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Taking Respect Seriously: Clinical Research and the Demands of Informed Consent

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There is broad agreement among research ethicists that investigators have a duty to obtain the informed consent of all subjects who participate in their research trials. On a common view, the duty to obtain this informed consent follows from the need to respect persons and their autonomous decisions. However, the nature of informed consent and the demands it places on investigators are open to dispute and recently have been challenged. Respect for persons, it has been claimed, does not require investigators to guarantee that the subjects enrolled in their trials comprehend the risk/benefit information disclosed to them or even that they appreciate the difference between research and therapy. According to this critique, the significance of defects in informed consent, like therapeutic misconception or unrealistic optimism, has been greatly exaggerated. This article reevaluates informed consent in clinical research in light of this critique. It not only rebuts the main points the critics raise, but also shows that other points they raise can be accepted by a doctrine of informed consent that resembles the common view in maintaining that autonomous authorization is central to informed consent.

Keywords: *clinical, informed consent, respect*

I. INTRODUCTION

Clinical research and medicine are entangled in contemporary practice. Despite this entanglement, the recognition that clinical research differs significantly from clinical medicine is the starting point for contemporary research ethics. Medical professionals have a duty to promote the best

medical interests of their patients within the constraints of the law and with the resources at their disposal. In contrast, investigators have a responsibility to advance generalizable scientific knowledge and ultimately to serve the medical interests of future patients. Investigators do not aim in the first place to provide research participants with the best possible care, since doing so may not serve the goals of their research. Attention to the differences between research and medical contexts has led many to argue that research ethics should not be grounded in a principle of medical beneficence, but rather in a principle of respect (Levine, 1988). There is now broad agreement among research ethicists that investigators have a duty to obtain the informed consent of all subjects who participate in their research trials. On a common view, the duty to obtain informed consent follows from the principle of respect. "Informed consent embodies the need to respect persons and their autonomous decisions" (Emanuel, Wendler, and Grady, 2000). However, the nature of informed consent and the demands it places on investigators are open to dispute and recently have been challenged. Respect for persons, it is claimed, does not require investigators to guarantee that the subjects enrolled in their trials comprehend the risk/benefit information disclosed to them or even that they appreciate the difference between research and therapy. According to this line of thought, the significance of defects in informed consent, like the therapeutic misconception or unrealistic optimism, has been greatly exaggerated. The following statements express this skeptical challenge.

> The dominant view is that it is permissible for investigators to proceed only if the subject's consent is "valid" and that the validity of the subject's consent is based on the subject's mental state . . . [However] when we approach consent from a bilateral perspective, it turns out that it may be permissible for investigators to proceed even if the subject's consent is not valid. (Wertheimer, 2011, 13)

> The very act of consent arguably entails a bare minimum of comprehension. Participants must comprehend both what it means to consent and a basic description of what they will undergo—an injection, for example. However, this minimal comprehension is fully consistent with a therapeutic misconception, since it includes nothing about the risks or benefits or the difference between research and care. (Sreenivasan, 2003, 2018)

> Protecting patients from research decisions made with deficient understanding of some required elements of information disclosure must coexist with respect for their right to make voluntary choices consistent with their preferences and values. In both of these respects, despite evidence of the therapeutic misconception, therapeutic misestimation, and unrealistic optimism, patients seeking cancer-fighting treatment can arguably give valid consent to phase 1 trials. (Miller and Joffe, 2013, 763)

These claims and the arguments that support them present an interesting and hitherto unaddressed challenge to the standard understanding of informed consent in clinical research. This article reevaluates informed consent in

clinical research in light of this challenge. It rebuts the main points the critics raise and shows that other points they raise can be accepted by a doctrine of informed consent that makes autonomous authorization a requirement. In addressing the challenge, the article aims to put the standard view on firmer ground.

II. SHARED RESPONSIBILITY AND THE NATURE OF CONSENT

The standard view of informed consent requires that participants in clinical research understand and appreciate the information that is disclosed to them.[1] Understanding and appreciating relevant information are necessary if potential research participants are to make autonomous decisions to participate or not participate in research trials (Beauchamp and Faden, 1986; Grisso and Appelbaum, 1998). There are hard questions to be asked about how much information participants must understand or how well they must appreciate it if they are to make autonomous decisions. But, advocates of the standard view agree that, at a minimum, understanding and appreciation include a good grasp of the risk/benefit information disclosed in the informed consent process, an awareness of the rights of research participants, and a recognition of the main differences between the research trial in which participants are enrolled, or considering enrollment, and beneficent medical care. Adequate understanding and appreciation must also include knowledge of the alternative treatment options available to participants outside of the trial and the risks and potential benefits they present.[2]

Yet, understanding and appreciation, however robust they are conceived to be, are achievements. And as critics of the standard view have pointed out, "in a shared relationship, successful communication is normally a shared responsibility" (Sreenivasan, 2003, 2016). A student may fail to understand calculus even though his teacher has done everything a teacher could be expected to do in explaining the subject to him. The student's failure to understand calculus may not be attributable to any failure on the teacher's part to live up to the duties that he has as a teacher. The same could be true of the failure of a research participant to understand information disclosed to her about a clinical trial.

