Optimal use of sequential trial designs in small populations

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Introduction

- Group Sequential Designs (GSD)
  - Proper incorporation of interim stopping rules
    - Multiple looks at accumulating data increase type I – error → compromise trial validity
- Possibility of early stopping
  - Stopping for efficacy/futility
  - Faster access to effective treatments
    - Identified as top priority by **patients** (ASTERIX)
  - Faster dropping of ineffective/harmful treatments

GSDs in small populations

- Suggested by research and EMA/FDA guidance as potentially useful for RCTs in small populations

Table 1. Published Reports–Neuronal Ceroid Lipofuscinosis Therapeutics.

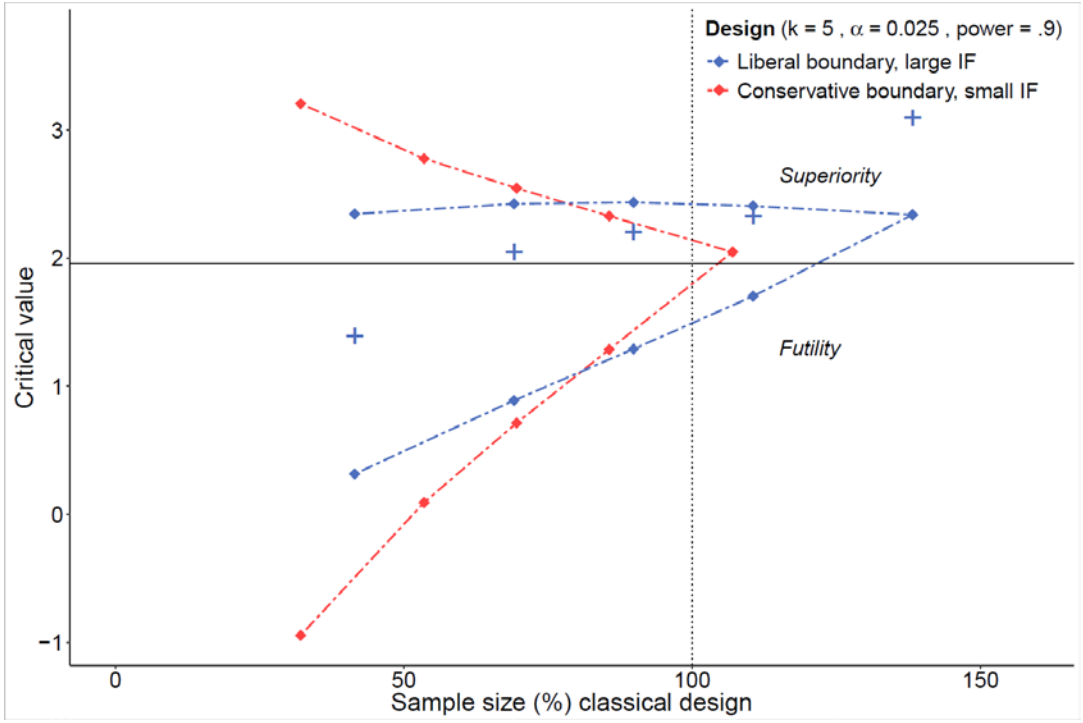
NCL type	Intervention	Indication	Sample Size	Outcome measure
Open-label, single-group clinical trials				
JNCL	Polyunsaturated fatty acids	Disease modification	5	(1) Serum lipoproteins, (2) IQ, (3) clinical signs and symptoms
LINCL, JNCL	Antioxidants (selenium, Vitamin E)	Disease modification	3	(1) Selenium, vitamin E, glutathione peroxidase levels, (2) clinical signs and symptoms
JNCL	Polyunsaturated fatty acids	Disease modification	6	(1) IQ, (2) test of motor impairment, (3) British ability scales, (4) clinical signs and symptoms
JNCL	Psychotropic medications (citalopram, olanzapine, risperidone, quetiapine)	Psychotic and affective symptoms	14	Clinical signs and symptoms
INCL	Transdermal fentanyl	Pain	5	Visual analogue pain scale
JNCL	Prednisolone	Disease modification	8	(1) UPDRS, (2) serum GAD antibodies, (3) clinical signs and symptoms
Open-label, historical-control clinical trial				
JNCL	Antioxidants (vitamin E, vitamin B2, vitamin B6, selenium)	Disease modification	43	(1) JNCL CRS, (2) clinical signs and symptoms
Open-label, parallel-group clinical trials				
JNCL	Antioxidants	Disease modification	46	(1) IQ, (2) Clinical signs and symptoms
JNCL	Antioxidants	Disease modification	125	(1) IQ, (2) plasma selenium levels, glutathione peroxidase activity, serum vitamin E level, (3) clinical signs and symptoms
JNCL	Levodopa or selegiline	Parkinsonism	21	UPDRS
Single-blind, placebo-controlled clinical trial				
INCL, LINCL, JNCL	Melatonin	Sleep disturbance	5	(1) Actigraphic recordings, (2) sleep log, (3) parent-reported sleep quality
Randomized, placebo-controlled, clinical trial				
JNCL	Antiparkinsonian drugs (orfenadrine, amantadine, levodopa + benserazide)	Parkinsonism	8	(1) Motor CRS, (2) ratings of videotaped tasks

