ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

FDA U.S. FOOD & DRUG ADMINISTRATION

Including People with Suicidal Ideations and Behaviors in CNS Clinical Trials: *Regulatory Perspectives*

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—no conflicts of interest to disclose—

Disclaimer

The views expressed in this presentation are the personal views of the speaker.

They should *not* be understood or quoted as being made on behalf of or reflecting the policy or position of the FDA, HHS, or the Federal Government.

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

Key Takeaways

- Include subjects with SIB in CNS clinical trials!
- Inclusion of subjects with active SIB in clinical trials (including placebo-controlled trials) is possible and has been done successfully in the drug development context
- Considerations for individual subject inclusion may need to go beyond SIB categories: clinical decision making should be involved
  - Consider the treatment development decision (or other purposes) your trial is intended to support
  - Consider how SIB relates to your target indication
- We are happy to help you work these things out, so please come talk with us about your development program!

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

What will **not** be covered

- **Assessment of SI/B as a Safety or Efficacy Outcome**
  - You can find FDA perspectives in previous talks posted on ISCTM's website (Kim, Fall 2019; Yaseen, Fall 2024)
- **Risk Mitigation Strategies**
  - E.g., Rescue protocols, Staff training requirements, Emergency procedures
  - Trial and indication specific; meet with us – we are happy to discuss!
- **Specific Inclusion and Exclusion Criteria**
  - Trial and indication specific; meet with us
  - In/exclusions can utilize measure-based operationalization but should be driven by clinical and trial considerations not the measures themselves

Including subjects with SIB consistent with long-standing FDA guidance

2005 Guidance to Industry on "Premarketing Risk Assessment" https://www.fda.gov/media/71650/download:

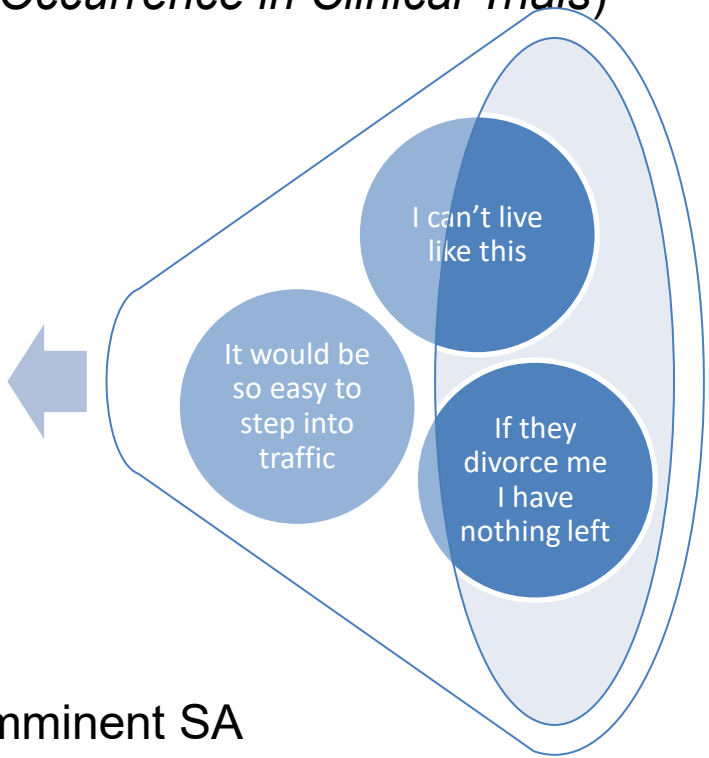
- Premarketing safety databases should include, to the extent possible, a population **sufficiently diverse to adequately represent the expected target population, particularly in phase 3 studies**.
- To the extent feasible, **only patients with obvious contraindications** or other clinical considerations that clearly dictate exclusion should be excluded from study entry.
- Inclusion of a diverse population allows for the development of safety data in a broad population that includes patients sometimes excluded from clinical trials… **Broadening inclusion criteria in phase 3 enhances the generalizability of the safety (and efficacy) findings**.

