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Considerations in the evaluation and determination of minimal risk in pragmatic clinical trials

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Abstract

The classification system for categorizing the riskiness of a clinical trial is largely defined by the body of federal regulations known as the Common Rule (45 CFR 46, Subpart A) and by regulations governing the US Food and Drug Administration (FDA) codified in 21 CFR 50. This rule is applied according to the interpretation of institutional review boards (IRBs) charged with overseeing the research. If a clinical trial is determined by an IRB to constitute "minimal risk," there are important practical implications: the IRB may allow waiver or alteration of the informed consent process; the study may be carried out in certain vulnerable populations; or the study may be reviewed by IRBs using an expedited process. However, it is unclear how the risk levels of pragmatic clinical trials (PCTs) should be assessed. Such trials typically compare existing, widely used medical therapies or interventions in the setting of routine clinical practice. Some of the therapies may be considered risky of themselves but the study comparing them may or may not add to that pre-existing level of risk. In this paper, we examine current research regulations and common interpretations of those regulations and suggest that current interpretation and application of regulations governing minimal-risk classification are marked by a high degree of variability and confusion, which in turn may ultimately harm patients by delaying or hindering potentially beneficial research. We advocate for a clear differentiation between the risks associated with a given therapy and the incremental risk incurred during research evaluating those therapies as a

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basic principle for evaluating the risk of a clinical study. We then examine two studies that incorporate aspects of PCTs and consider how various factors including patient perspectives, clinical equipoise, practice variation, and research methods such as cluster randomization contribute to current and evolving concepts of minimal risk, and how this understanding in turn affects the design and conduct of PCTs.

Keywords

Common Rule; Pragmatic clinical trial; Minimal risk; Patient-centered outcomes research; Institutional review board; Ethics committees; research; Ethics; research

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Pragmatic clinical trials (PCTs) compare widely used treatments for which there is known practice variation. Such studies are done because the evidence for the superiority of one treatment compared to another is either conflicting or lacking altogether.[1,2] PCTs provide data that can guide "real-world" clinical practice. Because these studies focus on treatments that are in widespread use, there is controversy about the degree to which enrollment in such trials adds risk above the inherent risks of the treatments themselves. In this paper, we will examine the concept of risk as it applies to these studies. The term "risk," as we use it, refers to a probability that harm will occur. The harm can be major or minor and also could be physical, psychological, dignitary, or economic. A study is of minimal risk when the probability of harm is sufficiently low and/or the particular harms that might accrue are sufficiently minor.

PCTs are done in a variety of clinical settings and involve patients whose illnesses may encompass a wide range of severity. Some of the interventions evaluated present very low risk to patients, while others may be associated with higher risks. In our view, the inherent riskiness of interventions should not be considered as a risk of the research if these same interventions would be used as part of routine clinical care for patients who are eligible for the study. The risks of the research are only those additional risks above the risks associated with the disease and interventions that are already used in routine clinical care.

In what follows, we elaborate on the crucial distinction between, on the one hand, the risks that arise because a patient has a serious illness that can only be treated with therapies that have known and serious side-effects and, on the other hand, the added or incremental risks of the research. We suggest that it is crucial, in such circumstances, to distinguish the incremental risks of the research from the inherent risks of the clinical situation in order to determine whether a study is of minimal risk.

Definition of minimal risk

The concept of "minimal risk" is a term of art that is embedded in the U.S. federal regulations governing research in human subjects known as the "Common Rule" (45 CFR 46, Subpart A). The Common Rule defines "minimal risk" as follows:

> *Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those*

> *ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*[3]

The U.S. Food and Drug Administration (FDA) uses the same definition in 21 CFR 50.[4] The standard of comparing risks of research with the risks of daily life has been controversial for two reasons. First, different people's daily lives involve different sorts of risks.[5] It is unclear whether the proper comparator is the risk of an individual person's daily life or an "average" person's daily life (whatever that might mean). Second, in the context of clinical research, the "routine physical and psychological examinations or tests" that a potential research participant might ordinarily encounter are quite different from those that a healthy person might encounter.[6] Again, the regulations are unclear as to how exactly the risks of daily life should be quantified in order to judge whether the risks of a proposed study exceed them.

In this article, we examine current definitions, interpretations, and applications of the minimal risk standard and their special implications for pragmatic clinical research. We also analyze the concept of equipoise and propose a way to think about whether clinical equipoise exists with regard to two or more widely used treatments. Then, we examine two case studies of research protocols that were approved as minimal-risk studies. Finally, we discuss ways in which current regulations ought to be interpreted in order to allow more flexibility in determining whether a study is of minimal risk.