Consider this example:

> A patient-subject is enrolled in an early phase cancer trial. The trial is not designed to benefit its participants, but rather to test the toxicity of the drugs administered in the trial. The patient-subject participates in a formal consent process and agrees to participate in the trial, but she does not have a good grasp of the information that is disclosed to her. She does not understand that the trial is not a form of therapy, and he does not appreciate the risks it presents to its participants. The investigator conducting the trial, however, lives up to his duties to take reasonable steps to ensure that this information is presented to the patient-subject in terms that she

can understand and appreciate. The investigator also has made reasonable efforts to counter therapeutic misconception, and he has tried to correct any unrealistic expectations for therapeutic benefit that the patient-subject may have.

In this example, the patient-subject's lack of understanding is not due to any failure on the part of the investigator. Does this mean that the patient-subject's consent, defective as it may be, is valid? Some critics answer affirmatively, and they claim that an affirmative answer shows that the standard view of informed consent is mistaken. Adequate understanding is not required for valid consent, since its absence may not be due to any failure on the part of investigators to discharge their duties.

Note that the force of the example is independent of the stringency of the duties of the investigators. To determine what is required of investigators—to determine what counts as reasonable steps to ensure understanding and appreciation—one needs to decide whether the targeted understanding and appreciation are very modest (a bare comprehension of what is going on, for instance) or more robust (the understanding and appreciation necessary for autonomous decision). Defenders of the standard view maintain that autonomous authorization is the appropriate target for informed consent in clinical research. The critics reject this target. This dispute is not engaged by the example.

Rather, the example encourages us to think about the more fundamental issue of the nature of consent. In particular, it encourages us to think about whether some kind of mental state is necessary for informed consent, or whether informed consent is simply a function of the behavior of the interacting parties. Three main positions on this issue have been articulated in the literature on consent: (1) mental states are necessary and sufficient for consent, (2) mental states are necessary but not sufficient for consent, and (3) mental states are neither necessary nor sufficient for consent (Alexander, 2014, 164–174). The critics' objection to the standard view requires them to accept the third of these positions. If appropriate mental states are necessary for consent, then even if investigators satisfy all their duties and responsibilities, their patient-subjects may still fail to consent. Hence, to reject the critics' view, one does not need to decide whether appropriate mental states are only necessary or whether they are also sufficient for consent.[3] One needs only to reject the view that mental states, such as those manifested by understanding, are not necessary for consent.

On its face, the claim that consent does not require appropriate mental states on the part of the consenting parties is very difficult to believe. Indeed, Sreenivasan (2003, 2018), in the passage quoted above, allows that "the very act of consent arguably entails a bare minimum of comprehension," which is close to an admission that mental states are necessary for consent. If this is correct, then even when investigators discharge all of their duties to the research subjects in their studies, we cannot conclude that they have thereby

secured their consent to participate in these studies. The valid point that understanding is a shared responsibility between investigator and research subject, therefore, does not show that certain mental states are not necessary for consent.

In rejecting the standard view, Miller and Wertheimer (2009) propose what they call the "fair transaction model" of informed consent (Wertheimer, 2011, 65). On this model, to determine whether research subjects have given consent, we should not look to the mental states of the consenting research subjects. We should focus instead on whether the investigator "has treated the research subjects fairly and has responded in a reasonable manner to their apparent or actual token of consent" (Wertheimer, 2011, 65). An account of consent transactions, they claim, must "account for the interests of those who solicit and receive consent," as well as those who give it (Wertheimer, 2011, 65).

The fair transaction model rests on a distinction between valid consent and morally transformative consent. Miller and Wertheimer appear to allow that the former may require appropriate mental states, but they contend that the latter does not. That is why they claim, "when we approach consent from a bilateral perspective, it turns out that it may be permissible for investigators to proceed even if the subject's consent is not valid" (Wertheimer, 2011, 13).

The fair transaction model fails to take adequate account of the distinction between blameworthy and wrongful conduct. Not all wrongful conduct is blameworthy, since the wrongdoer may have a valid excuse for doing what she did. In the example sketched above, the investigator is not blameworthy. He took reasonable steps to ensure that the information disclosed to research participants could be understood and appreciated, and he took reasonable steps to identify potential participants who were under a therapeutic misconception or suffered from other types of cognitive error. However, it does not follow that he has done nothing wrong in enrolling these participants. When investigators enroll subjects in their trials without their informed consent, then they may do wrong, even if they have done all that could reasonably be asked of them to ensure that the wrong did not occur.

