On the choice of doses for phase III clinical trials

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Challenges to development of new medicines

- Huge medical needs
- but # of new pharmaceuticals is decreasing
- Average development cost of the order 1 BUSD per new pharmaceutical
- Failure rate in clinical development may be 90%
- High requirements on ethics of clinical trials

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Lots of suggested remedies

- Omics
- Biomarkers
- Adaptive Designs
- Model-Based Drug Development
- …

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Key decisions in clinical development

- Programme and study design
- Dose
  - Dose-finding trials (phase II) are often too small to determine precisely the best dose
  - Has been suggested (e.g. by regulators) that two, rather than one, dose should be tested in confirmatory trials (phase III)

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Dose(s) in phase III ?

- Based on prior information, maximize
  P(prove at least one dose to be efficacious and "safe")
- Research questions
  - Find best dose for ph III
  - Find best pair of doses
  - Is one or two doses optimal?
  - Robustness

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Efficacy

- E_{max} model
- Parameters assumed known (may be relaxed)
- Stochastic data → Power function

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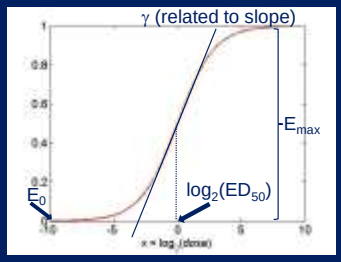
E_{max} model for efficacy, with known parameters:

$$\text{mean effect} = E_0 + E_{max} \cdot \frac{d^{\gamma}}{E_{50}^{\gamma} + d^{\gamma}}$$



WLOG: $E_0 = 0;\ E_{max} = 1;\ \log_2 ED_{50} = 0;\ \gamma = 1$

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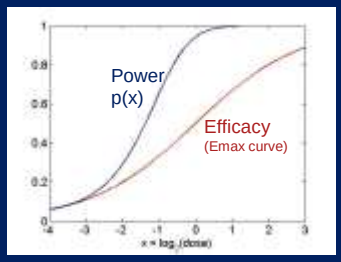
Assume i.i.d. normal residuals.
Mean effect translates into (2-sample) power, given total information = 100.



Total information =
= sample size divided by residual variance

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Safety

- True "Maximum Tolerated Dose" (MTD)
- Will observe whether doses in trial are <MTD
  - Dose d is "safe" iff d<MTD
  - Log dose follows probit model: P(safe) = q(x) = Φ(a·(b-x))
- (Bayesian prior + non-stochastic outcome)
- NB! Monotonicity: A lower dose cannot be "unsafe" if a higher dose is "safe"

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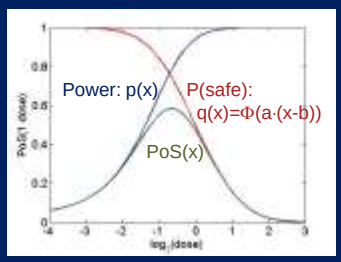
Probability of Success,
PoS(x)=p(x)·q(x)
when one single active dose is compared vs. placebo



In this graph, a=1 (shape) and b=0 (location).

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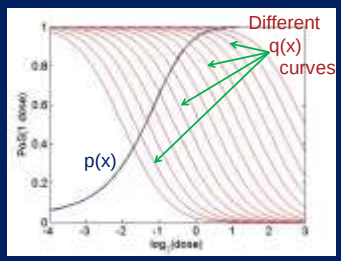
Family of safety curves



a=1 (shape parameter) and b∈[-2,3] (location parameter)

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- Case 1: One active dose, d, vs placebo
  - Equal split of total sample size
- Case 2: Two active doses, d_1 and d_2, vs placebo
  - Bonferroni correction
  - Sample size √2 larger in placebo arm
  - (May be relaxed)
- Optimal doses marked by *
  - One dose d*
  - Two doses d_1*, d_2*

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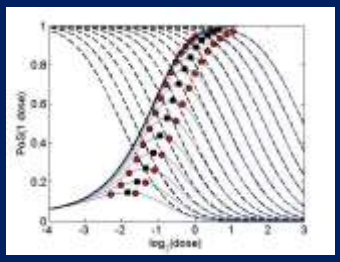
Power p(x)
Family of safety curves q(x)
Resulting PoS(x), with optimal dose(s) d_1*, d*, d_2*



- Optimal single (log) dose when p'(x)/p(x) = –q'(x)/q(x)
- d_2*/d_1* < 2 (Straightforward scaling for other γs.)

