

## Statistical Challenges: Designs for clinical trials with limited patient populations

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# Conflicts of interest (sorry!)



# What do statisticians contribute to clinical trial design?

- No rude answers please!
- Should be many things (I certainly do)
- Often seen as “the sample size calculation”
- But we are talking rare diseases; orphan drugs; orphan indications
- There are not many patients around
- Sample size calculations a bit irrelevant(?)

END OF TALK

# My beginnings...

## EU Regulatory Guidance



European Medicines Agency

London, 27 July 2006  
Doc. Ref. CHMP/EWP/83561/2005

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)**

**GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS**

<b>DRAFT AGREED BY EFFICACY WORKING PARTY / AD HOC GROUP ON CLINICAL TRIALS IN SMALL POPULATIONS</b>	May 2002 – January 2005
<b>ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION</b>	March 2005
<b>END OF CONSULTATION (DEADLINE FOR COMMENTS)</b>	September 2005
<b>AGREED BY EFFICACY WORKING PARTY</b>	July 2006
<b>ADOPTION BY CHMP</b>	27 July 2006
<b>DATE FOR COMING INTO EFFECT</b>	1 February 2007

# Regulatory Guidance

- Almost nothing at the time (early 2002)
- Tension about “upholding standards”
- “Nothing should contradict other guidance”

*and*

- Need for pragmatism, flexibility, etc.

# Regulatory Guidance

- Not a paradigm change
  - “The methods described [here] to increase the efficiency of the design and analysis are also applicable for studies in large populations...”
  - “...controlled trials with low statistical power in case of an important treatment effect may be preferable to no controlled studies.”
  - Trade-off between small amounts of high quality data and large amounts of low(er) quality data

# To control, or not to control? Is that the question?



- “Can’t do randomised trials because we haven’t got enough patients”
- “No point in having a control group because the trial would be severely underpowered”
- “No point in having a control group because there’s no chance to show any treatment benefit”

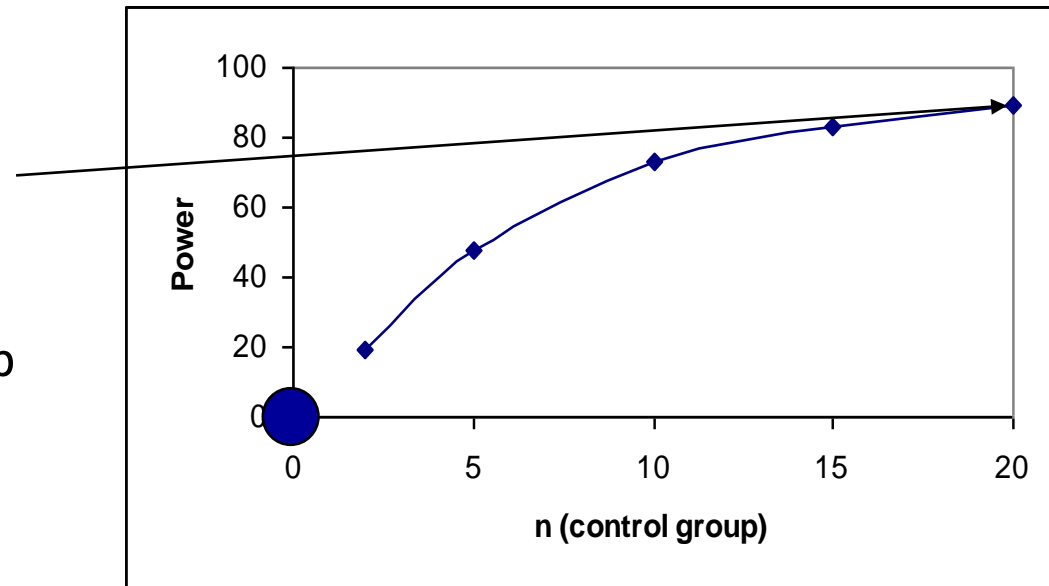
# Control group “not worth it”

## An example

Event rates 50% vs. 10%

Two (equal size) groups of 20 patients gives 85% power for a 1-sided test at  $\alpha=5\%$

What happens if the control group gets smaller and smaller?  
15, 10, 5, 2



What if the control group falls to size of *zero*?

– An “uncontrolled” study



# Control group “not worth it”

## An example

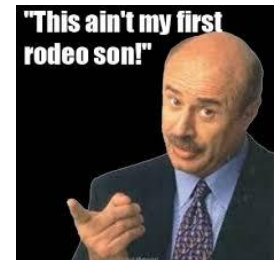


“I’m sorry but your study has zero percent power to demonstrate *any* treatment effect, of *any* magnitude. At least my study of 20 patients vs. 2 patients has 20% power, which is a lot better than not having a control group.”

