Dose rationale and innovative study designs in paediatric drug development

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Outline

* **Defining the clinical questions to be addressed in a clinical trial**

  Efficacy/Safety: Does the treatment work and is it safe?

  Dose rationale: It is efficacious and safe if the correct dose is used.

  Patient population: Who are the patients who benefit from the treatment?

* **Operational considerations**

  Clinical endpoints

  Study design: evidence generation vs evidence synthesis

  Bridging and extrapolation

  Data Analysis

* **Conclusions**

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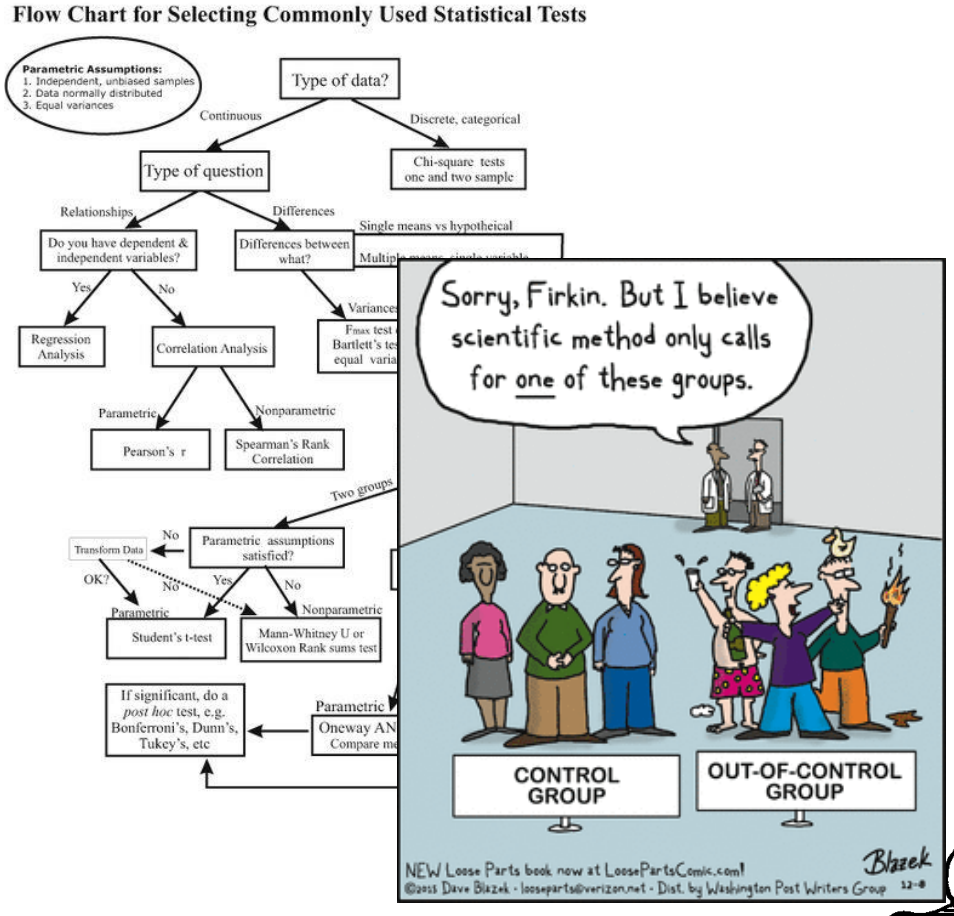
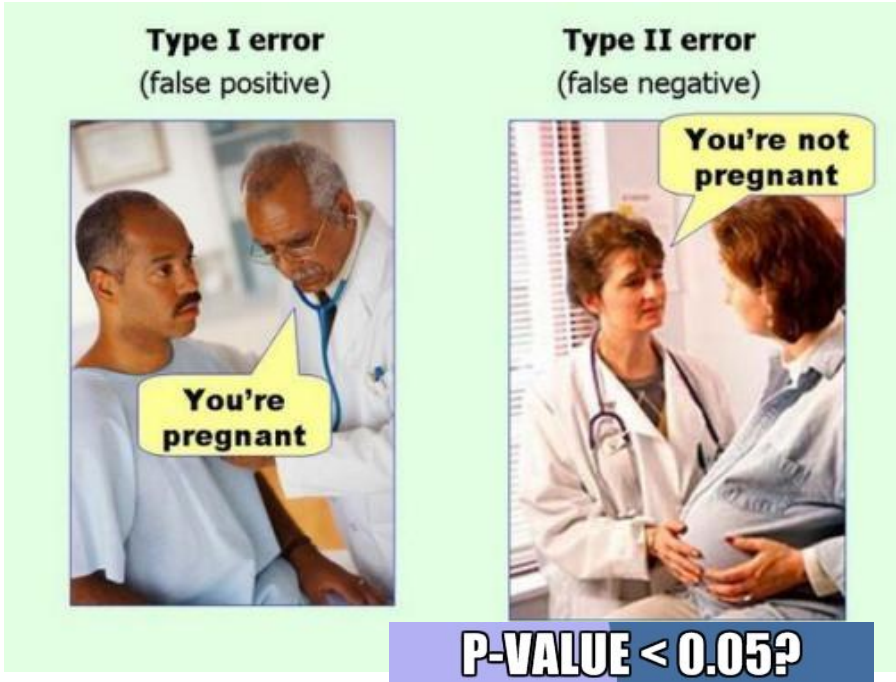
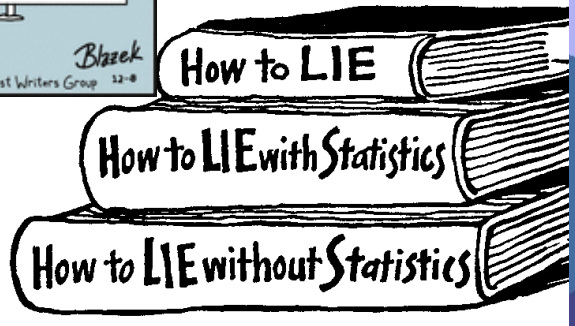
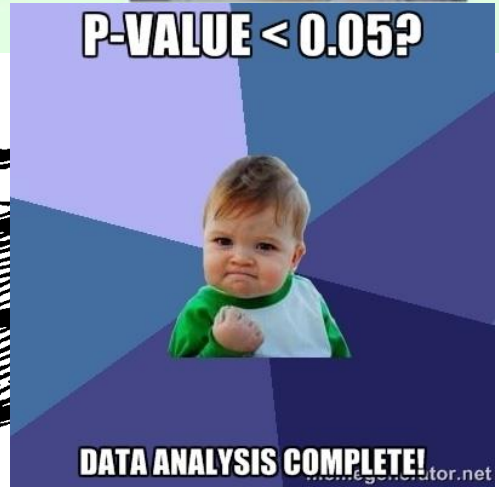
Why clinical studies fail

