A systematic application of good statistical practice in In-vivo studies

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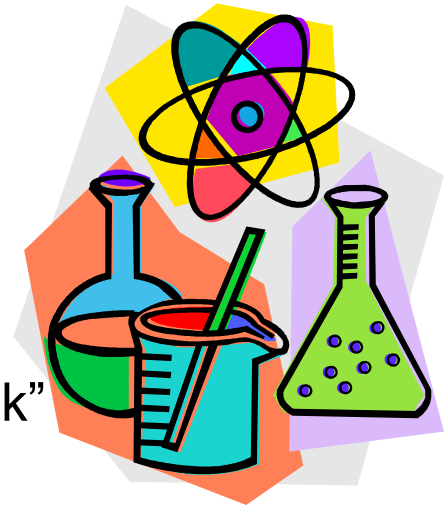
Why is systematic Good Statistical Practise important?

- Much of clinical research follows on from animal research.
- If animal studies fail to address internal and external validity, human predictions become less valid too.
- Each translational failure represents loss of invested capital.
- Poorly conducted studies give unreliable findings – unethical use of animals since not contributing to clinical benefit.

Increased benefit to patients

(Pound and Bracken et al. 2014, BMJ) + their comments

Preclinical robustness



- Even pre-clinical decisions have impact on “patient risk”
- Lack of systematic statistical support → missed opportunity to improve quality and confidence
- Impact of variability, bias and multiplicity often misunderstood – understanding key to improvement.
- Responsibility should be shared between statisticians, researchers and decision-makers.

Increased confidence in decisions.

(Peers et al. 2014, Nature Reviews)

Nature announcement: Reducing our irreproducibility

”We recognize that there is no single way to conduct an experimental study.”

Checklist:

- Describe methodological parameters
- Provide characterization of key reagents biological variability
- data deposition and presentation.
- Precise descriptions of statistics

(Nature, vol 496, 25 april 2013)

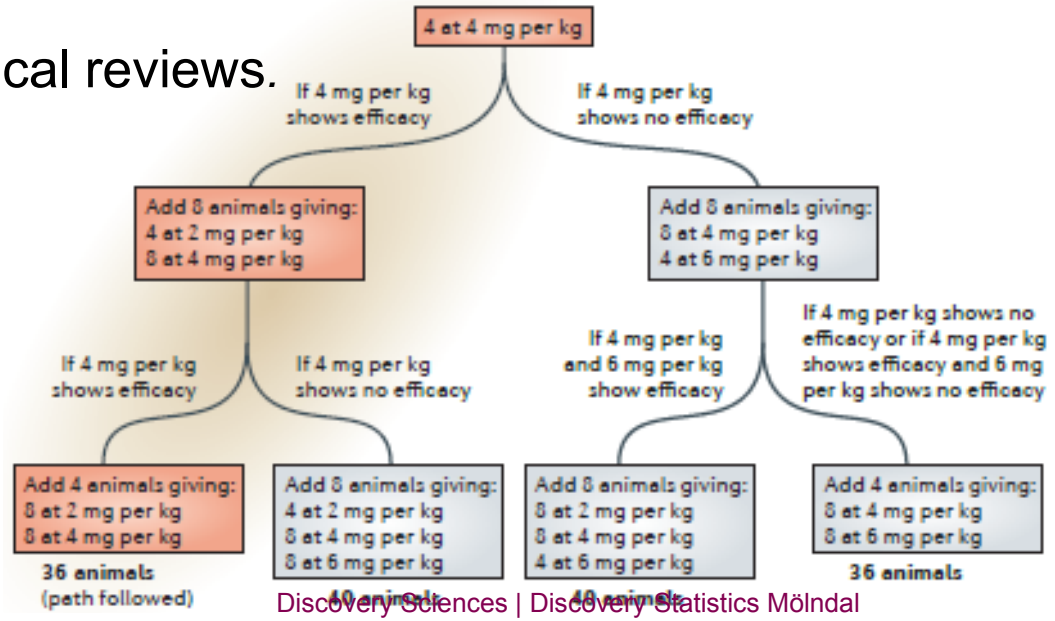
Can you trust your animal study data?

