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Concise Health Risk Tracking – Clinician-Rated (CHRT-C) 9-items

Considerations for Alto Neuroscience
ALTO-300-201 Clinical Trial



Brief Report

Suicide Rates in Clinical Trials of SSRIs, Other Antidepressants, and Placebo: Analysis of FDA Reports

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Objective: Previous reports suggesting that selective serotonin reuptake inhibitor (SSRI) use is associated with increased suicidal risk have not assessed completed suicides. The authors analyzed reports from randomized controlled trials to compare suicide rates among depressed patients assigned to an SSRI, other antidepressants, or placebo.

Method: Food and Drug Administration (FDA) summary reports of the controlled clinical trials for nine modern FDA-ap-

proved antidepressants provided data for comparing rates of suicide.

Results: Of 48,277 depressed patients participating in the trials, 77 committed suicide. Based on patient exposure years, similar suicide rates were seen among those randomly assigned to an SSRI (0.59%, 95% confidence interval [CI]=0.31%–0.87%), a standard comparison antidepressant (0.76%, 95% CI=0.49%–1.03%), or placebo (0.45%, 95% CI=0.01%–0.89%).

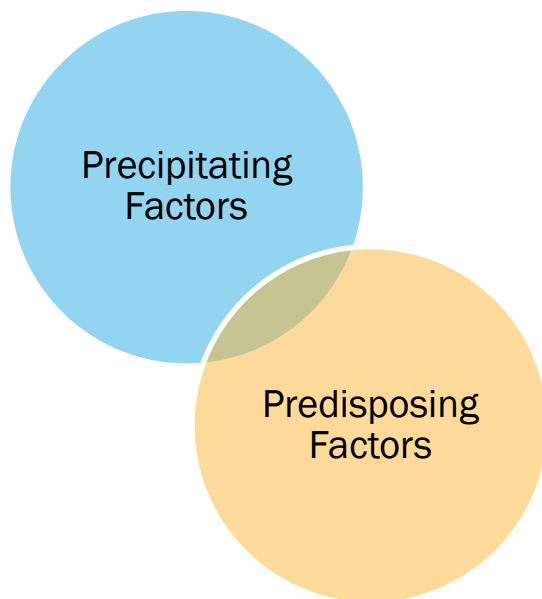
Conclusions: These findings fail to support either an overall difference in suicide risk between antidepressant- and placebo-treated depressed subjects in controlled trials or a difference between SSRIs and either other types of antidepressants or placebo.

(Am J Psychiatry 2003; 160:790–792)

- Monitoring suicidality risk following initiation of antidepressant treatment is essential in ALTO-300-201
- Per FDA, “during the initial few months of a course of antidepressant medication therapy or at times of dosage titration, patients should be monitored for worsening suicidality and unusual changes in behavior,” which can include:
 - Anxiety
 - Agitation
 - Panic Attacks
 - Insomnia
 - Irritability
 - Hostility
 - Aggressiveness
 - Impulsivity
 - Akathisia
 - Hypomania
 - Mania



Depression and Risk Factors for Suicidality



- **Suicidal ideation (SI)** (i.e., suicidal thoughts or ideas): broad term used to describe a range of wishes, contemplations, and preoccupations with death and suicide
- **Suicidal behavior:** any deliberate self-inflicted action that could cause a person to die, such as taking a drug overdose or crashing a car on purpose

Risk Factors for Suicide		
Risk Factor	Strength of Association with Suicide	Quality of Evidence**
Precipitating factors		
Drug and alcohol misuse	Strong	High
Access to lethal means	Moderate	High
Life events	Moderate	High
New diagnosis of terminal or chronic physical illness	Moderate	Moderate
Media effects ¹⁸	Weak	Moderate
Predisposing factors		
Neuropsychiatric disorders	Strong	High
Family history of suicidal behavior	Strong	High
Previous suicide attempt	Moderate	High
Adverse childhood experiences	Moderate	Moderate
Socioeconomic deprivation	Weak	Low

* Low quality indicates reported associations alone, moderate quality indicates reported associations that have been replicated in different settings, and high quality indicates associations that are supported by evidence from quasi-experimental studies or clinical trials.

