Symposium on Early Phase Dose Finding Methodology

Bayesian adaptive designs for phase 1 studies in healthy volunteers

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01 INTRODUCTION

Objectives:

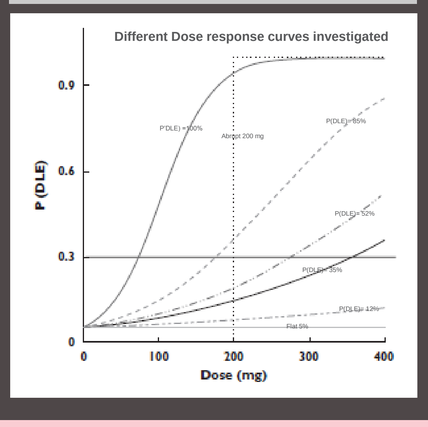
- Assess the **performance** of an innovative (Adaptive) approach that includes Bayesian adaptive designs in healthy volunteers. (several dose response curves investigated)
- **Comparison** with a more traditional approach (sequential)

Study designs:

- Single ascending dose
- Leap Frog design

Improvements:

- Standardization of the priors



02 METHODS

Endpoints :

Quality:
Focus on the variance and bias in the estimate of MTD

Efficiency:
Number of subjects
Duration of the trials

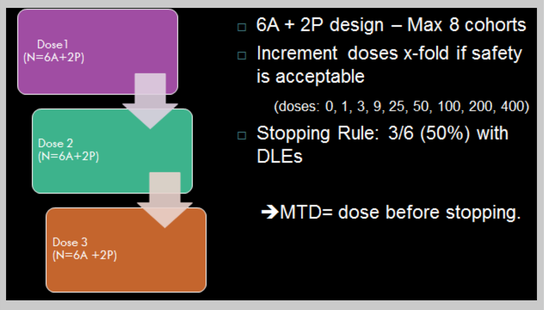
Safety:
Number of subjects overdosed

	Traditional (sequential)	Innovative (Adaptive)
MTD	≥ 3/6 subjects with DLE	Dose with P(DLE)=30%
Escalation	Modified Fibonacci	Closest dose to the MTD (model)
Cohort	6A+2P	3A+1P then 6A+2P
Dose levels	9 possible doses	15 possible doses Max 3 fold increase

Abbreviations	
MTD = Maximum Tolerated Dose	A= Active
DLE = Dose Limiting Event	P= Placebo
CV= Coefficient of variation	

Approaches (SAD):

Traditional (Sequential) 6+2

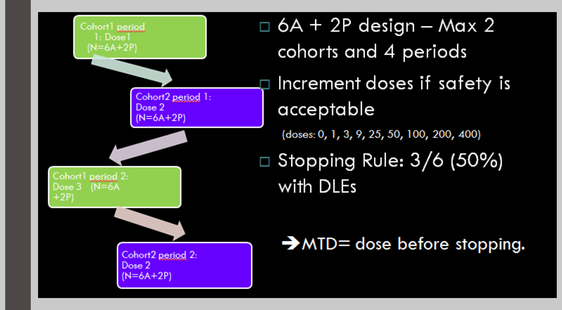


Innovative (Adaptive) approach

- Design:
  - 3A + 1P initially
  - Possible doses: 0,1,3,6,9,20,25,40,50,75,100,150,200,300,400
- Logistic Regression:
  - Model p(DLE) as function of dose
- MTD quantified:
  - Dose where p(DLE)=30%
- Next dose level:
  - Possible dose closest to predicted MTD
  - Maximum 3-fold increase in doses
- Example: MTD=5.8
  - Current dose=3 -> Next dose = 6
  - Current dose=1 -> Next dose = 3
- Stopping Rules:
  - MTD Found
    - Precision of MTD is strong (CV≤ 30%) or,
    - Any dose level is selected for the third time
  - MTD not Found
    - MTD is larger than highest possible dose (400mg) with high probability (>80%)
    - Maximum number of cohorts (16)

Approaches (Leap Frog):

