

# Suicidality and Risk of Suicide—Definition, Drug Safety Concerns, and a Necessary Target for Drug Development: A Brief Report

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**Objective:** To address issues concerning potential treatment-emergent “suicidality,” a consensus conference was convened March 23–24, 2009.

**Participants:** This gathering of participants from academia, government, and industry brought together experts in suicide prevention, clinical trial design, psychometrics, pharmacoepidemiology, and genetics, as well as research psychiatrists involved in studies of psychiatric disorders associated with elevated suicide risk across the life cycle. The process involved reviews of the relevant literature, and a series of 6 breakout sessions focused on specific questions of interest.

**Evidence:** Each of the participants at the meeting received references relevant to the formal presentations (as well as the slides for the presentations) for their review prior to the meeting. In addition, the assessment instruments of suicidal ideation/behavior were reviewed in relationship to standard measures of validity, reliability, and clinical utility, and these findings were discussed at length in relevant breakout groups, in the final plenary session, and in the preparation of the article. Consensus and dissenting views were noted.

**Consensus Process:** Discussion and questions followed each formal presentation during the plenary sessions. Approximately 6 questions per breakout group were prepared in advance by members of the Steering Committee and each breakout group chair. Consensus in the breakout groups was achieved by nominal group process. Consensus recommendations and any dissent were reviewed for each breakout group at the final plenary session. All plenary sessions were recorded and transcribed by a court stenographer. Following the transcript, with input by each of the authors, the final paper went through 14 drafts. The output of the meeting was organized into this brief report and the accompanying full article from which it is distilled. The full article was developed by the authors with feedback from all participants at the meeting and represents a consensus view. Any areas of disagreement at the conference have been noted in the text.

**Conclusions:** The term *suicidality* is not as clinically useful as more specific terminology (*ideation, behavior, attempts, and suicide*). Most participants applauded the FDA's encouragement of standard definitions and definable expectations for investigators and industry sponsors. Further research of available assessment instruments is needed to verify their utility, reliability, and validity in identifying suicide-associated treatment-emergent adverse effects and/or a signal of efficacy in suicide prevention trials. The FDA needs to systematically monitor postmarketing events by

encouraging the development of a validated instrument for postmarketing surveillance of suicidal ideation, behavior, and risk. Over time, the FDA, industry, and clinical researchers should evaluate the impact of the requirement that all central nervous system clinical drug trials must include a Columbia Classification Algorithm of Suicide Assessment (C-CASA)-compatible screening instrument for assessing and documenting the occurrence of treatment-emergent suicidal ideation and behavior. Finally, patients at high risk for suicide can safely be included in clinical trials, if proper precautions are followed.

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See the official consensus statement at [www.psychiatrist.com/suicide](http://www.psychiatrist.com/suicide).

Research on suicide has been plagued by a lack of definitional clarity and inaccurate reporting by health agencies and institutions.<sup>1,2</sup> The problem of definition has become more complicated since the introduction of the term *suicidality*, which lumps together suicidal ideation, self-injurious behavior, suicide attempts, and suicide despite very different consequences for the patient. The ambiguity of the term has often been overlooked in the major public and professional concern about “suicidality” as a potential treatment-emergent adverse event associated with various central nervous system (CNS) drugs.<sup>3–8</sup> The US Food and Drug Administration (FDA) has been at the center of a controversy among some medical professionals, as well as some in Congress, the media, and the general public, over 2 key questions: (1) whether there is a link between antidepressant drug use and the emergence of suicidal ideation and behavior (as well as rare reports of suicide) in children and adolescents and, if there is such a risk, why the FDA failed to detect and warn about this risk earlier, and (2) whether the “black box” warning on antidepressant drugs about the risk of treatment-emergent “suicidality” in pediatric patients resulted in decreased prescribing for this population and a

consequent reversal in the annual suicide rate decline among adolescents.<sup>9,10</sup>

In 2003, the FDA noted suggestions of increased suicidal ideation/behavior in studies of paroxetine in pediatric populations. The Agency requested sponsor data on possible “suicidality” among pediatric patients who had been treated with 8 other antidepressant drugs. The Agency conducted its own meta-analysis of data from 23 industry-sponsored trials and 1 trial sponsored by the National Institute of Mental Health (NIMH) on the efficacy of antidepressants in depressed children and adolescents.<sup>4,11</sup> The FDA commissioned a study by investigators at Columbia University to oversee the classification of all events in the pediatric antidepressant trials database that might represent “suicidality.”<sup>12</sup> On the basis of consensus recommendations and empirical findings regarding suicide-related definitions, the investigators developed the Columbia Classification Algorithm of Suicide Assessment (C-CASA), which systematically categorized suicide-related adverse events, as well as events that were reviewed and either were not suicidal or were events for which a determination of suicidal intent could not be made.

