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To: Division of Dockets Management (HFA-305)
Re: Docket #FDA-2012-D-0849

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to provide comments on the August 2012 revision of the FDA's Draft Guidance for Industry, titled *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials*. This revision was needed to provide greater clarity to the field and its release enhances the potential value of the data that are subsequently collected in clinical trials. We recognize the enormous effort the FDA has put into revising the draft guidance and note that although the draft guidance is considerably improved, there are still several points that can benefit from further consideration.

We appreciate that the FDA has taken [ISCTM comments](#) on the 2010 draft guidance into account in this revision. We feel this has strengthened the document, particularly the shift in language from "suicidality" to the less ambiguous phrase "suicidal ideation and behavior."

Sponsors, researchers, clinicians, and others working on clinical trials have gained a great deal of experience with implementing suicidal ideation and behavior (SIB) assessments since the release of the first draft guidance. The field has also seen advances in assessment methodologies such as the introduction of the electronic version of the C-SSRS (known as the eC-SSRS). Yet as the assessment of SIB has increasingly become a routine part of conducting clinical trials, many questions remain. The implementation of the recommendations remains challenging in many instances, and beyond implementation there are challenges related to the complexity of the analysis and interpretation of the data collected. The lack of guidance on the analysis and interpretation of SIB data continues to be a major gap for the field. The ISCTM welcomes the FDA intention and efforts to rapidly develop a separate guidance document addressing the analytical issues and statistical methods in detail.

We are pleased to submit comments and questions received from ISCTM members, including many who commented on the first draft and have been involved in implementing it in their trials as investigators or as sponsors. This document is divided into two sections: (1) General comments are provided in bullets below and (2) comments on specified lines are contained in the table that follows.

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GENERAL COMMENTS ON THE REVISED DRAFT GUIDANCE DATED AUGUST 2012:

- The revised draft guidance released in August 2012 continues to emphasize assessment as a more active and explicit way to capture safety parameters (AE reporting) in drug trials, and does not address potential research applications in which there is growing interest such as the possible positive effects of a drug on SIB as an explicit research outcome or as a primary endpoint. It should be clarified that the guidance focuses on SIB assessment as a means of generating safety data, not as the topic of study. Furthermore, we would like to call to your attention that there are sponsors interested in investigating SIB as a primary endpoint in clinical trials. Accordingly, additional insight into the FDA's view on this topic would be welcome.
- What level of cumulative clinical evidence would be necessary to allow a reduction in the frequency and intensity of SIB monitoring? The FDA should consider establishing a risk

threshold beyond which the additional scientific value gained from SIB assessments is too low to warrant continuing to monitor with the same intensity and frequency in all trials across a drug's life cycle. This guidance requires very resource-intensive data gathering that should be able to be reduced or omitted at some point. The example of electrocardiograms to monitor QTc is instructive in this context: early in development when little is known about a drug's effects, electrocardiogram monitoring may be frequent and intensive, however, as knowledge is accrued over time, it is common to reduce its frequency in later development phases or discontinue it altogether in populations determined to be at low risk. For SIB assessments, this might mean that once a low risk (or absence or reduction of risk) is established for a drug (or drug class) through experience in numerous trials, the frequency and intensity of assessment could be reduced or more narrowly limited, for example to populations with disorders where suicidal ideation and behavior risks are well recognized (e.g., depression, bipolar, PTSD).

