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Suicidal Ideation and Behavior Assessment: Implementation in Clinical Trials

WORKSHOP

Adam Butler & Michelle Stewart (Co-chairs)

ISCTM Autumn Conference

October 4, 2011

Amelia Island, FL

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AGENDA

Introduction & Background on work
• Workshop Objectives
• Ground rules
• Working Group membership
Presentation of Survey Results
• Review of ISCTM Suicidality Assessment
• Survey
• Survey Results
Discussion
• Interpretation of results
• Implications for clinical research
Next Steps
• Publication
• Targeting additional groups
• Additional analyses
Summary

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Workshop Objectives

- *Review and discuss data collected from survey assessing site experiences with implementing suicidal ideation and behavior (SIB) assessments in clinical trials in various phases of development*
- *Focus on interpretation of the results*
- *Understand implications for future work in this area*

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Ground Rules

- We are not here to debate the merits of any particular assessment scale/approach
- Focus on the data at hand

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Active Working Group Members

- Larry Alphs
- Adam Butler (Co-chair)
- Douglas Feltner
- William Lenderking
- Atul Mahableshwakar
- Clare Makumi
- Gary Sachs
- Michelle Stewart (Co-chair)

Working Group provided feedback on draft FDA guidance

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Background

- ISCTM sponsored two previous workshops
  - Oct 13, 2010 workshop
    - Speakers from FDA (Mitch Mathis), pharma sponsors (Phil Chappell, Pfizer) & academia (Jill Harkavy-Friedman, Columbia)
    - Discussion centered around draft guidance & sponsor experience with assessments
      - Several relevant issues were identified
  - Feb 21, 2011 dinner meeting/discussion
    - Objectives included defining issues r/t validating a new scale; recommendations for trials with SIB as an endpoint; and outline ongoing challenges
      - Discussion focused primarily on challenges

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Issues Identified

Highlights:

- Non-mental health PIs lack referral networks
- Raters show subtle bias when asking questions
- Some sites/PIs do not feel comfortable asking these questions
- Role of self-report in SIB assessments not well understood
- Desire for short, simple scales
- Cultural & religious issues are important yet under-recognized
- Good baseline history is crucial to understanding clinical trials results
- Concern in implementing SIB assessments in clinical settings or trials where not routinely done
- Language in draft guidance on special populations (e.g., AD) is vague
- Availability of multiple versions of scales creates problems
- Historically clinical trials have used a variety of approaches to assessing SIB such as text-string searchers
- Subjects cannot recall or do not always choose / want to be honest
- Some experts aren't certain how to interpret the data that emerges from trials (e.g., as DSMB members)

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2011 Site Survey

- Idea to conduct 2 surveys emerged from Feb dinner meeting
  - For (1) Sites and (2) Sponsors
  - Due to time constraints, we focused on the site experiences
  - Used the summary of previous meetings to develop questions
  - Goal was to design brief, Internet-based survey focused on site experiences
    - Survey did not ask questions about specific assessments or assessment modalities

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Survey Instrument

- Refer to handout

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Respondent information

The survey is very brief and should take only about 5 min to complete. Your input is important, please complete the entire survey.

Site Info

1. What is your role at the site?
    - Principal investigator (PI)
    - Rater
    - Coordinator
    - Other [TEXT BOX TO SPECIFY –limit 75 characters?]

2. Which of the following best characterizes your background?
    - Psychiatrist
    - Neurologist
    - Other physician
    - Psychologist
    - Nurse/social worker
    - Pharmacist
    - Other [TEXT BOX TO SPECIFY – limit 75 characters?]

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Clinical Trial Experience

3. How many trials has your site conducted in each of the therapeutic areas listed below that required prospective monitoring of suicidal thought and behavior?

NOTE: Prospective monitoring refers to a formal assessment that may be done via an interview with the subject or a form (paper or electronic) that the subject completes. Examples of assessments include the Columbia Suicide Severity Rating Scale (C-SSRS) and the Sheehan Suicidality Tracking Scale (S-STS).

