Prospective Suicidal Ideation and Behavior Assessment: An Internet Survey of Pharmaceutical Sponsor Practices

ISCTM Suicidal Ideation and Behavior Assessment Working Group

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INTRODUCTION

- In August 2010 the FDA issued a draft guidance requiring the prospective assessment of suicidal ideation and behavior (SIB) in clinical studies of psychiatric, neurologic and selected other indications [1].
- The intent of the guidance was that subjects experiencing SIB would be detected and appropriately treated and that data on SIB adverse events are collected in a more timely and standardized format.
- Since the appearance of the guidance and its revision in August 2012 [2], SIB assessments have been included in clinical studies spanning a wide range of indications, patient populations, geographic regions, and cultures.
- The ISCTM SIB Assessment Workgroup (ISAW) was formed in 2010 to understand the effects of the FDA guidance on clinical trial practices and to identify challenges in its implementation.
- To complement a previous survey of study site experiences and attitudes toward prospective assessment of SIB in clinical trials [3], the ISAW conducted an online survey of pharmaceutical companies to obtain information on current practices and challenges for sponsors in the implementation of SIB assessments.

METHODS

- A total of 30 items were developed for inclusion in the survey, including four questions on respondents' background.
- The survey was sent to 1447 industry employees at 178 pharmaceutical and biotech companies, using email addresses obtained from an ISCTM membership mailing list and from a contact list maintained by a vendor that provides clinical trial scientific services to pharmaceutical companies.
- The survey was implemented using the online survey software SurveyMonkey™, and data were collected from August 15, 2013 to September 20, 2013.
- Respondents were encouraged to discuss the survey questions with colleagues, if necessary, to provide information that best represented their company's practices and experiences with SIB assessments in clinical trials.
- Responses were summarized descriptively.

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RESULTS

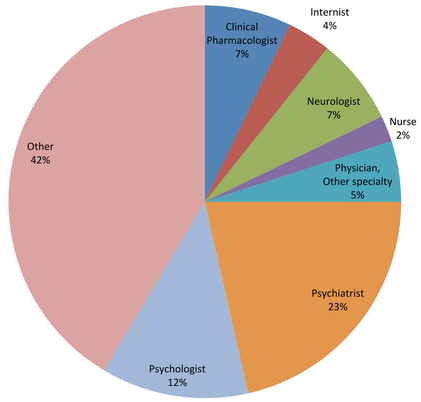
- A total of 132 responses from 50 different companies were collected for a response rate of 9.1%. Respondents with no involvement with the implementation of SIB assessments in clinical trials were excluded from further analysis, leaving a total of 89 evaluable responses representing 39 companies.
- A little over half of the respondents worked at large pharmaceutical companies (52%), with 35% from mid-sized, and 3% from small companies and/or biotechs.
- About 40% were physicians (23% psychiatrists); the majority (81%) worked in clinical development; and most had extensive experience in industry (60% >15 years) (Fig 1).
- Table 1 lists factors taken into account by sponsors in deciding whether to include prospective SIB assessments in clinical trials.
- Common CNS indications for which SIB monitoring was included are presented in Table 2. The most common non-CNS indications were fibromyalgia (41%) and insomnia or other sleep disorders (31%).
- Ninety-nine percent of respondents reported that SIB assessments were performed at both screening and baseline visits. The most common look-back periods at the screening visit were 1 month, 6 months, 1 year, and lifetime. At baseline the most common look-back interval was since the screening visit. (Table 3)
- A range of past time periods (from 1 month to lifetime) was used at screening to exclude subjects at risk of suicide.
- The majority of respondents (95%) reported utilizing the Columbia–Suicide Severity Rating Scale (C–SSRS)[4] and its IVR self-report version (eC-SSRS)[5]; 20% and 10%, respectively, reported using the Sheehan Suicide Tracking Scale (S-STS)[6] and the InterSePT Scale for Suicide Thinking (ISST)[7]. Some respondents reported using single suicide items from various scales (eg, HAM-D or MADRS). (Table 4)

Other sources of data used in the assessment of suicidal risk included information from the patient's family (73%), referring physician or medical care provider (64%), assisted living or nursing home staff (31%), and other informants such as friends or neighbors (12%). More than half of respondents (53%) also indicated that medical, psychiatric, and coroner records were used.

The majority of respondents indicated that subjects who report active SIB during the course of a clinical study are either (a) discontinued from the study and referred to a mental health professional for evaluation (44%), or (b) kept in the study and referred to a mental health professional for a risk assessment to determine if it were safe for the subject to continue in the study (53%). A small percentage of respondents (2 of 59, or 3%) indicated that subjects were discontinued from the study without a specific referral for further evaluation.

