HHS Public Access

Author manuscript

JAMA Psychiatry. Author manuscript; available in PMC 2015 June 26.

Published in final edited form as:

JAMA Psychiatry. 2013 December ; 70(12): 1363–1371. doi:10.1001/jamapsychiatry.2013.2105.

Addressing Risks to Advance Mental Health Research

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Abstract

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Objective—Risk communication and management are essential to the ethical conduct of research, yet addressing risks may be time consuming for investigators and institutional review boards (IRBs) may reject study designs that appear too risky. This can discourage needed research, particularly in higher risk protocols or those enrolling potentially vulnerable individuals, such as those with some level of suicidality. Improved mechanisms for addressing research risks may facilitate much needed psychiatric research. This article provides mental health researchers with practical approaches to: 1) identify and define various intrinsic research risks; 2) communicate these risks to others (e.g., potential participants, regulatory bodies, society); 3) manage these risks during the course of a study; and 4) justify the risks.

Methods—As part of a National Institute of Mental Health (NIMH)-funded scientific meeting series, a public conference and a closed-session expert panel meeting were held on managing and disclosing risks in mental health clinical trials. The expert panel reviewed the literature with a focus on empirical studies and developed recommendations for best practices and further research on managing and disclosing risks in mental health clinical trials. IRB review was not required because there were no human subjects. The NIMH played no role in developing or reviewing the manuscript.

Results—Challenges, current data, practical strategies, and topics for future research are addressed for each of four key areas pertaining to management and disclosure of risks in clinical trials: identifying and defining risks, communicating risks, managing risks during studies, and justifying research risks.

Conclusions—Empirical data on risk communication, managing risks, and the benefits of research can support the ethical conduct of mental health research and may help investigators better conceptualize and confront risks and to gain IRB approval.

Keywords

informed consent; research ethics; risk; mental health research

Introduction

With 26.2% of U.S. adults afflicted with a psychiatric disorder, improvements in psychiatric treatments are needed.[1] Despite advances for psychiatric disorders there has been increased public scrutiny over how mental health research is conducted and the risks to participants, particularly in the wake of concerns regarding non-published data on selective serotonin reuptake inhibitors and suicide,[2,3] studies on schizophrenia in which medication is withheld,[4] and increased litigation.[5] Researchers must proactively address risks—from minimizing risks inherent to study design (e.g., placebo controlled studies), to mitigating potential participant misunderstanding of the research purpose, to addressing risks of worsening symptoms during research participation (e.g., emergence of suicidal ideation or psychosis). Yet there are not always readily apparent means of addressing risks, particularly when those risks may be inherent in the overall research endeavor or associated with the illness itself, not the research. Institutional review boards (IRBs) and sponsors may halt or delay studies over concerns about participant risks. Increased investigator burdens because of real and perceived risks may discourage much-needed research. For example, suicide is

clearly associated with a history of depression and is the most serious potential outcome of depression, but only 10% of clinical trials examining SSRI efficacy between 1984 and 2001 included individuals with some level of suicidality. No SSRI efficacy trials in actively suicidal subjects currently exist.[6] Because the presence of suicidal ideation is a typical exclusion criterion in research, the community is left with 'evidence-based' guidance that is generalized to these excluded individuals. This pattern of exclusion has resulted in a dearth of evidence regarding treatment for individuals with varying degrees of suicidality. To facilitate research in this area, suicide should be treated as a negative outcome comparable to negative outcomes of other diseases - an undesirable yet to-be expected event.[7,8] To ignore this is to continue the unwarranted and unjust exclusion of these individuals.

Mental health researchers must strive to design ethical and scientifically sound research that does not ignore populations or kinds of research merely because of the difficulties involved. If mental health researchers continue to allow risks to discourage research, certain groups that could benefit from research will continue to be harmed by being understudied. Groups perceived as "high risk" deserve scientifically rigorous study as well. Researchers must be able to identify and communicate risks and potential benefits of this research to the public and regulatory bodies, demonstrate that they will manage risks effectively, and provide strong ethical justification for such research.

This article provides mental health researchers with practical approaches to: 1) identify and define various intrinsic research risks; 2) communicate risks to others (e.g., potential participants, regulatory bodies, society); 3) manage risks during the course of a study; and 4) justify the risks. These recommendations are the result of a systematic literature review, a public conference during which authors participated as speakers or panelists, a closed-door working session that included all of the authors, and subsequent email and phone conversations to formulate consensus recommendations. All authors participated in the writing and editing process.

