

# New Methods? New Thinking?

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# Example 1



**Incidence:**  
about 2 – 3 per  
1000 live births

**Prevalence:**  
>1 million affected  
in EU

**Sasha Browne, 3, has taken part in the first trial to treat cerebral palsy using stem cells taken at birth from the patient's umbilical cord. Her parents say her condition has improved**

***Stem cell first for cerebral palsy girl, page 4***



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*Stem cell first for cerebral palsy girl, page 4*

# Conflicts of Interest (apparent)

- Most of my income is from pharmaceutical companies
- Most of my income is from working on problems of (and developing medicines for) rare diseases



# Conflicts of Interest (real)

- Research funding and travel bursaries from MRC, EC & NIH
- All to work on methodological issues of developing medicines for rare diseases



# How is Sasha getting on?

“Look at the difference in her – her walking is streets ahead of what it was before...”

“We feel that there has been some general improvement in her motor skills and perhaps some improvement in her vision and cognitive ability.”



Sasha's *physiotherapist* told her parents “she believed the toddler's progress had been faster than that of other patients”

“We can't categorically say this is attributable to the stem cell infusion. However, we feel the improvement has potentially been at a faster rate than it may have occurred...”

Sasha was expected to need surgery to correct a squint... this has been postponed and may no longer be necessary. It is not known whether the stem cells brought about the improvement but Sasha's *ophthalmologist* said he could not rule out the possibility.

# What is a “rare” disease?

- “When you can’t get enough patents to do a reasonable (conventional?) clinical trial”
- Examples:
  - Stroke
  - Diabetes
  - ...
  - Cerebral palsy?
  - Malaria?
  - ...
  - Hutchinson–Gilford progeria
  - NP disease
  - MPS III



# The elephant...



# Example 2

- Hutchinson–Gilford progeria syndrome (HGPS)
- Premature aging, average age at death around 13 years
- Mental capacity unaffected
- Incidence ~ 1 in 4 million live births
- At time of trial, 34 known cases *worldwide*





# Efficacy

- 9 / 25 (exact 95% CI 18–58%) patients achieved >50% increase over pre-therapy in estimated annual rate of weight gain
- 16 / 25 didn't