- The goal of SIB assessment in trials is the collection of valid and reliable data. Yet its inclusion has added to the complexity of trials and the burden placed on subjects who elect to participate in them. Increased complexity and burden may ultimately compromise quality. Establishing and maintaining consistent, high-quality assessments across all visits and trials is not likely to be as simple, or as brief, as is suggested in the draft guidance document, notwithstanding the preliminary reports of the application of computerized SIB assessments cited in the guidance. There are also opportunity costs to including these endpoints as sponsors may have to forego the inclusion of other endpoints to reduce complexity and/or burden. The feasibility of some trials such as large simple trials (or certain trial designs) may be compromised to such a level that it becomes excessively burdensome.
- Additional clarification of circumstances when formal SIB assessments would be required is needed. For example, is the need for assessments driven primarily by clinical indication or subject population or by evidence that a new agent is CNS active?
- Efforts should also be made to rigorously assess the reliability, validity, and both scientific and clinical utility of data emerging from the recommended assessment methods, and using such information to refine further applications of the methods. Future revisions of this guidance should be based on systematic reviews of the research literature and, to the extent possible, the analysis of trial data on file with the FDA. Data emerging from implementing the previous version of the SIB guidance may be instructive to the FDA in this regard. Its consideration may provide empirical evidence to support many of the recommendations contained in the guidance. We encourage open reporting of what the FDA learns from analyses of SIB data on file, including meta-analyses. Further, the FDA also should periodically examine the performance and impact of the proposed assessment methods, including consideration of the challenges faced by sponsors and sites in implementing them. The agency might consider holding periodic public discussions to share its findings.
- The basic significance of "suicidal ideation" in predicting suicide risk remains far from clear and is not discussed. Suicidal ideation is a particularly complex, fleeting, changeable, and

difficult-to-assess dimension of human behavior, and its quantitative or predictive association with self-harm or actual suicide is tenuous. One study using the eC-SSRS for predictive purposes is mentioned in the guidance, but adequate assessment of the predictive value of proposed SIB assessment methods remains to be carried out.

- It is unclear to what extent the guidance reflects opinions widely held by suicide experts in the field or is based on the broader scientific literature concerning SIB. For example, are the definitions for terms such as “plan” or “method” ones commonly understood in the field? Another example of this would be the field’s view of the use of baseline history as assessed at one point in time as the basis for comparison for treatment-emergent SIB events.

COMMENTS ON SPECIFIC LINES IN THE REVISED DRAFT GUIDANCE:

Lines	Comments/Issues/Questions
28-30	Clarification about the role of the guidance with respect to screening (specifically regarding inclusion/exclusion criteria), in accord with ISCTM comments on the earlier draft, would be appreciated.
52/63	<p>The uniqueness, validity and utility of the 11 specific C-CASA categories have not been demonstrated. Is there evidence that all 11 categories provide exhaustive coverage of all possibilities? How do the categories relate to, or predict suicide attempts and suicides? As there are psychometric, statistical and clinical ramifications of having 11 categories, we suggest that more work is needed to ensure they are valid and useful categories.</p> <p>Suicidal ideation and attempts are indicative of increased risk but are far more frequent and very distant from actual suicide. Also, more than half of the general population reports having thought about suicide, though rarely with a plan or lethal intent. This might even be higher for a person who has a passing thought of “wanting to be dead”, which this guidance includes as a “passive suicidal thought.” Suicidal ideation, in particular, has questionable significance as a putative “adverse treatment effect,” and requires demonstrated value as a predictor of suicidal behavior if the efforts outlined in the guidance are to have credibility with the clinical-professional and general public.</p> <p>It is unclear from the guidance if there might really be 13 categories. For suicidal ideation, in particular, can we assume that the sub-categories listed will encompass all varieties of suicidal ideation? In terms of possible categories of “method,” “intent,” and “plan”, not all combinations of these considerations are covered. How do we handle cases that cannot be coded using the proposed categories, for example, when there is a method and a plan but no immediate intent?</p> <p>Existing data available to the FDA may provide information with which to address some</p>

