Bayesian dose selection strategy in biomarker trials: a case study using brain imaging.

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Statistical solutions to drug development

Imperial College London

Outline

- Biomarkers in early drug development
  - Case study using brain imaging
- Bayesian methods
  - Adaptive dose selection during biomarker trial
  - Predictive dose selection for phase II
  - Practical Issues
- Software
- Summary and Conclusions

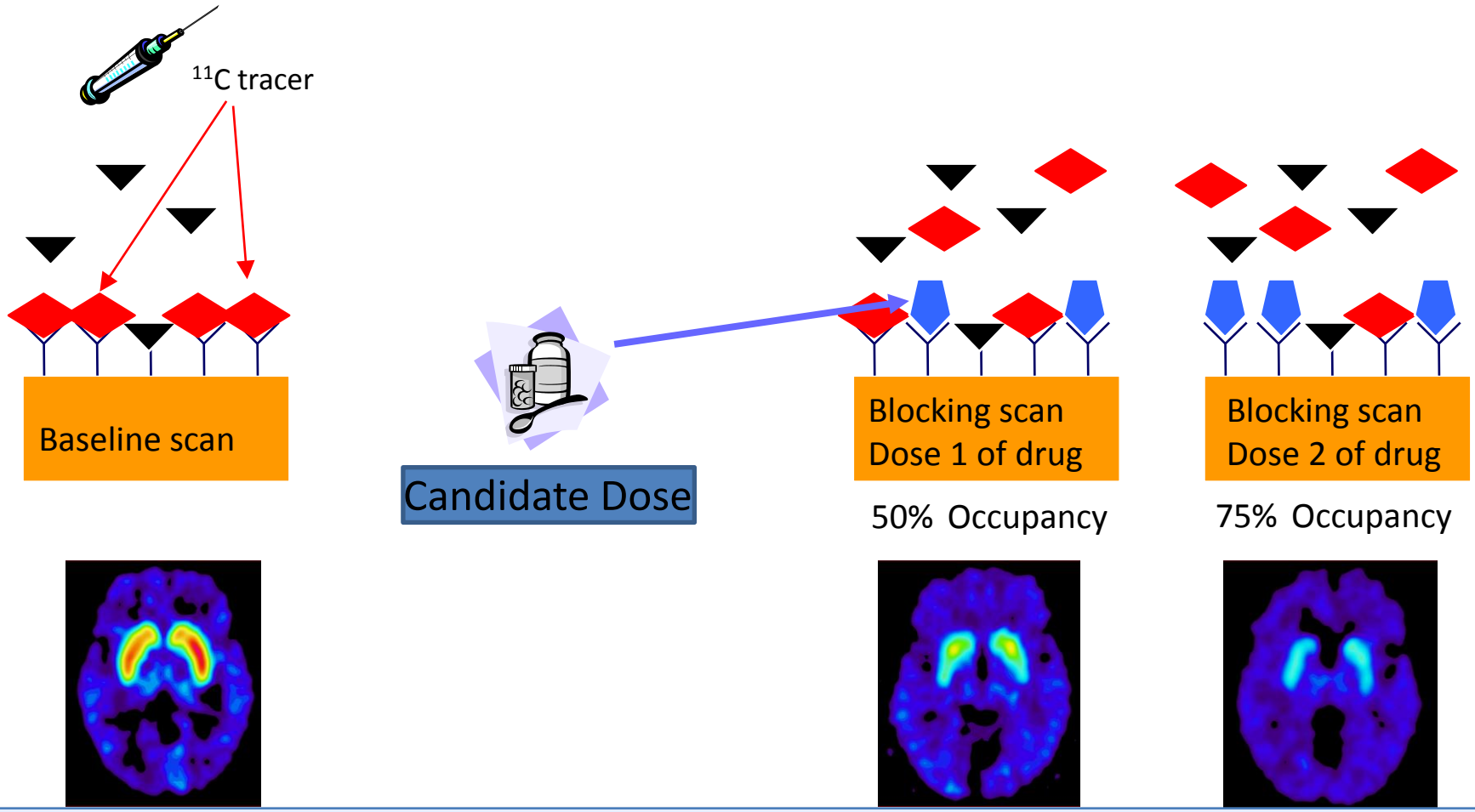
Biomarkers in Early Phase

- Early evidence of drug activity:
  - Proof of mechanism: drug-on-target assessment
  - Proof of principle: pharmacodynamic effect on disease phenotype
  - Proof of concept: clinical benefit to patient
- Go/No go decision and dose selection prior to phase II

Brain imaging case study

- Candidate is a highly selective antagonist of target receptors in the brain.
- Target receptor antagonism has been shown to improve disease symptoms in animal models.
- Proof of mechanism Phase Ib trial:
  - Demonstrate central receptor blockade in humans.
  - Using positron-emitted tomography (PET) scans with a ^{11}C-ligand being a marker of receptor availability.
- Before candidate enters a Phase II trial for the treatment of disease.

