C-CASA and C-SSRS in CNS Clinical Trials: Development and Implementation

Institute of Medicine
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Principal Investigator Columbia/ FDA Classification Project for Drug Safety Analyses
Principal Investigator Center for Suicide Risk Assessment Columbia University
Statement of Disclosure

- Funding from the FDA to develop and implement the suicidality classification system

- Institution (RFMH) has had research support as part of an effort to help execute the FDA suicidality mandates and requests

- No personal compensation at any time
Co-Investigators.

C-CASA Authors:
Kelly Posner, Ph.D.; Maria Oquendo, M.D.; Madelyn Gould, M.P.H, Ph.D.; Barbara Stanley, Ph.D.; Mark Davies, M.P.H.

C-SSRS Authors:
The Problem...

- Field of medicine challenged by lack of conceptual clarity about suicidal behavior and corresponding lack of well-defined terminology
  - In both research and clinical descriptions of suicidal acts
- Variability of terms referring to same behaviors, e.g., threat, gesture. Often negative and based on incorrect notions about seriousness and lethality in methods e.g., manipulative, non-serious
Consequences....

- Negative implications on appropriate management of suicidality and research
  - If suicidal behavior and ideation cannot be properly identified, they cannot be properly understood, managed or treated in any population or diagnosis

* Furthermore, comparison across epidemiological or drug safety data sets is limited, decreasing confidence in rates of suicide attempts
Consequences...

- Difficulty in interpreting the meaning of reported adverse events that occurred in drug trials
  - Adverse Events that should have been called suicidal may have been missed
  - Adverse Events may have been inappropriately classified as suicidal

Challenged risk findings and interpretability
“Research on suicide is plagued by many methodological problems... Definitions lack uniformity,...reporting of suicide is inaccurate...”
Reducing Suicide Institute of Medicine 2002

Alex Crosby, CDC
### Examples of The Problem

<table>
<thead>
<tr>
<th>Original Label</th>
<th>Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personality Disorder</td>
<td>10 y.o. male exhibited symptoms of PD of moderate severity and was discontinued, one day later pt. attempted to hang himself w/ a rope after dispute w/ his father. Investigator did not consider this an SAE but rather part of the PD</td>
</tr>
<tr>
<td>Accidental Overdose AND Neurosis</td>
<td>The overdose of 6 capsules of study medication was in fact intentional and in response to an argument with the subject’s mother.</td>
</tr>
<tr>
<td>Medication Error</td>
<td>The patient took 11 tablets impulsively and then went to school…the patient denied that it was a suicide attempt.</td>
</tr>
<tr>
<td>Hostility</td>
<td>Age 10: Before his mother’s call to the site and again after arguing with his stepfather, he wrapped a cord from the miniblinds around his neck, threatening to kill himself.</td>
</tr>
</tbody>
</table>
### More Examples of Difficulties in Adverse Event Labeling

<table>
<thead>
<tr>
<th>Original Label</th>
<th>Narratives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional Lab./Suicide Attempt</td>
<td>The patient is reported to have engaged in an episode of “automutilation” where she slapped herself in the face.</td>
</tr>
<tr>
<td>Suicide Attempt</td>
<td>Pt. had thoughts of killing self but had no intention of acting on them</td>
</tr>
<tr>
<td>Abdominal hernia</td>
<td>41-year old Caucasian male experienced a mild abdominal hernia that led to hospitalization and surgery 1 week later and the patient recovered. The patient experienced eventration after a laparotomy due to an abdominal wound caused by a self-inflicted gun shot.</td>
</tr>
<tr>
<td>Trauma</td>
<td>The patient made an attempt to stab himself in the abdomen on day 49 which resulted in minor injury only. This was not considered a true suicide attempt by the investigator and no action was taken...Hence it was not considered to be clinically significant</td>
</tr>
<tr>
<td>Suicide Attempt</td>
<td>Hitting his head on the wall... The patient explained it is like my thoughts are about to explode.</td>
</tr>
</tbody>
</table>

**Note severity goes both ways- labels more severe than they should be as well as less severe than warranted**
The patient, involved in the federal witness protection program for having testified against mobsters, died by apparent suicide. He made a call to a lawyer and said ‘please help, I’m going to die’. According to primary care physician and Investigator, the patient did not exhibit any signs of depression. There was no sign of despondency or hopelessness. The autopsy report stated the following: ‘cause of death: intra-oral gunshot wound of the head; how injury occurred: shot self; manner of death: suicide’...”

Reason to question labels!
How to Address this Problem?

- Columbia commissioned by FDA
- A common set of guidelines needed to be applied
- Data needed to be examined consistently
- Developed the research supported Columbia-Classification Algorithm for Suicide Assessment (C-CASA)\(^1\)
  - Mandated to be used in all antidepressant and anticonvulsant trials as well as other CNS agents, nonpsychotropic drug classes, including cannabinoid 1 receptor (CB1R) inverse agonists, montelukast sodium (Singulair)

Or Else......

- Critically important to answer question in a careful, thoughtful manner

- Erring in either direction would have adverse consequences:
  - Missing a signal of increased risk of suicidality would result in greater comfort than is warranted in the safety of these drugs
  - "False Signal" A premature decision on the strength of the signal could result in the overly conservative use of these drugs, or their lack of availability entirely for the entire population.

Laughren/FDA
C-CASA: How were Suicidal Adverse Events Classified?

Electronic text string search of database for these events
- Search of preferred terms for the following 2 text strings: “suic” or “overdos” “attempt; cut; gas; hang; hung; jump; mutilat; overdos; self damag; self harm; self inflict; self injur; shoot; slash; suic”
- Permitted exclusions for events that represented obvious false positives (e.g., “gas” in “gastrointestinal”)
- All accidental injuries, serious adverse events and deaths

Companies constructed narratives of events according to FDA/C-CASA guidelines and sent them to the Columbia group.
What is the Classification Scheme (C-CASA)?

Blue boxes = FDA “primary analysis” (includes events deemed suicidal).
Blue + green boxes = FDA “sensitivity analysis” (includes any event that could possibly be suicidal).
C-CASA Key Findings

- From Previous FDA Safety Analyses (Pediatric Antidepressants)
  
  - Excellent reliability (median ICC=.86)
  
  - FDA Audit C-CASA “robust and reproducible”
    excellent transportability.
  