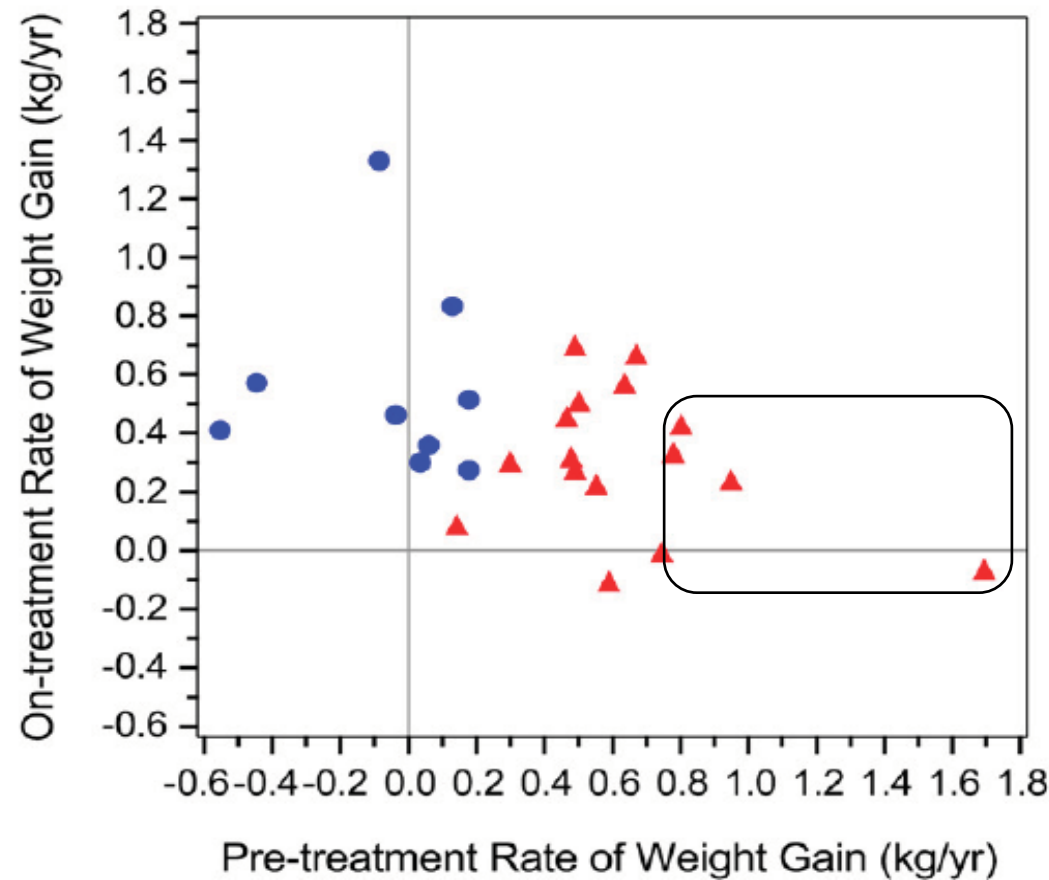
# Efficacy

- 9 / 25 (exact 95% CI 18–58%) patients achieved >50% increase over pre-therapy in estimated annual rate of weight gain
- 16 / 25 patients achieved <50% increase over pre-therapy in estimated annual rate of weight gain
- “Of note, the four patients whose rates before study were negative, all increased on treatment”

# Efficacy

“Of note, the four patients whose rates before study were negative, all increased on treatment”

What about the four “best” cases at baseline?



Blue ● achieve  $\geq 50\%$  increase  