IRBs and Minimal Risk Determinations

The minimal risk threshold has important practical implications. If an IRB determines that a research study is of "no more than minimal risk," the study may, if it meets other qualifications, be conducted with a waiver of the requirement to obtain informed consent (or with an altered consent process).[7,8] Such studies may also be given expedited review by IRBs, in contrast with studies judged to entail more risk. Expedited review, while still rigorous, is often much quicker than review by a full IRB.[9,10] In addition, the minimal risk threshold is a prerequisite for performing certain types of studies in vulnerable patient populations.[11] Thus, much rests upon whether an IRB designates a study as "minimal risk" or "greater than minimal risk."

One might therefore expect IRBs to have well-understood and widely agreed-upon methods for determining the risk level of proposed research. However, many studies of IRB decisions reveal tremendous variation in how IRBs classify risk level in identical studies.[12-21] As a result, investigators conducting a study with a single protocol at multiple research sites that have separate IRBs may find differences in whether their study is permitted, granted expedited review, or allowed to proceed with a waiver of the requirement for consent. The regulations themselves allow this sort of variability, and in some cases, this may be appropriate, because IRBs are designed to be responsive to the local culture of their own institutions. However, in multicenter trials, such variability becomes problematic, since it creates situations where the consent requirements differ at different sites, leading to potential selection biases in subject recruitment. In some cases, the differences are quite idiosyncratic and seem unlikely to reflect deeply rooted or ethically relevant cultural differences.[22]

However, idiosyncrasy is probably inevitable given the intrinsic vagueness of federal regulations that make reference to "ordinary daily life" as a benchmark for assessing risk. It is difficult to quantify the actual risks of ordinary daily life. IRBs may resort to intuitive but inaccurate impressions regarding the riskiness of everyday activity.[5] For instance: an ordinary activity such as a trip by car during rush hour poses a ~1/10,000 risk of serious injury and a ~1/100,000 risk of death in children.[23] However, a pharmacokinetic study that posed a 1/100,000 risk of death, but had no other adverse effects, was characterized as more than a minor increase over minimal risk according to 59% IRB chairpersons.[14] It would seem that such IRB chairs are making their own interpretive assessments of what constitutes acceptable risks. Alternatively, the risks of daily life for people with different types of illness can be considerable. Patients with serious diseases often require risky procedures or treatments that are part of their everyday lives.

In addition to variability surrounding the definition of minimal risk,[24] there is also uncertainty regarding what specific risks ought to be considered as risks of research, rather than as the inherent risks of the patient's disease or the risks of the treatments that the patient would have received even if not enrolled in a research project. This is particularly important when considering the incremental risks of PCTs because, as noted above, they compare treatments and interventions that are already in widespread clinical use.

As an example, consider a study such as the ADAPTABLE trial currently funded by PCORnet.[25] This study plans to test different doses of aspirin to determine which dose is most effective at preventing ischemic events (i.e., heart attack or stroke) in patients who have already been diagnosed with heart disease. Such patients are at high risk of recurrent ischemic events: researchers predict that about 8% of participants will die or experience a stroke or myocardial infarction over a 2-year period. We know from prior studies that almost all (>90%) these individuals take aspirin, which is part of the current standard of care for such patients. But doctors disagree about which dose is best. Almost 61% of doctors recommend 325 mg; 35.6% recommend 81 mg, and 3.5% recommend other doses.[26] So what is the risk of a prospective randomized trial comparing the two doses? It may seem odd to say that a study entails only minimal risk when 8% of study participants may die or have a stroke or an MI. But we believe that is the correct assessment, because the patients would be facing those risks anyway, and it is unknown whether participation in the study will increase, decrease, or have no effect on those risk levels. Thus, there is no reason to believe that being in the study any riskier than those patients' daily lives.

The Common Rule would seem to support this interpretation. It states that, when an IRB evaluates risk, it "…should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)."[11] Nevertheless, IRBs seem to have trouble applying this standard consistently.[27] Recent proposed guidelines from OHRP seem to suggest a different standard for evaluating the risks of research.[28-30] Those guidelines state in part that "…at a minimum, identified risks associated with a standard of care that are being evaluated as a purpose of the research, should certainly be considered 'reasonably foreseeable.'"[28] As in the past, many bioethicists have disagreed with OHRP's interpretation of the risks of

different types of research.[31] Such disagreements might lead to confusion among IRB members.

