

Suicidal Ideation and Behavior Working Group:

Consensus Meeting Topics Discussion

ISCTM Working Dinner Meeting

17 February 2015

ISCTM Dinner Meeting Agenda

Time	Agenda Item	Leader
6:45	Gathering for dinner	
7:00	Welcome & Introductions	L Alphs
7:10	Background	M Stewart
7:15	Models of Developing Consensus	S Marder
7:25	Proposed Consensus Topics Discussion <ul style="list-style-type: none">• Study design & methods to assess drugs to treat SIB• Developing “best practices” for SIB assessment in clinical trials	P Chappell JP Lindenmayer L Adler
8:25	Concluding remarks	L Alphs P Chappell M Stewart

Welcome

- Opening remarks
- Introductions

Culture of ISCTM Meetings

- Highly Interactive
- Presentations are to be short and start the conversation
- Creative, outside-the-box thinking is encouraged
- Audience participation is integral part of meeting's work
- No 'sacred cows'
- Be brief and as clear as possible
- No commercialism or 'product' promotion
- Thoughtful, respectful, but challenging
- A 'safe space'

Background on Current WG Effort

Objectives:

- Identify knowledge/practice gaps related to suicide ideation and behavior assessment that lend themselves to resolution through
 - ISCTM-sponsored consensus meeting in November 2015
 - Establishment of a follow-on ISCTM SIB working group

Rationale:

- In the past 10 years a vast knowledge base has been gained regarding the assessment of suicide ideation and behavior and its association with pharmaceutical interventions. Despite this, little systematic review of this work has been done.
- ISCTM has been an exception through the activities of several SIB working groups.
- We propose to continue this tradition by summarizing and prioritizing the methodological issues regarding assessment of SIB, its analysis and interpretation.

Working Group Product:

- A proposal to the ISCTM Executive Cmte for a consensus meeting to address issues identified as priorities by this working group, including an agenda and a plan for such a consensus meeting **OR** develop a follow-on ISCTM SIB Working Group to address these issues
- A white paper and/or published manuscript summarizing the work of this group.

Work Plan

Milestone	Delivery Date
Organization & brainstorming	Jan 9, 2015
Summary & prioritization of topics	Jan 23, 2015
Preparation for Working Group Dinner meeting	Feb 6, 2015
Working Group Dinner, ISCTM 11th Annual Scientific Meeting, Washington DC (Registration Required)	Feb 17 2015
Finalization of SIB Consensus Meeting proposal	May 2015
Presentation of SIB Consensus Meeting Proposal to ISCTM Scientific Committee	May 2015
<i>TENTATIVE: Consensus Meeting</i>	<i>Nov 2015</i>

Models for Achieving Consensus

Steve Marder

**ISCTM Working Dinner Meeting on SIB
Assessment**

17 February 2015

Consensus may be defined professionally as an acceptable resolution, one that can be supported, even if not the "favourite" of each individual.

Consensus is defined by Merriam-Webster as, first, general agreement, and second, group solidarity of belief or sentiment. It has its origin in the Latin word *cōnsēnsus* (agreement), which is from *cōnsentiō* meaning literally *feel together*. Consensus decision-making is thus concerned with the process of deliberating and finalizing a decision, and the social and political effects of using this process.

