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Risk Assessment in Clinical Trials

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Agenda

- UK Approach to Risk Adaption
- Risk Proportionate Approach
- Risk Assessment
- Risk Adaptive Monitoring: Defining & Documenting Monitoring Strategy
- Challenge to Risk Adaptive Approach
- Risk Adaptive and IMP management
- Inspection of Trials with Risk Proportionate Approach and Risk Adaptive Monitoring
- Summary

UK Approach to Risk Adaption

- Ad hoc working group including MHRA (GCP and CTU), Department of Health and MRC created a sub-group to look at risk stratification and one work stream was on risk adapted approaches

- The final document includes a simple risk stratification based on the IMP and guidance on a customised risk assessment

- MRC/DH/MHRA Risk Adapted Approach (issued March/October 2011) and Clinical Trial Notification Scheme (April 2011)

  http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Submittinganotificationforatrial/Submittinganotificationforatrial/Generalinformation/index.htm

Risk Proportionate Approach

- EU regulation
  Regulation (EU) No 536/2014 of the EU parliament and of the council of 16 April 2014 on clinical trials on medicinal products for human use
- EMA risk based quality management in clinical trials reflection Paper
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf
- MRC/DH/MHRA Risk Adapted Approach
  http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf
- FDA monitoring guidance
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf
- OECD Recommendation
  http://www.oecd.org/sti/sci-tech/oecd-recommendation-governance-of-clinical-trials.pdf
- Clinical Trial Transformation Initiative
  https://www.ctti-clinicaltrials.org/project-topics/study-quality
- Other publications
  (e.g. Adamon, Optimon, Transcelerate)
- And now addenda to ICH E6

Risk Proportionate Approach

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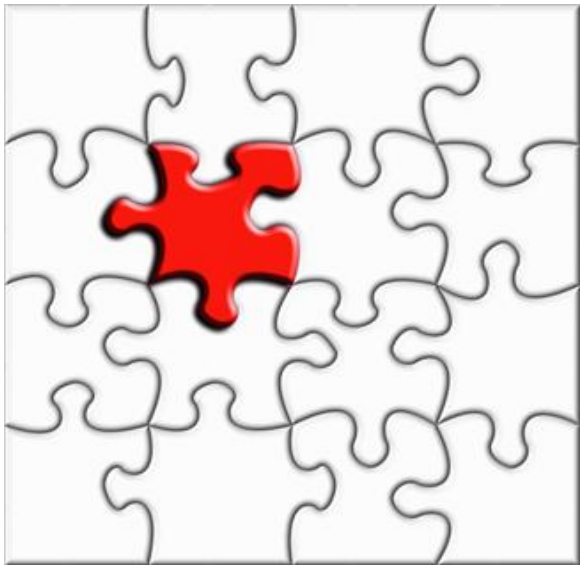
Possible modifications or simplification of "traditional" approaches (as allowed by legislation and within the principles of GCP)

- Risk Adaptive Monitoring
- IMP Management
- Safety Reporting
- Trial Master File
- Trial Authorisation
- etc.



