Adaptive Study Design in Early Phase Clinical Research

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Photo: Marcus Augustine

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Nice Sophia Antipolis, FRANCE

CLUB PHASE 1

AGAH

bapu

AHPPI

Association for Human Pharmacology in the Pharmaceutical Industry

Adaptive study design

One or more decision points are built into the trial design;

The subsequent conduct following that decision point depends on the data observed to that point

'without undermining the validity and integrity of the trial'

'Changes are made "by design", and not on an ad-hoc basis; therefore, adaptation is a design feature aimed to enhance the trial, not a remedy for inadequate planning.'

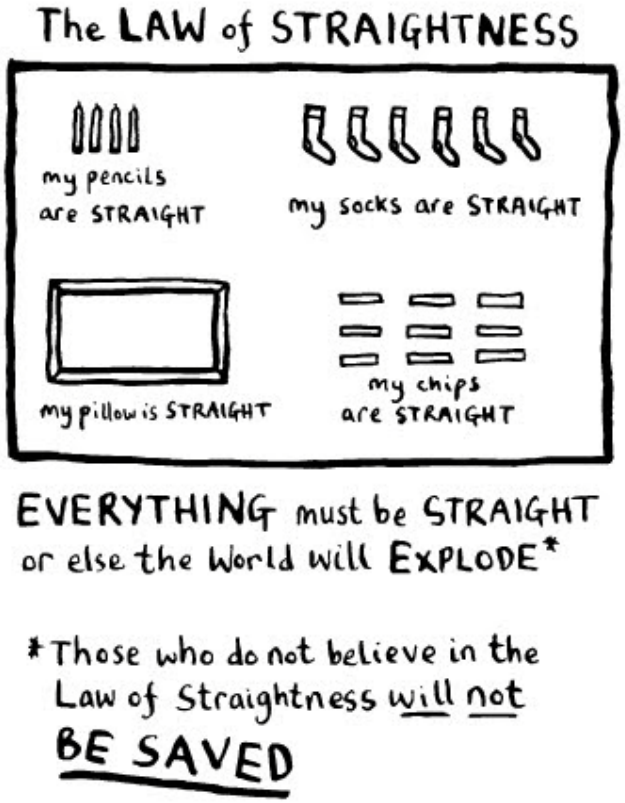
Paul Gallo et al.: Adaptive Designs in Clinical Drug Development – An Executive Summary of the PhRMA Working Group. Journal of Biopharmaceutical Statistics, 16: 275-283, 2006 http://www.qemini-grp.com/Bayes/PhRMA.pdf

The Law of Straightness

- How to manage the necessity to keep several possibilities of evolution with the needs of a detailed protocol?

The Law of Straightness

Edward Monkton



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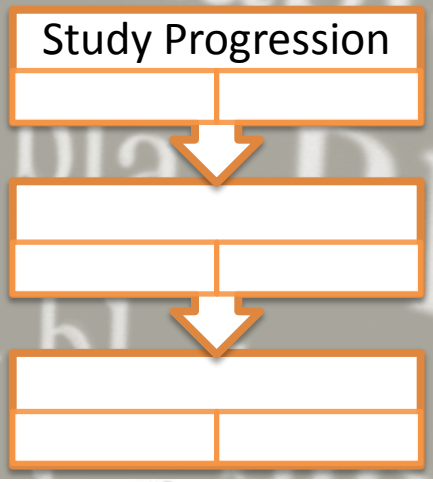
The Law of Straightness