What are Suicidal Ideations & Behaviors?

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

SIB

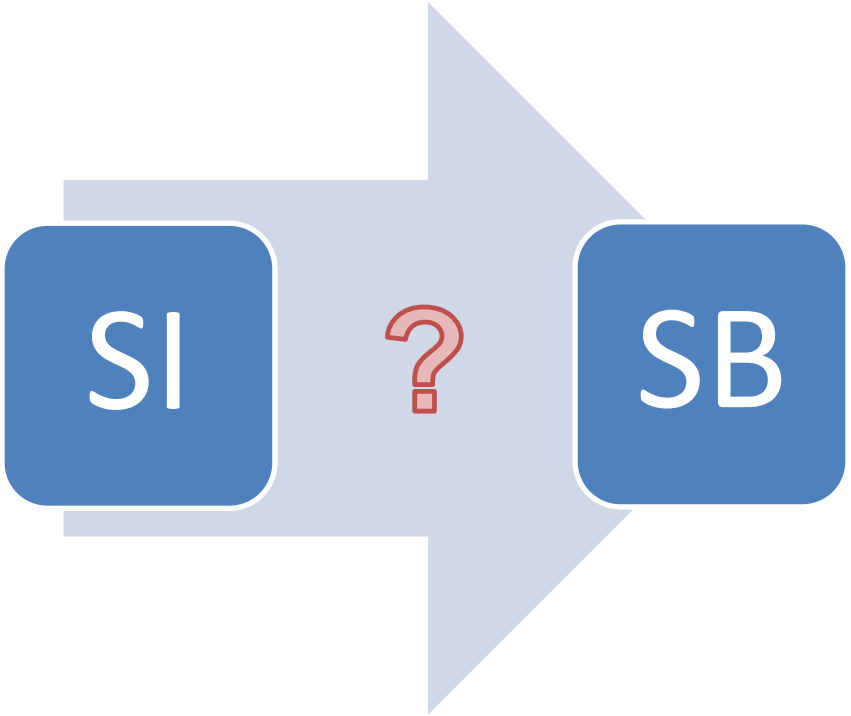
- **SI**=Suicidal Ideation
  1. Passive (wish to be dead)
  2. Active (no method & no intent)
  3. Active (method & no intent)
  4. Active (method and intent, no plan)
  5. Active (plan)
- **SB**=Suicidal Behavior
  1. **SD**=Suicide Death
  2. **SA**=Suicide Attempt
  3. Interrupted **SA**
  4. Aborted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



In/exclusion considerations

- Risk of inclusion to study
  - missing data?
  - need for protocol deviations
- Risk of inclusion to subject
  - trial compatibility with appropriate care
  - trial introduces new risk (e.g., discontinuation syndrome)
- Treatment Emergent SI/B interpretability

SI and SB Relationship



- Suicide remains difficult to prevent or understand on systematic level
- Suicide is heterogeneous
- Screening/monitoring relies heavily on self-report but SI/SB often occurs privately and may not be disclosed or may be minimized
- SI rarely leads to SB but is reliably identified as a risk factor in research literature
- SB (especially suicides) are rare in studies
- **Screening will always have major limitations**