Miller and Wertheimer only glancingly attend to the distinction between blameworthy and wrongful conduct (Wertheimer, 2011, 100). They claim that not much turns on the issue of whether a transaction is considered impermissible, but if it is considered excused or simply permissible. This is not correct; and the reasons why it is not correct can be appreciated by considering the moral situation of third parties. For example, consider the case of consent to sexual relations. If one person mistakes another's utterances as a token of consent, and proceeds to have sex with the other person, although in fact no consent has been given, then a third party can permissibly intervene to stop the sexual assault, even if the person committing the assault is blameless. However, if it is held that the sexual interaction is permissible because the person reasonably believed that he had the consent of the other, then the

third party would do wrong in intervening (Alexander, 2014, 106). Whatever one thinks of this example, one cannot think that nothing much turns on it. Similarly, in the example presented above concerning the investigator and research subject, a third party who discovered that a research participant did not understand or appreciate relevant information could justifiably intervene and demand that the investigator either secure the consent of the research participant or exclude her from his trial. But if the investigator's blameless conduct sufficed to make the recruitment of the participant into his trial permissible, then no such intervention would be justifiable.

The critics contend that understanding and appreciation of relevant information are a shared achievement between investigator and research subject. They claim that the most that can be asked of investigators is that they take reasonable steps to secure informed consent, and that to figure out what counts as reasonable steps we must consider the interests of those who elicit as well as those who give consent. These are reasonable points. Defenders of the standard view can accept them, but they do not establish that autonomous authorization is unnecessary for valid consent to participate in clinical research.

III. CONSENT EXCEPTIONALISM

Some critics of the standard view charge that it is committed to a dubious form of "medical exceptionalism" (Wertheimer, 2011, 15). The requirements of consent are taken to be special just because medicine is involved. In contrast, the critics contend that the requirements of consent in medicine are best understood by examining consent requirements in other contexts, such as market transactions, sexual relations, and family life.

Proponents of the standard view are committed to what we can call the *autonomous authorization claim for consent to clinical research* (AAC). Accepting this claim does not expose one to the charge of medical exceptionalism. Those who accept AAC could allow that when it comes to beneficent medical care autonomous authorization is *not* always a requirement of valid consent. For example, one could allow that a patient can give valid consent to an operation that is clearly in her best medical interests even if she does not have a good understanding of the risks and benefits it presents to her. As long as her physician discloses relevant information to her, he may do nothing wrong in proceeding with the operation, even though the patient's consent is not autonomous.

Those who would say that autonomous authorization is not a general requirement for valid consent in all medical contexts, but who affirm AAC, now might be charged with embracing "clinical research exceptionalism." And, this form of exceptionalism may look dubious as well. After all, some research trials promise their participants substantial medical benefits.

Participation in these trials allows participants to receive valuable medical care. If one rejects autonomous authorization for beneficent medical practice, then perhaps one should allow that valid consent to at least some research trials does not require autonomous authorization either.

To illustrate this point, Sreenivasan presents a hypothetical research trial that has "passed institutional review board assessment and has been independently assessed as having a favourable risk-benefit ratio. Furthermore, [he asks us to] suppose that the trial is not a phase 1 or other study in which benefit to society in knowledge gained is required to render the risk-benefit ratio favourable—i.e., that the risk-benefit ratio is favourable, even when direct benefit to the participant is the only benefit taken into account" (Sreenivasan, 2003, 2017). He then argues that such a trial is ethical, even if its participants enroll under a therapeutic misconception.

The key feature of Sreenivasan's example is that participation in the trial is known to be in the medical best interests of the participants.[4] It is the option that a beneficent physician would recommend to them. Participants in the trial could have an exaggerated expectation for benefit, either because they have unrealistic optimism about this event, or because therapeutic misconception leads them to believe that the risk/benefit ratio is even more favorable than it is. Sreenivasan suggests that these misunderstandings, while regrettable, should not undermine the validity of their consent. The misunderstandings do not "actually change the trial's risk-direct-benefit ratio" (Sreenivasan, 2003, 2017).

Sreenivasan's conclusion can be resisted. Even trials with a favorable risk-direct-benefit ratio do not provide their participants with genuine therapy. The treatment provided is not therapy that is individualized to their personal situation. (It should be borne in mind that patients have their own values and preferences and they need to evaluate the option to participate in a research trial in light of their individual concerns. Even when a trial has a favorable risk-direct-benefit ratio, as judged by an institutional review board (IRB), it may not be the best option for each patient considering it.) Further, a research trial can be stopped once its scientific purposes have been achieved, even though its participants believe that they would benefit from further treatment. To my mind, it is reasonable to demand that anyone who gives valid consent to a research trial should have at least a minimal understanding of these basic facts.

The main lesson of Sreenivasan's example, however, remains compelling. The more that the treatment provided by participation in a clinical trial resembles beneficent medical care, the less important it is to secure the kind of informed consent that is appropriate for clinical research in the standard case. How should proponents of the standard view respond to this lesson? The starting point for research ethics, recall, is the recognition that the practice of clinical research differs significantly from that of beneficent medical care.[5] With this in mind, proponents of the standard view should maintain

that AAC applies to clinical research in the standard case, but then allow for exceptions in nonstandard cases. AAC applies to certain contexts with certain features, they should say. When those features are not present, then AAC may not apply.[6]

This response requires one to spell out the features that characterize the standard case in clinical research and distinguish it from that of beneficent medical care. Four features can be highlighted.