	0 (None)	1-10 trials	11-25 trials	> 25 trials
Affective disorders				
Schizophrenia / Schizoaffective disorder				
Neurodegenerative (e.g., Alzheimer's, Huntington's, Parkinson's) (Select one)				
Epilepsy				
Pain				
Other CNS Diagnoses				
Other non-CNS diagnoses				

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Attitudes

Each item was rated as Disagree strongly, Disagree, Neither agree nor disagree, Agree, or Strongly Agree

1. Overall, the benefit of including suicidal thinking and behavior assessments in clinical trials is worth the additional burden.
2. The inclusion of suicidal thinking and behavior assessment in clinical trials has improved subject safety.
3. Our site uses the assessment of suicidal thinking and behavior to manage the safety of subjects enrolled in our clinical trials.
4. It has been easy to incorporate the assessment of suicidal thinking and behavior into clinical trials at our site.
5. It takes too long to administer an assessment of suicidal ideation and behavior during a clinic visit.
6. Subjects do not like to answer questions concerning suicidal thinking and behavior.
7. The training we have received on the assessment of suicidal ideation and behavior has been helpful.
8. The information subjects provide during the assessment of suicidal thinking and behaviors is valid and reliable.
9. The information we get from the scales used to assess suicidal thinking and behavior is the most relevant for judging a patient's suicide risk.
10. The raters at this site do not feel comfortable asking subjects questions about suicidal thinking and/or behavior.
11. Using suicide rating scales in our trials has provided clinical value.
12. Staff at this site feel prepared to handle reports of suicidal thinking and/or behavior.

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Benefits & Challenges

Instructions were to mark all that apply for each question

- What are the most challenging problems with respect to implementing the assessment of suicidal thinking and behavior in clinical trials? MARK ALL THAT APPLY.
  - Finding the correct version of the scale to use
  - Difficulty getting the correct language translations needed for our site
  - The amount of time it takes to do an assessment
  - Lack of adequate training to conduct these interviews and assessments
  - Difficulty getting an accurate history of a subject's lifetime history of suicidal thoughts and behaviors at baseline
  - Lack of a referral network for subjects with suicidal issues
  - Difficulty fitting this assessment into a typical clinic visit
  - Uncertainty about what to do if a subject has suicidal thoughts/behaviors
  - Other [TEXT BOX TO SPECIFY – limit 140 characters]
- What are the most important benefits with respect to implementing the assessment of suicidal thinking and behavior in clinical trials? MARK ALL THAT APPLY.
  - Helps identify subjects at risk of suicide
  - Makes running clinical trials safer
  - Improves our ability to provide care
  - Provides subjects with a sense that their safety is important and is being monitored
  - Will provide important prescribing information for prescribers
  - Can help identify drugs that may cause patients to become suicidal
  - Helps identify patients who may benefit from treatment
  - Reduces the stigma associated with suicidal thinking and behavior
  - Helps educate site staff on the importance of suicide-related issues in clinical trials
  - Other [TEXT BOX TO SPECIFY– limit 140 characters]

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Final Survey Questions

- Are you responsible for conducting assessments of suicidal thinking and behavior at your site?
  - Yes/no
- What country is your site located in?

- Please add any additional comments you have on the issue of assessing suicidal thinking and/or behavior in clinical trials: [TEXT BOX – 250 characters or less]

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Methods

Sample	• A list of 6058 study sites that had participated in at least one CNS clinical trial in the prior two years was obtained from an independent vendor's contact database. • An invitation to participate from the ISCTM Secretariat and a link to the online survey were distributed via email to a list of 6058 investigators, raters, and site staff with valid email addresses obtained from a vendor database. • Instructions encouraged respondents to speak with others at their site about their experiences implementing the assessment of STB and to provide one response from the site that reflected the broader experience.
Administration	Survey Monkey was used to collect responses. There was a with a 3-week deadline to respond.
Statistical analyses	Responses were summarized descriptively.

