Chapter 3
Treatment Emergent Suicidal Ideation and Behavior

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Abstract The concept of treatment emergent suicidality during clinical trials has been a subject of regulatory and research interest, especially since the early 1990s. A key series of analyses have shaped the regulatory environment for expectations of prospective assessment of suicidal ideation and behavior (SIB) in clinical trials. The development of a scale for prospective assessment of these events has been a key priority in order to detect emergent signs during the course of a clinical trial and to assist in patient selection criteria of suicide risk. The maturing regulatory environment and increasing evolution in thinking on definitions of SIB have underpinned significant changes in the main assessment scale, the Columbia Suicide Severity Rating Scale (C-SSRS), as well as in the standard adopted by the FDA for coding, summarizing, and analyzing SIB data, the Columbia Classification Algorithm for Suicide Assessment (C-CASA). For new drugs undergoing clinical development, assessment of SIB is incorporated into benefit/risk decision-making and continuing risk management approaches throughout the pharmaceutical industry and academia. A number of companies have developed internal guidances, which may include quantitative decision-criteria (i.e., based on binding data at CNS targets) or qualitative clinical judgment (i.e., based on mechanistic understanding

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and emerging safety profiles) of drug candidates that may require the inclusion of prospective SIB tools. In this chapter, we will provide an overview of the regulatory history surrounding treatment emergent SIB and will outline a number of structured qualitative steps for prospective SIB assessment.

3.1 Introduction

The detection of treatment emergent suicidal ideation and behavior (SIB) during clinical trials has been a subject of interest for researchers and regulators alike since the early 1990s with the controversial possibility that antidepressants might paradoxically contribute to the risk of suicide ideation (i.e., suicidal thinking) and suicidal behavior (i.e., suicide attempts, preparatory behaviors or suicide completions).

Research into suicide is fraught with methodological problems, including lack of definition and clarity. The problem of definition has been complicated by the use of the term "suicidality", which lumps together suicidal ideation, self-injurious behavior, suicide attempts, and completed suicide despite their very different consequences to the patient. The general term suicidality is not considered to be adequately specific or as clinically useful as more precise terminology (ideation, behavior, attempts, and suicide). In addition, epidemiological findings suggest that suicidal ideation is not a strong predictor of a suicide attempt, although approximately one-third of those who think about suicide at some point in their lives later make a suicide attempt (Nock et al. 2009a, b). Furthermore, psychological autopsy studies have found frequent expression of suicidal thoughts before completed suicide, with one meta-analysis showing 50–66 % of people who complete suicide have disclosed their ideation or intent to those around them (Cavanagh et al. 2003).

The use of more precise terms to describe SIB has now emerged following expert working groups, systematic historical clinical trial analyses, clinical trial methodology workshops and discussion with regulatory authorities. SIB refers to suicidal behavior (completed suicide, suicide attempts, interrupted attempts, aborted attempts, and preparatory acts toward imminent suicide) and suicidal ideation (active and passive). Suicidal behavior must be distinguished from self-injurious acts or behaviors without suicidal intent that may actually be a mechanism to gain attention and/or attempts to manipulate the environment.

The development of a scale for prospective assessment of these events has been a key priority in order to detect emergent signs during the course of a clinical trial and to assist in patient selection criteria of suicide risk. While it is important for prospective risk assessment to include specific focused questions on suicidal ideation, narrowing the time period for this has been the subject of methodological discussion. The expression of suicidal ideation and threats is relatively common. Therefore, it is difficult to identify the small percentage of a large number of ideators who will progress to a suicide attempt. Narrowing down the timeframe to

the past 12 months is one way to ensure better identification of those ideators who may subsequently be at greater risk of suicide attempt (Nock et al. 2009a).

In addition to considering the specific manifestations of SIB, it is important to recognize that there are other risk factors that influence the risk of suicide. There is no clearly defined combination of risk factors that has sufficient sensitivity and specificity to predict who among a group at risk will make an attempt or completion, or the circumstances or timing of this (Goodwin and Jamison 2007), as there are a number of general, chronic, and short-term risk factors for suicide. Interestingly, and somewhat surprisingly, subjects with depression and suicidal ideation, although a risk group, are not the leading group at risk for progression to a suicide attempt. Ideators with anxiety or impulse control disorders (i.e., conduct disorder and post-traumatic stress disorder, PTSD) showed a higher likelihood, or predictive power, for making a suicide attempt as reported in the National Comorbidity Survey Replication in US adults (Nock et al. 2009a, b). An anxiety disorder is an independent risk factor for suicidal ideation and suicide attempts. Comorbid anxiety and mood disorders have been shown to further increase the risk compared with a mood disorder alone (Sareen et al. 2005).

There have been a key series of analyses of drug classes that have shaped the development of scales, in particular, the Columbia scale and algorithm and the regulatory expectation of its broad application across many clinical trials. The most prominent of these are the meta-analyses of antidepressant clinical trial data that underpinned the FDA's conclusions that: (1) the risk of SIB was greatest among children and adolescents taking antidepressants versus placebo OR = 2.2 (95 % CI 1.4 − 3.6), followed by young adults aged 18–24 OR = 1.55 (95 % CI 0.91 − 2.7), and the risk appears to go down with age (e.g., ages 25–30, OR = 1.00; ages 31–64, OR = 0.77; ages 65+, OR = 0.39); and (2) the risk of suicidality was stronger for non-depressed psychiatric patients as compared with depressed ones. (Institute of Medicine 2010; Hammad et al. 2006; Stone et al. 2009). This latter finding led to ramifications for antidepressant and other centrally acting medicines, especially in indications other than depression. Other post hoc analyses have indicated that antiepileptic drugs (AEDs) might also increase suicide risk (FDA analysis 2008; Pompili and Tatarelli 2010; Pompili et al. 2010). Several recent studies, however, have yielded inconsistent findings in relation to risks with specific AEDs, nevertheless levetiracetam, lamotrigine, and topiramate were among the top three anticonvulsants associated with the highest observed risk of suicidal behaviors in at least two of the six reported analyses (FDA analysis 2008; Gibbons et al. 2009; Andersohn et al. 2010; Van Cott et al. 2010; Patorno et al. 2010; Olesen et al. 2010). Most of the studies as well as epidemiological studies identify psychiatric comorbidities in epilepsy as important factors that increase the propensity toward suicide and suicidal behaviors (Arana et al. 2010; Pompili and Baldessarini 2010).

