Assessment of Suicidal Ideation and Behavior:
Report of the International Society for CNS Clinical Trials and Methodology Consensus Meeting

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ABSTRACT

Objective: To develop consensus recommendations for assessment of suicidal ideation/suicidal behavior (SI/SB) in clinical trials.

Participants: Stakeholders from academia, industry, regulatory agencies, National Institutes of Health, National Institute of Mental Health, and patient advocacy organizations participated in a consensus meeting that was sponsored by the International Society for CNS Clinical Trials and Methodology and held November 17–18, 2015. Prior to the meeting, teams of experts identified key areas of consensus and dissent related to SI/SB. The most critical issues were presented and discussed in the consensus meeting.

Evidence: Literature reviews and a pre-meeting survey were conducted. Findings were discussed in pre-meeting working group sessions and at the consensus meeting.

Consensus Process: Five pre-meeting working groups reviewed (1) nomenclature and classification schemes for SI/SB, (2) detection and assessment of SI/SB, (3) analysis of SI/SB data, (4) design of clinical trials for new treatments of SI/SB, and (5) public health approaches to SI/SB. A modification of the RAND/UCLA Appropriateness Method was used to combine review of scientific evidence with the collective views of experts and stakeholders to reach the final consensus statements. After discussion, all attendees voted using an electronic interactive audience response system. Areas of agreement and areas of continuing dissent were recorded.

Conclusions: All 5 working groups agreed that a major barrier to advancement of the field of SI/SB research and the development of new treatments for SI/SB remains the lack of a universally accepted standardized nomenclature and classification system. Achieving alignment on definitions and classification of suicide-related phenomena is critical to improving the detection and assessment of SI/SB, the design of clinical trials for new treatments, and effective public health interventions.

J Clin Psychiatry 2017;78(6):e638–e647
https://doi.org/10.4088/JCP.16cs11417

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Suicidal thinking, suicide attempts, and death by suicide remain critical global public health concerns. The World Health Organization estimates that there were 804,000 suicides worldwide in 2012, with an annual global age-standardized suicide rate of 11.4 per 100,000 population.[1] More recent statistics in the United States indicate that from 1999 through 2014, the age-adjusted suicide rate increased 24% to 13.0 per 100,000, with greater increase since 2006, making suicide a leading cause of death.[2] In 2014, 9.4 million adults, 18 years or older, reported they had seriously thought about trying to kill themselves in the prior 12 months.[3] Among these, 2.7 million persons made suicide plans, and 1.1 million made a nonfatal attempt.[3] That same year, 42,773 persons were reported to have died by suicide.[4]

Yet, suicidal ideation (SI) and suicidal behavior (SB) remain underrecognized and undertreated. Efforts to improve this situation have been handicapped on many fronts, including the lack of a standardized nomenclature and disagreement on the diagnostic approach to individuals with SI/SB.[5] Given the growing public health problem, identification and management of persons at risk for suicide must be improved by utilizing better assessment approaches and preventative measures and finding better treatments.[6]

Historically, the treatment of SI/SB relied heavily on use of antidepressants. However, after extensive review of large data sets from multiple central nervous system (CNS) clinical trials, concerns arose regarding the possibility that antidepressants and other classes of CNS medications might be actually associated with an *increased* risk of SI/SB in subpopulations treated with these medications.[7–10] To address these concerns, in 2010 the US Food and Drug Administration (FDA) issued draft safety guidance for medications being developed and prescribed for psychiatric and neurologic indications. This draft guidance required the implementation of prospective assessments of SI/SB in all phases of relevant industry-sponsored clinical trials[11] and adopted the Columbia Classification Algorithm for Suicide Assessment (C-CASA)[12] as the standard for coding SI/SB data. In 2012, this guidance was revised

Clinical Points

- Suicidal ideation and suicidal behavior (SI/SB) are critical public health concerns but remain underrecognized and undertreated. The International Society for CNS Clinical Trials and Methodology supported a consensus meeting of stakeholders and experts in the field to develop recommendations for the standardization of SI/SB data collection and analysis and to guide the development of novel treatments for SI/SB.
- Recommendations included the following: (1) clear standards should be used to evaluate existing SI/SB assessments, (2) SI and/or SB should serve as the primary endpoint in treatment studies, (3) common data collection elements should be implemented to ensure comparability across studies, and (4) more work must be done on public health gaps, especially those related to stigma and cross-cultural issues.
- The primary barrier to advancement of SI/SB research and the development of new treatments for SI/SB remains the lack of a universally accepted standardized nomenclature and classification system. Achieving alignment on definitions and classification of suicide-related phenomena is critical to improving the detection and assessment of SI/SB, the design of clinical trials for new treatments, and effective public health interventions.

by expanding certain C-CASA coding categories while deleting others.[13]

In March 2009, an earlier consensus conference of representatives from academia, government, and industry was convened by the Department of Psychiatry at Beth Israel Deaconess Hospital in Boston, Massachusetts, to address issues concerning potential treatment-emergent "suicidality" and to consider the implications of the pending draft FDA guidance then being circulated.[14,15] Consensus recommendations were developed regarding the preferred terminology for suicide-related phenomena and the need for further validation of the C-CASA definitions, additional research on assessment instruments, more systematic monitoring of postmarketing events, and consideration of risk factors and moderator/mediator variables in the assessment of potential safety signals or efficacy in SI/SB treatment trials. Recommendations were also formulated for the inclusion of patients at high risk of SI/SB in clinical trials. Importantly, the consensus conference report highlighted the need to evaluate the impact of the new guidance over time to more fully assess its costs, risks, and benefits and the impact on drug development.

