PRACTICAL RISK MANAGEMENT IN EARLY PHASE CLINICAL TRIALS

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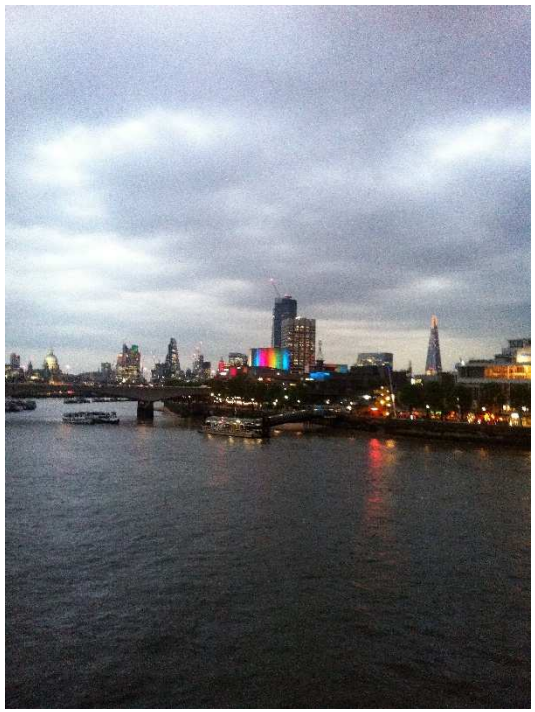

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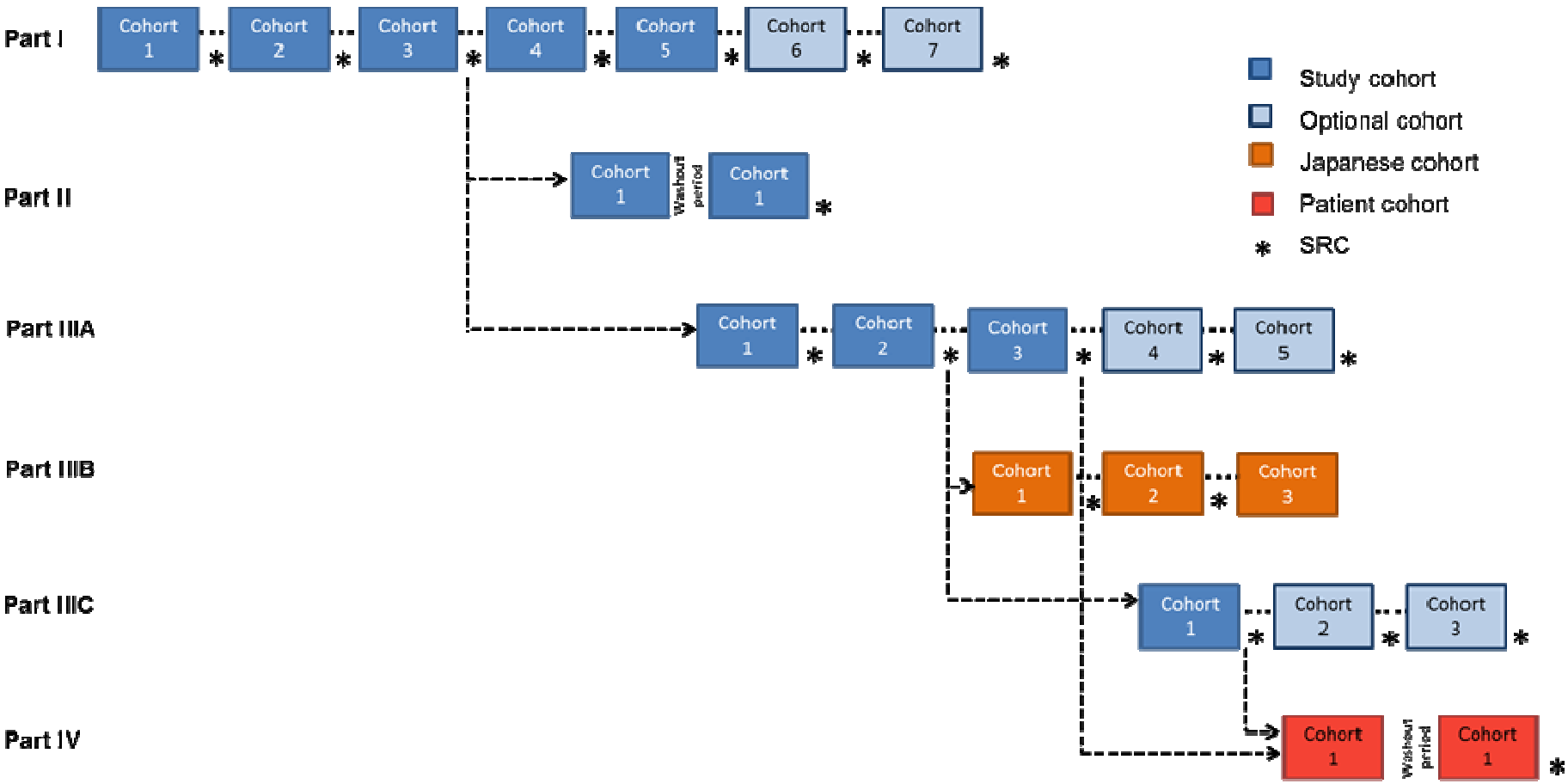
Background

