Psychometric and Statistical Considerations for Including Patients with SI/B in Clinical Trials

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Background and Disclaimers

- *Primary background in industry (pharma, CROs for 30 years)*
- *Now partly retired, working academia - clinical*
- *Licensed clinical psychologist, with specialized training in neuropsychology, statistics and psychometrics*
- *Applied experience in pharma advancing SI/B programs, scales, and psychometric development*
- *No actual or potential conflicts to report (past five years)*

The University of Texas at Austin
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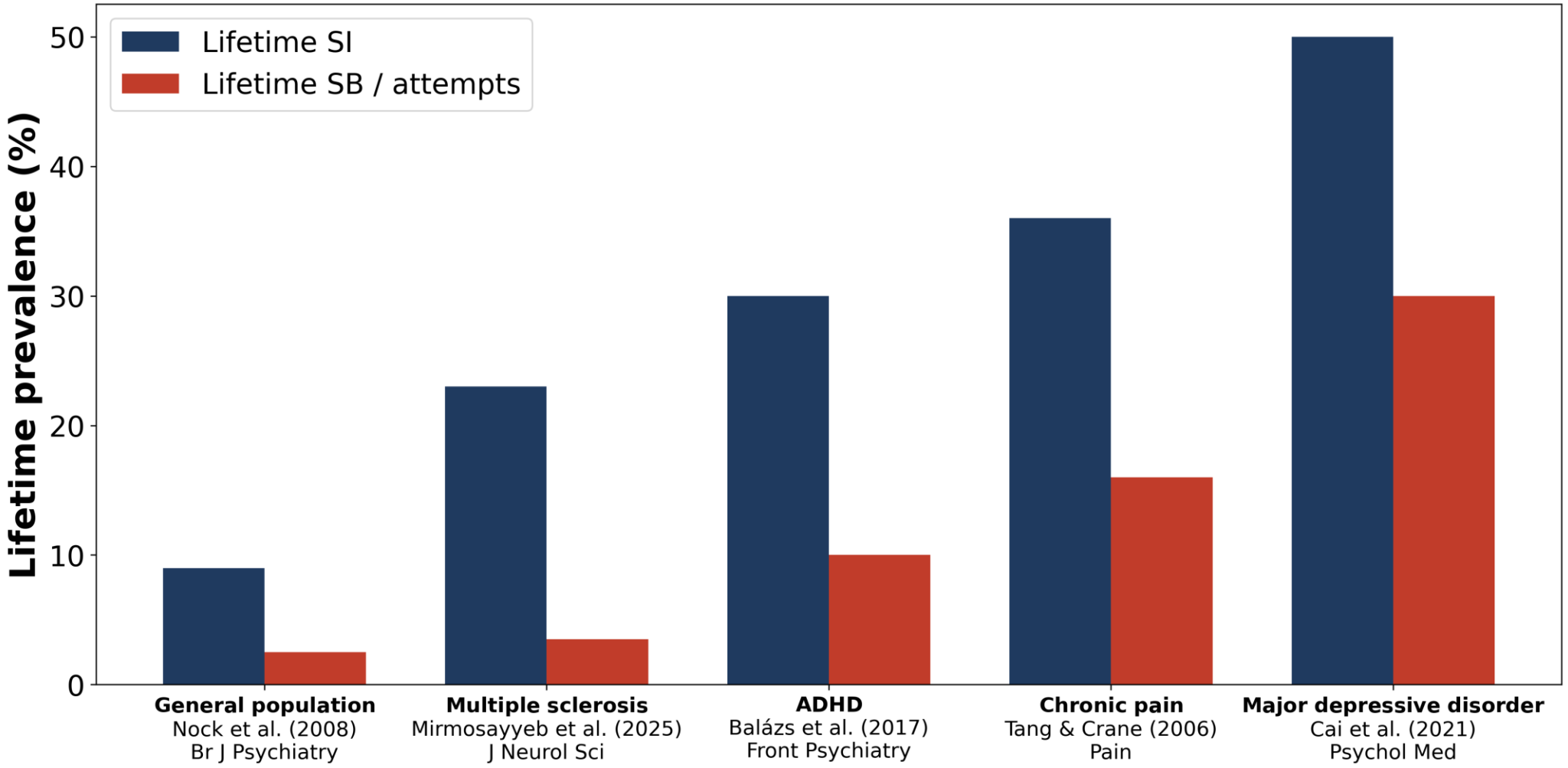
Context

