Suicidal Ideations and Behaviors:

Regulatory Perspectives

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—no conflicts of interest to disclose—

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(mentally add "But talk to us about your specific situation!" after everything I say)

- Diagnosis-representative population vs Suicidal sub-population vs Suicide-related outcome
- Context of what is known about the IP
- Look in DARRTS for suicide INDs, FDA label for suicide indications
- Value of well documented SAE reports
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- Panel requests:
- FDA perspectives on outcome measures, suicide death in a trial
- FDA perspectives on RWE for suicide prevention – need to look at guidance (probably very difficult to establish claim based on RWE); better to do a large controlled trial
- SI as an AE in a suicidal pop – forms of worsening should be reported as AEs
-
- Primary outcomes should measure how a patient feels functions or survives; for death and attempt this is relatively straight forward, however for ideation work should be done that the measure of suicidal ideation is in fact capturing a meaningful aspect of feeling or functioning. SI as epiphenom of patient distress vs contributor to patient distress, does it interfere with function?

Topics covered

- SIB categories
- Spectrum of target and study populations
- Approaching SIB as safety outcome
- SIB as efficacy outcome
- SIB as intercurrent event (ICE)

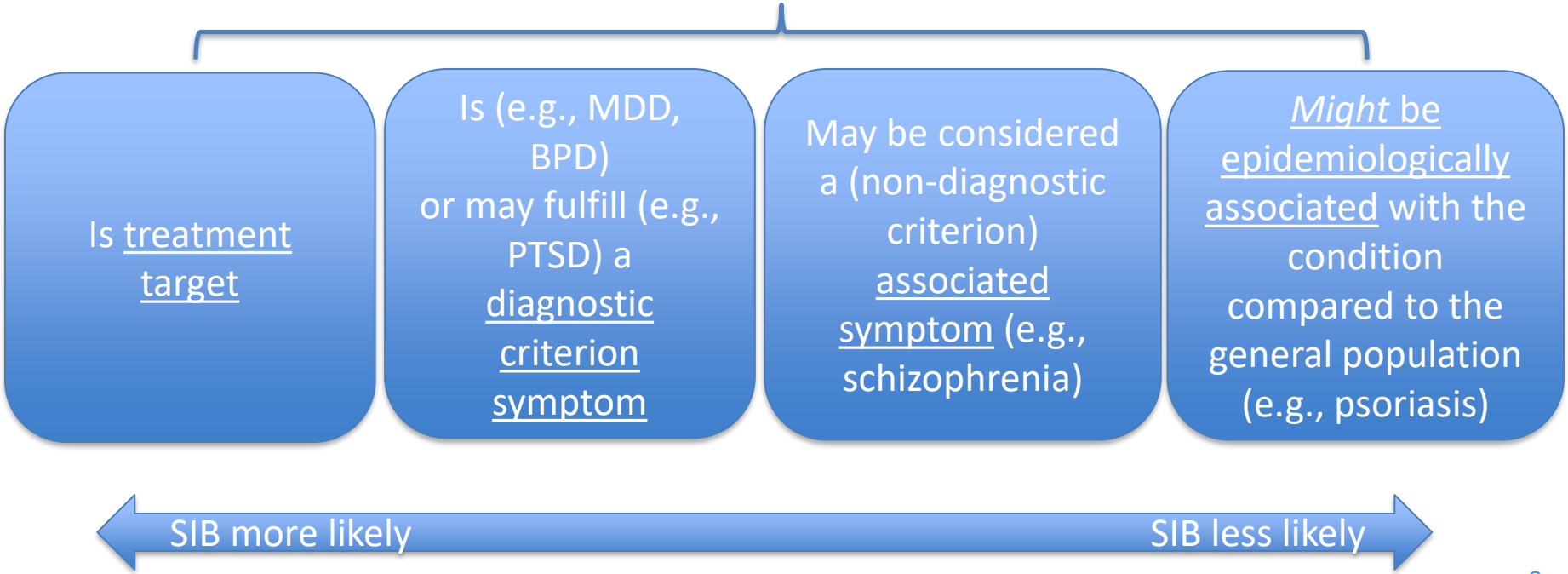
What are Suicidal Ideations and Behaviors (SIB)?