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Survey Results

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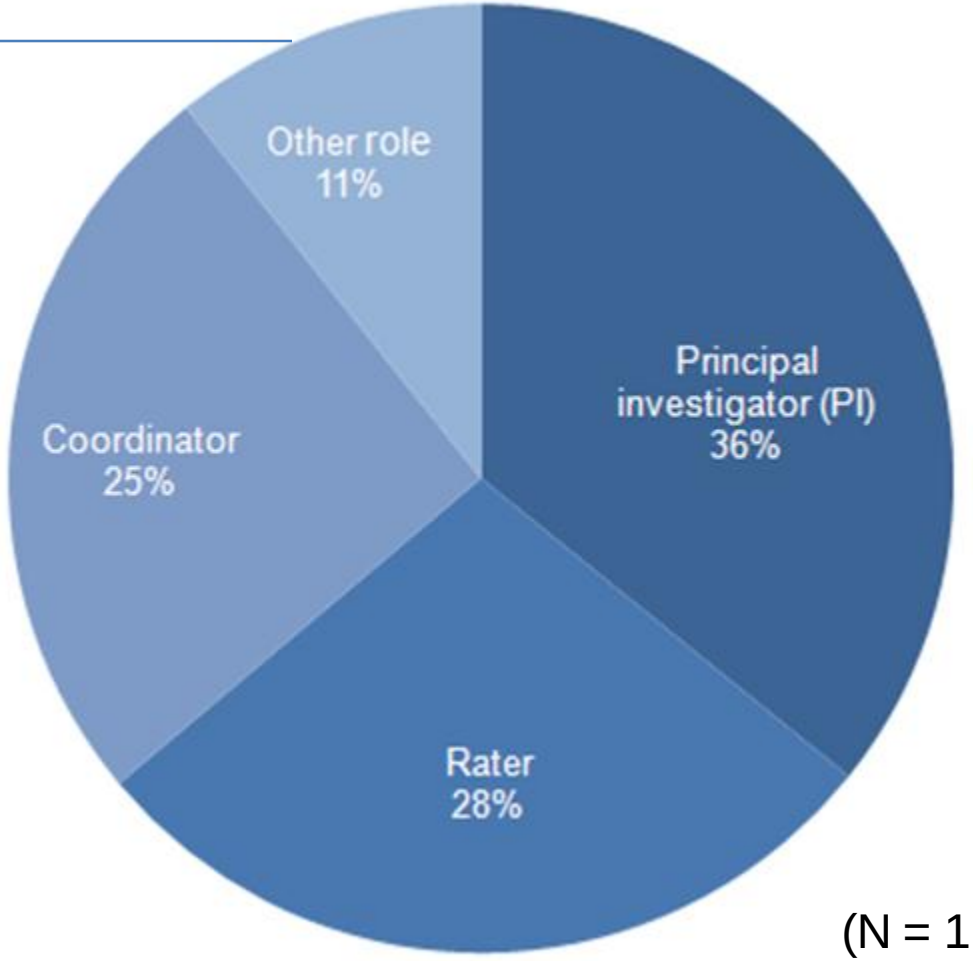
Role at Site

5% were sub-investigators
& rest had various roles or combination



(N = 1002)