How confident can we be in the robustness and reproducibility of preclinical animal data?

- Why do we need to improve the quality of preclinical animal studies?
- Improvement opportunities in design and conduct of animal studies.
- Outcomes of systematic statistical reviews.

36% reduction in study duration

36% reduction in animals used

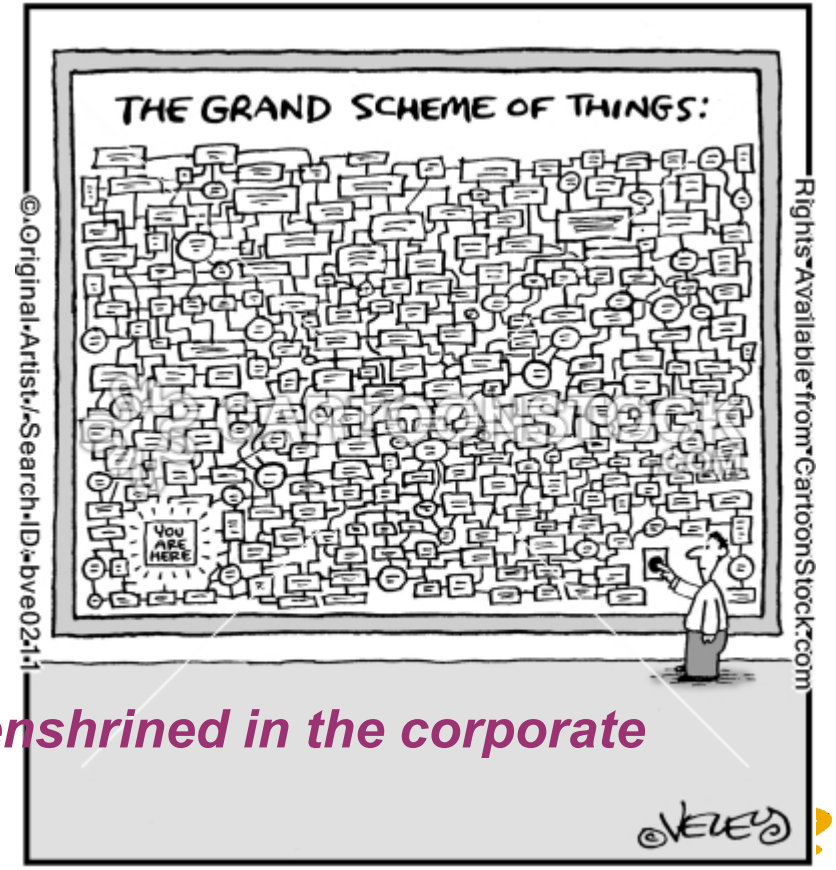


A systematic approach

Why? Integrating statisticians into in-vivo work at design stage to assure good science

Drivers:

- Helps to support AZ's external reputation
- Ensures that the data generated internally are of good quality
- Confident decisions
- Helps to make sure that our use of in vivo data in research is both ethical and appropriate.



The principles for this approach are enshrined in the corporate Bioethics Policy.

Supporting openness in animal research

Global Standard on Animal Care and Welfare

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Concordat on Openness in Animal Research