- “All-comers” will refer to current ideation and past behavior, not necessarily those at imminent risk.
- This presentation focuses on clinical trials for non-SI/B treatments.
- Field reconsidering “ultra-clean” samples. Regulators and NIH agree that trial eligibility should better reflect the target population at large.
- Prospective SI/B assessment of suicidality is common in many trials; it is required in industry trials studying CNS-active compounds.
- FDA SI/B guidance does **NOT** require, but can indirectly lead to, systematic exclusion of patients who endorse significant SI/B by using, e.g., C-SSRS cutoffs.
- University IRBs require comprehensive safety plans if SI/B is assessed, often prompting researchers to avoid scales and omit specific SI/B items.

Approximate Lifetime Prevalence of SI/B in Select Populations



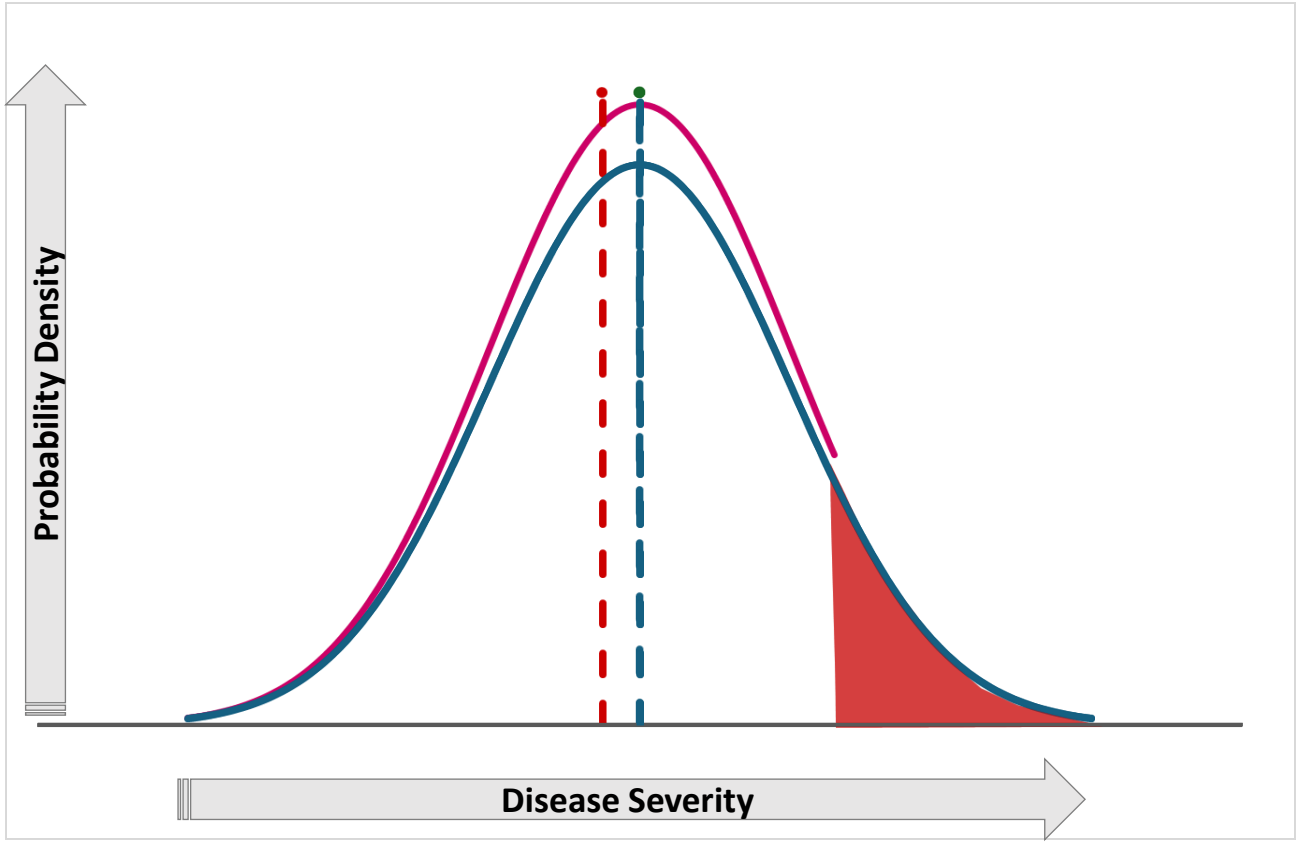
Downstream Consequences of Exclusion

Exclusion systematically alters the population estimand, leading to:

- reduced visibility of how treatment behaves in the full clinical spectrum
- systematic truncation of the severity distribution
- shifts in mean severity
- changes in variance structure, loss of measurement invariance
- misalignment of power assumptions
- reduced generalizability

These consequences emerge when they are not accounted for in trial design, measurement strategy, and power assumptions.