Red ▲ not achieved

# Regression to the Mean!

# Example 3

## An example of convincing evidence

Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials. *BMJ* 2003; **327**:1459–61.

Cuello C (rapid response) <http://www.bmj.com/cgi/eletters/327/7429/1459#44035>

“...skydiving student Sharon McClelland, 26, who amazingly survived a 10,000-foot plunge in September 1994 near Queensville, Ontario, into a marsh when her parachute malfunctioned”

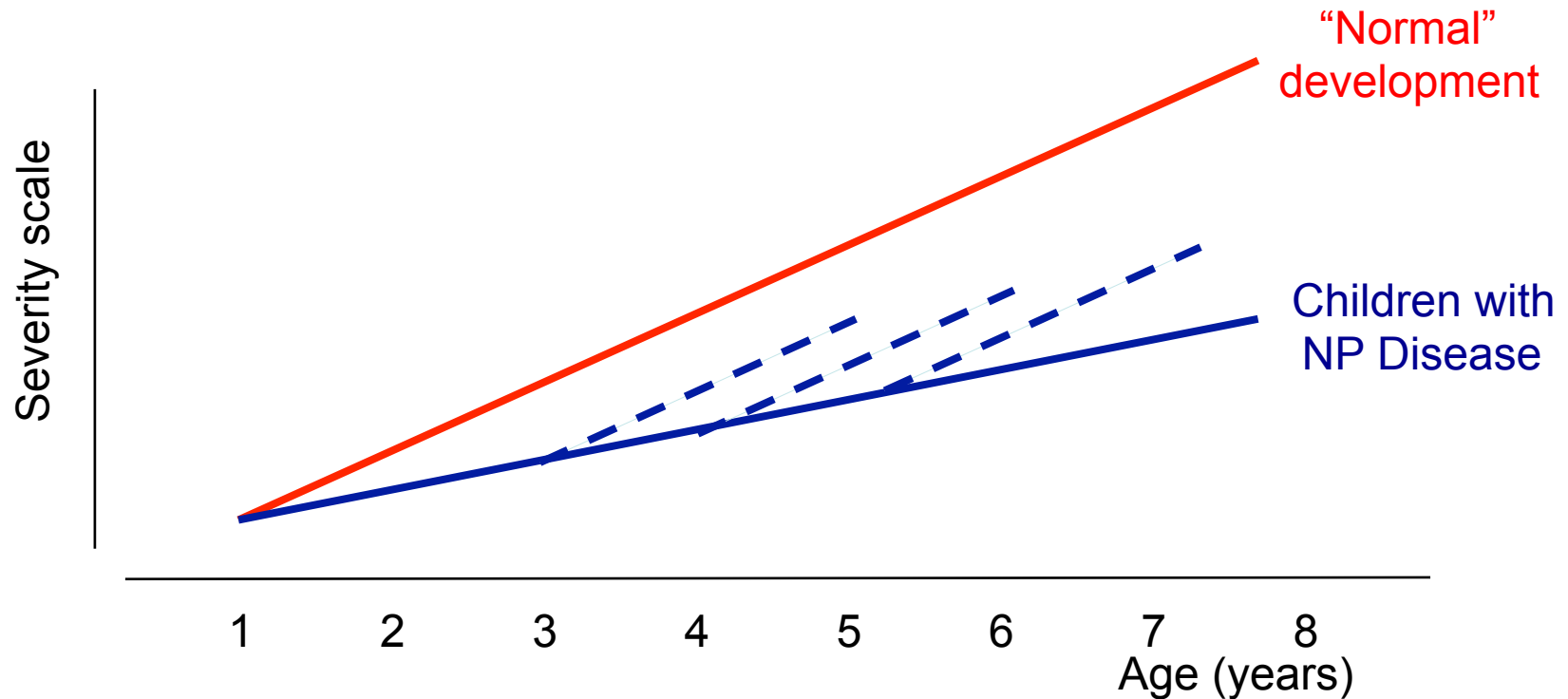
Temple R (rapid response) <http://www.bmj.com/cgi/eletters/327/7429/1459#44035>