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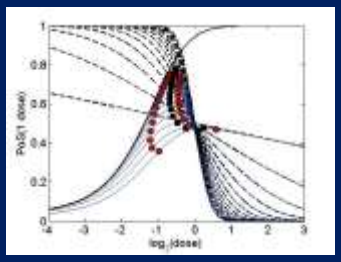
Varying shape parameter (with fixed location)



a∈[0.1,3] (shape parameter) and b=0 (location parameter)

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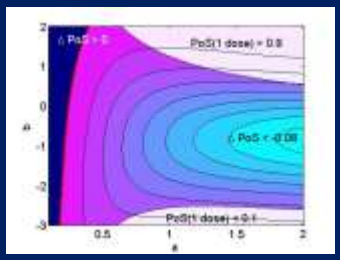
ΔPoS=PoS(2 doses)–PoS(1 dose).



One active dose is better than two, but …

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A number of factors may make two doses relatively more attractive

- Uncertainty in efficacy, e.g. prior on ED_{50}
- Optimal multiplicity procedure
- Optimal sample size split

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Difference in PoS, 2 vs 1 dose

	Weight	Recycling	Correlation	Scenario 1	Scenario 2
Bonferroni	No	No	No	-0.053	-0.024
Weighted Bonferroni	Yes	No	No	-0.052	-0.022
Holm	No	Yes	No	-0.026	+0.000
Weighted Holm	Yes	Yes	No	-0.012	+0.011
Dunnett	No	No	Yes	-0.045	-0.019
WD	Yes	No	Yes	-0.044	-0.018
RD	No	Yes	Yes	-0.022	+0.002
WRD	Yes	Yes	Yes	-0.011	+0.011

Smarter multiplicity corrections make 2 doses more interesting
Scenario 1 corresponds to power=0.8, PoS=0.6 (1 dose, Bonferroni)
Scenario 2 corresponds to power=0.9, PoS=0.7 (1 dose, Bonferroni)

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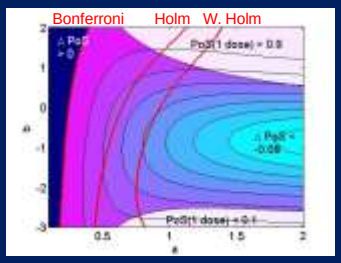
Red curves are boundaries for 2 doses vs 1 dose
(2 doses better to the left),
for Bonferroni, Holm and weighted Holm, respectively.



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Ongoing work

- Prior on ED_{50}
  - Leads to larger d_2^*/d_1^* ratio
  - More favorable for 2 active doses
- Prior dependence between efficacy & safety
- Optimal split of sample size
- Pooled analysis with closed testing

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Discussion, doses in phase III

- Can define optimal dose(s)
  - Requires explicit assumptions and criteria (cf. model-based drug development)
- One active dose is clearly best … under "naïve" assumptions and multiplicity corrections
- Move to more sophistication (and two doses might be better)
  - Prior for efficacy
  - Optimal multiplicity and sample size split
- Do we have to correct for multiplicity when higher dose is "unsafe"?

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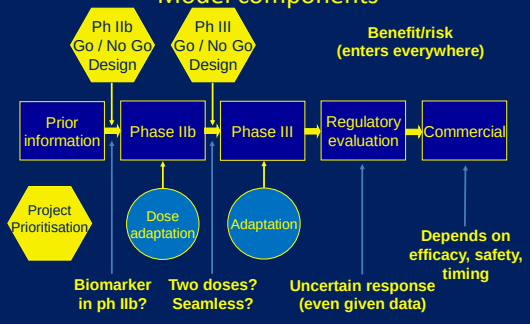
Adaptive Programme work stream: Model components



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General comments

- Multitude of highly relevant research problems
- Need more scientists involved
- … and need to spread results in the industry

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