Truncation of the Severity Spectrum



Conditional sampling shifts the mean severity downward.

Reduced Visibility of the Broader Clinical Spectrum

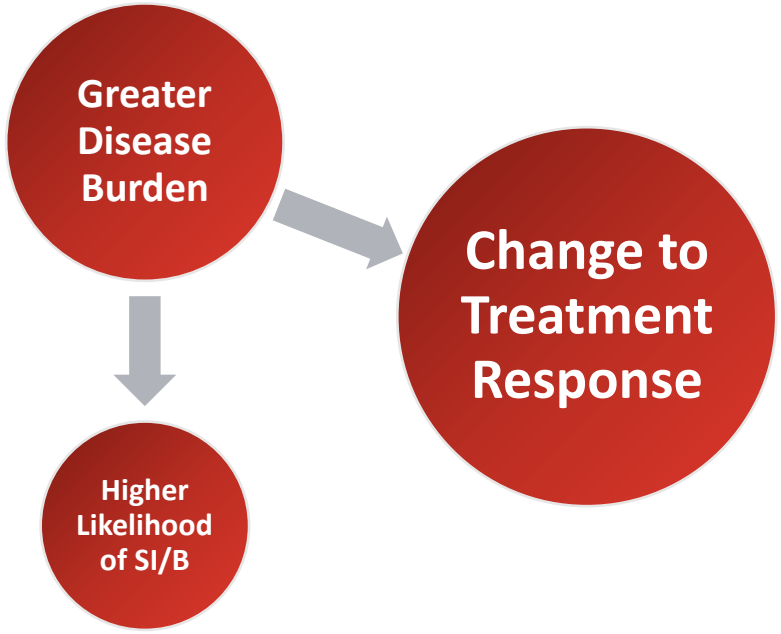
- Exclusion removes part of the, often known, severity range.
- Relationships between baseline severity and outcomes become partially unobservable.
- This limits:
  - subgroup observations,
  - model checking,
  - interpretation of secondary endpoints, including disability and quality of life.

Absence of observed effects ≠ absence of underlying effects

also

significant observed effects ≠ generalizable effects.

Potential Modification of Observable Treatment Response



Greater burden of disease is often associated with higher likelihood of SI/B

and may influence observable treatment response.

For example:

Migraine

Pooled prevalence is approx 15% for SI and 4% for SB (Pei et al, 2020, J Affect Dis). Greater number of baseline migraine days was associated with larger absolute reduction (Dodick et al, 2018, NEJM).

Multiple Sclerosis

Greater baseline inflammatory activity was associated with larger treatment effects (Kappos et al, 2007, Lancet Neurol).