In addition to the regulatory and clinical focus on identifying suicidal ideation associated with antidepressant use, research has been ongoing into potential genetic markers of susceptibility to treatment emergent suicidal ideation (TESI). Although family and twin studies have been conducted and have estimated the heritability of suicidal behavior to be 30–55 % (Brent and Mann 2005; Statham et al. 1998), no

such formal evidence has been established for TESI, probably due to the rareness and transience of the event that cannot be assessed by the usual genetic epidemiological methods. A genetic influence on this trait could be likely, based on a number of reports about the association of TESI with genetic markers (Brent et al. 2010; Perroud 2011). Two genome wide association studies (GWAS) have identified association between genetic variants and emergent or worsening suicidal ideation upon antidepressant treatment. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, variants in the genetic loci encoding papilin and the IL-28 α-receptor were identified (Laje et al. 2009). In the Genome-Based Therapeutic Drugs for Depression (GENDEP) study, a genetic marker in the vicinity of the *guanine deaminase* (*GDA*) gene has been associated with emergent or worsening of suicidal ideation (Perroud et al. 2012). In a recent GWAS study that investigated associations between TESI and single nucleotide polymorphisms (SNPs) in a naturalistic pharmacogenetic study of patients with depressive disorder, a subset of 14 SNPs were associated with TESI and had supportive genetic evidence (Menke et al. 2012). Of these, nine variants were located in or nearby genes previously linked to bipolar disorder (*RHEB*, *TMEM138* and *CYBASC3*) and one variant in a gene also associated with schizophrenia and neurodegeneration (*PIK3C3*). Despite the limited sample size, the results from this GWAS study suggest that genetic markers may be used as tools to identify patients at risk of TESI in the future.

3.2 Historical Perspectives and Regulatory History

Assessment of SIB in clinical trials continues to be an area of active regulatory concern. Reviewing the US regulatory history is important to put into context the current guidance for prospective assessment of SIB in clinical trials. The maturing regulatory environment and increasing evolution in thinking on definitions of SIB have underpinned significant changes in the main assessment scale, the C-SSRS, as well as in the standard adopted by the FDA for coding, summarizing and analyzing SIB data, the C-CASA.

While a number of global regulatory authorities have expressed interest in the prospective assessment of SIB in clinical trials, few other than the FDA have provided specific guidance on assessment tools and expectations for industry. The FDA issued a number of communications pertaining to the risk of SIB with individual drugs or classes of drugs via post-marketing safety updates. Thus, the regulatory history provides a useful background to the current global landscape and recommendations in the FDA Guidance document, as discussed below (see Fig. 3.1).

European Regulators were the first to post restrictions on the use of antidepressants. In 2003, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) initiated urgent safety restrictions to contraindicate the use of selective serotonin reuptake inhibitor (SSRI) antidepressants, with the exception of

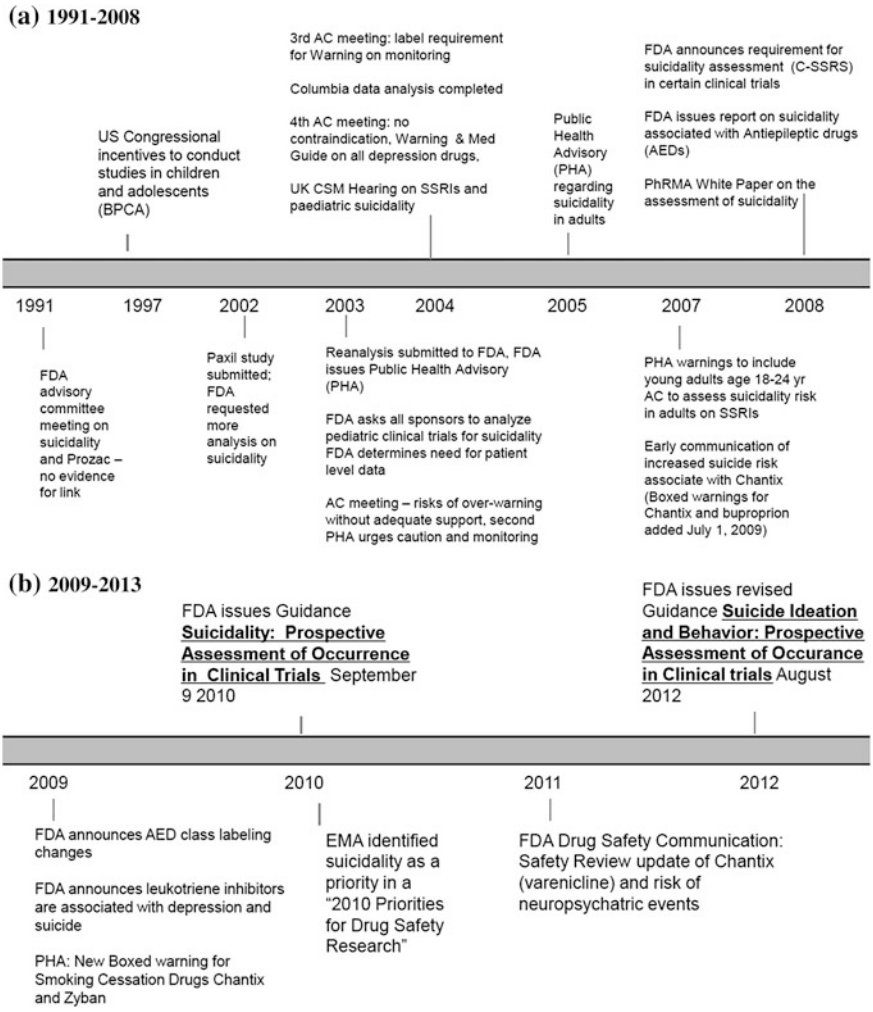

Fig. 3.1 Regulatory history and perspectives on SIB assessment. **a** 1991–2008 **b** 2009–2013

fluoxetine, in children and adolescents. This had followed comprehensive reviews of pediatric depression clinical trial data by the Committee on Safety of Medicines (CSM). The MHRA stated that "on the basis of this review of the available clinical trial data, CSM has advised that the balance of risks and benefits for the treatment of major depressive disorder (MDD) in under 18s is judged to be unfavorable for sertraline, citalopram, and escitalopram, and is unassessable for fluvoxamine. Only fluoxetine (Prozac) has been shown in clinical trials to have a favorable balance of risks and benefits for the treatment of MDD in the under 18s" (MHRA 2003).

Subsequently in 2004, after lengthy analysis and review of clinical trial data, FDA required that labeling of specific antidepressants carry black box warnings,

intended to alert healthcare providers and patients to increase monitoring of troubling symptoms. At the time of these regulatory actions, many public health and mental health professionals (MHPs) were concerned that deterring the prescription of antidepressants might lead to undertreatment of depression and in turn to an increase in suicide rates for untreated MDD. Two published studies highlighted this concern, indicating that between 2003 and 2005 in the US there was a 20 % reduction in prescription of antidepressants and, at the same time from 2003 to 2004, an increase in youth suicide rate by 14 % (Gibbons et al. 2007) and new diagnoses of depression in pediatric populations dropped by 44 % (Libby et al. 2009). In addition, previous pharmacoepidemiologic studies had reported that adolescent suicide rates had declined in the early 1990s, related to increasing use of antidepressant drugs in this population (Fergusson et al. 2000, 2005; Gibbons et al. 2006; Olfson et al. 2003; Sondergard et al. 2006; Simon 2006; Valuck et al. 2007).