C-CASA categories (adopted in 2012 draft guidance: *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials*)

- **SI**=Suicidal Ideation
  1. Passive
  2. Active (no method & no intent)
  3. Active (method & no intent)
  4. Active (method and intent, but no plan)
  5. Active (plan)
- **SB**=Suicidal Behavior
  1. **SD**=Suicide Death
  2. **SA**=Suicide Attempt
  3. Interrupted **SA**
  4. Aborted **SA**
  5. Preparatory actions (**PA**) towards imminent SA

Spectrum of SIB relation to target Pop

SIB in indications where SIB:



SIB as Safety Outcome

SIB as Safety Outcome

in indications where SIB:

Is treatment target	Is (e.g., MDD, BPD) or may fulfill (e.g., PTSD) a diagnostic criterion symptom	May be considered a (non-diagnostic criterion) associated symptom (e.g., schizophrenia)	Might be epidemiologically associated with the condition compared to the general population (e.g., psoriasis)
Include subjects		May include subjects (conder associated SIB importance in clin pop)	
SAE if hosp/death /adjudic. outcome	SAE if baseline SIB excluded or considered medically significant		
AE if new or significant adverse change from BL			

As safety outcome

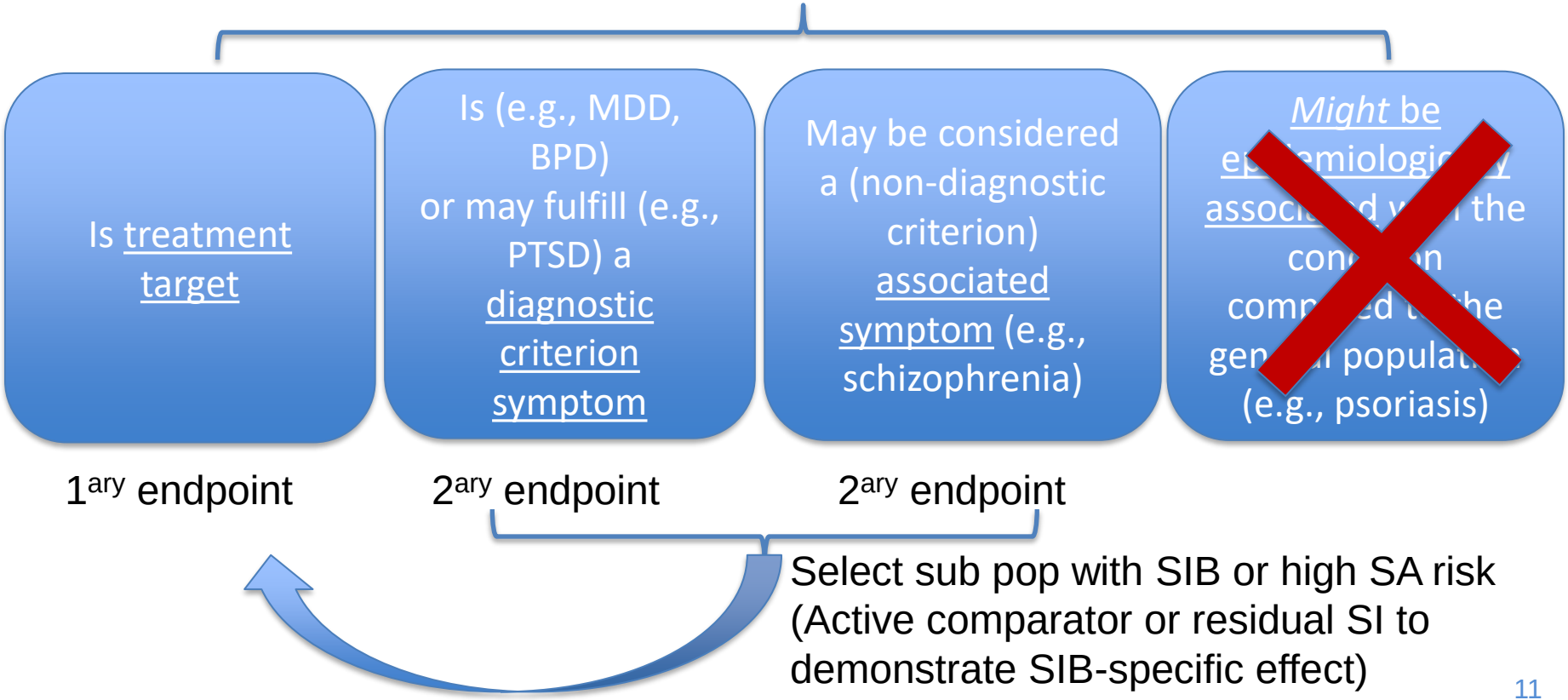
Lump vs Split:

- Provide finest grain possible (e.g., Aborted SA, with high/low potential lethality, interrupted SA with high/low potential lethality, High lethality SA, etc.)
- Signal can be analyzed with multiple grouping approaches.
- C-CASA adequate.

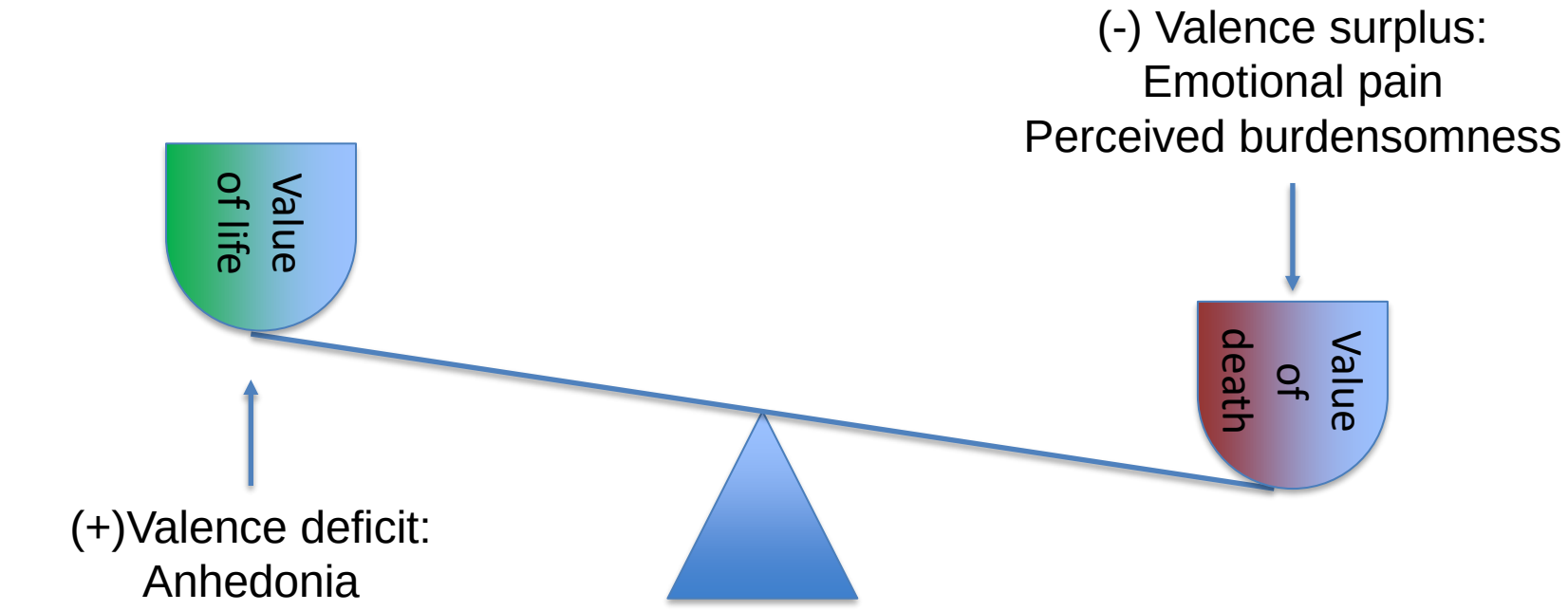
SIB as Efficacy Outcome

SIB as Efficacy Outcome

in indications where SIB:



SI as decisional balance



Endpoints – Feeling, Functioning, Surviving

- SIB spectrum: common (but SD is rare
- SIB spectrum vs Feeling, Functioning, Surviving:
  - SI → Feeling? SI→→Function? SI→→→Survival?
  - SA → Feeling? SA→Function? SA→→Survival?
  - SD=Survival (SD as an intercurrent event for other endpoint)

