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Making Progress in Clinical Trials for Suicide Prevention
A Review

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IMPORTANCE Suicide is a public health crisis, and despite renewed efforts to confront this problem, suicide rates continue to rise in the US. While suicide prevention encompasses a broad array of strategies, treatment development is lagging. Within this realm, clinical trials are the criterion standard for evaluating safety and efficacy of new treatments.

OBSERVATIONS Most clinical trials conducted among patients with mental illness have excluded patients at risk of suicide. Historical reasons for this include regulatory challenges, liability concerns, ethical questions, discomfort working directly with high-risk patients, and the belief that research is too risky for individuals at elevated risk for suicide.

CONCLUSIONS AND RELEVANCE Several considerations are provided for investigators in the design of trials targeting at-risk populations, including thoughtful selection of study outcome, use of time-to-event design and analysis (which may simultaneously satisfy ethical concerns and scientific aims), enrolling an enriched sample (eg, among patients recently discharged from the hospital), and provision of usual care in the comparator group. Caution should be exercised to avoid excessive or unreasonable safety requirements, which may lead participants to minimize self-report of suicidal ideation or to drop out of trials. Where possible, regulatory bodies (institutional review boards [IRBs] and data and safety monitoring boards) should consult with or include as members those with direct clinical experience with this high-risk population. An important ethical principle for IRB members and other regulators to consider is that suicide-related events are expected in this clinical population.

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Suicide is among the top 10 causes of mortality worldwide,[1,2] with more than 49 000 suicide deaths occurring in the US in 2022. Unfortunately, the suicide rate increased by 30% from 1999 to 2019.[3] Suicide-related visits to the emergency department also increased by 42% from 2001 to 2016.[4] For certain groups (eg, adolescents, young adults, and racial and ethnic minority youth), suicide risk has risen even faster in the last decade.[5,6] Past directors of the US National Institute of Mental Health (NIMH) have reiterated a call for renewed efforts to combat this public health problem and reduce the rate of suicide.[7]

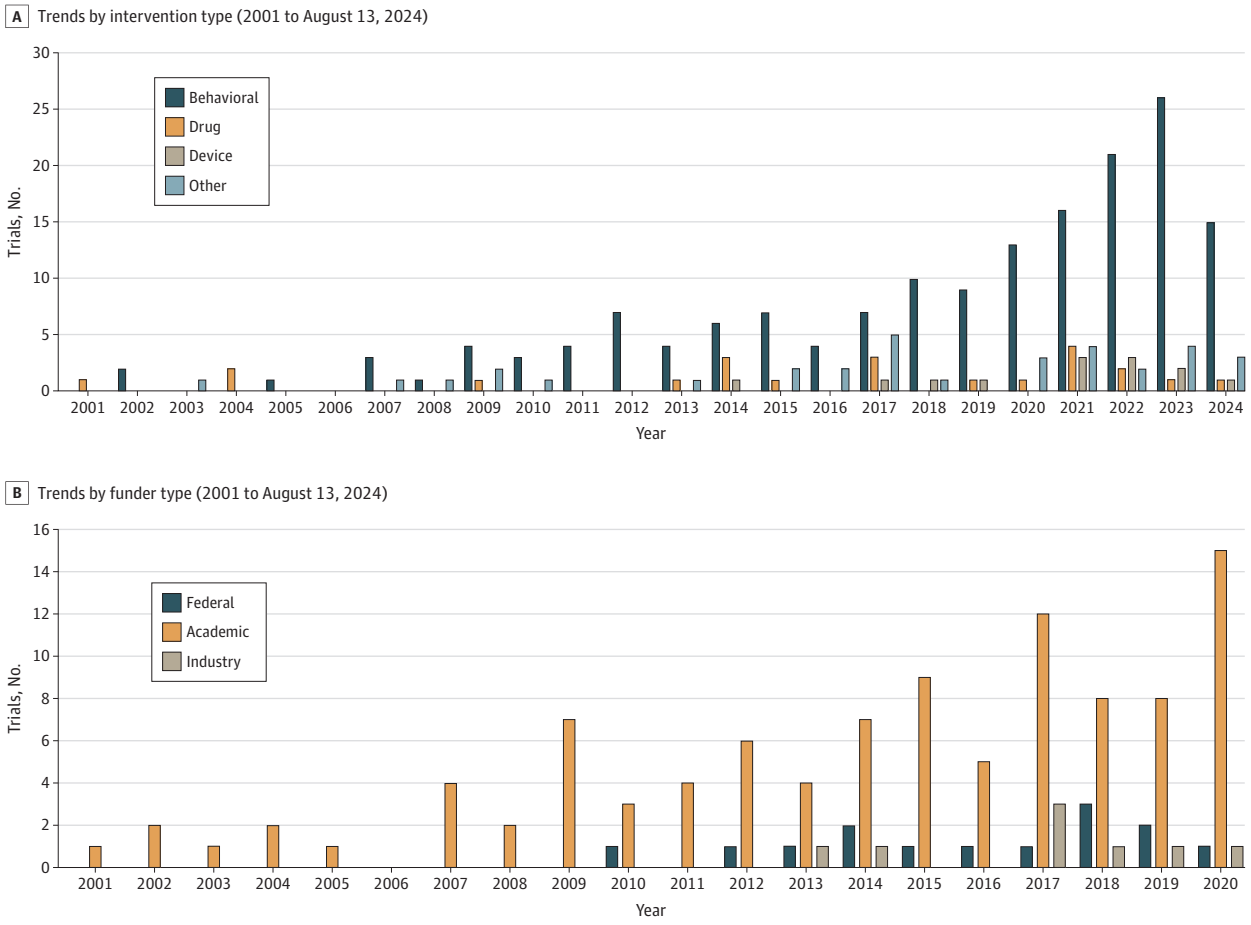
Suicide prevention research has focused on several strategies, including improving identification of at-risk individuals, treatment development, and means restriction. Within the realm of treatment development, conducting randomized clinical trials is the criterion standard for evaluating the safety and efficacy of new treatments.