EU Regulation

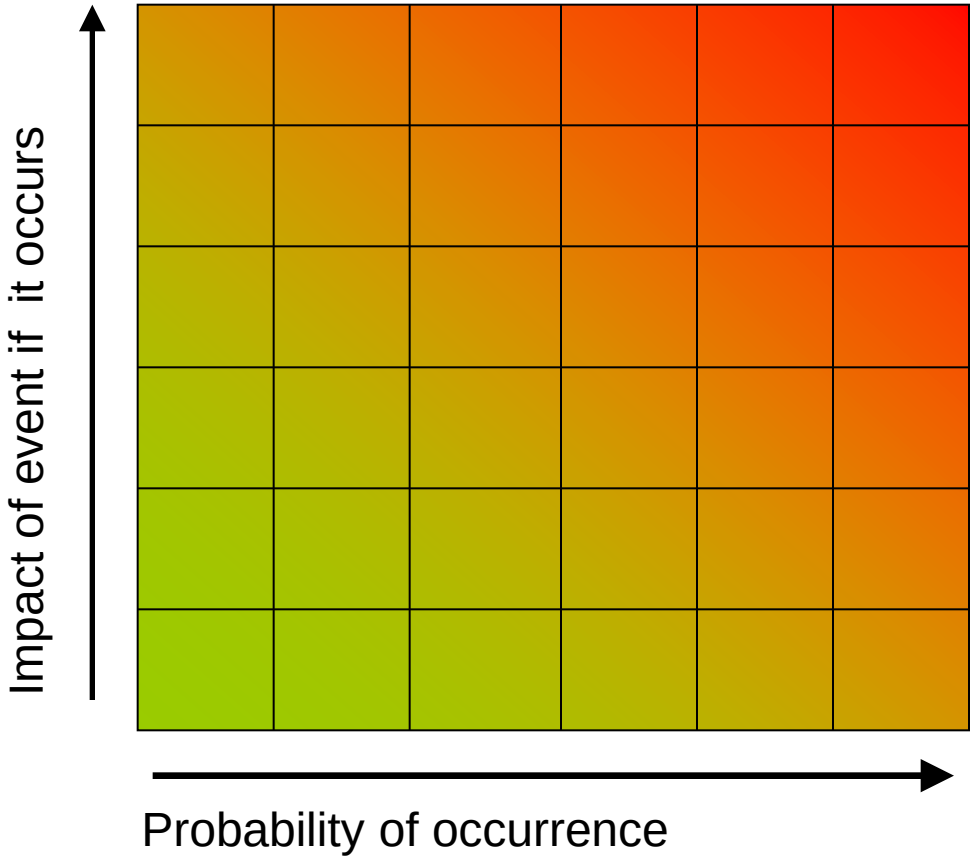
- Aims for risk proportionality to be taken into account throughout
- Risks associated with subject safety and data reliability and based on IMP marketing status
- Low intervention trials are defined (MHRA Type “A”)
- Low Intervention Trials/Risk Proportionate Areas:
  - “Less stringent rules”
  - Monitoring
  - TMF
  - Accountability/storage of IMP
  - Labelling of IMP
  - Insurance/Indemnification
- EMA Reflection Paper on Quality Risk Management

Risk Assessment

- Trial specific to assess hazards:
  - Risks to participant safety from IMP
  - Risks to reliability of results
  - Risks from trial clinical procedures
  - Risk to patient rights: consent & protection of personal data
  - Risks to compliance
- **WHAT MATTERS?**
- Mitigate or accept risks (Risk Management Planning)
- Used to develop the protocol and the **OVERSIGHT & MONITORING STRATEGY** to manage risk

Measuring risk

- Many methodologies - need for further research



Risk Assessment Factors

- Trial categorisation (A, B or C) {MRC/DH/MHRA approach}
- Bespoke risk assessment that will have comprehensively covered the aspects of the trial to highlight mitigations to be addressed by protocol design and monitoring strategy (for example):
  - Randomisation & Blinding
  - IMP – type, status, dosing methods, storage/handling requirements etc.
  - Complexity of the trial protocol and procedures
  - Novelty of the trial – for example, the use of new methods/equipment
  - Endpoint measurements
  - Size – multi-centre, multinational, number of subjects, data quantity
  - Subjects: vulnerable, patients or healthy volunteers
  - Type of investigator site and experience of site staff
  - Whether electronic data capture is being used
  - Complexity and ease of use of the Case Report Form (CRF)
  - Training requirements of monitoring staff, investigators and research teams
  - Type and effectiveness of central monitoring approaches available for the trial
  - Resource

Risk Minimisation – an example

- Background: IMP could cause Progressive Multifocal Leukoencephalopathy (PML)
- Plan
  - PML checklist
  - Evaluation Algorithm (part of study manual)
  - New neurological signs/symptoms potentially consistent with PML will be reviewed and adjudicated by an independent committee
  - Any diagnosis of PML will be considered an SAE
  - Specific study entry and exclusion criteria
  - Risk Minimization Action Plan for PML
  - Formal teaching and training for site personnel
  - Subjects will receive training and educational material prior to receiving treatment
  - Long term post study follow up safety assessment

Key problems seen with risk assessments reviewed

- Too late
- Not updated when required
- Not multi-disciplinary, not inclusive of the right people
- Risk areas not comprehensive / wrong focus
- Does not state the hazard/risk & impact
- Not communicated
- Just numbers – no description
- Defining the risk for the whole trial only

For more information on expectations see MHRA FAQS

http://forums.mhra.gov.uk/forumdisplay.php?1-Good-Clinical-Practice-(GCP)

Data Accuracy & Protocol Compliance

- The data accuracy and proper conduct of the trial can be influenced not only by detecting and correcting of errors and deviations retrospectively, but by prevention, for example, by appropriate trial design, training, communication and systems and resourcing that facilitate the conduct of the trial.

