Clinical Trial Database Analyses to Inform Regulatory Guidances

Suicidal Ideation and Behavior Assessment

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Overview

- Rationale for Suicidal Ideation and Behavior (SI/B) Assessment Guidance
- Key Issues to Address in Guidance Update
- SI/B Database Meta-Analysis Project
- Preliminary Recommendations

SI/B Safety Monitoring in Clinical Trials

- DPP issued a 2009 Guidance to Industry (revised 2012) on Assessment of Suicidal Ideation and Behavior (SI/B) in Clinical Trials after Antidepressant Boxed Warning
- SI/B safety monitoring should be done using scale that at least maps to Columbia Classification Algorithm for Suicide Assessment (C-CASA) criteria
- Recommended scale then was C-SSRS

SI/B Safety Monitoring in Clinical Trials

- FDA is in process of revising and updating this guidance (incorporate ISCTM SI/B Workgroup and other suggestions)
- Recommended SI/B monitoring at screening and at all study visits for multiple-dose trials and submission of scale data with any clinical study report
- Alternatives to C-SSRS can be submitted for approval for use as long as scales map to C-CASA

Key Issues for SI/B Guidance Update

- Clarify instances of use/which drugs
- Is C-CASA (or C-SSRS) useful for SI/B prevention?
  - Does it actually increase safety at all? Or just false positives?
  - How do results relate to AE reporting, and how should they influence AE reporting standards?

SI and SB Relationship

- Suicide remains difficult to prevent or understand on systematic level
- Suicide is heterogeneous
- Screening/monitoring relies heavily on self-report but SI/SB often occurs privately and is not disclosed or minimized
- SI in most cases doesn't necessarily lead to SB but is considered a risk factor in several studies
- SB (especially suicides) are rare in studies
- **Screening will always have major limitations**

SI/B Database Meta-Analysis Project

- Having received C-SSRS data from clinical trials since 2009, can we analyze it for trends to inform our guidance recommendations?
- Focus on antidepressant trials for now:
  - Enriched population for SI/B risk
  - Original source of SI/B assessment concern (with already coded database)
  - Fairly consistent mechanism of action and trial design (slightly varying time periods) and endpoints
- **Is more granular SI detection important for safety (i.e., SB prevention?)**

Database Challenges and Limitations

- HAM-D SI item did not map well to C-CASA
- Different studies used different primary depression scales and pre-2009, C-SSRS was not used
- General variability in studies (population severity, time period, dosing, etc.)
- Our preliminary coded database did not track by visit, only by maximum event severity during study (won't cover SI fluctuations at different timepoints within study)
- C-SSRS events do not always correlate with reported AEs

SI/B Database Meta-Analysis Project

- Compare events for Suicidal Ideation versus Suicidal Behavior detected on scales for any correlative trends
- Compare C-SSRS to single-item questions about suicide from HAM-D and MADRS or AE reporting

SI/B Database Meta-Analysis Project

- Analyze via positive predictive value (PPV) of various scales for SB events using hypothetical screening population rate comparators
- Analyze instrument event detection sensitivity using either internal scale comparison or outside comparator of recorded SI/B Adverse Events
- **Team of Analysts: Daniel Lee MD, Shamir Kalaria PharmD, Eugenio Andraca-Carrera PhD, Mark Levenson PhD, Catherine Hsueh PhD, Marc Stone MD, Kyle Richardville**

FDA Antidepressant Database

Crude total rates of reported SI/B during antidepressant trials was similar between drug and placebo.

Suicidal Ideation and Behavior Tabulation by Percentage (Total Pool)

		C-SSRS / CASA Categories					Total Events (yes/no)			
			Lifetime		Maximum – Study Endpoint		Lifetime		Maximum – Study Endpoint	
	Arm	Category	Suicidal Ideation	Suicidal Behavior	Suicidal Ideation	Suicidal Behavior	Suicidal Ideation	Suicidal Behavior	Suicidal Ideation	Suicidal Behavior
Total Pool	Anti-Depressant	0	61.1	88.5	84.0	99.7	24.2	2.8	11.1	0.4
		1	17.6	0.66	11.2	0				
		2	5.8	1.2	1.8	0				
		3	6.7	0.8	2.1	0				
		4	2.7	8.8	0.6	0.2				
		5	6.0	0.1	0.3	0.1				
	Placebo	0	59.3	88.3	81.2	99.7	25.1	3.0	12.9	0.4
		1	18.3	0.6	12.5	0				
		2	6.4	1.3	2.4	0.1				
		3	6.6	1.1	2.7	0				
		4	3.3	8.7	1.0	0.2				
		5	6.0	0	0.2	0				

Analysis and Table by Shamir Kalaria PharmD, ORISE Fellow

PPV Analysis: C-SSRS Screening Utility

Poor PPV rates even with enrichment of comparator population incidence.