- EMA's draft guideline FIH /early phase studies contains guidance on risk management.
  - Including stopping rules (aka toxicity rules)
- Toxicity rules contribute to 'go/no-go' decisions during clinical trial conduct.
  - Need careful consideration.

Aims of this presentation…

- Propose a systematic approach to applying the EMA's draft guidance on stopping rules in practice.
- Present template toxicity rules that can be modified to accommodate predicted/expected drug effects.
- Illustrate how the rules ensure:
  - Participant safety
  - Effective decision making
  - Ensure appropriate study progression

Example – First in Human Integrated Adaptive Protocol



Assessment of toxicities

A. The impact on the individual subject, e.g. whether IMP administration can be continued (therefore only applicable if subjects are due to receive more than one dose). This is determined using **individual toxicity rules**.

B. The impact on the cohort (i.e. that dosing regimen group) the individual subject is part of, i.e. in the following circumstances:

- If a cohort is split into different sub-cohorts (e.g. sentinel cohorts), the impact on those successive sub-cohorts – i.e. whether they can be dosed or not. This is applicable for single and multiple dosing regimens.
- If a cohort is due to receive multiple doses (e.g. a dose the following day or week), whether that cohort can receive further doses as per dosing schedule.

This is determined using **within-cohort toxicity rules**.

C. The impact on:

- Escalation to cohorts with expected higher exposures/longer dosing duration.
- Progression to successive parts of the study with an expected equal or higher exposure/longer dosing duration.
- Continuation or suspension of the overall study.

This is determined using **study progression toxicity rules.**

Individual Toxicity Rules

Grade (Severity)	Seriousness	Showing signs of reversibility (state time scale)	Action
I (Mild)	N/A	N/A	No action required
II (Moderate)	Not serious or serious	Yes	IMP administration may be continued, amended, temporarily suspended or discontinued in accordance with Investigator's clinical judgement and relevant algorithms for the treatment of toxicities
		No	IMP administration will be discontinued
III (Severe)	Not serious	N/A	IMP administration will be discontinued
	Serious (all except life-threatening and fatal)	N/A	IMP administration will be discontinued
IV (Life-threatening)	Serious (life-threatening but non-fatal)	N/A	IMP administration will be discontinued
V (death)	Serious (fatal only)	N/A	N/A

Within-Cohort Toxicity Rules

		No. of subjects affected		Toxicity Rules for continuation within a cohort (dosing regimen)	
Grade (Severity)	Seriousness	...in one SOC	..in total	Showing signs of reversibility (state time frame)	Action Note: in the event of suspension, continuation or extension of the cohort requires a substantial amendment.
I (Mild)	N/A	Any	Any	N/A	No action required
II (Moderate)	Not Serious	≤2	≤3	Yes	Dosing of the remainder of the dosing regimen can continue as per CSP. Dosing regimen can be extended.
		≥3	≥4	Yes	Dosing of the remainder of the dosing regimen suspended.
		N/A	1	No	Dosing of the remainder of the dosing regimen can continue as per CSP. Dosing regimen can be extended.
			≥2	No	Dosing of the remainder of the dosing regimen suspended.
	Serious*	N/A	1	N/A	Dosing of the remainder of the dosing regimen can continue as per CSP. Dosing regimen can be extended.
		N/A	≥2	N/A	Dosing of the remainder of the dosing regimen suspended.
III (Severe)	Not serious	N/A	1	Yes	Dosing of the remainder of the dosing regimen can continue as per CSP. Dosing regimen can be extended.
			≥2	Yes	Dosing of the remainder of the dosing regimen suspended.
			≥1	No	
III, IV, V**	Serious	N/A	≥1	N/A	

Study Progression Toxicity Rules (I)

Toxicity Rules to determine the following steps:

1. Escalation to cohorts with a higher expected exposure dosing regimen/longer dosing duration.
2. Progression to successive parts of the study with an expected equal or higher exposure/longer dosing duration..
3. Continuation or suspension of the overall study.