Fazel S, Runeson B. Suicide. N Engl J Med 2020; 382:266-274



ALT-300-201 Schedule of Assessments: CHRT-C and CHRT-SR-12

- The CHRT-C should be completed for all participants at **Screening Visit 1** with the focus on lifetime history of suicidal behavior (i.e., **CHRT-C Lifetime**). Current suicidal ideation should also be reported.
- Additionally, the CHRT-C should be completed at any visit whenever a participant’s CHRT Self-Report version (i.e., **CHRT-SR12**) reports a score of **2, 3, or 4** on **CHRT-SR12 items 10, 11, or 12**
 - The CHRT-C will further assess suicidality at those assessments, and the time period should be since the last study visit (i.e., **CHRT-C Since Last Visit**)

	Screening Period		Double Blind (DB) Treatment Period					Open Label (OL) Treatment Period				Follow-up Period
Visit Name	Screening 1	Screening 2 Biomarker Baseline	Day 1	Week 1	Week 2	Week 4	Week 6 DB EOT	Week 7	Week 8	Week 10	Week 14 OL EOT	Safety Follow-up
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Visit Window	-7 days	-7 days		± 3 days	±3 days	±4 days	±4 days	±3 days	±4 days	±5 days	-5 days	±3 days
CHRT-C	X											
CHRT-SR12		X	X	X	X	X	X	X	X	X	X	X

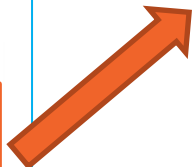


CHRT-C and CHRT-SR12 Form Comparisons

Figure 1. Concise Health Risk Tracking (CHRT) Scale

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
1. I feel as if things are never going to get better.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. There is no one I can depend on.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I have no future.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. It seems as if I can do nothing right.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I wish my suffering could just all be over.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Everything I do turns out wrong.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I feel that there is no reason to live.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I wish I could just go to sleep and not wake up.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. The people I care the most for are gone.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. I have been having thoughts of killing myself.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. I have thoughts about how I might kill myself.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. I have a plan to kill myself.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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Note. Shaded items reflect the 7-item CHRT scale.



- **CHRT-C (Lifetime)** is administered at the Screening Visit 1
- **CHRT-C (Since Last Visit)** is administered if participant scores **CHRT-SR12 items 10, 11, or 12** as either *Neither Agree or Disagree, Agree, or Strongly Agree* for subsequent visits

Concise Health Risk Tracking – Clinician-Rated (CHRT-C)

Ask patients the questions in bold italics. Please rate the patient's behavior over their lifetime (including current behavior)

YES NO	<p>1. Suicidal Ideation – passive (i.e., wanting to be dead) and/or active (i.e., method, intent, plan) SI present.</p> <ul style="list-style-type: none"> ▪ <i>In your lifetime did you think you might be better off dead or wish you were dead?</i> <p><i>Did you have any thoughts of harming or injuring yourself in any way?</i> If Yes:</p> <ul style="list-style-type: none"> ▪ <i>Have you thought about how you might do this?</i> ▪ <i>Have there been times when you seriously considered harming or injuring yourself?</i> ▪ <i>Do you intend to kill yourself or harm yourself in any way? Do you have a plan?</i> ▪ <i>How often do you have these thoughts? How long do they last?</i> <p>Frequency of suicidal ideation (select one):</p> <ul style="list-style-type: none"> ○ <i>Once per week or less</i> ○ <i>A few times per week</i> ○ <i>Once daily</i> ○ <i>Multiple times per day</i>
YES NO	<p>2. Suicide Attempt – patient made a suicide attempt (i.e., they engaged in a potentially self-injurious behavior associated with intent to die. Intent can be stated by patient or inferred by rater).</p> <ul style="list-style-type: none"> ▪ <i>Within your lifetime have you attempted to harm or injure yourself in any way with at least some intent that you might die as a result?</i> <p>If Yes:</p> <ul style="list-style-type: none"> ▪ <i>Can you tell me what happened? Was this an accident or on purpose?</i> <p>If On Purpose:</p> <ul style="list-style-type: none"> ▪ <i>Why did you _____?</i> ▪ <i>Were you trying to kill yourself when you _____?</i> <p>If "YES" list method: _____</p>
YES NO	<p>3. Non-Suicidal Self Injury (NSSI) – purposeful self-injurious behavior with no intent to die.</p> <ul style="list-style-type: none"> ▪ <i>In your lifetime, did you harm or injure yourself in any way without any intent to die?</i>
YES NO	<p>4. Preparatory Acts – Making preparatory acts toward imminent suicidal behavior (Person takes steps to injure self but is stopped by self or others. Intent to die is either stated by patient or inferred by the rater).</p> <ul style="list-style-type: none"> ▪ <i>Within your lifetime, have you done anything to prepare yourself for suicide or take any steps towards killing yourself?</i> <p>If Yes:</p> <ul style="list-style-type: none"> ▪ <i>What did you do?</i> ▪ <i>Were you thinking of killing yourself when you _____?</i> ▪ <i>Did you stop yourself or did someone else stop you before you harmed yourself?</i>
YES NO	5. Completed Suicide – Confirmed (i.e., Coroner's report, suicide note, other collateral information)
YES NO	6. Self-injurious behavior – Unknown Intent – Purposeful self-injurious behavior where associated intent to die is unknown and cannot be inferred
YES NO	7. Death (not enough information to classify as suicide)
YES NO	8. Other Injury – other not purposeful injury (accidental, psychiatric, medical), no deliberate self-harm
YES NO	<ul style="list-style-type: none"> ▪ <i>In your lifetime, have you had any accidental injuries requiring medical attention? Taken too much of your medication by accident?</i>
YES NO	9. Nonfatal Injury (not enough information to classify)

