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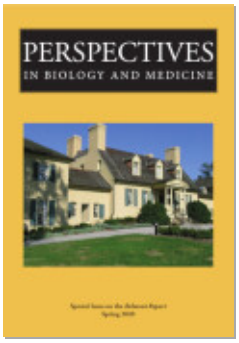

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ABSTRACT The *Belmont Report* attested to the cardinal importance of informed consent for ethical research on human subjects. Important challenges to securing informed consent have emerged since its publication more than 40 years ago. Among some of the most significant of these challenges are those that highlight social psychological factors that have the potential to impair the appreciation of relevant information disclosed in the informed consent process. Responding to these challenges requires us to think harder about the content of the principle of informed consent and the demands that it imposes on investigators. This article focuses on two challenges in particular, that presented by the so-called therapeutic misconception, and that presented by the psychological bias of unrealistic optimism. After outlining an account of the principle of informed consent as it applies to the research context, the article briefly reviews the empirical literature on the therapeutic misconception and the bias of unrealistic optimism. It then relates these phenomena to the principle of informed consent, paying special attention to the ethical demands they impose on investigators. The article concludes by considering how recent trends to integrate research and clinical care affect the main points it has advanced.

Ethical research on human subjects requires that subjects, if they have the capacity to do so, give free and informed consent to participate in the trials in which they are enrolled. This requirement, which is commonly referred to as the

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principle of informed consent, was prominently endorsed by the authors of the *Belmont Report* in 1978, and it remains widely accepted today. Yet while the principle of informed consent is by now almost universally accepted, the responsibilities that it imposes on those who conduct research on human subjects is a more contentious matter. New challenges to securing informed consent have emerged since the publication of the *Belmont Report*, and responding to these challenges requires investigators to think harder about the nature of informed consent and the demands that the principle of informed consent imposes on them. Two challenges in particular will be considered in this article, that presented by the so-called therapeutic misconception, and that presented by the psychological bias of unrealistic optimism. The first of these phenomena is specific to the context of clinical research, whereas the second applies to consent contexts more broadly.

The core idea of informed consent is well understood, but details and context matter. This article begins with an account of the principle of informed consent as it applies to human subjects research. It next reviews the empirical literature on the therapeutic misconception and the bias of unrealistic optimism, before relating these phenomena to the principle of informed consent, paying special attention to the ethical demands they impose on investigators. The final section considers how recent trends to integrate clinical research and medical care affect the main points advanced in this article.

The Principle of Informed Consent

The *Belmont Report* did not provide a complete statement of the principle of informed consent, but it identified some of the key elements and highlighted the fundamental concern that underlies it: "Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them" (National Commission 1978, 10). The concern in controlling what happens to us that is invoked is not simply an interest in control simpliciter, but in controlling what other people can and cannot do to us. Informed consent is interpersonal.

Informed consent serves both well-being and autonomy. It serves our well-being by helping to protect us from engaging in activities that could harm us, and by enabling us to cooperate with others in ways that further our interests. It serves our autonomy by giving us the power to shape our lives in ways that reflect our values. Different accounts of informed consent reflect differing assessments of the relative importance of protecting people from being exploited or manipulated by others, as against the good of allowing them to make decisions that they judge to be in their interests or consistent with their values. Setting the conditions of informed consent too low risks exposing people to too much harm; setting them too high risks preventing them from making the decisions that they want to make. Accordingly, some balancing of costs and benefits is required, and different accounts of the conditions of informed consent balance them differently.

Informed consent applies to interpersonal interaction generally, although its conditions and their stringency vary from context to context. For example, we should not expect a good account of consent for sexual relations to mirror a good account of consent for commercial transactions. It is common in medical ethics to assume that the principle of informed consent applies to both medical care and human subjects research. However, there are distinctive features of the research context to which the principle of informed consent, when it is applied to this context, must be responsive. Foremost among these is that the research context is always a potentially exploitative context, whereas this is not true of beneficent medical care. As the *Belmont Report* pointed out, some research trials are mixed, in that they contain therapeutic and experimental components, but if a trial contains any experimental component, then it is appropriately described as research. I come back to this point at the end of this article.

