Ethical Issues in Including Suicidal Individuals in Clinical Research

BY CELIA B. FISHER, JANE L. PEARSON, SCOTT KIM, AND CHARLES F. REYNOLDS

Although suicide was the 11th leading cause of death in the United States in 2000, the number of empirically validated treatments to reduce suicidality is small. Recent reviews indicate that the 20 or so trials focused on reducing suicidality per se have been limited with regard to statistical power to detect possible positive treatment effects.[1-3] Moreover, despite the fact that 90% of suicide victims have had a mental or substance abuse disorder, there are few clinical trials aimed at treating persons with mental disorders or substance abuse that also address suicidality. Rather, individuals perceived to be at risk for suicide are either excluded from the trial initially or withdrawn during the trial.

The paucity of studies and risk-aversive exclusion criteria for research on suicidality create an odd situation in medical practice in which few empirical studies are conducted to investigate treatments for conditions or disorders with fatal outcomes. Mortality rates for suicidal individuals will not decrease if these individuals continue to be treated with inadequate and unproven interventions. Randomized clinical trials to compare the efficacy and safety of pharmacological and behavioral interventions remain the gold standard of scientific evidence.[4-6] Participants in the workshop "Ethical Issues in Including Suicidal Individuals in Clinical Research" (see sidebar) agreed that suicidal individuals deserve treatments that have been empirically shown to be safe and effective, and that clinical trials must proceed with adequate ethical considerations and safety precautions.

Workshop participants also concurred that suicide research shared many common features with human subjects protection procedures implemented for investigations involving persons with mental disorders. For example, the principles underly to incorporating additional safeguards in obtaining informed consent, employing risk management for crisis situations, or withdrawing participants from trials for severe depression or schizophrenia appeared appropriate for research with suicidal persons. Numerous research opportunities were identified that could provide verification that such principles were applicable to suicide research and practices-e.g., assessing participants' understanding of the nature of the study and their appreciation of how study participation would affect them personally, determining the adequacy of various risk management strategies, or developing effective approaches to community consultation. Unlike most clinical trials for mental disorders, however, suicide prevention trials are premised on the fact that death or self-injury may occur during the trial. Thus some workshop participants argued that suicide research might in some ways be more analogous to research on fatal physical illnesses where deaths are an expected event and may even be used as an outcome variable.

Is Suicide Research Ethically Analogous to Clinical Trials Involving Persons with Terminal Physical Illnesses?

It was argued that aspects of suicide research comparable to research on terminal medical conditions might include the absence of empirically validated treatments to halt the disorder and the anticipation that death is one expectable outcome of the disease. Severity of illness and imminence of death are not criteria for systematically excluding patients with terminal

On the 7th and 8th of June 2001, the National Institute of Mental Health, the American Foundation for Suicide Prevention, and the National Institutes of Health Office of Rare Diseases, sponsored the meeting **Ethical Issues in Including Suicidal Individuals in Clinical Research.** Participants reflected a range of areas of expertise and viewpoints, including bioethics, plaintiff law, family members of persons who had died by suicide, mental health advocates, federally funded and pharmaceutical industry sponsored researchers, experts in research participant competency, the insurance industry, the Food and Drug Administration, and the Office for Human Research Protections. The purpose of the meeting was to discuss and expand on issues raised by institutional review boards for studies of suicide prevention that had either recently been approved or proposed by a number of the meeting participants. Here we present an expanded discussion of some of the key issues identified during the summative session of the meeting.

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physical illness from clinical research. For example, in research on endstage cancer, mortality rates for different arms of a randomized control trial are considered a baseline research risk or even an expected outcome. An analogous trial to prevent completed suicide, by definition, would need to compare rates of death between the experimental and control conditions. Deaths from suicide would be expected events.