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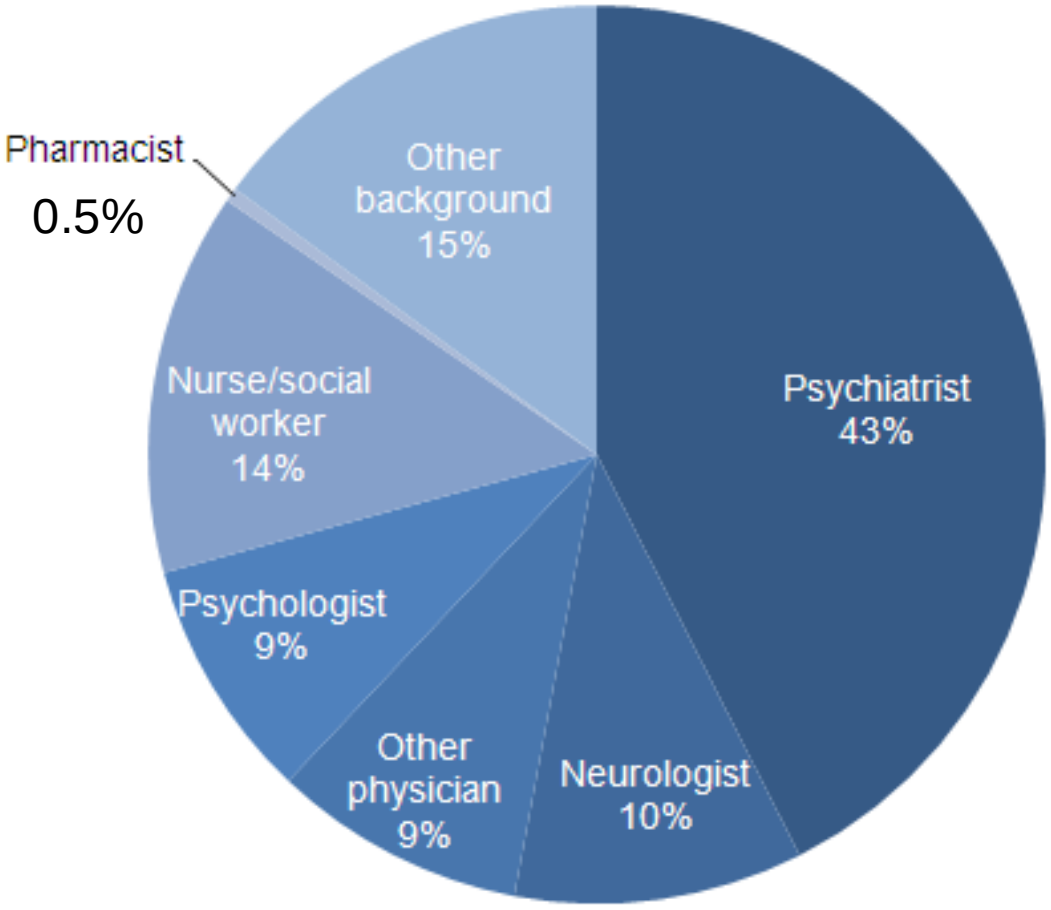
Respondent Background/training



(N = 998)

A total of 1004 responses were collected

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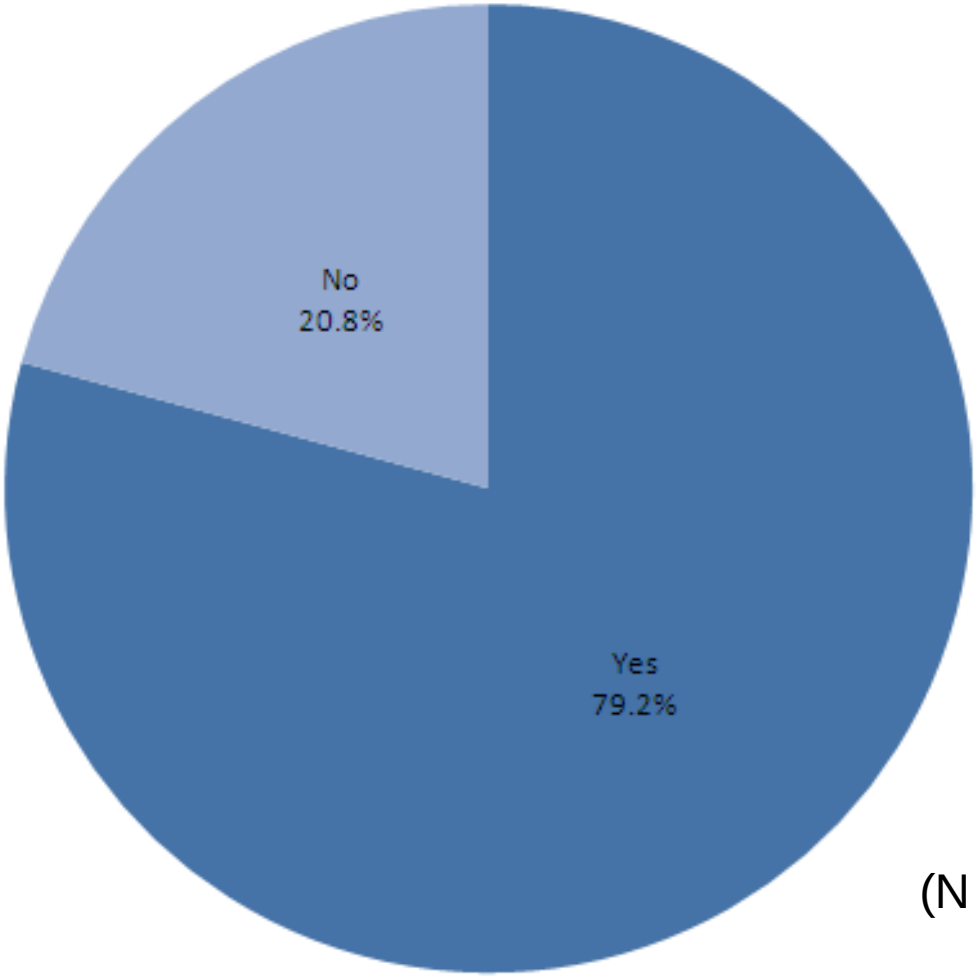
Responsible for conducting SIB assessments?