Estimates of “suicidality risk” were obtained for each drug relative to placebo, for selective serotonin reuptake inhibitors (SSRIs) as a group, and for all the evaluable trials using the C-CASA algorithm. *Suicidality* was defined as including completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, and suicidal ideation. Two additional categories were grouped as (1) indeterminate or potentially suicidal events or self-injurious behavior, suicidal intent unknown, and (2) injury events with insufficient information to determine whether they represented deliberate suicidal behavior. Because the data that the FDA collected came from studies that did not focus on suicidal ideation/behavior, this information was based entirely on the collection and documentation of adverse event information obtained through interviews by trained raters or medical personnel using open-ended questions (rather than a standard assessment instrument). Suicide item scores on depression rating scales failed to pick up a signal.<sup>4</sup>

*Importantly, no deaths from suicide were reported in any of the 24 pediatric trials involving 4,582 patients.*<sup>4</sup> An NIMH-sponsored multicenter trial<sup>4</sup> was the only individual study to show a statistically significant risk ratio for “suicidality” associated with drug treatment. For all indications, the risk ratio for “suicidality” was 1.95 (95% CI, 1.28–2.98), suggesting an increase in risk of “suicidality” broadly defined. When the analysis was restricted to just SSRIs for major depression, the confidence interval was still significant, but the risk ratio was somewhat diminished (1.66; 95% CI, 1.02–2.68). There was not a difference between results for ideation and behavior. Although the initial focus was on pediatric trials, studies in adults were later analyzed. The aggregate adult data set was much larger, with 99,231 patients in 372 trials.<sup>8</sup> The overall odds ratio (OR) for the primary endpoint of “suicidality” was 0.85 (95% CI, 0.71–1.02), suggesting a possible slight protective effect of the drugs, in particular in relation to

suicidal ideation. When the data were further examined by age cohort, these were the findings: in young adults (aged 18–24 years), the results were close to being statistically significant in terms of increased risk of “suicidality” (OR = 1.62; 95% CI, 0.97–2.71); in adults 25 to 65 years, the effect of antidepressants on “suicidality” was neutral; and, in patients 65 years and older, the trend was in the other direction (OR = 0.37; 95% CI, 0.18–0.76). In sum, the FDA found a suggestion of an age-related increased risk of “suicidality” associated with antidepressant treatment that was statistically significant only in the pediatric/adolescent age group.<sup>8</sup>

One of the most persistent questions about the FDA meta-analysis is the extent to which it can be considered definitive in establishing a cause-and-effect relationship between antidepressant drug use and the emergence of suicidal ideation and behavior in younger patients. A major problem with the FDA analyses was the lack of systematic and prospective data collection of the events of interest. Moreover, association in a meta-analysis does not equal causality, and data from case-control and other studies should be considered before more definitive statements can be made. A case-control study<sup>13</sup> of Medicaid beneficiaries from all 50 states who received inpatient treatment for depression compared suicide attempts and suicide deaths in severely depressed children (aged 6–18 years) and adults (19–64 years) treated with any antidepressant (vs controls). The results were consistent with the results of the FDA meta-analyses in adults and in children and adolescents. In contrast, autopsy studies of people who have committed suicide rarely have found evidence of recent exposure to SSRI antidepressants. In a study<sup>14</sup> in Utah of 151 teen suicides, only 4 of those who committed suicide had evidence of any psychiatric medication during a toxicology screen. In another study,<sup>15</sup> of 42 teen suicides, none of the individuals were treated with an SSRI during the last 2 weeks of life. In a third study,<sup>16</sup> an SSRI was detected in only 2 of 58 youths who committed suicide in New York City between 1993 and 1998. Many reports from different countries have shown an association between SSRI use and declining suicide rates.<sup>15–25</sup> Since SSRIs were introduced in the United States in 1988, the subsequent decline in suicide rates in children and adolescents has been attributed by some to the use of antidepressants during this period.<sup>26</sup> In 2004, there was an increase in the adolescent suicide rate,<sup>27</sup> which some researchers attributed to the publication of FDA safety concerns about antidepressants in young populations that had surfaced in 2003, and a possible consequent decrease in the prescription of these drugs to children and adolescents.<sup>10</sup> However, a decline in suicide rates in this age cohort in 2005<sup>28</sup> and 2006 (A. Crosby, MD, MPH; electronic communication of Centers for Disease Control and Prevention data; December 2010) would also need to be explained in the context of the same “black box” warning.

