# Complying with FDA Guidance on the Prospective Assessment of Suicidality in Clinical Trials

PEER REVIEWED

**In September of 2010 the FDA issued draft Guidance for Industry on Suicidality: Prospective Assessment of Occurrence in Clinical Trials. The purpose of this guidance is to assist sponsors in prospectively assessing the occurrence of treatment-emergent suicidality in clinical trials of drug and biological products. This guidance involves actively querying patients about the occurrence of suicidal thinking and behaviour, rather than simply relying on patients to report such occurrences spontaneously, followed by retrospective classification of events into suitable categories. The purpose of this CNS Watch is to outline the essential elements involved in prospective suicide assessment in trials of drugs with central nervous system (CNS) effects.**

## The FDA draft guidance

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf stems partially from the results of past meta-analyses of placebo-controlled pediatric and adult antidepressant trials that revealed a consistent signal for drug-related treatment-emergent suicidality for younger cohorts[1]. Additional meta-analysis of placebo-controlled trials of antiepileptic drugs (including those with various underlying pharmacologies) in both trials of epilepsy as well as psychiatric indications, also revealed a consistent signal for drug-related treatment-emergent suicidality[2]. More recent concerns regarding treatment-emergent suicidality for "non-psychiatric" drugs have also arisen, based largely on spontaneous reports. These "non-psychiatric" drugs have included isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss, implicating numerous therapeutic indications that are reviewed by multiple therapeutic divisions at the FDA.

However, the various case descriptions from these investigations were often incomplete, with baseline status that was not well defined. Furthermore, past examinations have been limited by great variability in the adverse event terms referring to essentially the same behaviours (e.g., threats, gestures). Some adverse events that should have been identified as suicidal may have been missed, while other adverse events may have been inappropriately classified as suicidal. A false signal could result in an overly conservative use of a desirable drug or unnecessarily restrict its availability. Alternatively, missing a signal of increased risk of suicidality would result in a greater sense of comfort with a drug than might be warranted. Of note, it has been suggested that misclassification typically results in an over-estimation of risk with a tendency toward significantly more suicidal events overall[3].

These shortcomings necessitate prospective assurance that patients in clinical trials who may be experiencing suicidality are properly recognised and adequately treated. Further, it is critical to ensure the collection of more timely and complete data on suicidality than has previously been collected so that in the future, suicidality detection is increased in both individual studies and in pooled analyses. Given this, the FDA recommends that "prospective suicidality assessments should be carried out in all clinical trials involving any drugs being developed for any psychiatric indications, as well as for all antiepileptic drugs and other neurologic drugs with CNS activity. Assessments should be conducted in both inpatient and outpatient trials, and even phase 1 trials involving healthy volunteers….. as even single doses of certain drugs used in challenge studies in vulnerable populations have been shown to induce suicidality."

In order to achieve this mandate, the FDA has advocated the use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). This instrument was developed by Kelly Posner, Ph.D. and others at the Center for Suicide Risk Assessment at Columbia University[4] to assist the FDA in coding suicidality data accumulated during the conduct of clinical trials of antidepressant drugs. The C-CASA is a retrospective instrument that utilises a series of probing questions to inquire about possible suicidal thinking and behaviour. Importantly, the C-CASA provides a set of preferred terms for use in coding, a critical step in preparation for analysis of these data, and the FDA has adopted the C-CASA as the standard for coding all suicidality data.

The prospective suicidality instrument of choice should therefore include all the key concepts (domains) identified in C-CASA related to suicide ideation (both active and passive), suicide behaviour (actual attempt versus preparatory actions), and non-suicidal self-injurious behaviours. The Columbia Suicide Severity Rating Scale (C-SSRS) http://www.cssrs.columbia.edu, also developed by Kelly Posner, Ph.D. and the same team of researchers at Columbia University, fully maps to C-CASA3 as the prospective counterpart of the C-CASA and is considered to be "automatic" with no additional steps needed; therefore, rendering the C-SSRS as a fully acceptable instrument from a regulatory perspective.

Sponsors may opt to utilise other suicidality instruments such as the Sheehan Suicidality Tracking Scale, the Beck Scale for Suicide Ideation, the Suicide Intent Scale, the Modified Scale for Suicide Ideation, or the InterSePT Scale for Suicide Thinking as judged appropriate for various patient populations; however, the use of these alternative scales should be discussed with the appropriate regulatory review division in advance. This is essential as other instruments, in conjunction with other assessments in a particular programme, may reliably collect the data necessary for coding to C-CASA terms, but may not truly accomplish the actual coding necessary. In those instances, narratives should be created and blinded classification of the narratives performed if the data are to be used in any pooled analyses.

The C-SSRS enjoys the most prevalent use in industry-sponsored trials to date, investigating patients in both numerous CNS and non-CNS indications. Rates for suicidal ideation and behaviour based on the C-SSRS have been seen as high as 10% in Major Depression studies, falling sharply to 3% in Generalized Anxiety Disorder studies, 1.2% in fibromyalgia studies, and 0% in pediatric Attention Deficit Hyperactivity Disorder studies. The agency suggests that "there are likely to be several different approaches to administering the C-SSRS, including investigator

administered or self-report (e.g., phone, computer)." These alternative approaches may be appropriate as long as the method is validated, the psychometric properties of the instrument are well-established, and there is some provision for formal training of raters to ensure reasonable accuracy and consistency in application of the instrument.