Majority of respondents had conducted SIB assessments

(N = 992)

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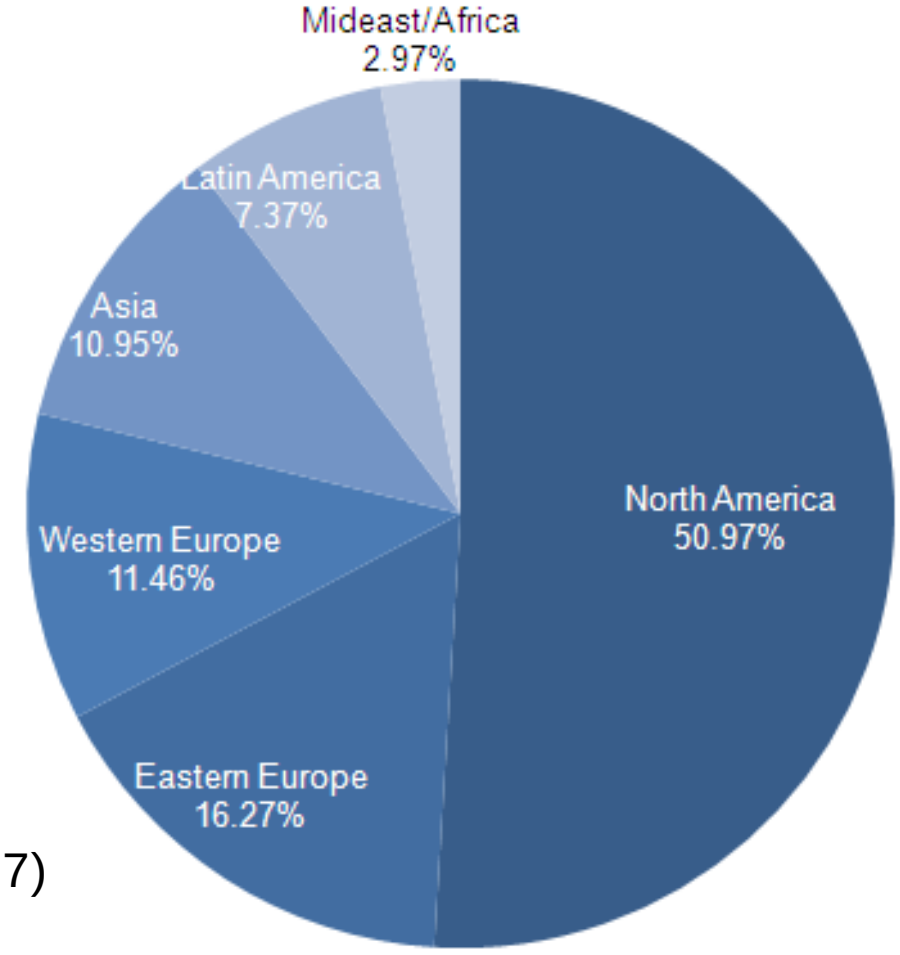
Geographic Distribution



