Integrated Protocols

From First in Human to Proof of Concept

EUFEMED, London 18 May 2017

Jorg Taubel MD FFPM
Richmond Pharmacology Ltd.,
St. George's University of London,
j.taubel@sgul.ac.uk

St George's University of London RICHMOND Pharmacology

The one thing to remember: Integrated adaptive Phase I clinical trials are safer for the participants, take less time and cost less.

Aims of adaptive studies

1. Safety
   --- ensures the welfare of participants
2. Efficiency
   --- preserves funding which is available for more research benefitting more patients

Both are worthwhile objectives

Why do adaptive studies: Examples

Responding to the wrong starting dose!

one good reason to allow flexibility to adjust a dosing regimen is that the starting dose may be wrongly predicted.
In small molecules using PKPB plus NOEL: actual C_{max} (AUC) is greater or below 3x the prediction in about 20% of cases.
[from data presented by 2 global Pharmaceutical companies]

The continuous assessment of data as it emerges

1. replaces uncertainty and risk with certainty!
2. Allows you to choose the right path to progress

“adaptive” sets a playing field

… rather than a set pathway.

Set boundaries:
- Starting dose
- Max exposure limits
  (mean and individual)
- Number of subjects
- Procedures
- Samples
- “Inconveniences”
- Etc.

Unforeseen Change:
Substantial amendment!

Approval is for a “worst case” defining a roaming space which is thought to be safe.

Trial Progression:
From emerging data
Regular ***formal*** review
Additions + Removal as per adaptive table

St George's University of London RICHMOND Pharmacology

Remove futile/unnecessary tests!

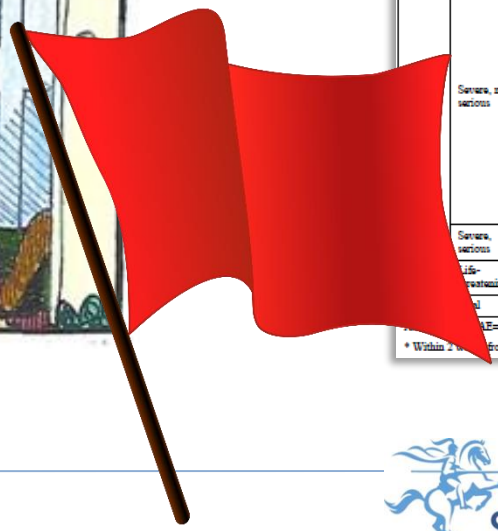
"… the percentage of data collected that ultimately goes unused varies by trial and may range from 15% to 30%, adding US$20– US$35 million in direct drug development costs for the average drug."[Lit[1]]

[1] Getz KA. With clinical data, less is more. Appl Clin Trials 2010; 19: 28–30

Adverse Events

A clear comprehensive set of toxicity rules.

Find more of these on http://researchcartoons.com/



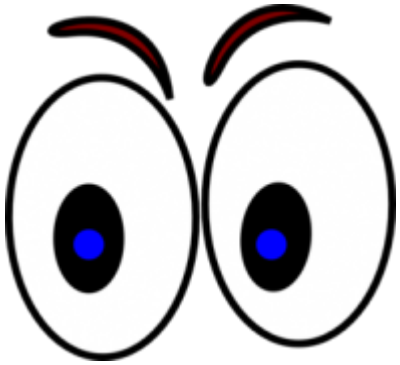
CTCAE Grade	Severity/ Seriousness	Reversibility	Number of Subjects Affected	Action	Effect on Dose Progression/Escalation
I	Mild	N/A	N/A		
II	Moderate	Showing signs of reversibility; i.e. event which shows signs of improvement in the judgment of investigator	≤2 subjects in different SOC	Next dose determined by SRC	N/A
			≤2 subjects in same SOC OR 3 subjects in different SOC*	Dose level may continue OR be extended AND Dose escalation on hold until results of continuation or extension are available	Following continuation or extension, dose escalation may proceed as per clinical study protocol
			≥3 subjects in same SOC OR ≥4 subjects in different SOC*	Dose level suspended	A lower (intermediate) dose level may be administered in the next cohort AND Dose continuation, extension, or escalation requires substantial amendment
		Showing no signs of reversibility	≥2 subjects*		
	Severe, not serious	Showing signs of reversibility; i.e. event which shows signs of improvement in the judgment of investigator	1 subject*	Dose level may continue OR be extended AND Dose escalation on hold until results of continuation or extension are available	Following continuation or expansion, dose escalation may proceed as per the clinical study protocol
			≥2 subjects*	Dose level suspended	A lower (intermediate) dose level may be administered in the next cohort AND Dose continuation, extension, or escalation requires substantial amendment
		Showing no signs of reversibility	≥1 subject		
	Severe, serious	N/A			
	Life-threatening	N/A	≥1 subject	Study suspended	Study continuation requires substantial amendment
	al				

AE=adverse event; N/A=not applicable; SOC=System Organ Class; SRC=Safety Review Committee

* Within 2 [illegible] from each dose

St George's University of London RICHMOND Pharmacology

Grapple with the worst case!