Since the FDA guidance was issued, prospective assessment of SI/SB has greatly expanded and has been widely implemented in relevant industry-sponsored clinical trials. These trials span a wide range of psychiatric and nonpsychiatric indications and many patient populations, geographic regions, and cultures. Implementation of this guidance has required enormous effort and resources, but significant challenges to capturing these data, ensuring their proper interpretation, and optimizing their value for improving public health have been identified.[16–18]

To gather information on sponsor experiences with prospective collection of SI/SB data, the International Society for CNS Clinical Trials and Methodology (ISCTM; https://isctm.org/) conducted 2 global surveys of pharmaceutical sponsors and clinical trial site investigators.[16,17] The results of these surveys identified important benefits of consistent SI/SB assessment for improving patient safety, as well as numerous challenges to applying the current FDA guidance. Among these were operational and statistical challenges that impact the quality of SI/SB data currently being collected and limitations of existing scales when assessing suicide risk, especially in cognitively impaired populations.[16–18]

Concurrent with the movement to characterize the possible adverse impact of CNS drugs on SI/SB, interest in providing better SI/SB treatments has been growing. Several interventions have been identified that may reduce SI/SB. Although only clozapine has been approved by the FDA for treatment of recurrent suicidal behavior in schizophrenia or schizoaffective disorders,[19] there are reports that other agents, such as lithium and ketamine, may reduce SI/SB in mood disorders.[20,21] In addition, several evidence-based psychosocial interventions[22–24] have been identified that specifically target SI/SB. Furthermore, growing biomarker research provides a promising potential to increase clinical trial cost-efficiency, fill knowledge gaps, and promote personalized medicine.[25] These emerging developments raise numerous questions related to optimizing study design, including appropriate population identification, choice of study endpoints, assessment instruments, and statistical analytic approaches.

In light of these challenges and the need to provide better guidance regarding SI/SB assessment, the ISCTM convened a meeting of key stakeholders and experts in the field on November 17–18, 2015, in Washington, DC. Its aims were to review what has been learned about the implementation of SI/SB assessments in industry-sponsored clinical trials since the draft FDA guidance was first issued in 2010, to work toward a consensus on the standardization of SI/SB data collection and analysis, and to develop recommendations to guide the development of novel treatments for SI/SB. In preparation for this meeting, teams of interested experts identified key issues related to SI/SB and explored potential solutions. Having established this background, representatives from academia, pharmaceutical sponsors, the US National Institutes of Mental Health (NIMH), the US National Institutes of Health (NIH), the FDA, and European regulatory agencies gathered, debated this work, identified areas of consensus, and delineated critical areas where additional work is required to move the field forward. Results of this work are summarized in this report.

CONSENSUS PROCESS

A modification of the RAND/UCLA Appropriateness Method guided the ISCTM Consensus Meeting.[26] This process combines a review of scientific evidence with the collective views of experts to reach consensus statements.

The major modification was that the goal was to reach consensus using a large group of diverse stakeholders rather than a smaller expert panel. To initiate the process, interested stakeholders were recruited (experts from within and outside ISCTM) and organized into 5 working groups (WG) in the following areas: (1) principles and characteristics of a standardized nomenclature and classification scheme for SI/SB; (2) best approaches to the detection and assessment of SI/SB across different patient populations; (3) analysis of SI/SB data at the study, program, and meta-analytic levels; (4) design of industry sponsored and nonindustry clinical trials and drug development programs for regulatory approval of medicines to treat SI/SB; and (5) development of research-based policies and educational initiatives to support optimal public health approaches to SI/SB. A total of 84 stakeholders participated in the 5 pre-meeting WGs (a list of pre-meeting working group members can be found at https://isctm.org/public_access/MANUSCRIPT/Pre-Meeting-Working-Groups-Consensus-Meeting-Methodological-Considerations-for-Suicide-Assessment-and-Clinical-Trial-Design.pdf).

Prior to the face-to-face meeting, each WG reviewed the current state of knowledge of their topic area, identified key issues where a consensus would be useful for the field, prioritized the issues through group discussion and literature reviews, and selected the most critical issues for presentation and discussion at the larger consensus meeting. The WGs also determined if there were important questions related to their topic areas where a consensus view already existed.

A pre-meeting survey designed by each of the 5 WGs was conducted to obtain a preliminary assessment of the prevailing views of key stakeholders regarding the critical issues in their topic area. The surveys were sent to the members of all the WGs, to individuals who had registered for the consensus meeting, and to key external experts (a total of 144 recipients). The survey results indicated areas where there was broad consensus and other areas where opinion was divided. The complete results of the pre-meeting surveys can be found at https://isctm.org/si-sb-pre-meeting-survey-results.

Prior to the consensus meeting, the WGs discussed survey questions that lacked broad consensus. When they were able to reach consensus among their members during the pre-work, the consensus opinion was brought forward to the meeting for review. Where consensus was not reached, the WGs prioritized the questions and assigned representatives to present divergent positions. Following the presentations and discussion at the consensus meeting, all attendees voted using an electronic interactive audience response system.

The consensus meeting was open to anyone who wished to attend. Announcements of the meeting were posted on the ISCTM website and e-mailed to ISCTM members, working group members, and identified thought leaders in the field. A total of 115 individuals attended the meeting, including 50 WG members, the 4 members of the Steering Committee, and 61 additional attendees who registered for the meeting but had not participated in the WG process (the list of participants is provided in Supplementary eTable 1). Attendees provided a broad representation of key stakeholders from academia, industry, the FDA and European regulatory authorities, the NIH and NIMH, and patient advocacy organizations such as the American Foundation for Suicide Prevention. A draft report on the output of the meeting was developed by the Steering Committee and WG Co-Chairs, who are the authors of this report, and circulated for review to all members of the WGs. Final editorial decisions rested with the authors of the report.

CONSENSUS MEETING RESULTS

The key outputs for each WG are summarized below. The full list of consensus statements and on-site voting results from all the WGs can be accessed at https://isctm.org/consensus-meeting-working-group-statements.

Nomenclature and Classification Working Group

There currently is no internationally agreed upon set of terms, definitions, or classifications for the range of thoughts, communications, and behaviors that are related to self-injurious behaviors, with or without the intent to die. Nor is there an agreed taxonomy that encompasses the full spectrum of what are clinically defined as suicide-related behaviors.[27] There remains much debate about what truly constitutes suicidal behavior and what is classified or labeled as other forms of self-injury, accidents, etc.[28–31] As a result, researchers cannot easily compare their study populations or the effectiveness of their interventions, and clinicians have difficulty translating research findings into practical applications when working with an individual at risk for suicidal behaviors.[27]

The WG was challenged to provide a nomenclature and classification system that would address the wide variety of concerns faced by a complex array of research and treatment settings. They decided to adhere to the principles and best practices for development of classification systems promulgated in the United Nations' Best Practice Guidelines for Developing International Statistical Classifications.[32] This document provides guidelines for the development of international statistical classification systems, outlining the essential attributes of a classification system: having a consistent conceptual basis, a clearly defined structure (eg, flat or hierarchical), mutually exclusive and exhaustive categories, and clear and up-to-date definitions.