Incident Treatment Emergent SI/B Rates in Post-2009 Antidepressant Trials

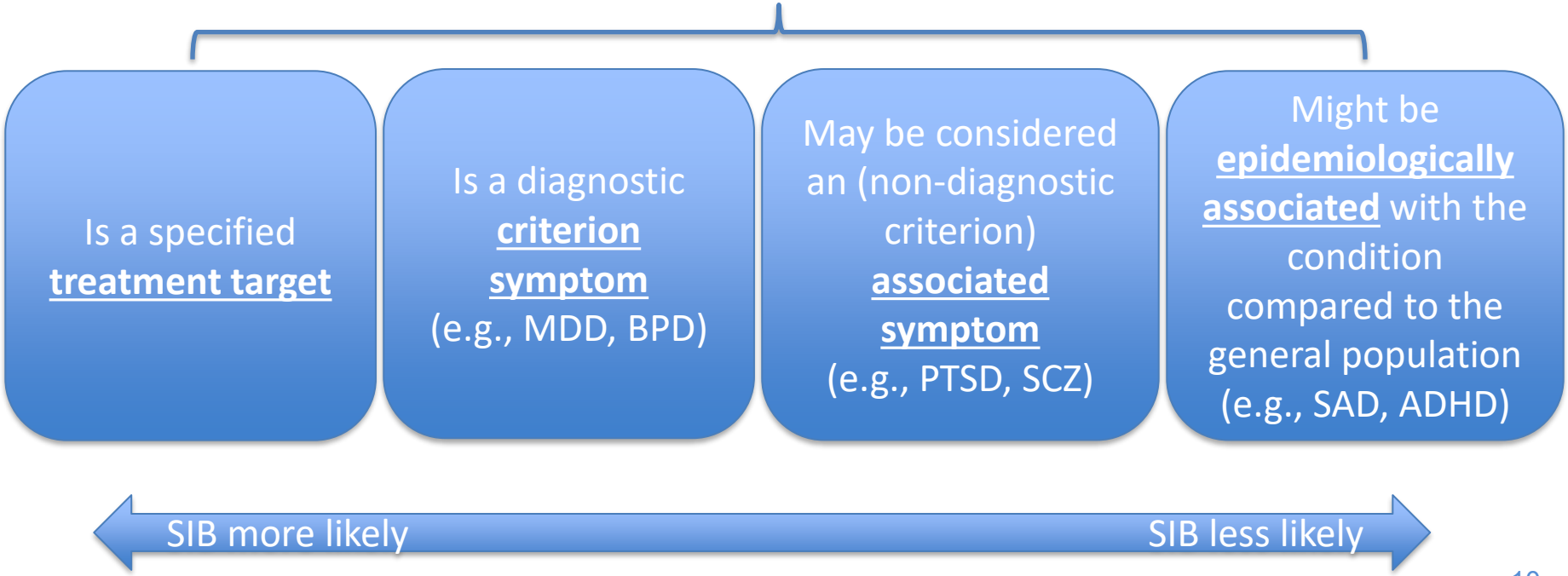
	N	Suicidal Ideation (%)				Suicidal Behavior (%)			
		HAMD	MADRS	C-SSRS	AE	HAMD	MADRS	C-SSRS	AE
Levomilnacipran	1297	16.3	51.2	26.1	24.1	0.07	0.54	2.5	0.38
Placebo	759	16.6	54.4	24.2	22.4	0.01	0.13	2.5	0.13
Vilazodone	233	66.5	53.6	21.9	0.50	0	0	0	0
Placebo	233	63.1	53.6	26.6	0.14	0	0	0	0
Vortioxetine	1169	10.0	56.8	15.1	0.3	0	0.26	0.26	0.1
Placebo	721	11.7	57.0	15.7	0.3	0	0.27	0.14	0
Active Control (Fluoxetine)	298	7.4	50.0	5.7	0.5	0	0	0	0.1