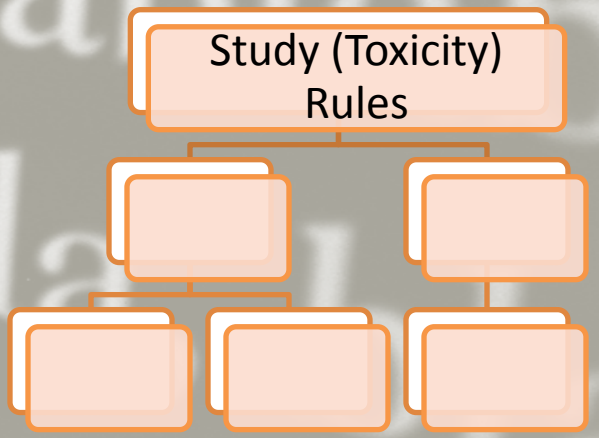
Clinical Study Protocol

A set of rules for the correct way to do an experiment

Adaptive Features	Limits

Controls





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The adaptive study design toolkit

Benefits:
Saving Time and Cost

By continuous and early decision making

By adjusting the study design taking into account data as it emerges

Funds are directed towards meaningful tests …

The Adaptive Features (*Type* of adjustments)

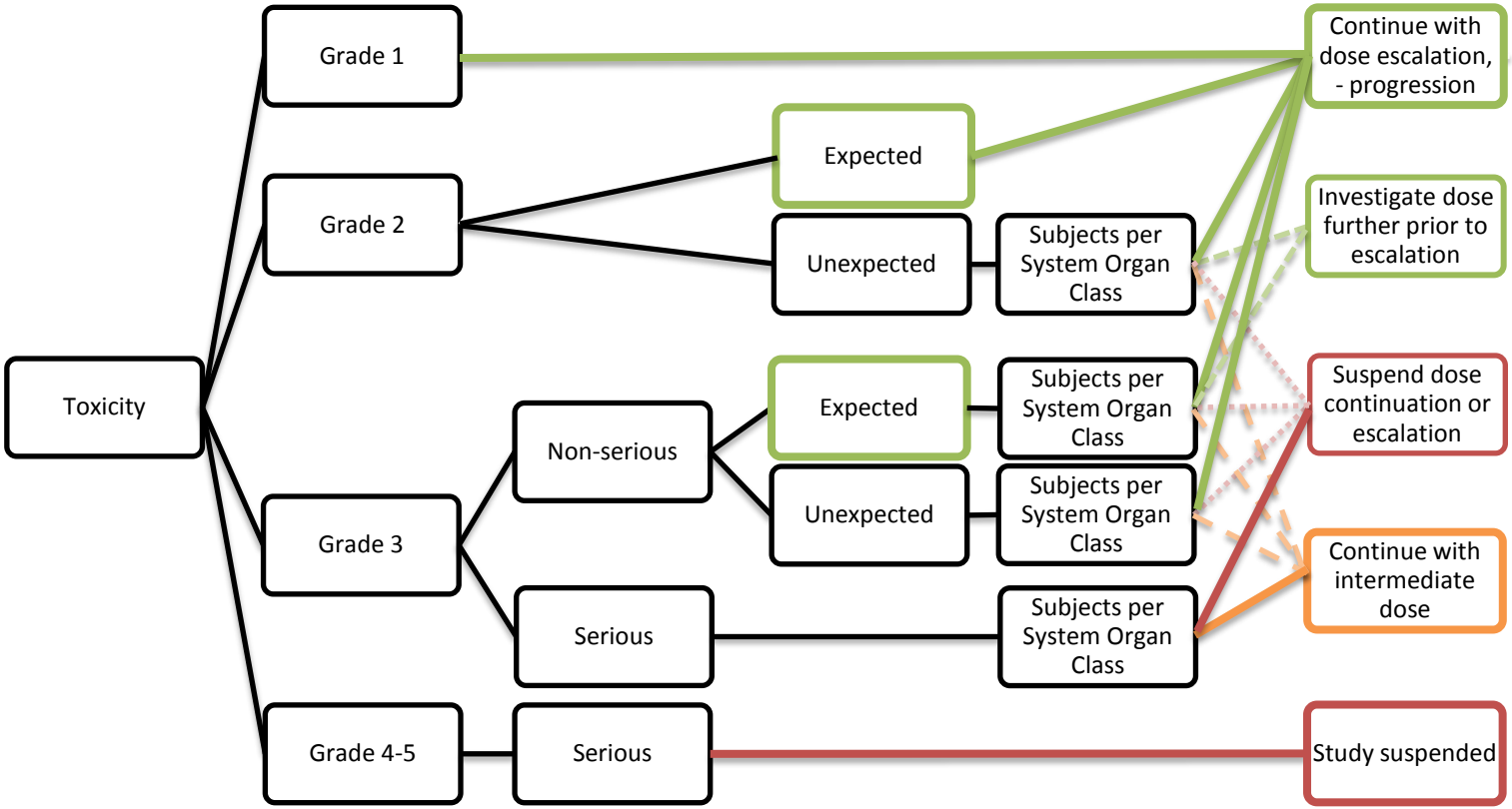
Potential changes with a reasonable likelihood of being required due to evolving data