Clearly, there is disagreement about what risks should be considered as risks of research as opposed to being considered as risks that would be present whether or not a person decides to participate in research. These different interpretations of federal regulations presumably lead to much of the variation in how IRBs apply the concept of minimal risk. Our view is that the risks associated with a person's disease or condition and risks associated with various treatments for that condition should *not* be considered research risks, even when a research project is designed to evaluate and compare the risks of those various treatments. Instead, those risks need to be disclosed as part of informed consent for treatment. The question for research purposes, then, is what additional information needs to be disclosed as part of informed consent for research.

Implications of IRB variability and risk aversion

In the context of multicenter studies, the variability in IRB risk determinations has two equally problematic possible implications. One is that the most risk-averse interpretations often become the guiding standards. That would occur if the protocol and consent process must be standardized. Such standardization would require conformity with the most restrictive IRB. Under this approach, more "permissive" IRBs would allow protocols that were approved by more risk-averse IRBs. Another possible implication is that the more risk-averse IRBs would accede to a protocol about which they harbored misgivings. In either case, the end result would be ambiguity about whether approval of the protocol was appropriate or not. There might also be ambiguity about whether a risk-averse stance was motivated by a belief that the protocol itself was actually risky to patients or, instead, by a desire to protect the institution from possible sanctions for deviating from federal guidelines. Further research is badly needed on these issues.

It is difficult to measure the net effect of this variability in risk-tolerance among IRBs. It may mean that fewer studies are carried out than would be the case if IRBs took a different approach. It is possible that potentially beneficial research may be delayed. It may also be the reason why, overall, the research enterprise in the United States is so safe for research participants. Clearly, any changes to the current system should be undertaken carefully, cautiously, and open-mindedly in order to determine the effects of those changes.

Risk, Benefit, and Clinical Equipoise

There are two important and intertwined concepts that inform the evaluation of the incremental risk of participating in a PCT. One is the concept of *practice variation.* The other is the concept of *clinical equipoise*. PCTs generally take place in situations in which there is well-recognized variation in the physician practice. Such variation is ubiquitous in modern healthcare and has been described with regard to most common clinical situations, including prescription drug use,[32] surgery rates for similar conditions,[33] costs of end-of-life care,[34] and many other things. Practice variation exists within the United States and within and among other countries.[35,36] It usually (but not always) reflects disagreement within the expert clinical community about which treatment approach is best for any particular patient.

The term “equipoise” is controversial. It refers to a state of mind that reflects genuine uncertainty about which treatment is best. It is always difficult to assess whether an individual is in a state of equipoise. Thus, Freedman coined the term “clinical equipoise,” which he defined as the circumstance that exists when there is “genuine uncertainty within the expert medical community,” even if each individual practitioner is confident that his or her approach is the best.[37]

Clinical equipoise is easier to measure than individual equipoise. In fact, the degree of practice variation within a community of practitioners who are well-informed of the state of existing evidence could be taken as a rough indication of the degree of clinical equipoise in that community. If, for example, we knew that exactly half of doctors preferred one treatment and half preferred another for identical patients, and all the doctors were well-informed of the state of existing evidence, then we could say that there was perfect equipoise. In many situations, we either do not know this, or we know that there are disagreements among the clinical community but those disagreements may not be evenly distributed. A greater or lesser degree of consensus among the clinical community about the best treatment would then correspond to a lesser or greater degree of justification, respectively, for conducting a PCT. It would also offer a way of assessing the likelihood that a participant in a research study would receive a different treatment than that person would have otherwise received as part of routine practice. To the extent that there is widespread practice variation, the resulting allocation of treatments will look very much like the allocation that will result from randomization.

The Problem of Dichotomizing Levels of Risk

Much of the variation in the regulation of research risks stems from policies that treat risk levels as a dichotomous rather than a continuous variable. If studies must either be minimal risk or greater than minimal risk, and if all studies in the latter category are treated similarly from a regulatory perspective, then any study that exceeds the minimal-risk threshold will be regulated in a fashion similar to that applied to the riskiest studies. This is especially problematic given evidence that IRBs tend to be very cautious, to the extent that anything riskier than a single blood draw is considered greater than minimal risk. This results in a misallocation of regulatory resources and might implicitly convey a false impression to research participants.