Unfortunately, the vast majority of randomized clinical trials conducted among patients with mental illness have excluded patients at risk of suicide.[8] One study notes that only approximately 10% of all trials of selective serotonin reuptake inhibitors from 1984 to 2001 included patients with suicidal ideation.[9] To our knowledge, there is no trial of standard oral antidepressants that includes patients with active suicidal ideation. Patients with suicidal ideation are also often excluded from clinical trials that target other mental illnesses, including schizophrenia. This has severely limited the field's ability to develop treatments that are effective in reducing suicide risk. It has also led to uncertainty regarding the effects (both therapeutic and adverse) that existing treatments have on patients at substantial risk of suicide in the community.[10-14]

Historical reasons for excluding patients at risk of suicide in clinical trials include regulatory challenges,[15] liability concerns, ethical questions, and the belief that research is too risky for individuals at elevated risk for suicide.[8] Many of these issues have also prevented investigators and sponsors from designing and conducting trials where the key outcomes of interest are related to suicide risk. Recognizing the great evidence gap that exists from decades of neglect of this issue, there has been increased interest recently in designing and conducting trials that enroll patients with clinically significant suicidal ideation or recent suicidal behavior (**Figure**). These include trials involving ketamine[16-18] or esketamine,[19-22] lithium,[23,24] and clozapine,[25] as well as psychotherapeutic interventions.[26,27]

In an effort to better inform those who are designing and conducting such trials, here we review and provide guidance on topics relevant to designing and conducting trials that purposefully recruit high-risk patients, including choosing the proper clinical settings from which participants are recruited, designing a proper comparator group, selection of outcomes, ethical considerations, and

Figure. Trends of Suicide-Related Randomized Clinical Trials Registered in the US Trial Registry (N = 230) by Intervention Type (A) and Funder Type (B)



Note: Data were drawn from the US Clinical Trial registry from the inception through August 13, 2024. Year was based on the start date of the trial, and 1 study with a start year of 2026 was not included. "Other" denotes studies focused on case management or diagnostic or screening interventions. See Supplement for systematic review details.

management of regulatory oversight (**Boxes 1** and **2**). The focus of this article is not on the merits of any particular investigational therapy in reducing suicide risk, but rather on the methods of the clinical trials used to evaluate these therapies in high-risk populations.

Research Participation Is Not Too Risky for Persons With Suicidal Ideation

One oft-cited reason why individuals at elevated suicide risk are not enrolled in trials is the belief that research participation is too risky for such persons.[8] This belief is often tied to several factors, including the possibility of receiving placebo, the fear that merely mentioning the possibility of suicide during assessments may worsen the mental health of vulnerable participants, or that trial participation may delay standard treatment in urgent situations.[28]

In 1 survey of research ethics committee members, 65% of respondents expressed concern that suicide risk might be exacerbated or reinforced by suicide research, in part due to requiring participants to recall their experiences.[29] When asked about the possibility of conducting research that includes suicidal patients, 1 survey respondent with significant experience in ethics replied that "these people need treatment first and foremost, not study." Such a response misses the significant limitations of current treatment options and the fact that research and access to standard clinical care need not be mutually exclusive.