Nonbeneficent Purpose: The purpose of clinical research is not to provide direct therapeutic benefit to its participants. Even if an investigator aims both to advance generalizable scientific knowledge and to benefit trial participants, the former aim is controlling.

Uncertain Prospective Benefit: Although the purpose of clinical research is not to provide direct therapeutic benefit to its participants, it does not follow that the research provides participants with no prospect for such benefit. Yet, in the standard case, the prospect for benefit is subject to great uncertainty.

Nonpersonalized Care: The study drug or treatment tested in the research trial is not tailored to the specific needs of individual trial participants.

Vulnerability: Those who participate as trial participants in clinical research are very often in a vulnerable position. Either they suffer from a serious illness or, if they are healthy volunteers, they often come from disadvantaged socioeconomic backgrounds.

Not every clinical trial has each of these features. A clinical trial could provide its participants with personalized beneficent medical care in conjunction with the nonbeneficent administration of an experimental drug or procedure. Further, as Sreenivasan's example illustrates, a clinical trial could provide its participants with a very probable and favorable prospect for direct therapeutic benefit. However, these possibilities are all clear departures from the standard case.

Some departures from the standard case are more significant than others. *Nonpersonalized Care* is an implication of *Nonbeneficent Purpose*, and *Vulnerability* would be less troubling if *Nonbeneficent Purpose* and *Uncertain Prospective Benefit* did not obtain. In contrast, the conjunction of *Nonbeneficent Purpose* and *Uncertain Prospective Benefit* is crucial to explaining why AAC is appropriate in the contexts in which it applies. Sreenivasan's example gets its force by rejecting *Uncertain Prospective Benefit*. But, standardly, clinical trials offer their participants a very uncertain prospect for benefit. Uncertainty about the efficacy of a proposed therapy, after all, is the rationale for conducting the research. If the investigators already knew that the experimental agent or procedure was more effective than standard therapies, then they would not need to conduct the trials in the first place.

The four features I have highlighted distinguish the research context from that of beneficent medical care. But, more needs to be said to respond to the

charge of clinical research exceptionalism. In everyday life, people encounter contexts in which their interacting partners have nonbeneficent purposes and where the benefits of interaction are uncertain. Further, in at least some of these interactions, one party is vulnerable to the other. Yet, it seems clear that we should not require autonomous authorization for consent to be valid in all of these contexts.

The next section argues that clinical research is a distinctive moral practice in which investigators have duties of respect to participants in their trials and that this fact about the practice, combined with the four features of the standard case, explain why autonomous authorization is a requirement of valid consent in this context. If this argument is successful, then when it is objected that in affirming AAC one still affirms a form of "clinical research exceptionalism," the reply is obvious. The standards of valid consent should be responsive to relevant features of a given context, and the features that characterize clinical research in the standard case explain why autonomous authorization is appropriate in this context.[7] To reject this modest form of exceptionalism would be to recommend a rigid form of consent generalism that is blind to the relevant differences between different contexts of consensual interaction.

IV. CLINICAL RESEARCH AS A MORAL ENTERPRISE

Physicians and the patients they serve share the same end. The point of the interaction between them is to advance the medical interests of the patient. No such alignment of ends is guaranteed, or even expected to obtain, in the investigator/subject interaction in clinical research. "So what?" it may be asked. Many consensual interactions in everyday life do not involve parties that share the same end. In business transactions, for example, it is commonly known that the interacting parties are each pursuing their self-interest and seeking to get the best deal they can get, even if this comes at the expense of the other party. We do not demand high-grade consent for these transactions to be valid.

Clinical research purports to be different from such everyday interactions, however. Influential reports, codes, and declarations attest to the fact that it purports to be a distinctive kind of moral enterprise.[8] These documents not only articulate a robust set of duties that include the requirement of informed consent but also go beyond it. Ethical interactions between investigators and subjects include the demand that risks must be minimized and potential benefits to subjects maximized within the constraints imposed by the research protocol (Emanuel, Wendler, and Grady, 2000). In addition, hospitals and research institutions routinely announce their commitment to respecting research participants, and they establish rules and policies to protect them. Research participants, it is claimed, should be thought of as

"partners" rather than "subjects" (Emanuel, Wendler, and Grady, 2000). And, importantly, effective enrollment of patients into research trials relies heavily on the trust that patients have in the physicians who recruit them to the trials.

The fact that clinical research is a moral enterprise of this kind does not show that it must be. Someone might argue that research should be modeled on the practice of self-interested market transactions. This would require a fundamental reform of current practice, a reform for which the critics have not called. Furthermore, the fact that clinical research purports to be a moral enterprise itself has ethical consequences. Subjects recruited into trials reasonably expect, and are encouraged to expect, that the investigators will treat them as respectful partners rather than as people to be exploited for the good of medical science. The generation of these expectations in the practice of clinical research affects the nature of the consensual interaction that occurs within it. If parties to market transactions were routinely unaware that they were in a competitive context, if they were encouraged to view themselves as collaborative partners, then concerns about potential exploitation would become more appropriate here as well.

