MHRA
Regulating Medicines and Medical Devices

Risk Adapted Application Process

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Medicines and Healthcare Products Regulatory Agency

Overview

- Background
- Risk Assessment and Adaptation
- Benefits
- Application Process for Clinical Trial Notifications
- Outcomes
- Notification Scheme 12 month review
- Updates following review

Background: Risk-proportionate approach to managing clinical trials

- 2009: MRC/DH/MHRA review of 2003 project to assist in interpretation of CTD in UK determined that risk adapted approaches for managing clinical trials was one of four areas that required attention

- Develop a process to facilitate the agreement of key stakeholders on the level of risk associated with a clinical trial

- Identify how risk adapted approaches for clinical trials can be achieved within the current regulatory framework

- Develop a risk assessment tool with guidance principles on how to manage and conduct clinical trials of IMPs in a risk proportionate way

Risk in Clinical Trials

- Risk – the likelihood of a potential hazard occurring and resulting in harm to the participant and/or an organisation, or to the reliability of the results.

- What does it mean?
    - Different things to different groups

- Will depend on roles and responsibilities with respect to the trial
    - A funder considers the scientific and financial risks
    - A sponsor is concerned about the legal and reputational risks
    - A healthcare organisation considers the compatibility of the trial with its duty of care to patients

Risk Assessment

- Identify potential hazards associated with the trial
- Asses the likelihood of those hazards occurring and resulting in harm
- Include:
  - Risks to participant safety in relation to the IMP
  - All other risks related to design and methods of trial (including risks to participant safety and rights, as well as reliability of results)
- Risk assessment will direct the mitigation activity required in the conduct of the trial and collection of data

Project value and advantages for applicants

- Framework for considering trial risks agreed with key stakeholders
- Regulatory agreement of IMP risk category with the CTA
- Reduced time and bureaucracy associated with approval of low risk trials
- Funding application based on trial risk assessment so necessary resources for the appropriate management plans included.
- More efficient and cost effective use of trial resources by sponsors
- The risk assessment and resultant plans contribute to inspection activities

Risk in Relation to IMP

- Assess risk associated with IMP
- Balanced against risk that a trial participant would be exposed to outside of the trial.
- Three-level categorisation:
  - **Type A**
  - **Type B**
  - **Type C**

Risk Categorisation

- **A = Comparable to standard medical care**
  - Trials involving medicinal products licensed in any EU Member State if:
    - *they relate to the licensed range of indications, dosage and form, or*
    - *they involve off-label use (e.g. paediatrics and oncology) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines*

- B **= Somewhat higher than standard medical care**
  - Trials involving medicinal products licensed in any EU Member State if:
    - *used for a new indication (different patient population/disease group), or*
    - *substantial dosage modifications , or*
    - *if they are used in combinations for which interactions are suspected*
  - Trials involving medicinal products not licensed in any EU Member State if:
    - *the active substance is part of a medicinal product licensed in the EU*

- **C = Markedly higher than standard medical care**
  - Trials involving a medicinal product not licensed in any EU Member State

New CT Regulation Proposal

- '**Low-intervention clinical trial**': a clinical trial which fulfils all of the following conditions:
  - (a) the investigational medicinal products are authorised;
  - (b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation or their use is a standard treatment in any of the Member States concerned;
  - (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

Risk-adaptive approaches within the scope of the Clinical Trials Directive

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	Non-Interventional	Type A	Type B	Type C
Adaptations possible?				
1. Reduced MHRA role for approval	*	Yes	No	No
2. Content of application	*	Yes	(Yes)	No
3. Labelling	*	Yes	(Yes)	(Yes)
4. Safety Surveillance	*	Yes	(Yes)	No
5. IMP management	*	Yes	(Yes)	(Yes)
6. Documentation	*	Yes	(Yes)	No
7. GCP Inspections	*	Yes	(Yes)	(Yes)

Risk Adaptations	Areas impacted
1. Reduced MHRA role in approvals	Notification v Approval
2. Content of application	a) IMP dossier b) Investigator's Brochure c) GMP Compliance
3. Labelling of trial drugs	a) Need for trial labelling b) Content of labelling
4. Safety Surveillance	a) Adverse Drug Event recording/reporting b) Safety Monitoring
5. IMP management	a) Tracking and Accountability b) Storage
6. Documentation	a) TMF Content b) Essential Documents retention times
7. GCP Inspections	a) Organisation and selection processes for routine GCP systems inspection b) Increase in routine GCP inspection reviews at the study level c) Frequency and duration of inspections

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Trial Management and Monitoring Plan

- Applicable to all trials
- Based on the risk assessment
- Include in CTA application
- Active sponsor and trial team oversight during the trial
- Moderation of management in response to emerging data and feedback on trial progress/conduct
- Guidance is available on the MHRA website (Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products)

Example safety monitoring plan – risks from IMP

Study Title:					
EudraCT:					
Sponsor:					
Risks associated with trial IMP/interventions ☐ **Type A** ≡ Comparable to the risk of standard medical care ☐ **Type B** ≡ Somewhat higher than the risk of standard medical care ☐ **Type C** ≡ Markedly higher than the risk of standard medical care		**Justification**			
IMP/Intervention	**Body System**	**Hazard**	**Likelihood (L,M,H)**	**Mitigation**	**Comments**
ABC 123	metabolic	hyperglycaemia	L	blood glucose monitoring	X hourly
	GIT	pancreatitis	L	amylase and lipase	daily
	GIT	raised transaminases	H	LFTs	daily
	CVS	prolonged QT interval	M	digital ECG, Holter monitoring	X Hours X hours
Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. IDMC, independent data review,...)					