It is worth noting that, for many decades, successful research programs have been conducted in medical disciplines where death is a distinct possibility and often an outcome of interest.[30] There are reasons why suicide risk in psychiatry trials might be considered differently than mortality risk in an oncology trial.[15] However, trials can and should be designed and conducted in ethical ways that allow for the assessment of an intervention vs a comparator group comprised of standard care.[30]

Ethical Considerations

There are unique ethical considerations when undertaking trials that enroll participants at risk of suicide. Historically, some institutional

Box 1. Key Considerations for Investigators on Designing and Conducting Interventional Trials Targeting Patients at Risk of Suicide

- In most cases in randomized clinical trials, the control group should be comprised of (at a minimum) the usual care a similar patient would receive in the community.
- In some contexts, trials that measure continuous outcomes and do not allow change in therapy would not be appropriate. In these cases, time-to-event analyses may be most appropriate, wherein a change in management due to worsening suicide risk (eg, initiation of electroconvulsive therapy) might constitute an event.
- Focusing on patients recently discharged from hospital will enrich the sample, given the high risk of this population.
- Care should be taken not to overgeneralize from high-risk clinical groups to nonclinical groups (eg, suicide prevention efforts in schools).

Box 2. Key Considerations for Other Stakeholders (Members of Institutional Review Boards [IRBs] and Data and Safety Monitoring Boards [DSMBs] and Funders) on Regulating the Conduct of Interventional Trials Targeting Patients at Risk of Suicide

- Wherever possible, DSMBs and IRBs should strive to include (or at least receive input from) members with direct clinical experience with high-risk populations.
- Stakeholders must recognize that suicide-related events (eg, attempts) occur regularly in these populations, and trials should not generally be stopped for 1 or 2 events.
- At the same time, members of the DSMBs that oversee such trials and regularly review group-specific outcomes should be aware of the possibility that some interventions may paradoxically worsen suicide risk.
- Stakeholders must also realize that requiring that care in the control group be far in excess of what is found in community settings can be counterproductive and burdensome to patients. Excessive safety requirements may lead participants to drop out or minimize their reporting of suicidal thoughts.

review boards (IRBs) may have insisted on excluding those at risk of suicide or objected to the use of suicide-related events as a study outcome.[29] Some have drawn comparisons to oncology research, where the outcome of interest is often death. In oncology, while investigational chemotherapy does confer serious risks on research participants, the risk of death is understood to be largely attributable to the illness. In psychiatry, some have argued that the conceptualization of the risk of suicide-related events as primarily due to participation in research is problematic. This is especially the case for trials that recruit from high-risk populations. In these trials, participants are, by virtue of their underlying condition, at elevated risk of suicide. Unless there are reasons to believe otherwise, the risk of suicide-related events in such trials should be framed as primarily due to the underlying condition. The potential risk that an investigational therapy designed to reduce suicide risk paradoxically increases it could be included in the informed consent process, but in most cases this would be a theoretical risk rather than one based on evidence.

Choice of Comparator

The choice of a comparator in randomized clinical trials has important ethical considerations. The withholding of treatment known to be effective (eg, assignment to placebo without facilitating concurrent access to standard of care) from a patient with suicidal ideation would generally not be considered ethical. Likewise, disallowing such patients from making treatment changes during the course of the trial is also fraught with ethical challenges.[15,31] Hence, conducting a randomized clinical trial where treatments are tightly controlled (with the purpose of isolating treatment effects) would be difficult in many contexts. Given this, the most logical choice of a comparator would be a group that receives usual care and in which treatments can change in response to transiently increased suicide risk. Participants randomized to the investigational group would receive the experimental therapeutic in addition to usual care. Those participants randomly assigned to the group that does not receive the investigational therapeutic would still receive active treatment. The level of care in the comparator group should, at a minimum, be equivalent to that of the care a patient not enrolled in the trial would receive in the community. Given the strong, nonspecific effects that are seen in most randomized clinical trials of mental illness (where outcomes in the comparator or placebo groups are typically superior to outcomes in community settings from active treatment), this would not usually be a concern. For example, the remission rate in the comparator group in the ASPIRE-I study of esketamine[20] (which received placebo plus a new antidepressant plus comprehensive usual care) exceeded 45% at 3 months, an unusually high rate for individuals with severe depression and acute suicidal ideation that required hospitalization.