The WG conducted a systematic evaluation of the currently used nomenclature and classification systems based on the United Nations best practice guidelines for classification systems.[32] (These reviews are available at https://isctm.org/nomenclature-and-classification). They found that current terminology and classification systems are inadequate to cover the large continuum of suicide or suicide-related thoughts and behaviors.

A high-level overview of the current classification systems is available in Supplementary eTable 2, and a comparison of

Table 1. Nomenclature and Classification Working Group: Key Consensus Statements

Key Consensus Statements	Caveat
There are 3 types of self-directed violence (SDV) or suicidal behaviors[26]: Nonsuicidal SDV Undetermined SDV Suicidal SDV	Although there were some conceptual disagreements, it was noted that, although not precisely the same concept, suicidal SDV was equivalent to "suicidal behaviors."
The category of "suicidal behaviors" or suicidal SDV includes 3 subtypes: Preparatory behaviors for death by suicide Suicide attempt Died by suicide	The working group struggled with whether to use the more colloquial terms "suicide" or "death by suicide" instead of "died by suicide." However, a strong argument was made that the fatal outcome of a suicidal behavior is that the individual *died by suicide*. Nevertheless, the feedback from the pre-meeting survey was not supportive of this term.

Table 2. Assessment Instrumentation Working Group: Key Consensus Statements

1. When selecting an instrument and method of administration for a study, one should consider the research settings (eg, academic, hospital, clinical research unit), study teams (eg, psychiatric vs nonpsychiatric, level of experience), and patient populations (eg, youth, elderly, cognitively impaired, acutely ill).
2. Evidence of both validity and reliability must be provided for formal use of an instrument in clinical trials. Reliability and validity of an SI/SB instrument must be demonstrated for the population to be studied, taking into account vulnerable populations and cultural relevance. This does not apply to experimental measures, which may be included alongside established measures.
3. Assessment tools for SI/SB must be translated into different languages taking cultural factors into account and ideally have demonstrated reliability and validity for use within the selected population.
4. Training should include information about the specific population being studied and the scales being used with attention to vulnerable populations.
5. Standardized instruments require manuals with specific instructions about administration, scoring, and interpretation as well as provision of evidence of reliability and validity.
6. For interviewer-administered measures, initial training, monitoring, and regular follow-up training of interviewers is recommended to maintain reliability and prevent drift.

Abbreviations: SB = suicidal behavior, SI = suicidal ideation.

the concepts and terms that comprise the major systems is provided in Supplementary eTable 3.

Consensus agreements. The members of the WG and the pre-meeting survey respondents uniformly endorsed the guiding principles that an optimal nomenclature and classification system for suicide terminology should be clinically relevant, comprehensive, reliable and valid, easily understood and applied, theory-neutral, and adaptable to public health needs. There was also broad agreement that definitions of suicide and suicide related phenomena should be free of value judgments and "culturally normative" (ie, broad enough to apply to a range of belief systems and cultures).

With some caveats, consensus was reached on a few specific terminology issues, including the types of self-directed violence and subtypes of suicidal behaviors or suicidal self-directed violence (Table 1).

Key challenges. The WG identified several key challenges to the development of a standardized nomenclature and classification system for SI/SB. Foremost among the specific challenges confronting the field is the lack of agreement on which terms are essential and how to define mutually exclusive categories, a critical characteristic for a successful classification system.[32] For example, in the absence of a clear and consistent definition of the term *suicide*, there is no consensus on the definition of terms that are related to the act of "death by suicide," such as *suicide ideation, suicide intent,* and *suicide attempt*.[5] There are also continuing disagreements about the meaning, connotations, and appropriateness of such terms as *suicidality, completed suicide, suicidal threat, suicide gesture, cry for help,* and *nonfatal suicide attempt,* especially when many of these terms are commonly used by mental health professionals and clinical researchers.[5]

Another critical challenge debated at length by the WG is the assessment of "intent to die" by suicide, which is generally viewed as a critical element for determining whether or not a self-injurious behavior is suicidal. Despite the high clinical relevance of this term, the "intent to die" may be difficult to understand and is not clearly defined.[5,27,33,34] A key challenge to the development of a standardized nomenclature is that the criteria for establishing "implicit" or "inferred" intent are open to a great deal of nuance and conjecture, especially when a patient who appears to have engaged in suicidal behavior denies the intent to die. There are no agreed-upon operational definitions for "implicit" or "inferred" clinical judgment regarding the presence/absence of intent when a patient denies it.

The third key challenge is what constitutes a suicidal ideation or thought. Must a suicidal thought by definition include an intention to die, or can there be suicidal ideations without intent? Is it appropriate to differentiate "active" vs "passive" ideation, or should suicidal ideation be conceptualized as occurring on a spectrum from "wishes to die" to "thoughts of killing oneself"?

In summary, although the WG was able to reach consensus on the types and subtypes of self-directed violence/suicidal behavior (Table 1), the present state of SI/SB nomenclature and classification remains fragmented, with multiple competing systems and with limited tools for "crosswalk" between them.[35] The development of a uniform standardized nomenclature and universally accepted classification system—which is a sine qua non for advancement of the field—remains an elusive but necessary goal.

Assessment Instrumentation Working Group

The standardized assessment of SI/SB is central to an improved understanding of SI/SB phenomena. A wide range of raters in varied settings administer SI/SB instruments in diagnostically diverse and potentially at-risk populations. This WG focused on the psychometric and implementation characteristics that would be desirable in an SI/SB assessment. In all, the group agreed to 31 statements with no areas of significant controversy. Table 2 summarizes key consensus statements developed by the group that reflect important considerations for selecting an SI/SB instrument.

