November 8, 2010

To: Division of Dockets Management (HFA-305)
Re: Docket # FDA-2010-D-0451

The International Society for CNS Clinical Trials and Methodology (ISCTM) thanks the Food and Drug Administration (FDA), for the opportunity to submit comments on the **Guidance for Industry "Suicidality: Prospective Assessment of Occurrence in Clinical Trials**." ISCTM supports the goals of the Draft Guidance to reduce the potential for suicidal behavior, ideation and attempts during drug treatment. We agree that prospective evaluation of suicidal behavior and ideation may add to a more complete assessment of risk to benefit ratio of drugs used in the treatment of psychiatric and non-psychiatric disorders. However, we find the document unclear or incomplete in a number of sections and provide this commentary for your consideration.

The ISCTM is a multi-disciplinary independent organization, devoted to promoting advances that address strategic clinical, regulatory, methodological and policy challenges that arise in the development and use of CNS therapeutic agents. This work is accomplished through partnership with persons in academia, industry, government, policy-making and the public.

Recognizing the importance of this document for our constituency, the ISCTM convened a working group to review and comment on the guidance.

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General Comments on the Guidance

- It would be helpful to begin this document with clearer descriptions of the scope of the guidance that is being provided. Relevant issues of scope are included in the document, but addressing this would be helpful for the reader. In particular is does this guidance only pertain to sponsors who conduct a study under an IND, to non-IND studies, to academic investigators studying drugs (eg clinicians, NIMH, the VA, etc.), to non-interventional studies conducted as part of general surveillance of risk/benefit, and/or to post marketing safety surveillance? Reference is made to this guidance serving 'as a focus for continued discussion among the FDA, pharmaceutical sponsors, the academic community and the public. Does this mean that studies conducted by any of these groups fall under the remit of this guidance? It would be valuable to define "pharmaceutical sponsors" in this context.
- The guidance could benefit from a definition of key terms early in the document that are not well defined by the guidance (e.g., suicidal ideation, suicidal behavior, and pharmaceutical sponsors. When key terms are used throughout the document, every effort should be made to use them precisely and consistently throughout the document.
- To better frame the intent of the guidance, the document should specifically state at the outset that the goal is to ascertain the risk of suicidal ideation and behavior for those receiving medication relative to comparator and/or placebo.
- The C-SSRS is best viewed as a semi-istructured questionnaire to elicit the information required to facilitate mapping events to the C-CASA categories. As such it is more a data collection tool or instrument to arrive at C-CASA classifications and not a "scale" in the sense that that term is generally used in psychometric literature. For example, there is no evidence that there is a latent construct that underlies the C-SSRS, that severity is quantified (e.g., as an outcome), or that its items cohere in a meaningful way. Thus we would recommend the term "assessment" be used rather than "scale" throughout the guidance.
- The guidance does not address study entry criteria, e.g., recommending thresholds for entering a clinical trial based on suicidal ideation and behavior. Does the FDA have any clarification regarding this issue relative to the guidance?
- The guidance should make clearer that the recommendations in the guidance are not intended for trials in which suicidal ideation and/or behavior is the primary or key endpoint. An example would be a trial in which a drug was being studied to show that it decreased suicidal ideation and behaviors. It is not clear that the C-SSRS would be the assessment of choice in such trials as it has not been developed to track severity or change in suicidal ideation.
- The detailed nature of the information that subjects are required to submit for these assessments may be too intrusive and culturally insensitive. This may contribute to attrition of subjects in clinical trials, as well as country/cultural bias in the validity of data generated, thus further complicating the analyses of available data.
- Because assessments recommended by the guidance will be used by many people with little understanding of suicide risk, a statement similar to the following should be added to the introductory remarks: "Assessments used to detect and monitor for suicidal ideation and behavior are not adequate to assess an individual's risk of future self-harm. The assessment of risk for future self-harm requires an evaluation by a competent professional."
- The guidance should acknowledge that there are limited published data to support the use of the C-SSRS for detecting suicidal ideation and behaviors in clinical trials and that additional data on the psychometric properties of the C-SSRS and similar assessments are needed.