Considerations of Informed Consent

Proper informed consent of patients who may be in an acute crisis is another important consideration. The challenge of true informed consent is to provide the participant with sufficient information for an informed decision but to avoid overwhelming them with so much information that they cannot grasp the key points of the study. This is particularly true in a trial that enrolls patients in an acute suicidal crisis. In trials enrolling participants in emergent settings during time-limited periods and in psychiatric crisis, it is particularly important that the consent process and consent forms are clear and concise and are not overly verbose and legalistic. Including infographics, educational videos, and an accessible contact to answer questions can be helpful.[32]

Another relevant aspect of the informed consent process is to acknowledge that clinical actions will depend on the participant's assessed level of risk. In other words, it may be useful for patients, especially those who are naive to treatment and/or research, to understand that disclosure of suicidal ideation will not necessarily lead to hospitalization.[33] Patients may believe that any disclosure of suicidal ideation will result in hospitalization, sometimes against their will. Clear communication of how risk is assessed may enhance the integrity of data collection regarding true suicidal ideation.[34] Nonetheless, suicidal ideation is often either minimized or sometimes absent in high-risk patients.

The informed consent process is also a critical time for collecting emergency contact information. This information can be used to safeguard participants if a patient cannot be reached but staff consider the patient at elevated risk, with possible need for intervention.

Table. Examples of Trials That Have Successfully Recruited From Emergency or Inpatient Settings and Other High-Risk Settings

Study acronym or author (NCT No.)	Sponsor	Recruitment setting	Primary outcome	Treatment
ASPIRE I and II (NCT03039192, NCT03097133)[20,21]	Janssen	Inpatient/hospitals	Change in depression at 24 h	Esketamine
Brown et al, 2005[26]	NIH	EDs post-suicide attempt	Group difference in suicide attempts	CBT
ENDURE (NCT04760652)[22]	NIH	Inpatient/hospitals	Feasibility[a]	Ketamine/CBT
Rudd et al, 2015 (NCT02038075)[27]	DoD	Inpatient/ED	Group difference in suicide attempts	CBT
KISA (NCT04578938)	NIH	Inpatient	Group difference in suicidal ideation	Ketamine/ cognitive training
OTX-202 (NCT05144685)	Oui Therapeutics	Inpatient/ED	Group difference in suicide attempts	Therapeutic app
InterSePT[25]	Novartis	Patients with recent suicide attempts	Group difference in suicide behaviors	Clozapine

Abbreviations: app, application; CBT, cognitive behavioral therapy; DoD, US Department of Defense; ED, emergency department; NCT, national clinical trial; NIH, US National Institutes of Health.

[a] Per requirements from the Request for Funding Applications, the ENDURE trial is a feasibility study, with a key secondary outcome being relapse among those who experienced substantial benefit following 2 weeks of esketamine therapy.

Choosing the Proper Clinical Setting From Which Patients Are Recruited

The rate-limiting step for most clinical trials in mental illness is the recruitment of eligible participants. Elaborate efforts to recruit participants (including advertising campaigns) and to ensure that participants are compliant with study protocols speak to some of these challenges. Companies have been created that ensure that research participants are not simultaneously enrolled in multiple conflicting trials. Including only a small number of participants who have no intention to consume the investigational product can greatly reduce the chance of detecting an efficacy signal.

In trials that aim to enroll high-risk patients, there is an opportunity to overcome many of these traditional challenges by enrolling from settings where high-risk patients regularly seek care. To generate an enriched sample, several such trials have successfully enrolled patients from emergency departments or inpatient units (**Table**).[21,22,26,35] The period following a hospital discharge is a time of extraordinary high risk for suicide[36]; a 2017 meta-analysis of 100 studies found that the rate of suicide death in the period following hospital discharge was 2078 suicide deaths per 100 000 person-years compared to a base rate of 11.4 per 100 000 person-years in the general population.[37] A UK-based study found that among suicide decedents who had any contact with the mental health system within 12 months of death, 24% of all suicide deaths occurred within 3 months of discharge from a psychiatric facility.[38]

Choice of Outcomes and Analytic Approaches

To maximize statistical power in many contemporary US Food and Drug Administration–registered trials of psychiatric treatments, a continuous outcome is often chosen with planned between-group comparisons to evaluate treatment effects. However, in suicide prevention trials, the outcomes of greatest interest are often discrete (eg, suicide attempts). In addition, many patients with recurrent severe suicidal ideation have learned to underreport suicidal ideation to avoid unwanted hospitalizations against their will. This can make it problematic to rely on suicidal ideation as a continuous outcome, strengthening the case for using discrete outcomes. Unfortunately, statistical power generally decreases when comparing discrete outcomes, especially for rare outcomes, necessitating much larger samples. One strategy to overcome this is to enhance statistical power by choosing statistical methods that allow for recurrent events (eg, multiple suicide attempts within participants) like Cox proportional hazards modeling and Poisson or negative binomial regression analyses.[39] However, if using this approach, 1 participant or a small number of participants with many events can disproportionately influence the outcome of the entire trial, producing a trial that is not generalizable or difficult to replicate.