Planned adjustments

The Limits (*Range* of adjustments)

Protocol Area	Adaptive features	Limits
Dose	Adaptable dose Fractionation Formulation	Starting dose Exposure limits Increments Minimum/Maximum no. of dose levels Minimum/Maximum no. of doses
Samples/Assessments	Flexible no. of samples and assessments Flexible timing of samples/assessments Additional (optional) types of samples and assessments	Minimum no. of PK/PD/Safety samples Minimum no. of safety assessments Maximum blood volume
Study Participants	Flexible no. of participants Optional cohorts	Minimum no. of evaluable subjects Maximum no. of randomised subjects
Timing	Flexible overlap of study parts	Minimum time to elapse between parts Maximum overlap

The Controls
Group Toxicity Rules



Maximum permissible risk, depending on the number of toxicities per SOC and in total

The Controls Study Progression Rules

Single Dose 1
Minimum PK/PD | Minimum Safety

Single Dose 2
Minimum PK/PD | Minimum Safety

Single Dose 3
Minimum PK/PD | Minimum Safety

Single Dose 4
Minimum PK/PD | Minimum Safety

Multiple Dose 1
Minimum PK/PD | Minimum Safety

Patient Dose 1
Minimum PK/PD | Minimum Safety

Ethnic Comparison Dose 1
Minimum PK/PD | Minimum Safety

Food Effect Dose
Minimum PK/PD | Minimum Safety

Interim blinded review by a Safety Review Committee

Change Management

- Necessity of amendments?
- How to adapt the Informed Consent Form?

‘Umbrella’ Protocols

- In case of a combined protocol, do we have to submit the results from the individual parts of the study before we are allowed to move forward to the next part? If yes, are blinded safety data sufficient?

Amendments for adaptive protocols

Adaptation	Substantial	Non-substantial	ICF* amendment	RA/REC * notification	RA/REC * authorisation
Use of adaptive features within limits and controls		yes	no	no	n/a
New adaptive features	yes		yes	yes	yes
Relaxing the limits	yes		no	yes	yes
Relaxing the controls	yes		no	yes	yes
Increasing the risk	yes		yes	yes	yes

*Medicines and Healthcare Regulatory Authority (MHRA) / National Research Ethics Service (NRES), UK

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Avoiding substantial amendments

- How to choose appropriate adaptive features?
- How to avoid the most common pitfalls when setting the limits and the controls?