Influence on Variance Structure and Power

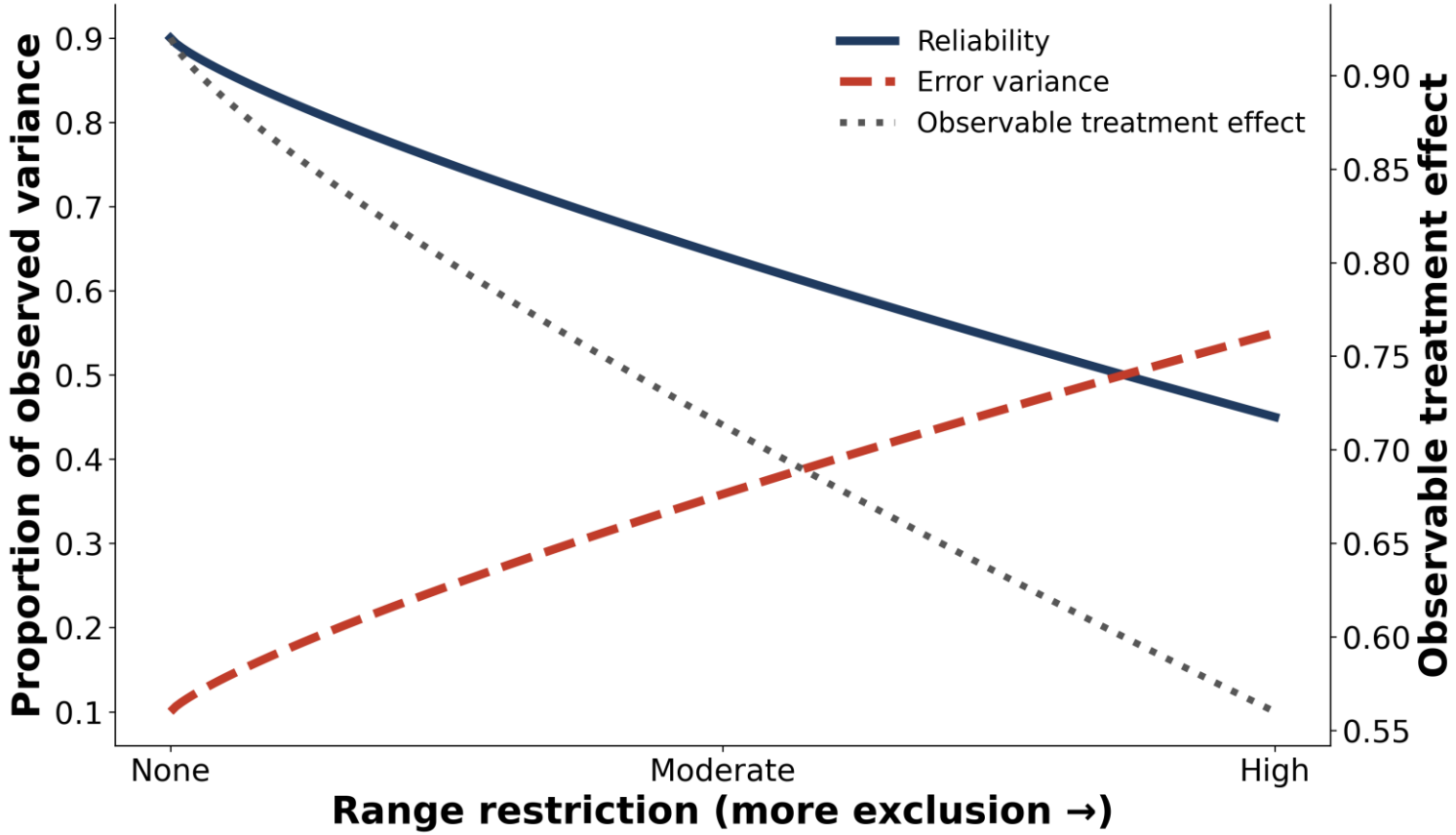
$$\sigma^2_{total} = \sigma^2_{systematic} + \sigma^2_{error}$$

$$\text{Treatment effect} = \frac{(\Delta_{tx} - \Delta_{control})^2}{\sigma^2_{total}}$$

Systematic Variance	Error Variance (e.g., inaccurate reporting)
Informative	Not informative
Reflects true differences that treatment may differentially affect	Reflects noise that obscures treatment effects
Inclusion of pwSIB increases systematic variance but not necessarily error variance	Exclusion of pwSI/B reduces systematic variance and reduces the ability to make accurate assumptions for power analyses

When informative variance is removed, power assumptions become less reliable even when sample size increases.

Exclusion = ↑ Range Restriction & ↓ Reliability



Range restriction reduces reliability, which in turn reduces the observable treatment effect.

Generalizability and Secondary Outcomes

- Quality of life, disability, and functioning are severity-sensitive.
- Range restriction also compresses these outcome distributions.
- Signal loss may occur even when the primary endpoint is unchanged.
- Real-world exposure reintroduces the truncated tail, with unpredictable results.
- Inclusion enables stratification and subgroup analyses that clarify how treatment effects vary across severity and functional burden.

Inclusion restores visibility of severity-sensitive outcomes that are otherwise systematically compressed.

Conclusions

- “Cleaner” samples are not necessarily more informative samples.
- Exclusion based on SI/B alters the population estimand.
- Reduced visibility is the first and least recognized consequence.
- Mean severity, variance structure, power assumptions, and generalizability follow.
- Broader inclusion increases visibility and allows for more accurate, reliable assumptions when designing clinical trials.

Broader inclusion improves inferential clarity.

Thank you!