- What is the applicability to certain Phase 4 trials? For example, would sponsors be expected to collect these assessments in real-world or non-interventional trials (e.g., large simple trials) where the goal is to follow regular clinical practice as much as possible and where data collection beyond that collected in standard clinical practice is therefore to be minimized?

Specific Comments

Line	Comment
48 (& 199-200)	The term "suicidality" is too broad and has been criticized because it bundles ideation and behavior. Early in the document it is recognized that "suicidality is a broad term that includes both ideation and behavior" that may have separate predictive meanings. The use of this term, in the guidance leads to confounding of issues and unclarity. We suggest using the phrase "suicidal ideation and behavior" as being more descriptive and appropriate. There is additional value in discriminating between suicidal ideation and suicidal behaviors for, although they may be related constructs, they are not continuous. In particular, measurement of severity and the ability of suicidal ideation and suicidal behaviors to predict future risk for death may require distinct approaches. Indeed, the nature of and meaning of suicidal ideation may vary over time. For instance, suicidal ideation that is prevalent in young females (teenagers) is much less frequently associated with later risk for death than is that of geriatric males.
49	Should state "…that occur during drug OR PLACEBO treatment." The guidance should specifically state that the goal is to ascertain the risk of suicidal ideation and behavior for those receiving medication relative to comparator and/or placebo.
51	In the guidance "suicidality" is referred to as an "event." It is not clear that suicidal ideation always represents a discrete event that can be readily captured.
87-88	The document indicates that an assessment instrument used to detect suicidal ideation or behavior must map to the C-CASA categories. However, the document then goes one to indicate that many of the codes of the C-CASA are not relevant. This statement should be clarifed to indicate that the mapping entails only those relevant categories.
115-117	Reference is made to the fact that Code 7 has predictive validity. Please provide citation for line 116 regarding the predictive validity of the C-CASA code 7.
118-119	Reference is made that codes 5 and 6 are indeterminate and unnecessary for prospectively assessing patients. Based on clinical experience, category 5 can be useful because it is not always possible to clearly ascertain suicidal intent for self-injurious behavior or whether a fatal event represents a death. We would argue that, if code 7 is valuable for collection,

codes 5 and 6 would have similar value. This is particularly true of events that may occur in cultures or subcultures where suicidal thinking or behavior is considered unacceptable.

If the FDA is not interested in codes 5, 6, and 9, do data on them need to be collected at all (beyond what would be needed for adverse event reporting if applicable)? Also would alternative instruments be expected to map to these codes or would psychometric validity only have to be identified for Codes 1, 2, 3, 4 and 7?

130 The guidance suggests that the C-SSRS represents an acceptable instrument for capturing data to be mapped to the C-CASA. The psychometric data supporting this are not referenced. Such references would be valuable to the reader. Also, since multiple versions of the C-SSRS exist, it would be valuable for the document to reference the particular versions of the C-CASA that are supported by this guidance.

140-142 Other assessment instruments do exist for suicidal ideation and behavior. It would be helpful if the guidance provided a list of other existing instruments beyond the C-SSRS and provide information on the status of these with the agency (e.g., if they are not fully accepted then this should be noted).

The guidance should further provide details on the standard of evidence that would be necessary for use of alternate assessments to be accepted by the FDA as alternatives to the C-SSRS.

149-155 (& 233-241) The guidance requires that instruments ask about various aspects of suicidal ideation (i.e., nonspecific; method but no plan or intent; method and intent but no plan; method, plan and intent) but all of them map to the same C-CASA code 4. The guidance should clarify that the subcategories mentioned in lines 147-162 are not a part of the C-CASA codes. If greater granularity on these subcategories is required by this guidance and needed for additional analyses, it should be recognized that this information cannot be recovered from the C-CASA categorization data alone. Is this guidance suggesting that additional classification beyond that provided by the C-CASA is necessary? If so, what is the basis for this requirement?