Code of Federal Regulations. 21 CFR 314.126. Adequate and well controlled studies  
“...**placebo concurrent controls, dose comparison concurrent controls, no treatment concurrent controls, active treatment concurrent controls, historical controls**”



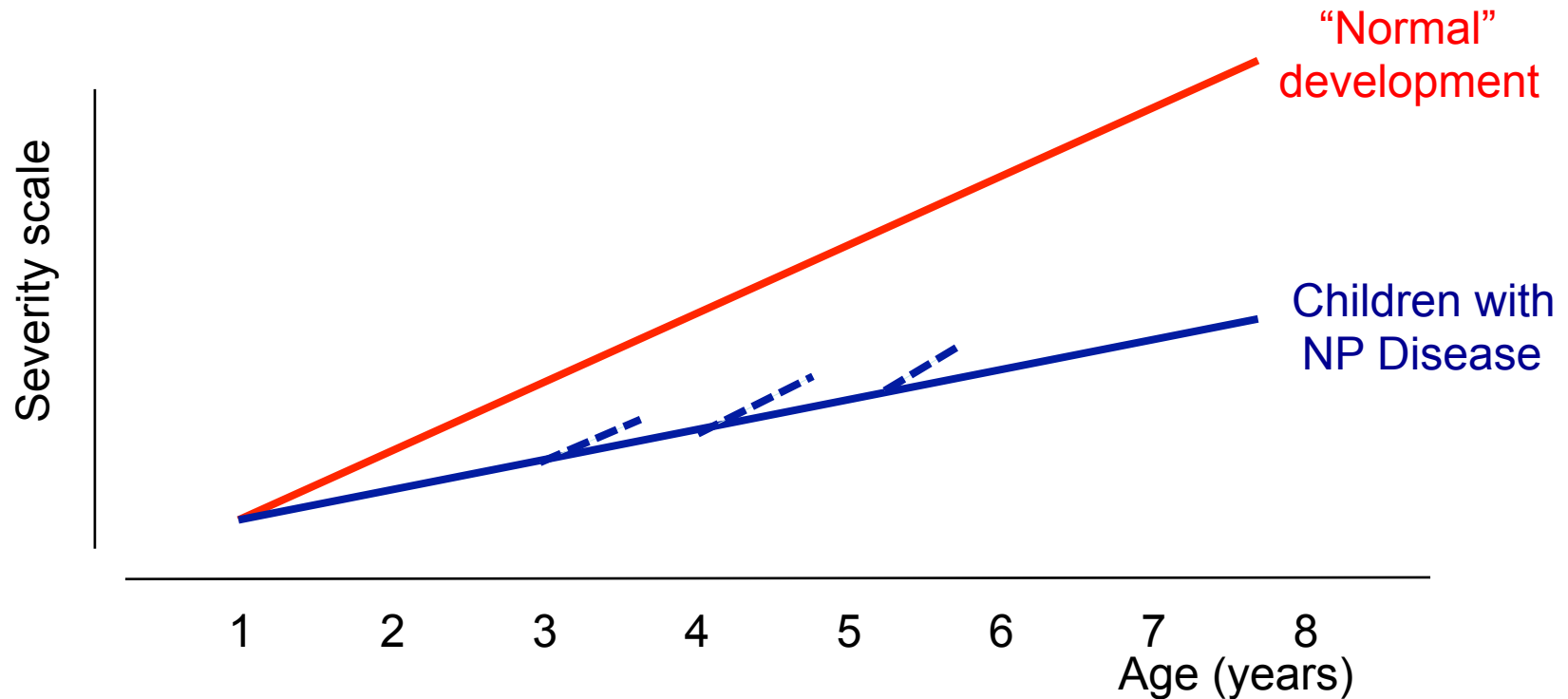
# Example 4

- NP Disease
- Prevalence (in EU) about 2000 patients
- **Plan A**



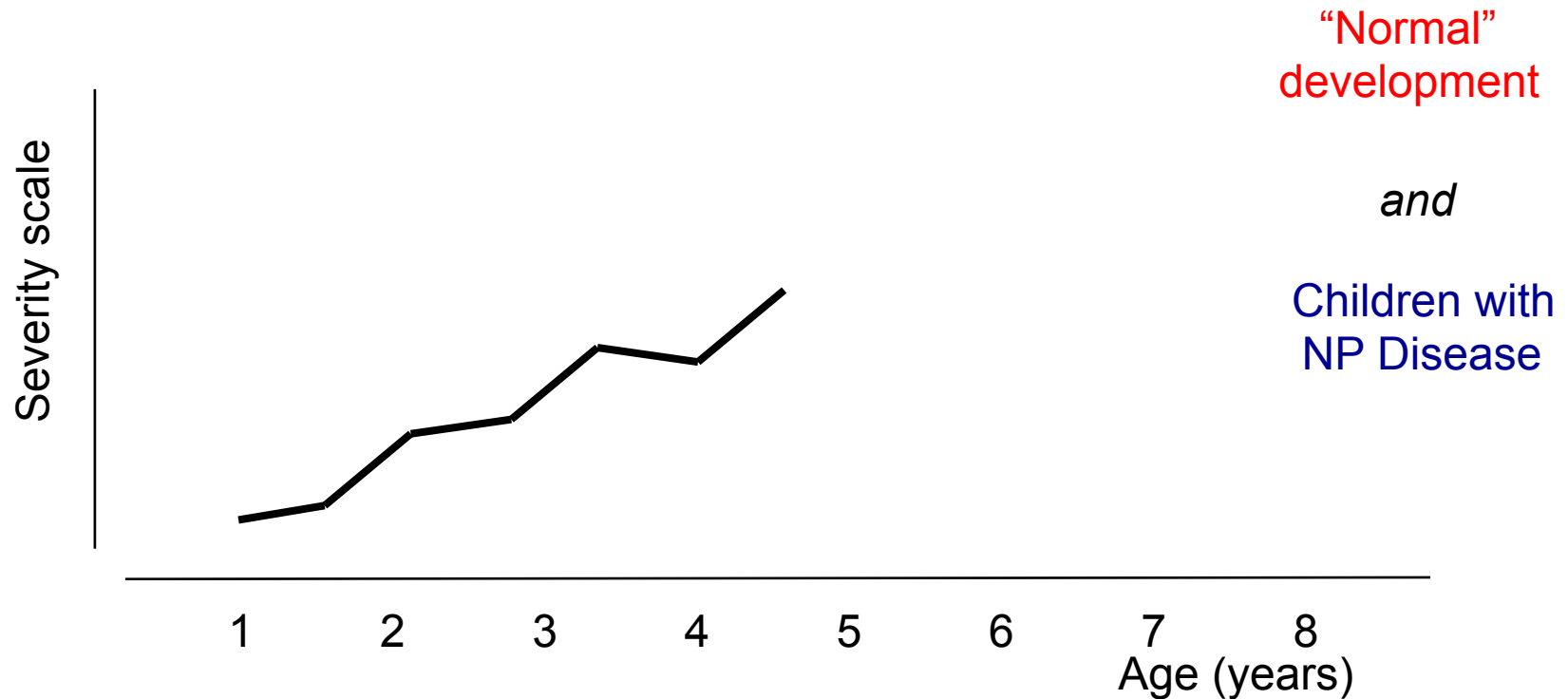
# Example 4

- NP Disease