- Focus on the reliability of the trial results not the data points

- Protocol compliance and study conduct are important for reliability of the results

- Statistical aspects – impact of error in relation to trial size and design

Oversight and Monitoring Strategy

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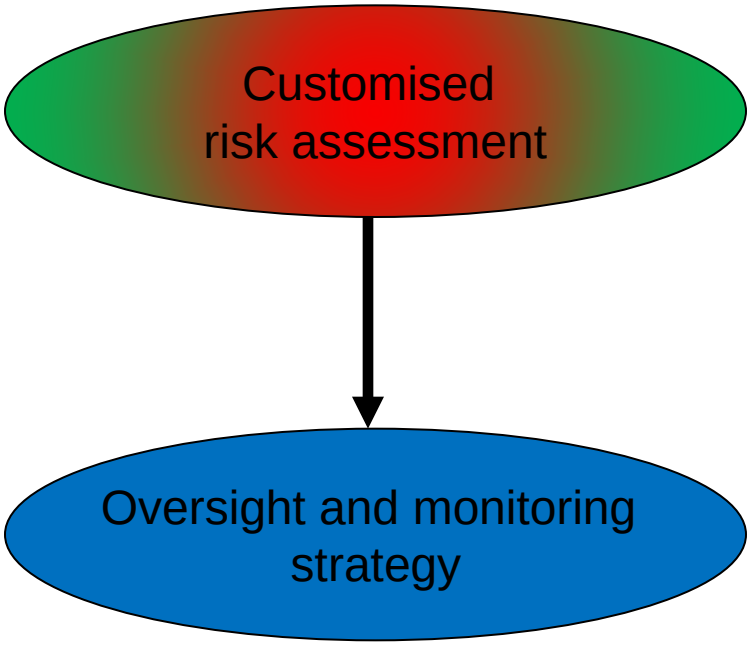
- Oversight and Monitoring can take many forms:

  - traditional on-site monitoring
  - central and statistical monitoring
  - peer review
  - trial steering committees and data monitoring committees
  - other remote activities (such as telephone calls, self-assessment/status or progress reports etc.)
  - Meetings

- Once the oversight and monitoring strategy has been decided, it should be **documented and must be followed**
  - Risk Assessment, Monitoring Plan, Safety Plans, Data Management Plans, Charters etc.

- The use of central monitoring transfers some additional activities to the investigator site & to data management/statistics and may impact on resources

Oversight and monitoring strategy



Documented in risk management plan

Documented in / supported by the Protocol, Plans, Charters, SOPs

Ongoing review in light of:
feedback from oversight + monitoring activities (triggers), protocol amendments, issues (program/trial/site level), DMC review, interim analyses, results from other studies etc.

Risk-based monitoring is consistent with ICH GCP, as the sponsor “should determine the appropriate extent and nature of monitoring”

Risk Adaptive Monitoring

- The monitoring activities should have been based on the vulnerabilities identified in the risk assessment that defines the priorities

- Should contain further risk-based flexibility within it to ensure that the monitoring tasks undertaken are risk- based and reflect accumulating information about compliance

- Feedback from the oversight/monitoring activities drives the risk adaptive approach to monitoring itself

  - Metrics from visits/central monitoring
  - Visit reports
  - Serious breaches etc.

  - TRIGGERS FOR ESCALATION (or de-escalation)
  - TRIGGER TO UPDATE RISK ASSESSMENT

Central Monitoring

- Data Management can be considered a form of central monitoring and should be risk based.
  - Data validation – data that is critical to the reliability of the trial results
  - Avoid excessive resource spent on raising irrelevant data queries
- Statistical: Trending and modelling to identify any unusual or extraordinary patterns/variance/distributions and sites appear to be “outliers”. Multivariate methods possible.
- Metrics used: SAEs reported, time to CRF completion, Number of deviations etc. with predefined criteria, thresholds or tolerance limits
- The use of all the data in this manner can potentially reveal issues that on-site monitoring would not be able to detect.
- New roles in central monitoring for statisticians. Increased interaction between monitoring, data management and statistics personnel.
- Organisations are developing quality metrics or key risk/performance indicators to assist in determining which investigator site should be visited (QA usually)