… and make appropriate provisions.

(Which is *not* to just hope for the best because it is thought to be unlikely)

Why do integrated studies?

- They offer considerable efficiencies
- Efficiency is a virtue
- **Speed differs from haste**
- They have proven to be safe
- Why “integrated” protocols need to be adaptive
  - Lorch et al. 2012
- How it can be done/things to consider
  - Lorch et al. 2014

Types of distinct studies rolled into one

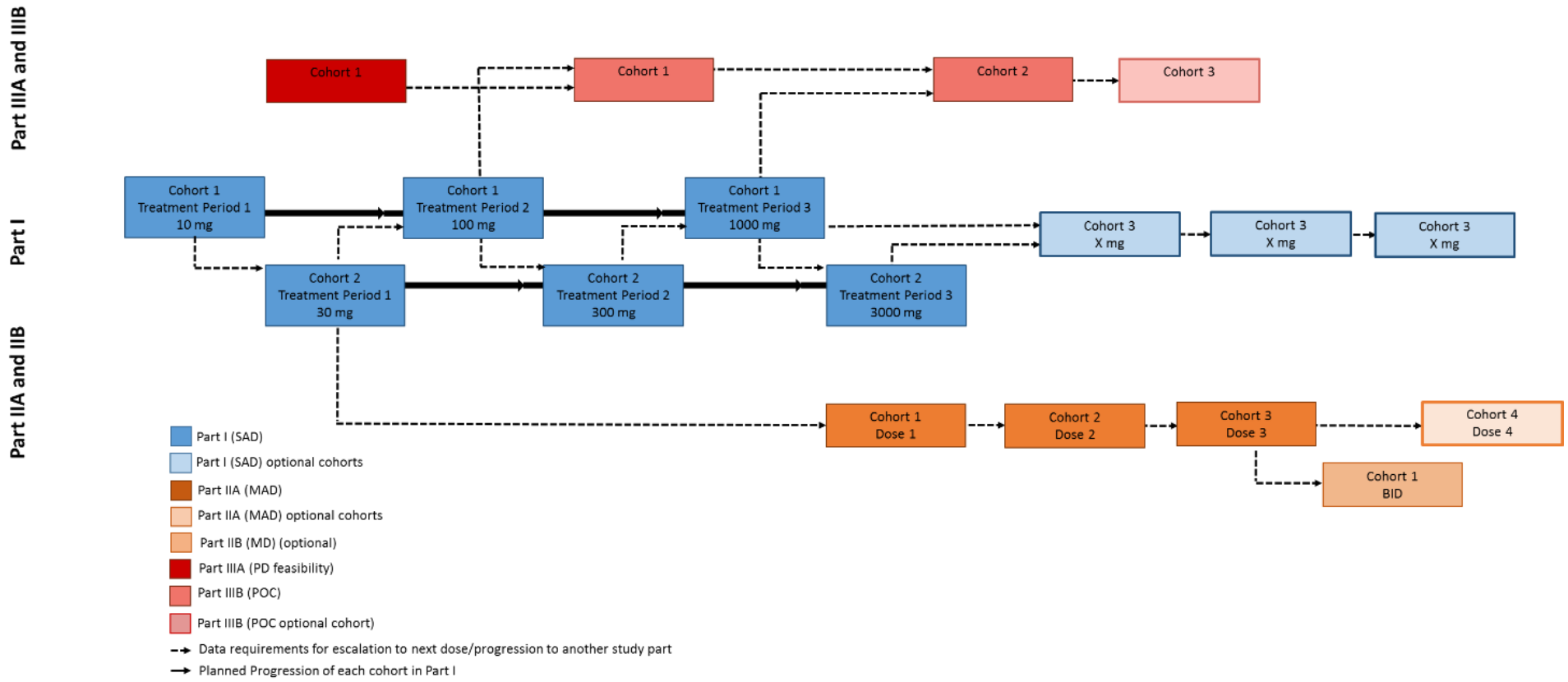
- SAD
- MAD
- Food Effects
- Formulations
- Elderly
- DDI
- Japanese (or other ethnic bridging)
- POC
- Cardiovascular safety (definitive QTc assessment)

By conducting these studies in parallel we learn from one part to the other and back!

