Choosing the Right Design and Analytic Approach for Trials Recruiting Patients at Risk for Suicide

Larry Alphs, MD, PhD

Past Positions: Novartis, Pfizer, Knoll, J&J, Newron, Denovo

Current Consultant: Denovo Biopharma, NetraMark, Neumarker

Focus of Talk

- Suicide prevention trial
- Other types of trials with suicidal patients
  - Similar considerations but different emphasis or responses

Considerations when Designing a Suicide Prevention Study

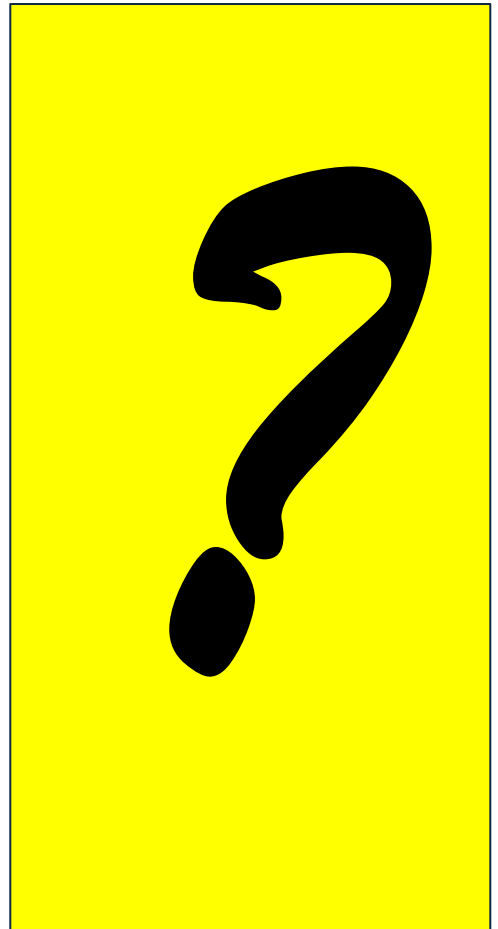
- Study goal
- Framing study question
- Definitions
- Patient population identification
- Endpoint selection
- Endpoint measures
- Study duration
- Study setting
- Patient Safety
- Blinding
- Selection criteria
- Analytic approaches

Treatment goal

- Prevention of death by suicide?
- Reduction of death by suicide?
- Reduction in suicidal thinking?
- Reduction of severity of suicidal thinking?
- Safety of novel treatment in patients at risk for suicide?

Well articulated study question

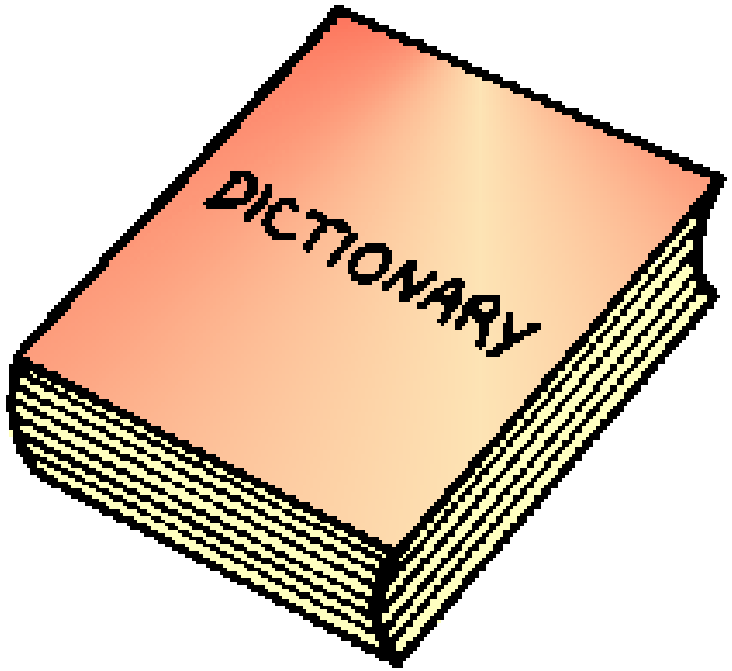
- Superior efficacy of treatment
- Superior value of treatment
- Population type exhibiting suicide ideation or behavior
- Severity of suicide ideation and behavior
- Duration of effect
- Treatment comparator