CHRT-C Items

Considerations for ALTO-300-201 Major Depressive Disorder



CHRT-C Items

The 9 items of the CHRT-C assess suicidality:

- Item 1: Suicidal Ideation
- Item 2: Suicide Attempt
- Item 3: Non-Suicidal Self-Injury (NSSI)
- Item 4: Preparatory Acts
- Item 5: Completed Suicide
- Item 6: Self-Injurious Behavior
- Item 7: Death
- Item 8: Other Injury
- Item 9: Nonfatal Injury

All CHRT-C items are scored as either **YES** or **NO** based on the certified rater's assessment of the participant's responses

		Concise Health Risk Tracking – Clinician-Rated (CHRT-C)	
Ask patients the questions in bold italics. Please rate the patient's behavior over their lifetime (including current behavior)			
YES	NO	1. Suicidal Ideation – passive (i.e., wanting to be dead) and/or active (i.e., method, intent, plan) SI present.	<ul style="list-style-type: none"> ▪ <i>In your lifetime did you think you might be better off dead or wish you were dead?</i> <p>Did you have any thoughts of harming or injuring yourself in any way? If Yes:</p> <ul style="list-style-type: none"> ▪ <i>Have you thought about how you might do this?</i> ▪ <i>Have there been times when you seriously considered harming or injuring yourself?</i> ▪ <i>Do you intend to kill yourself or harm yourself in any way? Do you have a plan?</i> ▪ <i>How often do you have these thoughts? How long do they last?</i> <p>Frequency of suicidal ideation (select one):</p> <ul style="list-style-type: none"> ○ <i>Once per week or less</i> ○ <i>A few times per week</i> ○ <i>Once daily</i> ○ <i>Multiple times per day</i>
YES	NO	2. Suicide Attempt – patient made a suicide attempt (i.e., they engaged in a potentially self-injurious behavior associated with intent to die. Intent can be stated by patient or inferred by rater).	<ul style="list-style-type: none"> ▪ <i>Within your lifetime have you attempted to harm or injure yourself in any way with at least some intent that you might die as a result?</i> <p>If Yes:</p> <ul style="list-style-type: none"> ▪ <i>Can you tell me what happened? Was this an accident or on purpose?</i> <p>If On Purpose:</p> <ul style="list-style-type: none"> ▪ <i>Why did you _____?</i> ▪ <i>Were you trying to kill yourself when you _____?</i> <p>If "YES" list method: _____</p>
YES	NO	3. Non-Suicidal Self Injury (NSSI) – purposeful self-injurious behavior with no intent to die.	<ul style="list-style-type: none"> ▪ <i>In your lifetime, did you harm or injure yourself in any way without any intent to die?</i>
YES	NO	4. Preparatory Acts – Making preparatory acts toward imminent suicidal behavior (Person takes steps to injure self but is stopped by self or others. Intent to die is either stated by patient or inferred by the rater).	<ul style="list-style-type: none"> ▪ <i>Within your lifetime, have you done anything to prepare yourself for suicide or take any steps towards killing yourself?</i> <p>If Yes:</p> <ul style="list-style-type: none"> ▪ <i>What did you do?</i> ▪ <i>Were you thinking of killing yourself when you _____?</i> ▪ <i>Did you stop yourself or did someone else stop you before you harmed yourself?</i>
YES	NO	5. Completed Suicide – Confirmed (i.e., Coroner's report, suicide note, other collateral information)	
YES	NO	6. Self-injurious behavior – Unknown Intent – Purposeful self-injurious behavior where associated intent to die is unknown and cannot be inferred	
YES	NO	7. Death (not enough information to classify as suicide)	
YES	NO	8. Other Injury – other not purposeful injury (accidental, psychiatric, medical), no deliberate self-harm	<ul style="list-style-type: none"> ▪ <i>In your lifetime, have you had any accidental injuries requiring medical attention? Taken too much of your medication by accident?</i>
YES	NO	9. Nonfatal Injury (not enough information to classify)	