A: General Population [Incidence 11.15 per 100,000]				
	Screen +	**Screen -**		
SIB +	**8**	**23,997**		**PPV: <1%**
SIB -	**3**	**75,992**		**NPV: 99.99%**
B: Depression Trial Population [Incidence 166.67 per 100,000]				
	Screen +	**Screen -**		
SIB +	**117**	**23,960**		**PPV: <1%**
SIB -	**50**	**75,873**		**NPV: 99.9%**
C: Enriched Trial Population [Incidence 1,000 per 100,000]				
	Screen +	**Screen -**		
SIB +	**700**	**23,760**		**PPV: 3%**
SIB -	**300**	**75,240**		**NPV: 99.6%**

Analysis and Table by Daniel Lee MD, Medical Officer, DPP

PPV Analysis: MADRS-SI Screening Utility

A: General Population [Incidence 11.15 per 100,000]				
	Screen +	Screen -		
SIB +	9	23,998		PPV: <1%
SIB -	2	75,991		NPV: 99.99%
B: Depression Trial Population [Incidence 166.67 per 100,000]				
	Screen +	Screen -		
SIB +	142	13,977		PPV: 1%
SIB -	25	85,856		NPV: 99.9%
C: Enriched Trial Population [Incidence 1,000 per 100,000]				
	Screen +	Screen -		
SIB +	850	13,860		PPV: 6%
SIB -	150	85,140		NPV: 99.8%

Analysis and Table by Daniel Lee MD, Medical Officer, DPP

PPV Analysis: HAM-D-SI Screening Utility

A: General Population [Incidence 11.15 per 100,000]				
	Screen +	Screen -		
SIB +	9	14,998		PPV: <1%
SIB -	2	84,991		NPV: 99.99%
B: Depression Trial Population [Incidence 166.67 per 100,000]				
	Screen +	Screen -		
SIB +	137	16,972		PPV: 1%
SIB -	30	82,861		NPV: 99.9%
C: Enriched Trial Population [Incidence 1,000 per 100,000]				
	Screen +	Screen -		
SIB +	820	16,830		PPV: 5%
SIB -	180	82,170		NPV: 99.8%

Analysis and Table by Daniel Lee MD, Medical Officer, DPP

Preliminary Results of PPV Analysis

- C-SSRS does not show significantly higher positive predictive value for SB events during antidepressant trials than HAM-D or MADRS-SI in trials using both (i.e., all are nearly equally poor)
- Results affected by extreme rarity of SB events in trials (thankfully): no good scale for SB prediction exists
- Similar trends found in other SI/B meta-analyses in literature

Franklin JC, Ribeiro JD, et al. Risk Factors for Suicidal Thoughts and Behaviors: A Meta-Analysis of 50 Years of Research. Psychological Bulletin, (2017) 143: 187-232.

Instrument Sensitivity Analysis

- Internal comparison of C-SSRS SI/B event detection to HAM-D or MADRS-SI in trials using C-SSRS and at least one of the other scales

Population	# of Trials	# of Drug Programs	N
Total Database	228	16	73,606
C-SSRS	26	6	12,301
C-SSRS + HAMD	12	4	5,561
C-SSRS + MADRS	19	4	9,591
C-SSRS + HAMD or MADRS	20	4	10,482
C-SSRS + HAMD + MADRS	11	4	4,670

Analysis and Table by Eugenio Andraca-Carrera PhD, et al, Department of Biostatistics, FDA

Preliminary Results of Instrument Sensitivity Analysis

- HAM-D-SI and MADRS-SI showed poor sensitivity for maximum SB events detected in study by C-SSRS
- HAM-D-SI and MADRS-SI showed higher sensitivity for maximum SI events detected in study by C-SSRS but limited specificity and poor PPV