Possible actions:

a) No action required.

b) Steps (1) and (2): On hold until results of full (or extended) dosing regimen are available, to which toxicity rules will be applied. (1) and (2) can then proceed, unless the data meet suspension rules.

c) Steps (1) and (2) require substantial amendment. Progression to successive cohorts or study parts is permitted only with dosing regimens with expected exposures/dosing durations below this current level (at which these toxicities were observed).

d) Study suspended (i.e. this dosing regimen AND all ongoing dosing regimens including those at lower exposures/shorter durations, and upcoming dosing regimens, are immediately suspended). Continuation of the study requires a substantial amendment.

Study Progression Toxicity Rules (III)

Grade (Severity)	Seriousness	Number of subjects affected:		Showing signs of reversibility (state time frame)	Action:
		...in one SOC	...in total		
I (Mild)	N/A	Any	Any	N/A	(a) No action required
II (Moderate)	Not serious	≤2	≤3	Yes	(b)
		≥3	≥4	Yes	(c)
		N/A	1	No	(b)
		N/A	≥2	No	(c)
II (Moderate) and serious (all except severe, life-threatening and fatal) -OR- III (Severe) and not serious		N/A	1	Yes	(b)
		N/A	≥2	Yes	(c)
		N/A	≥1	No	
III (Severe)	Serious	N/A	≥1	N/A	
IV (life-threatening)	Serious	N/A	≥1	N/A	**Study suspended** – (d)
V (Fatal)	Serious	N/A	≥1	N/A	

Study-specific adaptations

1. “Predictable” toxicities:

- Little or no Reference Safety Information (RSI) available
- The nature, occurrence and impact of potential risks are predictable through:
  - mode of action
  - non-clinical data
  - anticipated pharmacokinetics and –dynamics
  - class effects

Study-Specific Adaptations

1. Example:

In a FIH study (no RSI) in an immunostimulatory subcutaneous IMP, pre-clinical data predicted cytokine release would occur.

Individual toxicity rules:

Grade (Severity)	Diagnosis	Reversibility	Action
I (Mild)	Cytokine release syndrome	N/A	IMP administration will be discontinued
	Flu-like symptoms	N/A	No action required
	Injection site reactions	N/A	No action required
	All other toxicities	N/A	No action required

Study-specific adaptations

1. This example illustrates:

- How low grade toxicities that may indicate risk of ≥ Grade 3/serious ADR developing need cautious treatment.
- How further investigation of an ADR can be allowed for decision making.
- How to deal with reactions that are signs of efficacy.

Study-specific adaptations

2. “Expected” toxicities:

- Solid Reference Safety Information (RSI) available.
- Good knowledge of the nature, occurrence and impact of the potential risks.

Study-specific adaptations

2. Example cntd:

A Phase 1 DDI study tested the interactions of four NIMPs with the IMP in two separate, repeat-dose study parts (A and B). The Part A NIMP (magnesium) was expected to reach toxic levels.

Cohort/study progression toxicity rules:

*"If 2 or more subjects are **withdrawn** from the study due to clinically significant magnesium toxicity, Part A will be suspended; **Part B can continue**."*

Study-specific adaptations

2. Example cntd:

Individual toxicity rules:

Grade (Severity)	Diagnosis	Action
I (Mild)	Magnesium toxicity (defined as: Presence of clinically relevant signs and symptoms of magnesium toxicity with **confirmed** hypermagnesaemia on clinical laboratory tests)	The subject will not receive any further doses of MgSO4 or MgSO4/IMP and will consequently be withdrawn from the study
	All other toxicities	No action required

Study-specific adaptations

2. This example illustrates:

- How low grade toxicities that may indicate risk of ≥ Grade 3/serious ADR developing need cautious treatment.
- How further investigation of an ADR can be allowed for decision making.
- How to allow discontinuation of one part of a study whilst allowing another part to continue.
- How to simplify the rules and base them on withdrawals.

Conclusion…

Template toxicity rules can be modified for all early phase clinical trials.

They can be modified and simplified for predicted or expected drug effects.

This approach ensures:

- Participant safety
- Effective decision making
- Ensure appropriate study progression