	of these basic questions.
63-65	<p>The summary of changes from the 2010 version (lines 47-69) is helpful. The FDA has adopted what is described as “an expanded set of C-CASA categories,” which are variously referred to throughout the guidance as “preferred terms,” “categories,” and “preferred categories.” It would be helpful to select a single way to refer to these throughout the document.</p> <p>In lines 63-65 explicit mention is made that an assessment instrument must directly classify thoughts and behaviors to the “C-CASA categories”, not the expanded set. Was this reference to the original C-CASA categories intentional? Elsewhere in the document (e.g., lines 153-154) it states that instruments should classify events into the expanded set of 11 categories.</p> <p>Also, it remains unclear whether the FDA requires a complete reconciliation between C-SSRS events and the Adverse Events database beyond the reporting of serious adverse events; for example, is it necessary to record a non-serious AE of passive ideation for all subjects with an entry on passive ideation on the C-SSRS if there was no spontaneous reporting of such an AE at time of C-SSRS assessment?</p> <p>The hierarchy of categorization is not clear and becomes especially problematic and potentially confusing when a person exhibits multiple behaviors. Thus, if someone makes preparations for a suicide attempt, and makes an attempt, are one or two categories met or three because they also had “active suicidal ideation?”</p>
83-85	Subsequently published analyses [e.g., Gibbons et al., Suicidal Thoughts and Behavior With Antidepressant Treatment; Arch Gen Psychiatry. 2012; 69(6):580-587]] of the same data cited here should also be included in this section as additional context.
99/155	It should be noted that any assessment instrument is designed to assess either retrospective (past) or concurrent (current) behavior, but the instrument cannot collect data prospectively. It is a misnomer to refer to these as “prospective assessments.” The study design is prospective; the assessments themselves are retrospective or concurrent.
131-151 & Appendix A	<p>The expanded list and definitions that are provided are helpful, though questions and issues still remain:</p> <ul style="list-style-type: none"> • Previously all suicidal ideation mapped to a single C-CASA category. Is it the intent that each of these 5 categories of ideation now be summarized separately? • Although the footnote on page 4 notes that the definition of “plan” includes intent, from a clinical point of view, it may be that there is a method & plan with no intent. Beyond referencing the definitions given by the C-SSRS, what is

the rationale for not including this category?

- Why does the hierarchy of the items for suicidal ideation apparently progress to increasing levels of severity, whereas those for behavior progress towards decreasing levels of severity?
- The definition of “passive suicidal ideation” in Appendix A focuses on the wish to be dead. If a subject denies wishing to be dead but has recurrent thoughts of death or being dead, is that suicidal ideation? If not, what is the rationale for not including this?
- Are the definitions for “method” and “plan” ones that the field widely accepts? The definitions of these and “intent” should be provided. There would seem to be some ambiguities in these definitions, e.g., if a subject buys a rope or firearm “just in case”, but does not carry out a suicide attempt, would that be considered an “aborted” attempt?
- This section indicates that there are 11 preferred terms that will be required by the FDA in their revised suicide categorization. However, some potentially valuable classification groupings for suicidal ideation and behavior are omitted, and events observed in trials that are suggestive of SIB may not ultimately code to those events. It would seem valuable to include some or all of the terms available in the initial version to manage these more ambiguous cases:
 - Self-Injurious Behavior, intent unknown
 - Not enough information (fatal)
 - Not enough information (non-fatal)
 - Other (accidental, psychiatric medical), no deliberate self-harm
- It is not uncommon to see subjects report a more severe level of suicidal ideation (for example Active: method, intent, and plan) without endorsing less severe levels, e.g., wish to be dead. This suggests that the hierarchy of severity implied by this guidance is not valid and each category should be captured independently. Additionally, patient populations such as those with psychosis may not be able to articulate or differentiate different levels of suicidal ideation.
- Although some subjects have actual suicidal thoughts, others experience delusions and hallucinations that drive them to commit acts of self harm. Not infrequently, these people deny they are suicidal but describe the hallucinations as so strong that they feel compelled to act on them, despite having no intent to harm themselves. In other cases, they may become convinced they have special powers (e.g., to fly) that ultimately lead to self harm. How should these cases be categorized and what would be the criteria for categorizing them?
- What constitutes “Imminent suicidal behaviors”? What if a rope has been purchased “for some time in the future”? The fact that this guidance allows for a method, with no plan suggests that this is a possibility. What if a will is

