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.
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 1st 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>
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</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)* |
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| *Type C: markedly higher than that of standard medical care* | Trials involving a medicinal product not licensed in any EU Member State  
(A grading other than TYPE C may be justified if there is extensive class data or pre-clinical and clinical evidence)* |
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
Risk Adaption in Practice

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

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