Traditional (Sequential) 6+2



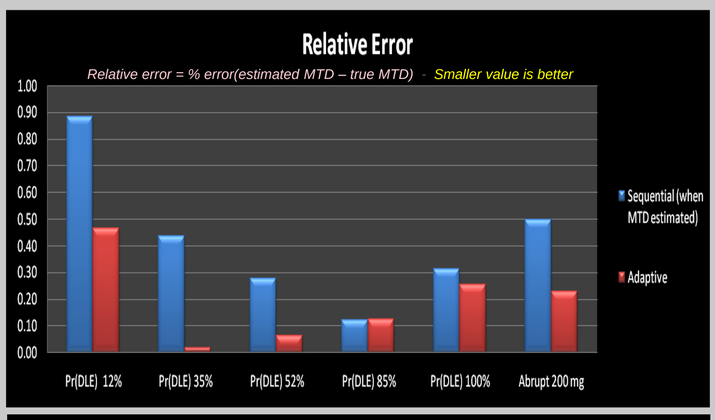
Innovative (Adaptive) approach

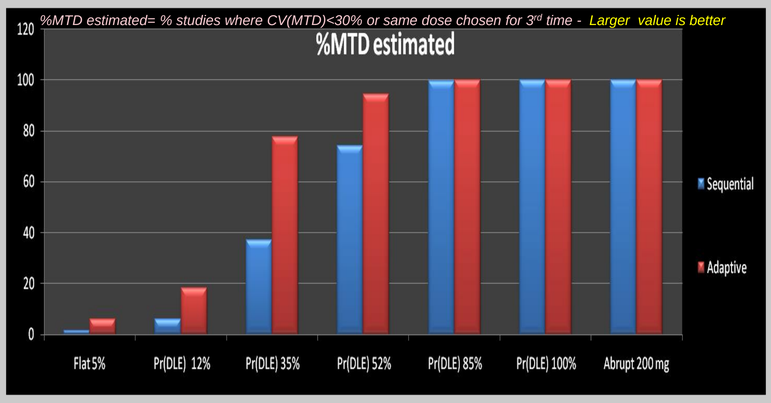
- Same as SAD
- Logistic Regression:
  - Model p(DLE) as function of dose and an random effect if more than one dose received
- Missing Data:
  - Subject with DLE are eliminated➔ less observations/subject
  - Difficulty to fit individual DLE profiles.
- How to overcome the problem?
  - Solution: Data augmentation
    Patients with DLE are removed from the study BUT we consider them as experiencing DLE for the next doses given to the cohort

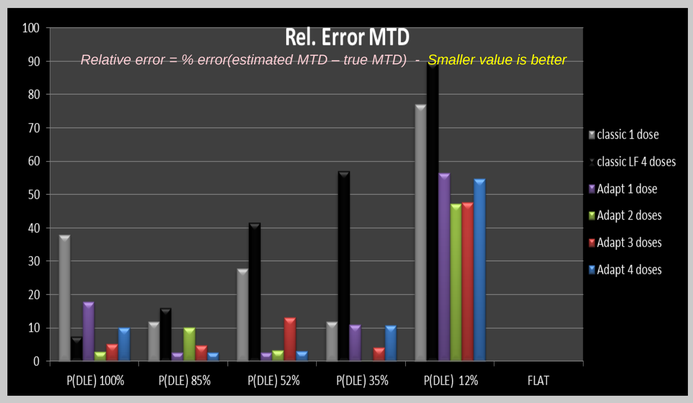
➔ Very conservative rule!