Table 3. Trial Design and Methodology Working Group: Key Consensus Statements

Trial Design and Endpoints
Prospective, double-blind, randomized, parallel-group, placebo-controlled studies are generally required for regulatory approval; however, alternate trials designs such as single-blind or non–placebo-controlled arms may be utilized. Study design should emphasize patient safety. If placebo is used, the length of the double-blind, randomized, controlled treatment period should be the minimum necessary to answer the study hypothesis. The length of any open-label extension or posttreatment follow-up period should be sufficient to ensure safety and adequately address secondary outcomes.
Suicidal ideation and/or behavior are the key efficacy outcomes. Both statistical and clinical significance should be addressed.
The study setting (inpatient, outpatient, or a combination) is dependent on the acuity of the patient population and the hypothesis being tested and must ensure the safe and ethical care of the patient population. The study should be conducted within the context of the highest level available of standard of care.
Safety assessments must identify clinically significant worsening of SI/SB. The protocol should specify actions to be taken in case of worsening of symptoms, including criteria for early withdrawal of treatment, and outpatient studies should consider criteria for hospitalization. In order to ensure patient safety and monitoring of risk/benefit, a Data Monitoring Committee should be utilized to review unblinded safety and efficacy data during the study. Interim analysis for futility should also be considered.
The collection of samples for candidate biomarkers should be included in SI/SB trials to support discovery and validation for future biomarker research.
The relative acuity of the SI/SB of the study population should align with the hypothesis being tested. If appropriate, participants with recent evidence of clinically significant, moderate to severe suicidal ideation or suicidal behavior should be eligible to enroll.
Subjects on concomitant medications or receiving nonstudy psychosocial interventions should be stable for sufficient time to minimize influence on SI/SB assessment.
General Issues
In relation to the scope of therapeutic intervention, a distinction should be made between acute treatment and long-term prevention of SI/SB.
For clinical development, SI/SB can be investigated either within diagnostic categories (eg, SI/SB in context of major depression) or across diagnostic categories (ie, as a transnosological syndrome that occurs in different disorders).
Engagement of individuals with lived SI/SB experience should be strongly considered during protocol development.

Abbreviations: SB = suicidal behavior, SI = suicidal ideation.

Scale developers should provide sufficient information to assess their instruments in terms of these characteristics.

The group proposed criteria for the selection of appropriate, effective, reliable, and valid SI/SB measures, outlined essential rater-training requirements, and emphasized that the selected instruments must be applicable to special populations and across cultures. Additional areas that merit further study include whether different assessments are needed for SI/SB as a safety versus efficacy endpoint, how best to ensure cultural adaptability, and the most appropriate formats and sources of information (ie, self-report, observation, informant report, paper and pencil, computerized assessments, interview, observation). For example, self-report of SI/SB may be a more sensitive approach to detect SI/SB than clinician-based assessments.[36] Finally, it was beyond the scope of this group to review the many SI/SB scales currently in use, but future efforts could examine the existing scales in light of the recommendations issued by this group. However, it must be noted that the lack of consensus on nomenclature and classification is a barrier to further scale development and refinement.

Trial Design and Methodology Working Group

SI and/or SB increasingly serve as the primary efficacy endpoint in pharmacotherapy and psychosocial interventional trials.[20,21,37,38] Yet, there is little consensus among researchers or regulatory agencies on the optimal design of such studies, whether the focus is on demonstration of efficacy or characterization of the benefit risk profile of potential new therapies. Inclusion of provisions to safeguard patients' safety and rights is a critical aspect of studies conducted in such vulnerable, high-risk patients. Finally, the execution of such studies must be feasible from an operational perspective.

The Trial Design and Methodology WG's objectives included the review of current methodological approaches and the development of consensus on the key medical and scientific requirements for the design of clinical studies and programs to study therapies to treat SI/SB, with particular emphasis on clinical trials for treatments seeking regulatory approval. Priority was given to identifying issues hindering the advancement of knowledge and technology development in this field. Safeguarding the well-being of subjects enrolled in clinical trials investigating potential SI/SB treatments is of paramount importance and should be a priority in designing clinical trials, but it was beyond the scope of this group to develop specific recommendations regarding the management of treatment-emergent SI/SB. Similarly, issues related to conducting SI/SB trials in pediatric populations were not specifically considered.

Key recommendations, which broadly address critical issues confronting researchers designing trials where SI/SB is the primary endpoint, are summarized in Table 3. These recommendations were derived from the principles of good clinical trial conduct. Given the lack of formal guidance from regulatory bodies on conducting studies targeting SI/SB as a primary endpoint, these recommendations were viewed as laying the groundwork for future elaboration. Although no formal recommendation was made regarding how to best determine the baseline level of SI/SB, the WG recognized that it is important to establish an initial baseline for comparison to gauge the impact of treatment.

The recommendation to collect candidate biomarkers followed review of emerging evidence for novel biomarkers such as inflammatory,[39,40] epigenetic,[41,42] and genetic factors.[43] Group members concluded that although it was premature to nominate specific biomarkers to be collected, researchers should be encouraged to collect biomarkers where possible to continue to develop the knowledge base in this area. Similarly, the study of SI/SB across diagnostic categories was seen as promising but still underdeveloped.

Statistical Analysis Working Group

Statistical analysis tools are important to understand safety or efficacy signals from SI/SB data. It is critical to define the research questions and relevant endpoints before proposing a statistical analysis approach. Yet, the most appropriate definitions of SI/SB endpoints, the granularity of those endpoints (ie, global measures of SI or SB versus subtypes of SI or SB), and appropriate statistical approaches to analyze SI/SB data remain ill-defined.

Key recommendations of the Statistical Analysis WG are summarized in Table 4.

The recommendation that the existing guidelines for the analysis of SI/SB data should be updated was based on the WG's review of the FDA guidance for industry on the prospective assessment of SI/SB in clinical trials[10,11] and on an article summarizing earlier consensus work by a group of statisticians from the pharmaceutical industry.[45] These sparse sources were deemed far from complete and the depth of coverage insufficient to provide direction on analyzing and interpreting SI/SB data, whether collected as a safety endpoint or as an outcome endpoint.