Analysis and Table by Shamir Kalaria PharmD, PhD FDA

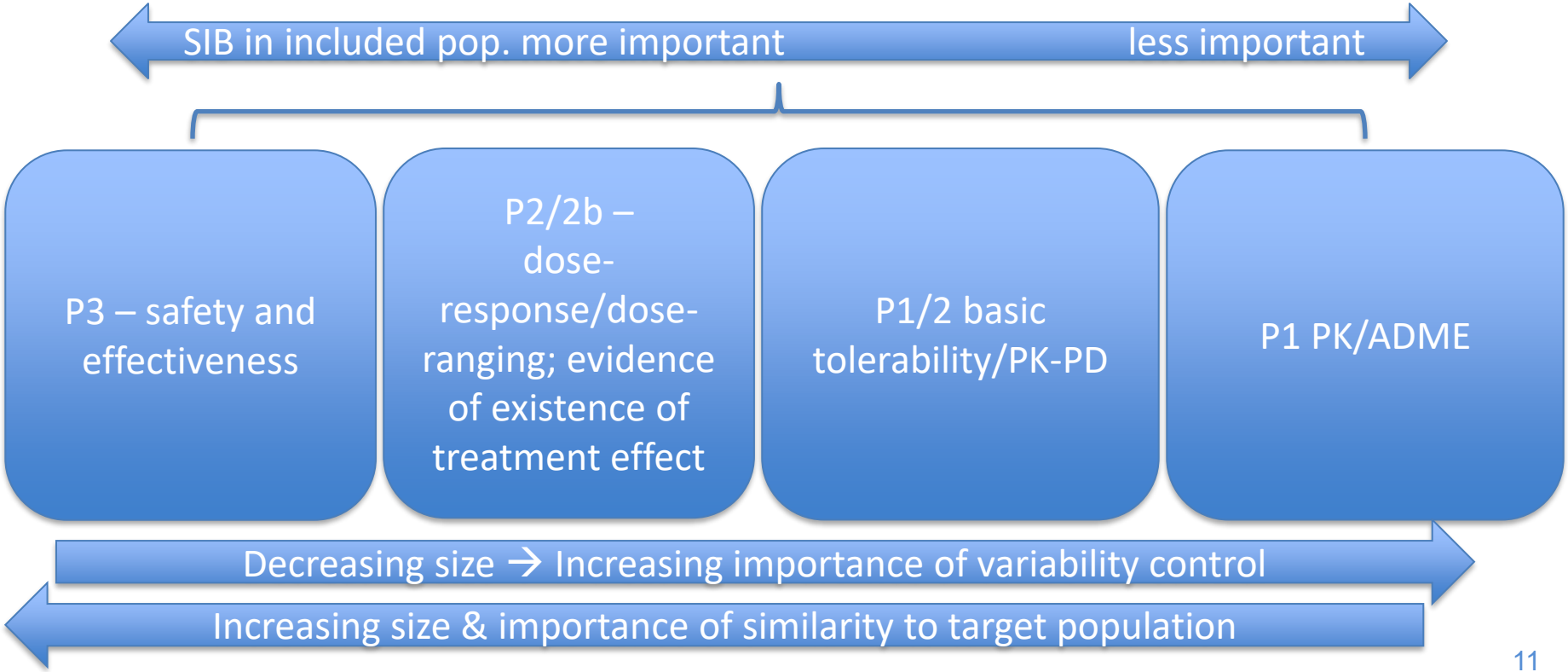
Spectrum of SIB

relation to target population

SIB in indications where SIB:



Spectrum of Development: relation to target population



Why (in/ex)clude where?

Trial size	Include	Exclude
small	When excluding is not important *(Medical ethical principles of Justice & Autonomy)*	Want early detection of potential SIB-related safety signal; rigorous **exclusion** might improve attribution of relatively rare events
LARGE	Include subjects to support generalizability of safety and effectiveness Oversampling may allow improved detection of SIB-related risks and benefits *(Medical ethical principles of Justice & Autonomy)*	Exclude subjects based on compatibility of clinical needs with trial operation, allowed/prohibited treatments Trial risks to individuals increase with sample size *(Medical ethical principles of Beneficence/Non-maleficence)*

	SIB required in Target pop.	SIB major comorbidity	SIB minor comorbidity	SIB ≤ general population
P1	Consider excluding	Consider excluding	Consider excluding	Consider excluding
P2	Include but consider limiting severity in proportion to evidence for benefit (e.g., 2a vs 2b)	Include but consider limiting severity in proportion to evidence for benefit/Consider oversampling	Include but consider limiting severity in proportion to evidence for benefit	Include but consider limiting severity in proportion to evidence for benefit
P3	Maximize inclusion	Minimize exclusion/ Consider oversampling	Consider oversampling if P2 or class signal	Consider oversampling if P2 or class signal

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