We believe that a more nuanced approach would be preferable. Studies that are very low risk but that might not be judged to meet current federal criteria for minimal risk ought not to be treated like the riskiest studies. Our idea is similar to one embodied in current regulations, which include a category of research that entails “a minor increase over minimal risk.” Currently, this category is only relevant for pediatric studies that offer no potential for direct benefit to participants and meet several other regulatory requirements. However, the concept of “minor increase over minimal risk” could be used in a different context, that of PCTs with adults, to characterize a type of study that might appropriately be carried out with a simplified consent process.

There are both conceptual and practical reasons to treat risk as a continuum, and to treat slightly risky studies differently than either minimal risk studies or high risk studies. Conceptually, such a spectrum better reflects the realities of PCTs in which the risks of being in the research study are likely to be comparable to the risks of being treated outside the research protocol. Many of these studies may pose risks of a sort that might properly be considered as a minor increase over minimal risk. In such cases, the consent process would focus on the known and anticipated differences between treatments for those who enroll in the research protocol compared with those who do not.

Low-Risk Studies in High-Risk Diseases: A Particularly Thorny Problem

One of the most complicated issues relevant to the categorization of risk is one that arises in the specific situation of PCTs performed in diseases that are themselves high-risk and for which currently available treatments also have known risks. These challenging situations require careful analyses to determine which risks should be attributed to the disease, which to the treatments that a patient would receive outside the study, and which are correctly attributed to the research itself. Below, we explore two recent examples of such studies. Two examples of such studies are the TASTE trial[38,39] of different interventions for myocardial infarction that was done in Sweden and the TiME study[40] of renal dialysis that is currently underway in the United States.

The TASTE Trial

The Swedish Thrombus Aspiration during ST-segment Elevation myocardial infarction (TASTE) trial enrolled hospitalized adults who showed signs of ST-segment-elevation myocardial infarction on electrocardiogram.[38,39] All such patients were treated with a revascularization procedure, and at the time of the trial, many patients were receiving thrombus aspiration and many were not. They were randomized to such a procedure either 1) without thrombus aspiration or 2) with thrombus aspiration as an adjunct therapy during their revascularization procedure.

At the time that the study was designed and implemented, there was substantial disagreement among cardiologists as to whether or not thrombus aspiration was safe and beneficial and constituted (or should constitute) standard care. There was both clinical equipoise among the cardiology community and known practice variation (of note: among 4,697 eligible patients who declined enrollment in TASTE, 75% underwent routine percutaneous revascularization while 25% underwent thrombus aspiration).[39]

So how should we assess the risk of participating in this study? At first glance, it seems preposterous to think of classifying this study as a low or minimal risk study. After all, it is a study of a potentially fatal condition for which a highly invasive procedure must be provided in a very urgent manner. And yet, the patients' condition and the different treatments were risks that the patients would face whether or not they were in the study. The only incremental risk of the study was any risk that traces to having one's treatment decided by a formal randomization procedure, rather than by one's physician based on individualized clinical judgment. As we discuss below, empirical data suggest that in the setting of clinical equipoise, randomization per se does not increase risks. There were no additional study

procedures or follow-up examinations, in part because, in Sweden, all cardiology patients have follow-up data entered into a national database. Thus, outcome information was available on all patients who were in the randomized trial. Such data will likely soon be available for many, though not all, U.S. patients as a result of the Clinical Data Research Networks that are being developed as part of the PCORnet project.

Thus, we believe that the TASTE study posed minimal incremental risk to study participants. In addition, we think that the modified approach to consent used by the TASTE investigators was both appropriate and permissible. The investigators did not waive consent altogether. Instead, patients were asked to provide oral consent after being given a brief (two-paragraph) oral description of the study. Patients who chose to enroll were asked to confirm their agreement by signing a written consent form within 24 hours.[38] This approach reflected an appropriate balancing of the particular circumstances of the study, the ethical commitment to seeking informed consent, an assessment of the risk level of the study, and the prevailing uncertainty and practice variation among expert cardiologists. We do not think, however, that many IRBs in the United States would have judged the TASTE trial to have been minimal risk. Thus, they would not have permitted the altered consent process. Certainly the “Draft Guidelines” recently issued by OHRP would not permit such a study to be categorized as minimal risk. We believe that the Swedish investigators and their IRB got it right.