Specific recommendations for updating the current FDA guidance included adding a section on the assessment of SI/SB as an efficacy endpoint and changing the expanded C-CASA coding system[13] so that the numeric codes for SI and SB move in the same direction with a change in severity (in the current system, they move in opposite directions). Additional recommendations included updating the guidance for the conduct of retrospective review of SI/SB data when prospective collection has not been done and developing a meta-analytic guidance specific to SI/SB. Meta-analysis of SI/SB data across clinical trials is possible as long as the different assessment instruments have been demonstrated to map to a common set of categories such as the expanded C-CASA categories used by the FDA.[13] Although not directly a statistical issue, additional guidance is needed on whether and how prospective SI/SB assessments should be done in special populations such as very young children, stroke victims, the seriously medically ill, or those with severe dementia,[18] given that there are no validated tools to use in these patients and their conditions may compromise their ability to provide reliable information.

This group also identified a number of additional critical gaps in the current knowledge base that present barriers to the development of standardized statistical approaches for the analysis of SI/SB data. These gaps include lack of agreement on the appropriate analytic approaches to be used when SI/SB is an efficacy endpoint and the current limited knowledge base regarding risk and protective factors for imminent SB (including moderators and mediators) that may need to be factored into analyses. Potential mediators and moderators of SI/SB should be defined a priori in a statistical analysis plan in order to provide prospective confirmation of any exploratory findings. Likewise, the lack of a commonly accepted and consistently applied definition for the relevant baseline window from which to gauge treatment emergent SI/SB, or worsening or improvement in SI/SB in treatment studies, hampers interpretation of SI/SB data collected in clinical trials.

Vast amounts of clinical trial SI/SB data have accumulated since the requirement for the prospective assessment of SI/SB in trials sponsored by industry and academic investigators was established.[10,12] An overarching recommendation of the Statistical Analysis WG was that a collaborative effort should be undertaken to share the existing clinical

Table 4. Statistical Analysis Working Group: Key Recommendations

1. Outcome SI/SB endpoints and measures should be well defined to enable pooled analyses across studies and to better understand mediator and moderator effects of other variables.[a]
2. In clinical trials in which SI/SB is a primary or key secondary objective, potential clinical and biomarker moderators or mediators, and potential protective factors should be collected using common data elements.[a]
3. Careful consideration should be given to adjusting for multiplicity when testing multiple hypotheses in clinical trials in which SI/SB is a primary or key secondary endpoint.
4. It is important to identify top predictors of imminent suicidal behavior and protective factors that may mitigate risk of imminent suicidal behavior.
5. In the context of randomized clinical trials, the possible relation between medication exposure (eg, drug concentration) and SI/SB should be further explored.
6. The available guidance for industry on the prospective assessment of SI/SB in clinical trials should be updated to better address issues related to the analysis of SI/SB data, or a separate guidance on analysis considerations should be developed.
7. A coordinated effort should be made to harmonize common data elements for SI/SB endpoints to ensure they are comparable across trials and sponsors.

[a]A mediator is an intermediate variable in a causal chain whereby an independent variable causes an outcome variable. A moderator is a qualitative (eg, sex, race, diagnosis) or quantitative (eg, serotonin levels) variable that affects the direction and/or strength of the relation between an independent or predictor variable and a dependent or criterion variable.[44]

Abbreviations: SB = suicidal behavior, SI = suicidal ideation.

Table 5. Education and Policy Working Group: Key Consensus Statements

1. Research and education related to tackling stigma and finding culturally sensitive ways to talk openly about suicide are critical components of policy development.
2. Better approaches are needed to identify individuals at imminent and long-term risk for suicide. Research to address this need should be tailored to specific at-risk groups (eg, older adults, children/adolescents, incarcerated individuals, Native Americans, military personnel, and veterans).
3. Comprehensive epidemiologic studies including identification of behavioral risk factors, the role of access to suicide methods, and analysis of the interactions of access and behavioral risks are greatly needed worldwide.
4. Improving clinical training and practice including identification, treatment, and management of SI/SB represents an unmet public health need that should be a focus of prioritized research.
5. Future research into suicide risk and management should involve population health stakeholders from diverse disciplines including health care, education, advocacy, community representation, individuals with lived experience of SI/SB, and other relevant groups to support development and implementation of effective evidence-based SI/SB policies.

Abbreviations: SB = suicidal behavior, SI = suicidal ideation.

trial SI/SB data (eg, from the placebo treatment arms of completed studies) so they can be systematically explored to help answer unresolved questions and to provide evidence-based guidance on the statistical analysis of SI/SB data. Additionally, data from various NIH epidemiology trials (eg, the National Comorbidity Survey, https://www.hcp.med.harvard.edu/ncs/) and large datasets such as the Collaborative Psychiatric Epidemiology Survey (http://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/20240) could be utilized to supplement clinical trials data.[46,47]

Education and Policy Working Group

The dissemination and implementation of findings from well-designed and conducted studies should inform clinical practice and policy development. This WG was charged with surveying the current state of policies and educational initiatives that aim to support optimal public health approaches to SI/SB. Through a review of the landscape of SI/SB prevention and intervention programs, the WG identified best practices in regional and community programs that merit application in broader settings. The review also identified key gaps in the measurement of the effectiveness of different programs and where more robust data could confer improvements and broader public health benefits. The diverse perspectives of patients, family/caregivers, clinicians, and public health policy makers were taken into account.

The Education and Policy WG developed statements for which there was broad consensus within the WG already and utilized the pre-meeting survey results and the consensus meeting to identify key statements (Table 5) reflecting the highest priority areas to focus on for translation of science in SI/SB research into effective education and policy.

Reducing the stigma associated with SI/SB, which has been identified as an aspirational goal for a number of national initiatives[48,49] and is considered to be a key first step in reducing suicide by many suicide prevention advocates,[50,51] was seen as essential.

There was also a strong consensus on the importance of a patient-centric approach (ie, treating the individual, not simply the disorder); the need for expanded and improved treatment options (whether behavioral, psychotherapy, or pharmacotherapy); utilization of a multidisciplinary approach; and strengthening current training programs to ensure clinicians better understand the nature of SI/SB phenomena and its treatment. Involvement of individuals with lived experience of SI/SB will be critical to the success of these efforts, to ensure efforts focus on what is most pertinent, meaningful, and impactful in prevention, intervention, or postvention efforts.

The need for increased funding for prevention research was seen as essential, particularly the development of screening methods and biomarkers that are sensitive and specific for the detection of imminent and long-term risk of suicide, as well as the generation of data to better define at-risk populations and ensure effective implementation of policy initiatives where they are most needed.