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# Example 4

- NP Disease
- Prevalence (in EU) about 2000 patients
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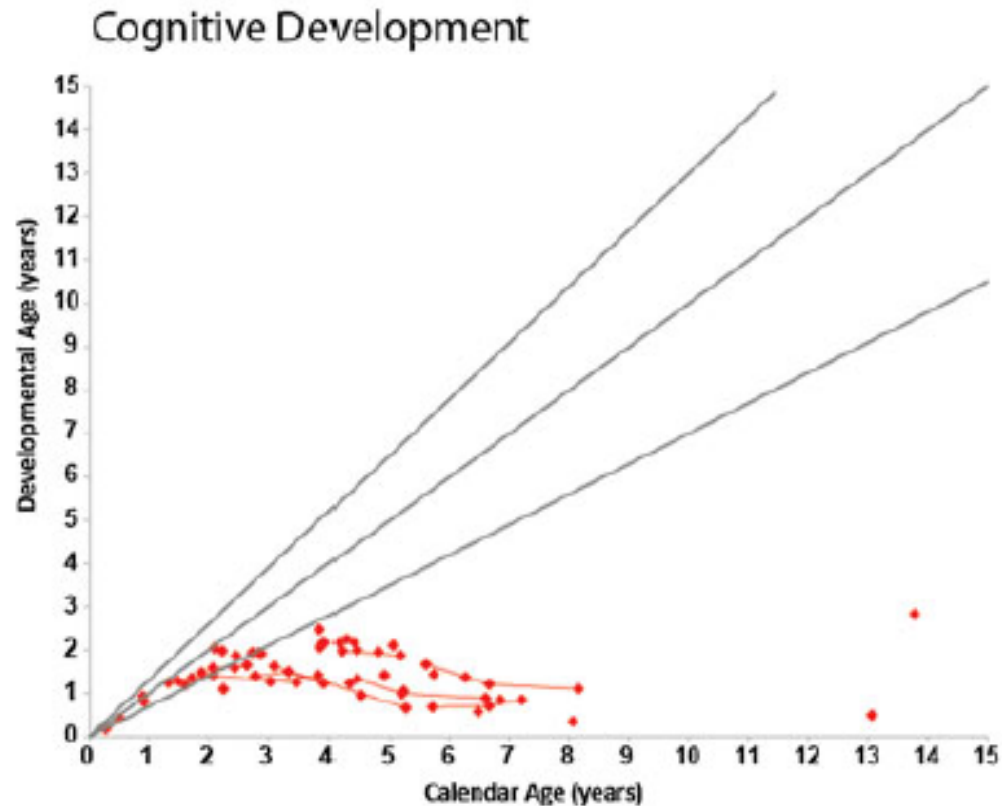


# Example 4

- NP Disease
- Prevalence (in EU) about 2000 patients
- **Plan B**
- **A randomised controlled trial**
  - Best standard of care (which isn't much)**
  - VS.**
  - Best standard of care + IMP**
- No patients denied best care
- Parents agreed to study design