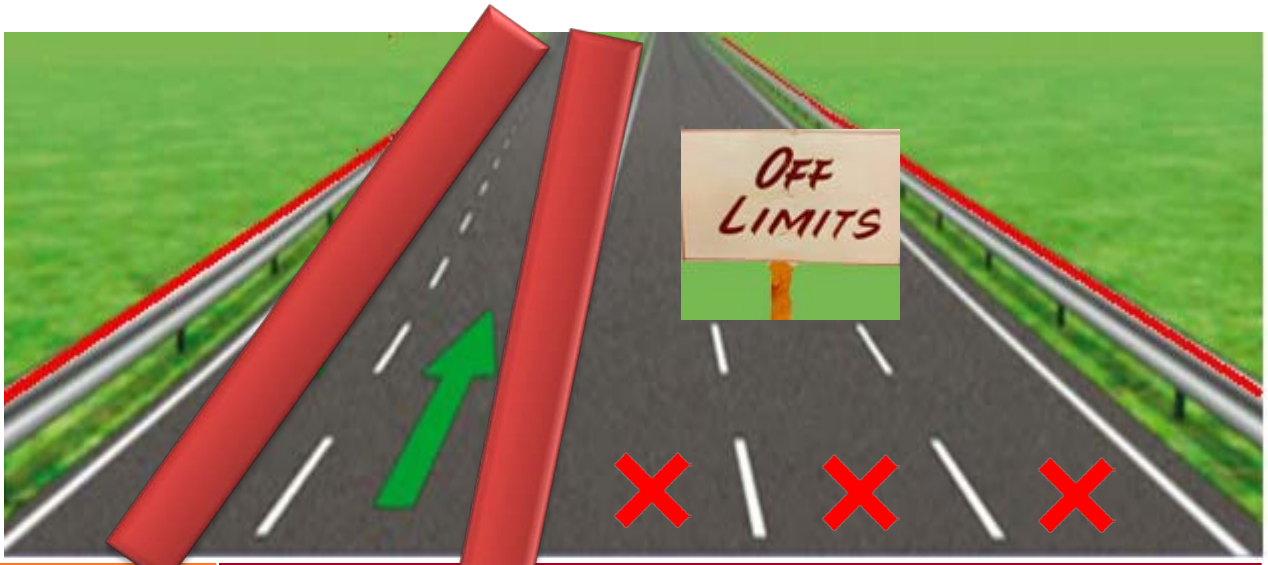
The Adaptive Features (*Type* of adjustments)

Adaptive Features

Planned adjustments	Potential changes with a reasonable likelihood of being required due to evolving data	Protocol Area
•Dose •Formulation •Overlap	•Fractionation •Number of doses to reach steady state •Change timing of assessments •Change number of assessments •**Additional/unnecessary types of assessments** (expected adverse events) •**Optional analysis of tests** •Include more/less subjects	Dose Samples/Assessments Study Participants Timing