CONCLUSION

Suicide remains an inadequately addressed public health concern with global impact. Developing consensus around key issues related to its identification and treatment is critical for rapidly advancing coordinated progress in this field. The 2015 ISCTM Consensus Meeting, which involved a diverse group of over 140 individuals from academia, industry, the FDA and European regulatory authorities, the NIH and NIMH, and patient advocacy organizations, represents an important milestone toward this goal. The consensus statements developed by this group provide a useful step for the broader group of stakeholders involved in this effort by clarifying key considerations for defining the nomenclature and taxonomy of suicide and improving methodological approaches for studying it.

During their discussions, issues related to SI/SB nomenclature and classification surfaced in all 5 Working Groups, highlighting its foundational role. There was strong consensus that achieving alignment on definitions and classification of suicide-related phenomena is critical for facilitating research, increasing collaboration, and improving the clinical utility of work in the area. Clear nomenclature and related definitions—particularly for areas such as suicidal intent and suicidal ideation—that are straightforward and nonoverlapping are needed for the field to advance. It is imperative to speak the same language (with the same definitions) when communicating with patients, family members, and policy makers and with each other as clinicians, researchers, and advocates.[31]

With respect to instrumentation, the participants articulated clear standards that can be used for judging among available instruments and for detecting measurement gaps requiring the development of new instruments. This

approach was driven by an understanding that suicide studies occur in different populations, different cultures, and different clinical and research settings and can have different goals. The participants agreed that instruments should generally be used only in populations in which reliability and validity have been demonstrated. Where these have not been demonstrated, validating instruments in populations of interest should be a high priority. The adaptation of instruments for cross-cultural use was also seen as important.

For interventional clinical studies of SI/SB, participants agreed that suicidal ideation and/or suicidal behaviors should be the primary endpoint(s). Patient safety should be a critical consideration in designing the trial and selecting the patient population for study. When regulatory approval is the focus, trials will need to meet rigorous standards, although typical design features such as double-blind and placebo control may not always be required. For example, in the case of clozapine, which is indicated in the United States for the reduction of suicidal behavior in patients with schizophrenia or schizoaffective disorder, the pivotal study was a large (956 patients), open-label design comparing 2 active treatments and using a blinded endpoint adjudication committee to ensure adequate treatment of a high-risk population.[19] Researchers should also clearly define whether the focus of study is treating individuals with acute SI/SB or preventing the recurrence (onset) of SI/SB in stable individuals. There was also consensus that studies should collect data on potential candidate biomarkers and that individuals with lived SI/SB experience should be consulted during protocol development to help ensure a patient-centered orientation.

Participants in the WG on the statistical analysis of SI/SB data identified several steps that could be taken to progress the field more rapidly. Introducing common data elements across clinical trials would ensure comparability of data across trials and sponsors, thereby facilitating analysis. These data elements should encompass SI/SB as a safety and primary endpoint, as well as moderators and mediators of SI/SB response. There was also a broad consensus on the need for updated regulatory guidance concerning SI/SB assessment in clinical trials (as safety or primary efficacy outcome), along with guidance on meta-analytic approaches to analyzing SI/SB data. The group also called for establishing a collaborative effort to leverage SI/SB data that has already been collected to help address several of the identified gaps.

The WG on policy and education issues highlighted the importance of designing studies that address key public health gaps in SI/SB, including characterizing and appropriately measuring SI/SB, identifying those at greatest risk, and incorporating measures to demonstrate effectiveness in reducing and preventing SI/SB. Addressing these gaps will enable better translation and adoption of research findings into policy initiatives and educational programs. Successful translation of findings from interventional studies to the real world will require ongoing dialogue between researchers, clinical trialists, patients, and clinicians with those responsible for policy implementation and education initiatives.

Obstacles to progress in SI/SB research were identified by all working groups. Many are attributable to a shortage of intellectual and financial investments in finding better approaches to the assessment and treatment of SI/SB as well as the persistent social stigma associated with suicide.[52] The efforts of the SI/SB WGs will be continued in some form under the aegis of the ISCTM. However, a major barrier remains the lack of a universally accepted standardized nomenclature and classification system. Overcoming this obstacle may require the establishment of an international task force similar to the NIMH-sponsored Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH MATRICS) initiative on cognitive impairment in schizophrenia[53] or to the Task Force on Nomenclature recently established by the International Association for Suicide Prevention.[31] To succeed, this effort should be broad and sustained, with engaged stakeholders from important constituencies such as regulators, industry, and academia who are willing to set aside considerations of competitive advantage or financial or intellectual interests to find common purpose in addressing this urgent public health concern.

The ISCTM Consensus effort represents an important step forward, and it has culminated in recommendations that can be adopted by the field. The consensus statements reflect input from key stakeholders and offer immediate guidance. This initiative also has highlighted the critical obstacles and gaps that remain. The challenges outlined by this effort should serve as a resounding call to action for the field.

Submitted: December 20, 2016; accepted April 21, 2017.

Potential conflicts of interest: **Drs Chappell, Stewart**, and **Ratcliffe** and **Ms DuBrava** are employees and shareholders of Pfizer, Inc. **Drs Alphs** and **Lim** are employees and shareholders of Janssen, Inc. **Dr DiCesare** is an employee of LeoBen Research. **Dr Harkavy-Friedman** is an employee of American Foundation for Suicide Prevention. **Dr Silverman** is an employee of Suicide Prevention Resource Center. **Dr Targum** is an employee of Clintara LLC. **Dr Marder** is an employee of Semel Institute for Neuroscience at UCLA and the VA Desert Pacific Mental Illness Research, Education, and Clinical Center.

Funding/support: This project was sponsored by the International Society for CNS Clinical Trials and Methodology, Nashville, Tennessee, which provided administrative and logistical support for the meeting, travel stipends to 2 attendees, and funding to support free access for the published article. Pfizer, Inc, and Janssen Pharmaceutical Companies are Sustaining Corporate Members of the ISCTM but did not provide direct funding for this project (2015 Sustaining Corporate Members).

Disclaimer: The opinions expressed in this article reflect those of the authors and not their respective employers or institutions. Participation in the working groups and attendance at the consensus meeting does not imply agreement with all the opinions expressed in this article.