The principle of informed consent regulates the rights and duties of investigators and adult research participants.[1] Sometimes investigators make commitments to research participants, such as committing to provide them with ancillary care or promising them post-trial access to study interventions that prove to be effective. These commitments create duties that did not exist prior to the consent. Likewise, by consenting to participate in a trial, research subjects make it permissible to include them in it, and they may thereby waive certain rights, such as the right to take medications that are inconsistent with the trial protocol. In these and other ways, informed consent helps to fix the rights and duties of the interacting parties.

The principle of informed consent also sets boundaries to valid consent. For example, the *Belmont Report* maintains that ethical research must have a favorable risk/benefit ratio. The best formulation of this requirement is a matter of debate, but the notion that some such restriction is necessary is widely accepted. This restriction is relevant to the principle of informed consent insofar as it renders invalid any consent to research that runs afoul of it. A full statement of the principle of informed consent for human subjects research, accordingly, needs to attend to all the ethical restrictions that bear on the permissibility of conducting it. When abstracted from this wider ethical context, the principle of informed consent is ripe for misapplication.

In the research context, coercion, duress, and undue influence are taken to invalidate consent. The principle of informed consent thus includes a condition of voluntariness. In addition to being voluntary, informed consent also must be based on an adequate understanding of what is being consented to. That is why investigators must disclose to potential research participants information that is

[1]Research involving children or adults without decision-making capacity presents special problems and is regulated by principles other than the principle of informed consent. The principle of informed consent also may not apply to certain special cases involving competent adults, such as research that involves deception (see Wendler, Miller, and Swartzman 2005).

relevant to the decision of whether or not to participate. Questions of what, and how much, information must be disclosed are difficult and require judgment (Veatch 2003). But the duty to disclose has a point: it is to provide potential research participants with the information that they need to understand if they are to make a rational decision to participate.

There is not consensus among research ethicists on all the requirements of informed consent. For example, it is sometimes claimed that even comprehension of the disclosed information is not necessary for consent to be valid (Sreenivasan 2003). This mistaken claim arises from the failure to distinguish the conditions of informed consent from the duties that these conditions ground. An investigator will not be at fault if she fully discharges her duties to secure informed consent from the research participants she enrolls in her trial, but it does not follow from her blamelessness that all research participants in her trial have given their informed consent.

The transition from disclosure to understanding is important, but it is not the endpoint. Research participants may comprehend disclosed information, but fail to appreciate it. Appreciation requires applying what one has understood to one's situation. Research on informed consent has found that people can comprehend information regarding their disease or the risks presented by a research trial without believing that this information applies to them. Research also has found that "factors associated with Understanding and Appreciation can vary independently of each other and are impaired by different factors" (Grisso and Appelbaum 1998, 44). As we will see below, appreciation helps to capture what is worrisome about both the therapeutic misconception and unrealistic optimism.

Failure to appreciate relevant information could be taken to indicate that one lacked the competence necessary for informed consent, and certain cognitive states and emotional disorders that impair appreciation fit this description. But others do not. In particular, various biases that "operate behind the back" of the agent may impair the individual's appreciation of relevant information (Elster 1983). Biases, like unrealistic optimism, are prevalent in human psychology, and they play both positive and negative roles in our lives (Kahneman 2011). If biases are relevant to informed consent in human subjects research, it is not because they undermine the competence to make decisions, but because they influence decision-making in ways that matter, given the values that underly the principle of informed consent.

To sum up, valid consent in research is free and informed. Free consent requires the satisfaction of the voluntariness condition, and informed consent requires the satisfaction of the understanding and appreciation conditions.

The Demands of Informed Consent

The principle of informed consent is compelling, but the details of its requirements matter. And one source of resistance to the principle of informed consent

is that it places excessive demands on investigators. By doing so, it either unjustifiably sets back laudable efforts to combat disease or breeds hypocrisy among those who pay lip service to it. In responding to these concerns, we confront a choice: either we can adjust the conditions of informed consent to the demands that it would be reasonable to impose, or we can allow that informed consent may not be secured, even if investigators have taken all reasonable steps to secure it.

There are compelling reasons to avoid the first of these options. Consider the difference between a fact-relative and an evidence-relative account of informed consent. On the fact-relative account, one can give informed consent, or fail to do so, even when the available evidence suggests otherwise. For example, an investigator may have a justified belief that all the participants in her trial have given their free consent to participate; but, unbeknownst to her, some have not done so. Perhaps they are subject to duress from others of which the investigator is unaware, and could not be expected to be aware. While in this kind of case the investigator is not appropriately subject to criticism, it remains the case that some participants did not give valid consent to participate.

