Integrated Protocols

From First in Human to Proof of Concept
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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 $C_{\text{max}}$ (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

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

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

Unforeseen Change:
Substantial amendment!

Trial Progression:
From emerging data
Regular formal review
Additions + Removal as per adaptive table
“... 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.”[Lit¹]

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/

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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)

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Experiencing – 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.

**Part I**
- Cohort 1 Treatment Period 1: 10 mg
- Cohort 1 Treatment Period 2: 100 mg
- Cohort 1 Treatment Period 3: 1000 mg
- Cohort 1 Treatment Period 4: 1300 mg

**Part IIA and IIB**
- Cohort 1
- Cohort 2 Treatment Period 1: 30 mg
- Cohort 2 Treatment Period 2: 300 mg
- Cohort 2 Treatment Period 3: 1300 mg
- Cohort 3
- Cohort 2 300 mg
- Cohort 1 1000 mg

**Part IV**
- Cohort 1 1000 mg
- Cohort 2 300 mg
- Cohort 3 1000 mg

**PK at every step!**
Including successful and validated intensive cardiac safety assessments

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Experience – First in Human Combination Protocols
Oral IMP -- Planned study design (N = up to 124)

Part Ai
Cohort 1  Cohort 2  Cohort 3  Cohort 4  Cohort 5  Cohort 6  Cohort 7  Cohort 8

Part Aii
Cohort 1  Cohort 2  Cohort 3

Part B
Cohort 1  Cohort 2  Cohort 3  Cohort 4  Cohort 5

Part C
Cohort 1  Cohort 1

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.
Integrated Adaptive Studies (IAS)

With careful planning and expertise of all stakeholders they are well possible.

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