CHRT-C Scale Format and Questions

Per CHRT-C guidelines, the clinician asks the participant to rate the extent to which each statement describes how the participant has been feeling or acting



For each item, ask the question in bold italicized text. For Item 1 (at the Screening visit), ask: ***“In your lifetime, did you think you might be better off dead or wish you were dead?”***

The question in non-bolded text can be asked for clarification: “Did you have any thoughts of harming or injuring yourself in any way?”



If the participant responds with “Yes,” ask all the remaining questions in bold italicized text for the item, starting with: ***“Have you thought about how you might do this?”***

The last follow-up question of Item 1 in bold italicized text assesses frequency of ideation by asking: ***“How often have you had these thoughts?”*** and ***“How long do they last?”***

- Ask all questions as written, in order to avoid ambiguity and ensure that the participant understands the instruction
- Provide clarification before beginning to ask the item-level questions
- For each item, the participant should endorse the level of agreement that they feel
- Equivocal answers (e.g., “not really,” “I don’t know,” “not all the time”) should be clarified and followed-up on



CHRT-C Item 1 Suicidal Ideation

Item 1 assesses passive and active suicidal ideation by asking:
“In your lifetime [or since the last visit], did you think you would be better off dead or wish you were dead?”

“Did you have any thoughts of harming or injuring yourself in any way?”

No

Yes

Move on to Item 2

- If the participant scored ≥ 2 on Item 10 of the CHRT-SR12 but denies that they would be better off dead or wish they were dead, continue to follow up to clarify the inconsistency between responses on the CHRT-SR-12 and CHRT-C
- Suicidal ideation (SI) presents in a "waxing and waning manner," so the magnitude and characteristics of suicidal ideation can fluctuate
- It is critically important for the rater to recognize that SI is a heterogeneous phenomenon that varies in intensity, duration, and character. As there is no "typical" suicide victim, there is no "typical" suicidal ideation

“Have you thought about how you might do this?”

“Have there been times when you seriously considered harming or injuring yourself?”

“Do you intend to kill yourself or harm yourself in any way? Do you have a plan?”

“How often have you had these thoughts? How long do they last?”
Frequency of ideation: Once per week or less, A few times per week, Once daily, or Multiple times per day



CHRT-C Item 2 Suicide Attempt

Participant made a suicide attempt (i.e., they engaged in a potentially self-injurious behavior associated with intent to die)
“In your lifetime [or since the last visit] did you attempt to harm or injure yourself in any way with at least some intent that you might die as a result?”

No

Yes

Move on to Item 3

“Can you tell me what happened?”

List Method

“Was this an accident or on purpose?”