The plausibility of the fact-relative account of informed consent bears on the demandingness issue. It would not be reasonable to demand that investigators guarantee that no one enrolled in their trials had failed to give informed consent. This is not reasonable, since at most we can demand that they take appropriate steps to see to it that informed consent has been obtained. If an investigator has taken those steps, and reasonably thinks that no one in her trial has failed to give their informed consent, then she has discharged her duties. But none of this establishes that informed consent has in fact occurred.

Those who insist that the conditions of informed consent should be adjusted to fit what it is reasonable to demand of investigators discount the possibility of blameless error (Jansen 2018). In the example I just sketched, the investigator may make a mistake—she may enroll a person in her trial who has not given informed consent to do so—but this error is not one for which she can be criticized. In reply, one might try to drive a wedge between the fact of informed consent and its success in effecting normative change. This approach is suggested by those who argue for a "fair transaction" model for informed consent (Miller and Wertheimer 2011). On this model, "B's consent token is morally transformative if B [a research subject] tokens consent or appears to token consent under conditions in which A [an investigator] has acted fairly towards B in obtaining B's consent" (Wertheimer 2010, 89). The fair transaction model shifts the focus from the satisfaction of the conditions of informed consent—voluntariness, understanding, appreciation—to the fairness of the circumstances under which A and B interact. If A does all that is required of her in soliciting B's consent, then she is morally permitted to enroll him in her trial.

The fair transaction model deserves more careful scrutiny than I can give it here, and it has the virtue of bringing the issue of the demandingness of the re-

quirements of informed consent to the forefront. Nevertheless, in downplaying the significance of the satisfaction of the conditions of informed consent, the model errs. It will be helpful to explain the root of this error before moving forward.

The values to research participants that the principle of informed consent serve, well-being and autonomy, are not secured by fair treatment from investigators. Fair treatment is a means to their securement, but it is an error to substitute the means for the ends. Recognition of this important point is consistent with allowing that researchers need to understand what their responsibilities are to those who participate, or desire to participate, in their trials, *and* that these responsibilities are sensitive to considerations of what can fairly be demanded of them.

The need to distinguish the demands that informed consent imposes on investigators from the conditions of informed consent can be further appreciated by considering cases in which they come apart. These are cases in which either the demands are satisfied, but the conditions are not met, or the conditions are satisfied, but the demands are not met. To illustrate these possibilities, consider the duty to disclose trial-related risk/benefit information to research participants. Two scenarios can be compared.

> *Scenario 1:* Ann [an investigator] does all that she can be fairly asked to do to disclose relevant information to Bruce [a research subject], but unbeknownst to Ann, and as a result of a random transcription error in the copying of the informed consent forms that are given to Bruce, some relevant information is not, in fact, disclosed to Bruce.
>
> *Scenario 2:* Ann culpably fails in her duty to disclose relevant information to Bruce. She willfully or carelessly withholds this information from him. However, unbeknownst to Ann, Bruce is aware of the information (perhaps another participant has discussed it with him) and gives his free and informed consent to participate in Ann's trial.

Ann's failure in scenario 1 is blameless, and her conduct is not open to criticism, but this does not the alter the fact that Bruce has consented to participate without adequate disclosure of relevant information. In contrast, in scenario 2, Ann's failure is culpable and her conduct is open to criticism. But her culpable behavior does not prevent Bruce from understanding what he needs to understand to give free and informed consent to participate in Ann's trial.

It might be objected that insisting on a sharp distinction between the conditions of informed consent and the demands that they impose on investigators makes the principle of informed consent objectionably unrealistic. Three points can be made in response. First, while the conditions and demands of informed consent need to be distinguished, they are tightly related. The point of the latter is to improve compliance with the former. Second, the question of how stringent the conditions of informed consent are differs from the question of how demand-

ing the requirements that they impose on investigators are. How realistic or unrealistic the conditions of informed consent are is a separate matter that needs to be investigated on its own terms. But, third, some measure of unrealism is in fact valuable, and it is well accommodated by insisting on the distinction between the conditions and demands of informed consent.