I. Defining and Identifying Risks

A. Challenges in Defining Risk in Research—The Belmont Report provides the ethical framework for U.S. research regulations and identifies five primary forms of harm relevant to research review and oversight.[9] These are summarized in Table 1.

In addition to recognizing the types of harms that study participation may pose, investigators and regulatory bodies must determine studies' overall risk level. While risk is an inherent aspect of human life and familiar to all, it is difficult to define operationally. Most regulatory and philosophical definitions of risk include three primary concepts: the *probability* and *magnitude* of *harm*. However, there is no agreed upon formula for determining risk level. The Common Rule recognizes two risk categories for adult research: 'minimal' and 'greater than minimal.' Minimal risk is "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".[10] Whose daily life and which examinations are routine are not specified and instead left to IRB judgment. The Department of Health and Human Services (DHHS) identifies three categories of risk for research involving children—minimal risk,

greater than minimal risk with prospect of direct benefit, minor increase over minimal risk with no direct benefit. Studies that do not fit these categories require special federal review.[10]

In order to foresee and address research risks, investigators must identify the types, probability and magnitude of harm their study poses and describe risk information in protocols and informed consent discussions and forms clearly. Regulatory bodies, such as IRBs, ultimately define the study risks relevant to review and determine whether the "[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result".[10] However, guidance about defining and evaluating risks and benefits is limited and often focused on determining the extent to which additional protections are needed for studies deemed to be higher risk. Researchers may educate IRB members about study risks, including a comparison of research risks across different types of studies, when they have data that might inform IRB determinations.

B. Research Summary: State of the Field—There is no consensus on how best to evaluate and rate research risk levels, and IRBs are inconsistent in how they evaluate risk. Shah et al found significant variability among IRB chairs' rating of risk level.[11] Similar studies of IRB practices have demonstrated inconsistencies in rating protocols as eligible for expedited review versus requiring full review, a determination based largely on assessment of risk level since expedited studies must be minimal risk.[12–14] This variability results in uneven participant protections and delays in start date for funded research.[14&15] These issues are magnified in large-scale multi-site studies, which can provide greater statistical power with more meaningful and generalizable outcomes yet require review by multiple IRBs.[14]

Despite data indicating that mental health research is as safe as most other medical research and that participants typically possess capacity to consent for themselves,[16–21] mental health researchers may find that IRBs, which are not required to and may not have members with substantive expertise in mental health research,[10] judge their studies as posing higher risks than comparably risky non-mental health studies and believe that potential participants are less likely to be able to understand risks and given informed consent.[22,23]

C. Tips for the Savvy Researcher—Strategies for appropriately identifying research risks are summarized in Table 2 and include:

1. Identify and define risks early in study development. The Research Protocol Ethics Assessment Tool (RePEAT), developed by Roberts,[24] essentially is a checklist thatcovers multiple ethical domains, including scientific merit of the protocol; risks and benefits; expertise, commitment and integrity of the research team; informed consent and decisional capacity issues; incentives for participation; confidentiality. Researchers can apply the RePEAT (or variations of it) to their protocols to ensure that ethically important research elements are proactively addressed.
2. Study proposals should explicitly identify and address foreseen potential risks; how these risks will be communicated to potential participants; and how emerging risks

will be managed, depending on risk level, once the study begins, including, but not limited to, the use of data and safety monitoring board or external monitors. Section II explores strategies for communicating and managing risks.

3. To conduct research with groups that IRBs often exclude due to their "vulnerability," mental health investigators may need to work harder than other investigators to document for IRBs evidence of research risks and of the decisional abilities of potential participants (who are likely to otherwise be perceived as "vulnerable") to understand risk information and provide informed consent. For example, researchers may collaborate with community advisory boards, review the literature, and conduct focus groups to support inclusion.

D. Further Research Needed to Advance the Field—A better understanding of participant and IRB views and decision-making regarding risk would assist researchers in designing studies. Future research should aim to identify and understand the risks that matter most to potential participants, including understanding their concerns about privacy violations, legal risks, social harms at the individual level, and the burdens of participating in studies. Finally, more research on how IRBs evaluate risk, perceive institutional risk, compare risks and potential benefits, and make decisions could help investigators explain studies better when applying for IRB approval. Such research might also identify areas for IRB education. For example, one study compared IRB member judgments of consent capacity of potential participants in oncology, chronic pain, and major depressive disorder research studies. Persons with major depressive disorder were judged as having significantly less consent capacity than those with non-mental health diagnoses even when IRB members were told of the high incidence of depression as a comorbidity in oncology and chronic pain patients. IRB members also judged the psychiatric study as posing greater legal risk to the institution than the other studies.[22,23] If these apparently inconsistent analyses of capacity and risk by IRBs are typical, it would be appropriate to develop educational interventions to help IRBs develop new strategies for evaluating studies. Knowing whether there is a significant difference between perceived and actual institutional risk might help facilitate research. Future research needs are summarized in Table 3.