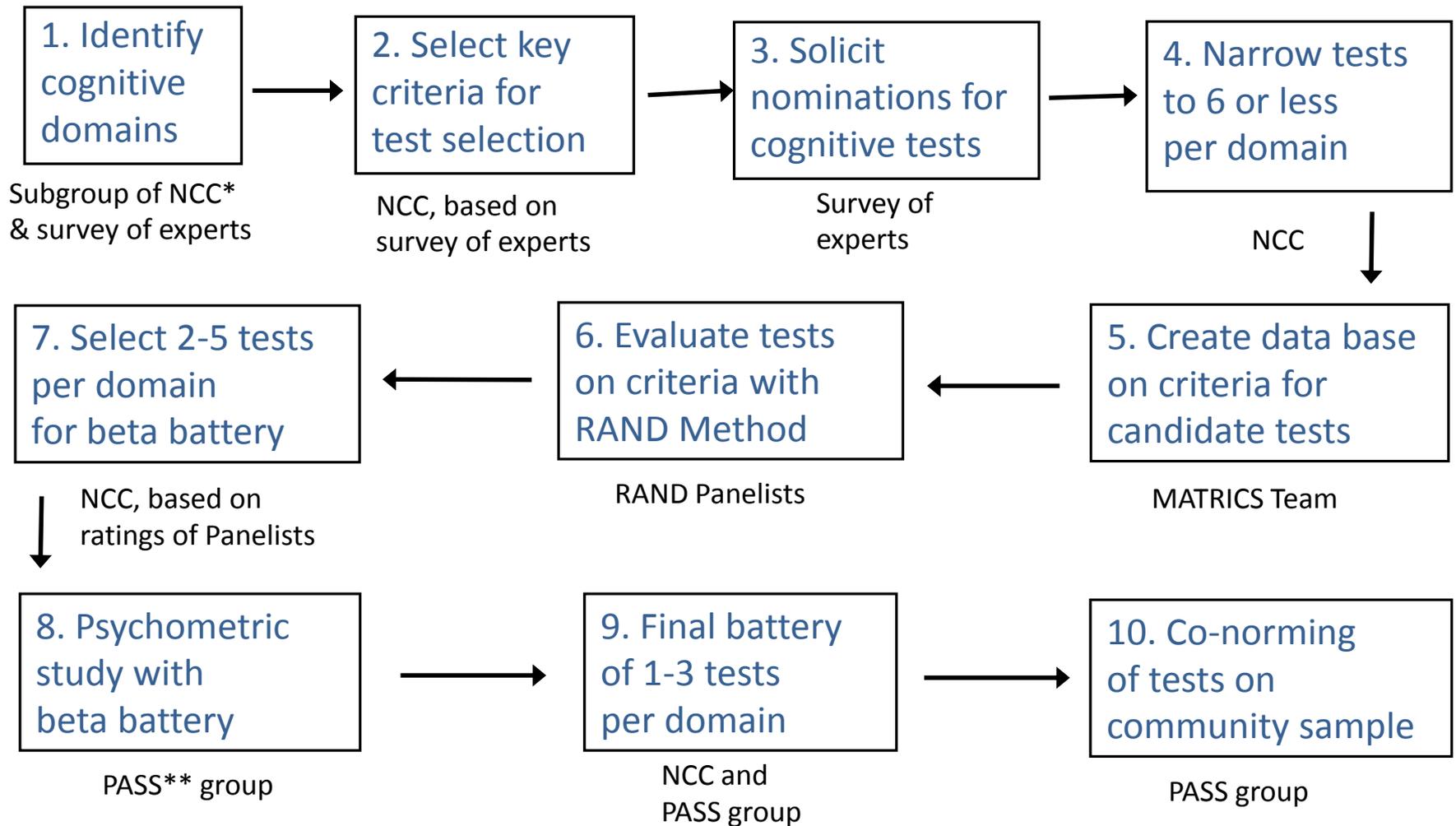
Quaker Decision-making

The goal is "unity, not unanimity." Ensuring that group members speak only once until others are heard encourages a diversity of thought. The facilitator is understood as serving the group rather than acting as person-in-charge. In the Quaker model, as with other consensus decision-making processes, by articulating the emerging consensus, members can be clear on the decision, and, as their views have been taken into account, are likely to support it.

Appropriateness Method

- Developed for reaching consensus on the appropriateness of medical interventions. Modified in MATRICS for decisions about cognitive battery, trial design, selection of most promising molecular targets.
- Requires first deciding on criteria for decision; then literature review to determine adherence to criteria, final decision made by a panel

Steps to MATRICS-NIMH Consensus Battery



*NCC: MATRICS Neurocognition Committee

**PASS: MATRICS Psychometric and Standardization Study

Method for negative symptom conference

1. Survey of most important questions requiring consensus
2. Opinion survey of meeting participants regarding selected questions
3. Priority is given to areas where there is disagreement
4. Individuals with opposing opinions are selected to defend their opinion at consensus meeting
5. Facilitator determines how presentations influenced opinions, defines differences, works to bring group to consensus

Method from Meyer Suicidality Consensus

- Relevant topics in agenda (i.e. the assessment instruments of suicidal ideation/behavior) reviewed and findings discussed in relevant breakout groups, in the final plenary session, and in the preparation of the article.
- Approximately 6 questions per breakout group prepared in advance by members of the Steering Committee and each breakout group chair. Consensus and dissenting views noted. Consensus in the breakout groups achieved by nominal group process.
- Consensus recommendations and any dissent reviewed for each breakout group at the final plenary session.