Experience – First in Human Combination Protocols

Oral IMP -- Planned study design (N = up to 145)

FSFV to LSLV 8-9 months plus 4 months for set-up to report
(excluding optional cohorts in YHV)



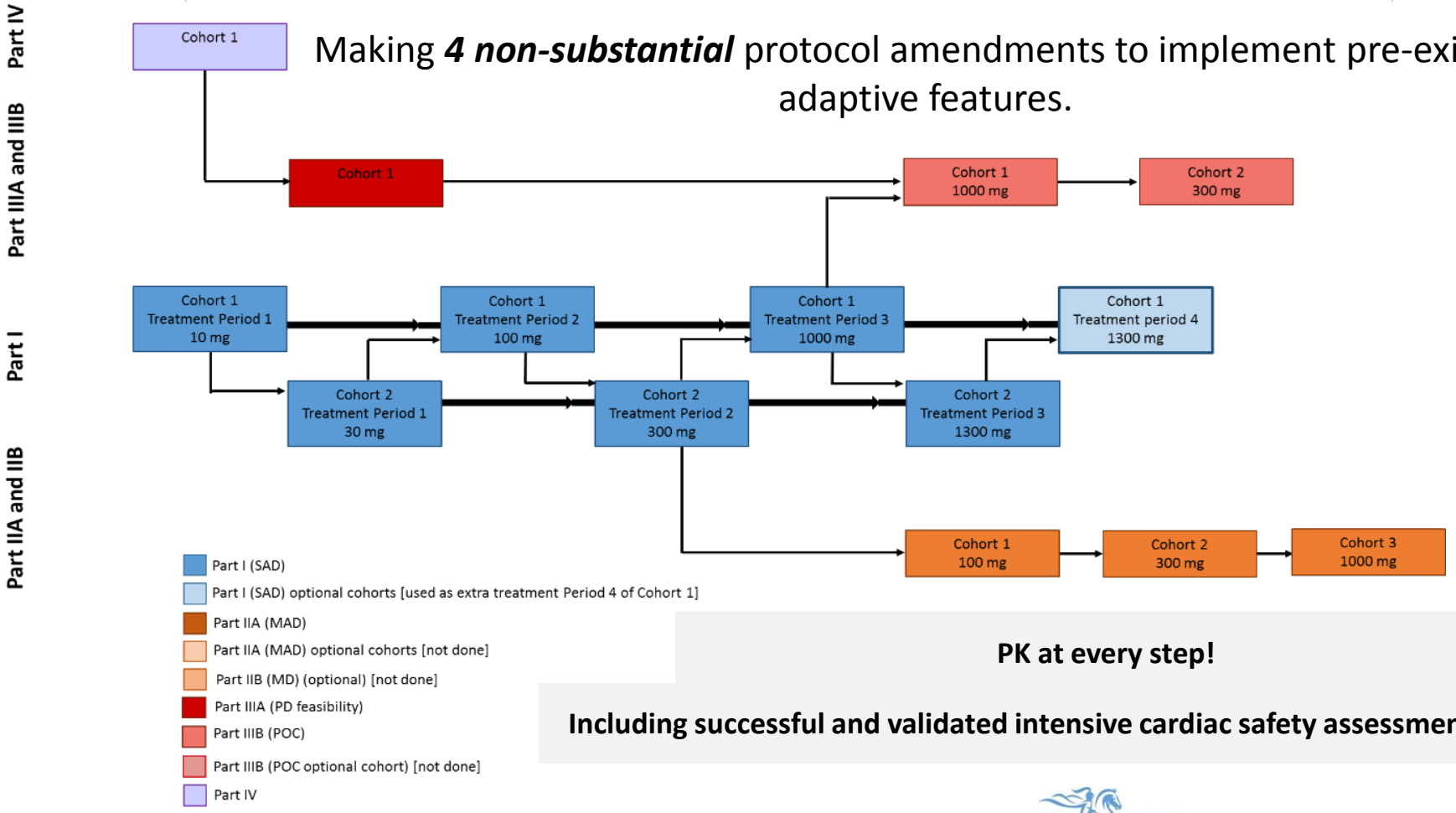
St George's University of London RICHMOND Pharmacology

Experience – First in Human Combination Protocols

What we ended up doing in N=48:

FSFV to LSLV 6 months; Study set-up 1st draft CSR: 11 months

Making ***4 non-substantial*** protocol amendments to implement pre-existing adaptive features.