II. Communicating Risks with Research Participants

A. Importance of Communicating Risks—The regulatory[10] and ethical[9] obligation to obtain informed consent from research participants (or their legally authorized representatives) requires effective risk communication.[25] Risk communication is an information sharing process in which investigators disclose research risks and benefits in language potential participants can understand and elicit their need for additional information, and participants understand and appreciate the information relevant to their research participation decision.

B. Research Summary: State of the Field—Numerous factors can impede effective risk communication for research participants. Individuals with certain mental health conditions may face additional barriers, some of which can be overcome with appropriate interventions.[26–30] Many barriers identified here are exacerbated by heavy reliance on

informed consent forms as the primary means for disclosing risks and on potential participants' spontaneously asking for further information or clarification.

1. Volume and Quality of Information. Risk information has five dimensions: identity, permanence, timing, probability and value/seriousness.[31] Effective risk communication requires disclosure, understanding, and appreciation of all five dimensions. Providing too much information at once, however, particularly without categorizing it or distinguishing between less and more significant and probable risks, impedes effective risk communication. Informed consent documents that incorporate required information from different sources can become long and difficult to read.[32] Risk communication involves both objective, factual information and subjective information whose relevance depends on individual values, goals and priorities. There may be a tendency to approach this process with a more legalistic/formalistic vision, whereby disclosure is seen as a standardized process without attention to the specific information particular participants might need and value.[33]

2. Poor Numeracy. Adults with average cognitive capacities do not always understand and use basic mathematical and statistical concepts well.[34,35] Understanding and appreciating risks requires a conceptual understanding of probability and basic mathematical skills. Poor numeracy interferes with this ability. If the person disclosing risk information does not understand these concepts well, disclosure may be inadequate.

3. Cognitive Biases. Tversky and Kahneman[36,37] and others have identified ways in which cognitive biases affect the understanding and interpretation of numerical information. Cognitive biases include framing (information about the chance of a risk materializing and not materializing is understood differently); compression (small risks appear greater than they are and large risks appear smaller); availability (culturally significant or otherwise well-known risks are overestimated); anchoring (risks are estimated relative to a familiar risk) and comparison bias (risk perception changes when given comparative risk information).[38,39]

4. Poor Literacy and Health Literacy. Poor health literacy is well-documented in the U.S.[40] and can interfere with understanding and appreciating research risk information. Risk information often is communicated in writing. Given the estimated number of functionally illiterate (40 million) and marginally literate (50 million) adults in the US,[41] written communication may be unreliable, particularly when written at a high reading level, as often is the case with research consent documents.[42,43] Poor literacy may pose special concerns in psychiatric research because adults with certain disorders may read several grades below their educational level.[43–46]

5. Poor Retention and Recall of Information and Working Memory Limitations. The decision to participate in a study is a series of decisions to enroll and remain in a study. Individuals must be able to recall information about the study, including risk information, to make these decisions. Individuals often have difficulty retaining and recalling risk information.[47–49] Working memory limitations also can impede

understanding and appreciation of risk information, which requires processing and manipulating significant amounts of information simultaneously. This poses special concern for potential participants with mental health conditions that adversely affect working memory, such as schizophrenia, mild cognitive impairment, Alzheimer's disease, and other forms of dementia.

6. The Subjectivity of Risk Information. Risk evaluation is value laden, and individuals may evaluate the same risks differently. Knowing which risks individuals would want disclosed can improve risk communication. This envisions a more subjective standard of disclosure over a purely formalistic approach (akin to an "information dump"), as discussed in clinical decision-making.[50]

7. Poor Communication Regarding Research Benefits. Potential participants must not only understand and appreciate research risks but evaluate them in light of the potential benefits of participation. Exaggerating risks, using vague information regarding benefits, or allowing potential participants to think that research participation poses greater personal benefit than it does can impede effective risk communication.[51]

C. Tips for the Savvy Researcher—Existing research suggests that specific practices can foster effective risk communication. These are summarized in Table 2 and include:

1. Use plain language (see www.plainlanguage.gov).

2. Use interactive informed consent processes that can foster decisional capacity, including understanding and appreciation of risks, among people with different learning styles and capacities.[27,30,50,52–54]

3. Use graphs, charts or other means of presenting information, particularly numerical information, to promote understanding among people with different learning styles and capacities.[55–57]

4. Assess capacity not only to determine whether a person is ready to give valid informed consent but because specific processes designed to assess capacity involve educational interventions that can foster understanding and appreciation.[58–60]

5. Avoid unnecessary vagueness and provide necessary information regarding research risks and benefits, distinguishing between probable and remote.[51,57,61–63]

6. Review research information periodically to address retention and recall.[61]

D. Further Research Needed to Advance the Field—There are few studies on risk communication involving actual participants or people contemplating enrollment in a real study. Studies about participation in hypothetical trials may not fully generalize to real-world decision-making contexts.

As summarized in Table 3, for each barrier identified, additional research is needed to better understand the nature of the barrier and identify cost-effective mechanisms that can overcome it. There also remain important normative questions, such as what level of

understanding and appreciation among potential participants is necessary for valid informed consent.[64]

III. Managing Risks

A. Definition and Importance of Managing Risks—High-risk studies are essential to improving knowledge of psychiatric disorders and effective treatment. Effective risk management during these studies is critical. IRBs, however, may pay little attention to the investigator's obligation to minimize risks[65] and either disapprove studies perceived as higher risk or approve studies with insufficient risk management plans. This makes it particularly important for mental health researchers to provide evidence based risk information and propose appropriate risk management plans when seeking IRB approval. Studies may be considered "high risk" because of the novel nature of the intervention; the study population is deemed high risk; the study targets risky behavior, e.g., suicidality or psychosis; or the study targets disorders where risky behaviors are features of the illnesses, e.g., depression or bipolar disorder. Automatic exclusion of "high risk" participants or removal of participants exhibiting risky behavior limits generalizability.[66] Risk management strategies instead focus on trying to initiate and maintain study participation in a safe manner.

B. Research Summary: State of the Field—Data safety and monitoring boards (DSMBs) may monitor studies, though they can be costly and there has been controversy about their independence from study sponsors. A July 2010 *New England Journal of Medicine* editorial proposed that DSMBs should be chosen and convened "under the aegis of an independent public body, such as…the Foundation for the National Institutes of Health…" and stated that they will be examining the independence of DSMBs for future manuscript submissions when appropriate.[67]

For longitudinal studies in populations at risk for fluctuating levels of decisional abilities, there is concern about diminishing capacity and the possibility of subjects being unable to protect their interests if new risks arise during a study. Use of third-party participant advocates who ensure that a research participant's interests remain protected during the course of a long term study should the participant exhibit diminished capacity may help researchers to allow individuals to remain in a study despite fluctuating or diminishing decisional capacity without adding significant costs. For example, the large-scale, 18-month-plus, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia trial examining long-term outcomes used such advocates.[68] At time of enrollment, participants designated an advocate. While advocates participated in the initial informed consent discussions, all participants had capacity to give consent. Advocates received training to determine whether the risk/benefit ratio acknowledged by the participant at time of enrollment had changed 'substantially and adversely,' thus no longer reflecting the participant's expressed interests. If so, participants were withdrawn. However if the risk/benefit ratio was not substantially altered, then the advocate could permit the participant to continue participation. Stroup and colleagues surveyed research personnel and a subset of participants and advocates when participants left or completed the study. A majority in all

groups favorably viewed the advocate process. Twelve percent of sampled participants believed the process negatively impacted their autonomy.[69]

Managing risk during a study may also involve altering standard study designs to address safety concerns and accounting for these changes in data analysis.[70,71] Consider the NIMH-funded randomized-controlled PROSPECT study (Prevention of Suicide in Primary Care Elderly–Collaborative Trial).[72] PROSPECT randomly assigned depression health specialists in primary care clinics (the study intervention) and measured depression and suicidal ideation rates in elderly primary care patients. These outcomes were compared with those in clinics that were assigned to an enhanced treatment as usual (TAU). Individuals with suicidal ideation were not excluded from participation and rates of suicidal ideation were examined over time. Unlike a true TAU clinical setting, all participants assigned to TAU received enhanced care in the form of increased psychiatric surveillance (screening and assessment). This enhanced TAU design created potential study limitations, but it was necessary for study design purposes (to initially identify cases and evaluate at follow-up study visits) and to meet stringent standards of assuring participants' safety.[73] Similar designs with high risk participants have been used in other clinical trials[74,75] and support to the notion that such approaches facilitate important research that otherwise would be constrained.