Subsequent to the regulatory reviews of antidepressant medication, TESI was the focus of further analyses for other classes of centrally acting drugs, particularly anticonvulsants, antipsychotics, and anxiolytics. These analyses resulted in a number of regulatory labeling changes and/or risk management actions as a result (see Table 3.1 for further details). Risk management actions typically focus on ensuring appropriate warnings and wording are reflected in patient materials, such as medication guides, as well as the physician prescribing information. Not all warning language in the product information includes both SIB. For example, product information for Strattera (atomoxetine) described suicidal ideation risks. While a number of the regulatory analyses and reviews were conducted as class reviews (e.g., antidepressants, antiepileptic drugs), not all assessments of SIB relied on data from across compounds (e.g., Strattera is the only ADHD medication with specific warning language for suicidal ideation). A consistent feature across the product labeling for compounds (Table 3.1) is the inclusion of other psychiatric symptoms that may be associated with increased risk of SIB, including mood disturbances, anxiety and/or disturbing thoughts. In addition, recent labeling inclusions for antidepressants have referenced a lowering of suicidal risk in the >65-year age group, based on reviews showing lowered relative risk of events in this age group.

3.3 US Regulatory Guidance on SIB

The result of the regulatory focus on SIB is the need to implement prospective assessment for treatment emergent SIB in clinical trials for CNS-active medicines. In addition, the same assessment tools can be used to measure prior history of suicidal ideation or behavior, and the implementation of other psychiatric screening tools are helpful to elucidate current or history of psychiatric comorbidities.

The FDA's first draft guidance document, entitled "Suicidality: Prospective Assessment of Occurrence in Clinical Trials" was issued in September 2010. The main rationale for this document was to "Ensure patients who are experiencing suicidality are properly recognized and adequately treated." In addition, the

Table 3.1 Summary of labeling changes for FDA reviews of different medication classes for suicidal ideation and behavior (as of March 2011)

Drug class	Drugs	Class labeling	Black box	Warnings	REMS	Med guide	Comments
Antidepressants		√	√	√		√	Black box—suicidality and antidepressants
							Children, adolescents, young adults
							Reduction in risk in 65+ years
Antiepileptics		√		√		√[a]	Warnings and precautions—suicidal behavior or ideation; antiepileptic drugs increase the risk of suicidal thoughts
ADHD							
	Strattera		√	√		√	Black box—suicidal ideation: children or adolescents
							Wording also in patient counseling info
	other stimulants					√	No focused language for suicidality
Antipsychotics (depression)							
	Abilify, Seroquel		√	√		√	Black box—suicidal thinking and behavior: children, adolescents, young adults
Smoking cessation							
	Chantix, Zyban		√	√	√	√	Black box—suicide ideation, suicide attempt and completed suicide reported in patients
Leukotriene inhibitors							
	Singulair			√			Suicidal thinking and behavior (including suicide)
	Accolate, Zyflo						Warnings for neuropsychiatric events *not* suicide

(continued)

Table 3.1 (continued)

Drug class	Drugs	Class labeling	Black box	Warnings	REMS	Med guide	Comments
Sedative/hypnotics							
	Lunesta	√		√		√	Suicidal thoughts and actions (including completed suicides)
							Also in dosing section
	Ambien	√		√		√	Suicidal thoughts and actions (including completed suicides)
							Warning in special populations (depressed patients)
	Ativan	√					Precaution and AE section
Acne							
	Accutane			√			Suicidal ideation, suicide attempts, suicide
							Patient informed consent for suicidal thoughts, suicide attempts, suicide
Other indications							
GERD	Reglan			√		√	Based on post-marketing events
							Warnings/CNS effects: suicidal ideation and suicide
Huntington's disease	Xenazine		√		√	√	Clinical trial events including completed suicide
Multiple sclerosis	Interferons	√		√			Suicidality based on post-marketing events

[a] *Note* in 2009 communication, all AEDs should have MedGuide, as of 1 Apr 2011, this has not occurred

guidance was intended to "Ensure collection of more timely and more complete data on suicidality to better detect increased suicidality in individual studies and in pooled analyses. This is important whether or not a particular drug is known to be associated with treatment-emergent SIB." Subsequently, in August 2012, the FDA issued a revised draft guidance document, entitled "SIB: Prospective Assessment of Occurrence in Clinical Trials". The revised FDA guidance reflects the FDA's current thinking on the importance of assessment of SIB in psychiatric and non-psychiatric drug trials conducted under Investigational New Drugs (INDs) and general principles for how best to accomplish SIB assessment in drug development.

The major revisions in the FDA's revised draft guidance of August 2012 include the following:

- The term *suicidality* is replaced with the phrase *suicidal ideation and behavior.*
- An expanded set of the C-CASA categories is provided, along with definitions and explanations.
- The advice on particular trials and patients that would need assessments of SIB and the timing of such assessments is revised.
- Concerns about the time burden of assessments are addressed.
- Questions about the possible value of the assessments providing protection for patients in the trials themselves are discussed.
- It is made clear that use of an assessment instrument that directly classifies relevant thoughts and behaviors into C-CASA categories eliminates the need for any additional coding.
- Additional advice on evaluation of alternative instruments is provided.

The scope of the revised FDA draft guidance encompasses both psychiatric and neurologic drugs as well as drugs for nonpsychiatric indications (e.g., isotretinoins, other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss). The revised FDA draft guidance was adopted by the Division of Psychiatry Products, and the Division of Neurologic Products. It is anticipated that the draft guidance will become the standard approach for other FDA divisions as well [such as the Division of Pulmonary, Allergy and Rheumatology Products (with regard, especially, to leukotriene-modifying drugs)]. It is unclear when the 2012 draft guidance will be finalized.