Acknowledgments: The authors thank Carlotta McKee, AA; Mary Bea Harding; and Lori Bales, BS, supported by International Society for CNS Clinical Trials and Methodology, for administrative and logistical support for the Working Groups and consensus meeting, and Margaret Driscoll, JD, supported by Pfizer, Inc., for project management support. Mss McKee, Harding, and Bales are full time employees of the ISCTM and report nothing to declare. Ms Driscoll is a full time employee and shareholder of Pfizer, Inc. The authors also thank all the individuals who participated in the Working Groups and the consensus meeting for their many contributions to this project.

Supplementary material: See accompanying pages.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.

Supplementary material follows this article.

THE JOURNAL OF
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Supplementary Material

Article Title: Assessment of Suicidal Ideation and Behavior: Report of the International Society for CNS Clinical Trials and Methodology Consensus Meeting

Author(s): Phillip B. Chappell, MD; Michelle Stewart, PhD; Larry Alphs, MD, PhD; Franco DiCesare, MD; Sarah DuBrava, MS; Jill Harkavy-Friedman, PhD; Pilar Lim, PhD; Sian Ratcliffe, PhD; Morton M. Silverman, MD; Steven D. Targum, MD; and Stephen R. Marder, MD

DOI Number: 10.4088/JCP.16cs11417

List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary material: Chappell et al.

Supplementary eTable 1. ISCTM Consensus Meeting Attendees and/or Pre-meeting Working Group Members

Lawrence	Adler	MD	University of Maryland School of Medicine
Munaf	Ali	BSc, MSc, PhD	Munaf Ali Consultancy, Ltd.
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Carla	Canuso	MD	Janssen Research and Development
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Wen-Hung	Chen	PhD	FDA
Wendy	Curran	BA	Turing Pharmaceuticals
David	Daniel	MD	Bracket
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John	Davies	MSs, BSc	GlaxoSmithKline
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Robert	Goldman	PhD	Sunovion
Veeru	Goli	MD	Pfizer, Inc.
Mark	Gordon	MD	Boehringer Ingelheim

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**Participated in pre-meeting working group and/or onsite meeting, but requests not to be listed as contributor to the manuscript.*

Participant names are listed by activity at the following links:

Pre-meeting Working Group Members

Consensus Meeting Attendees

Steering Committee

Supplementary eTable 2. Classification Systems Reviewed by the Nomenclature and Classification Working Group

Nomenclature and Classification Systems Descriptions			
	Description	Categorical Structure	Comment
FDA C-CASA (2010) [1]	Developed to assist FDA in retrospective analysis of possible suicide related AE's in meta-analyses of antidepressant trials.	Consists of 9 categories, including separate categories for CS, SI, SA, PB, and NSSIB (which were recommended for prospective assessment of SI/SB);and 3 categories for indeterminate events and 1 for accidental injuries (which were used in the retrospective meta-analyses)	Uses terms and concepts that are generally well understood and accepted by clinicians, has a flat (agnostic) organizational structure and is comprised of broadly defined domains and categories that are able to aggregate sufficient data to allow meaningful meta-analyses.
FDA Expanded C-CASA (C-SSRS) (2012)[2]	Provided an "expanded" set of C-CASA categories, based on the C-SSRS, for use in prospective assessment of SI/SB	Consists of 12 categories including 5 levels of SI and 5 levels of SB, each ordered by increasing severity (but in the opposite direction), and a separate category for NSSIB. SB includes CS, PB, and SA.	Finer grained categories may allow for more informative analysis of suicidal phenomena. The clinical relevance of the multiplicity of sub-categories of suicidal ideation is unclear. Restricted definitions of types of suicidal ideation leave out numerous potential combinations of suicidal phenomena that are clinically relevant.
WHO (DeLeo et al, 2006) [3]	Definitions and classification system for suicidal behaviors developed for the WHO/EURO multi-center study on suicidal behavior	Includes categories for Fatal SB, Non-Fatal SB with injuries, and Non-Fatal SB without injuries, as well as a category for Accidental Death. A flow chart is provided which guides clinicians through the progression of terms in a logically organized and consistent manner. Does not include SI.	This system allows for Non-Fatal SB to include self-initiated behaviors With or Without Intent to Die. Hence, Intent to Die is not a defining characteristic of suicidal behaviors. This system also does not account for the possibility of undetermined or uncertain behavioral states; nor does it include SI.
CDC Self-Directed Violence Classification System (2011) [4]	A set of uniform definitions of Self-Directed Violence (SDV) developed by the CDC for use by individuals and organizations interested in gathering public health surveillance data on SDV.	The overarching category of SDV includes 3 subtypes: Suicidal SDV, Undetermined SDV, and Non-suicidal SDV. Each subtype of SDV is further classified as Fatal or Non-fatal, and Non-fatal SDV of any subtype is further characterized as "Interrupted (by self or other) or "Other behavior (e.g., Preparatory). A list of unacceptable terms (i.e.,	Uniform definitions are available only for suicidal behavior and not for suicidal thinking and ideation, although the importance of assessment of ideation as a risk factor for suicidal behavior is recognized. Uses the SDV terminology which may not be universally acceptable and could be problematic in some cultures. Definitions of certain categories (ie, Other Suicidal Behavior, e g Preparatory) are ambiguous and do not clearly delineate the scope of the category. Inclusion of SDV acts with/without injury and interrupted by self/others in the same category sacrifices granularity which could be clinically relevant.

		"parasuicide," "failed attempt," etc.) is also provided. There are no uniform definitions for different types of SI, although SI is included among a list of data elements that can be collected as part of a surveillance system.	
MIRECC VA/DOD Self-Directed Violence Classification System (2011) [5]	Developed in collaboration with the CDC to provide a more inclusive set of terms to describe the full range of suicidal thoughts and behaviors. The terms used and definitions are fully compatible with the CDC's Self-Directed Violence Classification System. This system has been adopted throughout the VA and DOD.	Comprised of 2 major types or categories: Thoughts and Behaviors. Thoughts category includes 2 subtypes: Suicidal ideation and Non-suicidal SDV ideation. Behaviors category includes 4 subtypes: Preparatory, Suicidal SDV, Undetermined SDV, and Non-suicidal SDV. Modifiers used to further differentiate the subtypes of SI and PB (with intent, without intent, with undetermined intent) and SDV/SB (with injury, without injury, fatal, interrupted (by self or other)). System results in a total of 22 mutually exclusive terms and definitions that describe the range of suicidal thoughts and behaviors.	Well organized, hierarchically structured, and comprehensive. A companion Clinical Tool provides a methodology for clinicians for readily classifying clinical observations using the SDVCS classification system. System is not intuitive and complex (ie 22 different terms). The "undetermined SDV" and "non-suicidal SDV" categories may be challenging for clinicians to use in practice and could require extensive training and practice to be easily and correctly applied in classifying different clinical presentations (even with the aid of the Clinical Tool). The "self-directed violence" terminology may be unacceptable among some clinicians and across different cultures.