This last point bears directly on the significance of the therapeutic misconception and unrealistic optimism for informed consent in clinical research. In order to be reasonable, demands imposed on investigators must be sensitive to the costs of meeting these demands and the means of doing so that are currently available. For example, suppose that there is some defect in the informed consent process—call it Defect X—that is costly or difficult to detect, or for which there is no reliable tool for detection. These facts could make it unfair to require investigators to ensure that they never enroll participants in their trials who are subject to Defect X. Nevertheless, if there were good reason to believe that a significant number of research participants were subject to it, then the research community as a whole would have an obligation to develop cost-effective measures for detecting Defect X, assuming that there were promising avenues available for doing so. In this situation, while it would remain unfair to demand that individual investigators never enroll a participant in their trials who suffered from Defect X, the ethics of the clinical research enterprise would be called into question if the research community as a whole responded with indifference to the problem.

Therapeutic Misconception and Unrealistic Optimism

The theoretical points I have been advancing provide background for thinking about the significance for informed consent of the two phenomena that are the primary focus of this article. These phenomena can be helpfully viewed as potential real-world examples of the imagined Defect X. Responding to them requires attention to both the conditions of informed consent and the demands these conditions impose on investigators.

The better known, and more widely researched, of the two phenomena is the therapeutic misconception. Drawing on interviews of research participants in psychiatric trials, Paul Appelbaum and colleagues introduced the term in their pioneering paper on the topic nearly 40 years ago (Appelbaum, Roth, and Lidz 1982). Since then, the therapeutic misconception has been extensively studied, and it has been widely viewed as a serious impediment to informed consent in clinical research. The therapeutic misconception occurs when research participants confuse the context of experimental research with that of beneficent medical care. This confusion is thought to compromise either, or both, the understanding and the appreciation conditions of informed consent.

The measurement of the therapeutic misconception, however, is complicated by the fact that researchers use different methods for assessing it. A panel of

experts convened to discuss the therapeutic misconception observed that despite the substantial empirical work on it, "a consistent definition has not emerged in the literature" (Henderson et al 2007). Despite this, there is broad agreement among research ethicists and researchers on informed consent that the therapeutic misconception involves at least one of the following two basic errors: (1) falsely believing that treatment received in a research trial will be individualized to a participant's own situation,[2] and (2) falsely believing that the primary purpose of research is to provide therapeutic benefit to its participants, rather than to promote generalizable scientific knowledge.

Defined in these terms, the evidence for the therapeutic misconception among research participants across a wide range of clinical research trials is substantial. Despite some doubts that have been raised about the methods for measuring it (Kim et al. 2015; Weinfurt 2013), most scholars agree that it is prevalent in clinical research. A systematic review of the data on the therapeutic misconception from 44 clinical research studies found it to be pervasive, and the authors of the review summarized their results as follows:

> Our findings show that 31.1% of participants expressed inaccurate beliefs regarding the degree of individualization of their treatment, while 51.1% manifested an unreasonable belief in the nature or likelihood of benefit, given the methods of the study in which they were enrolled. A total of 61.8% of participants were judged to have a TM on one or both of these bases. (Appelbaum, Lidz, and Grisso 2004, 4-5)

A 2012 study of 220 patients from a variety of clinical trials found a somewhat lower rate of therapeutic misconception (Appelbaum et al 2012). Approximately 55% were found to harbor some misconception along one or more of three dimensions: the purpose of the trial, the degree of individualization of treatment, and the expectation for therapeutic benefit.

These findings reflected a permissive strategy for identifying the therapeutic misconception, insofar as any clear indication of it was taken to be indicative of the phenomenon, even if subjects also expressed contrary responses that suggested otherwise. The findings also took evidence of unreasonable expectations of benefit or unreasonable minimization of risks associated with trial participation as an indicator of the therapeutic misconception. This calls for comment. As the authors correctly noted, "misestimations of risk and benefits can occur for many reasons" (Appelbaum, Lidz, and Grisso 2004, 3). For example, they may result from simple failures of disclosure. In their review of the data, the authors thus attempted to identify those misestimations of risk and benefits that "occurred as a result of a misconception about the nature of research itself" (3).