3.4 The Columbia Suicide Severity Rating Scale

The 2010 draft FDA guidance recommended the use of a particular SIB assessment, the C-SSRS. This instrument was designed to be used prospectively in clinical trials and was intended to systematically ascertain and document the occurrence of suicidal events. These events were defined as indicative of SIB based on the use of the retrospective tool, the C-CASA (Posner 2009; see Table 3.2). The C-CASA was developed by Kelly Posner and her team at Columbia University. C-CASA

Table 3.2 C-CASA classification scheme from 2010 FDA guidance

Events	2010 C-CASA classification
Suicidal	1 Completed suicide
	2 Suicide attempt
	3 Preparatory actions toward imminent suicidal behavior (including interrupted attempt or aborted attempt)
	4 Suicidal ideation
Indeterminate	5 Self-injurious behavior with unknown intent: (suicidal or non-suicidal self-injurious behavior)
	6/9 Not enough information: (suicidal or "other") 6 Death 9 Non-death
Non-suicidal	7 Self-injurious behavior without suicidal intent
	8 Other: accidental, psychiatric, medical

Note Light gray boxes were FDA "primary analysis" (includes events deemed suicidal): *light and dark boxes* were FDA "sensitivity analysis" (includes any event that could possibly be suicidal)

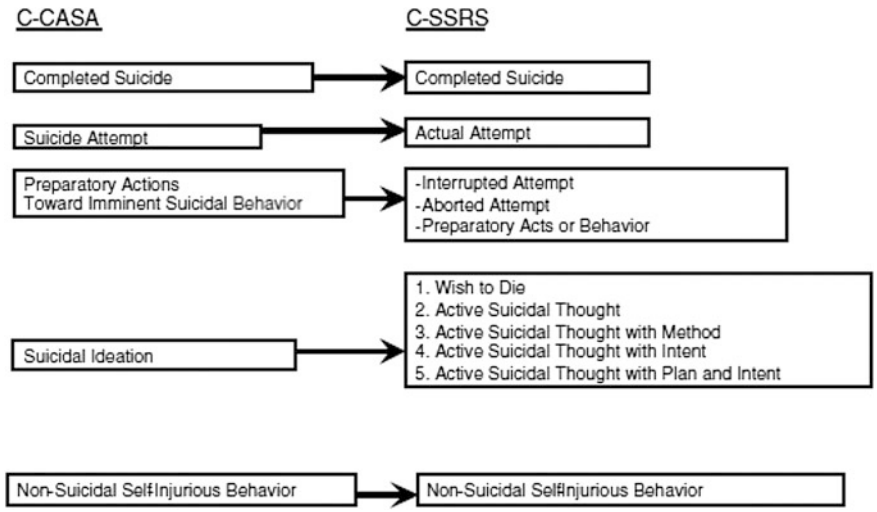

Fig. 3.2 C-SSRS and C-CASA mapping per Posner (2009)

provided a common language to classify SIB data derived from retrospective examination of clinical trial submitted to FDA.

C-CASA is the retrospective counterpart of the more detailed prospective classification instrument, the C-SSRS. It contains a 1–5 numerical rating scale for suicidal ideation of increasing severity (from a "wish list to die" to an "active thought of killing oneself with plan and intent"). By contrast, the C-CASA in the 2010 FDA guidance only had one ideation item (classification 4). How the C-CASA and C-SSRS mapping is done is shown in Fig. 3.2.

The 2012 revision continues to emphasize the use of the C-SSRS and highlights that it classifies SIB events directly to the 11 expanded C-CASA categories without the need for additional narratives or coding. This direct classification of events is viewed by the FDA as one of the C-SSRS's strengths.

The standard adopted by the FDA for coding, summarizing and analyzing SIB data in the 2012 revision of the draft guidance is an expanded version of the C-CASA. This version has 11 categories in total: 5 for suicidal ideation, 5 for suicidal behavior, and 1 for self-injurious behavior with no suicidal intent. Data collected for assessment (whether retrospectively or prospectively) must be classified into these 11 categories as defined by the FDA (see Table 3.3 for a listing of the categories).

The revised draft FDA guidance does state that other appropriate prospective SIB assessments can be used and instructs sponsors to discuss proposed alternatives with the relevant review division prior to implementing them. For example, the FDA's view of the Sheehan Suicide Tracking Scale (S-STS) and in particular its ability to classify SIB events into the 11 expanded C-CASA categories, is not clear at this time.

Table 3.3 Revised guideline (2012) suicidal ideation and behavior events and categories[a]

Category	Event
Suicidal ideation	
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	
1	Completed suicide
2	Suicide attempt
3	Interrupted attempt
4	Aborted attempt
5	Preparatory actions toward imminent suicidal behaviors
Self-injurious behavior, no suicidal intent	Self-injurious behavior, no suicidal intent

[a] From the revised FDA Guidance (August 2012): "according to the C-SSRS, the definition of plan includes intent (i.e., intent to complete suicide is implicit with the concept of plan). Thus, there is no need for the category *method and plan, but no intent.*"

3.5 European Regulatory Guidance

Unlike the FDA, the European Medicines Agency (EMA) has not yet produced a guidance document specific to assessing SIB in clinical trials. However, in 2010, the EMA identified SIB as a priority in a "2010 Priorities for Drug Safety Research" paper calling for increased research into suicide research methodologies (Issued 4 August 2009). Of particular interest in this paper, are methods to separate suicide associated with certain diseases from treatment for those diseases. In addition, SIB was incorporated into disease specific guidances as part of underlying disease as well as the risk assessment thereof. Disease-specific guidances that encompass suicidal ideation and behaviour include those for: Alcohol dependence, Attention Deficit Hyperactivity Disorder, Depression, Epileptic Disorders, Multiple Sclerosis, Obsessive Compulsive Disorder, Panic Disorder, Post Traumatic Stress Disorder, and Treatment of Smoking. The most recently issued guidances include a statement that C-CASA is an available tool that can be used in these assessments, although there is no explicit expectation to use this tool. Many European clinical trial investigators are familiar with use of the MINI neuropsychiatric interview for assessment of suicide risk at baseline, and have used depression scale suicide-specific items/questions for detection of suicidal symptoms. There is growing familiarity with the use of C-SSRS in global clinical trials, although the construct of the scale is still thought to be very US-centric. Product labels in Europe incorporate similar warning language in the *Special Precautions and Warnings for Use* section

of the Summary of Product Characteristics for all of the products with suicidality warning in the US Product Information.

3.6 Impact of FDA Guidance on Clinical Trials

For new drugs undergoing clinical development, assessment of SIB is incorporated into benefit/risk decision-making and continuing risk management approaches throughout the pharmaceutical industry and academia. A number of companies have developed internal guidances, which may include quantitative decision-criteria (i.e., based on binding data at CNS targets) or qualitative clinical judgment (i.e., based on mechanistic understanding and emerging safety profiles) of drug candidates that may require the inclusion of prospective SIB tools. In this section, we will outline a number of structured qualitative steps that are common throughout most large pharmaceutical companies.