CS = completed suicide; SI = suicidal ideation or thinking; SA = suicide attempt; PB = preparatory behavior or acts; SDV = self-directed violence; C-C-CASA = Columbia Algorithm for Suicide Assessment [ref], NSSIB = non-suicidal self-injurious behavior; AE= adverse event; MIRECC = Mental Illness, Research, Education, and Clinical Care Center; VA = Veterans Administration; DOD = Department of Defense

[1] United States Food and Drug Administration, Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry: Suicidality: Prospective Assessment of Occurrence in Clinical Trials: Draft. Sept 2010.

[2] United States Food and Drug Administration, Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. Division of Psychiatry Products, August 2012. http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm315156.htm. Accessed August 9, 2016.

[3] De Leo D, Burgis S, Bertolote JM, Kerkhof AJFM, Bille-Brahe U. Definitions of suicidal behavior: Lessons learned from the WHO/EURO multicentre study. Crisis 2006; Vol 27(1):4-15.

[4] Crosby AE, Ortega L, Melanson C. Self-directed violence surveillance: Uniform definitions and recommended data elements, Version 1.0. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2011.

[5] Brenner LA, Breshears RE, Betthauser LM, Bellon KK, Holman E, Harwood JE, et al. Implementation of a suicide nomenclature within two VA healthcare settings. Journal of Clinical Psychology Medical Settings 2011; 18:116-128.

Supplementary eTable 3. Comparison of Structure, Concepts, and Terms Comprising Four Current Suicide Classification Systems

Comparison of Structure, Concepts, and Terms Comprising Four Current Suicide Classification Systems [1, 2, 3, 4]				
Name of System	Expanded C-CASA (C-SSRS) (2012)[1]	Self-Directed Violence Classification System (SDVCS) (2011) [2]	CDC Uniform Definitions (2011) [3]	WHO/EURO Multicenter Trial (2006) [4]
Highest Level Group Terms, Classes, or Types		• SDV Thoughts • SDV Behaviors	• SDV (Self-Directed Violence)	• Subject Alive • Subject Deceased
Intermediate Classes or Subtypes	• Suicidal ideation (SI) • Suicidal behavior (SB) • Self-injurious behavior, no suicidal intent	• Non-suicidal SDV ideation • Suicidal ideation • Suicidal SDV • Preparatory behaviors • Nonsuicidal SDV • Undetermined SDV	• Suicidal SDV • Undetermined SDV • Non-suicidal SDV	• Self-initiated behavior ○ Without intention to die ○ With intention to die
Lower Level Outcome Domains or Terms	○ Active SI: Nonspecific (no method intent, or plan) ○ Active SI: Method, but no intent or plan ○ Active SI: Method and intent, but no plan ○ Active SI: Method, intent, and plan	○ Non-suicidal SDV ideation ○ SI, without suicidal intent ○ SI, with undetermined suicidal intent ○ SI, with suicidal intent		
	○ Completed suicide ○ Suicide attempt ○ Aborted attempt ○ Interrupted	○ Suicide ○ Suicide attempt, without injury ○ Suicide attempt, without injury interrupted by self or other ○ Suicide attempt, with injury ○ Suicide attempt, with injury interrupted by self or others	○ Suicidal SDV ▪ Fatal (suicide) ▪ Non-fatal • Suicidal SDV with or without injury (suicide attempt) e.g. interrupted (by self or	▪ Fatal suicidal behavior ▪ Non-fatal suicidal behavior • Without injuries • With injuries ▪ [Accidental death]

	○ Preparatory actions toward imminent suicidal behaviors	○ Non-suicidal SDV, preparatory ○ Undetermined SDV, preparatory ○ Suicidal SDV, preparatory	others) • Other suicidal behavior, e.g. preparatory	
		○ Nonsuicidal SDV, without injury ○ Nonsuicidal SDV, without injury interrupted by self or others ○ Nonsuicidal SDV, with injury ○ Nonsuicidal SDV, with injury interrupted by self or others ○ Nonsuicidal SDV, fatal	○ Nonsuicidal SDV ▪ Fatal ▪ Non-fatal • Nonsuicidal SDV with or without injury e.g. interrupted (by self or others) • Other nonsuicidal SDV, e.g. preparatory	
		○ Undetermined SDV, without injury ○ Undetermined SDV, without injury interrupted by self or others ○ Undetermined SDV, with injury ○ Undetermined SDV, with injury interrupted by self or others ○ Undeterminedl SDV, fatal	○ Undetermined SDV ▪ Fatal ▪ Non-fatal • Undetermined SDV with or without injury e.g. interrupted (by self or others) • Other undetermined SDV, e.g. preparatory	

C-SSRS = Columbia Suicide Severity Rating Scale

[1] United States Food and Drug Administration, Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. Division of Psychiatry Products, August 2012. http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm315156.htm. Accessed August 9, 2016.

[2] Brenner LA, Breshears RE, Betthauser LM, Bellon KK, Holman E, Harwood JE, et al. Implementation of a suicide nomenclature within two VA healthcare settings. Journal of Clinical Psychology Medical Settings 2011; 18:116-128

[3] Crosby AE, Ortega L, Melanson C. Self-directed violence surveillance: Uniform definitions and recommended data elements, Version 1.0. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2011.

[4] De Leo D, Burgis S, Bertolote JM, Kerkhof AJFM, Bille-Brahe U. Definitions of suicidal behavior: Lessons learned from the WHO/EURO multicentre study. Crisis 2006; Vol 27(1):4-15.