Practical Risk Management for Adaptive Integrated Early Phase Clinical Trials

Simon Coates[1], Jörg Täubel [1,2] and Ulrike Lorch[1]

[1]Richmond Pharmacology Ltd, UK; [2]St George's, University of London, UK

Background

Stopping rules (or 'toxicity rules') are a fundamental and essential part of risk management in early phase clinical trials. As well as being necessary for ensuring the safety of participants, they are also a requirement under the revision to the EMA's first-in-human and early clinical trials guideline1. In recent years the use of integrated protocols and adaptive trial design have resulted in early phase trials becoming larger and more complex. The increasing complexity of these trial designs raises potential issues with risk management, which, if complex, presents challenges for both regulators and investigators to implement. Therefore, there is a clear need for a standard, template or algorithm-based approach to risk management, in particular stopping rules. This poster presents a template approach to the design and implementation of stopping rules, which has been successfully utilised in many early phase clinical trials in the UK.

Methods

Toxicities (or adverse reactions, ARs) are one of the factors determining next steps in a clinical trial. Clear rules that can be systematically and consistently applied and state necessary actions when toxicities arise are therefore essential. In general, the assessment of toxicities is a series of three decisions:

Decision 1: The impact on the individual subject – can IMP administration be continued (therefore only applicable if subjects are due to receive more than one dose)? This is determined using **individual toxicity rules**.

Decision 2: 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**.

Decision 3: The impact on:

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

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

Consequently, the template toxicity rules were created to address each decision sequentially in a single table format. The template rules table, along with an explanation of how is was constructed, is shown below.

An objective grading system was selected to determine **severity. NCI CTCAE**[2] is the most comprehensive system. Other systems are available; the most appropriate one must be chosen, taking into account expected and predicted AEs.

Serious adverse events (SAEs) and non-serious AEs at relevant grades are listed separately as SAEs will require stricter rules than non-serious AEs.

Actions for individuals must clearly state the point at which a subject should be withdrawn from dosing.

Numbers: In principle, as the severity increases, the number of subjects required to trigger suspension of dosing decreases. Grade 1 would normally not trigger an action so no number needs to be set. In line with the EMA's guidance for serious and severe (≥Grade 3) ARs, 1 or 2 subjects respectively would suspend dosing. For Grade 2 ARs, the numbers need to be cautious enough that if a repeatable, clear safety signal is identified no further subjects are put at risk, but the numbers also need to balance the need to avoid counter-productive and premature study suspension. ARs in the same system organ class (SOC) in different subjects may point to a safety signal emerging, so fewer are needed to trigger an action compared to the total number of subjects with ARs (in different SOCs). The numbers in the template rules table have been used for cohort sizes of 4, 6, 8 and 12. Consider reducing the numbers if the sample size is smaller. **Reversibility** can be a built-in factor in the table, as ARs showing no evidence of reversibility prior to next planned dosing may need more cautious rules. The pharmacokinetics of the IMP and dosing schedule will determine the reversibility assessment period.

The **actions** required for any given scenario must be clear. The actions may include: (i) continuing as per protocol, (ii) investigating further (e.g. by increasing sample size - extending the dosing regimen), with no increase in exposure and/or dosing duration until investigation complete, (iii) continuing using interim dosing regimens only (i.e. lower exposure, shorter duration), with or without suspension of the ongoing regimen, (iv) suspension of the whole study, including all lower exposure/shorter dosing regimens.

		DECISION 1	DECISION 2				DECISION 3
		Individuals	Number of subjects		Showing signs of reversibility within [state time period]	Continuation within a dosing regimen	Escalation and/or progression
Grade (Severity)	Seriousness	Action	In one SOC	In total		Action NOTE 1: In the event of suspension, continuation or extension of the cohort requires a substantial amendment.	Action See text accompanying table* for explanation of decisions and actions.
I (Mild)	N/A	N/A	Any	Any	N/A	No action required	No action required (Action A).
II (Moderate)	Not serious	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.	≤2	≤3	Yes	Dosing of the remainder of the dosing regimen can continue as per CSP. Dosing regimen can be extended.	No action required (Action A). If a decision is made to extend the dosing regimen, Action (B) applies.
			≥3	≥4	Yes	Dosing of the remainder of the dosing regimen suspended.	Action (C)
			N/A	1	No	Dosing of the remainder of the dosing regimen can continue as per CSP. Dosing regimen can be extended.	No action required (Action A). If a decision is made to extend the dosing regimen, Action (B) applies.
				≥2	No	Dosing of the remainder of the dosing regimen suspended.	Action (C)
	Serious	IMP administration will be discontinued.	N/A	1	N/A	Dosing of the remainder of the dosing regimen can continue as per CSP. Dosing regimen can be extended.	Action (C)
III (Severe)	Not serious	IMP administration will be discontinued.	N/A	1	Yes	Dosing of the remainder of the dosing regimen can continue as per CSP. Dosing regimen can be extended.	No action required (Action A). If a decision is made to extend the dosing regimen, Action (B) applies.
				≥2	Yes	Dosing of the remainder of the dosing regimen suspended.	Action (C)
				≥1	No		
	Serious (all except life-threatening and fatal)	IMP administration will be discontinued.	N/A	≥1	N/A		
IV (life-threatening)	Serious (life-threatening but non-fatal)	IMP administration will be discontinued.	N/A	≥1	N/A		**Study suspended,** Action (D)
V (fatal)	Serious (fatal only)	N/A	N/A	≥1	N/A		

*Decision (3) determines the impact on study progression, which refers to the following potential steps:

1. Escalation to cohorts with a higher dose.
2. Progression to successive parts of the study with an equal or higher dose.
3. Continuation or suspension of the overall study.