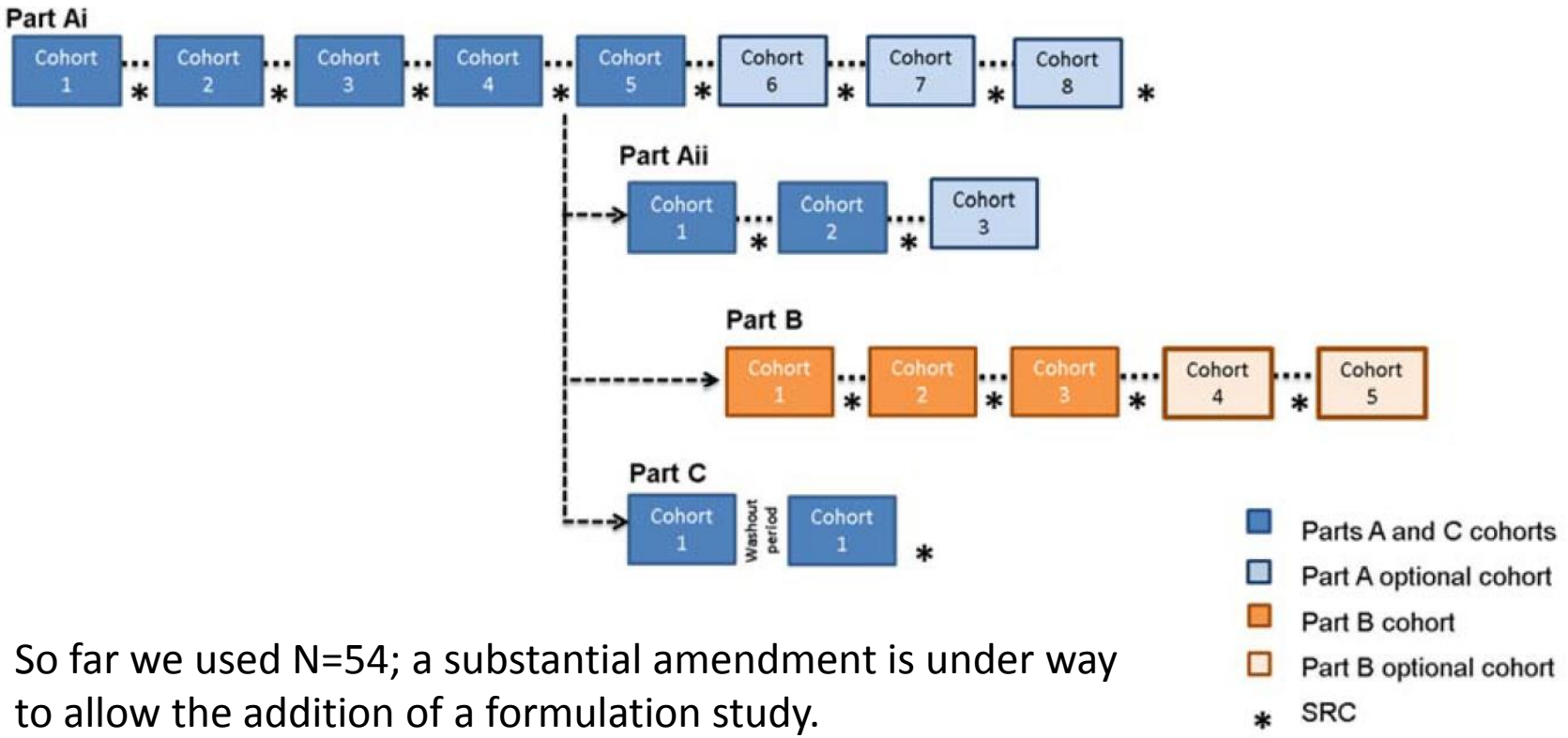
PK at every step!

Including successful and validated intensive cardiac safety assessments

St George's University of London RICHMOND Pharmacology

Experience – First in Human Combination Protocols

Oral IMP -- Planned study design (N = up to 124)



So far we used N=54; a substantial amendment is under way to allow the addition of a formulation study.