Suicidal behavior is strongly associated with completed suicide and should be assessed thoroughly to determine the potential lethality and context of the attempt

Accident

On purpose

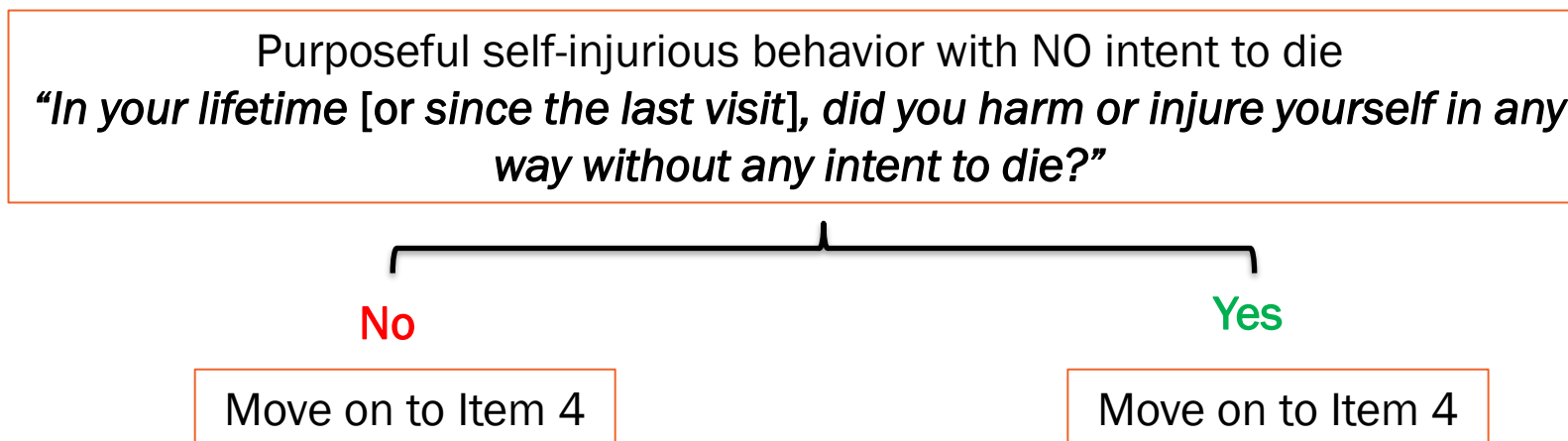
Move on to Item 3

“Why did you _____?”

“Why were you trying to kill yourself when you _____?”



CHRT-C Item 3 Non-Suicidal Self Injury (NSSI)



- Non-suicidal self-injury (NSSI): deliberate, self-inflicted destruction of body tissue without suicidal intent and for purposes not socially sanctioned
- NSSI includes behaviors such as cutting, burning, biting and scratching skin
- This item differentiates NSSI from self-injury with intent to die



CHRT-C Item 4 Preparatory Acts

Making preparatory acts toward imminent suicidal behavior
(Person takes steps to injure self but is stopped by self or others. Intent to die is either stated by the participant or inferred by the rater)
“In your lifetime [or since the last visit] have you done anything to prepare yourself for suicide or take any steps towards killing yourself?”

No

Yes

Move on to Item 5

“What did you do?”

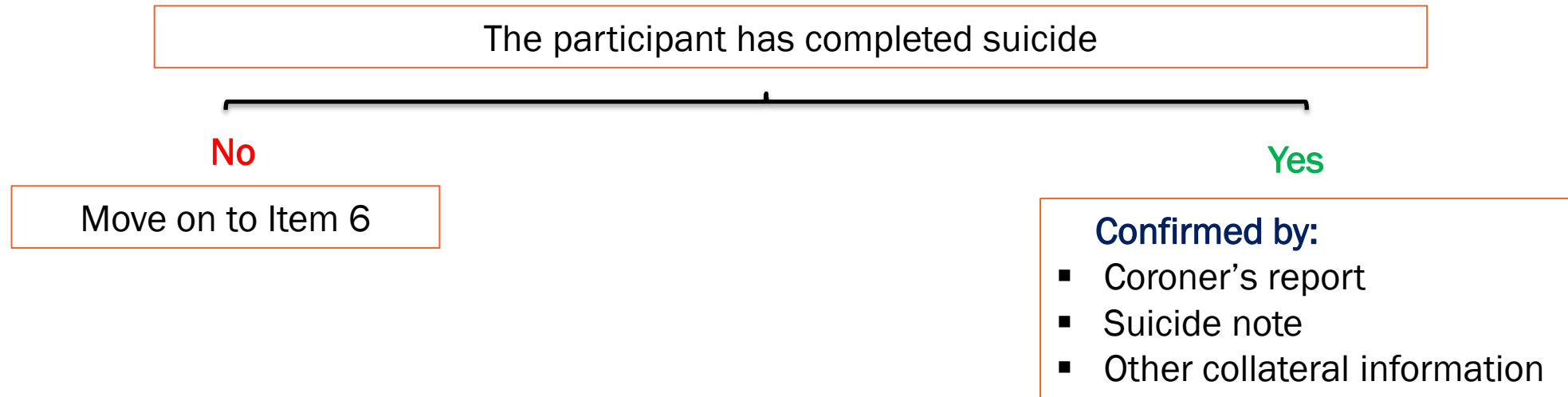
“Were you thinking about killing yourself when you ___?”