If "inevitable" or "expected" is understood as what occurs despite ongoing competent medical evaluation and treatment, then there is no ethically meaningful sense in which either the suicide or cancer scientist allows or causes a death if all participants receive competent medical evaluation and treatment throughout the trial. However, when clinical trials to reduce suicidality are proposed, there is often the perception that IRBs consider control group fatalities unacceptable research risks. It could thus be argued that ethical evaluation of research involving suicidal individuals has not been assessed equitably by IRBs compared to investigations involving other fatal disorders. Ideally, rescue procedures would serve as an outcome measure to compare two treatments for suicidality. However, valid risk assessment criteria and rescue procedures with long-term effectiveness have yet to be established. At present, for scientifically sound research on suicide prevention to move forward, and eventually benefit those at risk, death by suicide needs to be understood as an expectable event.

Reversibility of Suicide Risk. The ethical analogy with terminal illness trials is useful and valid, but may not be sufficient to justify analogous research designs for suicide and other fatal disorders. For example, it could be argued that assumptions about the malleability of suicide risk leave little comparability with research on terminal medical conditions. Unlike the majority of endstage medical disorders, suicide mortality is not considered inevitable. Most researchers assume that most suicides are preventable at least in the short run, and that very few cases would reflect an irreversible course of a disease process parallel to other endstage medical conditions. Thus risk-benefit assessments underlying suicide research presume that the course of disease is reversible, albeit often unpredictable, rather than inevitably fatal. In reality however, reversibility is short-lived; although restricting an individual's autonomy through hospitalization may seem preventive, there is research suggesting that such efforts confer little longer-term protection.[7]

Perceived Responsibility for Suicide Prevention. A second difference between suicide research and investigations of other fatal diseases lies in assumptions regarding the locus of control for suicide behavior and/or suicide prevention. Whereas the processes involved in endstage cancer are often attributed to factors, such as genetic predispositions or unintended exposure to viruses or carcinogens that are beyond the individual's or the clinician's control, suicide is often attributed to factors that the patient's and/or the health care provider could do something about. The public often assumes that a sense of personal responsibility, family support, and religious commitment are protective against suicide and that individuals can prevail over disease processes with regard to self-harming behaviors.

These assumptions are open to challenge, however. First, fluctuation in or dysfunction of personal responsibility or volition is often a key symptom of many psychiatric conditions that occur among suicidal individuals (which leads to special consideration of capacity to consent in research, as discussed below). Second, while there is some research to suggest that family support and religious participation may protect against suicidality, those factors alone may not be sufficient to overcome more potent risk factors.[8,9] As with other diseases, genetic liability and/or environmental exposures (for example child sexual abuse or other violent exposure, such as war) pose risks for suicidality for a significant subgroup of individuals.[10-12] There is no research to indicate that individuals, families, or or health care providers can simply summon up willpower or a strong wish that will keep an individual from engaging in self-harming acts over time. Rather, preliminary evidence would suggest that psychosocial, pharmacologic, and community-based efforts require systematic, multipronged, and sustained efforts to provide real protection against suicide.[13,14]

As the public become more aware that suicide risk is primarily associated with mental and substance abuse disorders, which are often chronic and potentially disabling, health care providers who treat these disorders are increasingly perceived to be responsible for preventing suicide This may be particularly the case among individuals who have attempted suicide, and even more frequently, surviving family members of a suicide victim. In this climate, perceived liability burdens to individual researchers and their institutions mean that few researchers are willing to conduct trials with suicidal individuals, which in turn has resulted in limited trials to reduce suicidality. Adequate insurance for researchers and their institutions (including IRBs) is needed to encourage further clinical trials in this area.

When Autonomy Clashes with Safety. When providers' responsibilities are divided, that is, when respecting a patient's autonomy clashes with assuring that patient's safety, further considerations arise for researchers. One challenge in mental health practice occurs when individuals assumed to be at imminent risk for suicide refuse more intensive treatments and involuntary treatment actions are considered. The same situation can occur in a clinical trial. Relatives and significant others who struggle with the desire to override a loved one's refusal to obtain appropriate treatment may have similar concerns in research protocols. Since researchers conducting clinical trials with suicidal individuals can anticipate the need for involuntary treatment, they can take steps to inform prospective participants and their family or significant others, if appropriate, about the possibility of such an event, and develop protocols consistent with their jurisdiction's

approaches to involuntary commitment.