Based on the 2012 revision of the FDA guidance, trials conducted under an IND in the following specific categories should address plans for SIB monitoring:

- *CNS Drug Candidates*:
  Prospective SIB assessments should be carried out in all inpatient and outpatient clinical trials involving any drug being developed for a psychiatric indication (i.e., those indications managed in the Division of Psychiatry Products), as well as for all antiepileptic drugs and other neurologic drugs with CNS activity. These trials include multiple-dose Phase 1 trials involving healthy volunteers. Questions on what constitutes CNS activity can be directed to the Division of Neurology Products, although some companies make this decision based on CNS clinical signs in preclinical studies, evidence of or expected brain penetration, as well as functional pharmacological data on typical CNS target receptors, ion channels, or transporters (typically through in vitro profiling).
- *Non-CNS drug Candidates*:
  Although prospective SIB assessments are not required for compounds/drugs that do not have overt CNS effects, there are some types of trials in this category for which the draft FDA guidance recommends that prospective SIB assessments be performed. This includes all clinical trials for drugs that are pharmacologically similar to drugs where possible signals of risk for SIB have been identified, including isotretinoin and other tretinoins, beta blockers (especially those entering the brain), reserpine, drugs for smoking cessation, and drugs for weight loss.

Leukotriene-modifying drugs are not explicitly discussed in the August 2012 Guidance; however, emerging regulatory intelligence for similar agents suggests that there is an expectation by the Division of Pulmonary, Allergy, and Rheumatology Products for inclusion of SIB assessment with agents acting in the leukotriene pathway.

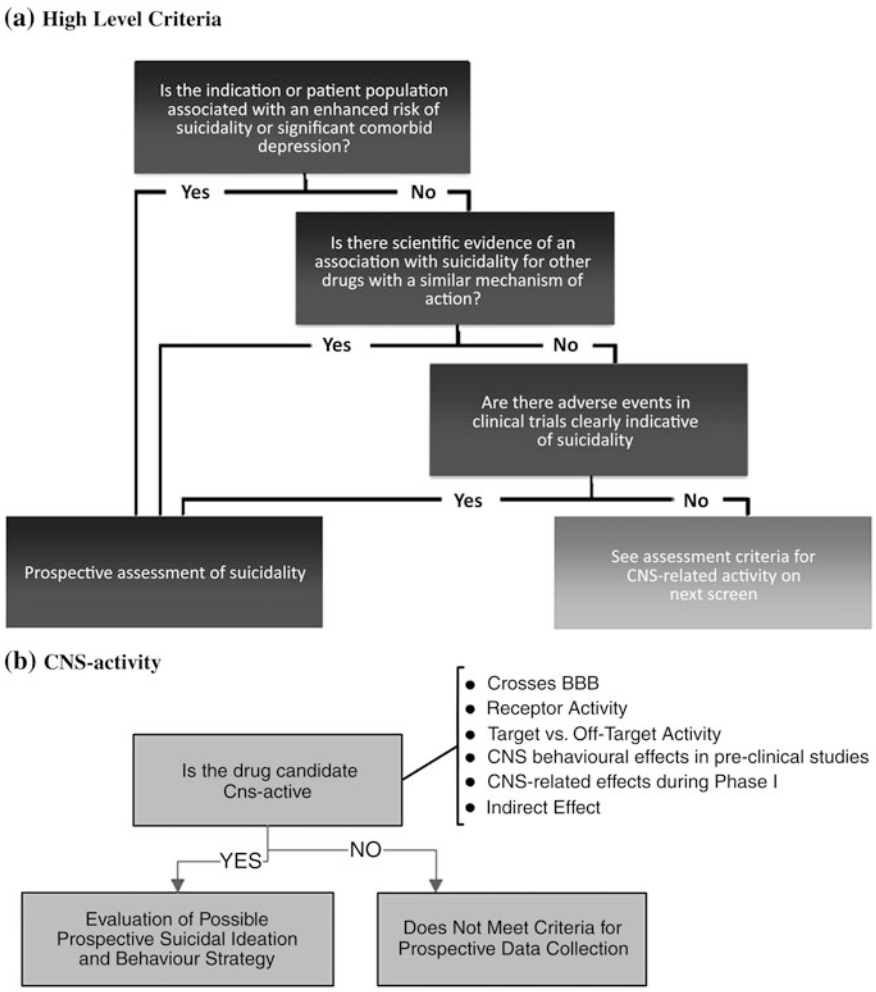

Fig. 3.3 Structured criteria for inclusion of SIB assessment in clinical trials **a** High level criteria. **b** CNS-activity

In addition to mechanistic assessment of new treatments under development, the underlying disease under study and patient population specific considerations need to be taken into account when evaluating prospective SIB assessment. In particular, if the intended indication is one in which the background rate of SIB is considered to be elevated compared with the general population, or if patients have overlapping comorbidity with mood and/or anxiety disorders, then prospective assessment of SIB is recommended. Figure 3.3 outlines a high level structured decision tree for evaluation of SIB in clinical trials.

Besides the C-SSRS or alternative structured SIB assessment tool, collection of narratives can also add valuable information, especially if there are additional notes

from MHP referral in response to the C-SSRS questions. A pre-planned Safety Narrative Plan for a trial should describe what events will require a narrative for the clinical study report and consideration should be made for events associated with SIB. Information for the narrative should be obtained from screening and baseline evaluations, data collected during the subject's participation in the trial and any MHP assessments. For drug candidates for which a medically significant SIB concern has not been identified, treatment emergent SIB adverse events that are spontaneously reported should have additional information collected at the time the event is reported to facilitate retrospective coding to C-CASA, if required. The following information is useful to obtain in a Narrative Guide to facilitate supplementary data collection and to help understand full details of a patient's risk for SIB.

Adverse events that may trigger a SIB narrative:

- Suicidal ideation
- Suicidal behaviors and gestures, including preparatory acts for suicide and actual attempts
- Self-injurious behavior or injury
- Completed suicides
- Adverse events that might initially appear accidental or unrelated to SIB, but could potentially have suicidal/self-injurious intent (Overdose, Poisoning, Intoxication, Motor vehicle accidents, Cuts/lacerations, Burns, Gunshot injuries)
- Other Deaths (drowning, asphyxiation/suffocation, etc.)
- Potential SIB-related adverse events or other clinical observations may, based on the judgment of the investigator, trigger a narrative. Suicidal Ideation

Supplemental data to collect for a SIB narrative:

- Suicidal Ideation
  - *Passive* ideation ("wish to be dead"; thoughts of wanting to be dead without plan or intent)
  - *Nonspecific* suicidal thoughts (general thoughts of killing oneself without actual intent or plan)
  - *Active* suicidal ideation (thoughts of killing oneself with actual plan and intent)
- Suicidal Behavior
  - Were there any *preparatory* acts? (Steps toward suicide such as buying a gun, hoarding medications)
  - Was there an *actual attempt*? (Including attempts stopped by the subject or interrupted by someone else)
  - Was there evidence that the patient *intended* to die by his/her behaviors? (Putting affairs in order, giving away personal possessions, writing a note)
- Was there *self-injurious* behavior without suicidal intent? (e.g., manipulative gesture)
- Was the event or behavior due to an underlying psychiatric condition?