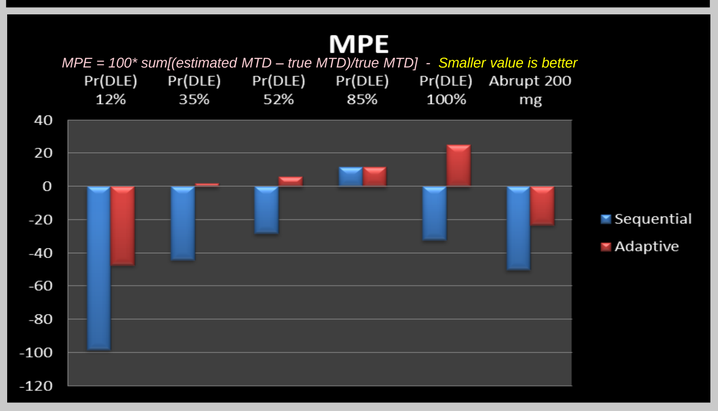
03 RESULTS

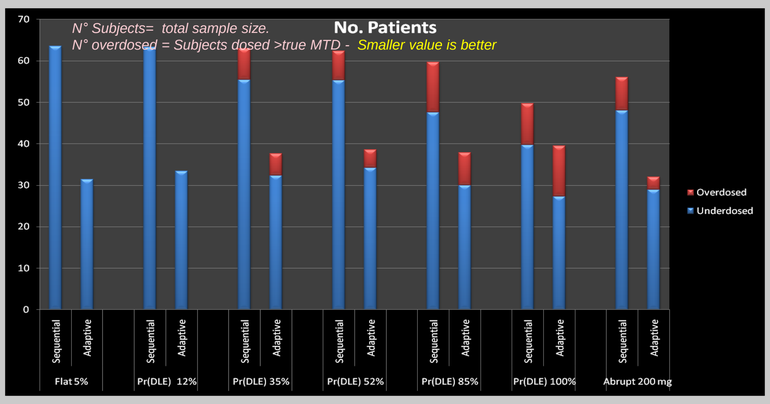
SAD

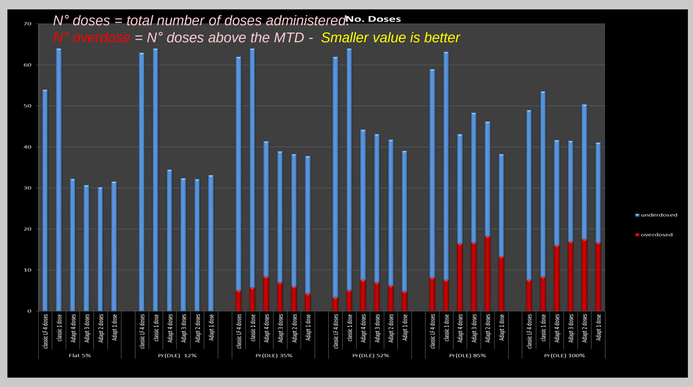


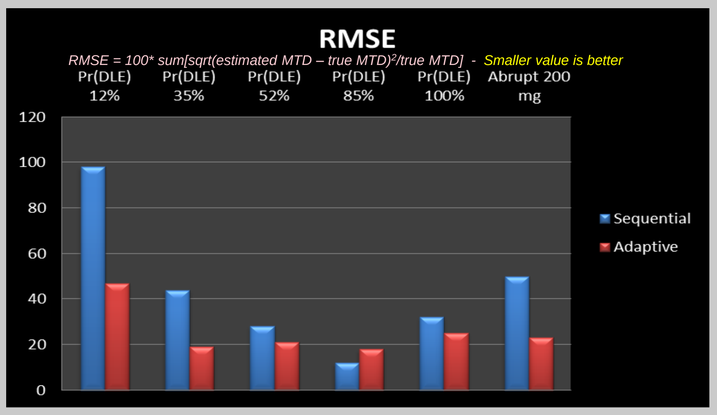


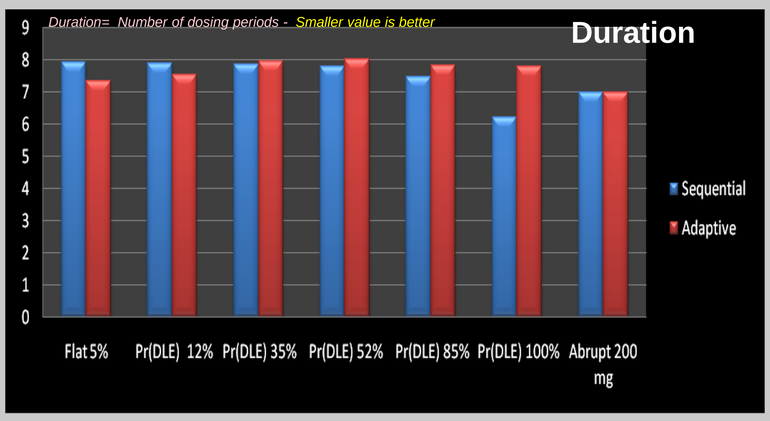


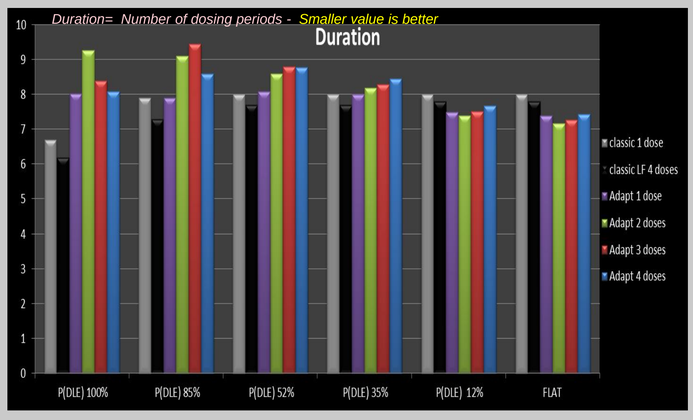












Results from 5000 simulations

04 CONCLUSION

01.Quality

MTD estimated more often

MTD estimated with better precision

02.Efficiency

A fewer number of subjects

Duration is equivalent

03.Safety

A fewer number of overdosed subjects

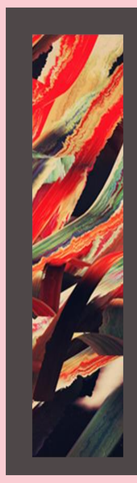
04. SAD Vs. LF

For Safety only, Leap frog is not necessarily better than SAD

05. Improvements

A new methodology to define the priors :

- avoid MCMC
- a clear meaning of the priors



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THANKS

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