Proposed Consensus Meeting Topic:
*What is current “best practice” for assessment of
SIB in clinical trials?*

Small Group #1
Presenter: Phil Chappell
ISCTM Working Dinner Meeting on SIB Assessment
17 February 2015

Sub-Team Participants

- Mark Bangs, Eli Lilly
- Heather Bryson, PPD
- Phil Chappell, Pfizer
- Franco Di Cesare, LeoBen Research
- John Greist, Healthcare Technology Systems
- Ebrahim Haroon, Emory University
- Michelle Stewart, Pfizer
- Joseph Palumbo, Mitsubishi Tanabe Pharma
- David Sheehan, Un of South Florida College of Medicine
- Christine Ulbricht, Un of Massachusetts Medical School

Overarching Theme

Based on the experience of investigators and sponsors since the issuance of the first FDA draft guidance (in 2010), what should comprise current “best practice” for assessment of suicidal thinking, suicidal behavior, and risk of suicide in patients participating in clinical trials of drugs that are centrally active, directly or indirectly?

Specific Questions To Be Addressed (1)

- What are the most critical psychometric properties and characteristics instruments used to assess SIB in clinical trials must have?
- Can a single SIB assessment instrument suffice for all studies and all patient populations? Do we need different instruments for different types of studies and patient populations?
- What properties should instruments used for assessment of SIB risk in *children* and in *patients with cognitive impairment* have? What additional studies need to be done to establish valid methods for SIB assessment in these patient populations?

Specific Questions To Be Addressed (2)

- What is the best method for assessment of SIB and making a clinical judgment of suicide risk in clinical trial subjects?
- What are the strengths and weaknesses of different approaches to the collection and integration of third party information in SIB assessments?
- What past time period should be used for assessment of SIB risk at the study screening visit?
- Is it possible to obtain an accurate and reliable assessment of lifetime suicidal thinking and behavior? What are the strengths and weaknesses of different approaches to doing a lifetime SIB assessment?

Specific Questions To Be Addressed (3)

- Who should perform SIB ratings and what qualifications and training should they have? How can we ensure raters are comfortable talking about suicide with patients?
- How should patients who are identified to be at increased risk of SIB or suicide during the course of a clinical study be managed to ensure their safety and the integrity of the study?

Why Should This Topic Be Supported

- Global internet surveys of sponsors and investigators conducted by the ISCTM SIB Workgroup have documented continuing challenges and inconsistencies in the conduct of SIB assessments in clinical trials.
- Consensus on current best practice for assessment of SIB in clinical trials would further the
 - Use of more standardized methods and approaches to SIB assessment in clinical studies across different companies
 - More accurate identification and characterization of benefit risk profile of new CNS drugs
- Best practices in a clinical trial setting also may be translated to clinical practice settings, leading to improved efficiency and effectiveness of suicide risk assessments.

- Deliverables
 - Consensus Meeting & White Paper for publication
- Impact
 - Identify pitfalls of current methods
 - Highlight knowledge gaps and directions for future clinical research
 - Increase awareness and interest (primarily, medical-scientific community and regulators)
 - Help establish more uniform and standardized approaches to the assessment of SIB in subjects participating in clinical trials, leading to more accurate characterization of the benefit-risk profiles of CNS active drugs.

Proposed Consensus Meeting Topic:

Clinical Trial Designs and Methods to Assess Drugs in Development for Treatment of Suicide Ideation and Behavior

Small Working Group #2

Presenters: J.P. Lindenmayer & L. Adler

ISCTM Working Dinner Meeting on SIB Assessment

17 February 2015

Clinical Trials Sub-Team Participants

- **Larry Alphas**
- **Larry Adler**
- **Heather Bryson**
- **Adam Butler**
- **Carla Canuso**
- **Franco Di Cesare**
- **Ebrahim Hooran**
- **Joe Hulihan**
- **Andrew Krystal**
- **Pilar Lim**
- **Jean Pierre Lindenmayer**
- **Cristiana Mayer**
- **Shane Mclerney**
- **Valentino Pironti**
- **David Sheehan**
- **Michelle Stewart**

Why Should This Topic Be Supported

- Suicide is the 2nd leading cause of death in adolescents and young adults (age 15-29).
- Every year, over 800,000 people commit suicide worldwide (40,000+ of these deaths in the US) and nearly 500,000 people visit a hospital annually for injuries due to self-harm behavior in the US
- Superior clinical methods and procedures to identify and monitor subjects at increased risk for suicide attempt are needed
- Pharmacological treatment may a valuable component of therapeutic intervention to mitigate the risk for suicide behavior
- There is no consensus on key elements of study designs aiming at evaluating therapeutic potential on drug treatments for SIB
- There is an additional number of “bottle-neck” knowledge (medical, scientific, regulatory) and methodological gaps preventing/slowing the development of drug candidates for SIB

