RISK BASED APPROACH TO CLINICAL TRIAL MANAGEMENT

THE ACADEMIC PERSPECTIVE

Nicola Muirhead PhD

YOU…

ACADEMIC TRIAL MANAGEMENT MODEL

- Trial Manager often = Trial Monitor
- Trial Team
- Impact on resources
- Build in efficiency and quality from beginning (pre-funding)
- Risk Assessment <-> protocol development. Organic, update
- ‘Trial vs study’

RISK ADAPTED APPROACHES

- Relevant documentation
- Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products (DH, MHRA and MRC, 2011)
- Categories based on risk associated c. IMP:
  - Type A: no higher than standard care
  - Type B: somewhat higher than standard care
  - Type C: markedly higher than standard care

OVERVIEW

- 3 examples of application of the risk adapted approach to clinical trial management (high risk areas)
  - Drug accountability
  - Consent
  - Drug dosing (provision to patient)

  (Papers in the public domain)
- Examples of applications of the risk adapted approach to monitoring

EXAMPLE 1 - OVERVIEW

- Multicentre, randomised, controlled open label phase 2/3 non-inferiority study
- Warfarin (control) vs. Rivaroxaban (novel anticoagulant), in thrombotic anti-phospholipid syndrome (APS)
- Rivaroxaban licensed: venous thromboembolism but directly applicable to APS?
- Non-CTIMP
- Type A
- N=116

RISK ADAPTED APPROACH

- Warfarin = control
- As per standard clinical care
- Managed entirely through community anticoagulation clinics
- No sponsor or study site responsibility or oversight
- No paperwork
- Data collection

REVIEW

- Positives:
  - Enabled the research/impossible without this approach
  - Safest: central management of warfarin = high risk
  - Support from MHRA, sponsor, sites, oversight committees
  - Reduced resource requirements
  - Guides development of systems and stakeholders
- Negatives:
  - No control, but no negative impact of this

EXAMPLE 2 - OVERVIEW

- Multicentre, non-randomised, single-arm, prospective comparison/diagnostic accuracy study in Crohn's disease
- Magnetic resonance enterography and small bowel ultrasound vs. reference standard
- No intervention , possibility of an additional arbiter test (local clinical decision)
- Non-CTIMP
- Type A
- N = 334

RISK ADAPTED APPROACH

- Applied across study, focus on consent = issue
- Patients not regularly attend site
- Consider risk
- Allowed patients to give consent on the day of PIS and consent discussion, if they want
- Rejected
- HRA: discussion, justification, support

RISK ADAPTED APPROACH

- HRA 17.01.2017: ‘no definitive guidelines or legislation regarding the appropriate amount of time (or minimum amount of time) that potential participants should be allowed in order to consider whether to take part in research or not’
- No standard requirement for 24 hours
- ALWAYS allow ‘as long as they need’

REVIEW

- Positives:
  - No need for additional visit (patient burden)
  - Reduced resource requirements
  - High level of up take
- Negatives:
  - None
  - Potentially: patients could fell rushed but no reports of this and staff well trained and competent – review and manage

CONSENT CONSIDERATIONS

- Medium:
  - Appropriate to the patient population
  - Multiple methods
- Ongoing process:
  - Manage and document this

EXAMPLE 3 - OVERVIEW

- Multicentre, open label, single arm, dose feasibility trial
- Acutely decompensating cirrhosis with serum albumin levels <30g/l (restore to >30g/l)
- Repurposing human albumin solution (HAS) as an immune restorative drug
- CTIMP
- N=80 (feasibility trial)
- Type B

RISK ADAPTED APPROACH

- Patient dosing (drug delivery)
- Majority of trial activities undertaken by trained trial staff
- Prescription
- HAS given daily by ward staff – not trial trained

REVIEW

- Positives:
  - Reduce resource requirements
  - Enables sites that couldn't otherwise participate = expand access to potential participants
  - Supports move to standard implementation of intervention if outcomes positive
- Negatives:
  - Adequate management of the IMP? Yes, prescribing by trained trial staff only

SUMMARY OF EXAMPLES

- Risk assessment – organic
- Build in quality by design
- Collaborate
- Is the RAA applicable to all areas of clinical trial management including high risk areas…..?

RAA TO MONITORING

- Resource intensive area (time and money)
- Vital to ensure quality and oversight
- Landscape changing: move to electronic data capture/records/essential documentation etc.
- Specifically highlighted in the documentation as area for RAA

ON SITE VS. CENTRAL

- Risk assessment dictates
- **On site:** Access to everything
- Relationships with site staff
- Discussions with site staff
- Resolution of findings at site
- **But:** Resource intensive (multicentre, distance)
- Confidentiality: data to site for SDV
- Logistics (PI time)

ON SITE VS. CENTRAL

- **Central:** resource reduced
- Move resource burden to site
- Look for data signals: within and across sites
- Build in automatic checks e.g. trends in data/clinic dates at weekends/out of range/X.0
- **But:** Full picture?
- No close out meeting, can't agree CAPAs/timelines in person
- Can't follow up at the time

ON SITE AND CENTRAL

- Mixed model
- Triggers lists
- Be flexible (type, frequency and intensity)
- Build in resource to support increased monitoring

FREQUENCY OF MONITORING ACTIVITIES

- Risk assessment
- May be different across sites depending on site/PI experience and your experience with that site
- Build in flexibility to increase or reduce frequency
- Triggers list
- Ensure sites are aware (no surprises)

INTENSITY

- Risk assessment
- Focus on relevant areas
- With Data Manager/statistician, identify key data points e.g. BP in a CVD trial vs. oncology
- % of the patients
- % of the Case Report Forms
- Flexibility to increase or reduce <- experience

SELF-REPORTED REVIEWS

- Provide forms to sites for self completion
  - Review Informed Consent Forms
  - SDV
  - Missing data: identify and source
- Trust the site
- Adequate training
- Open dialogue

MIXED MODEL

- Risk assessment (organic)
- Multiple methods working in harmony
- Buy in – not always appropriate
- Spectrum

SUMMARY

- Risk assessment (template) - organic
- Many ways
- Changes interaction with sites
- Mixed model
- Monitoring plan (template, SOPs, Policies)
- Flexibility – build in and embrace.
  Stakeholders on board including site. Training

TAKE HOME MESSAGE

- Positive development
- Supports efficient and high quality research whilst ensuring the participant and data are protected
- Minimising/eliminating redundancy
- Evolving and developing area
- Monitoring
- Risk assessment vital, update
- Collaborate, buy in, training, discussion

Questions….?

Thank you

n.muirhead@ucl.ac.uk