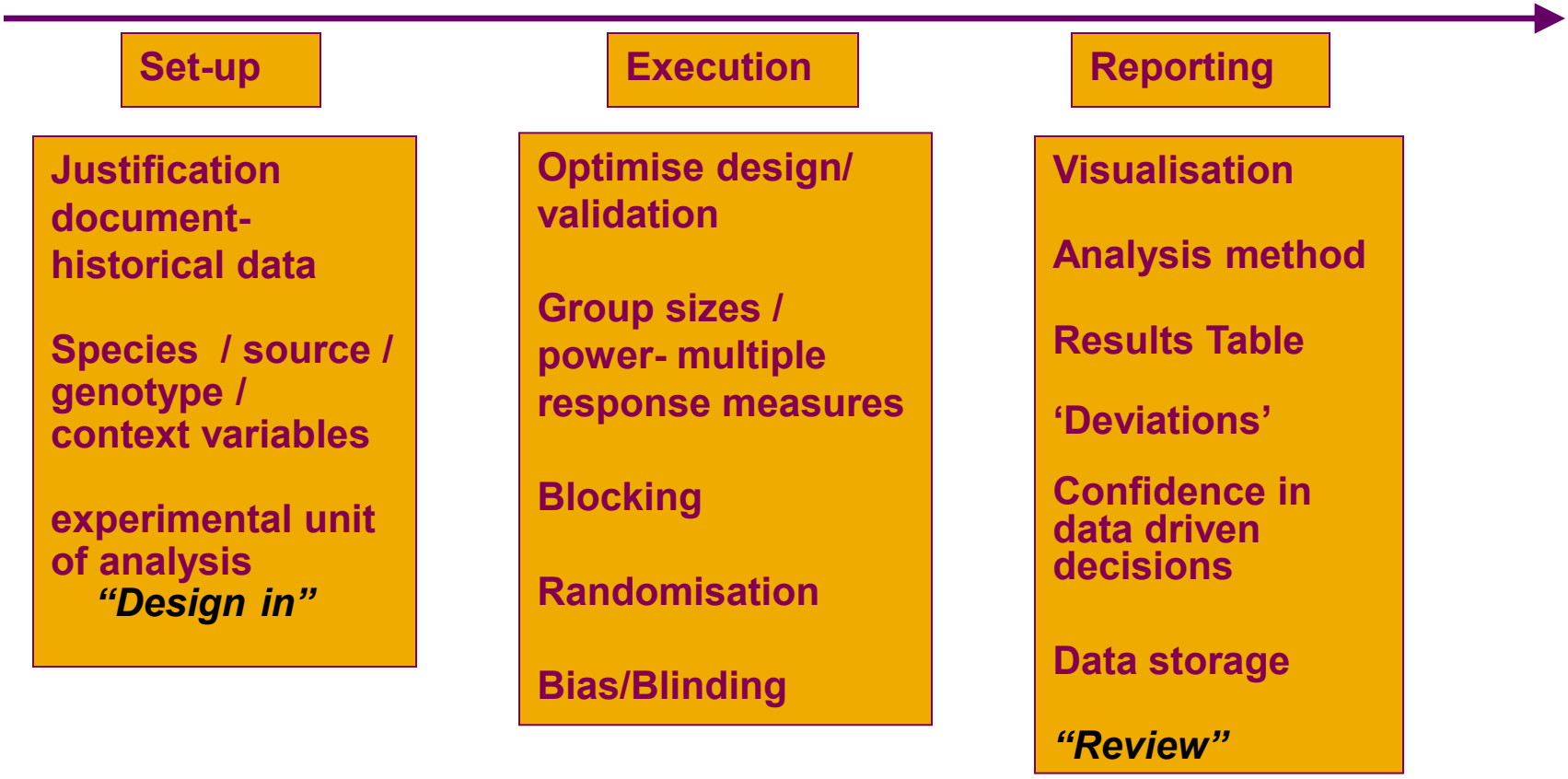
Commitment 1: We will be clear about when, how and why we use animals in research

Commitment 2: We will enhance our communications with the media and the public about our research using animals

Commitment 3: We will be proactive in providing opportunities for the public to find out about research using animals

Commitment 4: We will report on progress annually and share our experiences

GSP – Standards, Procedures



- GSP Standards documented – to promote consistent understanding
- GSP Procedures flowchart – to reflect priorities for statistician engagement