Monitoring Action

- Escalation could include tele/video conferences, training, on site visits etc.
- Intensity of monitoring oversight and/or visits are high initially and then decreases where compliance is acceptable
- High intensity for unknown/new sites with little trial experience compared with sites used many times by the sponsor, decrease where compliance has been determined to be acceptable
- Resources and process needed to escalate by a monitoring intervention should be available
- Processes overseen by the project manager/chief investigator/trial steering group. Rationale for the change should be documented
- Appropriate for the monitoring to focus or have more detailed review (intensity) on different areas within a trial or in different trials. (see examples in MHRA GCP Guide 7.3.2)

Evidence of Complying with the Strategy

- Records of contact/visits to sites retained
- Evidence of central monitoring activities regarding data should be retained, for example reports generated from interrogating the database, documents received from investigator sites, evidence of review
- Records of decisions/escalation activities

Challenges to Risk Adaptive Approach

- Is there an acceptable methodology?
- If I implement a risk proportionate approach and risk adapted monitoring am I increasing my risk of inspection findings?
- Will inspectors be consistent when looking at trials with a risk proportionate approach and using risk adaptive monitoring?
- How much can I adapt?
- Will trials categorised as “Type A” be inspected?
- How can I implement a risk adapted approach yet comply with ICH GCP?

Challenge to Risk Adaptive Approach (cont.)

- *"The investigator/institution ….., should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). … should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subject… should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s)…."* (ICH GCP 4.6.3)
- MHRA Type A /Low interventional trial – normal clinical practice risk assessed as sufficient and the additional requirements above add no value to reliability of results/safety of subjects
- *"All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification."* (ICH GCP 2.10, UK SI 2004/1031 (as amended))
- Global trials (countries may have ICH GCP a legal requirement) & trials for Marketing Authorisations

Risk Adaptive Monitoring and GCP

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified. (ICH GCP 5.18.3)

Systems with procedures that assure the quality of every aspect of the trial should be implemented (complied with). (ICH GCP 2.13, UK SI 2004/1031)

Risk Adaptive Monitoring and GCP

- Risk adaptive monitoring is consistent with ICH GCP, as the sponsor should determine the extent and nature of monitoring
- Site visits, for assessment, initiation, routine and close down may not always be necessary – the risk assessment could identify the exceptional circumstances mentioned in ICH – the role of central/statistical monitoring is underestimated in ICH GCP
- 100% SDV is not necessary
- Occasionally, only a limited amount of monitoring may be necessary for oversight
- No validation of effectiveness of approaches, but traditional approach has failures

Risk Adaptive and IMP management

- IMP and comparator(s) used within their authorisation.
  - Normal prescribing practice; No requirement for:
    - Shipping receipt and destruction records and Drug accountability, provided the sample size is acceptable to account for the variability in drug compliance. Alternatively, if the sample size is small, subjects may be asked to complete a diary card or return the remainder of the prescription
    - Recording batch numbers and/or expiry dates, unless part of routine practice
- IMP and comparator(s) used off label but use is an **established** and supported by published evidence: as above
- Single-/double-blinded trial with unblinded operator preparing IMP/ comparator/placebo (all with MA)
  - Normal prescribing practice is acceptable
  - No requirement for accountability of bulk receipt, return and destruction
  - Trial specific dispensing log or worksheet, batch no, second checker, retention of used vials required

Inspection of Risk Adaptive Trials

- Type A and low intervention trials should have a lower likelihood of inspection

- All documentation to be made available for inspection (risk assessment, documents relating to monitoring strategy, outcome of monitoring [records/reports])

- What about non-compliance in areas not covered by monitoring? (e.g. data discrepancies in non SDV'd data)

- Non-compliance ⇨ findings
  - Impact
  - Root cause (not identifying risk, not following strategy [e.g. escalation])
- Training of inspectors

MHRA Approach

- Meet with stakeholders to identify areas of risk adaptation
- Invite stakeholders to provide working examples of risk adaptation
- Review protocol, study manual and safety report plans
- Publish FAQs, GCP Guide, MHRA website
- Publish real examples of Risk Assessments to encourage wider adoption

Summary

- Risk proportionate approach is supported by MHRA
- Good and comprehensive risk assessment process is critical
- Risk adaptive monitoring is consistent with ICH GCP
- Methodology and its evaluation is still developing
- Provide or facilitate provision of examples to help sponsors

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Thank You

Any Questions?

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