

Risk based approach to management of clinical trials



Why risk based approach

- ‘Specific modalities’ – recognised the concept that not all trials are the ‘same’ wrt demonstrating GCP compliance
- Increasing interest and focus on risk proportionate approaches
 - EFGCP workshop – Barcelona (Jan 2010)
 - ESF Investigator driven trials
 - Commission consultation
- Currently much is possible but no real guidance!



Current activity

- Adamon project – ‘Risk analysis and risk adapted on-site monitoring in non-commercial clinical trials’
Clin Trials 2009; 6; 585 originally published online Nov 6, 2009;
- EMA Inspectors WG – reflection paper on risk based Quality Management
- Clinical Trials Facilitation Group (CTFG)
- European Commission – Consultation
- Clinical Trial Transformation Initiative (CTTI)
- UK project on risk adapted management of clinical trials

Project Objectives

The MHRA logo is a dark blue oval with the letters 'MHRA' in white, bold, sans-serif font.

1. Develop a risk assessment tool with guidance principles on how to manage clinical trials of IMPs in a risk proportionate way
2. Identify how risk adapted approaches for clinical trials can be achieved within the current regulatory framework.
3. Develop a process to facilitate the agreement of key stakeholders on the level of risk associated with a clinical trial.



Risk based approach?

- What does it mean?
 - ⇒ Different things to different groups
- Will depend on roles and responsibilities with respect to the trial
 - Sponsors
 - Investigators
 - Trusts
 - Funders
 - Ethics Committees
 - Regulatory Assessors
 - Regulatory Inspectors
 - Insurers

Project Scope



- Focus on risks inherent in the protocol for
 - Participant safety to the trial intervention
 - due to the trial intervention
 - due to clinical procedures
 - Participant rights
 - due to inadequacy of the consent process
 - due to failure to protect participant data
 - Data credibility/reliability of results
- Identify, and if possible, integrate/align with other relevant initiatives in this area (UK, EU, RoW)

General Considerations

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- The public may be put at risk by a clinical trial in two main ways:
 - Participants in the trial may be damaged by failure to adequately control the risks to their safety and rights, and
 - Future patients may be put at risk by misleading results.
- Trials are about data
- Data must be generated, stored, analysed and reported robustly and be verifiable
- In obtaining data subjects safety and rights must be assured
- Principles of GCP provide a structure for this

General Considerations

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- Not all trials carry the same potential risks in all areas
- Risk mitigation measures do not need to be the same for all trials
- Currently there is no agreed language on description of risk and its assessment
- OR what this actually means in terms of GCP compliance activity



Risk proportionate clinical trials management

Two broad categories:

- IMP related activities
- Trial monitoring activities



IMP related activities



Trial Safety Risk

- Assess risk associated with trial interventions (IMP)
- Assess risk in relation to normal standard care based on judgement of investigator/sponsor
 - Comparable to standard care (Low)
 - Somewhat higher than standard care (Moderate)
 - Markedly higher than standard care (High)



LOW: no higher than risks of standard medical care

e.g. Trials involving licensed medicinal products:

- if they relate to the licensed range of indications, dosage and form
- off-label use, e.g., in paediatrics, in oncology if this off-label use is established practice, i.e. if sufficient published evidence and/or guidelines referring to this exist.

(may be possible to justify in other situations where there is extensive clinical experience and no reason to suspect a different safety profile in the study population)

MODERATE: somewhat higher than risks of standard medical care

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e.g. Trials involving licensed medicinal products if:

- such products are used for a new indication (different patient population/disease group) or
- substantial dosage modifications are made for the licensed indication or
- if they are used in combinations for which interactions are predicted or about which little information is known or
- new formulations or route of administration if this is likely to be associated with a different adverse event profile



HIGH: markedly higher than risks of standard medical care

Trials involving an unlicensed drug

- e.g. Phase 1, 2 & 3 development trials

(It may be possible to justify a lower risk grading where there is extensive class data or evidence from pre-clinical and clinical evaluations)

Safety Monitoring Plan



The potential risk of trial interventions is...	Examples of types of clinical trials
<p>LOW: comparable to that of standard medical care</p>	<p>Trials involving licensed medicinal products:</p> <ul style="list-style-type: none"> - if they relate to the licensed range of indications, dosage and form - off-label use, e.g., in paediatrics, in oncology (allowed are moderate dosage modifications, transition from relapse to primary therapy, transition to other disease stages or states of severity, use in new combinations if interactions seem improbable), if this off-label use is established practice, i.e., if sufficient published evidence and/or guidelines referring to this exist
<p>MODERATE: higher than that of standard medical care</p>	<p>Trials involving licensed medicinal products if:</p> <ul style="list-style-type: none"> - such products are used for a new indication (different patient population/disease group) or - substantial dosage modifications are made for the licensed indication or - if they are used in combinations for which interactions are suspected
<p>HIGH: markedly higher than that of standard medical care</p>	<p>Trials involving an unlicensed drug</p>



Risk adapted activities possible for lower-risk trials

Pre-trial:

Simplified IMP Dossier – SmPC

Simplified labelling

MA IMP exemption for hospitals/Health centres

Different qualifications of investigator

Trial management procedures

Trial conduct:

Nature and extent of subject safety monitoring

Nature and extent of trial monitoring

Safety reporting

IMP tracking and accountability processes

Content of Annual Safety report

Post trial:

Retention time of essential documents

Safety monitoring plan



- Develop generic guidance indicating:
 - examples of each level
 - examples of expected activity levels for each level
 - concept of the 'safety monitoring plan'
- Investigate potential for Regulatory approval for 'safety plan'

Safety Monitoring Plan



Risk Mitigation to ensure Safety of Participants

Table 2:

Study Title:				
Risks associated with Therapeutic Interventions <ul style="list-style-type: none"> <input type="radio"/> LOW ≡ Comparable to the risk of standard medical care <input type="radio"/> MODERATE ≡ Higher than the risk of standard medical care <input type="radio"/> HIGH ≡ Markedly higher than the risk of standard medical care 			Protocol No. EudraCT No.	
Justification: Please briefly justify your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):				
What are the key risks related to therapeutic interventions you plan to monitor in this trial?			How will these risks be minimised?	
Body system/Hazard	IMP	Activity	Frequency	Comments
GIT – raised transaminases	ABC 123	LFTs	2-weekly	Transient & reversible
CVS – prolonged QT interval	ABC 123	Digital ECG, Holter monitoring	X hours X hours	Arrhythmia

Risk based approach for assessment

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- Potential for harmonised assessment around the safety monitoring plan concept (CTFG, Commission)
- Low risk - CTA notification only
 - Issues of:
 - time, audit trail, limited benefit re documentation



Trial monitoring



Trial Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable Regulatory requirement(s).

- ICH E6: *Good Clinical Practice*
- Part of good management of a study

Risks to participant safety and rights from study procedures

- Clinical procedures
 - Risk compared to standard care
- Consent
 - Risk of inadequate consent compared to a fully competent adult with a chronic condition
- Protection of personal data
 - All personal data must be handled and held securely, but are any particularly sensitive data being collected?
- Identify areas of vulnerability
- Specify mitigation and management plan
- Can trial monitoring detect/reduce potential for error?

⇒ **Targeted monitoring plan**

Risks to reliability of data and results

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Risks associated with potential for 'error' in conduct of trial

- Design
 - Procedures
 - Data collection methods
-
- Identify areas of vulnerability
 - Specify mitigation and management plan
 - Can trial monitoring detect/reduce potential for error?

⇒ **Targeted monitoring plan**

Issues listed in risk assessment tool for reliability of trial results (1)

Eligibility

- Does the trial require very precise assessment of eligibility for results to be applicable to the target population?

Randomisation method

- Is there any possibility that the randomisation schedule would differ from that described in the protocol or that treatment allocation might be predicted prior to randomisation?

Intervention

- Is it a complex intervention/treatment regimen in which might be applied incorrectly?

Masking/blinding

- If it is required is there any risk that it could be ineffective?

Assessment tool for risks to reliability of trial results



Category	Particular risk (Yes/No)	If yes, list specific concerns	If yes, how will risks be minimised?	If yes, could monitoring methods help to address concerns (specify)
<u>Eligibility</u> • Does the trial require very precise assessment of eligibility for results to be applicable to the target population?				
<u>Randomisation method</u> • Is there any possibility that the randomisation schedule would differ from that described in the protocol or that treatment allocation might be predicted prior to randomisation?				
<u>Intervention</u> • Is it a complex intervention/treatment regimen in which might be applied incorrectly?				

Common monitoring approaches

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- Trial oversight
 - e.g. TMG, TSC, IDMC,
- Remote routine monitoring
 - e.g. telephone contact, training teleconferences, recruitment monitoring, data returns, investigator meetings
- Central monitoring
 - e.g. eligibility checks, missing/invalid data, adherence to study protocol, unusual data patterns, external verification
- On-site monitoring
 - e.g. review of site training/resources, adherence to study protocol, review of clinical records, source data verification
- ***Evidence needed on efficacy and cost-effectiveness***

Risk-adapted monitoring strategy



		Concerns identified in the risk assessment of trial protocol and procedures (other than the intervention)	
		No	Yes
Overall assessment of risk of the intervention	Low	L Central monitoring of protocol adherence and data quality. No requirement for site monitoring unless there are concerns identified from central monitoring	L+ As outlined in L, plus appropriate monitoring of the issues/procedures identified in Appendix 3.
	Moderate	M Central monitoring of safety data quality and timeliness as well as protocol adherence and quality of other trial data. Triggered visits for poor data return or protocol adherence concerns as well as unusually low or unusually high frequency of SAE reports where between site comparisons are possible. Consider site visits to a sample of other sites to review systems and check for unreported safety events.	M+ As outlined in M plus appropriate monitoring of the issues/procedures identified in Appendix 3 as well as the more intensive monitoring of safety data and other data quality and protocol adherence, plus triggered and random site visits as outlined on the left.
	High	H More intense site monitoring than above to check accuracy of safety data	H+ As outlined in H, plus appropriate monitoring of the issues/procedures identified in Appendix 3.



Next Steps

- Continue UK development work – tools, worked examples, testing, consultation
- Early concepts presented to CTFG
- Presentation 9th June to EU GCP IWG
- Align with CTTI
- ? MRC methodology work on monitoring