And 2 equal-sized groups of 10 (or 11) give us about 50% power

Response:

“Well, but I would treat all of those 20 (or 22) patients with the active[?] treatment, and I would be able to compare them to historical controls”



“But your small trial has 20% power (even on its own) *and* I can compare the results to historical controls as well”

# Control group “not ethical”

## What’s the control?

- Everyone should get best standard of care (even if that is pretty minimal / palliative care)
- Then some patients (50%, maybe) get new treatment *as well*, and the other patients (50%, maybe) don’t...  
... but they stay on their palliative care
- That’s randomisation to a control group (possibly placebo, possibly “no *additional* treatment”)
- Randomisation and/or placebo-treated, does *not* mean best standard of care needs to be withdrawn

# Control group “not ethical”

## What’s the alternative?

- Everyone should get best standard of care (even if that is pretty minimal / palliative care)
- The patient is not included in the trial (because the trial is “unethical”)
- The patient continues to get best standard of care
- Patient is denied the chance to get experimental treatment
  - *And that’s ethical !?!*

# and US Regulatory Guidance

## **Rare Diseases: Common Issues in Drug Development Guidance for Industry**

### ***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Jonathan Goldsmith at 240-402-9959, or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**August 2015  
Rare Diseases**

- August 2015...  
and still draft!

# Regulatory Guidance

- Historical controls
  - “Within-patient comparisons in a relentlessly and predictably progressive disorder might provide sufficient data to support a benefit–risk assessment. However, in other situations comparative trials may be needed/expected.”
  - “In general, studies using historical controls are credible only when the observed effect is large in comparison to variability in disease course (e.g., substantive improvement in outcome is observed with treatment in a disease that does not naturally remit).”



# Regulatory Guidance

- Overall evidence of Effectiveness and Safety
  - “When conducting a benefit-risk assessment for a drug for a **serious or life-threatening illness**, FDA also recognizes that greater risks may be accepted for a treatment that is an advantage over available therapy. This reflects FDA’s commitment to expediting the availability of drugs for **serious diseases** as soon as it can be concluded that the benefits of the drugs exceed their risks, while preserving appropriate standards for safety and effectiveness, especially when these **patients have unmet needs**, as is often the case with patients with rare **diseases**”

# Case study

- L-glutamine Endari<sup>®</sup> for sickle cell disease
- FDA Oncologic Drugs Advisory Committee 24<sup>th</sup> May 2017
- Voted 10 vs. 3 to approve
  
- Small effect size problem
- Big missing data problem
- Missing data (dropout rate): 36% (active) vs. 24% (control)

# Case study

- L-glutamine Endari<sup>®</sup> for sickle cell disease
- FDA Oncologic Drugs Advisory Committee 24<sup>th</sup> May 2017
- Voted 10 vs. 3 to approve
- Brian Rini, acting chair of ODAC:  
“My ‘yes,’ like many of the [votes], was difficult. This could have gone either way. This is clearly a bad disease - worse than cancer in many ways, mostly from a stigma standpoint - and to complete two randomized studies is a major accomplishment. Our job, however, is to recommend approval of drugs not based on desperate need, but based on good data.”