The controversy about treatment-emergent suicidal ideation and behavior intensified with a subsequent FDA meta-analysis of 199 placebo-controlled trials of 11 different antiepileptic drugs.<sup>29</sup> The Agency reported a statistically significant drug/placebo difference in treatment-emergent

“suicidality” (68% of which was suicidal ideation), with 142 outcome events among 43,892 research participants (0.3% of the sample). The FDA required the addition of “warnings and precautions” (but not a black box warning) to the label for the anticonvulsant drugs, in spite of concerns from neurologists and patient advocacy groups about possible consequent medication nonadherence. The FDA now requires that all participants in clinical trials of CNS-active drugs be evaluated at baseline and during active treatment using a scale that maps to C-CASA to detect suicidality as a potential treatment-emergent adverse event. The Agency has also encouraged studies of drugs to reduce the risk of suicide in high-risk patients. The C-CASA terminology favored by the FDA represents an effort to define *suicidal ideation*, *suicidal behavior*, *non-suicidal self-injurious behavior* and *accidental injuries* in the context of treatment-emergent adverse events in clinical trials. It will be important to determine the broader utility and validity of the C-CASA definitions across cultures in clinical efficacy studies and epidemiologic research. Clinicians, in particular, need to know how to weigh possible risks and benefits associated with anxiolytic, antidepressant, and other CNS-active drug treatment. Treatment-emergent suicidal ideation and suicidal behavior may be influenced by risk or protective factors that were not fully considered in the clinical trials databases. How should these factors be considered in the context of drug safety and efficacy questions? Moreover, the typical exclusion from industry-sponsored pivotal trials of patients with significant suicidal risk (based on recent suicidal behavior and/or severity of suicidal ideation) has served to limit the information available to practitioners about the effects of approved drugs on these high risk-patients in their practices.

To address the issues that have emerged in recent years concerning potential treatment-emergent “suicidality,” a consensus conference of participants from academia, government, and industry was organized to bring together experts in suicide prevention, clinical trial design, psychometrics, pharmacoepidemiology, and genetics, as well as research psychiatrists involved in studies of major depression, bipolar disorder, schizophrenia, substance abuse/dependence, and other psychiatric disorders associated with elevated suicide risk across the life cycle. The objective was to achieve consensus on the following issues:

1. Definitions: to seek consensus on the value of the term *suicidality* or alternatives, as well as the relative advantages and disadvantages of instruments proposed for assessing the occurrence, severity, and intent of suicidal ideation and behavior in clinical trials of CNS drugs.
2. Risk factors: to seek consensus on risk factors and moderator and mediator variables that should be considered, and their relative weight, in evaluating the question of treatment-emergent adverse events related to suicidal ideation/behavior/intent and suicide and to evaluate the efficacy of pharmacotherapy in reducing the risk of suicide in high-risk patients.
3. Evidence: to consider the relative merits, limitations, and standards of evidence (“logic of inference”) of data analyses from randomized controlled trials (RCTs), meta-analyses of published and unpublished data from RCTs, and population-based studies in assessing the question of treatment-emergent adverse events related to suicidal ideation and behavior.
4. Ethics: to consider possible ethical and scientifically sound study designs that include research participants at risk of suicide in clinical trials in which suicidal ideation, suicidal behavior, or suicide is a potential treatment-emergent serious adverse event and in which elevated risk of suicide is the target of pharmacotherapy intervention.

The conference was convened in Washington, DC, on March 23–24, 2009, by the Department of Psychiatry at Beth Israel Deaconess Medical Center, Boston, Massachusetts, and organized by Best Practice Project Management, Inc. Conclusions arising from the conference are the basis of this report.

## DEFINITIONS

1. *Suicidality* should be abandoned as a term.
2. *Suicidal ideation*, *suicidal behavior*, and *suicide* are preferable terms; operational definitions for these terms should be formulated and disseminated and should work in translation across languages and cultures.
3. The FDA endorsement of C-CASA offers a uniform standard for defining these terms, but it is not yet fully clear how these definitions will meet different requirements in the prospective assessment of treatment-emergent suicidal ideation and behavior, in assessment of treatment efficacy (reducing the risk of suicide in high-risk patient groups), in population-based case-control studies, and in postmarketing drug surveillance.