“Did you stop yourself, or did someone else stop you before you harmed yourself?”

This item assesses active suicidal behavior in the form of preparatory acts, which can include writing a suicide note, identifying a means to kill oneself (e.g., locating a bridge or tall building to jump from, purchasing a firearm, determining a lethal dose of medication), or taking specific steps to commit suicide that were interrupted or aborted (i.e., someone stopped the act, or the participant decided not to complete the act after initiating it)

CHRT-C Item 5

Completed Suicide



Completed suicide: death that is known or reasonably suspected to have resulted from an intentional act of the deceased



CHRT-C Item 6 Self-Injurious Behavior

Unknown intent – Purposeful self-injurious behavior where associated intent to die is unknown and cannot be inferred

No

Move on to Item 7

Yes

Move on to Item 7

An individual may engage in self-injury without suicidal intent for a variety of reasons, including in order to:

- Receive attention or access to a preferred object or activity
- Escape from or avoid low preferred activities such as activities of daily living, work, or academic demands
- Provide sensory input to an area of the body or reduce pain



CHRT-C Item 7 Death

Death (not enough information to classify as suicide)

No

Move on to Item 8

Yes

Move on to Item 8



CHRT-C Item 8 Other Injury

Other not purposeful injury (accidental, psychiatric, medical), no deliberate self-harm
“In your lifetime [or since the last visit] have you had any accidental injuries requiring medical attention? Have you taken too much of your medication by accident?”

No

Move on to Item 9

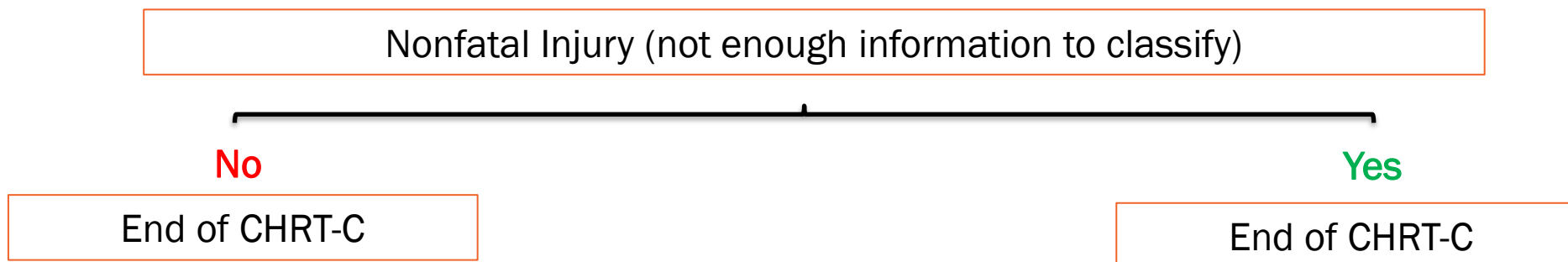
Yes

Move on to Item 9

It is important to verify whether the injury was purposeful or not and determine the manner of injury and what treatment was required



CHRT-C Item 9 Nonfatal Injury



Nonfatal injury: bodily harm (can be unintentional or violence-related) resulting from severe exposure to an external force or substance or a submersion



Summary of CHRT-C Administration in ALTO-300-201



- Assessment of suicide risk is a critical safety component of the ALTO-300-201 study
- The CHRT-C is administered at the Screening visit and at any subsequent visit for which the participant scores 2 or higher on CHRT-SR12 items 10, 11, or 12
- For each CHRT-C item, questions in bold italicized text should be **read verbatim** to the participant and follow-up questions should be asked when necessary
- All available information should be used when completing the CHRT-C, including collateral information such as coroner's report, suicide notes, medical records, and reports from other clinical assessments



Thank you!

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