Clinical research, in brief, is and purports to be a moral enterprise in which investigators openly acknowledge duties to respect and care for those who participate in their trials. Exploitation may be wrong in all contexts of interaction, but it is a more serious wrong conduct when it occurs within relationships committed to mutual respect and based on trust. Investigators' willingness to exploit research participants, or unwillingness to take steps to guard against inadvertently exploiting them, is not consistent with the moral character of the research enterprise. However, and importantly, if subjects autonomously consent to participate in the trials, then concerns about exploitation are muted, if not entirely eliminated. Autonomous authorization is a requirement of valid consent in clinical research, at least in the standard case, because it is a safeguard against exploitation.[9]

Critics of the standard view might respond that the minimally demanding consent they favor is sufficient to protect research subjects from exploitation. Minimally demanding consent, as the critics themselves emphasize, is not compromised by therapeutic misconception, failures to accurately understand risks and benefits, or cognitive biases that interfere with the realistic appreciation of relevant information. This means, however, that minimally demanding consent offers no protection against exploitation that takes advantage of these vulnerabilities. To see this vividly, consider an investigator who deliberately cultivates the therapeutic misconception and deliberately presents risk/benefit information in a manner designed to distort its appreciation in an effort to meet his recruitment goals. If such an investigator secured minimally demanding consent from each participant recruited, this would hardly establish that no exploitation had occurred.[10]

It might be said that minimally demanding consent combined with strict IRB review would suffice to protect research subjects from exploitation. If IRBs systematically excluded all trials with an unfavorable risk/benefit ratio, then subjects would not be given the option to consent to participate in trials that could exploit them. However, research subjects should be permitted to participate in trials with unfavorable risk/benefit ratios.[11] These trials can advance morally valuable research, and if participants consent to them autonomously and for the right reasons, there need be no ethical problem. In general, one is not exploited if one's main reason for participating in research is altruistic. The ethical character of a trial can depend on the motivations of its participants (Jansen, 2009). That is why IRB approval needs to be supplemented with a requirement of informed consent and why a minimally demanding form of consent is an insufficient safeguard against exploitation.

V. EXPLOITATION AND PATERNALISM

A more demanding form of informed consent, such as autonomous authorization, is necessary if informed consent is to protect research subjects from exploitation in clinical research in the standard case. Yet, respect for the autonomy of research participants and potential research participants is in tension with paternalistic restrictions that are designed to protect them from their own decisions. This gives rise to the concern that insisting on autonomous authorization for participation in clinical research, especially if the requirements of autonomous authorization are very demanding, is in fact not respectful of potential research participants, since it may prevent them from enrolling in a trial, even when doing so is consistent with their values and preferences. The effort to respect potential research participants by protecting them from exploitation, a little paradoxically, can result in disrespect to them by failing to honor their own decisions about whether or not to participate in the trials for which they are eligible.

This problem—we can call it the exploitation/paternalism problem—is sometimes said to be present in early phase cancer trials, and it will be useful to consider the problem as it applies in this area. In discussing the standard case, and in particular *Uncertain Prospective Benefit*, I noted that an uncertain prospect for benefit could still be a wager that it made sense to take. Phase 1 cancer trials may present such a wager to cancer patients who have exhausted all other therapeutic options. In an interesting discussion of early phase cancer trials, Miller and Joffe argue that, although the prospect of direct therapeutic benefit from participation in these trials is very low, given the grim circumstances of the participants involved, they could rationally judge that the prospect for direct therapeutic benefit was good enough to justify their participation in these trials. Suppose that this judgment is correct. This would not show that participants could not also rationally judge that the

prospect for direct therapeutic benefit was not good enough to justify their participation in these trials. In this circumstance, rationality would neither favor nor oppose participation in the trial.

Thinking that someone could rationally consent to participate in an early phase cancer trial on the grounds that he is seeking effective cancer treatment shows that we cannot conclude that this motivation for participation in itself is evidence of irrationality. But, possible rational consent is a very weak standard. And, when a participant could both rationally consent and rationally decline to consent, it would seem that it would be especially important to ensure that her actual decision, not a decision that she could possibly rationally make, is one that is not distorted by misunderstandings and bias. This kind of situation is one in which AAC would seem to be particularly appropriate.

Some critics of the standard view, however, reject this conclusion. Valid consent to participate in early phase cancer trials, they claim, "should be understood as the minimal threshold for permissible interpersonal conduct," and defects in understanding and appreciation, such as those associated with therapeutic misconception and unrealistic optimism, do not compromise this minimal standard (Miller and Joffe, 2013, 763). Invoking the paternalism concern, they claim that "it would be disrespectful of patients to paternalistically exclude them from trial participation on the basis of these types of defects in understanding or appreciation" (Miller and Joffe, 2013, 763). This point is an important objection to AAC. If taken too far, autonomous authorization becomes an obstacle that prevents potential research participants from making choices that were fully consistent with their values and concerns, thus frustrating their autonomy rather than furthering it.