## Assessment Instruments

1. At this juncture, the most important criterion for international clinical trials with relevance to the United States would appear to be how well an instrument conforms to C-CASA. While the FDA has invited other instrument developers to match their assessments to the C-CASA definitions and requirements, the Columbia Suicide Severity Rating Scale is the only method thus far endorsed by the FDA.
2. Scale-derived composite measures of severity for each of the proposed assessment instruments need to be validated or abandoned.
3. The assessment instrument should be clinician-administered, with information furnished by the patient and, wherever possible, augmented by other informants.
4. Semistructured interviews should have good anchor points.

5. Self-administered forms need to be validated against clinician ratings and judgment. Moreover, leaving the determination of intent up to the patient may complicate efforts at matching to C-CASA, which relies on rater assessment.
6. The measurement of suicidal ideation involves different, but sometimes overlapping, considerations than the measurement of suicidal behavior in efficacy and safety studies. Suicidal ideation can be assessed as a continuous measure, while suicidal behavior is probably best evaluated as a definable endpoint or as a “time to event” measure of efficacy.
7. The individual’s understanding of intent and potential lethality of suicidal behavior, irrespective of its actual lethality, is important in assessing such behavior.
8. Assessment of efficacy with respect to suicidal ideation requires longitudinal measures of improvement, worsening, and no change on measures of severity.
9. Use of standard time intervals for the assessment of suicidal ideation is critical. This may vary by study (last day/last week/last month), but it must be consistent across the study, and it must be reasonable in terms of memory/recall. “Since last visit” is not a standard time frame.
10. Key psychometric criteria for treatment studies are validity, severity of ideation, test-retest reliability, sensitivity to change, predictive validity/specificity, and interrater reliability.
11. Secondary psychometric criteria should also be considered, including requirements for training, validity in both safety and efficacy applications, and internal consistency.
12. Simplicity of licensing, cross-cultural and multilingual validity and equivalence for international studies, ease of administration by trained nonprofessional raters or computer, specified assessment intervals, and costs of training and staff time related to the assessment instrument are of particular interest to industry sponsors.

### **RISK FACTORS AND MODERATING AND MEDIATING VARIABLES**

Because suicide assessment instruments by themselves do not necessarily provide a complete assessment of factors that may be associated with suicidal ideation, suicidal behavior, and suicide, it will be important to consider how evidence-based or putative risk factors (and moderating and mediating variables) should be considered selectively in clinical trials. The following list of variables is not meant to be prescriptive or limiting, but it is suggestive of the factors that might be important to consider in planning safety and efficacy studies: age and other demographic information, the presence of specific psychiatric and medical disorders (including substance abuse/dependence [including tobacco smoking]), monitoring of direct and indirect measures of substance use in patients with a current or recent history of alcohol or drug abuse/dependence, feelings of helplessness and hopelessness

and other symptoms associated with suicidal risk in specific groups (such as poor sleep quality in the elderly), family history of suicidal behaviors (including lethality and method), recent stressors related to work or relationships, and the presence/absence of social support from friends, family members, coworkers, and coreligionists. Blood drug level data or other markers of medication adherence should be collected during the course of the trial. Because genetics play a key role in differentiating treatment response to medication, including treatment-emergent suicidal ideation/behavior and treatment efficacy, DNA sampling should be considered as an important domain for data collection. The protocol and informed consent form should enable DNA data collection during the course of a clinical trial, including the analysis of deidentified data at a central location, with allowance for analysis long after the conclusion of the trial.

To address questions about possible moderating or mediating factors that could account for age-related differences in antidepressant treatment-emergent suicidal ideation and behavior, additional hypothesis-testing studies should be encouraged. As an initial step, existing large data sets should be examined to determine whether younger patients have greater sensitivity to activating side effects, or side effects in general, compared with adults. If differences are identified, it would be useful to track self-report and behavioral measures of treatment-emergent hostility, agitation, and impulsivity during antidepressant clinical trials of adolescents to examine the relationship between these measures and the emergence of suicidal ideation/behavior. As a further step, exploratory laboratory studies could be conducted to ascertain whether SSRIs and serotonin-norepinephrine reuptake inhibitors produce differential activation in depressed adolescents (compared with depressed adults) using behavioral measures at baseline and during drug treatment.