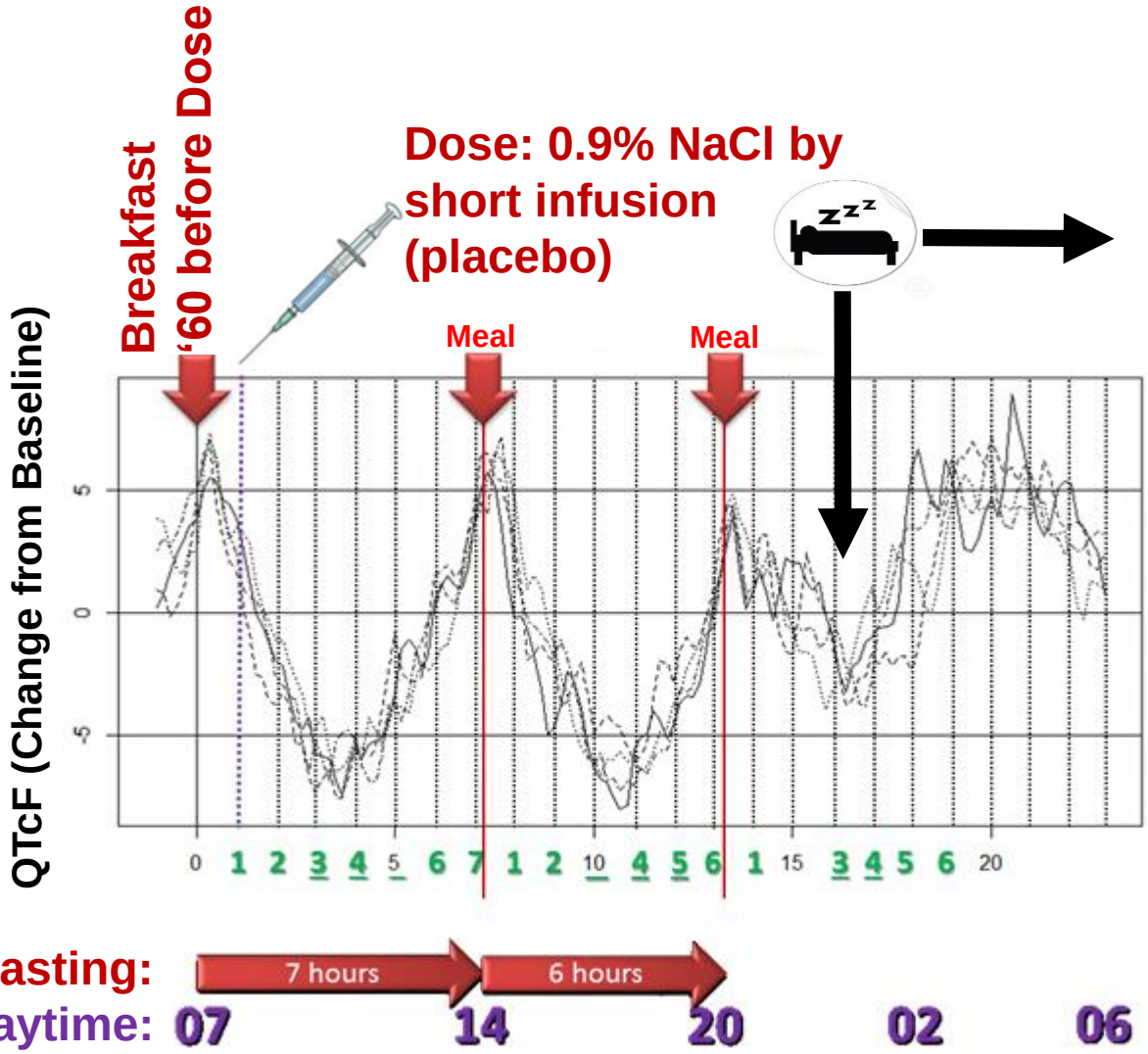
Types of distinct studies rolled into one

- SAD
- MAD
- Food Effects
- Formulations
- Elderly
- DDI
- Japanese (or other ethnic bridging)
- POC
- **Cardiovascular safety (definitive QTc assessment)**

By conducting these studies in parallel we learn from one part to the other and back!

Integration of ICH E14 compliant cardiac safety assessments in FTIM and other Phase I healthy volunteer studies – using the effect of a meal on QTc to assess the assay sensitivity (study specific internal validation)

Effect of a meal on QTc: 24 hour time course



A meal sets into motion a physiological response which results in a change in cardiac repolarisation. Therefore it is a *true effect* and the effect size of ~8ms is significant.

St George's University of London RICHMOND Pharmacology

Integrated Adaptive Studies (IAS)

With careful planning
and expertise of all stakeholders
they are well

Integrated adaptive Phase I clinical trials are safer for participants, take less time and cost less.