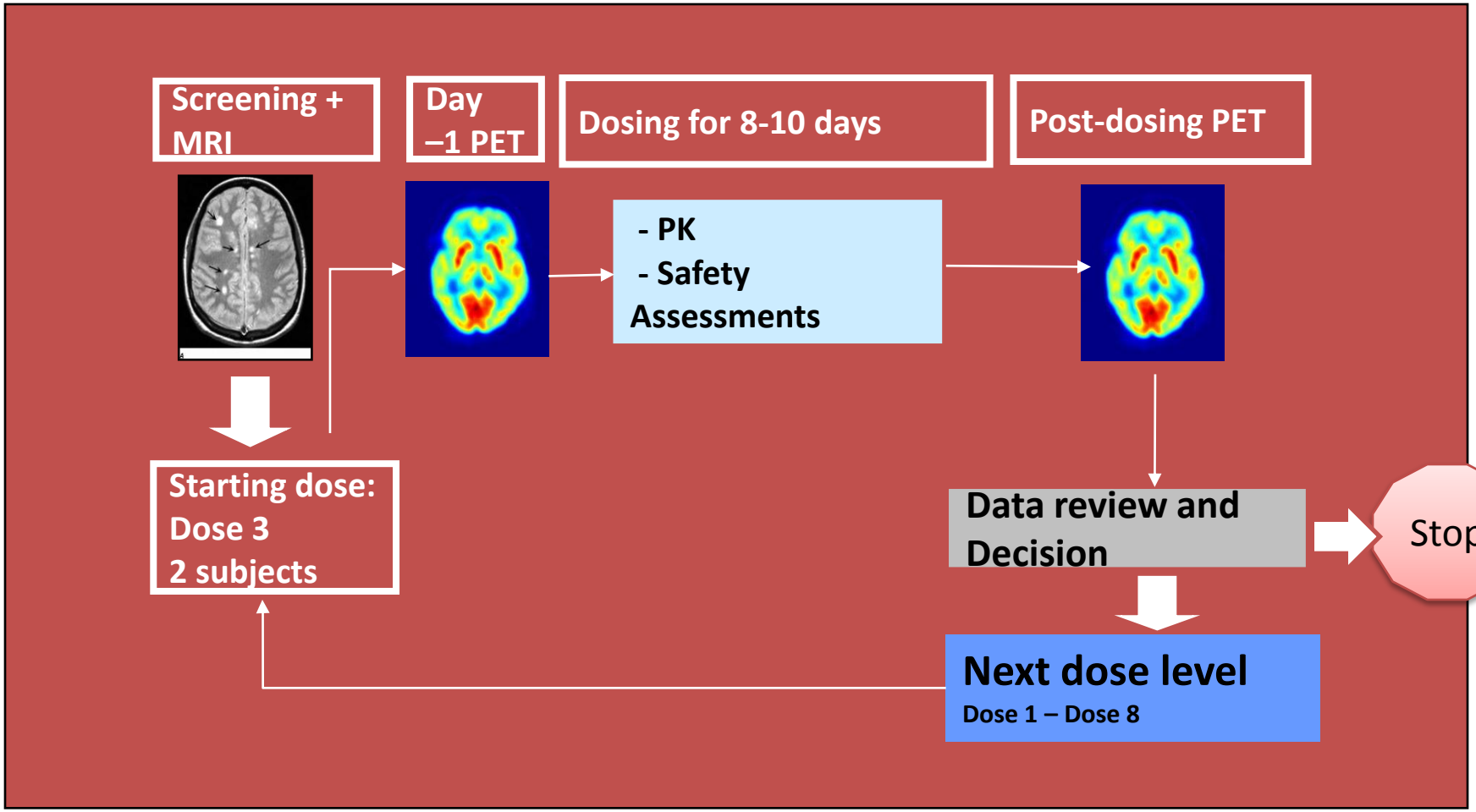
Receptor-Occupancy PET



Goals:

1. To determine the doses of candidate at which target receptors are saturated.
2. To assess the relationship between receptor occupancy and candidate dose.