Another strategy for improving statistical power with discrete outcomes is to create composite variables that aggregate multiple types of outcomes. Researchers have combined multiple types of suicidal behaviors into 1 outcome,[40] such as the composite outcomes of suicidal ideation, suicide attempts, and documented suicide risk assessments[41] and suicide death, suicide-related emergency department visits, and suicide-related hospitalization.[42] For example, the InterSePT trial of clozapine[25] included a composite outcome of suicide attempt, hospitalization, or significant worsening of suicidal ideation.

Although composite outcomes can improve statistical power by increasing event rates, this method can also obscure conclusions about treatment effects. Certain forms of suicidal ideation seem to be inherently unstable and can wax and wane quite rapidly. Furthermore, effects on the most frequent outcome (eg, suicidal ideation, which is less severe than nonfatal suicide attempt) may be driving the significance of any finding. Moreover, a decrease in less severe outcomes (eg, nonfatal suicide attempt) may obscure an increase in a more severe outcome (eg, suicide death). Relatedly, suicidal ideation and suicidal behaviors, for example, are known to respond differently to treatments—improvements in suicidal ideation have been observed across many different types of psychiatric treatment, but reductions in suicidal behaviors have only been observed consistently in a handful of treatments, such as cognitive behavioral therapies.[43,44] Reductions in suicidal ideation, therefore, do not necessarily translate to reductions in suicidal behaviors. Finally, if an intervention leads to a reduction in suicide attempts but an increase in hospitalization because participants are more likely to seek help when in crisis, this finding might be obscured if both events are part of the composite outcomes. Researchers using composite outcomes should be aware of the drawbacks of such an approach. The

reporting of treatment effects on each element of the composite outcome is strongly encouraged to help mitigate these drawbacks.

If using suicidal behavior as an outcome, a competing risk survival model may be an appropriate analytic approach. This approach estimates the probability of a primary event occurring (in this case, suicidal behavior) in the presence of other events that may affect this primary event or prevent it from occurring, such as hospitalization.

Not all modern trials enrolling high-risk patients have adhered to this formula of using discrete outcomes. The ASPIRE trials[20,21] used a continuous outcome (severity of depression), which was assessed 24 hours following the initial dose of the investigational therapy. By assessing the primary outcome so closely following randomization and enrollment, the ASPIRE trials[20,21] were able to avoid challenging issues that come from a continuous outcome in a trial where concomitant treatment changes cannot be strictly controlled due to ethical reasons.

Safety Monitoring

IRBs, independent safety monitors (ISMs), and data and safety monitoring boards (DSMBs) have the authority to stop the conduct of a clinical trial based on safety concerns. We argue that IRBs should refrain from stopping the conduct of a study based on a single or a few events, unless these events are clearly due to gross aberrations in the way a protocol should have been carried out. Instead, DSMBs, which have more content and statistical expertise and can evaluate aggregate data across study groups, should fulfill the role of determining whether an intervention being investigated to reduce risk paradoxically increases it. Investigators should strive to compose DSMBs that have at least 1 member with direct clinical experience with high-risk patients. Standard methods exist in other disciplines wherein DSMBs stop trials because the active intervention paradoxically harms rather than helps patients. Trials that enroll patients at high risk for suicide should be modeled after the examples of other fields, where trials are conducted that enroll high-risk patients.[45,46]

Usual Care in Community vs Research Settings

It is critical that patients randomized to the comparator group receive usual care that is at least as good as they would receive in the community. Given the high level of resources and oversight that typically exists in randomized clinical trials, this is usually not an issue. However, caution should be exercised such that this care is not excessive, burdensome to patients, or counterproductive. For example, requiring study staff to call patients daily or multiple times per day if any (even chronic or passive) suicidal ideation is present can result in patients becoming frustrated, altering their reporting (ie, minimizing), or even withdrawing from the study, leaving them with less care. When providing oversight to such trials, IRBs should consult with clinicians who have direct clinical experience with this patient population outside of research settings to ensure the proposed safety measures are reasonable.