  - This FDA safety analysis using C-CASA comprised
    1/3 different events than earlier analysis relying
    on pharmaceutical labels (substantial turnover)
Misclassification can lead to over estimation of risk

- More suicidal events overall, but fewer events were labeled suicidal attempts - **50% reduction in attempts** (Posner et al. 2007)

- Safety analysis using C-CASA (Hammad et al. 2006) had more precise estimate of risk (tighter confidence interval) compared to a prior analysis relying on an sponsor ratings (Mosholder, 2004).

- This is consistent with previous findings that misclassification leads to overestimation of true risk (Jurek et al. 2005).
### C-CASA Singulair: 1/13/09 FDA Update

<table>
<thead>
<tr>
<th>Company</th>
<th>Merck</th>
<th>Astra Zeneca</th>
<th>Cornerstone Therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Montelukast</td>
<td>Cornerstone Therapeutics</td>
<td>Zileuton</td>
</tr>
<tr>
<td># Placebo Cntrld Trials</td>
<td>41</td>
<td>45</td>
<td>11</td>
</tr>
<tr>
<td># Px</td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
</tr>
<tr>
<td></td>
<td>9929</td>
<td>7780</td>
<td>7540</td>
</tr>
<tr>
<td>Suicidal Ideation Events</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal Behaviors</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Completed Suicides</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1 (0.01%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Limitations of the Data: Lessons Learned

- Studies not designed to assess suicidality
- Association does not mean causality
- Alternative Explanation to Causal Link - Ascertainment Bias
  - Spontaneously generated not systematically elicited
  - Med subjects potentially have more contact with provider consequent to the more common occurrence of physical side effects. (more face-to-face time to hear about suicidal incidents)
  - Possibly accounts for differential rates among subjects receiving drug versus placebo in any safety analysis
Systematic vs. Spontaneous Data: Different Results

In pediatric antidepressant safety analysis, systematically collected data (suicide items from HAM-D, CDRS-R, MADRS, and K-SADS) did not confirm the risk shown by the adverse event data.

- **Worsening**: Increase in the suicidality item(s) score of pertinent depression questionnaires relative to baseline, regardless of subsequent change

- **Emergence**: Same concept as above, but with normal baseline score

In Treatment for Adolescents with Depression Study (TADS), C-CASA utilized

- **Systematic assessment (SIQ Jr)** did not confirm risk
Many other subsequent analyses show same thing......

- Large data sets from sponsors, item data shows no risk
- Always same direction, if AE shows nothing, item data shows improvement of suicidality
- 5 year pediatric SSRI (Escitalopram) study using C-SSRS

Emslie et al. AACAP 2008
C-SSRS Findings: Prospective Adolescent Depression Trial

Number of Pediatric MDD Patients with Increase in Suicidal Ideation and Behavior During Trial by Treatment Group

- 8-Week Trial (N enrolled = 312, N completed = 259)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Active Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal Ideation</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>(10.2%)</td>
<td>(9.2%)</td>
</tr>
<tr>
<td>Suicide Behavior</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(2.5%)</td>
<td>(1.5%)</td>
</tr>
</tbody>
</table>

- No significant difference between treatment groups.

Emslie et al. AACAP 2008
## C-SSRS Findings: Obesity Trial

### Comparison of Retrospective and Prospective Data

<table>
<thead>
<tr>
<th></th>
<th>Retrospective C-CASA&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Prospective C-SSRS Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Phase</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Double-blind</td>
<td></td>
</tr>
<tr>
<td><strong>Number of Patients</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>8600</td>
<td>~ 5600</td>
</tr>
<tr>
<td><strong>Suicidal Ideation</strong></td>
<td>452</td>
<td>12*</td>
</tr>
<tr>
<td><strong>Suicidal Behavior</strong></td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>1</sup> Stemmed from positive responses on PHQ-9

<sup>2</sup> Double-blind phase ranged from 12 to 104 weeks; Extension phase was 52 weeks

<sup>3</sup> Maximum number of patients entering the extension phase of the trials

* Markedly lower rates of suicidality with systematic monitoring
How to Fix the Problem...
Columbia - Suicide Severity Rating Scale

- Systematic administration of tool designed to track suicidal adverse events and change across a treatment trial
  - In context of multi-site NIMH trial (Treatment of Adolescent Suicide Attempter Study),
  - In response to need for a measure of suicidality severity and change

- “Prospective counterpart” of the FDA-commissioned system (indicated in C-CASA article, Posner et al, 2007); C-CASA is retrospective C-SSRS

- Way to get better safety monitoring and avoid inconclusive results

- This is why FDA and other regulatory authorities are often recommending or asking for C-SSRS in ongoing or future studies.
Columbia-Suicide Severity Rating Scale
Posner, Brent, Lucas C, Gould, Brown, Fisher, Zelazney, Burke, Oquendo, & Mann

- Developed by leading experts/collaboration with Beck’s group U Penn and U Pittsburg/evidence-based
- Feasible, low- burden (typical admin time a few minutes)
- Ages 6 - elderly
- Uniquely assesses both behavior and ideation (full range)
- Addresses need for a summary measure of suicidality

For all C-SSRS inquiries contact: posnerk@childpsych.columbia.edu
Simply....

1-5 rating for suicidal ideation, of increasing severity (from a wish to die to an active thought of killing oneself with plan and intent)
  - Can be two questions;
    - Have you wished you were dead or wished you could go to sleep and not wake up?
    - Have you actually had any thoughts of killing yourself?