Trials Using C-SSRS and At Least HAM-D-SI or MADRS-SI	C-SSRS versus HAM-D-SI	C-SSRS versus MADRS-SI	C-SSRS versus HAM-D-SI with Both Studies	C-SSRS versus MADRS-SI with Both Studies
Maximum SI Event Sensitivity	89%	95%	88%	97%
Maximum SI Event Specificity	69%	59%	70%	56%
Maximum SI PPV	41%	33%	43%	36%
Maximum SB Event Sensitivity	5%	1%	5%	2%
Maximum SB Event Specificity	100%	100%	100%	100%
Maximum SB PPV	N/A	N/A	N/A	N/A

Analysis by Eugenio Andraca-Carrera PhD, et al, Department of Biostatistics, FDA

Preliminary Results of Instrument Sensitivity Analysis

- HAM-D-SI and MADRS-SI do not capture SB events in trials to the same degree as C-SSRS; they may capture more SI events than C-SSRS but with poor specificity
- C-SSRS may be more specific overall in detecting SI/B events, and better at detecting drug-related SI/B trends
- Still may not correlate with any predictive value for SB events, in part due to rarity of events
- Pending: Comparative Analysis to SB events reported as AEs as external comparator
- Initial Trend: C-SSRS and all scales detect more SI/B events than AE reporting

Preliminary Considerations and Recommendations

- How to Balance Screenings' Poor Predictive Value with Sensitivity for N-of-1 Situations:
  - Ethical Dilemma: Is the goal getting an identified individual to a psychiatric assessment no matter what? Are numerous false positives worth the burden of avoiding any SB event? Or do these numbers indicate that screening type doesn't really matter?
  - Flexibility re: type of SI/B screening used
  - For now, still use C-CASA level screening criteria and still screen at each clinical visit
  - Include any CNS-effect drug

Summary-Future Directions

- AE comparative analysis (threshold for reporting)
- Self-report versus clinician-reported scale results
- Analyze by-visit SI data for any intrastudy trends
- Other drug class (antipsychotics, stimulants) meta-analyses
- Different scale head-to-head comparisons
- **All analyses will be of limited applicability due to SB event rarity**

Summary-Future Directions

- New considerations with rapid-acting antidepressants and SI/B as both efficacy and safety endpoint (timing of SI/B measures around drug dosing, different scale considerations)
- Updated FDA Guidance expected sometime this year


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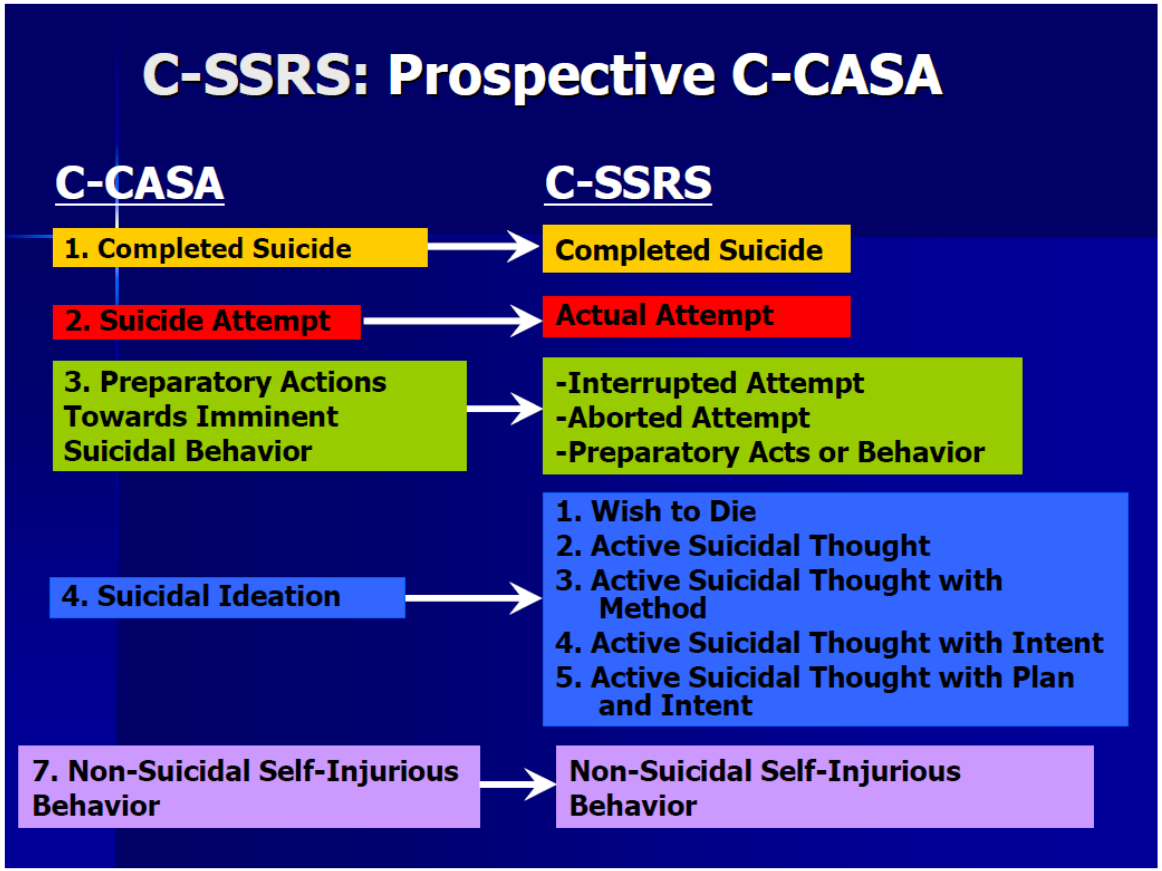
C-CASA Recoding Scheme