The TiME Trial

The Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial[40] (NCT02019225) offers another example of a high-risk disease/treatment context for which the incremental risks posed by the study are quite low. A cluster-randomized PCT currently under way at U.S. hemodialysis centers, the TiME trial is examining the effect of extended (minimum of 4.25 hours) dialysis on the endpoints of all-cause mortality, hospitalization, and quality of life in patients with end-stage renal disease (ESRD) who require maintenance hemodialysis. The optimal duration of dialysis in this very ill patient population is not currently known. A series of observational studies[41-45] suggests a possible survival advantage for extended dialysis. There is at least one study, however, that did not find this survival advantage.[46] At present, there is known practice variation among dialysis centers in the duration of dialysis.

TiME is randomly assigning approximately 400 dialysis treatment centers to either usual care (i.e., no trial-specified duration for hemodialysis) or to extended (minimum 4.25 h) hemodialysis for newly admitted patients who are initiating treatment with maintenance hemodialysis during the study enrollment period (a total of ~6,400 patients). The trial was determined to constitute a minimal risk study and was granted a waiver of informed consent under the provisions specified in 45 CFR 46.116.[47] Consent is not sought beforehand from patients receiving dialysis at participating centers; however, all patients are provided with information about the study that includes contact information for patients with questions about the study. Posters with similar information about the study are also posted in the dialysis centers. The trial is being conducted using an opt-out mechanism for patient participation. That is, even though randomization is by center, patients at each center can opt out of participation.

The TiME trial is studying a serious medical condition in a population at substantial risk for morbidity and mortality. Despite this, the study was deemed to be minimal risk. We believe this judgment to be correct because we do not believe that treatment assignment by randomization increases the risks to study subjects. In addition, the TiME trial was granted a waiver of the requirement for informed consent because it would likely introduce imbalances across treatment groups; hence a requirement for individual consent would make the research "impracticable."

One could ask whether the TiME trial met the criteria for a waiver of consent only because the study required a cluster-randomized design. This was certainly an important consideration. It would have been impracticable—that is, difficult or impossible—to conduct the research by randomizing individual participants because of an inability to maintain true "usual care" at facilities with participants in both treatment groups—especially since, for an individual participant, randomized treatment assignment would occur before the duration of a usual-care session was established. However, we would particularly emphasize that for a study to qualify for waiver of consent, it must be both impracticable if consent is required and of minimal risk. We think that the TiME trial met both of these criteria.

Does Randomization or Treatment by Protocol Cause More than Minimal Risk?

When treatment effects are modest, randomization is a critical method for ensuring that valid inferences can be made regarding the causes of differences in outcomes associated with an intervention. A considerable body of evidence suggests that, in the setting of clinical equipoise, randomization per se does not increase risk or decrease benefits for participants in RCTs, compared with individualized physician-patient decision making based on clinical judgment.[48-51] While it would be ideal to have a randomized trial of randomization versus individualized treatment assignment, the data from retrospective meta-analyses are quite robust. Still, it should be noted that the spectrum of risks and benefits engendered by random assignment to one of two or more treatments may differ from the expected risks and benefits of treatment selection by the patient and doctor based on weighing the available evidence. Risks can be relevant to decision-making even when they are minimal. They may also be pertinent if they are of very different kinds of harms, as happens when, for example, a randomized trial compares outcomes for a medical treatment and a surgical one.

The Curious Situation of Cluster-Randomized Trials

Cluster-randomized trials (CRTs) typically involve interventions deployed across large numbers of research subjects within a system that may involve a classroom, a clinic, a hospital unit, or a geographical space such as a county or neighborhood.[52] Obtaining individual informed consent in such setting may be impracticable. However, if one believes that consent is always necessary when the risks are more than minimal, then the impracticability of obtaining consent—should not, by itself, justify waiver of the requirement for consent and indeed this interpretation is reflected in current regulations.

Instead, it would mean that studies that are of greater than minimal risk and in which it is impracticable to get consent should simply not be done.

That is not quite the prevailing situation. It is apparent from studies like the TiME trial that, under current U.S. regulatory frameworks, studies may be done using a CRT design that could not be done if randomization took place at the individual level. To see how this is true, one might imagine a study in which individual patients were to be randomized to two different dialysis regimens as they are in the TiME CRT. Few IRBs would approve a waiver or alteration of consent for such a study. Yet in both the actual and putative designs, the risks are identical and patients would have a 50/50 chance of being assigned to one treatment or the other. If such treatment assignment in itself led to a level of risk that was greater than minimal, then waiver of consent should not have been permitted in the CRT design. Whether the research would be practicable if consent were required is a different issue, but, for this discussion, we are assuming that it would be.