Competence to Consent

Suicide research holds out the promise of producing knowledge and treatments that can enhance the life opportunities of those who suffer from suicide-related disorders, such as depression, schizophrenia, and substance abuse disorders. However, fluctuating cognitive deficits, including depressed or delusional thoughts where death is sought, raise some critical ethical questions. How is an investigator to protect the dignity of persons at risk for suicide and respect their autonomy to consent to research participation, while at the same time insuring that ill-informed or incompetent choices do not jeopardize their welfare or leave them open to exploitation?[15]

It is important to note that at present no study has assessed the competency to consent to research of individuals assumed to be at risk for suicide, outside of studies focused on assisted dying. In psychiatry practice, a patient's desire to die often triggers a focus on conditions that can impair decisionmaking capacity, such as severe depression or psychosis. Nonpsychiatric health care providers treating physical illnesses may also face refusal of care situations or disinterest in treatment approaches, but there is more often a presumption of competency in the individual with the physical illness[16] (assuming the illness is not directly affecting brain functioning[17]). It is becoming more apparent that health care decisionmaking can be influenced by an individual's physical and mental health status as well as his or her social context. Because nonpsychiatric providers often fail to assess mental status and social contexts, they may presume a greater degree of competence in patients who present with physical complaints. Yet patients who are medically ill may be as impaired—or as competent—as many psychiatric patients.

Several approaches to informed consent have been developed or proposed to ensure a balance between participant autonomy and safety. Appelbaum and his colleagues have pioneered interview methods to evaluate the consent capacity of adults with psychiatric disorders.[18,19] These methods enable investigators to assess broadly whether prospective participants are able to: (1) communicate a choice regarding their willingness to consent or dissent to research participation; (2) understand the nature of the research; (3) appreciate the personal consequences of research participation; and (4) reason about participation, including weighing research risks and benefits. However, the level of capacity that should be ethically required for autonomous consent may vary depending on the risk-benefit calculus and other aspects of the specific research context. Reframing capacity to give informed consent as a matter of "goodness-of-fit" between the prospective participant and the context in which consent is sought broadens the assessment of capacity to consent beyond assessment of the participant's mental status to include examination and minimization of those aspects of the consent setting that can exacerbate prospective participants' vulnerability.[20,21]

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Ways to reduce vulnerability and enhance prospective participants' capacity to give meaningful consent include encouraging them to review consent information at home when they have time to consider the personal consequences of participation carefully and seek advice from family and friends; and providing opportunities for reconsent over the course of a study.[22] Engaging family members or significant others in consent procedures for clinical trials as part of the ongoing treatment and/or assessment of individuals with cognitive impairments due to mental disorders has also been proposed to safeguard consent and ongoing oversight during study participation.[23-25] When implementing options such as surrogate consent or advance directives for research, achieving an optimal balance between respect for participant autonomy and protection requires that investigators: obtain agreement from the prospective participants that proxy oversight or assistance is a desirable means of protecting their interests; allow participants to have a role in selecting the person who will assist in the consent decision and the opportunity to communicate their wishes and concerns regarding participation to the consent partner; and insure that participants retain the right to refuse participation.[26] Few of these options have been researched with regard to treatment trials to reduce suicidality.

