of her own time on a project that does not provide social or scientific value. Physician-investigators should make an obligation to publish both negative and positive results a condition of their participation in a study, and they should demand a right to view the data from other sites where the study is occurring.

That said, a major thrust of my thesis has been that the investigator, subject and research ethics board are not the only stakeholders in the human research project

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[123] (Medicine, 2011)

[124] (Canadian Institutes of Health Research, December 2010, p. 152)

who are morally relevant when deciding what research is ethical. Since there are other stakeholders, it is worth considering what roles they could play in ensuring the integrity of human research.

Medical journals and other publications

Medical journals also have an interest in helping the project of human research to continue and thrive. Medical journals rely on a stream of new human research projects and articles produced by physician-investigators and other medical scientists in order to continue to produce their publications. It is therefore in the interest of medical journals and other such publications to do what they can to discourage research practices or policies that undermine the integrity of the human research project, since it is the proper functioning of human research that provides them with the articles that they publish.

A medical journal can carefully examine papers under consideration for publication, looking for studies that appear to be problematic phase IV seeding studies. They can refuse to publish studies that are designed in such a way that they are inefficient from a scientific point of view, but efficient from a drug marketing point of view.

Medical journals can help to protect the human research enterprise by maintaining high standards for scientific rigour. Many phase IV seeding studies are statistically underpowered, or ask a question that has little scientific value. By refusing to publish an article about a question that is unimportant, a medical journal serves its own interests, by keeping its own standards of publication high, and helps to protect the institution of human research.

Further, medical journals and other such publications can publish criticisms of phase IV studies and highlight the impact that such trials have on human research as a collaborative project.

Professional associations

All physician-investigators and many other medical staff that support human research are members of a professional association: Each province in Canada has a college of physicians and surgeons. Registered nurses are members of another professional association, as are a great many other therapists, technicians, technologists and other medical professionals who make human research possible.

Professional medical associations have a great amount of power in determining what conduct is appropriate for their members. The college of physicians and surgeons, for example, decides who can practice medicine within the province it governs. It also maintains standards of practice through peer assessment and disciplinary hearing in cases of misconduct or incompetence.

Professional associations for medical staff also have an interest in protecting the integrity of the human research enterprise, since their members constitute many of the essential stakeholders in human research. These professional associations could use their considerable power in order to protect the integrity of human research.

Research institutions

As I have argued, human research is not merely a private transaction between a physician-investigator and a subject. The help and resources of various institutions—hospitals, research centres, universities, etc. is one of the externalities that all human research relies on. All these institutions are affected by the use of their resources whenever they participate in human research, and their resources are limited.

Universities, research centres and hospitals could restrict what research is pursued using their facilities. There is no lack of ideas for phase IV trials—of all the drug trials recommended by the FDA, 71% of them were classified as 'pending,' meaning

that the study has not been initiated.[125] These institutions could mandate that priority be given to phase IV trials that answer questions of higher scientific and social value. The way in which these research centres' resources are used could be restricted to only protocols that are designed to be efficient (and not just efficient at marketing drugs). Institutions could adopt a policy of registration and a requirement that negative results be published along with the protocol used in the drug study.

Pharmaceutical industry

It is tempting to cast the pharmaceutical industry as the villain, but it is just as much in the interest of the pharmaceutical industry as it is in the interests of physician-investigators, human subjects, and the medical community that the integrity of the human research enterprise be protected. Ultimately, pharmaceutical companies will be unable to pursue their interest in marketing a product without sustained cooperation of other actors who are indifferent if not uncomfortable with these motivations. It is in the best financial interest of the pharmaceutical industry for them to establish policies and practices that protect the integrity of the human research enterprise. If the pharmaceutical industry does not protect the human research project—and even protect human research from phase IV seeding studies, which seem to have been designed to *promote* the interests of pharmaceutical companies—it is jeopardising the very thing that the pharmaceutical industry depends on, namely, a healthy environment for collaboration among the various stakeholders in the human research enterprise.

Corporate sponsors have duties to protect the personal welfare interests of volunteers by not submitting risky phase IV studies, because of the impact that such studies would have on the integrity of human research.

Human research is possible because physician-investigators, human subjects, research institutions, universities, and the pharmaceutical industry work together.

[125] (Thiel & Delden, 2008, p. 415)

They each have their own individual goals and motivations, and for each of them, there are conditions that are more or less conducive to the achievement of those goals. If the pharmaceutical industry acts in such a way that no one will want to, or be able to cooperate with them, then human research will either not happen, or it will be severely hindered in its ability to produce new and valuable knowledge. In either case, this will hurt the pharmaceutical industry.

The pharmaceutical industry should aim for honesty and transparency in the goals of its research. One of the reasons the ADVANTAGE study was so controversial was because after the fact, internal emails revealed Merck's duplicity. One email said explicitly, "It may be a seeding study, but let's not call it that in our internal documents."[126] Physician investigators, and even the journal that published the study both felt tricked.

For the sake of pharmaceutical industry, as well as the sake of all the other stakeholders in the human research enterprise, there should be greater transparency about the intentions and the behind research like phase IV studies.

Ultimately, it is in the best interests of the pharmaceutical industry to be honest and transparent, and to conduct phase IV drug trials that make a valuable contribution to medical science.

[126] (Hill, et al., 2008, p. 255)

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