Training research staff how to assess and manage risks and anxiety-provoking situations (e.g., using role play) has been shown to be effective.[76,77]

C. Tips for the Savvy Researcher—Investigators may implement a number of strategies to manage research risks. Three principal strategies are:

1. Researcher ethics consultations. Such consultations involve interaction between researchers and other stakeholders in the research enterprise and one or more individuals knowledgeable about the ethical considerations in research, regarding an ethical question related to any aspect of planning, conducting, interpreting, or disseminating results of research related to human health and well being. The purpose of the interaction is to provide information; identify, analyze, and/or deliberate about ethical issues; and recommend a course of action."[79, p. 3] McCormick et al reported that psychiatric researchers were more likely than other researchers to find such services useful.[78]
2. Plan for ongoing research staff training regarding the use of management plans and ways of responding to different situations. The principal investigator or a qualified co-investigator should be readily available to research staff during the study.
3. Identify situations that necessitate a written risk management plan. Such plans may include tools such as checklists for easy and systematic implementation of specific plan elements. Studies examining specific risky behavior require explicit procedures that include frequent assessment and crisis intervention when needed. For example, if investigators anticipate psychiatric emergencies, the plan should address how these will be handled, who will be involved and how, and to what extent confidentiality will be protected. Management plans may include a protocol

for handling dropouts from the study and for obtaining follow-up information or for maintaining an up-to-date list of multiple ways to contact participants. Risk management plans should clearly delineate the roles of research team members and the relationship between researchers and clinicians in managing safety. These plans should be detailed in the protocol, and elements relevant to participant rights or willingness to participate should be disclosed during the informed consent process.

D. Further Research Needed to Advance the Field—Further research to create evidence-based risk management plans and train investigators on risk management is needed. This is especially important given the need for more research in high risks areas such as suicide. Research to develop empirically based guidance about risk management in mental health research would benefit researchers and regulatory bodies alike. This research agenda should include further examination of the specific types of risky situations necessitating intervention and the specific interventions that are effective; the roles and responsibilities of researchers, clinicians and clinician-researchers with respect to risk management; and the perspectives of participants, families and regulatory bodies about the use of risk management strategies in research that carries greater than minimal risk.

IV. Justifying Risks

The Belmont Report and current regulations consistently require that risks be evaluated in light of potential benefits to participants and society; research that is scientifically invalid or otherwise lacks value is unethical insofar as it wastes resources and unnecessarily exposes subjects to risk.[64,80] Protecting the scientific validity of a study requires management of conflicts of interest that have the potential to bias the conduct or reporting of a study.[81] Trust in psychiatric research has been harmed by reports of investigators who conducted research of questionable validity with inadequately disclosed and unmanaged conflicts of interest.[82]

One frequently heard criticism of mental health research is that, despite years of research, the field has made few significant advances.[83] However, at least two federally-sponsored studies have shown that available treatments for psychiatric disorders are comparable in efficacy to treatments in other medical specialties [84,85] The lack of research on some types of patients may explain the lack of progress in some areas. Moreover, the development of beneficial treatments is often extremely complex, involving false starts, competing interests, and stigma. These factors are illustrated well in the research history of Lithium, which has been proved effective as both an acute and maintenance treatment[86,87] in bipolar disorder, and is FDA-approved for these indications. Several studies show that lithium significantly reduces rates of suicide.[88,89] Yet despite sixty years of clinical use, lithium has not been systematically and thoroughly studied in either pediatric[90] or geriatric[91] populations. Furthermore, there have been few controlled studies of lithium in “dual diagnosis” populations, e.g., patients with both bipolar disorder and substance abuse/dependence.[92] Ironically, suicide rates are highest in elderly populations, with affective illness a potent risk factor,[93] suggesting that the potential benefit of research in this population is reasonable relative to the risks. Similarly, “dual diagnosis” status (bipolar/substance use disorder) is associated with poor prognosis and treatment resistance.[92,94] Thus, two populations at

significant risk for morbidity and mortality are understudied with respect to lithium treatment. Reluctance to undertake research in these groups may stem from legitimate concerns regarding lithium's side effects and potential toxicity;[95] however, other factors may be at work. For example, unlike many anticonvulsants and "atypical" antipsychotics, lithium receives little marketing support from pharmaceutical companies.[96] The role of *stigma* surrounding lithium must also be considered. One non-professional website observes that, "Lithium…conjures up images of zombies, and everyone seems to think that it zaps your brainpower. While some users do end up feeling this way, the majority do not."[97] Clearly, if IRB members, researchers, or potential subjects buy into the "zombie" myth, research on lithium is likely to be impeded—notwithstanding a World Health Organization study estimating that lithium treatment saved over $145 billion in hospitalization costs in the U.S. between 1970 and 1994.[98]