- Was the event or behavior due to an accident or underlying medical condition?
- If a Completed Suicide
  - How and where did the patient kill himself/herself?
  - How was the patient discovered and by whom?
  - Did the patient leave a note?
  - Did the patient make or relay active plans or preparations? Were there any warning signs?
  - Was a triggering event identified?
  - Did the patient overdose on study drug?
- Did the event occur in the context of any of the following: Symptoms of depression, mania, psychosis, Drug or alcohol abuse

Useful information to determine relevant risk factors:

- Social*/family stressors
- School/academic stressors (e.g., failing classes, lack of peer acceptance)
- Drug/alcohol use by subject
- Physical or sexual abuse
- Traumatic personal event—specify
- Depressed mood/despair/hopelessness
- Severe psychotic symptoms (e.g., command voices, guilt delusions)
- Comorbidity (physical or mental)
- (*Social stressors might include separation, bereavement, moving house, financial, legal, medical, unemployment, housing, dependents, workplace stress)
- Is there a history of *previous* suicidal ideation/plans or attempts?
- Previous suicidal ideation or plans
- Previous suicidal attempts or behaviors
- Is there a history of *previous* deliberate self-injurious behaviors
- Is there a family history of suicide ideation/plans/behaviors or completed suicide?
- Is there a family history of psychiatric illness, substance or alcohol abuse/dependence?

Is there any previous psychiatric history in the subject and/or family not documented above?

3.6.1 Phase 1 Studies

The FDA Guidance (August 2012) specifies that in multiple dose inpatient Phase 1 studies, the SIB assessment should be completed at any visit where a symptom assessment (scheduled or unscheduled) is conducted, but is not necessary when non

symptom assessments are performed (e.g., vital signs). For multiple dose studies with dosing periods longer than 1-week in duration, it is helpful to extend the SIB assessment to be administered at least weekly while the subject is being dosed. The SIB assessment can also be administered at the discretion of the investigator, based on any reasonable concern, at any time during the study.

According to the revised FDA Guidance (August 2012), it is no longer necessary to perform prospective SIB assessments in Phase 1 single dose trials in healthy volunteers or in microdose trials (i.e., using doses that are not expected to have a measurable pharmacological effect). However, SIB adverse events that are spontaneously reported in this category of trials should have additional information collected at the time the event is reported (see above narrative guide insets).

If a positive finding suggestive of SIB is detected in a Phase 1 study, an SIB risk assessment (by a qualified mental health professional) should be completed within a clinically reasonable timeframe as determined by the study principle investigator, taking into account the severity of the finding and subject history.

3.6.2 SIB Assessment in Phase 2/3 Blinded, Controlled Trials

This section will focus on the use of screening instruments to exclude or assess the baseline risk of subjects entering in psychiatric and neurologic clinical trials, and the detection of potential treatment emergent SIB. A number of scales in addition to the required C-SSRS assessment are often implemented by many companies conducting clinical studies. As the C-SSRS is a clinician-administered scale, it is often helpful to balance this with self-rated instruments or other instruments that assess psychiatric comorbidity also.

3.6.3 Selection and Screening Instruments: Psychiatric Trials

Studies of adult subjects with psychiatric indications are now expected to include the C-SSRS, and many companies also include a self-rated instrument such as the Suicidal Behaviors Questionnaire-Revised (SBQ-R; Osman et al. 2001) at the screening visit to detect possible SIB. In typical practice, a risk assessment is required by a qualified MHP to assess whether it is safe for the subject to participate in the trial if the subject's responses on any of the screening instruments indicate: (1) the subject may have had suicidal ideation associated with actual intent and a method or plan in the past year, (2) any history of suicidal behavior in the past 5 years, (3) any lifetime history of serious or recurrent SIB, (4) the subject meets criteria on the SBQ-R (i.e., total score ≥ 8), or (5) in the investigator's judgment a risk assessment is required. (The recommended look-back period for suicidal

behavior is 5 years; however, a longer look-back period may need to be used dependent on the patient population or indication.)

A qualified MHP is a clinically-qualified MHP with appropriate training in the assessment of suicide risk, according to local clinical practice standards and regulations, who would normally evaluate the risk for SIB in a patient. In the United States, in addition to psychiatrists (board certified or board eligible), clinically qualified MHPs include the following: (1) Psy. D. or Ph.D. level Clinical Psychologists, (2) licensed Master's level Clinical Social Workers (LCSW), or (3) licensed Psychiatric Nurse Practitioners (PNP), who have specific training and experience in the assessment and management of acutely suicidal patients. The qualification of MHPs has been the subject of previous regulatory scrutiny of clinical trial conduct, and therefore these details are critically important to the quality of data obtained in such clinical trials.

3.7 Selection and Screening Assessments for Adult Patients (Neurologic Indications)

Studies in adult subjects with neurologic indications (epilepsy, neuropathy, stroke, etc.) are expected to include the C-SSRS, and other instruments such as the Suicidal Behaviors Questionnaire Revised (SBQ-R), and the Patient Health Questionnaire-8 (PHQ-8; Kroenke and Spitzer 2002) are helpful at the screening visit to detect possible SIB and depression. Subjects may either be excluded or have a risk assessment done by a qualified MHP to assess whether it is safe for them to participate in the trial if the subject's responses on any of the screening instruments or other screening information indicate:

- Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the C-SSRS.
- Previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS.
- Any lifetime history of serious or recurrent suicidal behavior. [Non-suicidal self-injurious behavior is not a trigger for a risk assessment unless in the investigator's judgement it is indicated.]
- SBQ-R total score ≥ 8.
- Clinically significant depression: PHQ-8 when the total score ≥ 15.
- The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria.
- In the investigator's judgment a risk assessment or exclusion is required.

3.8 Detection of Emergent SIB During the Course of Clinical Trials (Psychiatric and Neurologic Indications)

Studies of adult subjects in psychiatric and neurologic indications typically include the C-SSRS at every visit to detect possible SIB. At the baseline (randomization) visit, if there are "yes" answers on items 4, 5, or on any behavioral question of the C-SSRS, a risk assessment should be done prior to randomization by a qualified MHP to determine whether it is safe for the subject to continue to participate in the trial. At post-baseline visits, if there are "yes" answers on items 4, 5, or on any behavioral question of the C-SSRS, a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial.

Subjects who answer "yes" on items 4, 5, or on any behavioral question of the C-SSRS *on more than one occasion* during a trial should either have their SIB managed appropriately by the Principal Investigator (PI) together with a qualified MHP (or the PI alone if the PI is a qualified MHP), or be discontinued from the trial, depending on the specifics of the subject and the trial. Studies that allow for the possibility of subjects with recurrent SIB of this severity to continue to participate in the trial must provide guidance on how to manage SIB of this severity in the study protocol. One example of how to operationalize the National Institute of Mental Health (NIMH) guidance on managing suicidal subjects in clinical trials has been published (Nierenberg et al. 2004). When there is a positive response to any question on the C-SSRS, the PI should determine whether an adverse event has occurred. Data collected from SIB assessments such as the C-SSRS directly map to the 11 categories the FDA has adopted in the August 2012 guidance for classifying SIB events.