(N = 977)

Overall
43% from US
57% from outside US

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Clinical Trial Experience

	% of Responses by Therapeutic Area (N = 1000)			
	None	**1-10 trials**	**11-25 trials**	**> 25 trials**
Affective disorders	32.1%	49.1%	10.8%	8.0%
Schizophrenia / Schizoaffective disorder	40.8%	46.0%	8.9%	4.2%
Neurodegenerative (e.g., Alzheimer's, Huntington's, Parkinson's)	42.9%	44.9%	7.0%	5.2%
Epilepsy	80.7%	16.8%	1.7%	0.8%
Pain	62.0%	32.7%	2.8%	2.5%
Other CNS Diagnoses	45.0%	40.9%	7.5%	6.6%
Other non-CNS diagnoses	66.9%	23.6%	3.2%	6.3%

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Attitude Items

	Disagree strongly	Disagree	Neither A/D	Agree	Agree strongly
1. Benefit is worth the burden	3.4%	7.9%	16.2%	47.7%	24.7%
2. Has improved subject safety	1.9%	6.7%	17.8%	47.1%	26.5%
3. Site uses to manage the safety of enrolled subjects enrolled	2.9%	8.7%	14.1%	48.4%	25.8%
4. Easy to incorporate into clinical trials	2.1%	7.3%	18.9%	49.5%	22.1%
5. Takes too long to administer	13.9%	45.6%	22.4%	15.2%	2.9%
6. Subjects do not like to answer questions	9.8%	38.9%	25.8%	21.0%	4.4%
7. Training received has been helpful	1.8%	6.3%	24.0%	50.3%	17.6%
8. Information subjects provide is valid and reliable.	0.8%	7.1%	27.7%	56.1%	8.2%
9. Information obtained is the most relevant for judging a subject's suicide risk	2.8%	15.5%	33.7%	41.7%	6.1%
10. Raters at this site do not feel comfortable asking about SIB	32.2%	43.4%	13.4%	9.6%	1.3%
11. Has provided clinical value	2.2%	7.3%	26.1%	50.6%	13.8%
12. Staff feel prepared to handle SIB reports	1.3%	3.7%	12.8%	55.8%	26.3%

(N = 997)

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Most Important Benefits

Benefit	%
Helps identify subjects at risk of suicide	84.5%
Makes running clinical trials safer	61.4%
Provides subjects with a sense that their safety is important and is being monitored	58.8%
Helps educate site staff on the importance of suicide-related issues in clinical trials	57.5%
Can help identify drugs that may cause patients to become suicidal	55.7%
Improves our ability to provide care	49.9%
Helps identify patients who may benefit from treatment	42.3%
Reduces the stigma associated with suicidal thinking and behavior	35.7%
Will provide important prescribing information for prescribers	28.3%
Other	2.2%

(N = 868)

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"Other" Response Categories - Benefit

Sample Comments
The assessment seems a good way to track that the question was asked
Helps differentiate real suicidal ideation with intent from just words or anger
Create a good alliance with the patient
Helps to identify exclusion criteria in clinical trials
Regulatory framework for a governmental agency to fight criticism of medications it approves
It adds to the comprehensiveness of evaluation in clinical trials and in practice. Time /effort spent is rewarded with lives saved
Eliminates spurious reporting of non-suicidal behaviors.

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Most Difficult Challenges

Benefit	%
Difficulty getting accurate information on a subject's lifetime history of suicidal thoughts and behaviors at baseline	54.5%
The amount of time it takes to do an assessment	27.9%
Lack of a referral network for subjects with suicidal issues	27.1%
Finding the correct version of the scale to use	25.5%
Difficulty getting the correct language translations needed for our site	24.0%
Difficulty fitting this assessment into a typical clinic visit	22.4%
Lack of adequate training to conduct these interviews and assessments	21.7%
Uncertainty about what to do if a subject has suicidal thoughts/behaviors	18.7%
Other	12.7%

(N = 876)

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"Other" Response Categories - Challenges