	<p>written with a hope to die, but there is no other plan? Is that considered preparatory?</p>
<p>157-159,330</p>	<p>This section provides an extensive detailed description of the C-SSRS. It is unclear why so much focus is given to a particular scale and appears to promote its use. It seems premature to pick one measure over others as there is much work yet to be done regarding the psychometric properties of most instruments, as well as comparisons across measures and across investigators.</p> <p>The psychometric properties of the C-SSRS are referenced, but the information provided is somewhat limited and may be flawed. Would it not be better to articulate the specific psychometric properties to be met by any SIB instrument and criteria by which to evaluate the reliability, validity, and predictive value of any rating method?</p> <p>With respect to the issues raised in this section it should be noted that assessment of suicidal status and history at baseline, especially regarding lifetime suicidal thoughts or behaviors, may yield unreliable and unverifiable data. Many subjects may not remember or be willing to fully disclose their pasts; in addition, distant thoughts or acts may not be scientifically or clinically relevant to SIB encountered during a trial. Consideration should be given to whether the retrospective time frame for baseline assessment should be confined to a shorter pre-specified time prior to study entry that can be more reliably recalled (e.g., 6 or 12 months) and, thus, is more clinically meaningful.</p> <p>A standard reference period for making historical comparisons for treatment-emergent events would ensure consistency across studies and allow for better reference and interpretation. We acknowledge, however, that there is no empirical basis for setting such a threshold at this time. We encourage the FDA to use the existing databases they have to examine this issue and formulate a standard reference period. One study that might be used for this purpose is the InterSePT study. Considerations of other potentially relevant risk factors such as substance abuse history, history of suicide attempts, recency of the last suicide attempt, may also need to be taken into consideration.</p> <p>A recent global online survey of CNS clinical trials sites, sponsored by ISCTM, examined the implementation of the first draft FDA guidance and found that 51% of respondents (N=1004) identified obtaining an accurate baseline lifetime SIB history as the greatest challenge in conducting SIB assessments. (CITATION: ISCTM Suicidal Ideation and Behavior Assessment Working Group: Butler, A, Stewart, M, (Co -chairs) and members Alphs, L, Chappell, P, Feltner, DE, Lenderking, WR, Mahableshwarkar AR, Makumi, C, and Dubrava, S. Study Site Experiences & Attitudes toward Prospective Assessments of</p>

	<p>Suicidal Ideation and Behavior in Clinical Trials: Results of an Internet-based Survey; 2012; submitted to Innovations in Clinical Neuroscience). If baseline data are unreliable, their use as a comparison for changes observed during a clinical trial for treatment-emergent events raises questions. Further study on the best way to elicit lifetime SIB history and the use of these retrospective data as a comparison for treatment-emergent events is sorely needed. [NOTE: These survey data can be shared with the FDA if deemed appropriate.]</p>
155-173	<p>This section provides an extensive, detailed description of the C-SSRS. If the use of the C-SSRS is not <i>required</i> by the FDA, why is so much attention devoted specifically to it? This appears to promote its use. Can the FDA confirm whether there are any other scales that would be accepted?</p> <p>We would like to note that it seems premature to pick one measure over others as there is much work yet to be done regarding the psychometric properties of most instruments, as well as comparisons across measures and across populations.</p>
163-164	<p>The emphasis on accessing and integrating all available relevant data (from family, friends, caregivers, health care providers, hospital records, coroner's reports, etc) into the C-SSRS appears to be a new recommendation in this revision. In the context of a clinical trial, "information from all potential sources" seems excessively broad, imprecisely defined, and possibly unrealistic. What is the FDA's guidance on how this should be operationalized? How would this be accomplished and documented for computerized assessments?</p> <p>Is there any evidence to indicate that information from outside sources is any more valid than what is obtained from subjects? In other words, do we know what is gained in incremental validity by the use of data from outside sources? The use of such external data also raises concerns about privacy and confidentiality that may be difficult to anticipate and adequately address in the informed consent.</p>
166-173	<p>The citations for the psychometric properties of the C-SSRS are a welcome addition to this version, but the available reports leave several questions. For example, the Brent, Greenhill, et al. (2009) article does not fully address inter-rater agreement and it is not clear which version of the C-SSRS was used in that study. In addition, the abstract cited as Pumariega, et al. (2011) from the Eastern Nursing Research Society (ENRS) does not appear in the society's conference proceedings. Another abstract (see citation below) was found for a poster on the same topic, but the title and author list are different. The poster with a different title reports on psychometric work completed on an abbreviated form of the C-SSRS dated 2009 (no citation was given for that abbreviated version). The methods section describes the use of "clinical vignettes" to assess inter-rater reliability; it is not clear how these vignettes were presented to raters and whether they were written documents or videotapes, which would seem far removed</p>