If answer is “No” to both, No more questions on ideation

There are four behaviors assessed, few questions required
  - Provides definitions and questions to figure out how to classify behaviors
Improved Ascertainment.... Definitions are Important

- All items include definitions for each term and standardized questions for each category are included to guide the interviewer for facilitating improved identification
  - Behavioral definitions from Columbia Suicide History Form (Oquendo, 2002)
  - Ideation definitions from NIMH Brown, Conwell, Posner, Burke Ideation Project
Additional Features Assessed

- Lethality of Attempts; Compilation of Beck Medical Lethality Rating Scale
- Other Features of Ideation: Intensity
  - Frequency
  - Duration
  - Controllability
  - Reasons for Ideation
  - Deterrents

*All these items significantly predictive of completed suicide (on SSI)/ minimum amount of info needed for tracking and severity*
C-SSRS Format and Administration

- Allows for utilization of multiple sources of information
  - Any source of information that gets you the most clinically meaningful response (subject, family members, records)

- Semi-structured – flexible format
  - Questions are provided as helpful tools – it’s not required to ask any or all questions - just enough to get the appropriate answer
  - Most important: gather enough clinical information to determine whether something should be called suicidal
Suicide Attempt Definition

A self-injurious act committed with at least some intent to die, *as a result of the act*

- There does not have to be any injury or harm, just the **potential** for injury or harm (e.g., gun failing to fire)
- Any “non-zero” intent to die - Does not have to be 100%
- Intent and behavior must be linked
- Intent can sometimes be inferred clinically from the behavior or circumstances
  - If denies intent to die, but thought that what they did could be lethal
  - “Clinically impressive” circumstances - highly lethal act where no other intent but suicide can be inferred (e.g., gunshot to head, taking 200 pills)
1. The patient wanted to escape from her mother’s home. She researched lethal doses of ibuprofen. She took 6 ibuprofen pills and said she felt certain from her research that this amount was not enough to kill her. She stated she did not want to die, only to escape from her mother’s home. She was taken to the emergency room where her stomach was pumped and she was admitted to a psychiatric ward. ______

2. Young woman, following a fight with her boyfriend, felt like she wanted to die, impulsively took a kitchen knife and made a superficial scratch to her wrist; before she actually punctured the skin or bled, however, she changed her mind and stopped. ______

3. Patient was feeling ignored. She went into the family kitchen where mother and sister were talking. She took a knife out of the drawer and made a cut on her arm. She denied that she wanted to die at all (“not even a little”) but just wanted them to pay attention to her. ______

4. The patient cut her wrists after an argument with her boyfriend. ______

5. Had a big fight with her ex-husband about her stepson. Took 15-20 imipramine tablets and went to bed. Slept all night and until 4-5 pm the next day. States she couldn’t stand up or walk. Called EMS – taken to the ER – drank charcoal and admitted to hospital. Unable to verbalize clear intent, but states she was well aware of the dangers of TCA overdose and the potential for death. ______
Suicidal Behavior

<table>
<thead>
<tr>
<th>SUICIDAL BEHAVIOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Check all that apply, so long as these are separate events; must ask about all types)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Actual Attempt:</th>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <strong>There does not have to be any injury or harm, just the potential for injury or harm.</strong> If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>☐</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Have you made a suicide attempt?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you done anything to harm yourself?</td>
</tr>
<tr>
<td>Have you done anything dangerous where you could have died?</td>
</tr>
<tr>
<td>What did you do?</td>
</tr>
<tr>
<td>Did you ______ as a way to end your life?</td>
</tr>
<tr>
<td>Did you want to die (even a little) when you ______?</td>
</tr>
<tr>
<td>Were you <strong>trying to end your life when you ______?</strong></td>
</tr>
<tr>
<td><strong>Or did you think it was possible you could have died from ______?</strong></td>
</tr>
<tr>
<td>Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:</td>
</tr>
<tr>
<td>Total # of Attempts</td>
</tr>
<tr>
<td>🅰️</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>☐</td>
</tr>
</tbody>
</table>

**May help to infer intent**

**Important:** Shows you did the appropriate assessment and decided it should not be called suicidal
Various Uses of C-SSRS Within a Study

- Treatment benefit outcomes
- Safety outcomes
- Clinical safety monitoring
- Coordinated efficiently with other measures
- Epidemiological

- Easily coupled with inclusion/exclusion
  - In past exclusion arbitrary e.g. “serious risk”? (criteria can be operationalized and assessed by C-SSRS
    e.g. past attempt ever - early phases; recent attempt - later phase; current ideation (intent or plan)
  - Inclusion/exclusion varies/allows you to assess variables
Advantages and Uses....Clinical Safety Monitoring and Management

- Improved Documentation
  - Training on the scale can improve investigators approach to AEs as a whole and documentation of them

- Specify parameters for triggering referrals to mental health professionals
  - Eg., 4 of 5 on ideation item to indicate need for immediate referral
  - Decreases unnecessary referrals, exclusion, and burden – very important for non-psychiatric trials
One Example: FDA Document, How C-SSRS Is Used

Endocrinology -
- C-SSRS to be administered at baseline, then at each visit throughout the duration of the trial
- Baseline:
  - A subject should be excluded from the trial if he/she has any suicidal ideation of type 4 or 5 on the C-SSRS in the last month
- During Study Conduct:
  - A subject should be referred to a Mental Health Professional (MHP) if he/she has any suicidal ideation of type 4 or 5 on the C-SSRS

*See later slides for more details*
Assessment Periods/ Time Frames

Flexible, amenable to study or clinical need

- Baseline/lifetime history
- Screening: Recent/Last Week/Past Month/6 months
- Since last assessment (whatever time period that may be)
“Already- Enrolled Subjects” Version

- Some good data better than no good data

- 2 Baseline Periods
  - Prior to Study Entry (lifetime)
  - Study Start to first C-SSRS administration
Baseline Information and Improved Adverse Event Determinations

- Comprehensive baseline history

- Necessary to better determine if adverse event is related to intervention ("new or different")
  - Investigators asked to make judgments re relationship to treatment
  - If have an event and had something similar prior to study start speaks to relationship to tx or lack thereof
Constellation of Neuropsychiatric Sequelae

- What do we actually need to assess and how?
- Is paired with other psychiatric measures
- Example of “package” to assess key sx: suicidality, depression, anxiety
  - Depression (e.g., PHQ-9)
  - Anxiety (e.g., GAD-7)
  - Suicidality (C-SSRS)
Baseline:

- A subject should be excluded from the trial if he/she has:
  - A baseline PHQ-9 score of 15
  - Any suicidal behavior in the last month
  - Any suicidal ideation of type 4 or 5 on the C-SSRS in the last month
    - Type 4 indicates Active Suicidal Ideation with Some Intent to Act, Without Specific Plan
    - Type 5 indicates Active Suicidal Ideation with Specific Plan and Intent
- The GAD-7 score at baseline need not be the basis for exclusion from a trial
Guidance: During Study Conduct

(research-supported cut-points; Williams et al.)