Given the importance that clinical researchers assign to the presence of “psychic anxiety” in their assessment of suicidal risk, it will be important to clearly define the term, to try to differentiate this state from other anxiety states and disorders, to improve methods of assessment, and to determine the optimal frequency of measurement necessary to establish a clear link to the emergence of suicidal ideation/behavior and risk of suicide. In particular, it is critical for clinicians to know whether failure to reach remission of the anxiety state is associated with a higher risk of suicidal behavior. Clinicians will want to know how personality traits and/or a personal past history of child abuse and other potential moderators influence suicide risk in their patients and the risks and benefits of antidepressant drug treatment.

Finally, it is important for the NIMH to continue to invest in focused, hypothesis-testing research to identify potential biologic markers of suicidal behavior and suicide risk.<sup>30–35</sup>

### **WEIGHING THE EVIDENCE: PROTECTING THE PUBLIC**

While meta-analyses of data from efficacy trials that were conducted before drug approval constitute one

important source of information, the FDA should use its new postmarketing surveillance powers to access pharmacoepidemiologic databases from the United States and abroad to advance the type of cross-design synthesis that can more clearly delineate drug safety regarding suicide-associated risk. Assessment approaches now rely heavily on the acquisition and integration of information from premarketing studies and from spontaneous postmarketing reports of adverse events. Recommendations about relative benefits and risks should draw on information from broader data sources while capitalizing on more modern statistical and epidemiologic tools. The Agency needs to systematically monitor postmarketing events and, toward this end, should encourage the development of a validated instrument for postmarketing surveillance of suicidal ideation, suicidal behavior, and suicide. This should enable the FDA to aggregate and utilize data from randomized and nonrandomized studies, administrative databases, epidemiologic studies, and US-based and non-US-based pharmacoepidemiologic resources. This broad-based paradigm would be consistent with public health approaches that have defined risk of exposure to a variety of environmental toxins, including the relationship between smoking and the full range of negative health outcomes.

Ultimately, the FDA, the clinical research community, and the pharmaceutical industry will need to obtain a better handle on the costs, risks, and benefits of the broad screening requirement for suicidal ideation, suicidal behavior, and suicide risk across all CNS drugs in development; the impact of the requirement on drug development in this therapeutic area; and the risks of failing to implement the new policy. For example, will the FDA require a therapeutic class-based black box warning on a new drug with a novel mechanism of action, even if that drug fails to show a signal of increased suicidal ideation, suicidal behavior, or suicide across all premarketing studies?

### ETHICAL CONSIDERATIONS IN CLINICAL TRIALS INVOLVING HIGH-RISK INDIVIDUALS

In light of studies that have demonstrated the ethical and clinical feasibility of including patients with suicidal ideation and/or recent suicidal behavior as participants in clinical trials,<sup>36,37</sup> it is difficult to argue in favor of common practice that excludes patients from clinical trials who are deemed to be at risk of suicide. Because many patients with these symptoms will be receiving medications (after FDA approval) for which there are no systematic premarketing data on the associated risks and benefits related to suicidal ideation, suicidal behavior, and suicide, priority should be given to implementing ethical procedures to include such patients in clinical trials, just as patients with other life-threatening illnesses are routinely included in premarketing studies of new medications for their conditions. Consensus conference participants agreed with the following general principles regarding the inclusion of patients with suicidal ideation or recent suicidal behavior in clinical trials:

1. Suicide prevention or risk reduction must be a legitimate outcome variable, not just a safety variable.
2. Trials for those at significant suicide risk should not be placebo controlled, unless it is an add-on design. The model would be comparable to the requirements related to clinical trials of anticonvulsant agents, in which all patients receive established treatments in order to reduce the risk of death or serious injury from seizures in placebo-treated patients. In these studies, half of the subjects receive an add-on placebo and half receive the experimental treatment.
3. Noninferiority studies are required if there are approved drugs with established efficacy in reducing risk of suicide for a disorder (eg, clozapine in schizophrenia).
4. The consent process needs to inform that suicidal ideation and behavior are either possible treatment-related serious adverse events or targets of treatment and delineate what the limits of confidentiality will be if the patient becomes suicidal. Consent should also explain that if patients wish to withdraw from the study, they will be assessed for acute suicide risk and may be treated clinically.
5. Staff must be trained in risk assessment and crisis management. The critical threshold for project approval at each site must include a vetted risk management protocol, validated staff training, and appropriate emergency and urgent care resources to implement a high-risk study. The latter includes 24-hour availability of senior clinicians for evaluation and for hospitalization.
6. A hierarchy of evidence-based, severity-based interventions should be available to follow in case of suicide risk.
7. The proper balance of research assessment and clinical care should be carefully calibrated. Although more frequent contact may suppress events, if both arms have the same frequency of contact, the data will be valid.
8. Frequency of assessment should be consistent with standard treatment of the underlying condition and the requirements of the experimental treatments being evaluated, with the option of more contact as clinically indicated. More frequent monitoring of ideation, behavior, and intent via telephone or the Internet can be of value, especially in monitoring high-risk-related ideation such as "psychic anxiety," and feelings of hopelessness, as well as the emergence of significant stressors and ongoing or emergent drug and alcohol use.
9. A guide-based protocol should be available to research participants (eg, the treatment model described by Stanley et al<sup>38</sup>) to provide them with tools for self-assessment and self-management of suicidal ideation during the clinical trial.
10. A Data and Safety Monitoring Board (which should include experts on suicide risk) should be involved throughout the study.