	<p>from the type of interviews used in clinical trial settings. Furthermore, the use of the C-SSRS in that study was as a screening instrument for inpatient hospital admissions at a community hospital – very different from its use in clinical trials to monitor changes in SIB. Further clarification of these citations, their content, and their reporting in peer-reviewed, readily accessible journals would allow a better evaluation of the instrument’s properties.</p> <p><u>Poster citation found at Eastern Nursing Research Society website:</u> Stavarski DH, Millsaps U, Pumariaga AJ, Posner K, et al. Suicide Screening In A General Hospital Setting: Initial Results. Poster presented at Eastern Nursing Research Society 2011 annual conference, Philadelphia, PA.</p> <p>It should be noted that some of these articles appear to refer to older versions of the C-SSRS instrument than the one that is currently in widespread use. Validation of an instrument is never really complete, and it is usually updated as additional information comes to light or as new versions are developed. As noted in the Study Endpoint and Labeling Division’s (SEALD) guidance on patient-reported outcomes, instrument revisions typically require additional psychometric work to verify their properties and confirm that the changes haven’t fundamentally affected how it performs. In addition, the validation of any SIB assessment with respect to outcomes, especially regarding the association between subjective reports of ideation and suicidal behaviors, remains extraordinarily challenging.</p> <p>In summary, the methods of assessment currently recommended in the draft guidance rely primarily on the C-SSRS rating methods, but the level of documentation of the reliability and validity of this method, its psychometric characteristics, and whether the numerical values obtained are quantitatively scalable and its validity based on association with suicidal behavior or suicide—all in specific relationship to applications in treatment trials and with peer-review and public availability—remain incomplete.</p> <p>Would it not be better to articulate the specific criteria by which the reliability, validity, and predictive value of any rating method will be evaluated?</p>
191-193	<p>The draft guidance asserts that SIB assessments need not take much time and cites as evidence a report from a study using the eC-SSRS, a version of the C-SSRS that is not yet widely used. There are likely differences between the times required for a rater-based interview and the computerized self-report versions of the C-SSRS. Research citations should be provided for evaluations of the paper-based interview version of the C-SSRS for subjects with positive and negative findings. Likewise, estimates for time spent obtaining and integrating information from “other sources” should also be included in the guidance. Without this information, the full picture of the time required for these assessments is incomplete.</p>

193-196	Is the eC-SSRS an equally acceptable alternative to the rater administered C-SSRS, as the draft guidance seems to imply?
212-213	The draft guidance recommends that instruments be able to integrate information from sources outside an interview or electronic assessment conducted solely with the subject. It would be helpful to clarify circumstances in which such supplemental information should be sought. If a trial participant denies all ideation and behavior, to what extent is the sponsor responsible for confirming this, or is outside information only relevant in positive or more ambiguous cases?
225-226	<p>It would be useful to provide guidance on standardizing interview techniques to be used to elicit SIB information with the C-SSRS or other instruments. This would include how to limit the elicitation of information of questionable value or validity and efforts to support comparability across raters and trials. The precision of wording is important – a rigorous standardized language approach may miss events (as can occur when it is not wording the patient would use), yet allowing excessive unstandardized language across different interviewers may likewise lead to problems such as the omission of questions.</p> <p>In the discussion of training, it should also be noted that clinical skill and expertise are often required to fully assess SIB.</p>
264-270	<p>The description of when an event is to be considered a discrete event is not clear. Parameters for determining if events are discrete within a limited time frame or continuous over a long period of time (as in an ongoing state) are needed, particularly when, as noted in lines 264-265, subjects themselves may be making these distinctions on the eC-SSRS.</p> <p>Furthermore, the language concerning the classification of all discrete events (esp. lines 269-270) should be made more prominent given that in the past, some sponsors reported only the most severe event for a given interval.</p> <p>In the FDA’s forthcoming guidance on analyzing the data collected from SIB assessments, it would be useful to provide more detail on both defining a discrete event and what should be reported.</p>
277-284	Will the FDA consider label modification in favor of an investigational medicine when pooled analyses (e.g., using the C-SSRS) demonstrate non-significant or no risk to patients? Also, how and when would SIB findings suffice to justify removal of a warning of possible suicidal risk, such as that now pertaining to antidepressants for juveniles and young adults, and to anticonvulsants generally, or to indicate evidence of a benefit (such as that now apparent from FDA meta-analyses for antidepressants among patients over age 65 years)?