Other risks

1) risks to participants associated with
   - a) the clinical procedures specified by the protocol;
   - b) failure to obtain fully informed consent;
   - c) failure to protect personal data; and
2) risks to the reliability of results

A similar process is suggested for all these areas of risk:

- Review the protocol to identify whether or not it contains any aspects that materially increase the risks in areas outlined below.
- Identify the specific potential hazards, and
- For each hazard identified, consider the appropriate mitigation, management and optimal monitoring strategy.

Risk Area: (see issues to be considered below)	Particular risk identified? (Yes/No)	If yes, specify concerns	If yes, can the risks be minimised? Specify any mitigations/ Adaptations	If yes, could monitoring methods help to address concerns? (Specify)

Notification scheme- overview

- **Notifications can only be made for certain 'Type A' trials**
  - Default approval after 14 days
  - Limited review by MHRA
  - Potential for MHRA to object to Notification → full assessment
  - Amendments:
    - **Not Substantial** if within SmPC
      - no submission required
    - **Substantial** if beyond SmPC
      - submission and MHRA approval required (normal timeframe)

Notification scheme: eligibility criteria

- ‘Type A’ trials with products licensed in any EU Member State if:
  - they relate to the licensed range of indications, dosage and form
  - they involve off-label use (such as in paediatrics and oncology, etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines

  – Acceptable evidence would include NICE guidelines or peer-reviewed publications (include summary)

Notification scheme: eligibility criteria

- Trial may include randomisation of subjects to different marketed products.
- Placebo controlled trials in patients will not be permitted
  - exceptions?
- Double-dummy trial designs may be permitted depending on the nature of the placebo and any modifications to the marketed product
  - all IMPs, including placebo, must be licensed in an EU MS
- Trials in which the marketed product has been modified, for example by over-encapsulation, will not be permitted
- Repackaging and/or relabeling of the marketed product will be permitted
  - no anticipated effect on product Quality.

Submitting a notification to the MHRA

- Who can apply?
  - Sponsor or authorised representative.
  - Must be established in European Community or have a legal representative who is.
- Where do I apply?
  - Submit electronic documents (PDF or Word files) on a labelled disk (EudraCT number, description of content, company name, date).
  - Usual address (Information Processing Unit, Area 6, MHRA, etc.).
- Fees
  - From April 2013 →No fee
  - If objection to notification by MHRA → assessment fee applies

What to send

- For the submission to be valid it must contain a file for each of the following:
    - Covering Letter, which includes a statement that this is a submission under the notification scheme
    - Clinical Trial Application Form + valid xml
    - Protocol
    - SmPC
    - Justification for absence of labelling (or the content of trial-specific labelling if this will be used)
    - Justification for the absence of a manufacturer's authorisation (or a copy of the authorisation for each manufacturing site involved in repackaging of the marketed product where this site is not a hospital or health centre)