3.9 Special Population Considerations

Populations that require special consideration include children and adolescents, the elderly, cognitively impaired subjects, and subjects with illnesses associated with significant mortality (e.g., oncology trials shortly after first diagnosis or following relapse). For cognitively impaired subjects and children, involvement of a third party (e.g., proxy) to assist with completion of SIB assessments can often be useful and may be necessary.

3.9.1 SIB Assessment in the Elderly (>65 Years)

Elderly subjects and subjects with illnesses associated with significant mortality may think about death or dying in an adaptive way (Bartels et al. 2002; Szanto et al.

2003). This is often termed "death ideation" and is different from suicidal ideation. As such, evaluation of SIB in the elderly requires the clinician to distinguish bereavement and end of life ruminations from suicidal ideation. In addition, research clinical trials enrolling the elderly should have clearly articulated inclusion/exclusion criteria with respect to SIB and psychopathology, which may increase suicide risk.

As with other studies in adults for psychiatric (non-dementia) indications, studies of elderly subjects in psychiatric indications should include at the screening visit the C-SSRS and include a self-administered scale such as the SBQ-R. In neurologic indications, the PHQ-8 is helpful to detect possible depression. A risk assessment should be done by a MHP skilled in the evaluation of SIB in the elderly by virtue of training or experience (e.g., psychiatrist, geriatric psychiatrist/licensed clinical psychologist, geriatrician or neurologist, social worker or psychiatric nurse practitioner) to determine whether it is safe for the subject to participate in the trial in the same way as for other adult patient. Treatment emergent SIB should be assessed using the C-SSRS at every visit throughout the study.

3.9.2 Patients with Alzheimer's Disease or Mild Cognitive Impairment

In the FDA's revised draft guidance, August 2012, the inclusion of prospective SIB assessments in studies of patients with Mild Cognitive Impairment and in studies of patients with mild to moderate Alzheimer's Disease (or other dementia) are recommended. In subjects with a diagnosis of Mild Cognitive Impairment, involvement of a third party (e.g., proxy) to assist with completion of SIB assessments may be required, depending on the severity of cognitive impairment. In subjects with a diagnosis of Alzheimer's disease, the assessments should not depend solely upon patient self-report, but should systematically utilize information provided by third parties such as spouses, caregivers, or the patient's medical providers.

The 2012 version of the FDA guidance indicates that prospective SIB assessments in studies of patients with advance cognitive impairment such as severe Alzheimer's Disease may be omitted under some circumstances, although FDA needs to be consulted prior to the finalization of the study protocol.

In addition to the C-SSRS, studies of subjects with MCI or mild to moderate Alzheimer's Disease should include additional tools at the screening visit such as the SBQ-R and the Cornell Scale for Depression in Dementias (CSDD; Alexopoulos et al. 1988) or the Neuropsychiatric Inventory (NPI; Cummings et al. 1994; Cummings 1997) Depression/dysphoria domain to detect possible SIB and depression, respectively (Kaufer et al. 1998; Wood et al. 1999). Selected additional questions from the NPI may be added to assist in identifying the behavioral aspects of dementia. (It should be noted that the NPI Depression/dysphoria domain is not an adequate substitute for the CSDD as a screen for DSM-IV Major Depressive Disorder in AD.)

Special considerations for risk assessment, above and beyond those mentioned above, include the endorsement of clinically significant depression as determined by the scores on the CSDD or the NPI Depression/dysphoria domain with additional optional information provided by other items of the NPI (e.g., Agitation/Aggression, Apathy/Indifference, Irritability/Lability).

Although the C-SSRS is widely used in studies of patients with MCI, Alzheimer's Disease, and other dementias, it has not been specifically validated for the prospective assessment of SIB in elderly or cognitively impaired patients nor does it have scope for caregiver input. Integration of information from third parties (spouses, caregivers, medical providers) essential in this patient group, but there have been no systematic studies on:

- The best method of obtaining third party input to SIB assessments,
- Who is qualified to provide third party input
- At what level of cognitive impairment third party input is necessary
- How discrepancies between patient and caregiver input should be reconciled

Additional challenges in assessing SIB in patients with dementia include:

- the tendency of elderly to minimize symptoms of depression,
- the reluctance of many elderly to speak directly about thoughts of suicide
- the risk of confounding age appropriate "death ideations" with passive suicidal ideation
- interview burden in patients with physical limitations (visual and hearing problems, motor impairments)
- complicated by progressive cognitive and functional decline associated with dementia.

3.9.3 Children and Adolescent Patients

Studies of adolescent subjects (age 12–17) in psychiatric indications that do not involve cognitive impairment (as in the case of mental retardation or autism) should include the adult version of C-SSRS at the screening visit. Additional validated scales such as the SBQ-R or the Suicidal Ideation Questionnaire (SIQ; Reynolds 1987) or SIQ-junior (SIQ-JR; Reynolds and Mazza 1999) should also be considered to enhance the screening for subjects at risk. The use of alternative instruments to the C-SSRS would have to be discussed and agreed upon with the FDA *prior* to study start. If the SIQ/SIQ-JR is chosen, the SIQ should be used for subjects aged 15–17, while the SIQ-JR should be used for subjects aged 12–14. The risk assessment for participation in the study needs to take into account not only the C-SSRS answers, but also scores on the SBQ-R and/or suicide specific items on the SIQ/SIQ-JR. For non-psychiatric indications, the Quick Inventory of Depressive Symptomatology—Self-report (QIDS-SR; Rush et al. 2003) should also be administered to screen for depression at the screening visit.

The risk assessment must be done by a clinically qualified child and adolescent mental health provider (MHP). In the United States, in addition to Child and Adolescent Psychiatrists (board certified or board eligible), clinically qualified MHPs include the following: (1) general psychiatrists, (2) Psy. D. or Ph.D. level Clinical Psychologists, (3) LCSW, or (4) PNP who have training and experience in the diagnosis and treatment of children and adolescents with psychiatric disorders. In other countries, the risk assessment should be done by a clinically-qualified MHP who would normally evaluate the risk of suicide in children and adolescents, according to local clinical practice standards and regulations.

Studies of adolescents (age 12–17) in psychiatric and neurologic indications should use the adult version of the C-SSRS at every post-screening visit to detect possible SIB as described above for adult psychiatric and neurologic indications.