- **New Criteria:**
  - **Suicidal ideation (SI)**
    1. **Passive**
    2. **Active: Nonspecific (no method, intent, or plan)**
    3. **Active: Method, but no intent or plan**
    4. **Active: Method and intent, but no plan**
    5. **Active: Method, intent, and plan**
  - **Suicidal behavior (SB)**
    1. **Preparatory actions towards imminent suicidal behaviors**
    2. **Aborted attempt**
    3. **Interrupted attempt**
    4. **Suicide attempt**
    5. **Completed suicide**
  - **Self-injurious behavior, no suicidal intent**

C-SSRS to C-CASA Coding



SI/B Scale Examples

- **Beck Scale for Suicidal Ideation (BSSI)**
- **Montgomery-Asberg Depression Rating Scale (MADRS)-SI**
- **Scale for Suicidal Ideation (SSI)**
- **Hamilton Rating Scale for Depression (HAMD)-SI**
- **Beck Depression Inventory (BDI)-SI**
- **Quick Inventory of Depressive Symptomatology (QIDS)-SI**
- **Sheehan Suicidality Tracking Scale (S-STS)**
- **Columbia-Suicide Severity Rating Scale (C-SSRS)**
- **InterSePT Scale for Suicidal Thinking (ISST)**
- **Suicide Ideation and Behavior Assessment Tool (SIBAT)**
- **Clinical Global Impression of Severity of Suicidality Scale (CGI-SS)**

HAM-D-SI and MADRS-SI

- **HAM-D-17/21:**
  - Question 3: Suicide
    0=Absent
    1=Feels life is not worth living
    2=Wishes he/she were dead
    3=Suicidal ideas or gestures (*Codes to multiple C-CASA categories*)
    4=Attempts at suicide

- **HAM-D-24:**
  - Question 3: Suicidal Thoughts
    0=Absent
    1=Life is not worthwhile but no wish to die
    2=Wishes to die (e.g., not waking up next morning) but no plans to take life
    3=Vague but still active plans to take own life
    4=Has certain plans to take own life

- **MADRS:**
  - Question 10: Suicidal Thoughts
    0=Enjoys life or takes it as it comes
    2=Weary of life. Only fleeting suicidal thoughts.
    4=Probably better off dead. Suicidal thoughts are common, and suicide is considered a possible solution, but without specific plans or intent
    6=Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Other SI/B Drug Endpoint Data

- **Clozapine** - 2-year International Suicide Prevention Trial (Meltzer et al, 2003). However, drug is administered daily and long-term unlike ketamine.
- **Lithium** has had several meta-analyses showing likely reduced risk of suicide, particularly in depressed patients. (Cipriani et al, BMJ 2013)
- **Antidepressant** meta-analyses have shown equivocal data, with possible increase in SB in children/young people up to age 25 (leading to FDA boxed warning) but reduction in adults and the elderly. (Stone et al, BMJ 2009)