- Reduction in sample size (study duration) key in small populations

Augustine EF, Adams HR and Mink JW, Clinical Trials in Rare Disease: Challenges and Opportunities, *J Child Neurol,* 2013

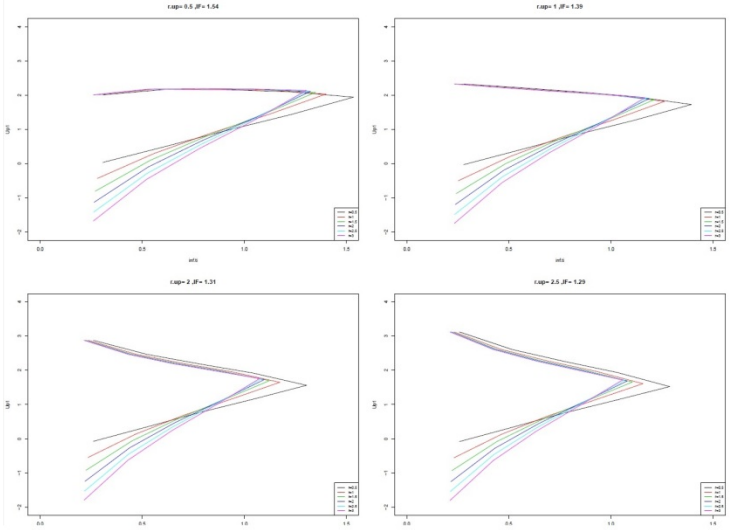
Design choices in GSDs

- Boundaries – trade offs
  - Especially relevant with a small (maximum) sample size

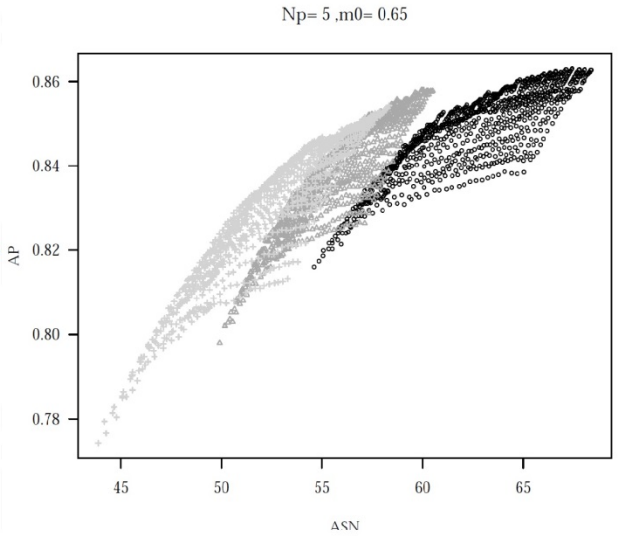


Optimal boundaries

- For small sample sizes, frequently overlooked boundaries (*t*-)correction is essential
  - Type I error control
- Historical information may be utilized to derive optimal boundaries, given maximum sample size and correction
  - Incorporating uncertainty about parameters involved, given limited data – *design prior*



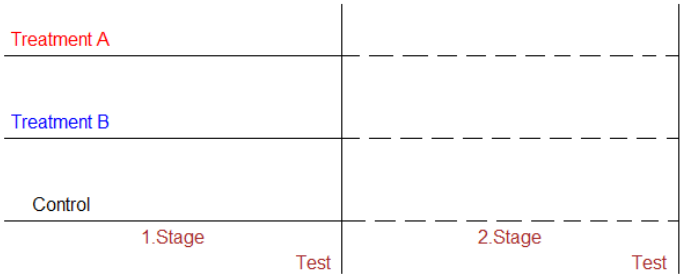
prior



Nikolakopoulos S, Roes KCB and van der Tweel I, Sequential designs with small samples: Evaluation and recommendations for normal responses. *Statistical Methods in Medical Research*, 2016, epub ahead of print

Multi-arm GSDs

- **Potential of multi-arm trials**:
  - Lower sample sizes than having separate trials for each treatment
  - Possibility of head to head comparisons between different treatments
  - More patients are randomized to a treatment arm due to the common control arm



- **Stopping rule:**
  - *Separate stopping*:
    Treatment arms, for which a stopping boundary is crossed, stop.
  - *Simultaneous stopping*:
    If at least one null hypothesis can be rejected the whole trial stops.