Recently, a computer automated version of the C-SSRS (the eC-SSRS) that utilises an interactive voice response (IVR) system, was tested and validated by ERT/Healthcare Technology Systems in both control volunteers and psychiatric patients supporting both the feasibility and validity of the eC SSRS for prospective monitoring of suicidality for use in clinical trials5. The eC-SSRS interview maps directly to and populates the C-SSRS / C-CASA which, as discussed, is important as instruments should ideally map to C-CASA preferred terms without additional effort (e.g., creation and blinded classification of narratives). In comparison to the traditional C SSRS, the eC SSRS is self-reported and eliminates queries, thereby reducing reconciliation efforts, resulting in cleaner data and faster database lock, and importantly reducing site burden and costs. Site staff are immediately notified of any suicide risk for follow-up by a clinician, with any findings ultimately superseding self-ratings. Over 29,000 eC SSRS assessments have been performed to date with a completion rate of 99.9% from the first 15,000 assessments analysed. The majority of these assessments have been negative for suicidal ideation and behaviour (98.5%). The mean time to completion for these negative assessments was 3.7 minutes – with the shortest test path composed of six questions. The remaining 1.5% of the positive responses take twice as long on average to complete (7.8 minutes) - with the longest test path composed of 19 branched questions http://www.cssrs.columbia.edu/docs/HTS_Suicidality_Poster_ISCTM_20OCT2010.PDF.

It has been suggested that the eC-SSRS may promote increased patient candour, actually rendering the quality and reliability of the data better than the clinician-rated version, with some evidence of fewer false negatives[3]. Similar findings have been seen in past studies that have shown the superiority of automated assessments when querying sensitive subject matters such as substance abuse, sexual function, and even suicidality[6]. Certainly one of the best features of data collected via any IVR or interactive web response (IWR) system is that data are stored electronically for integration across studies and subsequent analyses. There are of course some practical considerations in using the eC-SSRS in clinical trials. For example, this measure cannot be reliably conducted in those too young to comprehend the assessment (typically under age six), those who are demented (e.g., MMSE <24), those who have a severe developmental disability, or those who are acutely psychotic. In these instances the traditional C-SSRS should be utilised. Alternatively, the eC-SSRS could be completed by a knowledgeable and responsible care-giver[3].

Ultimately the actual choice of suicidality assessment instrument is at the discretion of the sponsor. However, there is clear guidance regarding when the assessments should be conducted. In general, guidance demands that prospective suicidality assessments "should be conducted at baseline and at all planned visits at which other clinical assessments are to be carried out in a study for which suicidality assessments are considered appropriate. For certain drugs (e.g., those with particularly long elimination half-lives), it may make sense to include follow-up assessments even after dosing has stopped. These assessments should also be conducted at any unplanned visits at which other clinical assessments are needed." Practically, for Phase I studies, these assessments should be conducted minimally upon screen, entering the study unit (baseline) and leaving the study unit.

It is important for all researchers developing drugs that may have CNS effects or even side-effects to incorporate prospective suicidality assessments into their clinical development programmes, or be prepared to discuss the rationale for opting out of the assessments with the appropriate regulatory review division very early in the development programme. For the most part, psychiatry drug developers have embraced this guidance and are routinely using prospective suicidality assessment scales in their development programmes. More reticent drug developers who may be wary of the additional encumbrances that this assessment may entail should be encouraged by the fact that systematically assessing suicidality risk can actually reduce a sponsor's overall burden.

*References*


1. *Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, Hammad TA, Temple R, and Rochester G. Risk of Suicidality in Clinical Trials of Antidepressants in Adults: Analysis of Proprietary Data Submitted to U.S. Food and Drug Administration. BMJ, 339:b2880 (2009).*
2. *FDA. FDA Advisory: Suicidality and Antiepileptic Drugs. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM100190. (2008), visited on 2 May 2011.*
3. *Posner K, Griest J, and Federico M. Prospective Assessment of Suicidality in Non-Mental Health Indications. Webinar presented by ERT/HTS. www.ert.com (6 April 2011).*
4. *Posner K, Oquendo MA, Gould M, Stanley B, and Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants, Am J Psychiatry. 164:1035-1043 (2007).*
5. *Mundt JC, Greist JH, Gelenberg AJ, Katzelnick DJ, Jefferson JW, and Modell JG. Feasibility and validation of a computer-automated Columbia-Suicide Severity Rating Scale using interactive voice response technology. J Psychiatr Res. Dec;44(16):1224-8 (2010).*
6. *Greist JH, Gustafson DH, Stauss FF, Rowse GL, Laughren TP, and Chiles JA. A computer interview for suicide-risk prediction. Am J Psychiatry. 130(12):1327-32 (December 1973).*



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