All patients deemed at risk of suicide may not be eligible for participation in RCTs. Patients deemed to be at serious and imminent risk of suicide and medically unstable patients should generally be excluded from these clinical trials. There may be a need for a “cut-off” of severity related to the seriousness and potential lethality of recent suicidal behavior, urgency of suicidal ideation, assessment of intent, and other variables, unless an inpatient lead-in is included, as was done by Oquendo et al.<sup>39</sup> Inclusion and exclusion criteria should include an evaluation of risk by a mental health clinician, following initial screening on a scale to assess ideation and past suicidal behavior.

## CONCLUSION

In the past decade, reports of increased “suicidality” associated with antidepressant and other CNS-active medications have made more urgent the need to accurately and consistently define terms associated with suicide, identify patients at risk, and measure the effects of treatment (both positive and negative) on suicidal ideation, behavior, and risk. This consensus statement is a snapshot of where things stand on this issue in 2009–2010. It is not the last word, just the best that could be distilled from a consensus conference and postmeeting paper preparation by a large, complex group with diverse interests and perspectives. Participants agreed that the term *suicidality* is not as clinically useful as more specific terminology (*ideation, behavior, attempts, and suicide*) that can be defined more precisely across data sets from clinical trials and pharmacoepidemiology and that can be more readily understood by clinicians and the public. Most participants applauded the FDA’s effort to promote standard definitions and definable expectations for investigators and industry sponsors by endorsing the terminology in C-CASA. Currently, there is no consensus on the value or validity of composite scores of severity on any of the available assessment instruments. Their developers should continue their research to address the most important uncertainties regarding utility, reliability, and validity of the scales in identifying suicide-associated treatment-emergent effects and/or a signal of efficacy in suicide prevention trials. All assessment instruments should include a recommendation that would define the point at which a patient should be referred to an experienced mental health professional for a thorough assessment of suicide risk (eg, intent). No scale can, or should, replace clinical judgment where life-and-death issues are concerned.

The FDA needs to build on its new authority to systematically monitor postmarketing events by encouraging the development of a validated instrument for postmarketing surveillance of suicidal ideation, behavior, and risk within informative large health care–related databases in the United States and abroad. By utilizing and synthesizing data from multiple sources, the Agency will be in a far stronger position to define drug-related risks and benefits in many more patients in much broader settings than in a typical RCT. Over time, the FDA, industry, and clinical researchers should evaluate the impact of the current Agency requirement

that all CNS clinical drug trials must include a C-CASA-compatible screening instrument for assessing and documenting the occurrence of treatment-emergent suicidal ideation and behavior. This evaluation should consider the costs and benefits of the broadly applicable mandate, the relevance of including specific risk factors and moderating and mediating variables in the database, and the impact of the mandate and the associated data-gathering requirements on the development of CNS-active compounds and on the health and safety of the public.

Finally, patients at high risk for suicide can safely be included in clinical trials, if proper precautions are followed. They need to be included to enable premarket assessments of the risks and benefits of medications related to suicidal ideation, suicidal behavior, and suicide in such patients. Clinical trials in which suicide is the primary target of treatment will need to be large and of longer duration than the usual 8-week study. Informed consent must explain that suicidal ideation and behavior are the outcome measures, what the limits of confidentiality are should a patient become suicidal, and what assessment and treatment patients will receive if they withdraw from the study. Each research participant should be provided with a suicide prevention plan with steps to follow if they recognize warning signs of imminent suicidal behavior. A balance between research assessment and clinical care can be established such that patients are safe and results are valid.

**Drug name:** clozapine (Clozaril, FazaClo, and others).

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**Consensus conference participants:** See list at [www.psychiatrist.com/suicide](http://www.psychiatrist.com/suicide)

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