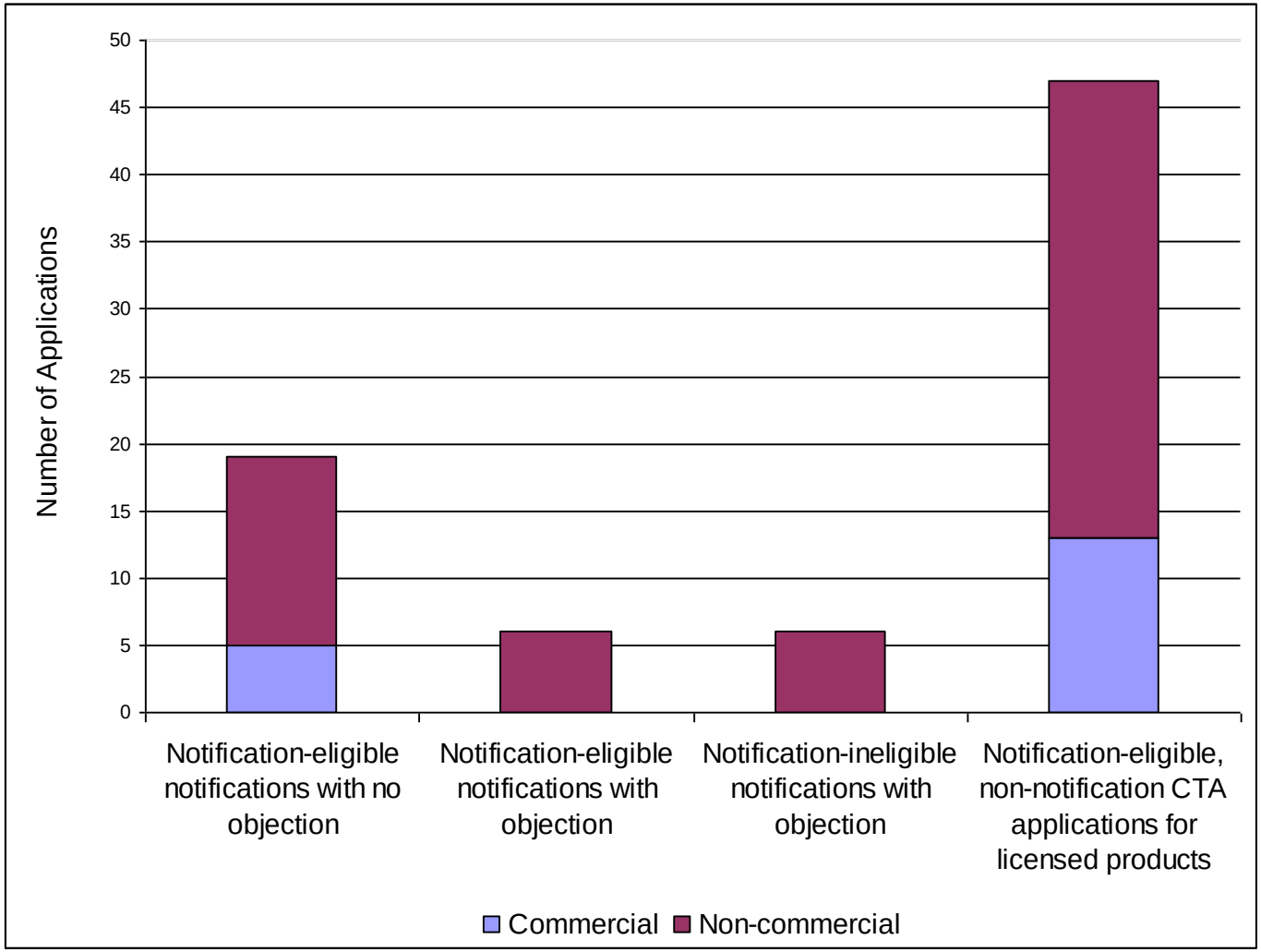
Timeframe and outcomes

- Notification acknowledged by the MHRA.

- **No MHRA Objection Raised**
- Trial may go ahead 14 days after receipt of a valid notification.
- Acknowledgement letter will act as the authorisation (email confirmation).

- **MHRA Objection Raised**
- Applicant (as named in Section C1 of the application form) will be informed of the MHRA objection by email and by post within 14 days of receipt of the valid notification.
- Submission enters standard process for assessment of a CTA application.
- Invoice for fee
- Initial assessment will be performed within 30 days of the initial valid submission.

12 month review



12 month review

- Limited uptake by sponsors
  - Low awareness?
  - Limited appeal?
  - Time to integrate into working practices?
- Usage by commercial vs. non-commercial sponsors
- Reasons for objection
- Clarification of eligibility criteria

Actions from review…

Proposal	Implementation
Email confirmation of authorisation	From 1st November 2012
Removal of fee	From 1st April 2013
E-submission	TBC (discussions in conjunction with IRAS)
Improve communication with applicants (reasons for objection, assessor contact details for feedback)	1st November 2012
Review of MHRA website	Launched 1st April 2013

Hints and Tips

- **Application Form**
  - Ensure contact details are complete and accurate
- **Covering Letter**
  - Clearly state that the submission is for notification
- **Protocol**
  - Comply with the guidance in the community guideline on GCP.
  - Include all currently authorised amendments
  - Definition of the end of the trial
  - Statement on safety reporting by investigators to sponsor
  - Evaluation of anticipated benefits and risks
  - Where product is not being used strictly within the terms of its SmPC, a rationale/justification for its use

Hints and tips

- **Labelling**
  - Trial-specific labelling is not required where the IMP:
    - has a marketing authorisation in the UK
    - is being used within the terms of its marketing authorisation
    - is dispensed to a trial participant in accordance with a prescription given by an authorised healthcare professional and is labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994 that apply in relation to dispensed relevant medicinal products.
  - Where a sponsor chooses to use trial-specific labelling, information on the content of the labelling should be provided.

- **Manufacturer's Authorisation**
  - Required or not required?

Further information

- **MHRA website**
  - Notification scheme
    - http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Submittinganotificationforatrial/Submittinganotificationforatrial/index.htm
  - FAQ and Discussion Forum
    - http://forums.mhra.gov.uk/forumdisplay.php?22-Risk-adaptive-approach