  - Alternatively, might consider SI & SB a little bit of each

    But…can still be tricky as ordinal/continuous outcomes:
    - E.g., passive SI may reflect severe chronic distress or be intrusive and impairing while active SI with method may reflect transient equal or lesser distress in a different patient or be less frequently intrusive & therefore less impairing
    - Concern at group level may be mitigated by adequate sample size and randomization
    - At individual level may be more uncertainty SI and SB may comprise various phenomena and processes
- ClinRO/PRO Should be well-constructed/validated – FDA Guidance on PRO qualification highlights important considerations

Example CGI-SS-r:

"Considering your total clinical experience with suicidal patients and all information available to you, how suicidal is the patient at this time?"

* Consider seriousness/lethality of any plan or suicide attempt in the overall rating

Rating	Guide to Rating
0 – Normal, not at all suicidal	Not suicidal
1 – Questionably suicidal	Minimal ideations; little if any impulsivity for suicide; few risk factors; many protective factors and no impact on function.
2 – Mildly suicidal	Occasional ideations; little if any impulsivity for suicide; few risk factors; adequate protective factors and no or minimal impact on function.
3 – Moderately suicidal	Intermittent ideations; with possible impulsivity for suicide; may or may not have plan or recent attempt*; several risk factors; protective factors may outweigh risk factors and some impact on function.
4 – Markedly suicidal	Regular ideations with intent or potential for impulsive actions for suicide; may or may not have plan or recent attempt*; multiple risk factors outweigh protective factors; and marked impact on function.
5 – Severely suicidal	Frequent ideations with intent; well-worked-out suicide plan; may or may not have recent attempt*; multiple risk factors outweigh protective factors; and major impact on function.
6 – Among the most extremely suicidal patients	Nearly constant suicidal ideations and intent; well-worked-out plan and preparation underway or recent attempt*; and severe impact on function.

- 10 C-CASA categories for SIB →
- Many potential SIB-related effects to target →
  - Define clinical question of interest (and corresponding estimand) carefully
  - Many potential alternative ways to lump outcomes
  - Multiple supportive endpoints possible and encouraged to assist in interpretation of findings
  - **Talk with us to reach agreement on key endpoint(s) as soon as possible!**

Example: Clozapine

SIB efficacy claim support

- Prospective, randomized, open-label, active-controlled evaluating flex dosing of clozapine vs olanzapine. Extensive concomitant psychotropics allowed: 84% with antipsychotics, 65% with anxiolytics, 53% with antidepressants, and 28% with mood stabilizers. There was significantly greater use of concomitant psychotropic medications among the patients in the olanzapine group.
- 956 patients with schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be at risk for recurrent suicidal behavior and at least 1 of:
  a. SA or Hosp. to prevent SA within past 3 y.
  b. Moderate-to-severe SI with a depressive component or with command hallucination within one week prior to their baseline evaluation.

1ary outcome - time to event including:

(1) significant SA, including SD

(2) hospitalization due to imminent suicide risk, including increased level of surveillance for suicidality for patients already hospitalized

(3) worsening of suicidality severity as demonstrated by “much worsening” or “very much worsening” from baseline in the Clinical Global Impression of Severity of Suicidality as assessed by the Blinded Psychiatrist (CGI-SS-BP) scale.