- A subject should be referred to a Mental Health Professional (MHP) if he/she has:
  - A PHQ-9 score 10
  - A GAD-7 score 10
  - Any suicidal behavior
  - Any suicidal ideation of type 4 or 5 on the C-SSRS

- A referral to a MHP should also be made if in the opinion of the Investigator it is necessary for the safety of the patient

- If a subject’s psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the patient, at the discretion of the MHP, should be continued in the trial
Why item data isn’t sufficient (e.g., HAM-D, PHQ-9, and MADRS)

**HAM-D**
3. Suicide
0 = Absent
1 = **Feels life is not worth living**
2 = Wishes he were dead or any thoughts of possible death to self
3 = Suicidal ideas or gestures
4 = Attempts at suicide (any serious attempt rates 4)

**PHQ-9**
Thoughts that you would be **better off dead** or of **hurting yourself** in some way

**MADRS**
10. Suicidal Thoughts
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.

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 as a possible solution, but without specific plans or intention.
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Data confirms that when item followed by C-SSRS, eliminate cases that should not have been called suicidal

**Can reduce false positives**
Feasibility

Iatrogenic
- Asking about suicidality doesn’t cause distress or suicidality (Gould et al., JAMA 2005)

Feasibility
- Investigators
- Subjects - no withdrawal

Who can administer the C-SSRS?
- Need to be trained
- Do not have to be a Mental Health Professional to administer this scale; thousands of health professionals have been trained
- Examples: Any type of physician, psychologist, clinical social worker, mental health counselor, nurse, coordinator
C-SSRS in Clinical Trials

- Trials in Phases I-IV
- Few thousand sites internationally, psychiatry and non-psychiatry
- Over 90 different languages for all versions
- Drug/placebo; active controls; open maintenance
- Range of interventions: pharmacologic, device, psychotherapy, ECT
Training and Implementation

- Administration Training
  - Approximately 20-30 minutes
  - Trained thousands of health practitioners across the world via webex, phone, etc
  - Training DVD for the IM training and supplemental rater turnover
  - Interactive training tool in development
  - Higher level “Train the Trainer” program

- Various Modalities
  - Paper
  - Centralized Raters
  - Phone
  - Self-report version/IVR
How Do We Think About These Outcomes?

- Association with underlying condition (shouldn’t vary across groups)
- A suicidality instrument for RCTs primarily needs to systematically collect info to determine if an occurrence meets criteria for a nosological category; it is not to predict future behavior or characterize state/trait
- To provide between group differences
- Also has risk assessment features
How to Make Sense of the Data

- Most Important/Primary Data
  - Identification of suicidality: Ideation and Behavior
  - Categorical distinctions

- Treatment emergent ideation – need to account for baseline level of ideation

- Important to evaluate changes – worsening &/or improvement in ideations and behaviors

- Secondary Data/Used for Clinical Monitoring/Descriptive
  - Operationalize changes – Severity and intensity of ideations and nature and lethality of behaviors
Different Sources of Input = Same Output (e.g., eC-SSRS)

<table>
<thead>
<tr>
<th>SUICIDAL IDEATION</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Wish to be Dead</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Non-Specific Active Suicidal Thoughts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Active Suicidal Ideation with Specific Plans and Intent</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>INTENSITY OF IDEATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (1-5)</td>
</tr>
<tr>
<td>Duration (1-5)</td>
</tr>
<tr>
<td>Controllability (0-5)</td>
</tr>
<tr>
<td>Deterrents (0-5)</td>
</tr>
<tr>
<td>Reasons for Ideation (0-5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUICIDAL BEHAVIOR (Check all that apply: so long as these are separate events: must ask about all types)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed Suicide</td>
</tr>
<tr>
<td>Actual Attempt</td>
</tr>
<tr>
<td>Interrupted Attempt</td>
</tr>
<tr>
<td>Aborted Attempt</td>
</tr>
<tr>
<td>Preparatory Acts or Behavior</td>
</tr>
<tr>
<td>Any Suicidal Behavior</td>
</tr>
<tr>
<td>Non-Suicidal Self-Injurious Behavior</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Answer for Actual Attempts Only (Lethality Section)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most Lethal Attempt</td>
</tr>
<tr>
<td>Date: / / /</td>
</tr>
</tbody>
</table>

| Actual Lethality/Medical Damage (0-5)             |
| Potential Lethality: Only Answer if Actual Lethality=0 (0-2) |
Tailored for Population Specific Data Collection

### SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes,” ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is “yes”, complete “Intensity of Ideation” section below.

<table>
<thead>
<tr>
<th>Question</th>
<th>Since Last Visit</th>
<th>Postcard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Wish to be Dead</strong>&lt;br&gt;Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.&lt;br&gt;Have you wished you were dead or wished you could go to sleep and not wake up?</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2. Non-Specific Active Suicidal Thoughts</strong>&lt;br&gt;General non-specific thoughts of wanting to end one’s life/commit suicide (e.g. “I’ve thought about killing myself”) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.&lt;br&gt;Have you actually had any thoughts of killing yourself?</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</strong>&lt;br&gt;Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, “I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it and I would never go through with it”.&lt;br&gt;Have you been thinking about how you might do this?</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</strong>&lt;br&gt;Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to “I have the thoughts but I definitely will not do anything about them”.&lt;br&gt;Have you had these thoughts and had some intention of acting on them?</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5. Active Suicidal Ideation with Specific Plan and Intent</strong>&lt;br&gt;Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.&lt;br&gt;Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being
What drugs should be prospectively evaluated?