Addressing 10 key areas

For each of the GSP principles, sufficient details are given to:

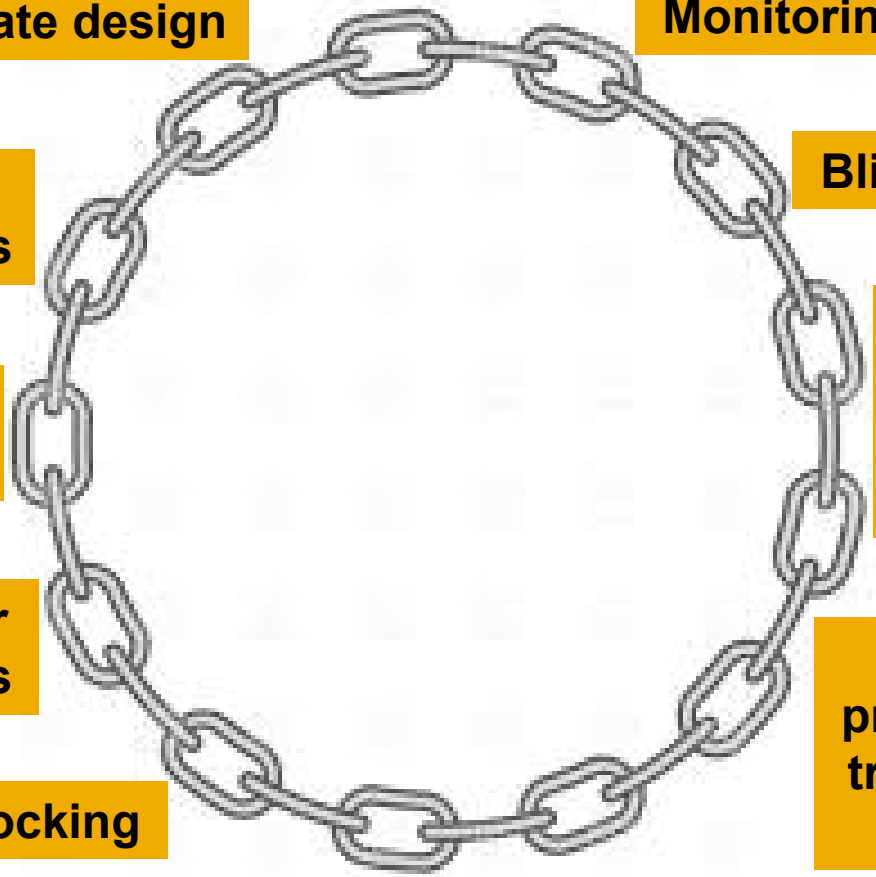
- **Justify the outcome qualifier (Green, Amber, Red)**
- **Act as a reference to scientists: what to do and how to do it**

***Practical constraints* and *animal welfare* are always weighed against the risk for bias.**

The Principle is:	Outcome	Qualifier
Carried out (statistical risk addressed)	Green	1
Not carried out (statistical risk outweighed by other considerations)	Green	2
Not relevant (no statistical risk identified)	Green	3
Not reviewed	Amber	
Not carried out (statistical risk, neither addressed nor outweighed by other considerations)	Red	

Agreed outcome of discussions is documented in a statistical health check and the study is deemed compliant with Good Statistical Practice.

The document



Appropriate design

Monitoring

Appropriate reference groups

Blinding

Planned statistical analysis

Appropriate order for sample processing and analysis

Justification for animal numbers

Appropriate processing order for treatment, sampling and termination

Blocking

Randomisation to treatment groups

Conclusions

- **Applying the practice in decision making process leads to enhanced external reputation for integrity and transparency**

- **We become confident that we have the right design at the first time conducting experiments**

- **This systematic approach serves as a stepping stone for information translated to clinical stage.**

- **Value of extra input and spending more time for planning needs to be visible and understandable to all.**

- **Key to success: Get all the scientists on board.**

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