Number of responses	Category
25	Comment on specific scale
10	Problems with cognitive impaired populations
14	General comments – unable to categorize
9	Difficulty with subject information (unreliable/difficult to obtain or verify)
6	Predictive validity of these scales in not known
4	MDs must do these scales
3	Routine issues (e.g., problems entering into electronic data capture program)
2	SIB is assessed by another scale
2	PI availability

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Open-Ended Response Categories

Number of responses	Topic	Sample verbatim response
15	Comment on specific scale	Kelly Posner PhD designed the CSSRS for non-clinicians yet sponsors won't allow non-MD's to administer the scale. The makes visits less efficient and takes time from the MD.
14	General comments that scales are clinically relevant; important to assess Suicidality in clinical trials	Assessment of suicidality is simple and important tool to safety in clinical trials.
13	General comments about SIB assessments (e.g., too long/complicated/convoluted)	We need better and more reliable scales!
11	Problems with use in cognitively impaired populations	The use of "scales" in dementia trials is a fig leaf and provides meaningless information.
5	Rater issues	Allowing trained coordinators who are not MDs to use the scales may improve reporting as subjects have the most comfort with the coordinator
4	Patients self-report of symptoms is problematic/unreliable/difficult to obtain	It is unclear how truthful the patients are regarding their symptoms, however, there is value in at least, asking the question
4	Patients benefit directly from assessing SIB	Benefit that subjects have better awareness & understanding that suicide ideation may occur as a side effect & that this should be reported as it can be addressed.
2	Use of scales cross-culturally causes problems	The assessment should be differed based upon country to country. It should be depend upon depression level of different people of different origin.

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Conclusions

- First study to look at this topic
  - Generally the implementation of SIB assessments in clinical trials is viewed positively
  - Majority see clear-cut benefit in subject safety
  - Yet issues remain with implementation
    - Difficulty with subject self-report, especially at baseline
    - Obtaining correct versions/translations of scales
    - Fitting assessment into clinic visit & time
    - Training to administer scales
    - Lack of referral network or uncertainty how to handle positive SIB reports
    - Problems with use in cognitively impaired populations
    - Predictive validity of SIB assessments is unknown
    - Some dissatisfaction with currently available scales

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Comparison to Anecdotal Info

How do our results match?

- ✓ Non-mental health PIs lack referral networks
- Raters show subtle bias when asking questions
- Some sites/PIs do not feel comfortable asking these questions
- Role of self-report in SIB assessments not well understood
- ✓ Desire for short, simple scales
- ✓ (half-check) Cultural & religious issues are important yet under-recognized
- Good baseline history is crucial to understanding clinical trials results
- Concern in implementing SIB assessments in clinical settings or trials where not routinely done
- ✓ Language in draft guidance on special populations (e.g., AD) is vague
- ✓ Availability of multiple versions of scales creates problems
- Historically clinical trials have used a variety of approaches to assessing SIB such as text-string searchers
- ✓ Subjects cannot recall or do not always choose/want to be honest
- Some experts aren't certain how to interpret the data that emerges from trials (e.g., as DSMB members)

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What New Did We Learn/Hear?

- Training on SIB assessments is an issue
- Requirement that an MD must do the scale add complexity
- Most sites don't feel it takes too long to do these assessments
- Most sites have done < 10 trials using SIB assessments
- Sites focus on safety of patients they see and see less connection to label that may emerge based on results
- Predictive validity of scales is of concern to sites
- A variety of individuals with varying backgrounds are serving as raters

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Limitations

- Study was limited by Internet-based survey approach
  - Sampling was not representative of all clinical trials sites
    - We drew from a list of sites involved in CNS trials
  - No verification of responses (all is self-report)
  - One response per site may not capture full experience at the site
  - No comparison to what approaches were used prior to the implementation of formal SIB assessment using scales/instruments

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Next Steps?

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Thank you!

Back up slides

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Other CNS Diagnoses	45.0%	40.9%	7.5%	6.6%
Other non-CNS diagnoses	66.9%	23.6%	3.2%	6.3%

	DS	D	Neither A/D	A	AS
1. Benefit is worth the burden	3.4%	7.9%	16.2%	47.7%	24.7%
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