Statistical vs. scientific rigour









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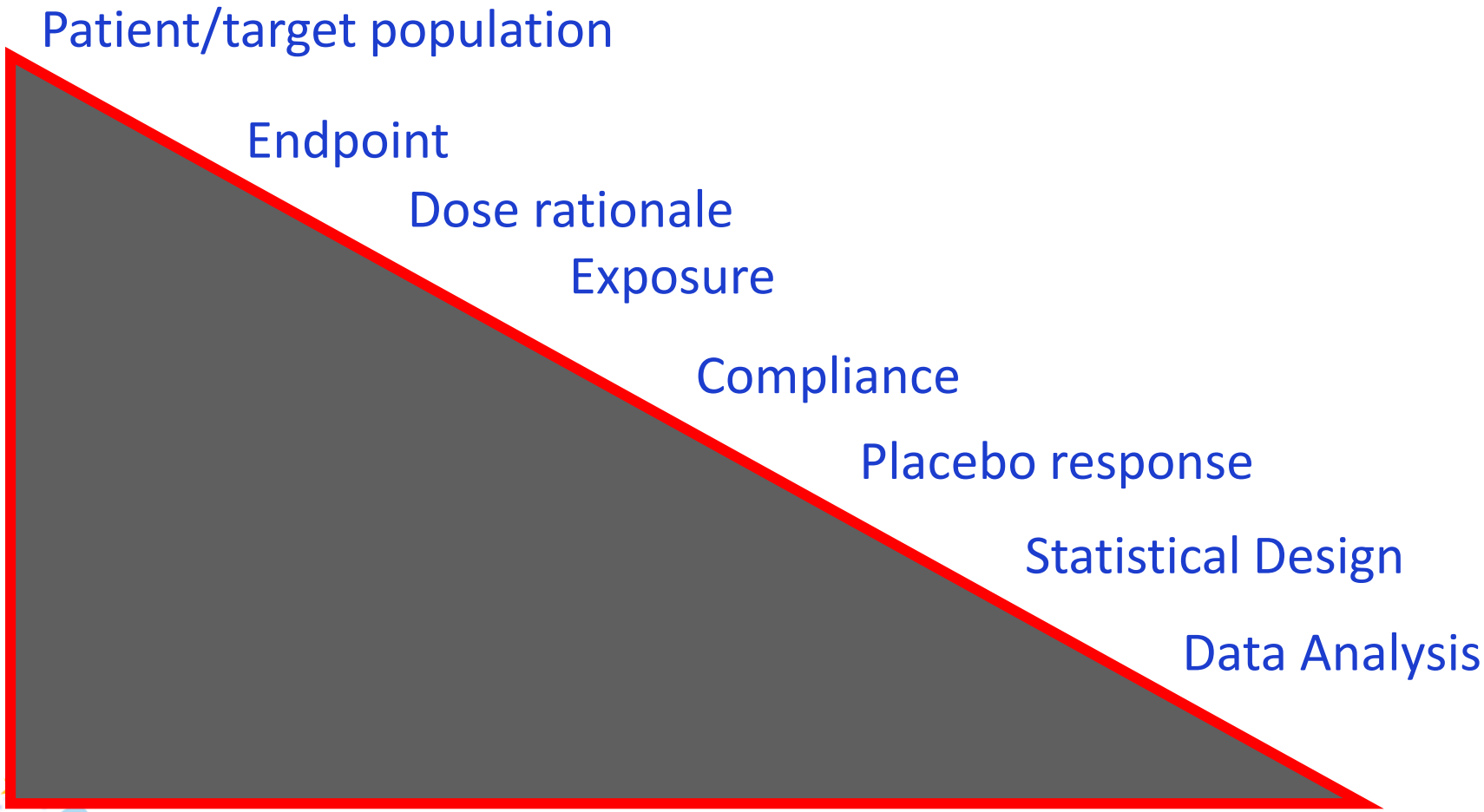
Why clinical studies fail



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WHAT IS THE APPROPRIATE DOSE?
WHAT IS THE APPROPRIATE SCALING FACTOR ?

BJCP British Journal of Clinical Pharmacology

What is the right dose for children?

Massimo Cella[1], Catherijne Knibbe[1], Meindert Danhof[1], Oscar Della Pasqua[1,2,*]

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British Journal of Clinical Pharmacology

