Fraud and misconduct in clinical studies

P

h

a

r

m

a

T

i

m

e

s

I

n

t

e

r

n

a

t

i

o

n

a

l

C

l

i

n

i

c

a

l

R

e

s

e

a

r

c

h

e

r

o

f

t

h

e

Y

e

a

r

F

r

a

u

d

&

M

i

s

c

o

n

d

u

c

t

i

n

C

l

i

n

i

c

a

l

S

t

u

d

i

e

s

S

t

a

g

e

2

E

s

s

a

y

C

h

a

l

l

e

n

g

e

Q

u

e

s

t

i

o

n

Fraud and misconduct in clinical studies can be challenging to detect! What tools and techniques could you use on-site and off-site to identify potential fraud and misconduct.

What could lead you to suspect fraud/misconduct when monitoring? What steps would you take if you suspected fraud and misconduct at site?

Introduction

Clinical trials have become an integral part of healthcare, redefining tomorrows standard of care; thus, much weighs on their data and results. Despite heavy regulation (1, 2), data falsification and fabrication continues (3, 4). Monitors must be able to detect the signs of possible fraud and misconduct (F&M).

Fraud Vs Misconduct

Intent to deceive distinguishes fraud from misconduct; fraud is considered a deliberate deception for personal gain (5), whereas misconduct is unintentional. In both instances, the safety of subjects and the reliability of data is jeopardised.

Fraud can broadly be classified as the (6):

- fabrication (i. e. creation) of
    - data (e. g. patient identities, physical examinations, biological specimens)
    - documents (e. g. ICFs, diaries, scan reports)
- falsifying data (i. e. altering or omitted existing records)

Misconduct is serious or repetitive failure to comply with the study protocol, GCP and regulatory requirements. Examples include inadequate staffing, poor attention to detail, lack of understanding of regulatory requirements and poor management. Although unintentional, it can falsify the data.

Tools & Techniques to Identify the Warning Signs

GCP dictates that sponsors must monitor their clinical trials, as it facilitates data accuracy, integrity and completeness (7). Monitors may face ominous signs, such as significant differences or implausible trends at one site or of all patients under the care of a single investigator would (8, 9), requiring vigilant investigation.

ONSITE TOOL OR TECHNIQUE	HOW?	WHAT COULD APPEAR SUSPICIOUS?
Face-to-Face Communication	– Open ended questions. – Non-verbal communication. – Consistency with all site staff.	– Gathering information such as ‘ timepoints’; e. g. notified that staff member is on annual leave, however their account has been used to enter data into the

		eCRF.
		– Are pharmacy aware of the patients and does drug dispensed reflect this?
Analysing & Reviewing Original Source Documents	– Ensure originals/ wet-ink are provided for SDV.	– Photocopying with fine marks: could indicate white-out usage.
	– Reviewing screening data: are patients eligible? Do they exist?	– Photocopied questionnaire/ source data – where is the wet ink?
	-Patients or investigator signatures discrepancies.	– Signatures differs each
	– Medical	

notes/ clinic letters to check genuine patient attendance – Consistencies of ink/ pen. – Implausible trend of visit dates, patient initials, dates of birth. – Recurring or identical lab values or test results (e. g. bloods, ECG).	time a patient reconsents? – Site requested to add missing information to a document (e. g. questionnaire or ICF). Notice the document has been amended/ completed but patient has not attended clinic. – Same pen/ ink would not be used be on all

		source documents. – Same handwriting: has one member of staff preformed all trial related tasks? – Two patients, same initials and date of birth: one patient, screened twice?
Pharmacy Logs	– Match IxRS report? – Dose drug that been delivered to	– Rare for 100% drug compliance across all patients.

	the site match what has been dispensed and/ or returned?	
	– Is compliance 100% across all patients?	
Pharmacy Accountability of Stock	– Is drug dispensed in a similar fashion (e. g. all tubes of cream or blister packs pressed in exact same way).	– A high level of perfection or similarity would be suspicious. – E. g. no two patients would dispense a tube of cream identically.
OFF-SITE TOOL OR TECHNIQUE		

		– Rapid recruitment/ few withdrawals
RMB Software	– Reviews data holistically to assess patterns and trends in patient populations or techniques against other trial sites to identify outliers.	– Few/ no SAEs or concomitant medications compared to other sites. – Few AEs reported vs patients enrolled. – Late reporting of SAEs.
Audit Trails	– Exist for eCRFs, ePROs, etc. Can track when data was entered, if it was modified and by whom.	– Timepoints: data entered on a weekend, national holiday or

		when key staff are known to be away. – ePRO/ diary completed within 1 day.
RAVE/ eCRF	– Remote compliance checks of data: • Visit schedules • Assessment dates	– Patients visit, or assessment is on a weekend, national holiday or when key staff are known to be away. – Prefect protocol and patient adherence to visit

		schedule. – Matching dates across patients for visits/ too many visits on a single day. – Recurring or identical lab values or test results (e. g. bloods, ECG).
Remote Monitoring Calls	*With Site:* – Open ended questions. – Review findings from audit trails, eCRF and RBM software – Review missing date,	– Same as above.

	screened patient, ICFs *With Pharmacy:* – Review dispensing logs and cross match with IxRS report. – Do these match data in eCRF?
Statistical Methods	– Statisticians can detect ‘ strange’ data patterns and outliers (10, 11).

