

# Consensus Meeting on Methodological Considerations for Suicide Assessment and Clinical Trial Design: Design & Methodology Working Group Consensus Statements

## Description/Overview:

The Design & Methodology Working Group (WG) was charged with developing consensus statements regarding clinical trials in which suicidal ideation and/or behavior (SIB) is the primary outcome endpoint, ie, where SIB is the target of treatment. The focus was primarily on clinical trials for pharmacotherapies but the general design issues are broadly applicable to other types of interventions.

## Objective of WG:

Review current approaches and develop consensus on the key medical and scientific requirements for design of clinical studies and programs to be used for regulatory approval of therapies to treat SIB.

## Scope and Activities:

1. Supporting evidence and rationale for use of drugs to treat SIB
2. Compare design approaches: Independent, trans-nosological identification (ie, across primary psychiatric or medical diagnoses) vs. linked to diagnosis (e.g. as a symptom of depression or anxiety)
3. Review study design considerations (including subject benefit-risk assessment for study participation) for treatment trials and make recommendations
4. Review acute and maintenance designs and make recommendations
5. Review patient selection and make recommendations
6. Review considerations around use of placebo and make recommendations
7. Review outcome measures and make recommendations
8. Review use of biomarkers applied to SIB treatment trials, *develop considerations and recommendation*
9. Review management of suicide risk in clinical trials and make recommendations

## Statements Voted on at F2F Meeting on Nov 18

Statement	N	% Strongly Agree	% Agree	% Disagree	% Strongly Disagree	% DK
1. The primary goal of SIB treatment is to reduce suicidal ideation and/or behavior.	85	75%	18%	4%	4%	--

2. Suicidal ideation and/or behavior are the key efficacy outcomes for clinical trials in SIB.	85	52%	39%	6%	2%	1%
3. For the purpose of SIB clinical development planning and trial subject enrollment, subjects with recent evidence of clinically significant (moderate to severe) suicidal ideation or suicidal behavior should be eligible to enroll.	88	73%	25%	1%	1%	--
4. Evaluation of suicidal ideation and behavior for eligibility and as outcomes in SIB clinical trials can be based on a dimensional or categorical approach.	85	49%	32%	5%	2%	12%
5. For the purpose of clinical development planning and of enrolling subjects in SIB trials, SIB can be investigated either within or across diagnostic categories.	86	63%	27%	5%	3%	2%
6. Knowledge gaps on the underlying neurobiology and pathophysiology should not prevent us from investigating suicidal ideation and behavior as a trans-nosological syndrome in SIB clinical trials.	86	69%	26%	3%	--	2%
7. For the purpose of demonstrating clinical benefits/efficacy, it is of interest but not essential, to determine whether clinically significant changes in SIB are distinct from changes in the concurrent psychiatric disorder(s).	83	55%	24%	12%	1%	7%
8. In relation to the scope of therapeutic intervention a distinction should be made between acute treatment and long term prevention of SIB.	88	76%	19%	1%	1%	2%

9. The collection of samples for candidate biomarkers should be included in SIB trials to support discovery and validation for future biomarker research.	85	66%	27%	6%	--	1%
10. Policy, including relevant informed consent procedures, should be developed to encourage biobanking as well as to ensure broader access to biobanked specimens.	81	68%	23%	1%	1%	6%

**Statements Not Voted On at the Face-to-Face Meeting in November**

The statements listed below were ones that the group had reached consensus on prior to the F2F meeting in November and thus were not voted on at the meeting.

Statement 1:

Suicide is a major health problem and there is an urgent need to establish guidelines for the design of clinical trials to identify effective treatments that reduce suicidality and to support regulatory approval of effective treatments.

Statement 2:

Prospective, double-blind, randomised, parallel group, placebo-controlled studies are required for regulatory approval.

Statement 3:

The length of the double-blind, randomized, controlled treatment period should be the minimum necessary to answer the study hypothesis and the length of an open-label extension or post-treatment follow-up period should be sufficient to ensure safety and adequately address secondary outcomes.

Statement 4:

The study setting (inpatient, outpatient, or a combination) is dependent on the acuity of patient population, hypothesis being tested and must ensure the safe and ethical care of the patient population.

Statement 5:

Efficacy assessments should encompass the multiple dimensions of suicidal ideation and behavior, as well as broader dimensions of suicidality, and must have established psychometric properties, including

validity and reliability (inter-rater, test-retest). Ideally, assessments should be validated in the population to be studied.

- i) Both clinician- and patient-related assessments may be considered, and for patient-rated outcomes, different modes can be considered depending on the study setting and patient burden (e.g., Interactive Voice Response System, diary). The protocol must clearly define the primary outcome and how it will be measured.
- ii) The analysis of efficacy should include both statistical significance and clinically meaningful change over time as part of the analysis plan.
- iii) For assessments completed by a rater (eg, clinician), appropriate training and documentation of training is required. If the mechanism of the study treatment is potentially unblinding, blinded raters are recommended. Interrater reliability should be established if applicable.

Statement 6:

Stratification is recommended for comorbid conditions and where practicable, concomitant central nervous system (CNS) medications.

- i) Subjects should be stable on concomitant CNS medications for sufficient time to minimize influence on SIB assessment (eg, 6-8 wks) and on current dose for specific time period (eg, 2-4 wks).
- ii) If subjects are receiving psychosocial interventions such as therapy, they should be well established in that therapy (eg, have been receiving care for 3-6 mos) with no anticipated changes (in frequency, modality, or therapeutic approach) for the duration of the trial.

Statement 7:

Assessments of safety must identify clinically significant worsening of suicidality. 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.

- i) In order to ensure patient safety and monitoring of risk/benefit, a Data Monitoring Committee is required to review unblinded safety and efficacy data during the study. Interim analysis for futility should also be considered.
- ii) Careful consideration of assessments to minimize type II error.

Statement 8:

The acuity of the study population with respect to suicidality should align with the hypothesis being tested and enrollment ultimately will be dependent on both the clinician's judgment of suicidality risk

and assessments/scales to determine inclusion/exclusion criteria as defined by the protocol.(Note dependency with item #2 under No consensus list.)

Statement 9:

Engagement of patients during protocol development should be strongly considered.

### **Areas Where There Was No Consensus:**

The Design & Methodology WG identified several key areas and issues where there is currently no consensus in the field, but which have the potential to have an impact on the design and conduct of clinical trials with SIB as the primary endpoint. These are areas/issues that are critical and pressing, and which must be resolved before the field can progress.

1. Experimental Trial Design: Use of active control, Standard of Care or Treatment As Usual.
2. Issues related to the identification of appropriate patients to enroll in studies:
  1. Classification of patients on suicidality spectrum is needed to ensure population of appropriate acuity is enrolled; need to address how to handle at the individual level because literature has shown that risk cannot be predicted at the individual level, although may be possible at group level
  2. Trans-nosological or specific patient population (eg, depression with SIB, Post-Traumatic Stress Disorder with SIB) to be enrolled in studies.
  3. Terminology is critical to the field. The definitions of terms such as suicidality, suicidal ideation and suicidal behaviour were not be addressed by this subgroup but nomenclature is a key issue impacting clinical trial design.