Practical Risk Management for Adaptive Integrated Early Phase Clinical Trials

Simon Coates¹, Jörg Täubel¹,² and Ulrike Lorch¹
¹Richmond Pharmacology Ltd, UK; ²St 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 that 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 that should form the basis for both sponsors 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

An objective grading system was selected to determine severity. NCI-CTCAE is the most comprehensive system; other systems are available, the most progression toxicity rules may be chosen, taking into account expected and predicted AEs.

Serious adverse events (SAEs) and non-serious AEs at relevant grades are listed separately; 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Actions for individuals must clearly state the point at which a subject should be withdrawn from the dosing regimen.

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 no established safety profile or specific risk identified), or they can be adapted for specific IMPs or trial designs.

Adaptations for trial designs: Which determine if one of the three of the template toxicity tables are needed, e.g. if a single cohort is used, only with dose escalation or progressive 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” AEs (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 be included in scope of risk management. (3) “Unexpected/unpredicted” - those that could arise with any compound at any stage of drug development.

Modifications for predicted drug effects:

Situation: IMPs with non-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, time-limited or reversible effects. Consequence: The possible actions for each of the three “tiers” are determined using individual toxicity rules. 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, (iii) increasing in exposure and/or dosing duration until investigation complete, (iv) continuing using interim dosing regimens only (i.e. lower exposure, shorter duration, (v) suspending dosing in the whole study, including all lower exposure/dosage dosing regimens.

Modifications for expected drug effects:

Situation: IMPs with 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, time-limited or reversible effects. Consequence: The possible actions for each of the three “tiers” are determined using individual toxicity rules. 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, (iii) increasing in exposure and/or dosing duration until investigation complete, (iv) continuing using interim dosing regimens only (i.e. lower exposure, shorter duration, (v) suspending dosing in the whole study, including all lower exposure/dosage dosing regimens.

References

1. EMMA/CHMP/SWP/23867/07 Rev 1. 10 November 2016

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.