The Suicidality Data Coding Form in Appendix B does not collect this level of information and many sponsors may not routinely database this level of detail which means it would not be available for later analyses without additional effort and specification in the database. Is it the intent of the FDA that such data regarding method, plan and intent be available? Will any additional tools be required to track method, plan and intent, and maintain what appears to be the guidance's hierarchical classification? Are details about method, plan, and intent important information to gather in an randomized clinical trial? These items would appear to be more appropriate for a tool to assess suicide risk. The guidance appears to be concerned with documenting adverse events related to suicidal ideation and behavior rather than assessing suicide risk per se. It is unclear what the value of some of the detail is to FDA since it will not be summarized in the C-CASA data from

trials. This distinction seems to be only tangentially related to the focus of the guidance, unless an alternative classification system is being proposed.

With respect to suicidal ideation, as noted in the guidance, it can be present with varying levels of ideation. Some forms of ideation may not carry as much weight as others and little is known about the predictive validity or other psychometric properties of these specific aspects of ideation (i.e., nonspecific; method but no plant or intent; method and intent but no plan; method, plan and intent). There may be other aspects that are also important to assess that are will not be collected (e.g., controllability, deterrents, etc). Tools could be developed to capture severity or type of suicidal ideation but they will all map to the same C-CASA category .

What is meant by "intent" in this context: Intent to die or intent to carry through with a suicidal plan? It is possible that patients may intend to carry out a plan but have no intent to die (e.g., when motivated by attention-seeking).

The interpretation of "method" seems straightforward, i.e., what the respondent would do or how he/she would kill him/herself. Does "plan" in this context then refer only to time and place? Method would seem to be part of a plan.

156-161 & (226-231) The guidance requires that instruments ask about three types of preparatory actions: preparatory acts, interrupted, and aborted, but all 3 map to the same C-CASA code 3. As with the suicidal ideation domains, the guidance should clarify that these subcategories mentioned in lines 156-161 (& 226-231) are not a part of the C-CASA codes. And as noted for the suicidal ideation levels, if greater granularity on these types is needed for additional analyses, it cannot be recovered from the C-CASA category data alone. Similarly, the Suicidality Data Coding Form in Appendix B does not collect this level of information and many sponsors may not routinely database this level of detail which means it would not be available for later analyses without a great deal of effort that may entail going back to sites to try and recover the details. Is it the intent of the FDA that such data should be available?

Providing detail at this level on rare events such as aborted and interrupted attempts may contribute to noise. The detail that a suicide attempt was interrupted would not be expected to contribute to greater understanding of whether a drug has any impact on suicidal ideation and behavior. Hence collecting such information would impose additional burden without contributing to the primary objective of safety monitoring.

164-165 Clarity is needed that this should refer only to terms relevant to C-CASA codes 1-4 and 7, as they are described in lines 112-116 of the draft guidance.

177-179 The sentence about "other instruments" is not clear and it is not obvious what value its inclusion in this guidance provides.

183 We agree that appropriate training is critical to implementation. The guidance could

include more clarity on who should deliver the training, and how it should be administered. Our recommendation is that training be done by qualified experts with appropriate experience and training but not necessarily a requirement that it be done by the person who developed the assessment.

"Accuracy and consistency" could be clarified or defined in more detail, possibly with examples of how these requirements would be satisfied. Is it necessary to quantify the accuracy and consistency of raters or is it sufficient to show that appropriate training was provided?

186-187 "Psychometrics" is a broad term. Elaborate more on what psychometric properties should be examined for alternatives. Will inter-rater reliability suffice? Is there a definition for "well-established?" Will one study be sufficient to argue an alternative is acceptable? Are there requirements for how this should be documented?

The guidance should clarify that it is the psychometric properties that are important for the intended purposes of the instrument (detection and classification) that should be characterized.

The authors also note that the C-SSRS does not have any published psychometric validation data beyond comparisons of interview and IVRS formats (NEED TO ADD CITATION FOR Mundt, Greist, et al.). This information should be referenced in this document.

202-203 The guidance says that any prospective assessment of suicidality be "designed for the immediate coding…to C-CASA categories…." What is meant by "immediate" in this context? Should this coding be done at the site before the patient leaves?

Many sponsors are collecting data while the patient is at the site then mapping the responses to C-CASA categories through programming algorithms at a later date, often following database lock when the rest of the study data are analyzed. Sites are instructed to refer patients as needed based on responses to the assessment so there is no delay in seeking follow-up care if needed; it is just that the mapping to C-CASA categories may occur at a much later time.