Managing Suspected Fraud & Misconduct

Suspected F&M can be difficult to manage; without adequate evidence it could lead to a breakdown of the relationship with that site. Therefore, in the first instance the monitor should attempt to obtain any missing data and documents to confirm that the CRF data is supported by original source;

often a reasonable explanation exists. This may involve repeated requests, but they should not accept denial to source documents.

The current climate of risk-based monitoring has seen a reduction in 100% SDV (12, 13); so, checking the legitimacy of source documents bears increased importance when F&M is suspected. Therefore, any missing information (e. g. ICFs) and sudden corrective actions should be questioned. Inconsistencies in signatures, dates, ink or photocopies may be subtle but should all be investigated to rule out F&M.

If no reasonable explanation can be sort the monitor could consider 100% SDV for a suspect site or patient. Alternatively, a ‘ for cause’ audit could be conducted, as per the sponsors SOP. The findings could be used to compile a written case report.

If appropriate to escalate, the study manager should be notified, without alerting the site or persons suspected, who would then escalate to the QA team in line with applicable local policies. A detailed explanation of the monitors findings and supporting evidence would be required (i. e. the case report). This would facilitate further investigation, prior to approaching the site or investigator.

Although not a legal requirement, the MHRA (14) and EMA (15) encourages the reporting of all confirmed instances of clinical trial F&M as serious breaches.

Conclusion

F&M is uncommon and can be difficult to detect (3, 4, 16). Monitors must be proactive in differentiating transcription errors from deceit and poor management. A high level of perfection and precision at any site would raise suspicion and warrant further investigation; but the context must also be considered. Having the tools and techniques is key to enable monitors to act as whistle-blowers and ensure the impact of F&M on patients and data integrity is prevented, or at least minimised, while equally maintaining site relations.

References

1. McLaughlin P, Sherouse O. The McLaughlin-Sherouse List: The 10 Most-Regulated Industries of 2014. 2016. Available from: https://www. mercatus. org/publication/mclaughlin-sherouse-list-10-most-regulated-industries-2014.
2. Lellis C. 10 Most Regulated Industries in the U. S. 2018. Available from: http://www. perillon. com/blog/10-most-regulated-industries-in-the-us.
3. George SL. Research misconduct and data fraud in clinical trials: prevalence and causal factors. Int J Clin Oncol. 2016; 21(1): 15-21.
4. Carlisle JB. Data fabrication and other reasons for non-random sampling in 5087 randomised, controlled trials in anaesthetic and general medical journals. Anaesthesia. 2017; 72(8): 944-52.
5. Sheehan JG. Fraud, conflict of interest, and other enforcement issues in clinical research. Cleve Clin J Med. 2007; 74 Suppl 2: S63-7; discussion S8-9.

6. Gupta A. Fraud and misconduct in clinical research: A concern. Perspect Clin Res. 2013; 4(2): 144-7.
7. International Council for Harmonisation. INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2). INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH); 2016.
8. Polanin-Huk J, Huk J, Filip R. Fraud and misconduct in clinical research.: Journal of Pre-Clinical and Clinical Research; 2010. p. 158-60.
9. Jessen J, Robinson E, Bigaj S, Popiolek S, Goldfarb NM. Unreported clinical research fraud and misconduct. . Journal of Clinical Research Best Practices; 2007. p. 1-5.
10. Knepper D, Lindblad AS, Sharma G, Gensler GR, Manukyan Z, Matthews AG, et al. Statistical Monitoring in Clinical Trials: Best Practices for Detecting Data Anomalies Suggestive of Fabrication or Misconduct. Ther Innov Regul Sci. 2016; 50(2): 144-54.
11. Jaffer U, Cameron AE. Deceit and fraud in medical research. Int J Surg. 2006; 4(2): 122-6.
12. TransCelerate. Position Paper on Risk-Based Monitoring. 2014.
13. Tantsyura V, Dunn IM, Fendt K, Kim YJ, Waters J, Mitchel J. Risk-Based Monitoring: A Closer Statistical Look at Source Document Verification, Queries, Study Size Effects, and Data Quality. Ther Innov Regul Sci. 2015; 49(6): 903-10.
14. MHRA. GUIDANCE FOR THE NOTIFICATION OF SERIOUS BREACHES OF GCP OR THE TRIAL PROTOCOL.: Medicines and Healthcare Regulatory Agency; 2018.

15. EMA. Guideline for the notification of serious breaches of 4 Regulation (EU) No 536/2014 or the clinical trial protocol.: European Medicines Agency; 2017.

16. George SL, Buyse M. Data fraud in clinical trials. Clin Investig (Lond). 2015; 5(2): 161-73.

17. Abbreviations

ADRAdverse drug reaction

AEAdverse event

CIConfidence interval

CRFCase report form

ECGElectrocardiogram

F&MFraud and misconduct

GCPGood Clinical Practice

ICFInformed consent form

QAQuality assurance

PROPatient reported outcomes

RBMRisk based monitoring

RCTRandomised controlled trial

SAESerious adverse event

SDVSource data verification

SOPStandard operating procedure