	In general, a discussion of how SIB data could be appropriately addressed in a product label – either as part of this guidance or the forthcoming guidance on statistical analysis of SIB data – would be very useful to the field.
286-304	For pre-pubertal children, as well as mentally retarded or demented subjects, and subjects whose native language differs from that of the investigators, appropriate and feasible means of assessing suicidal risks remain especially poorly developed, and the potential adverse effects of attempting to do so remain to be evaluated. The challenge of assessing young children (e.g., < 11 years) who may not have reached sufficient cognitive maturity to understand the concept of death is acknowledged in the revised Guidelines, but empirical evidence is needed. It would be helpful to have better characterization of the psychometrics of existing scales, their linguistic validation, and ages at which children can understand these concepts. Again, the FDA has existing data that may be able to shed some light on these questions.
289-291	<p>The guidance mentions the use of “alternative assessments” when dealing with populations in which assessment can be difficult, although the conditions under which these might be used and the purpose of including them should be better characterized. Would they be held to the same standards outlined on lines 223-226, e.g., classifying to the 11 expanded C-CASA categories? How would such data be collected and would alternative assessments be used to inform a drug’s SIB risk potential? Would they appear in the label or be used in meta-analyses?</p> <p>We agree that omitting SIB assessment for clinical trials in the later stages of dementia is appropriate. However, how subjects enrolled in trials for early stages of dementia (e.g., MCI) should be assessed calls for further clarification. The ability of such subjects to complete the assessments may wane as the trial progresses, and thresholds need to be defined at which it may no longer be possible for them to provide valid responses on the C-SSRS (or other SIB assessment instrument).</p>
295-298	Clarification is needed regarding the recommendation to use the C-SSRS in special populations, particularly children, the mentally retarded or demented persons. Evidence that such applications have acceptable reliability and validity is lacking.
312,317	Statements about SIB risk levels in multiple dose trials conducted in healthy volunteers seem contradictory. “Short-term” trials should be defined.
310-325	<p>The heading for section 3a refers only to single-dose trials but the section also addresses multiple-dose trials. It would be useful to provide a separate section for multiple-dose trials to further clarify that they are to be handled differently.</p> <p>Additional guidance on the timing of assessments of SIB in multiple-dose escalation trials in healthy volunteers is needed. The current guidance indicates that SIB</p>