210-212 The guidance seems to suggest that every instance of suicidal ideation be captured. This is not practicable. Issues of definition, memory, culture and of frequency make it impossible to reliably and meaningfully to capture every suicidal 'thought.' Capturing this information would require a careful definition of what constitutes an episode or "event" of suicidal ideation in terms of onset and offset, and in terms of frequency. If a subject has many thoughts every day should each be captured?

253 It is unclear what is meant by concluding that 'the suicidality question has been resolved until all the data are in hand.' It is unlikely that suicidality data will ever be 'all in hand.' A discussion of risk:benefit of this collection would be valuable. At what point can it be

concluded that a drug is associated with an increased risk of suicidal behavior or ideation? Is it determined on the basis of a number of observations? How many? Is it determined on over a period of observation in individuals? If so, what is that period of observation? Should it be relate to the half-life of the drug?

Similarly, at what point is the risk for suicidal ideation or behavior considered so low as to be of no interest?

255-267 The discussion of "challenging populations" in which it may be acceptable to forego assessment of suicidal ideation and behavior does not provide much detail. The definitions of the populations are vague and there are other populations beyond those listed here where these assessments may be difficult, especially those that are acutely ill. For example, there are numerous issues with acute stroke patients, certain HIV populations, and very young children such as those enrolled in epilepsy treatment trials.

There are clinical measures used in the mild-to-moderate AD population that rely on assistance from caregivers and it is reasonable to believe that a similar approach to suicidal ideation and behavior would be as reliable as these other measures, so that it may be reasonable for clinical trials in AD to include assessment of suicidal ideation and behavior. Data, of course, are largely lacking for supporting the validity of using any given method for detecting suicidal ideation and behavior in the AD population.

If alternative assessments are acceptable, the guidance should provide a list of suitable ones beyond the C-SSRS and what they would be used for. For example, the Neuropsychiatric Inventory could be used to assess depression/dysphoria in an AD population but would not directly monitor suicidal ideation and behavior. The guidance should provide additional clarity about this issue.

The use of the C-SSRS in children age less than 11 is unlikely to provide valid information. The language used in the C-SSRS is not appropriate to the language abilities of young children and the ability of very young children to conceptualize of suicide will vary depending on their level of cognitive development. Assessing suicidal ideation and behavior in children, particularly younger children, should be given greater consideration and discussed in greater detail.

Studies in critical care settings with drugs that have CNS actions may also not be suitable for collection of suicidal ideation and behavior data, whether due to medical morbidity of patients or the issue of frequency of other assessments. The guidance speaks to populations with cognitive impairment, but not those who are otherwise seriously compromised due to acute illness (e.g., acute stroke patients, myocardial infarction, closed head trauma).

277, 288-289, 332 The guidance indicates that assessments for suicidal ideation and behavior be done at all planned visits at which other clinical assessments are done. In Phase 1 studies (especially those conducted in-patient) there are often frequent assessment schedules, including ones

& 343 that occur multiple times in one day (e.g. collection of multiple blood samples or in a TQT study continuous monitoring of the EKG). Given this issue, the guidance should provide additional information on the timing for the assessment of suicidal ideation and behavior in trials such as Phase 1 studies where there are frequent scheduled clinical assessments.

What recommendations are made for unplanned visits?

328-332 Clarification is needed regarding which drugs are covered for Division of Neurological Products (DNP). The guidance appears to indicate that all drugs submitted under IND's to DNP would require suicidal ideation and behavior monitoring. If the thought is any CNS active drug should be monitored, this could mean any drug that crosses the blood brain barrier, e.g., antibiotics.

Appendix B The coding form provides an idea of what type of data the FDA wants to receive. Is it the intent of the agency that this should be used to develop a CRF that must be used at every visit? Will it be necessary to database individual responses to questions on the assessment tool, e.g., the C-SSRS?

As noted elsewhere in these comments, many sponsors are electing to database responses to assessments such as the C-SSRS, then use programming algorithms to map the responses to C-CASA categories at a later date, generally following database lock when the rest of the study data are analyzed.