[2]Certain aspects of the research design in some trials may be individualized to the needs of individual patients (Kimmelman 2007). In such cases, the belief that the relevant aspects were individualized to one's personal situation would not be a false belief, and so would not indicate a therapeutic misconception.

Determining the causal factors that give rise to unrealistic assessments of risk and benefit, however, is challenging, especially when more than one factor may be at work. This brings us to our second phenomenon, the bias of unrealistic optimism. This bias has been extensively studied in social psychology, and it has been found to be prevalent among participants in early-phase oncology trials. Unrealistic optimism refers to an event-specific bias, whereby people believe they are less likely to experience negative outcomes and/or more likely to experience positive outcomes than similarly situated others. Applied to clinical research, unrealistic optimism is present when participants believe that they are more likely to benefit or less likely to experience adverse consequences from trial participation than similar others who are participating in the trial. It is a bias insofar as it interferes with the rational appreciation of risks and benefits.

There are different ways to measure unrealistic optimism. In a typical study, people are asked to compare their own susceptibility to a risk, or benefit, associated with a specific event compared to others with similar characteristics. This comparative method does not require knowledge of an objective standard of risk or benefit, which is often unavailable. Thus, in principle, people could be unrealistically optimistic about an event, in this comparative sense, while having an accurate assessment of the likelihood of the event in the objective sense. But, in fact, a number of studies have found that people who are unrealistically optimistic in the comparative sense are also unrealistic in the objective sense (Shepperd et al. 2013).

Might this bias account for a significant amount of the expectations for benefit commonly observed among research participants? If research participants expect substantial therapeutic benefit from a trial that promises little to no benefit, then is this necessarily problematic? Commentators on informed consent in human subjects research sometimes point to the ambiguity of expressions of optimism (Horng and Grady 2003; Weinfurt 2013). Perhaps when research participants express an unrealistic expectation for benefit from trial participation, they are simply expressing a positive statement about their future rather than making any kind of mistake. There is likely some truth in this. But unrealistic optimism, understood as a bias, is not mere hopefulness about a future event. Nor is it a product of dispositional optimism—in other words, having a positive outlook on life. In the social psychological literature on unrealistic optimism, careful efforts have been made to distinguish it from these other conceptions of optimism (Jansen 2011; Radcliffe and Klein 2002).

When writers confidently assert that optimism regarding one's participation in a research trial is never a problem from the standpoint of informed consent (Horng and Grady 2003), they are most charitably interpreted as referring to event-specific hope or dispositional optimism. Determining the significance of unrealistic optimism for informed consent to participate in clinical research is, in contrast, a much more complicated matter. It requires an assessment of how

significantly the bias interferes with the rational processing and appreciation of relevant risk/benefit information among those who manifest it.

A substantial body of empirical work has been done on unrealistic optimism and its effects on risk-related decision-making and behavior (Weinstein 1980; Weinstein and Klein 1996). Recently, this approach to studying optimism has been applied to participants in research trials. The results from the few studies that have been undertaken suggest that unrealistic optimism is prevalent among trial participants. For example, a study that I and my research team conducted on participants in early-phase oncology trials found that the bias was present when patient-subjects were asked about the possibility of their cancer being controlled by drugs administered in the trial, experiencing health benefits from participation in the trial, and not experiencing health problems from the drugs administered in the trial (Jansen et al. 2016). This study found no significant correlation between unrealistic optimism and dispositional optimism. Further, it found that there was no significant correlation between unrealistic optimism and patient-subject understandings of the purpose of the trial in which they were enrolled, thereby indicating that unrealistic optimism is distinct from the therapeutic misconception.

Researchers have found that unrealistic optimism is evoked when an event is perceived to be controllable. The greater the subject perceives the event to be subject to her control, the more likely it is that she will manifest the bias with respect to that event (Klein and Helweg-Larson 2001). In line with this, Jansen et al found a significant correlation between unrealistic optimism and perceptions of control with respect to each of the events that evoked the bias in their study (Jansen et al. 2018). This result fits well with findings from other studies of the decision-making process of early-phase cancer trial participants. One study found, for example, that 44% of respondents reported that participation in the trial gave them a sense of control over their cancer (Agrawal et al. 2006). This same study found that participants expected to benefit from the trial, while at the same time believing that the trial would not benefit most of its participants. Thus, it is reasonable to infer that perceptions of control, and in this case illusory perceptions of control, played a role in evoking the unrealistic expectations for personal therapeutic benefit that were observed.