It is also important to determine which benefits matter most to participants and when and why they matter most. Some data suggest that the interests of researchers and funding agencies do not always align with those of participants, the primary stakeholders in mental health research. For example, mental health consumers tend to prioritize more than researchers a focus on alternative treatment modalities (such as nutritional or self-help modalities), iatrogenic harms, and qualitative research.[99,100]

Conclusion

The ethical conduct of research requires investigators to identify, communicate and manage risks effectively. Investigators' efforts to identify and communicate research risks and potential benefits clearly, demonstrate knowledge of participants' perceptions of risks and the kinds of potential harms that most concern them, document potential participants' capacity to give informed consent, and develop plans to monitor risks during the study and identify new risks may help researchers improve their studies and collaborations with IRBs. For individual investigators, providing IRBs with tables that explain risk information and clear management plans may be useful. Continued research is required to advance researchers' and IRBs' understanding of how best to identify, define, effectively communicate, and manage risks. Such efforts are essential to facilitating much needed mental health research.

Acknowledgments

This publication was made possible by the National Institutes of Health (NIH), National Institute of Mental Health (grant 1R13MH079690) and the NIH National Center for Advancing Translational Science (grant UL1 TR000448). Dr. Dunn reports serving as a Consultant in 2012 to Lilly, Inc.

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Table 1

The Kinds of Harms Identified in the Belmont Report

Kind of Harm	Illustrations
Psychological	Boredom, anxiety, embarrassment, depression, or exacerbation of a psychological condition
Physical	High blood pressure, sexual dysfunction, death, or exacerbation of a physical condition
Legal	Legal fines or imprisonment
Economic	Lost time at work or medical bills
Social	Stigmatization, harm to reputation, harm to relationships

Table 2

Strategies for the Savvy Researcher

Defining/Identifying Risks	Communicating Risks	Managing Risks
• Identify possible concerns about risk or decisional capacity that might affect a study prior to submitting a proposal • Use tools such as RePeat to identify risks and benefits systematically • Address anticipated concerns about risk and decisional capacity in research proposals • Describe potential research benefits and compare those to the risks explicitly • Describe for sponsors and IRBs the process for communicating and managing risks	• Plain language • Interactive informed consent processes • Interactive process to assess decisional capacity • Provide risk information in different formats • Be as specific as possible and avoid vague risk and benefit language • Periodically review relevant risk information with participants	• Use research ethics consultation services or other opportunities to discuss research risks with individuals not affiliated with the study but knowledgeable about research ethics • Plan for ongoing staff training • Ensure availability of senior investigators who may help research staff address emerging issues in a study • Devise a risk management plan that includes detailed information on how different anticipated risks will be managed, how safety will be monitored, what will happen when a participant drops out of a study, the roles and responsibilities of different members of the study team with respect to risk management, and how the effectiveness of the risk management plan will be evaluated during a study.

Table 3

Research Needs

Defining/Identifying "Risk"	Communicating Risks	Managing Risks
• How do potential participants and families/ surrogates, investigators, and IRB members define risk? • What risks are most worrisome to potential participants? • What benefits matter most to potential participants, surrogates, and society? • How do IRBs make decisions regarding risks and how do they compare risks and benefits?	• What techniques are most effective for improving participant understanding of research risks? For example, what practices6 – Help individuals to sort and manage significant amounts of information? – Help individuals understand numbers and probabilities? – Reduce cognitive biases? – Improve understanding of health information? – Facilitate communication of information typically provided in writing? – Enhance retention and recall of information? – Promote the exchange of information that matters most to potential participants? • What variables affect understanding and appreciation of risk information?	• What "toolkits" may investigators employ to help develop and implement effective and comprehensive risk management strategies? • What are effective ways to train research staff to manage risk, particularly in higher risk studies? • Are there risk management strategies that should be used when clinicians also serve as investigators? • How do participants, researchers, and IRBs respond to different risk management plans?

Note: In answering research questions about the views and assessments of participants or populations of potential participants, it is important to attend to individual differences.