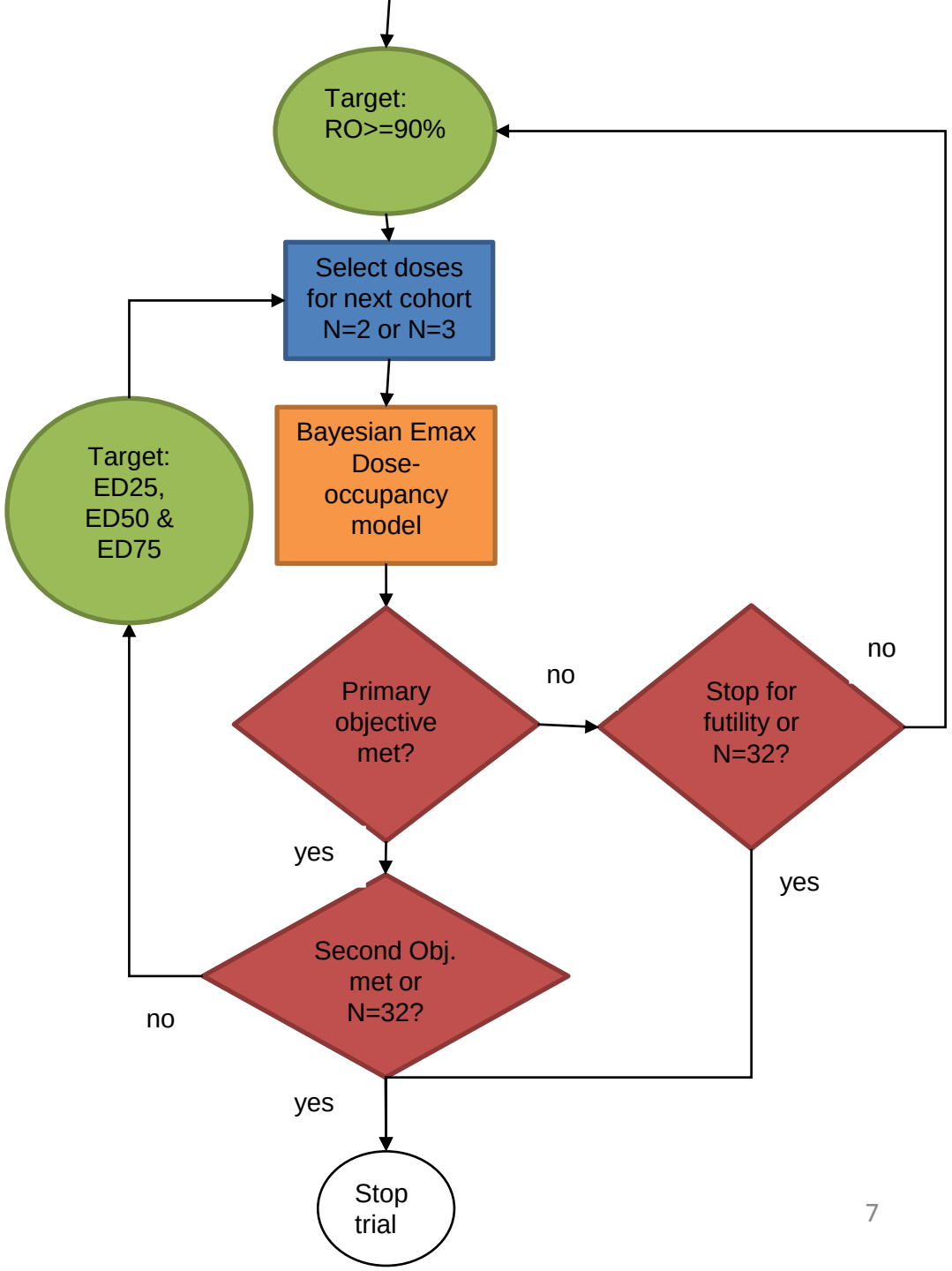
Adaptive Study Design



Decision Tree

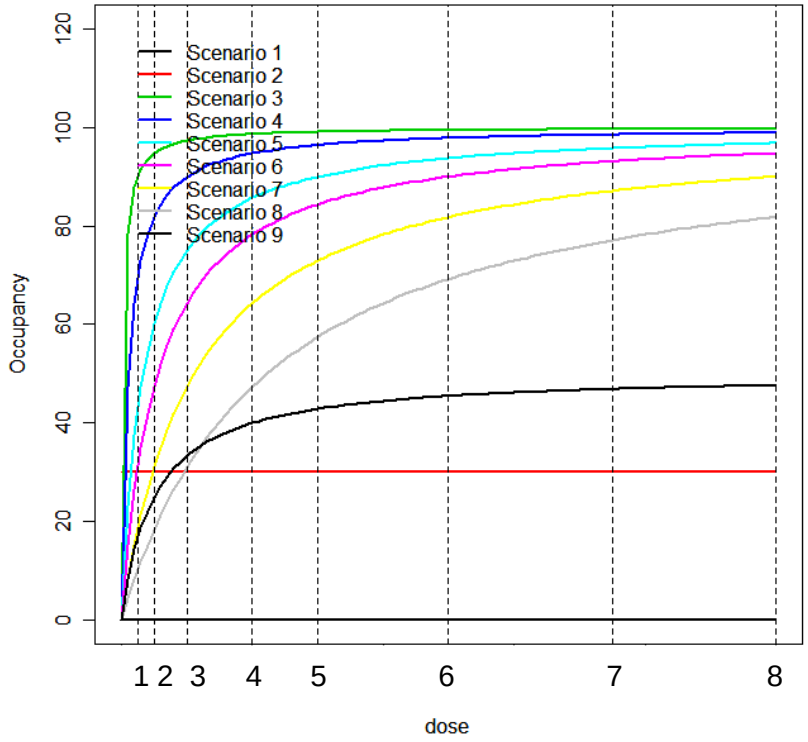
Stopping Criteria

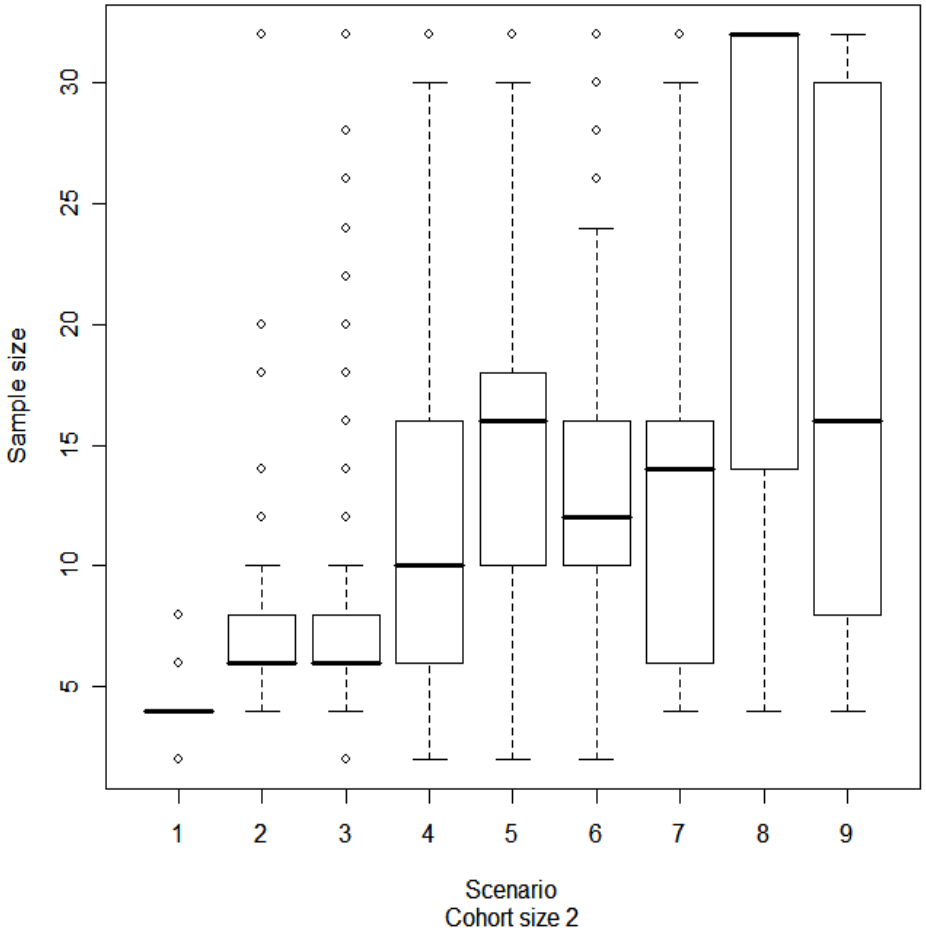
- Primary objective:
  CV(ED90%) <30%
- Secondary objective:
  CV(ED50%) <30%
  or ED50% < Dose 1
- Futility:
  Pr[Max RO<50%]>85%
- Maximum size:
  N=32