**CNS**
- All CNS Indications
- Underlying conditions associated with suicide (e.g., Chantix and Singulair)

**Non-CNS**
- Any brain pathophysiology
- Any AE Concern
**C-SSRS used in Government, Industry, & Foundation sponsored intervention studies**

**Psychiatric**
- MDD
- Major Depressive Episode Associated with Bipolar I Disorder
- Refractory Depression
- Bipolar
- GAD
- OCD
- ADHD (w/ and w/o Dyslexia)
- Schizophrenia
- Personality Disorders
- Alcohol Dependence
- Bereavement
- Tardive dyskinesia
- Tourette’s

*Basically All Psychiatric Disorders*

**Healthcare Conditions**
- Healthy Volunteers
- Overweight patients
- Obesity
- Diabetes
- Interstitial Cystitis/ Painful Bladder Syndrome
- Eczema
- Smoking Cessation (w/ and w/o Schizophrenia/Schizo Affective Disorder)
- Cancer Survivors
- Insomnia
- Cardiovascular Disease
- Non-alcoholic Steatohepatitis
- Overweight with Type 2 Diabetes
- Group Intervention for OEF/OIF TBI Survivors and Families

**Non-Psychiatric**
- Metabolic disorders
- Traumatic Brain Injury
- Alzheimer's
- Dementia
- Huntington Study Group
- Fibromyalgia
- Epilepsy
- Epileptic patients with renal impairment
- Chronic Headaches
- Neuropathic Pain due to Multiple Sclerosis
- Diabetic Peripheral Neuropathic Pain
- Peripheral Neuropathic pain
- Osteoarthritis pain
- Lower Back Pain
- Restless Leg Syndrome

---

*50*
What we are seeing.....

- MDD: adults approx. 10%
- GAD: 3%
- Non-alcoholic Chronic Liver disease: < 1% (liver disease associated with depression & suicidality; no referrals triggered)
- ADHD: ages 6-12, 0% ideations & behaviors
- Cardiovascular: 1-2% (no referrals triggered)
- Obesity: <1% (no referrals triggered)
- Obesity with Depressed Patients: 1.25% ideation or behavior
## C-SSRS Data from Blinded GAD Trial

### Lifetime History of Suicidal Ideation and Behavior Obtained at Baseline and Incidence Rates During Trial

<table>
<thead>
<tr>
<th>C-SSRS Item</th>
<th>Lifetime (N=908)</th>
<th>During Trial (N=908)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ideation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wish To Be Dead</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Non-Specific Active Thoughts</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Active Thoughts Without Intent To Act</td>
<td>23</td>
<td>3%</td>
</tr>
<tr>
<td>Active Thoughts With Some Intent—No Plan</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Active Thoughts With Plan And Intent</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td><strong>Behavior</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual Attempt</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Total Number of Attempts</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Interrupted Attempt</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Aborted Attempt</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Preparatory Acts Or Behavior</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal Behavior</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with One or More Positive Responses on C-SSRS</td>
<td>12.4% (N=113)</td>
<td>3%</td>
</tr>
</tbody>
</table>
C-SSRS Findings: Prospective MDD Clinical Trial (N=376)

<table>
<thead>
<tr>
<th>C-SSRS Item</th>
<th>Total Events/Subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ideation (N Events)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Wish To Be Dead</td>
<td>322</td>
<td>86%</td>
</tr>
<tr>
<td>(2) Non-Specific Active Thoughts</td>
<td>55</td>
<td>15%</td>
</tr>
<tr>
<td>(3) Active Thoughts Without Intent To Act</td>
<td>35</td>
<td>9%</td>
</tr>
<tr>
<td>(4) Active Thoughts With Some Intent—No Plan</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>(5) Active Thoughts with Plan and Intent</td>
<td>4</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Behavior (N Events)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparatory Acts or Behavior</td>
<td>1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Interrupted Attempt</td>
<td>1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Aborted Attempt</td>
<td>1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Actual Attempt</td>
<td>1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>N Subjects with &gt;=1 Positive Ideations</strong></td>
<td>163</td>
<td>43%</td>
</tr>
<tr>
<td><strong>N Subjects with &gt;=1 Positive Behaviors</strong></td>
<td>4</td>
<td>1%</td>
</tr>
</tbody>
</table>
Baseline from Fibromyalgia Trial

- Based on 496 patients
- Wish to be dead - 8.67%
- Suicidal Thoughts - 4.23%
- Ideation w/out Intent - 3.23%
- Ideation w/out plan - 2.22%
- Ideation plan intent - 2.42%
- Actual Baseline - 0%
- Nonsuicidal baseline - 0.4%
- Interrupted baseline - 0%
- Aborted baseline - 0%
- Prep acts baseline - 0.4%
- Behavior present baseline period - 1.41%
- Completed suicide - 0%

Total: 22.98%
Fibromyalgia Trial

- Based on 1888 CSSRS forms
- Wish to be dead - 0.64%
  - Suicidal Thoughts - 0.21%
  - Ideation w/out Intent - 0.16%
  - Ideation w/out plan - 0.11%
  - Ideation plan intent - 0.05%
- Actual Baseline - 0%
- Nonsuicidal baseline - 0%
- Intersuicidal baseline - 0%
- Aborted baseline - 0%
- Prep acts baseline - 0%
- Behavior present
  - baseline period- 0.05%
- Completed suicide - 0%

Total: 1.22%
C-SSRS Current Uses

- World Health Organization-Europe: 100 Best Practices for Adolescent Suicide Prevention
- AMA Best Practices Adolescent Suicide
- Japanese National Institute of Mental Health and Neurology
- Israeli National Suicide Prevention Program
- Korean Association for Suicide Prevention
- Planned statewide dissemination in Victoria, Australia – Health and Law Enforcement agencies
- Drug and Alcohol Addiction Centers
- National Institute on Alcohol Abuse and Alcoholism: NIAAA
- Commissioned by VA to do online training for clinical trials
- Center of Excellence for Research on Returning War Veterans
- Hospitals and Community Clinic Settings
  - Inpatient and ERs; general medical and psychiatric, Crisis services, Special Needs Clinics, VA’s
- Surveillance Efforts; CDC Definitions are Columbia Defns
- AFSP/Developing Centers Registry Project
- NIH-medically ill
- Suicide Section of SCID
- Clinical Practice, nationally and internationally
- Schools (Middle Schools, High Schools, and College Campuses)
C-SSRS Psychometric Properties
Reliability and Validity: Adults

- Pilot registry study NIMH Developing Centers and AFSP
- Multi-site trial at 3 psychiatric EDs (N=121)