Presentation of Consensus Topics

- The working group reviewed many areas of interest and examined them for possible need of consensus.
- The following criteria were used for selection:
 - Topics with significant data and agreement in the field: low need for consensus
 - Topics with little data: Consensus difficult to achieve
 - Topics with conflicting data and divergent opinions in the field: Chosen for consensus

Basic terminology, clinical model, and construct validity

- Is there a general consensus on what *suicide ideation/behavior* (SIB) is?
- If yes, should the current terminology on *suicide ideation/behavior* be further specified to make it more clinically meaningful and valid, including the introduction of new terms (i.e. “imminent risk of”, “self-harm”) and a clearer definition of the current ones?
- What is/are the appropriate clinical model(s) to work in?

Clinical indication/label

- Are these clinically relevant and differentiable conditions worth a labeled indication?
 - Acute suicide ideation
 - Chronic suicide ideation
 - Acute suicidal behaviors
 - Chronic suicidal behaviors
 - Imminent suicide risk
- Should the targeted indication be general (i.e. “*suicide ideation/behavior*”) or specific to clinically relevant aspects of SIB (i.e. suicide behaviour or suicidal ideation, etc.) ?

Patients/target population

- Should SIB be considered “trans-nosological” (independent from primary psychiatric diagnosis; similar to RDocs) or associated to a psychiatric diagnosis?
- Should the primary criterion for inclusion be evidence of SIB (or specific components of it) regardless of psychiatric co-morbidity or, alternatively, should SIB be considered secondary/associated to a known psychiatric diagnosis (i.e. schizophrenia, bipolar disorder, PTSD, etc.)?

Expected therapeutic response/clinical benefits

- Should the drug treatment benefit the patient by decreasing the severity of SIB and the duration over a period of time of SIB?
- Should the drug treatment be limited to reduce the risk for suicide behaviour?
- Should the drug treatment benefit other clinical elements associated with SIB (i.e. hopelessness, level of depression, etc)?

Clinical assessment methods to detect treatment effects in drug trials

- Consensus is needed to define clinical assessment methods, which are reliable (including demonstrated sensitivity to change and specificity to change), valid (including trans-cultural adaptations), and cost-efficient to evaluate severity and duration of SIB
- Is there consensus on a gold standard method currently available?
- Is there consensus on a compelling need to develop new methods? If so, in what areas are they needed?
- Is there consensus on patient-reported outcomes (PROs) instruments?

Consensus Questions on Study Design

- *Acute vs. Maintenance SIB or Chronic (Preventative) Design* for SIB: What is best design for each?
- *Use of placebo*. Is a parallel group/placebo-controlled trial design allowed, specifically in phase 2 studies to evaluate therapeutic efficacy?
- What is the *historical duration of SIB* for an adequate enrichment design?
- *Comparator*. Is Clozapine the gold standard to treat SIB? If not, any other drug treatment may be considered as a gold standard for SIB?
- *Is an “add-on” design* the preferred design to evaluate therapeutic potential?
- *Adaptive or enrichment designs*. Are they adequate to evaluate SIB in phase 2 trials?
- Should we consider a trial design for SIB generically (trans-nosologically) or for specific sub populations? What about age subgroups?

Biomarkers

- Should biomarkers be included in studies targeting SIB as an indication?
- What is a biomarker? MRI, EEGs, genes, protein measures (blood, saliva, CSF)
- Assess change in biomarkers over time (need to assess at BL and f/up points) to examine sensitivity to change and relationship to treatment and validate against other accepted measures
- Propose to use in conjunction w/C-SSRS as the putative “gold standard” to have common basis for comparison (though other scales could also be used). Eg, will be able to look at lifetime risk & biomarkers.
- Form consortium (or other mechanism) to explore biomarker in non-competitive space
- Propose list of specific biomarkers to be included at a minimum (to drive consensus about which biomarkers minimally needed)

Safety risks

- Are there rebound/ withdrawal reactions for SIB expected? If yes, how is this safety risk to be mitigated by trial design.
- Could elements of the informed consent procedure and repeated assessments of SIB in a short time-frame increase the risk for suicide behaviour?

Concluding Remarks

Thank you for your participation