	<p>assessments should be performed at the same time as other clinical assessments in multiple-dose healthy volunteer studies. However, commonly the major clinical assessment performed in such studies is an inquiry whether the subject has experienced adverse effects of any kind. Adverse effect inquiries may be repeated many times a day (e.g., hourly following the initial dose of study drug for the first 24 hours) or at least daily throughout the typical multiple-dose escalation trial. It seems counter-productive to perform concurrent SIB assessments at the same frequency. We recommend that in multiple-rising-dose tolerance phase 1 studies, SIB assessments should be completed at the screening visit, prior to dosing on day 0, on the last dosing day, and at the follow-up/closeout visit. For multiple –rising-dose tolerance studies with dosing periods longer than one-week in duration, we recommend that SIB assessments should be administered at least weekly while the subject is being dosed. SIB assessments should also be administered at the discretion of the investigator, based on any reasonable concern, at any time during the study.</p>
327	<p>It is good to have a measure of past SIB levels to provide a basis for comparison in cases of treatment-emergent events, however, the more appropriate comparison may be to a more recent timeframe rather than lifetime, especially in light of the difficulties of getting reliable baseline data noted above.</p> <p>It is mentioned that the assessments should be conducted at <u>baseline</u>, as well as at all later planned visits. Sponsors normally conduct the C-SSRS assessment at the <u>screening</u> visit. Many of the inclusion/exclusion criteria we use in our studies often refer to past lifetime suicide attempts, so it is important to collect this at the screening visit. Suggest that it be made clear in the guidance that the C-SSRS instrument be used to collect suicide history data at either the screening or baseline visit.</p>
338-340	<p>The guidance recommends that the SIB assessment should be done at the time of other symptom assessments for inpatient multiple-dose studies. Can the FDA better define “symptom assessments?”</p> <p>Additionally, these assessments can be done multiple times in a very short period of time for some studies such as those conducted in Phase 1. If symptom assessment is done several times in a 24-hour period, is it the FDA’s intention that SIB be assessed each time?</p>
349-352	<p>There has also been no systematic study of the validity of the data obtained when a SIB assessment is implemented in an ongoing study. From a practical standpoint, it can be difficult to implement these assessments in an ongoing study, e.g., the different recall periods (prior to entering the study, since the study began) for the different versions can be confusing for subjects.</p>

354-356	<p>Allowing sites to “individually decide” how to address the issue of SIB assessment in trials that are nearing completion could result in inconsistent or biased reporting. We suggest the FDA recommend that sponsors develop a consistent, documented approach to be used across all sites.</p>
360-365	<p>The section on prospective assessments in large simple trials is ambiguous and does not provide adequate guidance to sponsors. It asserts that the inclusion of SIB assessments would add little burden, but does not specify when and how such assessments should be done.</p> <p>What is the basis for the statement that “increasingly these types of assessments are becoming part of clinical practice”? A reference or citation is needed. Further clarifications about possible exceptions and more direct guidance is needed.</p> <p>If the FDA’s intent is that prospective SIB assessments should be included in large simple trials, this conflicts with the goal of having these trials be conducted as close as possible to real-world clinical practice. We urge the FDA to re-consider and omit the requirement for SIB assessment in these trials because although it may seem to be a small burden, it is beyond the purpose of such trials.</p>
371	<p>The guidance should include a discussion of the limits of SIB assessment in clinical trials (e.g., it may not detect all subjects at risk) to better orient the public to realistic expectations.</p> <p>For example, even though most persons at risk for suicide have talked about suicide in the past and have seen a clinician in the months preceding suicide, they typically do not announce their suicidal inclinations at the time of acting on them. Indeed, they may deny suicidal ideation, plans, or intent, even when actively queried, as in an SIB assessment.</p>
407-420	<p>The draft guidance states that “it is plausible that certain drugs and pharmacologic profiles” will “prove not to be inducers of suicidal ideation and behavior.” This statement is scientifically implausible since one cannot prove a null hypothesis, regardless of the amount of data collected. Moreover, there is a risk of potentially misleading “statistical significance” when the database considered becomes huge, but the level (e.g., one in thousands of cases) or nature of risk (ideation without behaviors) remain clinically trivial. Therefore, it is critical that the FDA set up prospective safety thresholds for determining what constitutes a clinically meaningful increase in incidence. For example one case of suicidal ideation in 5,000 drug-treated versus 10,000 placebo-treated patients has far different implications from similar relative risks for life-threatening suicide attempts.</p>
416-417	<p>We agree that requiring all drug development programs to include SIB assessments</p>

	would be excessive and is not warranted at this time. The effort that would be required seems disproportionate to the potential marginal benefits.
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