100% sensitivity and 98% specificity for correctly classifying attempts versus no attempts compared to classifications by hospital staff

Convergent validity:
- Severity of ideation highly correlated with severity of ideation on the SSI (r=.69, p<.001)
- Intensity of Ideation total score moderately correlated with the SSI total score (r=.55, p<.001)
- Actual Lethality score was moderately correlated with the Beck Lethality Scales score (r=.55, p<.001)

Reliability:
- Moderate internal reliability of the Intensity of Ideation 5-item measure (Cronbach's alpha = .59)
SSI Total Score by Highest Level of Ideation on the C-SSRS

F (5,185) = 14.35, p < .001
Currier, Brown & Stanley (2009)
C-SSRS Psychometric Properties: Adolescents - Convergent & Discriminant Validity

- Convergent validity:
  - Strong positive relationship between C-SSRS and SIQ-Jr over time, p < .001
  - Baseline C-SSRS suicidal ideation severity item & suicidal ideation intensity scale significantly correlated with SIQ-Jr and CDRS-R suicide item (r’s range from .52 - .57, p < .001)

- Discriminant validity:
  - Baseline C-SSRS suicidal severity ideation item NOT correlated with CDRS-R change in appetite item r = .07, difficulty sleeping item r = .06, fatigue item r = -.08, or somatic item r = -.07.
As the severity of suicidal ideations on the C-SSRS decreased over the trial, the SIQ-Jr scores decreased in a similar pattern, $p<.001$.

Sample (n=259) of pediatric patients (ages 12 to 18) in an RCT evaluating escitalopram relative to placebo to treat MDD.
C-SSRS Psychometric Properties: Adolescents - Predictive Validity & Reliability

- Predictive validity:
  - Reporting lifetime suicidal ideation on C-SSRS at screening associated with increased chance of reporting suicidal behavior, Fisher’s exact test \( p = .0008 \), during the trial.

- Reliability:
  - Internal consistency reliability of intensity of ideation subscale (for lifetime ideation) = .74.
Inter-Rater Reliability

- Treatment of SSRI-Resistant Depression in Adolescents
- N=49
- 100% for Behavior
- 90% for Ideation (p<.001)

(Brent, Emslie, Clarke et al. AJ P, 2009)
“We know that whether or not these drugs actually cause suicidal thought or action is a question we have to answer, but up until now, none of the clinical trials for the drugs were set up to address the question,” says Posner. “Either way we have to get the right answers. It’s critical to know about drugs that pose risk, but debunking false notions of risk is equally important to the public health.”

“...the FDA hopes that by using Posner’s methods, they may be able to find categories of people who might be at risk for suicide on a particular drug...and in whom it can safely be prescribed” says T. Laughren.
Conclusions

- Intervention trials using prospective and systematic measurement of suicidality would more clearly delineate the relationship between suicidal adverse events and medication treatment.

- Consistent and systematic assessment (e.g., C-SSRS) can provide more meaningful data within a study, as well as across studies, improving pooled analyses.

- Just as important for safety—need appropriate identification, avoid false positives.

- Improved assessment of suicidal events is necessary to better inform risk benefit analyses.
C-SSRS: Prospective C-CASA

**C-CASA**

1. Completed Suicide
2. Suicide Attempt
3. Preparatory Actions Towards Imminent Suicidal Behavior
4. Suicidal Ideation

**C-SSRS**

1. Completed Suicide
2. Actual Attempt
   - Interrupted Attempt
   - Aborted Attempt
   - Preparatory Acts or Behavior
3. Preparatory Actions Towards Imminent Suicidal Behavior
4. Active Suicidal Thought
5. Active Suicidal Thought with Method
6. Active Suicidal Thought with Intent
7. Active Suicidal Thought with Plan and Intent

**Non-Suicidal Self-Injurious Behavior**

7. Non-Suicidal Self-Injurious Behavior
### Other Categories Become Obsolete with Prospective data collection

<table>
<thead>
<tr>
<th>C-CASA</th>
<th>C-SSRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Self-injurious Behavior, Intent Unknown</td>
<td></td>
</tr>
<tr>
<td>6. Not Enough Information: Death</td>
<td></td>
</tr>
<tr>
<td>9. Not Enough Information: Non-Death</td>
<td></td>
</tr>
<tr>
<td>8. Other (Accident; Psychiatric; Medical)</td>
<td></td>
</tr>
</tbody>
</table>

**C-CASA**: Not Applicable - Unknowns are eliminated with Prospective Data Collection (These C-CASA categories created ONLY to make sense of limitations of retrospective adverse events.)

**C-SSRS**: N/A: No Indication of Suicidal Ideation or Behavior
Most Profound Change in Drug Development Regulation in 16 Years

“Researchers at Columbia University have developed a questionnaire to help systematically assess suicidal thoughts and behavior. The Food and Drug Administration is now requiring that drug companies adopt the methodology in their clinical trial.”
Clinician Screen Not Adequate

- "Structured Interview May Better Detect Adolescent Suicidality: Simpler 2-Question Screening Approach by Trained Clinicians Falls Short" (Medscape Medical News, 2008)

- Screening method (without a measure) over-detected suicidal ideation & under-detected suicidal acts

Holi et al. 2008 BMC Psychiatry
Correspondence from the EMEA to the London Times

“European legislation for both clinical trials and marketing authorization of medicines has established clear procedures to report and evaluate any suicidal event. The use of the Columbia University Questionnaire to systematically assess suicidal thoughts and behaviors has been required for a number of ongoing developments in the context of the EMEA Scientific Advice procedure. In addition, the issue of suicidality is regularly addressed during pre-authorization evaluation of new medicines (centralized procedure and also referrals in the context of mutual recognition and decentralized authorization procedures), usually at the time of the initial assessment report (Day 80) of the Agency’s Committee for Medicinal Product for Human Use (CHMP) and when specific questions are issued to the Applicant at Day 120. Suicidality may be addressed by reports, as mentioned above, but also during the evaluation of new medicinal products based on: a Central mechanism of action; for example a Central Nervous System active substance like a new anti-epileptic, a target population, like patients suffering from major depression, bipolar disorder, or frequent concomitant conditions in the target population, like depression/anxiety during smoking cessation.
"We give the scale at every session as part of best practice," Toll says. "We are not predicting that they are suicidal, but if they are, we will attend to it. I'm pleased to say we've not found anyone suicidal."