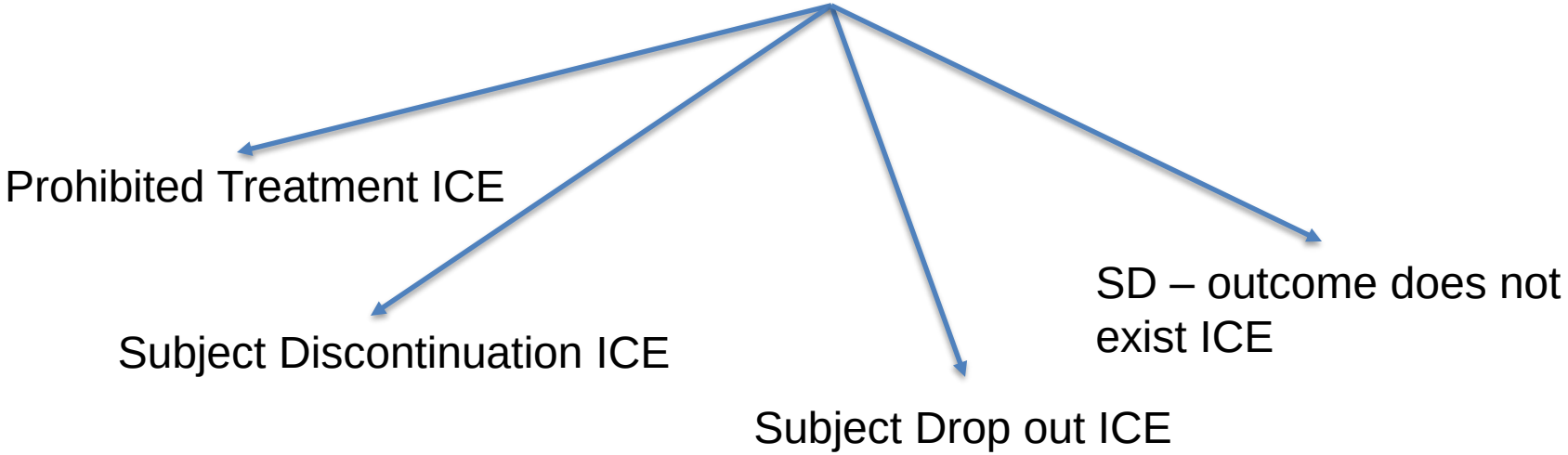
A determination of whether or not a reported event met criterion 1 or 2 above was made by the Suicide Monitoring Board (SMB), a group of experts blinded to patient data.

Example: Esketamine

SIB efficacy claim support

- 2 RDB parallel arm fixed dose 4-week trials of ESK+SOC vs PBO+SOC in ~200 adults w/ moderate-to-severe MDD (MADRS total score >28) and active SI w/ intent (C-SSRS >=4)
- SIB outcome – was 2ary efficacy measure was the change in Clinical Global Impression of Suicidal Severity - Revised (CGI-SS-r) score at 24 hours after first dose (Day 2). (derived from CGI-SS-BP unsed in clozapine InterSEPT study)
- An SIB claim was **NOT** supported – ultimately, SIB risk enrichment of MDD population provided a population where the benefits justified risks of treatment

SIB as ICE


Prohibited Treatment ICE
Subject Discontinuation ICE
Subject Drop out ICE
SD – outcome does not exist ICE

SIB is :	Trigger for prohibited Tx	Cause for Tx discontinuation	Cause for subject drop-out	Cause for outcome non-existence (SD)
Tx Target	Hypothetical or composite, Tx policy could be reasonable in certain contexts	Tx Policy	Consider composite or LOE imputation	Composite
Criterion symptom of target indication	Hypothetical or Tx policy could be reasonable in depending on context, could consider composite	Tx policy	Consider composite or LOE imputation	Consider composite or LOE imputation
Associated with target indication	Hypothetical or Tx policy could be reasonable in depending on context	Tx policy	Imputation aligned with discontinuation	LOE imputation or Imputation aligned with discontinuation
Potential association with target indication	Hypothetical or Tx policy could be reasonable in depending on context	Tx policy	Imputation aligned with discontinuation	Imputation aligned with discontinuation

Questions and Answers

Q: Could RWE support an SIB efficacy claim?

A: In principle, yes; might be most applicable to an SD claim where very large data are needed to detect an effect. But see https://www.fda.gov/media/152503/download:

Many issues would need to be addressed, e.g.,

- Confounding by indication, beliefs and changes in beliefs about relation of available treatment to suicide risk.
- Strength and reliability of propensity scores
- Secular trends in SD, SA, availability of means
- Secular trends in prescribing
- Drug-drug interactions
- Locality differences in high lethality means (e.g., gun ownership)
- Informative censoring
  - So: talk (and talk some more) with us about your RWE plan for such a claim.

Conclusions

https://commons.wikimedia.org/wiki/File:Hephthalite_horseman_on_British_Museum_bowl_460-479_CE.jpg

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