Setting The Limits

When the limits are too restrictive…



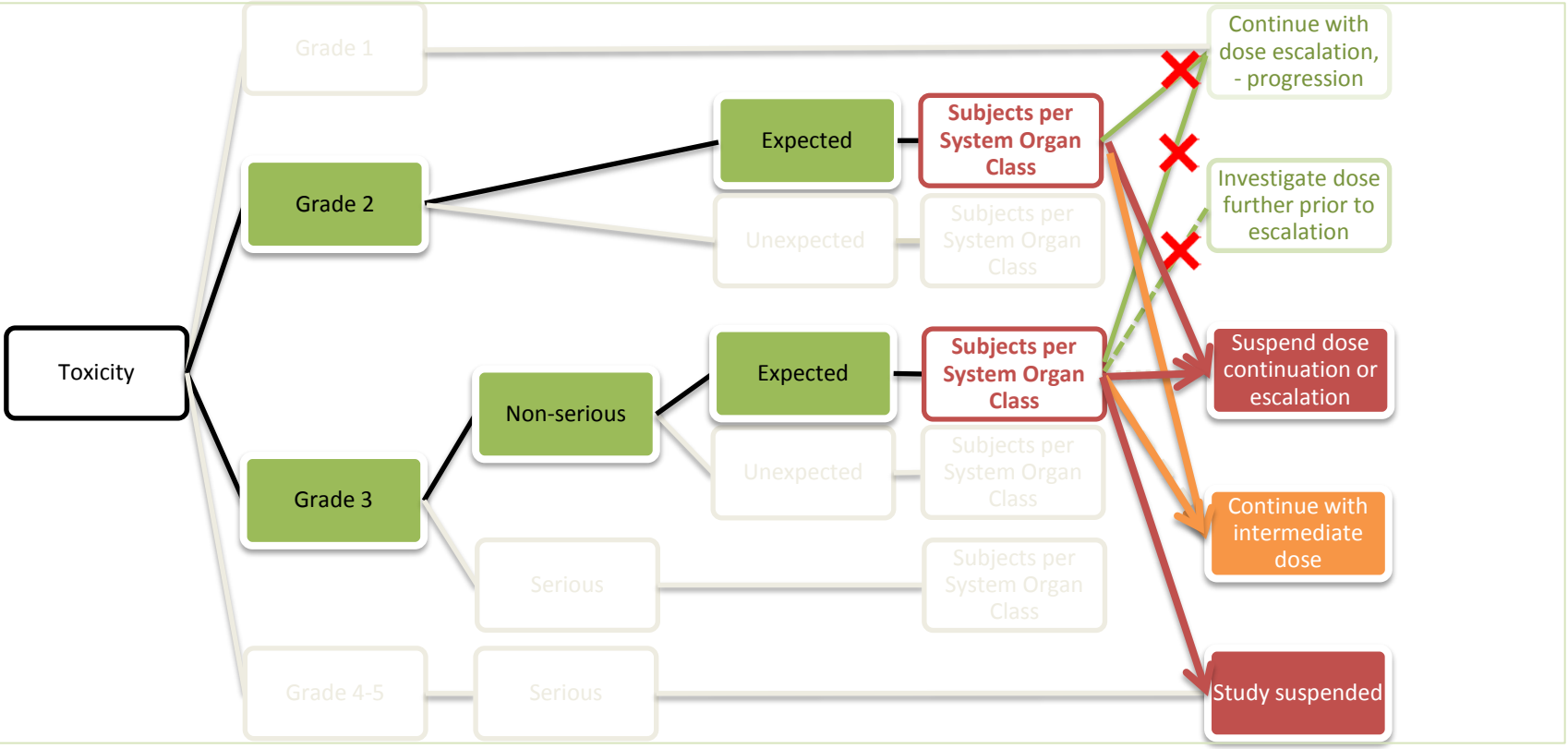
Protocol Area	Adaptive features	Limits
Dose	**Adaptable dose**	**Exposure limits:** 'Dose escalation will be stopped if the mean exposure (AUC and or Cmax) at a dose level exceeds […] •which was achieved in a previous study with an acceptable safety and tolerability profile •observed at NOAEL in the X-week study in (species) after X mg/kg/day administration. If available data justify exceeding the aforementioned exposure limit a substantial amendment will be written and submitted to the Regulatory Authority and the REC for approval.' **Higher exposures may be safe and desirable**