# Example 5

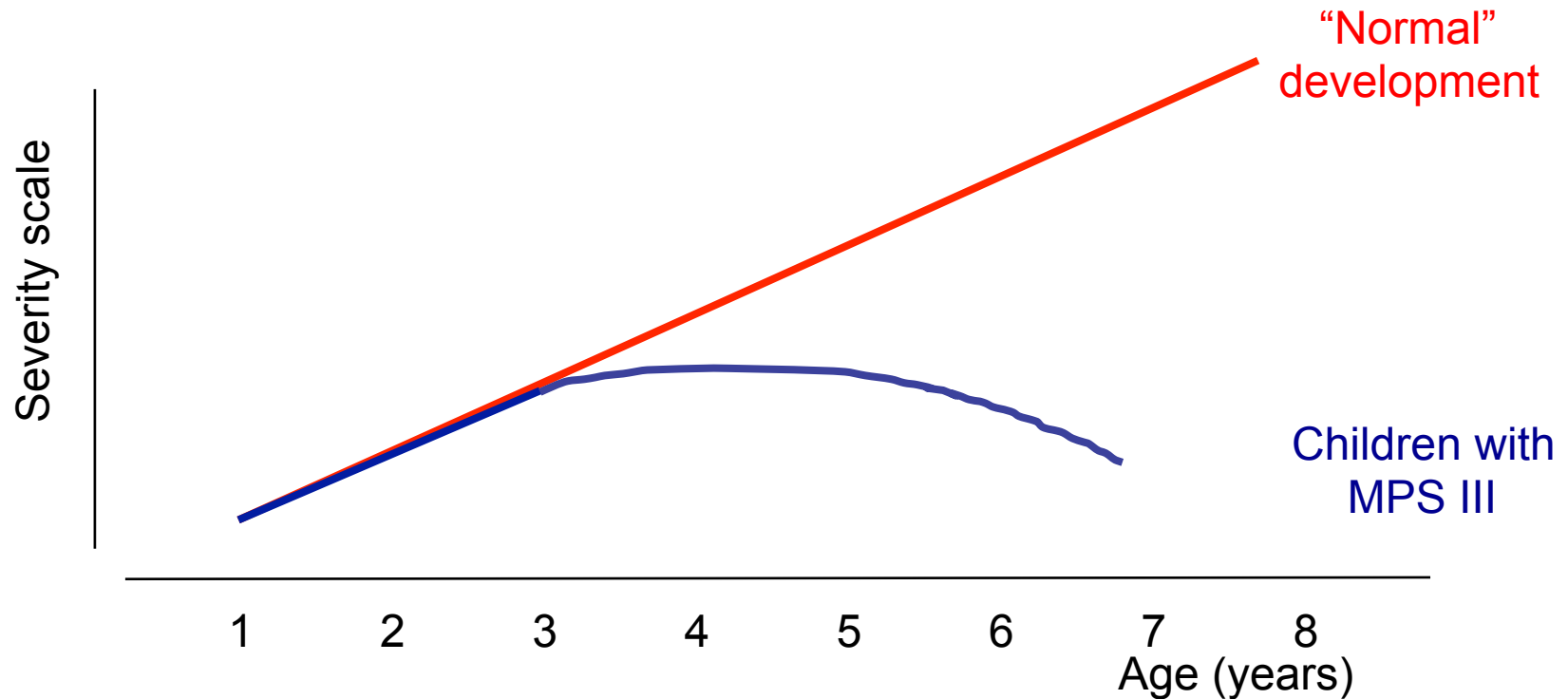
- MPS III
- Prevalence (in EU) about 50 patients





# Example 5

- MPS III
- Prevalence (in EU) about 50 patients
- **Plan A**



# Example 5

- MPS III



- Parents reaction to placebo control...???

# Example 6

- Infantile Spasms
- Incidence 1:5000 – 1:2500 live births

“To evaluate the efficacy, comparisons will be made with data from closely matching infants in the XXX study, within a Bayesian statistical model...”