Autonomous authorization does not require people to have perfect comprehension of all relevant information and to exhibit perfect rationality in processing the information and applying it to their situation. Proponents of autonomous authorization have long emphasized this point (Feinberg, 1986; Beauchamp and Faden, 1986). What is necessary is that a person has an adequate grasp of the relevant information and that he or she exhibits a sufficient level of rationality in processing and applying it. The hard issue is how to add more substance to the rather vague notions of adequacy and sufficiency.

In considering this issue, two different types of error need to be considered. They concern, respectively, what Wertheimer calls the negative and positive dimensions of autonomy:

> The *negative* dimension of a person's autonomy encompasses an agent's interest in *not* undergoing interventions or *not* acquiring commitments unless such interventions are the result of her autonomous choice. The *positive* dimension of a person's autonomy refers to her interest in being able to facilitate interactions with others in order to bring about a desired result. (Wertheimer, 2011, 66)

Giving insufficient weight to the negative dimension of autonomy leads to one type of error; giving insufficient weight to the positive dimension of autonomy leads to another type of error. Applied to the context of clinical research, the two types of error can be formulated as follows:

Type 1: A participant consents to enroll in a clinical trial, but she would not have done so if she had a better understanding and appreciation of the nature of the trial and the risks and benefits it presents to her.

Type 2: A potential participant to a clinical trial who desires to enroll in it is prevented from doing so because it is determined that he has an inadequate understanding and appreciation of its nature and the risks and benefits it presents to her. However, were she to have an adequate understanding and appreciation of these issues, she would have consented to enroll in the trial.

By making the requirements of informed consent very stringent, we minimize the risk of Type 1 error. But by doing so, we increase the risk of Type 2 error. In a similar way, by making the requirements very lax, we minimize the risk of Type 2 error, but increase the risk of Type 1 error.

A satisfactory account of both valid consent and autonomous authorization must address the issue of how to balance the risks of the two types of error. Wertheimer provides no account of how to do so. He says only that an account of consent must be sensitive to both the negative and positive dimensions of autonomy. Wertheimer claims that informed consent to participate in clinical research is just "one species of the more general category of consent transactions" (Wertheimer, 2011, 66). Since different contexts of consensual interaction will call for different approaches to balancing the negative and positive dimensions of autonomy, it is not surprising that an approach that focuses on the general category of consent transactions is not well placed to offer an informative account of how to balance the two types of error in the specific context of clinical research.

My strategy is to argue against a natural view of how to do the balancing—a view I will call the equal weight view—and to defend an alternative view on which reducing the risk of Type 1 error should take priority over reducing the risk of Type 2 error.[12] This alternative view supports AAC. I then will address the paternalism concern raised by Miller and Joffe.

Type 1 errors raise concerns about exploitation. Investigators should not take advantage of the deficits in understanding and appreciation of vulnerable subjects so as to further the goals of their research. Doing this violates a duty of respect that investigators owe to those they enroll in their trials.[13] If this is right, then research participants have a claim against investigators that they are not subject to this kind of exploitation. In contrast, Type 2 errors do not violate any claim on the part of these participants. Potential research participants have an interest in participating in the trials in which they desire to participate, but they do not have a right or a claim to do so. Since Type

1 errors involve the violation of a claim, and Type 2 errors do not, priority should be given to minimizing the former over the latter.[14]

One might resist this argument by claiming that research participants do not have a claim not to be exploited by investigators. In some circumstances, people may not have claims against exploitation. But if clinical research is a moral enterprise, one in which investigators have duties of respect toward research participants, then research participants do have claims against being exploited.[15] The claims of the subjects correspond to the duties of the investigators.

An alternative way to resist the argument is to claim that potential research participants do in fact have a claim to participate in the research trials in which they desire to participate. After noting that clinical trials differ importantly from medical care, Miller and Joffe observe that "patients considering phase 1 trials, when motivated by therapeutic benefit, are faced with making treatment decisions in the research context" (Miller and Joffe, 2013, 763). It might be thought, then, that such patients have a treatment-based claim to participate in the trials if they desire to do so. The argument I have presented, on this view, rests on the questionable assumption that avoiding risks is more important than offering benefits to potential subjects. Yet, in response, no potential research participant has a treatment-based claim to participate in a research trial. The criteria of eligibility for participation in a research trial are determined by the scientific purposes of the trial and by the ethical requirements that apply to its administration. To think that research participants have a treatment-based claim to participate in a research trial is to confuse the context of research with that of beneficent medical care and thereby to succumb to a version of the therapeutic misconception.

Thinking that potential research participants do not have a treatment-based claim to participate in research trials does not show that they cannot be treated disrespectfully by exclusion from the trials. For example, if someone were excluded from a cancer trial on the basis of race or gender, then this could constitute disrespectful treatment. This brings me to the paternalism concerns expressed by Miller and Joffe. One could argue that while potential research participants have no treatment-based claim to participate in research trials, they do have a claim against being excluded from participating in these trials for paternalistic reasons. Type 2 errors, one could claim further, violate this claim against exclusion for paternalistic reasons and so Type 2 errors just as much as Type 1 errors violate the claims of research participants and potential research participants. Therefore, one could conclude, there is no case for giving priority to the minimization of Type 1 errors over the minimization of Type 2 errors.