Benjamin Toll goes onto say “The community-at-large benefits from this type of screening when its citizens are appropriately and adequately treated”
Structure and Scaling

- Screening Questions: 2 for ideation, 4 for behavior (if answer is no to 2 ideation questions, go to behavior)
- Approx 17 items
- No global score; some categorical and some severity information, specified for behavior and ideation
  - Categorical-types of ideation and behavior, total # of occurrences
  - Scaling component, several continuous scale variables
    - Lethality
    - Intensity
- Categorical responses do not require narrative description: optional (training includes how, more important in non-psychiatric areas where it can serve as a QA mechanism; and facilitates AE descriptions)
Press claimed reports were being hidden however, the initial analysis completed by Dr. Mosholder ("FDA Scientist") was completed with pharmaceutical company rated adverse events e.g. "slap in the face"

No consistent definitions of suicidal events were used between companies

Hence, these analyses were considered to be unreliable.

Findings warranted further examination (e.g., Prozac, Zoloft, Effexor)
Blinding of Event Narratives to Avoid Bias

- Received from Company blind to all potential drug identifying information:
  - Drug name
  - Company/sponsor name
  - Patient identification numbers
  - Active or placebo arm
  - Any and all medication names and types (e.g. tx with other meds may be associated with a particular antidepressant side effect profile and thus could potentially bias)
  - Primary Diagnosis/Indication of study

- Additional Blinding of potentially biasing information:
  - Original label of event given by investigator or sponsor
  - “serious” or “non-serious” labels
Columbia Classification Algorithm for Suicide Assessment: Codes

**Suicidal**
1. Completed Suicide
2. Suicide Attempt
3. Preparatory Actions Towards Imminent Suicidal Behavior
4. Suicidal Ideation

**Indeterminate**
5. Self-injurious Behavior Intent Unknown
6. Not Enough Information: Death
9. Not Enough Information: Non-Death

**Non Suicidal**
7. Self-Injurious Behavior Without Suicidal Intent
8. Other (Accident; Psychiatric; Medical)
Children’s Depression Rating Scale

—SUICIDAL IDEATION—

Understands the word *suicide*, but does not apply the term to himself/herself. .......................... 1

*Sharp* denial of suicidal thoughts. .......................... 2

Has thoughts about suicide, or of hurting himself/herself (if he/she does not understand the concept of suicide), usually when angry ....................... 3

Has recurrent thoughts of suicide. ....................... 4

Has made a suicide attempt within the last month or is actively suicidal. ....................... 5

Poznanski & Mokros 1996


Brown, G. K., Currier, G., & Stanley, B. (September, 2008). Suicide Attempt Registry Pilot Project. Invited presentation for the National Institute of Mental Health annual meeting of the Developing Centers for Intervention and Prevention of Suicide, Canandaigua, NY.

**SUICIDALITY TRACKING SCALE (STS)**

(From MINI Tracking, Module C. Copyright Sheehan et al 2006 revision)

**RATING INSTRUCTIONS:**

1. **Over the past week did you suffer any accident?**
   - □ NO  □ YES
   
   **IF NO, SKIP TO QUESTION 2.**
   **IF YES, ASK:**

1a. **to what extent did you plan or intend to hurt yourself in that accident (either passively or actively)?**
   
<table>
<thead>
<tr>
<th>not at all</th>
<th>a little</th>
<th>moderately</th>
<th>markedly</th>
<th>extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

   **IF THE ANSWER TO QUESTION 1a IS 0, SKIP TO QUESTION 2.**
   **IF IT IS SCORED ≥1, ASK:**

1b. **Did you intend to die as a result of this accident?**
   - □ NO  □ YES

<table>
<thead>
<tr>
<th>3. want to harm yourself or to hurt or to injure yourself?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. think about suicide?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. plan for a suicide?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. take active steps to prepare for a suicide attempt in which you expected or intended to die?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. Over the past week did you injure yourself intentionally?</th>
</tr>
</thead>
</table>
| □ NO  □ YES

   **IF NO, SKIP TO QUESTION 8.**
   **IF YES, ASK:**

   Over the past week, how seriously did you:

<table>
<thead>
<tr>
<th>7a. deliberately injure yourself without intending to kill yourself?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. attempt suicide?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

**TOTAL**
S U I C I D A L  I D E A T I O N

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes," complete "Intensity of Ideation" section below.

1. W i s h t o b e D e a d
   Subjectmachine thoughts about a wish to be dead or commit suicide or wish to take over and not wake up.
   Have you wished you were dead or wish you could go to sleep and not wake up?
   [ ] Yes, describe:

2. N o n - S p e c i f i c A c t i v e S u i c i d a l T h o u g h t s
   General, non-specific thoughts of wanting to end one's life/suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself.
   Have you actually had any thoughts of killing yourself?
   [ ] Yes, describe:

3. A c t i v e S u i c i d a l I d e a t i o n w i t h o u t M e t h o d s (N o P l a n) w i t h o u t I n t e n t i o n t o A c t
   Subjectmachine thoughts of suicide and has thought of at least one method during assessment period. This is different from a specific plan with time, place or method details worked out (e.g., "I thought of方法 to kill myself but a specific plan with time, place or method details worked out")
   Have you had these thoughts and did you have any intention of acting on them?
   [ ] Yes, describe:

4. A c t i v e S u i c i d a l I d e a t i o n w i t h S o m e I n t e n t i o n t o A c t, w i t h o u t S p e c i f i c P l a n
   Subjectmachine thoughts of suicide, but has a specific plan with time, place or method details worked out (e.g., "I thought of method to kill myself in a specific plan with time, place or method details worked out")
   Have you had these thoughts and had some intention of acting on them?
   [ ] Yes, describe:

5. A c t i v e S u i c i d a l I d e a t i o n w i t h S p e c i f i c P l a n and I n t e n t i o n t o A c t
   Subjectmachine thoughts of suicide, but has a specific plan with time, place or method details worked out (e.g., "I thought of method to kill myself in a specific plan with time, place or method details worked out")
   Have you had these thoughts and had some intention of acting on them?
   [ ] Yes, describe:

I N T E N S I T Y O F I D E A T I O N

The following features should be rated with respect to the most severe type of ideation (i.e., 1-3 from above, with 1 being the least severe and 3 being the most severe). Ask about time of the most severe ideation.