Setting The Limits

Safe,
but not
over-restrictive

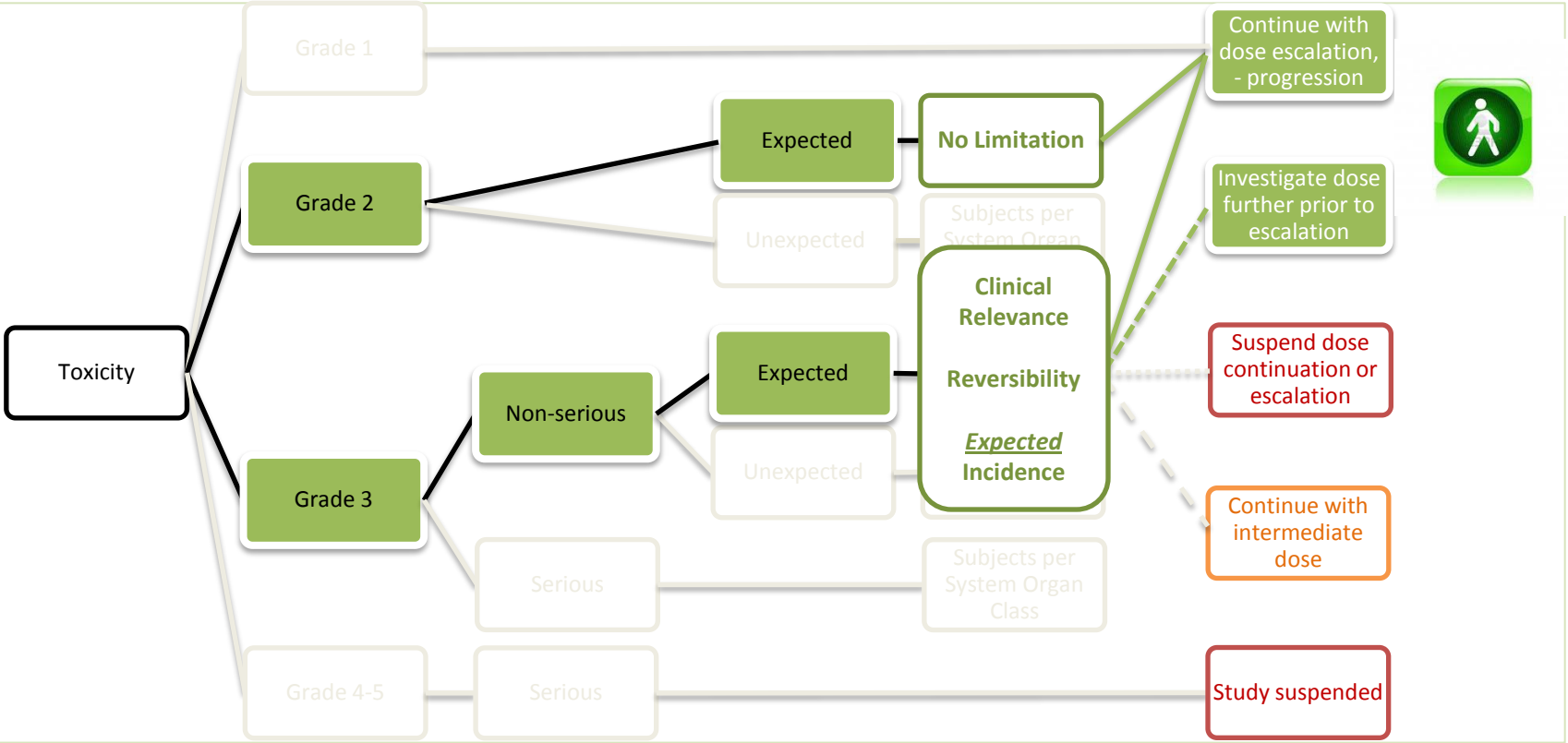
Protocol Area	Adaptive features	Limits
Dose	**Adaptable dose**	**Exposure limits:** **What are the margins based on**: (pre-clinical safety pharmacology/ toxicology or clinical toxicities)? Are the toxicities: **Clinically significant? Reversible?** **Relevant for single and or multiple dosing?** **Easily monitored** in a well controlled setting (e.g. QTc, laboratory)?

Group Toxicity Rules



When one is overcautious…

Group Toxicity Rules



***Proceed* with caution**

Group Toxicity Rules

‘Umbrella’ Protocols

- SAD and MAD alone or combined:
  - Any advantage concerning time frame?

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‘Umbrella’ protocols

+

=

Saves significant time & cost

−

=

Saves time & cost

−

=

Time Savings

Total Actual Time Savings in 18 of 29 adaptive Studies which saved time stratified by the type of adaptive features used:*

+

=

10/14 umbrella studies
Saved on average 77 (21-140) days

2/14 umbrella studies completed **neutrally** compared to conventional non-adaptive (sequential) design as adaptive design features were not used

2/14 umbrella studies delayed
21 days against planned schedule due to the need for substantial amendments (i.e. lack of adaptability)

−

=

8/15 non-umbrella studies
Saved on average 33 (7-63) days

*Lorch U, Berelowitz K, Ozen C, Naseem A, Akuffo E, Taubel J (2012) The practical application of adaptive study design in early phase clinical trials: a retrospective analysis of time savings. Eur. J. Clin. Pharmacol. 68:543–551.

