Regulatory Agencies and Quality in Clinical Trials
Risk Adaptive Approach
Aims of the Agency

- Protecting public health through regulation, with acceptable benefit-risk profiles for medicines and devices.
- Promoting public health by helping people who use these products to understand their risks and benefits.
- Improving public health by encouraging and facilitating developments in products that will benefit people.
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Risk Adaption – what is it?

• OECD – Global Science Forum
  - Risk based approaches
    - Stratified
    - Customised

• EMA
  - Reflection paper
    - Risk based Quality management in clinical trials

• UK
  - AMS report
  - Growth Agenda
  - DH/MRC/MHRA project
MRC/MHRA/DoH Project Scope

• Focus on *risks inherent in the protocol* for
  
  • Participant safety to the trial intervention *due to the trial intervention & clinical procedures*
  
  • Participant rights *due to inadequacy of the consent process & failure to protect participant data*

• Reliability of results

• Implementing a risk based Quality System
  
  ➔ Informed protocol development
  ➔ Targeted management and monitoring plan
Approach

- Work within current legislation/guidance

- Identify what can be done differently/less of for certain types of trial?
  - Application process
  - Conduct of the trial

- Implement and develop guidance
Risk based approach for assessment

• Type A trials - CTA notification only to MHRA
  • Default approval after 14 days
  • Limited triage/assessment internally
  • Potential to object to Notification – full assessment
  • Amendments
    • Not substantial if within SmPC (Type A) – no submission needed
    • Submission for substantial – beyond SmPC

• Live from 1\textsuperscript{st} April 2011
1. Intervention Safety Risk

- Assess risk associated with trial interventions (IMP)
- Assess risk in relation to normal standard care
  - Comparable to standard care (Type A)
  - Somewhat higher than standard care (Type B)
  - Markedly higher than standard care (Type C)
## Intervention Safety Risk – Type A

<table>
<thead>
<tr>
<th>Trial Categories based upon the potential risk associated with the IMP</th>
<th>Examples of types of clinical trials</th>
</tr>
</thead>
</table>
| Type A: no higher than that of 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 (such as in paediatrics and in oncology etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines |
## Intervention Safety Risk – Type B

<table>
<thead>
<tr>
<th>Trial Categories based upon the potential risk associated with the IMP</th>
<th>Examples of types of clinical trials</th>
</tr>
</thead>
</table>
| **Type B: somewhat higher than that of standard medical care** | Trials involving medicinal products licensed in any EU Member State 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 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  
(A grading of TYPE A may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population)* |
## Intervention Safety Risk – Type C

<table>
<thead>
<tr>
<th>Trial Categories based upon the potential risk associated with the IMP</th>
<th>Examples of types of clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Type C: markedly higher than that of standard medical care</em></td>
<td>Trials involving a medicinal product not licensed in any EU Member State</td>
</tr>
<tr>
<td></td>
<td>(A grading other than TYPE C may be justified if there is extensive class data or pre-clinical and clinical evidence)*</td>
</tr>
</tbody>
</table>
2. Non IMP risks

- Risks related to the design and methods of the trial
  - participant safety and rights
  - reliability of results

- Multi-factorial and less amenable to simple categorisation at the trial level.

- Must be assessed independently and mitigation plan developed
  
  - Identify areas of vulnerability
  - Specify mitigation and management plan
  - Can trial monitoring detect/reduce potential for error?

  ➔ **Targeted management and monitoring plan**
  ➔ **Informed protocol development**
Impact on Authorisation

- Type A trials - CTA notification only to MHRA
  - Default approval after 14 days
  - Limited triage/assessment internally
  - Potential to object to Notification – full assessment

- Amendments
  - Not substantial if within SmPC (Type A) – no submission needed
  - Submission for substantial – beyond SmPC
11 trials have gone through the Risk Adaptive Process since April 2011
Implementation & Plans

- Risk Adaptation implemented 1\textsuperscript{st} April 2011
- Appendix 2 (Guidance for risk assessment etc) has been piloted by a group of CTUs
- Appendix 2 to be reviewed and issued (anticipate September)
- The GCP inspectorate will produce guidance on areas where risk adaptation would be appropriate.
  - First guidance will be on monitoring
- Consultation on guidance and examples
- Web to contain guidance and populate with examples (provided via inspection, volunteered or forum)
- Development and planned publication of GCP Guide
Risk Adaptation Areas

IMP

Monitoring & Sponsor Oversight

CT Pharmacovigilance

Training

Laboratories

Quality Systems & QA

Data Management

Statistics

Reporting

Computer Systems

Trial Master Files & Archiving
<table>
<thead>
<tr>
<th>Risk Adaptations</th>
<th>Areas impacted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reduced MHRA role in approvals</td>
<td>Notification v Approval</td>
</tr>
</tbody>
</table>
| 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                     |
Thank you for your attention

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