<table>
<thead>
<tr>
<th>Type #1(1-5)</th>
<th>Description of Ideation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Frequency

How many times have you had these thoughts?
(1) Less than once a week
(2) Once a week
(3) 2-5 times in week
(4) Daily or almost daily
(5) Many times each day

Duration

When you have the thoughts, how long do they last?
(1) Flitting - few seconds or minutes
(2) Less than 1 hour
(3) 1-4 hours
(4) 4-8 hours
(5) More than 8 hours persistent or continuous

Controllability

Could you stop thinking about killing yourself or wanting to die if you wanted to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with lots of difficulty
(5) Can't control thoughts

Deterrents

Are there things someone or something (e.g., family, religion, pain of death) that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Unsure if deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you

Reasons for Ideation

What sort of reasons did you have for thinking about wanting to die or killing yourself?
(1) Mostly to get attention, revenue or reparation from others
(2) Mostly to get attention for reasons or reparation from others
(3) Mostly to get attention for reasons from others
(4) Mostly to get attention, revenue or reparation from others
(5) Mostly to get attention for reasons or reparation from others
**SUICIDAL BEHAVIOR**

*(Check all that apply, so long as these are separate events; must ask about all types)*

<table>
<thead>
<tr>
<th>Actual Attempts:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A potentially self-injurious act committed with at least some wish to die, or a recent effort. Behavior was part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intentional desire to associate with the act, it can be considered an actual suicide attempt. There does not have to be any injury or harm, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun blows so no injury results, this is considered an attempt. Inherent intent: Even if an individual denies intent to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor story). Also, if someone denies intent to die but they thought that what they did could be lethal, intent may be inferred.</td>
</tr>
<tr>
<td>Have you made a suicide attempt?</td>
</tr>
<tr>
<td>Have you done anything to harm yourself?</td>
</tr>
<tr>
<td>Have you done anything dangerous where you could have died?</td>
</tr>
<tr>
<td>What did you do?</td>
</tr>
<tr>
<td>Did you ___________ in a way to end your life?</td>
</tr>
<tr>
<td>Did you want to die (even a little) when you ___________?</td>
</tr>
<tr>
<td>Were you trying to end your life when you ___________?</td>
</tr>
<tr>
<td>Did you think it was possible you could have died from ___________?</td>
</tr>
<tr>
<td>Or did you do it purely for other reason / without ANY intention of killing yourself likely to elude stress, feel better, get sympathy, or get something else to happen? (Self-injurious behavior without suicidal intent)</td>
</tr>
<tr>
<td>If yes, describe:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interrupted Attempt:</td>
</tr>
<tr>
<td>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act of not for that, actual attempt would have occurred.</td>
</tr>
<tr>
<td>Observed: Person has pills in hand but stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.</td>
</tr>
<tr>
<td>Observation: Person has gun pointed toward self, gun to take away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.</td>
</tr>
<tr>
<td>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</td>
</tr>
<tr>
<td>If yes, describe:</td>
</tr>
</tbody>
</table>

| Aborted Attempt: |
| When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by someone else. |
| Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? |
| If yes, describe: |

| Preparatory Acts or Behavior: |
| Acts or preparation toward making a suicide attempt. This can include anything beyond a verbalization or thought such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). |
| Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? |
| If yes, describe: |

| Suicidal Behavior: |
| Suicidal behavior was present during the assessment period? |

### Answer for Actual Attempts Only

<table>
<thead>
<tr>
<th>Actual Lethality/Medical Damage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = No physical damage or very minor physical damage (e.g. unbruised cheeks).</td>
</tr>
<tr>
<td>1 = Minor physical damage (e.g. lacerations, scratches, bruises, mild bleeding, minor swelling).</td>
</tr>
<tr>
<td>2 = Moderate physical damage: medical attention needed (e.g. concussion but sleepless, somewhat responsive, second-degree burns, bleeding of major vessels).</td>
</tr>
<tr>
<td>3 = Severe physical damage: medical hospitalization and usually extensive care required (e.g. concussion with severe burns, third-degree burns, minor burns to 20% of body; extensive blood loss can occur; major fractures).</td>
</tr>
<tr>
<td>4 = Extreme physical damage: medical hospitalization with intensive care required (e.g. severe injury without fractures, third-degree burns to 20% of body; extensive blood loss with unstable vital signs; major damage to vital organs).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential Lethality: Only Answer if Actual Lethality=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely lethality of actual attempt: if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun locks so no medical damage, laying on tara table with incoming turn but pulled away before fall).</td>
</tr>
</tbody>
</table>

| Yes No |
|--------|--------|--------|
| Enter Code | Enter Code | Enter Code |
| Enter Code | Enter Code | Enter Code |

| Initial-Earliest Attempt Date | Most Recent Attempt Date | Most Recent Lethal Attempt Date |

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### Other Categories Become Obsolete with Prospective data collection

<table>
<thead>
<tr>
<th>C-CASA</th>
<th>C-SSRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Self-injurious Behavior, Intent Unknown</td>
<td>Not Applicable - Unknowns are eliminated with Prospective Data Collection (These C-CASA categories created ONLY to make sense of limitations of retrospective adverse events.)</td>
</tr>
<tr>
<td>6. Not Enough Information: Death</td>
<td></td>
</tr>
<tr>
<td>9. Not Enough Information: Non-Death</td>
<td></td>
</tr>
<tr>
<td>8. Other (Accident; Psychiatric; Medical)</td>
<td>N/A: No Indication of Suicidal Ideation or Behavior</td>
</tr>
</tbody>
</table>
Example: Item data versus C-SSRS - Use C-SSRS rates of ideation lower

- Large scale obesity drug program

- PHQ-9: 452 suicidal ideations reported (8600 subjects) over 12 to 104 weeks (during RCT phase)

- C-SSRS: 12 suicidal ideations reported (5600 subjects) over 52 weeks (during extension phase)