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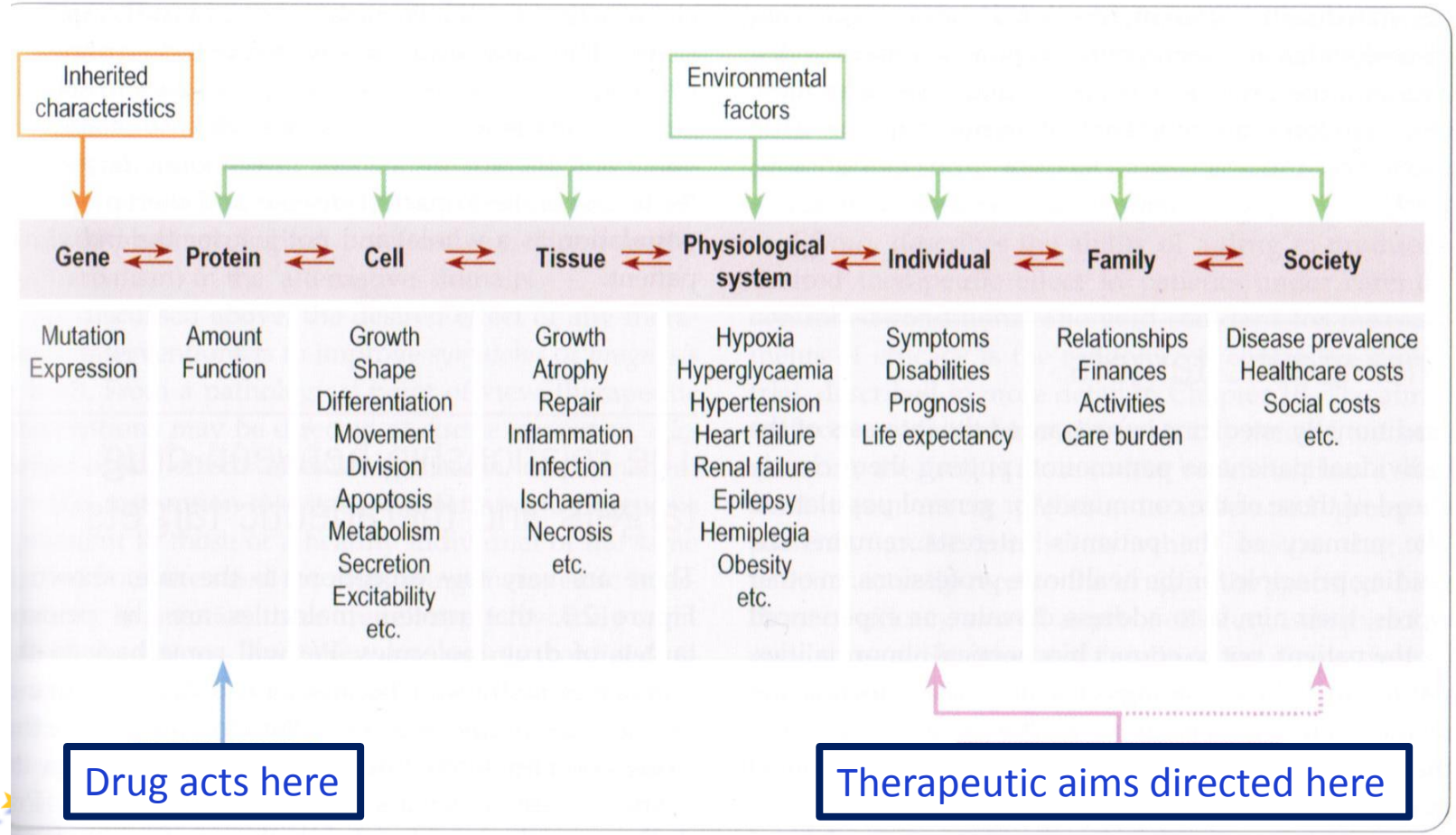
Endpoints: Clinical efficacy and outcome measures



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The paediatric population(s)

Pre-term 3 months 7 months 1 year 2 years 3 years 4 years 5 years

12 years 17 years

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Clinical Trial Simulations

Four basic questions:

How to

- Model
- Quantify
- Explain
- Take advantage of

→ Variability

Principle :Non-linear mixed effects modelling, Bayesian hierarchical models

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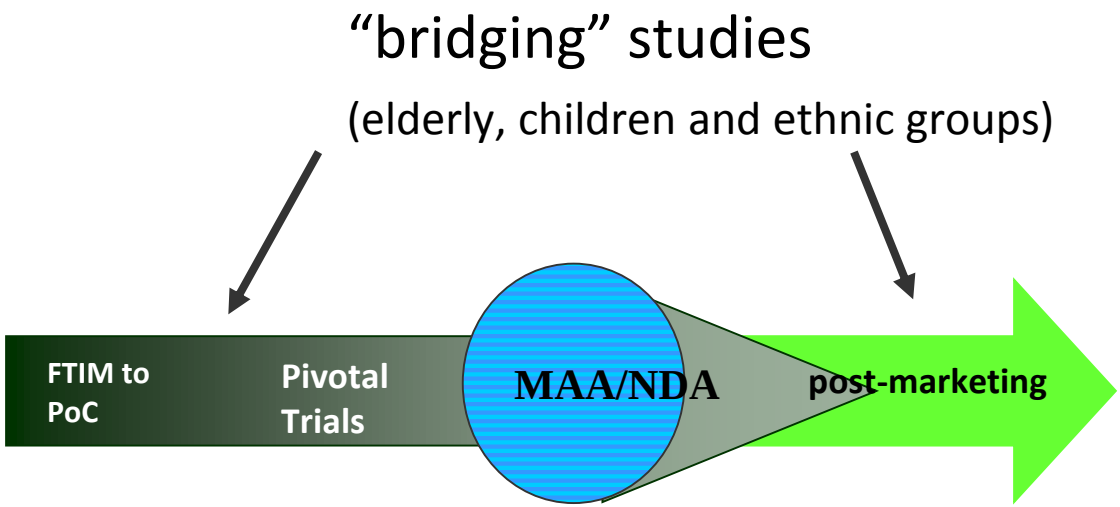
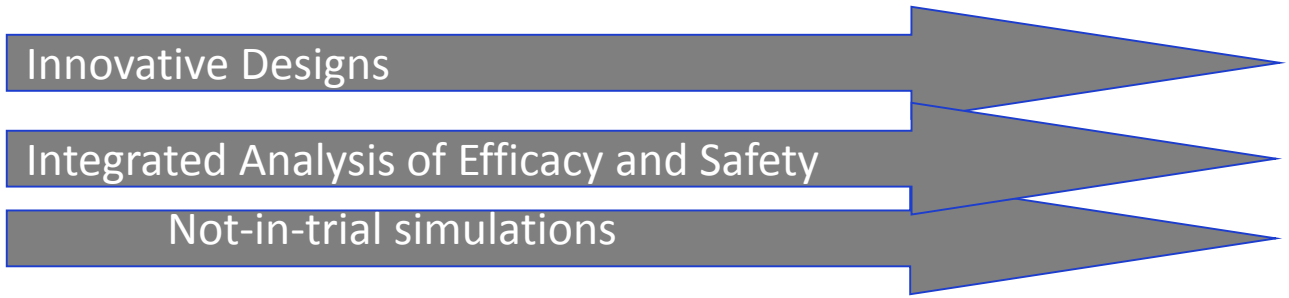
Not-in-trial simulations

Predicting treatment outcome in real-life populations





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Summary

- **Quantitative methods are required in paediatric research**

  - Intrinsic and extrinsic sources of variability
  - Information from direct evidence is incomplete or cannot be generated
  - Personalised medicine

- **Dose adjustment, titration and dosing algorithms can be evaluated in silico before exposing patients to potentially inefficacious or suboptimal interventions**
  - Evaluation of what-if scenarios
  - Inferences from bridging and extrapolation concepts

- **Methods are available that ensure informative study designs, eliminating unnecessary procedures and minimising the experimental burden on patients**
  - Optimal experimental design
  - Sparse sampling

- **Conclusions**

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Conclusions

In vivo veritas, in silico modus

Clinical decisions often require quantitative assessment of the benefit-risk balance. Decisions can be supported by a range of methods that enable:

1. Assessment of scenarios which are difficult to observe in clinical trials (e.g. due to practical challenges or other clinical complexities)

2. Optimisation of the design of experimental protocols, yielding accurate data on drug and disease properties

3. Integration of oncoming and existing historical data, which can then be used as basis for personalisation of treatment

4. Appropriate, patient-tailored treatment and dosing recommendations

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