Planning Activity: Trial Simulations

- 9 dose-response scenarii simulated



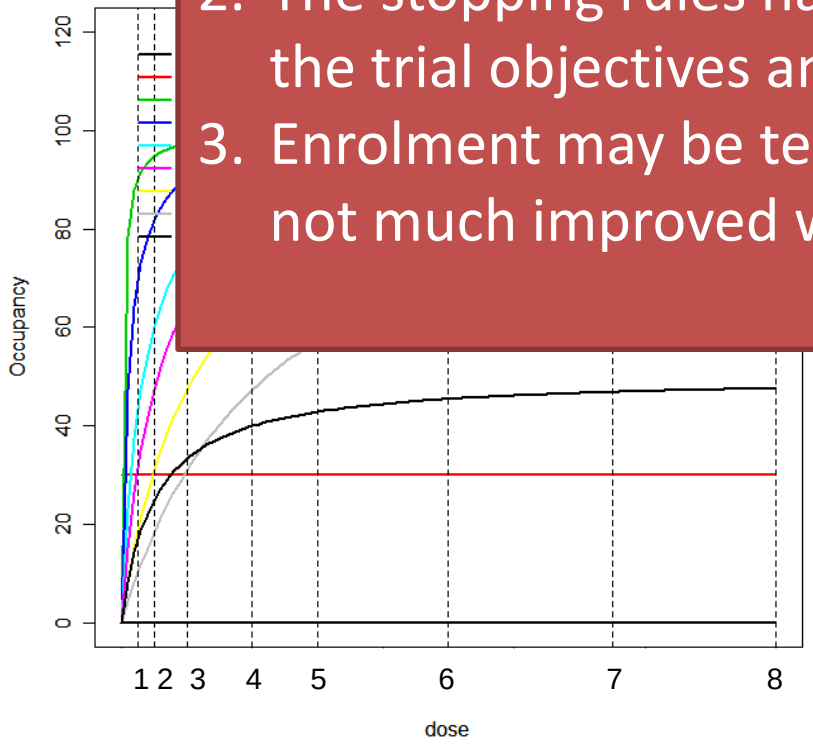


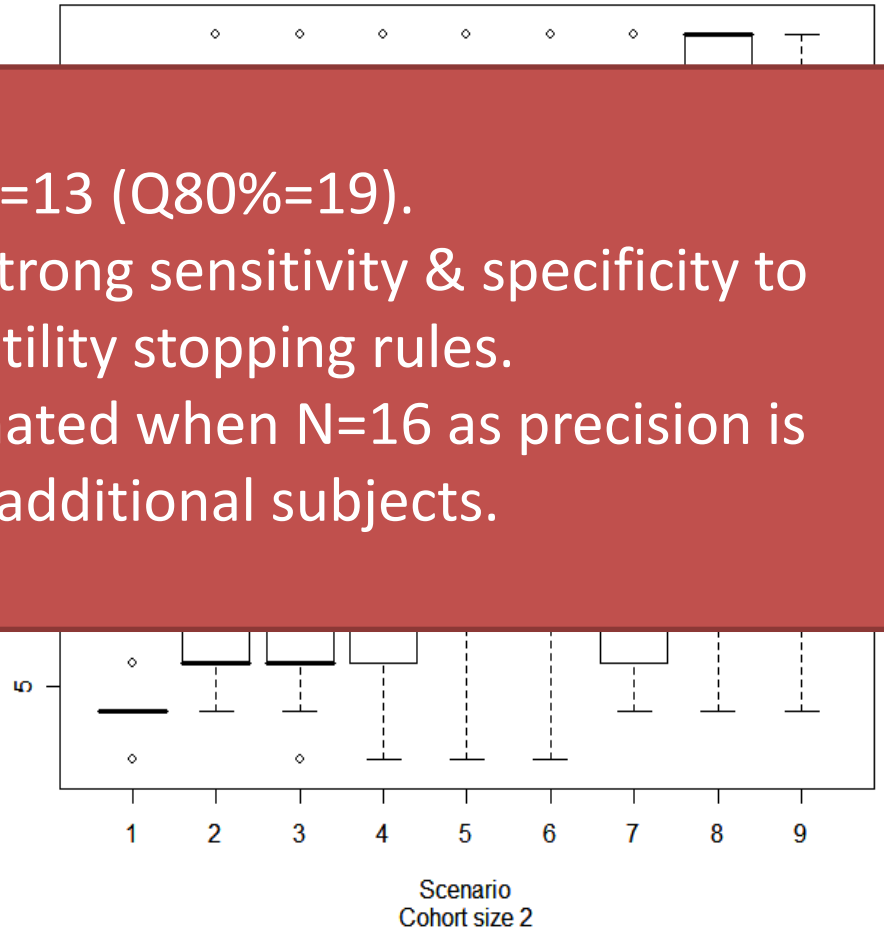
Planning Activity: Trial Simulations

- 9 dose-response s

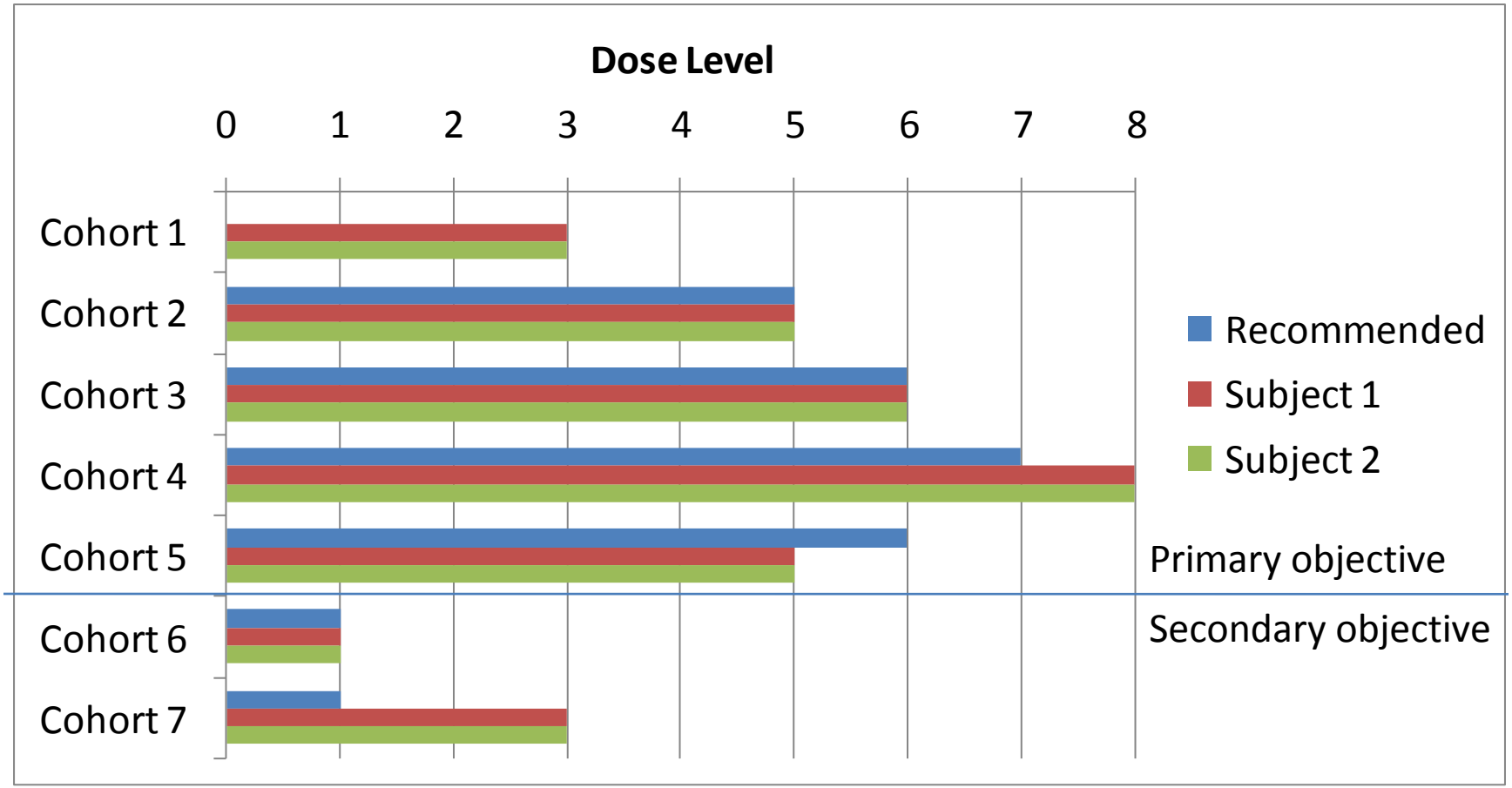
<u>Conclusions:</u>

1. Expected sample size is N=13 (Q80%=19).
2. The stopping rules have strong sensitivity & specificity to the trial objectives and futility stopping rules.
3. Enrolment may be terminated when N=16 as precision is not much improved with additional subjects.