Randomized Clinical Trials

The investigator's responsibility to conduct scientifically valid research often necessitates randomly assigning participants to experimental treatment and control conditions. Ethical justification for randomization requires that there be no known differences among the relevant outcomes (theoretical equipoise) or that there is a current or likely dispute among experts in the clinical community as to which condition is superior in all known respects (clinical equipoise).[27] For some disorders, such as bipolar disorder and schizophrenia, some newer treatments and augmentation strategies used to manage these disorders appear promising for conferring suicide protection, so that standard treatments for these disorders have been used as control

conditions.[28] Beyond these disorders, however, few treatments have been empirically established to reduce suicidality, and more stringent design is required to ethically justifiy assignment to a control group receiving minimal active treatment-e.g., if adequate monitoring and rescue procedures are in place. Two issues, however, have reduced the likelihood that study designs will include placebo or minimal active treatment control groups. First, ethical concerns have been raised about the use of placebo or nontreatment control groups for suicide research because of public and clinical perceptions that certain basic services are at least minimally effective.[29] Second, suicidality is often comorbid with depression, substance abuse disorders, and other psychiatric conditions for which there are known effective treatments. This has led many investigators to use treatment as usual (TAU) as a control condition.

Treatment as Usual Designs. Using treatment as usual as the control arm in a randomized clinical trial can present challenges for suicide researchers. Approaches used to reduce suicide risk are variable across different practice settings, and some local practices may not meet standards of expert opinion regarding best practices. To improve consistency of practice across control arms in multisite, and to assure uniform assessment and safety monitoring procedures for experimental treatment and TAU controls, some suicide treatment investigators have enhanced components of TAU services. Thus in many current clinical trials aimed at reducing suicidality, all participants receive more monitoring and more intensive (and sometimes higher quality) care than would be available outside the research protocol. While this effort provides increased safety for the research participants, there may be additional treatment effects from enhanced TAU that reduce the power to detect differences between TAU and the experimental treatment. Preliminary data from one multisite study involving depressed older adult primary care patients, however, suggested that increased monitoring and feedback in the TAU group had little impact on rates of suicide ideation or depression.[30] Future attention to the methodological issues inherent in TAU are needed for both suicide prevention and other "effectiveness" research efforts.[31]

Treatment Risks. One aspect of conducting research with suicidal individuals that has less risk than other high mortality conditions is the nature of the treatment. In comparison to many other medical treatments for high mortality conditions, (particularly endstage cancer treatments for example) treatments for suicidal behavior are minimally iatrogenic. To date, only one study of curriculum-based suicide prevention efforts for youth has reported mild untoward effects.[32] Although there has been theoretical speculation and case reports of adverse effects with certain medications,[33] an analysis of published papers linking serotonin, SSRIs, and aggression suggests that SSRIs are particularly effective in reducing violence to self and others.[34] The consensus among workshop participants was that to date there is no persuasive empirical evidence that SSRIs induce suicidality. Suicidal ideation or behaviors may be identified during treatment not because they are iatrogenic, but because the patient may not have reported suicidal ideation during initial assessment or because fluctuations in suicidal ideation are part of the course of the illness (e.g., depression, personality disorder).

Future Challenges and Directions

Clinical Judgment and Imminent Risk. Clinical judgment about the severity of suicide ideation and the imminence of suicidal behavior has remained the mainstay of decisions to exclude or withdraw high-risk individuals from research protocols. That the behaviors on which these judgments are based are in fact reliable indicators of fatal behaviors in the near term has rarely been demonstrated, however. Moreover, the reliability, uniformity, and validity of these judgments across different studies have yet to be determined. Failure consistently to use validated clinical assessment techniques is one cause of the variability of risk-benefit calculations applied by institutional review boards striving to meet recent federal requirements for data safety monitoring. Consequently, one important area of research is the development of validated approaches that can support consistent clinical judgments across studies.