The possible actions:

No action required.

A. (1) and (2): On hold until results of extended
B. dosing regimen are available, to which toxicity rules will be applied. (1) and (2) can then proceed, unless the data meet suspension rules. (3): Whilst awaiting results of extended dosing regimen, any dosing regimens on lower dose levels can continue; progression to successive cohorts or study parts is permitted only with doses below this current level (at which this toxicity was observed).
C. (1) and (2) require substantial amendment. (3): Dosing regimens on lower dose levels can continue. Progression to successive cohorts or study parts is permitted only with dosing regimens with expected exposures below this current level (at which these toxicities were observed).
D. Study suspended (i.e. this dosing regimen AND all ongoing regimens, including those at lower exposures, are immediately suspended. Continuation of the study requires a substantial amendment.

Note: toxicity rules can be amended during a trial. However, the amendment is substantial (i.e. needs competent authority approvals) if the potential risk of the study has increased.

Results and discussion

The template toxicity rules shown above have been used in multiple early phase studies in the UK. They can be used in their template form (e.g. where there is no established safety profile or specific risk identified), or they can be adapted for specific IMPs or trial designs.

Adaptations for trial designs: Determine which of the three of the template toxicity rules tables are needed, e.g. if the proposed study is a single cohort only with no dose escalation or successive cohorts/study parts, study progression toxicity rules (decision 3) may not be required.

Adaptations for expected or predicted toxicities: Toxicity rules must cater for three broad categories of toxicities: **(1) "Expected"** - IMPs in the first year of clinical development (including FIH studies), usually have no Reference Safety Information (RSI) and therefore no "expected" ARs (so any SAE = SUSAR). After the first year of clinical development there is usually an RSI (or SPC) containing any "expected" effects. **(2) Predicted** - mode of action, PD effects, class effects and pre-clinical data may give an indication of potential/predictable effects which should form the basis of risk management. **(3) "Unexpected/unpredicted** – those that could arise with any compound at any stage of drug development.

Unexpected/unpredicted toxicities can usually be addressed with template toxicity rules. These must then be adapted for each IMP, taking into account any expected or predicted toxicities and their potential severities. Those that are potentially serious or life-threatening will need more cautious rules, while those considered a drug-effect (e.g. desired) and not a "toxicity" will be suitable for less cautious rules. Therefore, toxicity rules will need to balance the need to maintain subject safety whilst ensuring that the occurrence of mild or moderate expected/predicted effects does not trigger premature study termination. The same factors need to be considered for any NIMPs.

Modifications for predicted drug effects:

Situation: IMPs with no/limited RSI. However, the mode of action predicts drug effects, including some which may be potentially serious.

Rules: Modify the rules so that they cater for the worst-case scenario for fundamental risks. Ensure there are multiple options available for other, lower risk scenarios so that the study is not prematurely suspended, e.g. for non-severe, non-serious predicted drug effects.

Example: In a FIH study (no RSI) in an immunostimulatory subcutaneous IMP, pre-clinical data predicted cytokine release would occur. The potentially life-threatening cytokine release syndrome (CRS) was not predicted, however, but was scientifically possible so very cautious rules for this were built in. Local and systemic immunostimulatory effects (flu-like symptoms and injection site reactions) were predicted and, being neither life-threatening and their occurrence indicating drug efficacy, required less strict rules.

To minimise risk, individual rules were tightened to withdraw subjects at Grade I for CRS, but not for the other immunostimulatory effects:

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

For cohort/study progression, cytokine release syndrome rules were cautious but didn't always trigger cohort or study suspension, instead mandating confirmatory investigations before continuing/stopping. For flu-like symptoms and injections site reactions, larger numbers were permitted before triggering any action as these effects were regarded as low risk and an indication of efficacy.

Modifications for expected drug effects:

Situation: Detailed RSI, which may include potentially serious expected drug effects. The frequency at which these arise is understood; their presence in one or two trial individuals is less predictive than the RSI of further individuals in the cohort being affected after continued dosing. Therefore, keep the rules simple.

Rules: It is essential to have clear individual toxicity rules, in particular to define the point at which a subject needs to be withdrawn. This may involve distinct rules for each significant ADR listed in the RSI (or SPC).

For studies using NIMPs where the SPC is the RSI (e.g. in drug interaction studies), consider rules that allow suspension of one NIMP study part whilst continuing study parts with other NIMPs and/or the IMP. Toxicity rules for the NIMP follow the same principles discussed above.

Example: 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. For individuals, the rules were very strict – withdrawal at Grade 1.

For the cohort, the rules allowed discontinuation of magnesium (i.e. Part A) whilst allowing Part B to continue.

"This study (both Parts A and B) will be suspended if 2 or more subjects are withdrawn from the study due to an AR at least possibly related to IMP.
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."

Here, the rules were simplified and based on withdrawals.

Conclusions

This adaptable, template approach to toxicity rules demonstrates how a systematic, objective and consistent approach to the risk management of large integrated trials can be simple yet robust, ensuring participant safety whilst facilitating effective decision making and trial progression.

References

1. EMEA/CHMP/SWP/28367/07 Rev. 1, 10 November 2016.
2. CTCAE 4.03. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

RICHMOND Pharmacology
www.richmondpharmacology.com

St George's University of London