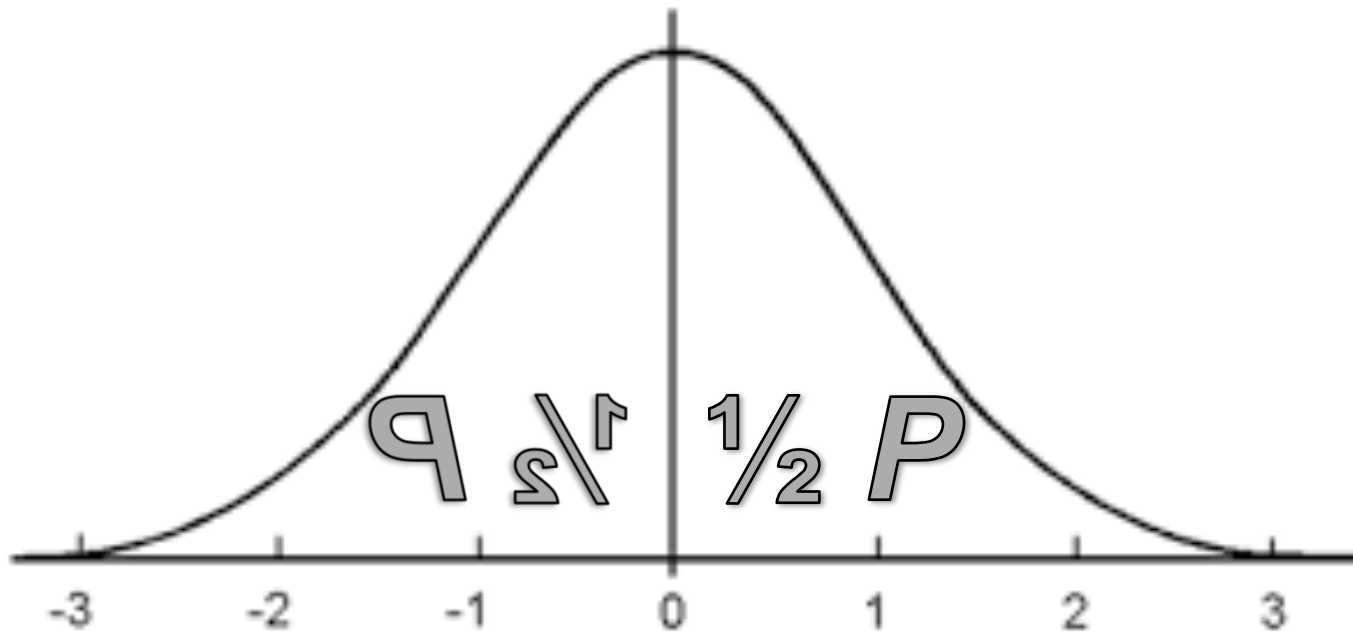
# Example 6

- Infantile Spasms
- Incidence 1:5000 – 1:2500 live births

“To evaluate the efficacy, comparisons will be made with data from closely matching infants in the XXX study, within a Bayesian statistical model. We are planning a simple frequentist approach to the statistical analysis of data from this study.”

“If we are able to use Bayesian methods, we anticipate that the sample size requirement will reduce significantly from that given below...”

# Playing with $P$ -values





# Playing with $P$ -values



# Standards of evidence

CHMP. Guideline on clinical trials in small populations.  
London: EMEA, 2006.

- Meta-analyses of good quality randomised controlled trials that all show consistent results
- Individual randomised controlled trials
- Meta-analyses of observational studies
- Individual observational studies
- Published case-reports
- Anecdotal case-reports
- Opinions of experts in the field

*Let's turn back  
about 40 years*

# Standards of evidence

Hill AB. The environment and disease: Association or causation?  
*Proceedings of the Royal Society of Medicine* 1965; **58**:295–300

1. Strength of association
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

“None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer which is more likely than cause and effect?”

# Standards of evidence

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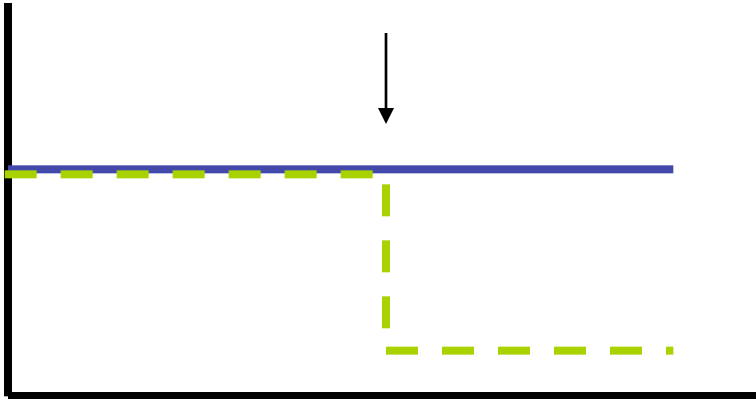
“What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect.”