Definitions

Definitions needed in Suicide Prevention Trials

- Suicide
- Suicide attempt
- Imminent suicide risk
- Non suicidal self injury



Patient Population

ISSUES TO CONSIDER

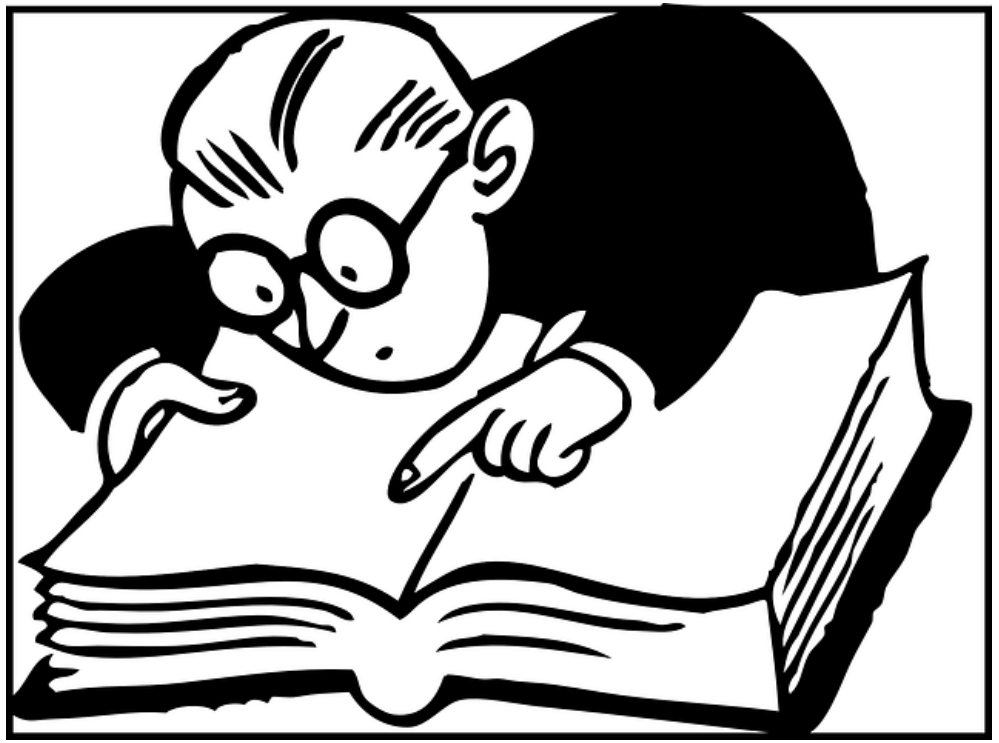
Not all suicide risk is the same

- Prior history of suicide attempt
- Family history
- Support system
- Prior methods
- Personal history risk factors
    - Concomitant diagnoses: Depression/Anxiety/PTSD
    - Medical history: Head Trauma
    - Stress/Loneliness/Support Systems
    - LGBTQ status
    - SIBAT Demographics Module

Endpoint Selection

Alternatives

- Improvement on **suicide severity scale**
  - Missing data
- **Time to event**
  - Identification of event and time
  - Have events been missed?
  - Verification of event
  - Missing data
- **Composite endpoint**



Endpoint Assessment Considerations for Suicide Prevention Trials

- **Scale Change:** C-SSRS, SIBAT CGI-Suicide Severity , ISST-Plus, Other?
  - Onset of significant change; duration of change
- **Event reduction:**
- What events count ?
- Distinguishing events: accidents, newspaper accounts of unexplained death
  - Number of events
    - What if a patient has multiple events?
  - Time to event
- **Combination**
- **Biomarker/Machine learning approaches**

Study duration

- What is the study question?
- What is the target product profile?
- How suicidal are subjects at point of randomization?
- How quickly is a change expected?
    - What is the durability of the treatment effect?

Study Setting

- **Inpatient**
  - “Contextual” response of inpatient care
  - Cultural issues: Use and duration of hospitalization; type of support
  - Ethical Issues: Ethical evaluations may differ by specific setting
- **Outpatient**
  - Support system
  - Loss to follow up
  - Cultural issues and support systems

Patient Safety

- Type of study: novel treatment vs real world
- Nature of interventions to prevent suicide
- Frequency of follow up

Ethical Imperative: All participants involved MUST work to prevent suicide behavior

Blinding

- Can study be blinded?
- Is it ethical to blind the study?
- If an unblinded study, will analyses be blinded?

Patient selection criteria

- Dependent on study question
- Suicide severity
- Suicide subpopulation
  - Depression/Schizophrenia/ Bipolar/PTSD/Combat/Rape/ Imprisonment
  - SIBAT Demographic module

Analytic Approaches

- Frequentist: change from baseline severity
- Time to event
- Combined endpoints
  - Special analytic methodology, e.g. Wei, Lin, Weissfeld
- Machine learning

- Studies involving persons at risk for suicide are highly desirable

- Designing trials involving suicidal patients requires
  - Well articulated study question
  - Extensive, careful decision-making around design
  - Careful attention to safety and ethical considerations.

Thank You