

SMA Summit on Drug Development

Session 5 Clinical Trial Design

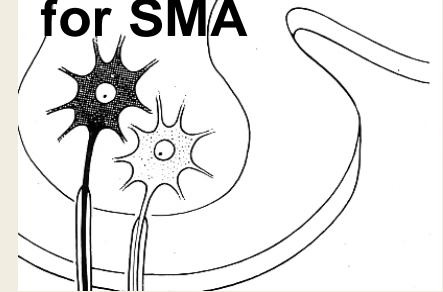




MOTOR NEURON CENTER



**PNCR Network
for SMA**



Issues in SMA Clinical Trials

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SMA Summit on Drug Development

**Hyatt Bethesda, Maryland
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Bottleneck in SMA Drug Development

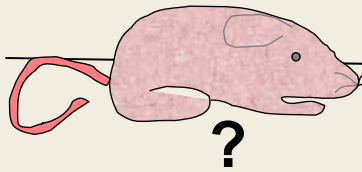
Preclinical Testing



Foundations

Industry

Academic
Labs



Multiple drug candidates

Phase I Phase II Phase III

Small pool of patients

Limited resources



In vitro

In vivo



1. Efficient Phase II Designs – possible approaches

Is Phase III evaluation warranted?

Conduct an early efficacy test

FUTILITY STUDY

Select drug to be tested (first) or rank drugs?

Select between alternative drugs

SELECTION PROCEDURE

Avoid gaps between Phases of conventional trials

ADAPTIVE DESIGNS

SEAMLESS DESIGNS



Futility Design

- H0: Drug is effective.
- Reject H0 if there is significant evidence of non-superiority (often at the one-sided $\alpha=0.1$ level)
- If H0 not rejected, there is inadequate evidence of non-superiority
- Given adequate power, this justifies proceeding to Phase III
- False negative error more important
- Avoid missing effective treatment
- False positive can be identified in phase III
- Counter-intuitive to spend resources on identifying futile medications
- When multiple candidate drugs and limited resources, futility design can be efficient
(Levin B, The utility of futility, Stroke 2005)



Selection Procedure

Selection paradigm rather than formal hypothesis test for dose selection

No interest in guarding against Type I error under the assumption of equal efficacy

Rather, interest resides in making a required selection

If both drugs were equal, we would be indifferent to the selection (therefore type I error unimportant)



Continuous Drug Evaluation Adaptive Designs

avoid gaps of traditional drug development through seamless phase 2-3 designs (e.g. Ceftriaxone/ALS study)

Use observed data to adapt

- Sample size
- Randomization fraction
- Drop or add treatment arm
- Reduce variability by dropping sub-population
- Problems: type 1 error, blinding, bias



2. Biomarkers and Surrogate Endpoints

Shorten observation period

Early signal of biological efficacy

proof-of concept

Biological marker has to be validated against
clinical outcome



3. Increase likelihood of success by optimizing dose regimen

If licensed for other disease, consider assessing in this new therapeutic indication

maximum tolerated dose

Basic safety

Pharmacokinetics

Small Phase Ib studies in the targeted population prior to larger efficacy trials (e.g. NPTUNE Phase I Study of SPB in SMA)



4. Reliable and Sensitive Clinical Measures

Clinically meaningful

Low patient burden

Cost-effective

Capturing wide range of population

Reliable

Allowing for data collection off-site

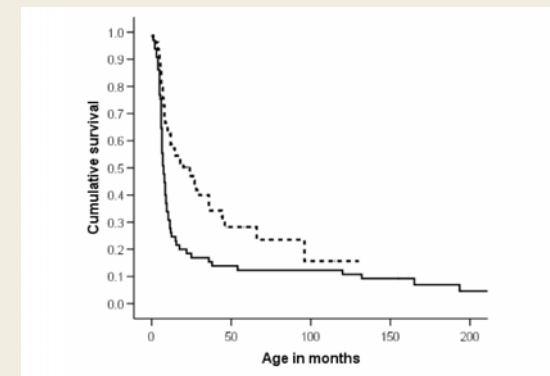
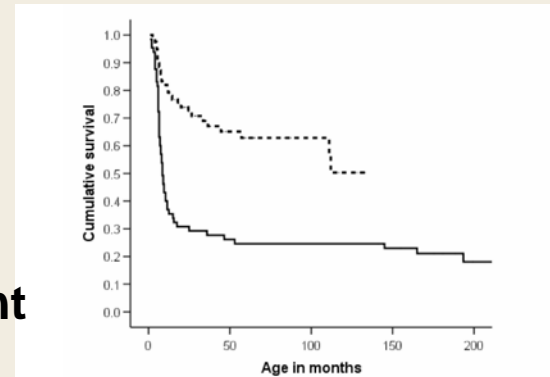
Sensitive to change



5. Efficacy trials need to be placebo-controlled whenever possible

Historical data may not be suitable

- **Data from international SMA patient registry**
- **n=143**
- **YOB 1980-1994 (n=65) vs.**
- **YOB 1995-2006 (n=78)**
- **Significant increase in survival**
- **Proactive care reduces mortality**





6. Modern data management and trial coordination

rapid communication

Timely availability of data

Facilitates data quality control

Efficient for multi-center trials

7. Recruitment

- Patient education on the need of clinical trials
- Partnership with patient advocacy groups
- Involving patients in planning stage
- Patient centered visit schedule that minimizes burden to participants
- Proactive advertising

- Form sufficiently large trial groups
- Carefully select inclusion criteria
- Obtain feasibility data early
- Conservative estimates of recruitment rates
- Cover geographically appropriate area based on prevalence estimates
- Foster collaboration between investigators and clinical trials groups so that trials can expand if needed



8. Improve Dataset used in Future Trial Planning

Data repository with placebo group data

requires:

Comparable data across trials

- a. Core of common design features
- b. Core of common data elements

Quality control

Governance

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