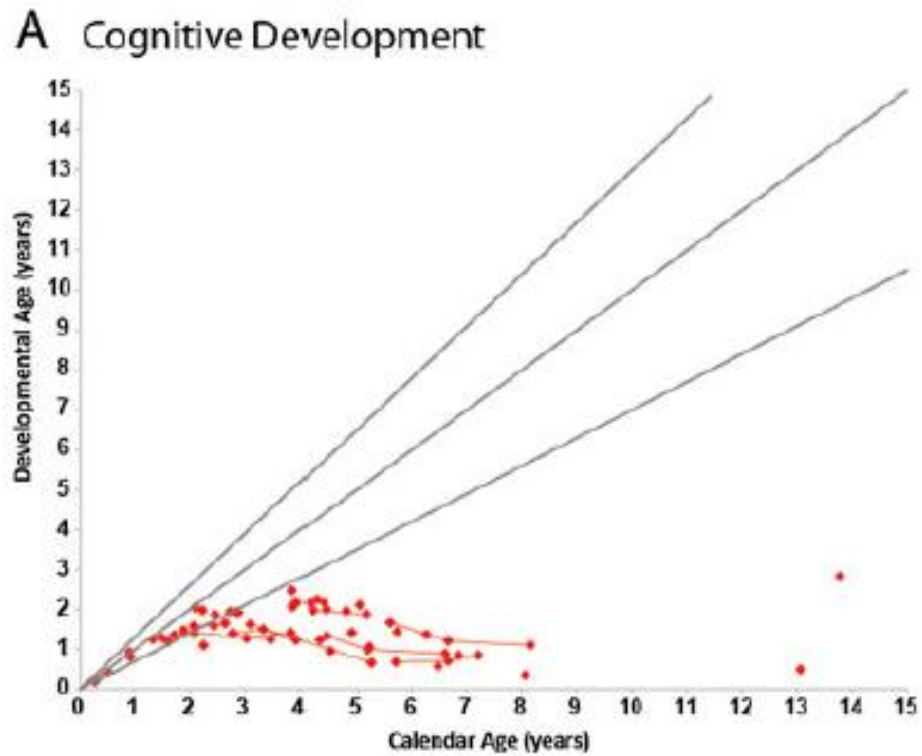
# Case study

## MPS IIIA

- Mucopolysaccharidosis type IIIA
- Sanfilippo syndrome type A
  
- MPS IIIA
  
- Incidence about 1:100,000\*

\* Meikle et al., JAMA, 1991

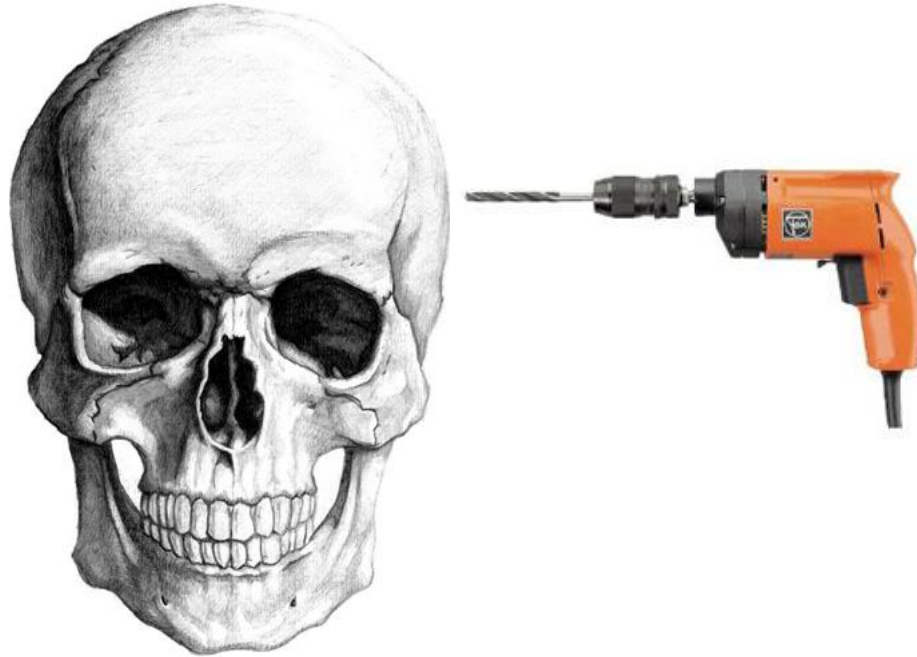
# Case study MPS IIIA



# Case study

## MPS IIIA

- How the treatment is given...



- Patients' [parents'] reactions to placebo???

# Bayesian desperation...

- “Can’t we use Bayesian methods?”
- The good news:
  - A Bayesian approach will combine what you already know with new data you collect
- The bad news:
  - A Bayesian approach will combine what you already *believe* with new data you collect
- Don’t confuse knowledge with belief; and belief with hope

## Bayesians in clinical trials: Asleep at the switch

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“It is difficult for physicians [and others] to keep in mind how bad things may be with an untested intervention, in the face of the reality of how bad things are without it.”

“...the more passionate the investigator [or parent??], the greater the protection the priors require from their strongly held opinion.”

# back to the MPS IIIA Case study

- Solution ??? ...
  - “Sanfilippo A Multi-national Observational Study” (“SAMOS”)
- Press release (30<sup>th</sup> May 2017)
  - “SAMOS is particularly important as there is currently no validated biomarker in MPS IIIA that reflects CNS disease progression and response to future therapy. SAMOS has therefore been **designed** to evaluate clinical change in **untreated MPS IIIA patients**. As agreed with the regulatory authorities, this international multi-center study is to function as a **non-concurrent control group** for the upcoming Lysogene Phase II/III pivotal gene therapy trial, scheduled to start during the first quarter of 2018.”

# To close...

- It's largely about design
- It's about execution
- “Quality always matters”
- It's about thinking “totality”

And we need to think *specifically* about *this* problem, not just pick up a (generic) textbook on clinical trials