This seems (to me) what gets forgotten.  
One size does *not* fit all.

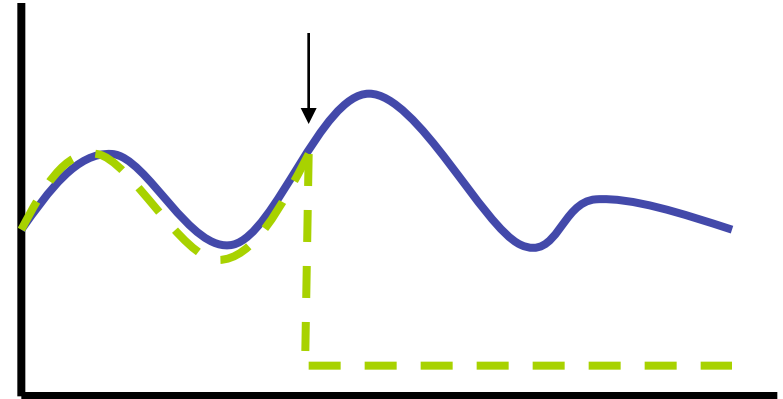
*Levels of evidence* might be consistent  
but *criteria of evidence* need not be.

# Context-specific evidence

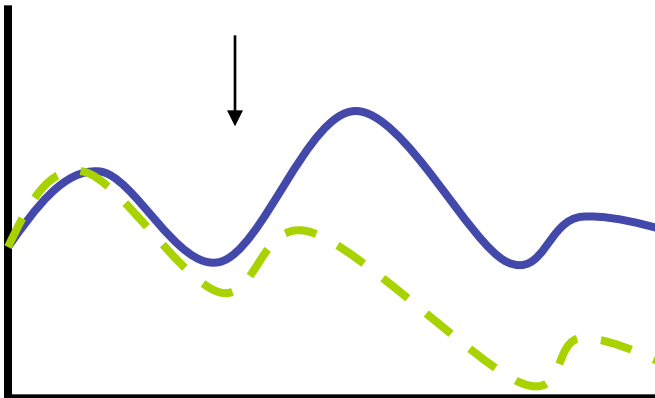
Stable disease, with sudden effect



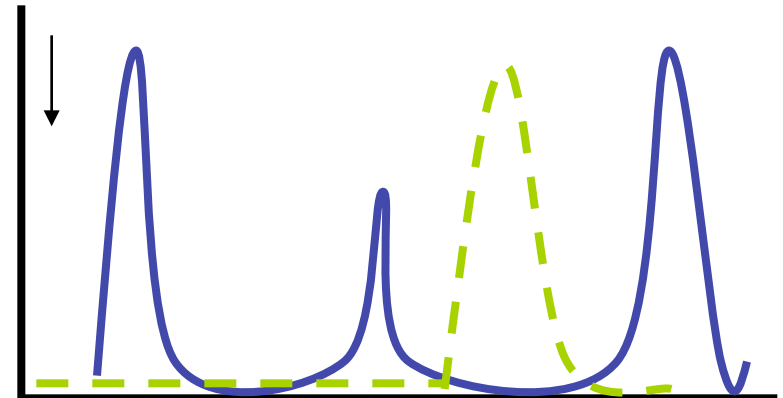
Fluctuating, with sudden effect



Fluctuating, with gradual effect



Episodic, with partial effect





# Context-specific evidence

## Acknowledgement of different sources of evidence

Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials. *BMJ* 2003; **327**:1459–61.

What causes death or major trauma?

Speed of hitting the earth.

Parachutes slow you down.

So they probably reduce incidence of death and major trauma.