Few instruments for assessing risk for suicide have been assessed for efficiency in detecting risk in treatment trials,[35] but approaches have implications for establishing both clearer treatment outcomes and appropriate inclusion and exclusion criteria. For example, some efficacy studies of mental health interventions will need to exclude individuals at risk for suicidality. If these studies do not apply sufficiently sensitive measures as the basis for exclusion (beyond a single suicidality item from a depression scale), it remains difficult to determine the heterogeneity of their participant cohorts. Routinely using more refined measures of suicidality across studies, would also better support the utility as a treatment outcome of participant withdrawal due to suicide risk from the study. So too unless more refined measurements are applied, the opportunity is lost for a trial to detect possible untoward treatment effects of increased suicidality, or conversely, efficacy for reducing emergent suicidality.

Obtaining Adequate and Representative Samples. Suicide is a low-incident event with high personal and social costs. Suicidality is a state that arises from a variety of conditions and stressors, and is frequently the product of an accumulation of risk factors. It is often comorbid with other forms of psychopathology, such as depression, schizophrenia, or borderline personality disorder, which means that a single cluster of factors is unlikely to predict suicidality across individuals and populations. Lack of a defined set of period-specific predictive variables (who will attempt suicide and when) in turn makes it difficult to carry out prospective studies. As a result, researchers often recruit individuals who have a prior history of

attempted suicide, or members of populations known to have a high frequency of self-harming or high-risk behavior.

Given the low base-rate and multifactorial nature of suicidality, and the challenges of prospective research,it is difficult to conduct individual, small-scale studies with the requisite statistical power to support clear conclusions. Large, multisite studies are often needed to ensure adequate enrollment of individuals at risk within the typical five-year life of a federally funded treatment trial. Recruitment across sites can be uneven, particularly when there is geographic variation in community understanding of and trust in research. This is especially true for members of certain ethnic minorities who may have a historic legacy of distrust of medical research, whose culture may not conceptualize suicidality as a treatable condition, or whose community looks upon suicidal behavior as an immoral act or a cause for family shame.

Community Consultation. Community consultation is a valuable way to enhance recruitment efforts, especially in ethnic minority communities in which there is a legacy of suspicion and distrust of federally funded research.[36-38] Community consultation enables investigators to learn about and tailor ethical procedures to meet prospective participants' expectations and concerns about suicide research. This may be particularly important for multisite studies in which understanding and engagement in research will vary across sites. To understand the perspectives of individuals who differ from the investigator in life experiences, worldviews, needs, power, social status, culture, and material and personal resources requires bidirectional teaching and learning. This process assumes that both scientist and participant come to the research enterprise as experts: The researcher brings expertise in the scientific method and extant empirical knowledge, and the prospective participant brings expertise about the concerns and expectations he or she has regarding the prospect of research.[39-41]

This model can be used to strengthen the applicability of research designs to community mental health services by consulting with local practitioners (physicians, psychologists, social workers, nurse practitioners), hospital administrators, health insurers, and others in the community—such as the clergy or school teachers—who are knowledgeable about the opportunities and practical constraints of suicide prevention and treatment in their communities. This may be particularly important where the transfer of research-based knowledge about clinical care in mental health to front-line treatment settings has historically been consistently poor.

Investigators can use community consultation procedures to share with prospective participants their views on how and why it is important to study suicidality scientifically through clinical trials and other research, and to debate areas of current ethical concern. In turn, prospective participants, and/or their community representatives (e.g., family members, school principals) can share their perspectives on the value of a proposed study and their reactions to the risks and benefits of planned procedures.[42] Information from community consultation at the outset of research design is needed to produce sound evidence for the selection of specific ethical and risk management practices that can enhance the potential for more positive and uniform IRB review of suicide research across multiple research sites.

Moving Forward

While investigators who choose to conduct clinical research treatment with individuals at high risk for suicidal behavior face significant challenges, with careful consideration, researchers willing to test treatments for suicidal individuals can anticipate ethical and safety dilemmas and address them in safe, just, and systematic ways. Research opportunities with regard to capacity to consent, validity of risk assessment measures, and community collaboration can be easily incorporated into ongoing research efforts. Workshop participants concluded that there is much to be optimistic about with regard to respectful and safe treatment development for persons at risk for suicidality.

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