Thus far research on unrealistic optimism has been conducted primarily on adult participants in early-phase cancer trials. Further work is needed to confirm its prevalence in other populations of research subjects. However, assuming the bias is prevalent among research participants, it is natural to wonder about its impact on their decision-making. Is the bias consequential for their decision to enroll? Since unrealistic optimism has been shown to be consequential for behavior in other contexts, it is reasonable to presume that it is consequential for behavior in the research context as well. To test this presumption in a follow-up study, my team compared the unrealistic optimism scores of those who had agreed to participate in an early phase cancer trial with those who declined to participate

(Jansen et al. 2017). We found that the acceptors exhibited unrealistic optimism and the decliners did not. The decliners also scored better on questions designed to test the appreciation of risks associated with trial participation.

More research is needed on the decision-making processes of those who decline to participate in research trials. But if unrealistic optimism does indeed play a consequential role in the decision to enroll in a research trial, then it should concern those who are genuinely committed to informed consent. Along with the therapeutic misconception, the bias of unrealistic optimism may go a long way in accounting for the expectations for therapeutic benefit that trial participants have long been found to harbor.

Responding to the Defects

Explanation is one thing; practical response is another. Suppose that it is agreed that the therapeutic misconception and unrealistic optimism impair informed consent to participate in research, either by invalidating it or by diminishing its quality. Do they ground demands on investigators to respond to them? If so, how? These questions bring us back to our imagined Defect X.

A survey of empirical work on informed consent and clinical research concluded that "investigators have no reliable tools to achieve informed consent," and that the current regulatory system is "flying blind" (Flory, Wendler, and Emanuel 2008, 658). If this conclusion were correct, then investigators could not reasonably be expected to combat defects such as therapeutic misconception or unrealistic optimism. They might know that these defects were present among the pool of potential research participants, and they might believe that these defects compromised informed consent, but, short of shutting down clinical research, they could not know how to eliminate them. This situation would be unfortunate, "as inadequately informed research participants are less able to protect themselves either from exploitation or from the inherent risks of research" (Flory, Wendler, and Emanuel 2008, 658). The authors of this survey, accordingly, call for more empirical work on improving informed consent, which is indeed an apt response if the defects that generate concern fit the mold of Defect X.

But is it true that there are no reliable tools for assessing the therapeutic misconception and unrealistic optimism? In recent years, sophisticated tools have been developed for identifying these defects. Investigators could use these tools to screen potential research participants, and to exclude those who manifest the defects. Alternatively, the screening could be used to identify participants who are good candidates for additional interventions (Appelbaum et al. 2012). The tools, moreover, appear to be reliable. A therapeutic misconception questionnaire based on three decades of research on the topic is now readily available (Appelbaum et al. 2012). And, while the tools for measuring unrealistic optimism in clinical research have not been extensively applied in this context, they are modeled on

questionnaires that have been successfully employed by social psychologists to study the phenomenon in other health-related contexts. Finally, the administration of these tools is cost-effective and not overly time consuming. Given all of this, there is no reason why IRBs could not require investigators to screen for both of these defects prior to enrolling research participants in their trials.

An important issue of interpretation remains. The therapeutic misconception and unrealistic optimism questionnaires yield scalar assessments: they measure the degree or magnitude of the defect they target. Those who are committed to informed consent can reasonably disagree over where to set the threshold that marks a potential research participant as exhibiting too much therapeutic misconception or too high a degree of unrealistic optimism. Free and voluntary decisions need not be perfectly rational, bias-free decisions, but some level of irrationality or bias surely does call them into question (Elster 1983).

The conditions of informed consent, as I pointed out above, can be set high or low. This issue is distinct from the issue of how demanding the conditions are—in other words, how difficult or costly it is for investigators to meet them, whether they are high or low. But what considerations should guide us in setting the conditions? The key to answering this question is to grasp that there are costs on both sides. Conditions that are set too low expose research participants to exploitation; conditions that are set too high prevent potential research participants from participating in research when doing so would serve their interests and values. Some balancing of costs is therefore called for, even if there is no precise method for doing so.