Simultaneous stopping ↔ trial objective:
Identify at least one treatment that is superior to control.

Separate stopping ↔ trial objective:
Identify all treatments that are superior to control.

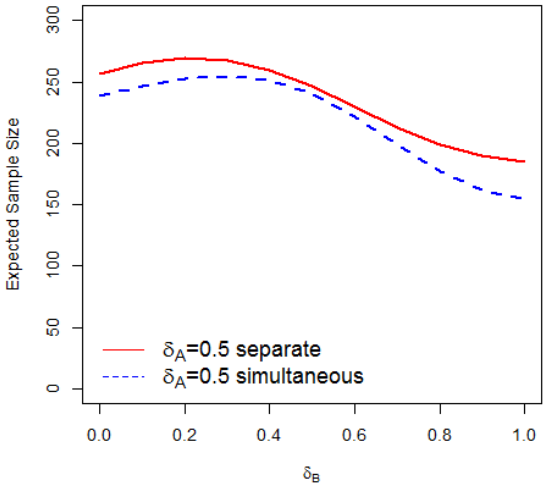
Simultaneous stopping in multi-arm GSDs

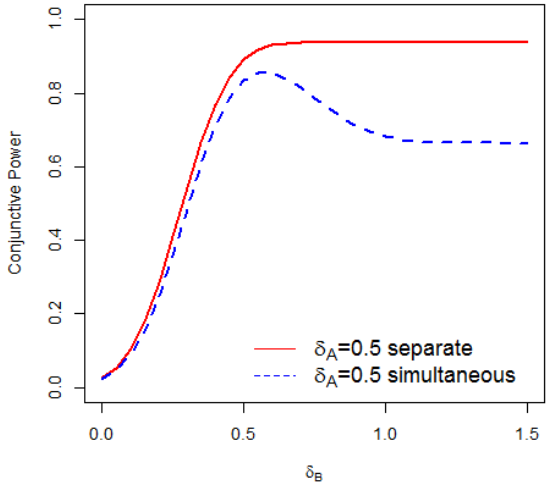
Advantages

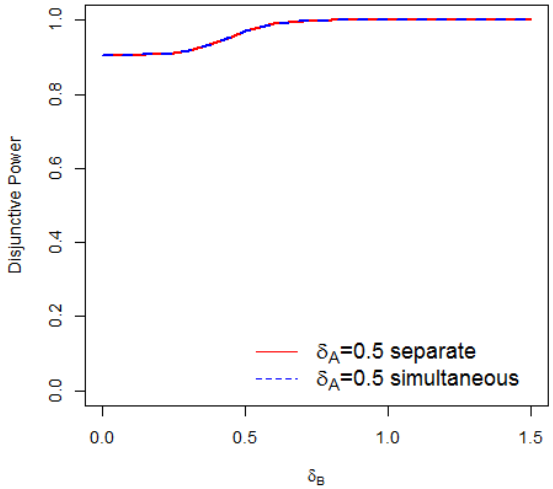
- Randomizing to control group as soon as an efficacious treatment has been found is unethical in life threatening diseases
- Lower expected sample size
- Same power to reject any null hypothesis (*disjunctive*)
- Improved boundaries can be applied to regain some of the power to reject all null hypotheses

Disadvantages

- Lower power to reject all null hypotheses (*conjunctive*)
- The simultaneous stopping rule must be adhered to
  - If improved boundaries are used
- Stopping only based on efficacy endpoint, treatments might differ in safety
- Less information available about all treatments







Urach S and Posch M, Multi-arm group sequential designs with a simultaneous stopping rule. *Statistics in Medicine,* 2016, 35: 5536–5550

Conclusions

- GSDs points of attention when implemented in a small population setting
- Particularly in small populations, any reduction in sample size could translate to significant benefit (time)
- Boundaries can be optimized for
  - Historical information
    - Design prior taking logistical concerns & correction into account
  - Inferential goal
    - For simultaneous stopping, lower ASN is possible (fixed disjunctive power)
    - Some of the conjunctive power can be regained by relaxed boundaries

Discussion points

- Suitability of GSDs for small populations (rare diseases)
- Issue of trade off efficiency/ information gain magnifies
- In chronic conditions with high unmet need / organised patients, recruitment might be fast (despite small samples)
- Response time / Recruitment ratio crucial
- Diseases classification (WP5) of importance for design implementation