- About half of the respondents (53%) reported that their company prepared separate summaries for each study for SI and SB, while a third of respondents (33%) reported their company summarized SI and SB data together. A minority (8%) indicated their company did not have a standard approach for summarizing study level data.
- Forty percent of respondents reported that, in addition to prospective assessment of SIB, their company performed retrospective, post-hoc analyses of potential suicide-related adverse events, using computerized search of verbatim adverse event reports and submission of narratives for external adjudication.
- Major challenges for implementing SIB assessments faced by sponsors are presented in Table 5.

FIGURE 1: Training Background of Respondents



N=132
Other includes basic science, statistics, clinical pharmacology, pharmacy, social work, project management, regulatory affairs, and epidemiology.

TABLE 1: Factors Considered In Deciding If a Study Should Include SIB Assessments (N=83 respondents)*

	N	%
Psychiatric or neurologic drug product	79	95.2
CNS active compound	65	78.3
Disease under study	61	73.5
Regulatory announcements and policies	61	73.5
Patient population	59	71.1
Evidence of SIB for other drugs of the same class	45	54.2
CNS effects in Phase 1 trials	40	48.2
Adverse events indicative of SIB	39	47
Capacity of patient population to understand	36	43.4
CNS behavioral effects in animal studies	31	37.3
Type of study (eg, Phase 1 PK or single dose study)	31	37.3
Potential for indirect CNS effects	29	34.9
Background rates of SIB	22	26.5
Micro vs macro dosing study	9	10.8
Other	4	4.8

*Respondents were instructed to select all that apply.

TABLE 2: CNS Indications Including Prospective SIB Assessments in Clinical Trials (N=81 respondents)*

	N	%
Schizophrenia	64	79
Depression	61	75.3
Bipolar disorder	39	48.1
Alzheimer's disease or other dementia	36	44.4
Anxiety	34	42
ADHD	26	32.1
Pain	26	32.1
Mild Cognitive Impairment	20	24.7
Parkinson's Disease	16	19.8
Epilepsy	16	19.8
Autism	15	18.5
Multiple Sclerosis	9	11.1
Suicidal ideation and behavior	8	9.9
Alcoholism	7	8.6
Substance abuse	7	8.6
PTSD	7	8.6
Opioid dependence	5	6.2
Stroke	3	3.7
Amyotrophic Lateral Sclerosis	3	3.7
Traumatic Brain Injury	1	1.2
Other**	12	14.8

*Respondents were instructed to select all that apply.
** Other included Down's syndrome (2), migraine (3), binge eating (1), hypoactive sexual desire disorder (1)

TABLE 3: Look Back Periods Used at Screening and Baseline for SIB Assessment*

	Suicidal Ideation		Suicidal Behavior	
Screening Visit (N=73)	N	%	N	%
Lifetime	46	63.0	49	67.1
10 years	2	2.7	4	5.5
5 years	4	5.5	6	8.2
1 year	23	31.5	19	26.0
6 months	31	42.5	18	24.7
1 month	13	17.8	10	13.7
2 weeks	4	5.5	3	4.1
1 week	6	8.2	5	6.8
Other (SI and SB together)**	13	17.8		
	Suicidal Ideation		Suicidal Behavior	
Baseline Visit (N=72)	N	%	N	%
Lifetime	15	20.8	16	22.2
10 years	2	2.8	2	2.8
5 years	3	4.2	3	4.2
1 year	15	20.8	14	19.4
6 months	8	11.1	8	11.1
1 month	13	18.1	13	18.1
2 weeks	8	11.1	7	9.7
1 week	9	12.5	9	12.5
Other (SI and SB together)***	31	43.1		

*Respondents were instructed to select all that apply.
**Other text comments for Screening included: 15 years (1), 2 years (5), 2 months (1), varies depending on indication and study population (2), unsure (2), and since last visit (1).
*** Other text for Baseline included: since last visit (24), unsure (3), varies by study design (2), 2 months (1).

TABLE 4: SIB Assessment Instruments Employed for Screening, Baseline, and Tracking SIB in Clinical Trials (N=67)*

	Screening		Baseline		Tracking	
	N	%	N	%	N	%
Columbia Suicide Severity Rating Scale (C-SSRS)	64	95.5	64	95.5	63	94
IVR version of CSSRS (eC-SSRS)	12	17.9	12	17.9	12	17.9
Sheehan Suicide Tracking Scale (S-STS)	14	20.9	15	22.4	15	22.4
Suicidality module of the Mini Neuropsychiatric Interview	15	22.4	7	10.4	6	9
Concise Health Risk Tracking – Clinician Rating (CHRT-T)	0	0	1	1.5	1	1.5
Concise Health Risk Tracking – Self Rating (CHRT-SR)	0	0	1	1.5	1	1.5
InterSept Scale for Suicide Thinking (ISST)	7	10.4	7	10.4	7	10.4
InterSept Scale for Suicide Thinking – Plus (ISSTPlus)	4	6	4	6	4	6
Beck Scale for Suicide Ideation	3	4.5	4	6	3	4.5
Suicide Behaviors Questionnaire	2	2.9	0	0	0	0
Paykel Suicide Scale	0	0	0	0	0	0
Suicide item of the HAM-D	18	26.9	18	26.9	17	25.4
Suicide item of the MADRS	20	29.9	21	31.3	21	31.3
Suicide item of the PHQ-9	5	7.5	4	6	5	7.5
Suicide item of the IDS/QIDS	5	7.5	6	9	7	10.4
Suicide item of the CDRS	3	4.5	3	4.5	4	6
Don't Know	1	1.5	0	0	0	0
Other**	7	10.4				

*Respondents were instructed to select all that apply.
** Includes screening, baseline, and tracking.

