MRC Hubs for Trials Methodology Research

MRC Clinical Trials Unit Hub

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Central and on-site monitoring – a retrospective review of findings

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Can central monitoring techniques identify on-site monitoring findings? A review of findings from selected monitoring reports in a phase III trial.

- Aim: to assess the type and proportion of on-site monitoring findings that can be identified through the use of other central monitoring techniques.
- Methods: retrospective analysis of on-site monitoring findings
  - Findings extracted and individually assessed to see if they could have been detected in the trial database or through other central means

MDP301 trial

- Setting: Microbicides Development Programme 301 trial.
- Randomised, placebo controlled IMP trial of microbicide gel to prevent vaginally acquired HIV infection, conducted in 6 sites in east and Southern Africa
- 9385 healthy women enrolled, 4 wkly clinic visits for 12 or 24 months follow up
- Intensive on-site monitoring plan designed to complement trial management processes as results were intended to support licensing application to US FDA had they been positive

MDP301 trial monitoring

- Trained staff visited sites according to pre-specified schedule
- Checking informed consent forms, data management systems, pharmacy accountability
- Source data verification
- Findings: critical, major or other
- Common database in place at each site including double data entry system for validation
- Combined database at CTU
- Query module designed to allow detection of missing data, missing CRFs, defined inconsistencies and to enter query resolutions

Retrospective review process - methods

- Sample of monitoring reports purposively selected
- Individual findings extracted
- Findings assessed to determine if they could have been identified centrally during the trial.
- Findings relating to data points in individual ppt folders and on CRFs
  - Would they have been identified in list of query types or inconsistency checks documented in data manager guide?
  - If not, could a query have been developed and included that would have identified it centrally?
- Findings not relating to data points ie TMF review, trial processes and procedures
  - Could some other central process have been implemented to identify it?

Summary of review findings

Summary	N (%) from monitoring reports	From PMBe reports
Participant files reviewed	104	12 mth period ~ 36 monitoring visits
Study visits covered by review	324	
Monitoring findings	**268**	**9** (3 critical, 6 major)
Findings identified on trial database as well as directly during on site monitoring	75 (28%)	-
Findings assessed as being possible to have been identified using other central monitoring strategies	141 (52.6%) (2 major)	7 (3 critical, 4 major)
Findings identified from errors on the CRF that would not have been entered onto the database	38 (14.2%)	-
Findings assessed as unlikely to have been identified without a direct review of the ppt folder or through other central monitoring process	14 (5.2%)	2 (2 major)

Composite central strategy to identify finding

Central strategy	N (%) of total monitoring findings
Specific data check could have been implemented	70 (49.6%)
Central receipt & review of ppt info (inc translations)	22 (15.6%)
Central receipt & review of spec testing logs	17 (12.1%)
Central receipt & review of screening/enrolment logs, IC forms, delegation of responsibility logs	12 (8.5%)
Central receipt & review of reg docs	6 (4.2%)
Central receipt & review of source data on NAEs	2 (1.4%)
Central receipt & review of pharmacy accountability docs	1 (0.07%)
Central receipt & review of translated CRFs	1 (0.07%)
Fax back confirmation of docs filed	6 (4.2%)
Review of delay between date of visit and date data entered onto CRF	2 (1.4%)
Including all written text/comments on database	2 (1.4%)
Total	141

Central strategy considerations and the use of data checking

- Does everything need checking?
- Size of trial – number of sites, participants, volume of data/information, site visit schedule
- Type of trial – level of risk to participants

- Who decides what to check and how?

- Queries can be written for any linked data in a trial

- Someone needs to define the checks
- Financial burden
  - Programming – writing and testing
  - Central management - running and chasing
  - Site management – responding

Conclusions

- Central monitoring – trial related QC activities
- On-site visits/monitoring – where central review or RA indicates increased cause for concern

- Benefits of on-site meetings
  - 2 way communication
  - Discussion around logistics of practical application of procedures
  - Identify training gaps
  - Team spirit increases accurate and complete data collection

What is this study informing?

- Plan – develop and prospectively test central monitoring strategy to provide empirical evidence of good practice
- Methods of appropriately targeting sites for more intensive monitoring
- Assess usefulness and value of individual strategies

- Yet to think in detail about protocol – any collaborative interest from other Hubs?

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Findings assessed as not possible to identify by other central means

Finding	**N**
Initial lab test triggered notable event report. Lab result not confirmed so event not considered notable. Database not updated to reflect this.	1
Transcription errors (within normal limits for lab ranges)	2
Source lab results missing from ppt folder	2
Inconsistency between written and followed procedures	3
Erroneous forms in/missing from ppt folder – entry correct on database	2
Meds documented in source notes incorrectly transcribed to CRF	2
Ppt referral detailed in source notes but not on CRF	1
Incorrect answer given on CRF only identifiable from source notes	1
Total	14

Critical/major findings

Finding	Severity	Central strategy to identify finding
Problems with re-consent process	Critical	Requesting re-consenting logs from sites
Inappropriate drug dispensing	Critical	Database query
Problems with site compliance with procedures	Critical	Central generation of TMF, receipt and review of updates
Protocol procedures followed inappropriately	Major X 4	Database query
Site persistently unprepared for monitoring visits	Major	None defined
Decline in GCLP standards and lack of maintenance of QC system	Major	None defined