Two ideas, I believe, should guide us in thinking about this matter. First, as a rule, avoiding the first kind of cost should take priority over avoiding the second: researchers have a negative duty to avoid exploiting research subjects, but no positive duty to provide them with an opportunity to participate in research (Jansen 2006, 2018; but see Miller and Joffe 2013 for an alternative view). Second, the stringency of the conditions should be sensitive to the risk/benefit profile of the research trials to which they apply (Appelbaum et al. 2012). Degrees of unrealistic optimism in particular become more tolerable as the research trial presents lower risks.

These ideas bring us back to the claim that the principle of informed consent applies differently in the research context than in the medical context. This claim may seem hard to sustain when research and medical contexts become blurred. To this issue I now turn.

Blurred Boundaries

There are two main ways by which the boundaries between research and medicine can be blurred. Research trials can include both experimental and therapeutic components, or access to experimental agents can be presented as genuine

"treatment" options. Neither type of blurring presents a fundamental challenge to the analysis presented here, but both complicate it.

The first way of blurring the boundaries integrates personal care with the research protocol. If a patient-subject receives both medical treatment and experimental agents in a trial, then the purpose of the trial is not as clear cut: it has both a scientific purpose and a therapeutic purpose. Still, the primary purpose of the trial remains scientific, because the medical treatment could be provided independently of the trial. This is why the authors of the *Belmont Report* judged that the presence of any experimental component is sufficient for the activity as whole to count as research. The therapeutic misconception will occur in these integrated trials whenever participants fail to understand that their primary purpose is scientific, and unrealistic optimism will be present when patient-subjects have unrealistic expectations of the risks and benefits presented by the overall package of interventions they will receive from the trial.

The second way of blurring the boundaries raises more challenging issues. It involves adopting a therapeutic orientation toward research. (Miller and Rosenstein 2003). Clinical research is defined by its purpose and by its mode of operation (for example, not providing individualized treatment to participants). It is not defined by its probable effects. Yet patient-subjects understandably will be in interested in the probable effects of participation in a trial, and, in light of these effects, they may decide that participation is in their best medical interests. If this decision is irrational or not warranted by the available evidence, then it is problematic. But suppose that it is a rational decision. For example, suppose that the trial is in the medical best interests of some of its participants. In this kind of case, it may not be problemmatic for a trial participant to adopt a therapeutic orientation toward the research (Kimmelman 2007), and indeed one could so without harboring a therapeutic misconception.

How then should the possibility of trials of this kind affect the analysis of the ethical significance of the defects of informed consent that I have presented? I have been treating the therapeutic misconception and unrealistic optimism as two types of defects that have similar normative upshots. But in cases where it is appropriate to adopt a therapeutic orientation toward the research trial, their normative significance plausibly diverges. Even in trials that are in the medical best interests of their participants, the therapeutic misconception remains worrisome (Kimmelman 2007). Patient-subjects, as noted in the *Belmont Report*, should be "given the opportunity to choose what shall or shall not happen to them," but if they fail to appreciate that they are participating in a research trial and instead believe that they are receiving personalized medical care, then they do not know what they are doing and thus have not really chosen to do it. However, unrealistic optimism, as I have explained, need not be a consequence of the therapeutic misconception, and thus its presence can be consistent with an accurate understanding of the differences between research and medicine. The concern about

unrealistic optimism in clinical research primarily centers on exploitation. But if the intervention one receives in the trial is in one's best medical interests—if it is, for example, as good as or superior to any treatment one could receive outside of the trial—then the concern about exploitation is muted.

The significance of this point is easily exaggerated. Calculating risk/benefit ratios for research trials is challenging (Rid and Wendler 2018). Uncertainty in clinical research is the norm. The favorable risk/benefit ratio restriction is commonly understood to include prospective benefits to future patients. Trials that satisfy this restriction do not thereby present favorable risk/benefit profiles to the participants themselves. And there are strong incentives for investigators and the institutions that support them to overstate the therapeutic promise of the trials they conduct. Still, granting all of this, the point stands. To the extent that it can be determined that the risks and benefits to participants of trial participation resemble the risk/benefit profile they would receive from standard medical care, unrealistic optimism on the part of trial participants becomes significantly less problematic from the standpoint of informed consent.

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