Operational challenges

- What are the operational challenges in the pharmacy?
- Packaging of IMP, is there any waste related to this kind of design?

Pharmacy

Planning

- Prediction of *all* potentially required dosage forms and quantities
- Lower than anticipated dosages may be required (IMPD & manufacture)

Speed

- Dosing soon after

Interim blinded review by a Safety Review Committee

requires

- Flexibility
- Efficient processes and templates
- Resident QP

Fractionation of manufacturing runs

- Requires strictly controlled processes
- Increases unit costs
- Increases retention samples

Operational challenges

- Does adaptive study design require additional efforts for investigator training?

Training & Delegation
Data capture

Documentation

- **Of adaptive changes:** Non-substantial amendments
- **Of practical impact:** Study Operations Manuals

Communication

- Electronic **Training** Management Systems
- Electronic **awareness and competency** check systems

Delegation

- Electronic **delegation** depending on competency and/or awareness
- Scheduling and **resource management** systems

Data capture

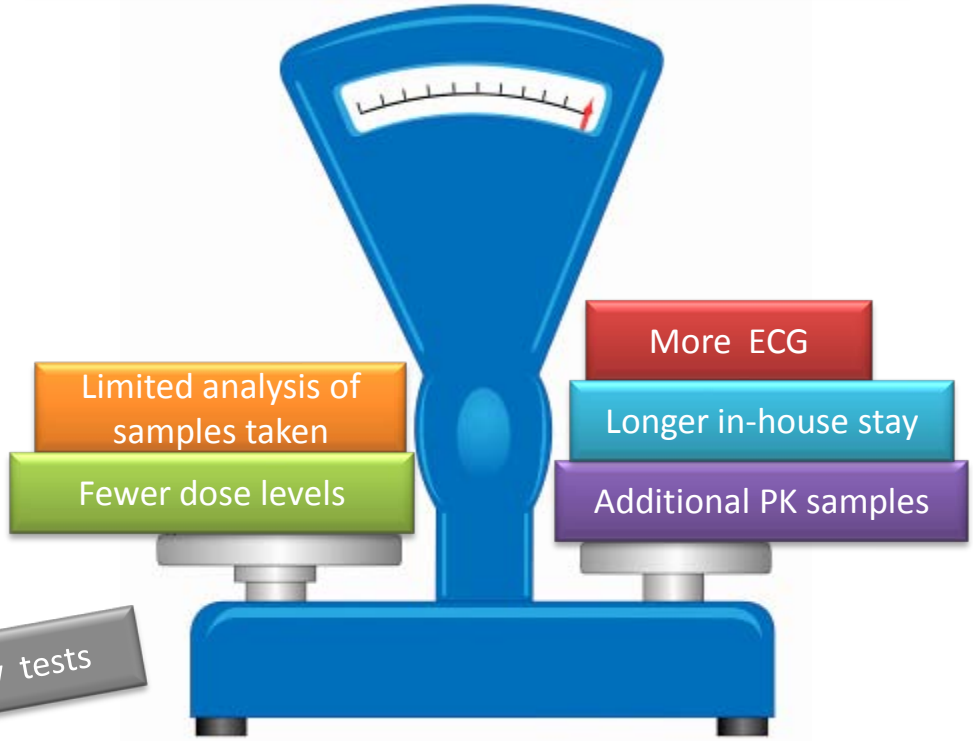
- Use of **easily adaptable data capture** systems

Operational challenges

- How can I manage the study budget using adaptive design?

Rational budget management

Add what is *essential*
Take away what is *not necessary*
Analyse data *as and when needed*



Thank you

To improve is to change; to be perfect is to change often.

Winston Churchill

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