This prompts one of two conclusions. Either individual patient consent should be required for the CRT design, or the requirement for individual consent could be waived or altered in any study design that involves randomization on the individual level if the study would permit such a waiver in a situation where a study was designed using cluster randomization.

We favor the latter conclusion, though we would also suggest that the appropriate response, as in the TASTE study,[38] would not be to waive the consent requirement but to modify it. A modified consent could tell people that a study is taking place, the goals of the study, and the alternatives. As in TASTE, it is likely that the alternatives would entail being offered a choice of the treatments that are being evaluated as part of the study. One solution to this would be for the federal regulations to clarify whether there are situations in which waiver of consent would not be permitted but modification of consent would be. As is, the regulations suggest that in order to modify consent, it is necessary to first waive the requirement for an unmodified consent.

This analysis of one CRT suggests a general rule that might be used to determine whether a study is of sufficiently low risk that the requirement for consent might be waived or altered. If a study using a cluster-randomized design were approved with a waiver of the requirement for consent, then a study of the same interventions that employed randomization at the level of the individual should also qualify for altered or waived consent. This approach would properly lead to a rethinking of the formal requirements of a consent process. For minimal-risk studies, a minimally burdensome consent process might be appropriate. In some cases, such a consent process might also be more effective in helping prospective research participants to focus on the most important elements of a study, rather than on the many other issues that are required to be described in a “full” informed consent document.

Patient Perspectives and Minimal Risk

A major implication of the minimal-risk classification is that it allows informed consent to be waived or altered. One of the key concerns is that such waivers or alterations might erode the core ethical principle of respect for patient autonomy. As policies regarding consent are

developed and evaluated, it will be crucial to incorporate patient perspectives on the need for consent in different research studies and the preferable processes for obtaining it.

Research on patient attitudes regarding participation in studies without their consent gives conflicting results. A 2007 Institute of Medicine survey[53] found that only 1% of respondents supported allowing researchers to use their personal health information without their consent, while 8% said they would be willing to provide advanced consent for future studies without the further need for consent, and 19% said that so long as an IRB was overseeing a study and their identity would never be disclosed they would be willing to forego being asked for consent. In addition, the 2014 publication of a social-media study that investigated "emotional contagion" by manipulating information appearing on individual Facebook pages without the knowledge or consent of the research participants[54] was met with a largely negative public reaction.[55]

However, recent empirical investigations of patient attitudes toward research ethics in general and toward research on medical practices in particular suggest that patient attitudes may be quite nuanced and represent a complex spectrum of preferences for consent and notification, depending on the degree of perceived risk and potential for benefit.[56,57] In the future, as access to the internet continues to grow, direct involvement of patients in protocol design, including even broad "crowdsourcing," could provide a direct means of assessing patients' views about minimal risk and appropriate consent.

Minimal Risk and Informed Consent

There is clearly confusion among IRBs and disagreement among bioethicists as to how the concept of minimal risk ought to be defined and operationalized. Much of this confusion arises from a conflation of the concepts of minimal risk and "incremental" or "attributable" risk. If all of the risks of treatments that are to be studied must be considered as risks of research (as the OHRP draft guidance suggests),[28] then the only studies that will be considered as minimal risk will be those in which the treatments themselves are of minimal risk. Very few treatments meet such a standard. But if, on the other hand, the risks of research are considered to be only those incremental risks that are associated with the research procedures themselves (as opposed to the treatments that are being studied), then many studies should be deemed as minimal-risk studies. This approach would need to be carefully evaluated. In particular, studies should focus on whether prospective research subjects understand the ways in which pragmatic trials evaluate medical treatments and understand the potential risks and benefits of being or not being in a study.

There is almost universal agreement about one central principle: transparency is crucial. People need to understand when or if they are being involved in research (or their data is being used for research purposes). They also need to know whether there are any risks that might result from such research studies. They need to be provided accurate information in a format that is understandable. People are not well-served or respected by requirements for consent that exaggerate the risks of research or inaccurately minimize the risks of different treatments that are in common use. Finding the right balance between transparency, accuracy, and empowerment will require that we clearly differentiate both the risks and

potential benefits of therapies from the risks and benefits of evaluating those therapies. Doing so will lead to a system that is more patient-centered, more philosophically consistent, and more ethically defensible than the system that exists today.

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