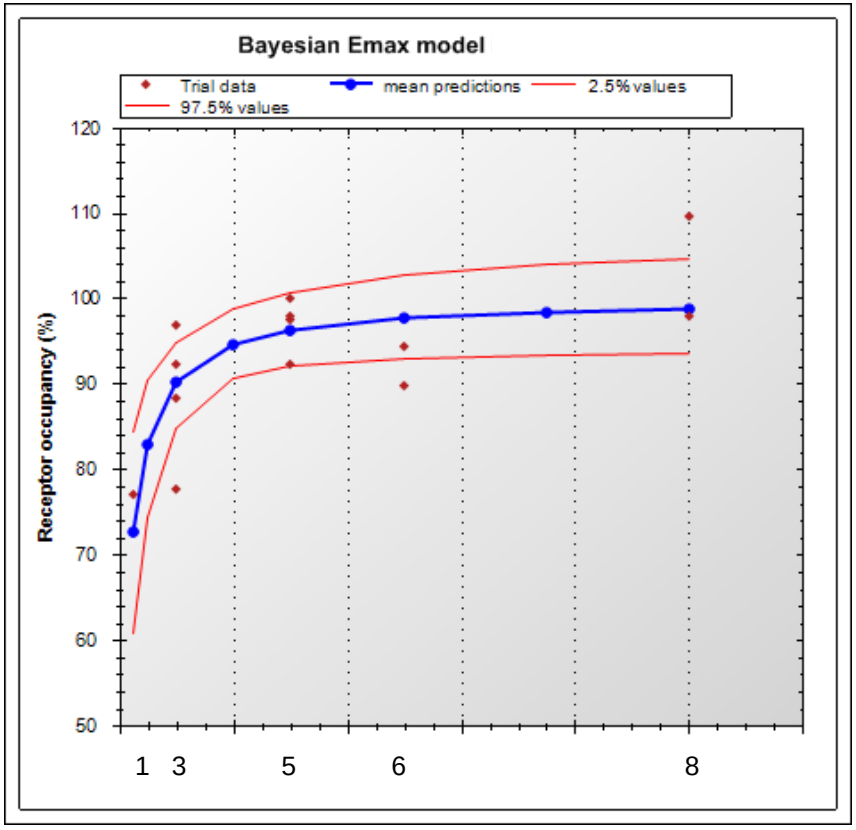


Adaptive Dose Selection Summary



Final Emax Model Fit

	Mean (mg)	Median (mg)	Precision (%)
ED90	~Dose 3	~Dose 3	28%
ED50	< Dose 1	< Dose 1	51%



- The study was positive.
- The primary objective was met:
  - The ED90 was precisely estimated.
- The secondary objective was not met:
  - The ED50 lacked precision
  - For practical reasons, precision could not be improved by adding patients.

Predictions

- Goal: Recommend doses for phase II
- How: Posterior predictive distribution

  Predicting Receptor Occupancy in future patient:

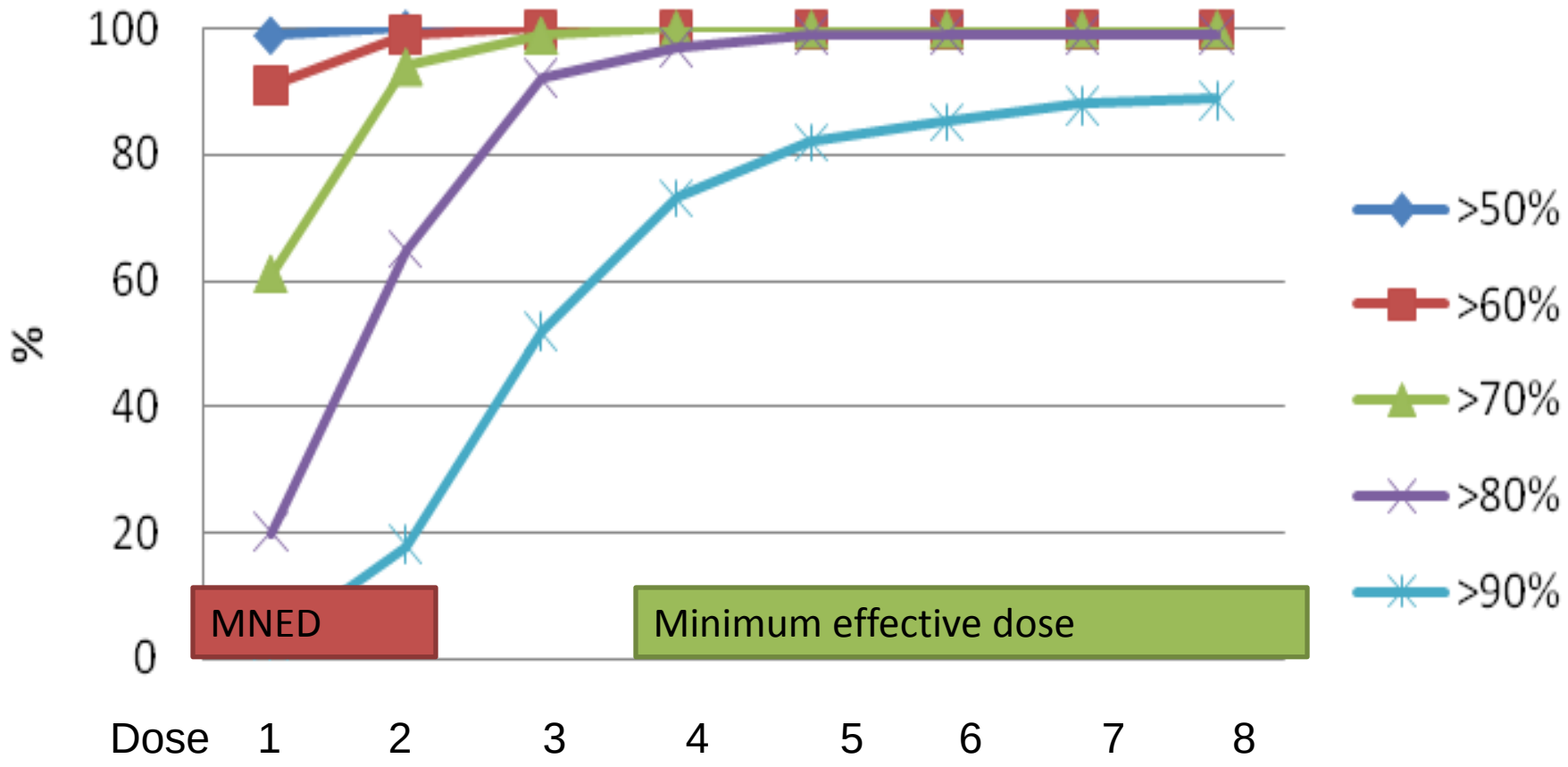
  - Given current data, and
  - Unconditionally to any fixed parameter value.

$$p(RO_{new} \mid RO) = \int p(RO_{new} \mid \theta, RO)\, p(\theta \mid RO)\, d\theta$$

Then, estimate proportion of future patients with RO above a target value

$$p(RO_{new} > \%\text{Target} \mid RO)$$

Percentage of subjects above RO target



Practical issues

- The following issues arised during the interim reviews:
  - drop-outs/ missing data:
    - Bayesian update possible with N=1!
  - Change in calculation method of receptor occupancy:
    - Challenging but expected when dealing with new biomarker that lacked formal validation
  - Expiration of CT material for low dose strengths:
    - Led to early stopping prior to secondary objective being met.
  - A few selected doses different from recommendation:
    - Decrease in efficiency was still quantifiable using on Bayesian utility function.
- The following issue arised during the phase II prediction:
  - Possibly different populations in Biomarker and Phase II trials.
    - Predictive model adjusted for population PK.

Software

- Decimaker:
  - User-friendly GUI to WinBUGS/R
  - Performs all Bayesian analyses:
    - Trial simulations
    - Adaptive allocation
    - Predictive modeling

www.decimaker.com

Summary and Conclusions

- Biomarker trials are run prior to phase II to
  - Terminate early unacceptable candidates
  - Select doses in an optimized manner
- Bayesian methods enable decision making
  - Summarize all available information
  - Quantify probability of success
  - Permit utility-based dose selection
- Case study was a success:
  - Study design validated using simulations
  - Delivered decision-enabling information
  - Flexible to deal with practical issues
  - Buy-in from all involved parties: physician, PK, site, sponsor…

Thank you!

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Any Question?