The Role of Funders

Leaders of the NIMH have set a goal to reduce suicide rates in the US. This goal has been accompanied by several suicide-specific Requests for Applications as well as funding of several suicide prevention research centers.[47] These initiatives represent important investments toward reducing suicide rates.

Following broader shifts toward greater stewardship over clinical research, some funders recently heightened oversight of clinical research that involves participants at risk for suicide. In practical terms, this means that the funders sometimes involve themselves in either the IRB or DSMB oversight of the study.

Unintended Consequences of Funding Agencies

While such a shift is well conceived, it can inadvertently impede progress in suicide research. When supporting this type of research, funding agencies should strive to consult with or include as reviewers those with direct clinical experience treating high-risk populations. When funding agency personnel and reviewers do not have such experience (or do not consult with those that do), trials may be required to institute safety measures that far exceed what patients would encounter in community settings, thereby introducing potential risks and costs that participants would not otherwise be exposed to (eg, dispatching law enforcement or requiring emergency psychiatric evaluations in response to disclosure of suicidal ideation). Fortunately, our experience is that most investigator-initiated research provides a reasonable level of oversight. However, in our judgment, it would be most appropriate for funding agencies to cede regulatory and ethical oversight of the trial to IRBs and DSMBs independent of the funder, as happens with most clinical research, including high-risk trials in other disciplines.

The Ethics of Assessing Suicide Risk

In trials that include patients at risk of suicide, investigators and regulators must consider what research teams are obligated to do if a patient reports suicidal ideation. Regulators, investigators, and clinicians should know that the mere presence of suicidal ideation is a poor predictor of suicide death (or even of nonfatal suicide attempt).[48,49] If there is a significant change in risk and research teams are actively surveilling research participants, then investigators and regulators have an obligation to respond.

However, if safety protocols are excessive, patients may alter the way they report suicidal ideation in order to avoid excessive calls or other intrusive monitoring. For example, for a patient with chronic suicidal ideation (without a history of attempt or a current plan or intent), daily calls to check in would likely not be appropriate and may influence the patient to alter the way he or she reports suicidal ideation (eg, minimizing it). Excessive monitoring may also influence patients to drop out of trials, leading to a situation where, paradoxically, they have less monitoring and care.

The tension between the scientific aims of a trial (to detect group differences in suicide-related events, suicide-related events must be present) and the ethical obligations to protect participants can potentially be resolved through use of time-to-event analyses, where a significant change in management (in response to the detection of a significant change in risk) is considered an outcome, and/or through the use of naturalistic, longer-term follow-up intervals with relatively infrequent assessments, designed to detect any lasting protection that may endure following the conclusion of all study treatments.

Conclusions and Considerations

For far too long, patients with substantial risk of suicide have been excluded from most clinical trials. Fortunately, renewed interest has emerged to be more inclusive in trial criteria. A number of interventional trials have even specifically targeted patients at high risk of suicide with the goal of developing interventions to prevent suicide.

To facilitate this important research going forward, we offer considerations for key stakeholders.

Considerations for Investigators

- Time-to-event and count data analyses may simultaneously satisfy ethical concerns as well as scientific aims of a given study.
- For ethical reasons, the comparator group in most randomized clinical trials should (at a minimum) receive care that is at least equal to usual care in the community. An exception would be for controlled studies on inpatient units, where continuous monitoring is possible.
- A focus on the period following hospital discharge will provide a highly enriched sample. However, care should be taken so as not to overgeneralize from this high-risk clinical group to nonclinical groups (eg, suicide prevention efforts in schools or communities).

Recommendations for Other Stakeholders (Members5 of IRBs, DSMBs, and Funders)

- IRBs should consider and determine a priori the number of events that would be expected in the clinical sample enrolled. This information would then be useful if the number of events occurring during the study is within acceptable numbers.
- We argue that in studies enrolling high-risk patients, IRBs should refrain from closing a study based on a small number of suicide-related events, as such events would usually be expected due to the study condition. An exception would be if investigators made gross violations to the way a protocol and care should have been carried out.
- Generally, safety concerns (in the case that a treatment group is doing unexpectedly worse) should be specified in the DSMB and rest with the ISM or DSMB, who have access to aggregate data across groups and are more likely to have specific expertise in this area.
- Wherever possible, DSMBs and IRBs should include or incorporate input from providers with direct clinical experience with this high-risk population.

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