TABLE 5: Challenges Encountered in Implementing SIB Assessments in Clinical Trials (N=57 respondents)*

	N	%
Cross-cultural differences in acceptance of SIB assessments	23	40.4
Site difficulty in obtaining adequate baseline history	21	36.8
Translations of SIB rating instruments into relevant language	20	35.1
Investigator/rater discomfort with asking about SIB	18	31.6
Inadequate training of raters to administer SIB ratings	17	29.8
SIB assessment instrument version control	16	28.1
Having to exclude or discontinue people when they report SIB	14	24.6
Site not prepared to handle suicidal patients	11	19.3
Investigator/rater discomfort with managing SIB	10	17.5
Site difficulties referring patients who report SIB for mental health evaluations	10	17.5
Failure of sites to respond to positive reports of SIB by study subjects (ie, continuing subject in the study when subject should have been excluded)	8	14
Patient resistance to responding to questions about SIB	7	12.3

*Respondents were instructed to select all that apply.

LIMITATIONS

- Limitations of the study included relatively low survey response rate and the possibility that there were multiple respondents from the same sponsor. Also, due to the wording of some questions, it was not possible to tell if responses referred to past or current practices.

CONCLUSIONS

- The results of this survey of pharmaceutical companies confirm that prospective assessment of SIB has been incorporated in industry sponsored clinical trials across a wide range of CNS and non-CNS indications.
- In line with the FDA's objective that subjects with SIB receive appropriate treatment, nearly all respondents reported that subjects who develop SIB during clinical trials are referred to a mental health professional for follow up.
- The most common SIB assessment instrument used is the C-SSRS, although other instruments such as the S-STS and the ISST are also used.
- Supplemental identification of suicide-related information by study sponsors remains common, and challenges remain regarding standardization of retrospective assessment timeframes and differing approaches to summarizing and analyzing SIB-related study data.
- Taken together, these results suggest that inconsistent reports of SIB within study datasets may occur and that integration of data across studies remains a concern.

REFERENCES

[1] Guidance for Industry: Suicidality: Prospective Assessment of Occurrence in Clinical Trials. U.S. Department of Health and Human Services. Food and Drug Administration Center for Drug Evaluation and Research (CDER), Division of Psychiatry Products, August 2010.

[2] Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. U.S. Department of Health and Human Services. Food and Drug Administration Center for Drug Evaluation and Research (CDER), Division of Psychiatry Products, August 2012.

[3] Stewart M, Butler A, Alphs L, Chappell PB, Feltner DE, Lenderking WR, et al. Study site experiences and attitudes towards prospective assessments of suicidal ideation and behavior in clinical trials: Results of an internet-based survey. Innov Clin Neurosci 2013:10(5-6 Suppl A):20S-28S.

[4] Posner, K, GK Brown, B Stanley et al., 2011, The Columbia-Suicide Severity Rating Scale (C¬ SSRS): Internal Validity and Internal Consistency Findings From Three Multi-Site Studies With Adolescents and Adults, Am J Psychiatry, 168:1266-1277.

[5] Mundt JC, Greist JH, Jefferson JW, Federico M, Mann JJ, Posner K. Prediction of suicidal behavior in clinical research by lifetime suicidal ideation and behavior ascertained by the electronic Columbia-Suicide Severity Rating Scale. J Clin Psychiatry 2013 Sep;74(9):887-93.

[6] Coric V, Stock EG, Pultz J, Marcus R, Sheehan DV. Sheehan Suicidality Tracking Scale (Sheehan-STS): Preliminary Results from a Multicenter Clinical Trial in Generalized Anxiety Disorder. Psychiatry (Edgmont). 2009 Jan;6(1):26-31.

[7] Lindenmayer JP, Czobor P, Alphs L, Nathan AM, Anand R, Islam Z, Chou JC. InterSePT Study Group. The InterSePT Scale for Suicidal Thinking reliability and validity. Schizophr Res. 2003; 63:161-70.

DISCLOSURE: ISCTM supported the implementation of the survey with staff time and funding; the affiliations of all authors are given above; the authors report no other conflicts of interest.

Poster presentation at the 10th Anniversary ISCTM Meeting held in Washington, DC, 18-20 February 2014.