This argument is more developed than any argument presented by the critics of AAC, but it still cannot withstand scrutiny. Even if it is assumed that potential research participants have a general claim against exclusion for

paternalistic reasons—an assumption that can be challenged—the argument does not work (Jansen and Wall, 2009). Investigators can have nonpaternalistic reasons to exclude potential research participants. Obviously, an investigator may exclude a potential research participant if the enrollment targets for the scientific design of the trial have already been met. Investigators also may exclude a potential research participant if they have reason to believe that the person has been subject to undue pressure to participate and thus the decision to participate is not a voluntary one. For parallel reasons, investigators may exclude research participants because they take seriously their duty to avoid exploitation in recruiting participants to their trials. The concern with avoiding Type 1 errors is not a concern that needs to be expressed, or is best expressed, in the language of paternalism. If this is right, then Type 2 errors, while they may be regrettable, need not violate any claim on the part of potential research participants.

This section has argued that on a respect-based approach to informed consent in clinical research, there is good reason to give priority to minimizing Type 1 over Type 2 errors. We should reject the equal weight view. The argument does not imply that absolute weight should be given to avoiding Type 1 errors. Positive autonomy implicates real interests, even if it does not ground a claim to participate in research trials. A satisfactory account of the demands of AAC will not completely ignore these interests. But once it is granted that priority should be given to avoiding Type 1 errors, the case for holding that autonomous authorization is compromised if research participants do not understand or appreciate the nature of the trials in which they participate or the risks and benefits they present, is compelling.

VI. THE STANDSTILL OBJECTION

Critics of AAC sometimes express unease about articulating the demands of informed consent for clinical research. If the demands are specified clearly, and if they require research participants to understand and appreciate relevant information, then much of current practice may be called into question. As Sreenivasan observes, if the therapeutic misconception invalidates informed consent and "if the therapeutic misconception is widespread, enrolment [*sic*] in many clinical trials should then be brought to a near standstill, which seems unacceptable" (Sreenivasan, 2003, 2016).

The unease expressed by these remarks is understandable, since research trials are crucial for continuing efforts to combat disease. Bringing them to a standstill would set back the interests of countless future patients. Yet, although understandable, there is nonetheless something odd about the unease. Suppose that we discovered that coercion and deception were much

more pervasive in clinical research than we had thought. Much current practice, we learn, involves tricking or forcing participants into trials in order to meet recruitment targets. It would be odd to respond to this disturbing discovery by proposing that we should not insist on voluntariness as a condition of ethical enrollment in clinical trials because doing so would bring research to a near standstill, which is unacceptable.

The standards and demands of informed consent are critical standards that we use to assess and criticize current practice. But if the standards and demands are adjusted to fit current practice, then they cannot perform their critical function. That is why the "standstill objection," as we might call it, is odd. Rather than adjust our ethical standards to current practice, we should adjust current practice to fit our ethical standards.

A different way to formulate the standstill objection is available. Rather than adjusting the requirements of informed consent to fit current practice, one could allow that current practice fails to meet the standards of informed consent, but insist nonetheless that current practice is justified. On this view, the prospective benefits to future patients made possible by clinical research justify overriding the claims of subjects not to be subjected to research trials without their informed consent. Charles Fried, in an early and insightful discussion of the ethics of medical experimentation, concluded that there is no reason to assume that a satisfactory resolution can be reached between the societal imperative to have research go forward and the demand to respect the rights and claims of all parties involved in the research (Fried, 1974). He called for candor and open acknowledgment of the ethical tension involved in clinical research, and it is arguable that research ethicists should be more willing than they have been to follow his counsel.

Notwithstanding this point, two main worries lie behind the standstill objection. Securing autonomous authorization for participation in clinical trials might prove to be prohibitively costly or it might make it too difficult for investigators to recruit participants to their trials.[16] Neither worry looks particularly troubling, however, so long as autonomous authorization is not construed to require perfect comprehension of all relevant information or perfect rationality in processing relevant information and applying it to one's situation. There is little reason to think that correcting the therapeutic misconception or counteracting the negative effects of certain well-understood biases must be prohibitively expensive. If the research community were committed to this goal, it could be achieved without bringing valuable research to a halt.[17] Nor is there good reason to think that investigators could not recruit subjects to their trials if these defects in informed consent were corrected. Of course, if it turned out that informed consent did indeed pose a real threat to recruitment goals to valuable research, then we would confront the need for candor to which Fried alluded.

VII. CONCLUSION

Clinical research is justified by its prospective results. Gains in medical knowledge and potential improvements in treatment for future patients justify spending social resources on the enterprise and imposing risks on research participants. But, clinical research is not fully justified unless research participants are treated with respect by those who conduct and oversee clinical trials. A key component of this respect is to secure the informed consent of all participants.