There are challenges in using the C-SSRS in this population, given the limited psychometric data available. While the C-SSRS has been validated in adolescents aged 12–17, no psychometric data is available for any version of the instrument in children <12 years of age. In addition, there have been no studies of the validity and reliability of the pediatric version of the C-SSRS. The pediatric version for children 6–11 years of age has age appropriate probes (see the children's baseline screening assessment on the C-SSRS website at http://www.cssrs.columbia.edu/documents/C-SSRS6-23-10-ChildrenBaselineScreening.pdf). There is general guidance on how best to conduct joint interviews of the child and parent, but only limited specific guidance on how to do this in children of different ages and developmental stages, which can be a complication in clinical trials in this patient group. The instrument has been simplified for use in this age group, with the intensity subscale (with the exception of frequency) omitted in this age group. The lethality section needs to be addressed by a parent if the subject is younger than 13 years old.

The revised draft FDA guidance (August 2012) acknowledges that assessment of suicidal thoughts and behavior in young children is challenging since they are not at a point of cognitive development that allows for an understanding of the concept of death. In such cases, it is recommended to discuss potential options, including a waiver, directly with the FDA. In studies of children age ≤11 years and in children and/or adolescents with disorders involving cognitive impairment (e.g., mental retardation or autism), the use of specific scales needs to be customized appropriately.

3.10 Special Considerations for Use of the C-SSRS: Look-Back Period

The revised 2012 FDA Draft Guidance (2012) states that the C-SSRS "is conducted at baseline (this would be a lifetime SIB assessment) and at each patient visit." Use of a lifetime assessment for the purpose of determining treatment emergence or between group differences could be very problematic in certain patient populations (e.g., lifetime assessments in elderly subjects might artificially inflate the baseline).

Table 3.4 Recommended look-back periods for SIB assessments

Visit	Look-back period	Purpose
Screen	Lifetime[a]	Provides lifetime SIB history; meets FDA recommendations and, per this guidance, for determination if a risk assessment should be obtained in children and adolescents before subject can be randomized
Screen	1 year active suicidal ideation; 5 years suicidal behaviors	Per this guidance, for determination if a risk assessment should be obtained before subject can be randomized
Baseline	Since last visit (screen)	Detect emergence of SIB since screen visit
Baseline	1 month active suicidal ideation; 3 months suicidal behaviors	Provides recent history of SIB to be used in determining treatment emergence

[a] In children and adolescents, the lifetime look-back should be used to determine if a risk assessment is required prior to enrolment of the subject

There is ongoing debate over what is the most relevant look-back period for measuring baseline SIB status (Table 3.4).

The definition of the baseline look-back period can significantly impact ability to detect both treatment emergent SIB adverse events (worsening) and beneficial effects of treatment (improvement). Longer look-back periods (as in lifetime assessments) may inflate baseline rates of suicidal ideation or suicidal behavior, particularly in the elderly or in conditions with high background rates of SIB. In addition, a longer look-back period may capture SIB events that are remote from the time of the study and not relevant for determination of current status and are sensitive to recall bias or selective recall. In addition, look-back periods used in study exclusion criteria need to be selected with care to avoid overlapping of the exclusion look-back period with the baseline look-back period, which could lower baseline rates.

Currently, clinical trials methodologists (Gassman-Meyer et al. 2011) recommend the approach of obtaining a more recent SIB history for the purpose of determining treatment emergence (i.e., 1 month look-back from the Baseline Visit for active suicidal ideation and a 3 months look-back for suicidal behaviors). A summary of the recommended look-back periods for SIB assessments at the Screening Visit and at the Baseline Visit is provided in the following table. Different baseline look-back periods may have greater pertinence depending on the patient population and indication under study.

Post-baseline SIB can be displayed without regard to recent history, or as treatment emergent, new onset, or worsening relative to recent history. In general, the recommended look-back period for recent history is 1 month for suicidal ideation and 3 months for suicidal behavior. Any incident of reported post-baseline SIB is typically defined as a new onset if the subject reported no ideation and no behavior during the recent history period. Treatment emergent SIB includes both new onset and worsening. Worsening of existing SIB is defined as movement to a higher numbered C-CASA ideation category than was reported during the recent history period. A subject who reports on-study behavior is considered to have

worsened provided no behavior was reported during recent history, regardless of reported ideation during recent history. On-study movement to a lower number behavior category is considered worsening.

3.11 Special Considerations for Use of the C-SSRS: Analysis

One of the critical unresolved questions and issue with the 2012 revised FDA Draft Guidance (2012) on SIB remains the lack of detailed guidance on statistical analysis of SIB clinical trial data. In particular, how analysis might be impacted by the use of "expanded" C-CASA, which increases the multiplicity of categories.

There are no formal analysis recommendations for C-SSRS and C-CASA data, however, there are precedented formats for data presentation. No formal statistical hypothesis testing is recommended for individual studies as only few events are typically observed, and a listing of the events or descriptive summary statistics will often suffice. Exceptions may occur with large trials or trials in which an "enriched" population is under investigation. If statistical analyses are to be performed, then exact estimation (and testing) methods should be considered.

Subject listings of both expanded C-CASA categories as well as the underlying scale data are helpful. In addition, a summary table of C-CASA categories for life-time, recent history, and post-baseline should be considered. Alternately, C-CASA summaries may be displayed by visit. Tabulation of new onset, worsening, and/or treatment emergent SIB relative to recent history is also helpful to assess treatment emergent SIB risk in selected populations, such as schizophrenia or depression, where there could be a sufficient number of events for meaningful interpretation.

It is important to exercise caution when pooling data across studies and to account for variability associated with methods of data collection (retrospective vs. prospective, different prospective SIB scales, etc.), as well as varying patient populations, extent of exposure, and cultural norms.

There is not one standard analysis as yet and the most appropriate analyses for any given program will depend on the population and compound under study. Sufficient analyses need to be conducted to characterize the level of SIB present in the clinical trial database.

The primary focus of analyses of program level data is to accurately estimate the rates of SIB in the treated and the placebo groups. There are several analysis methods available for the evaluation of SIB at the program level, including the examples highlighted below:

- Odds Ratio (OR)
- Incidence Rate
- Exposure Adjusted Incidence Rate
- Time-to-Event Analyses
- Sensitivity Analysis Methods to corroborate findings or assumptions

3.12 Conclusion

Despite the absence of specific analysis guidance by regulatory agencies, the prospective assessment of SIB in industry sponsored trials is now standard practice. With the growing use of the prospective tools, there are a number of emerging issues that have been encountered, including the specific challenges mentioned above. In addition, there are emerging data on the psychometric qualities of SIB assessments currently being used in clinical trials that warrant further study and the growth of trials in challenging and vulnerable patient groups (i.e., dementia, young children, and children and adolescents with autism) now means that valid assessment methods are of increasing priority. SIB assessment in these patient populations may require a range of different tools and approaches, which can be adapted to their changing cognitive and functional status. An additional challenge is the need for guidance on the best method to obtain and integration of third party input for such patient populations also. There also continue to be questions about the selection and training of raters, and this can become not only a regulatory quality issue, but also one of importance to clinical quality when conducting large, global clinical trials.

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