The critics of the standard view discussed in this article do not challenge the requirement of informed consent directly. Instead, they argue that its demands should be interpreted minimally. On the minimalist view, valid consent to participate in research does not require that participants understand or appreciate relevant information. Proponents of the minimalist view often contrast it with a higher or more aspirational mode of consent, a mode of consent that they say is desirable, but not required for consent to be valid (Miller and Joffe, 2013, 763). Against this view, I have argued that clinical research is a distinctive moral enterprise and that there are features of the practice, at least in the standard case, that explain why it is appropriate to demand that informed consent in this context must meet a standard of autonomous authorization, even if autonomous authorization is not necessary for consent to be valid in other contexts of consensual interaction. Autonomous authorization is not a maximally demanding standard that requires participants to have perfect knowledge and perfect rationality, but it does require them to understand and appreciate the nature of the trials in which they participate, as well as the risks and benefits such trials present.

To take informed consent seriously in clinical research, we must take its demands seriously, and we must be willing to adjust current practice so that it honors the principle of respect that informs contemporary research ethics.

NOTES

1. In some special contexts, such as emergency research, informed consent may not be a requirement for ethical research. I ignore these contexts here.

2. In this article, I am concerned with clinical research conducted on patient-subjects. Research on healthy volunteers raises additional issues that I will not mention.

3. Some writers on consent argue that it is a performative activity. It occurs only when communication occurs, and communication consists of outward behavior. See Dougherty (2016). This view is consistent with the standard view.

4. We need to assume that in Sreenivasan's example participants in the trial could not receive superior treatment outside of the trial. In other words, the favorable risk/benefit ratio presented by the experimental treatment is better than any alternative treatment available.

5. The same lesson is suggested by the examples provided by Truog et al. (1999). They argue that informed consent should not be required for trials that satisfy the standard of clinical equipoise and for which "no reasonable person should have a preference for one treatment over any other" (Truog et al., 1999, 805). In defending what they call the "difference position," Miller and Brody (2003, 20) claim that "the ethics of clinical trials must start with the realization that medical research and medical treatment are

two distinct forms of activity, [and thus] governed by different ethical principles." The argument I am putting forward can be understood to be an implication of the difference position. The standards of informed consent appropriate for research are not the same as those for beneficent medicine.

6. Proponents of the standard view could claim that it is important to draw a bright line between research and therapy because doing so is a safeguard against mistake and abuse. For this reason, nonstandard cases of clinical research that resemble beneficent medical care should be treated like standard cases when it comes to the demands of informed consent. This claim is a supplement to, and not a necessary part of, my defense of AAC, however.

7. Wertheimer seems to acknowledge this point. Toward the end of his discussion of the Fair Transaction Model, he allows that a fully developed account of fair transaction could show that investigators in clinical research have duties to take active steps to counteract the therapeutic misconception, and perhaps other autonomy-impairing defects, among research participants. See Wertheimer (2011, 105).

8. These include The Nuremberg Code, The Declaration of Helsinki, and The Belmont Report, as well as many others.

9. One of Wertheimer's examples of morally transformative consent that does not meet the standard of autonomous authorization is the consent that people give to gamble in casinos. No one has ever seriously claimed that the gambling industry is a moral enterprise based on respect and trust. See Wertheimer (2011, 81–82).

10. In this example, the investigator cultivates misunderstandings and failures of appreciation, and this is wrong for many reasons; investigators can take advantage of these same failures even if they do not deliberately encourage them. When they do so, they exploit research subjects for the good of their research.

11. Perhaps trials with an extremely unfavorable risk/benefit ratio to participants should not be permitted. Maybe there is an upper limit to how much risk a research participant should be allowed to assume, even with their autonomous consent. A discussion of this issue is not possible here.

12. A reviewer points out that one could appeal to the idea that it is morally worse, other things being equal, to cause harm than to fail to support the view that avoiding Type 1 errors should take priority over avoiding Type 2 errors. This idea can supplement the argument I present, but it is not essential to it.

13. Investigators could have duties to respect research subjects without its being the case that these duties are owed to the research subjects. Thus, investigators could do wrong in disrespecting research subjects without wronging them. However, if a research subject is wrongfully exploited, then he is plausibly wronged. And, as I have explained, Type 1 errors raise concerns about disrespectful exploitation.

14. For help in formulating this point, I thank Steven Wall.

15. If research subjects have a claim against being subject to disrespectful exploitation, could they waive this claim? It is a difficult question. My sense is that if they can waive this claim, then they must do so autonomously. Their waiver should not be done in ignorance or misunderstanding about the nature of the trials they are considering joining.

16. In this spirit Sreenivasan (2005, 370) writes: "a predictable consequence of enforcing a requirement of adequate comprehension will be to imperil clinical research of considerable moral value and importance. Hence, our justification for this requirement had better be pretty impressive, so as to warrant a moral cost of that magnitude."

17. See Wendler (2004) for an interesting discussion of how to approach this task in ways that are feasible.

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