Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

ePRO: MHRA Case Study

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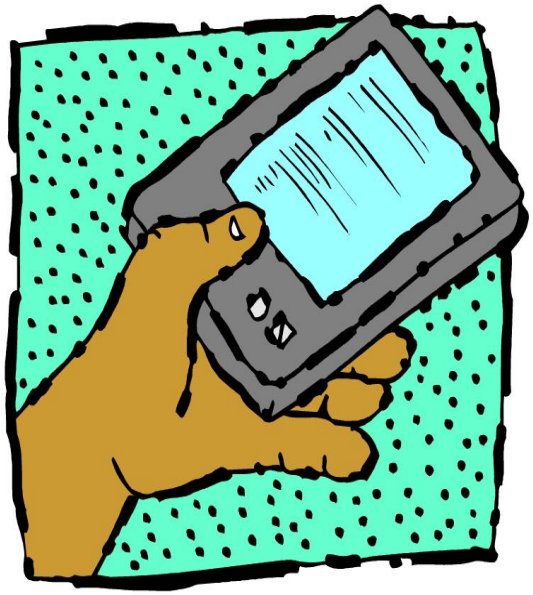
What is ePRO

"An electronic patient-reported outcome (ePRO) is a patient-reported outcome that is collected by electronic methods.

ePRO methods are most commonly used in clinical trials, but they are also used elsewhere in health care".



ePRO: Inspection Case Study

- Haemophilia trials inspected using electronic patient diaries (EPD) to track:
  - IMP administration dates;
  - Bleeding episodes;
  - Responses to treatment.

- EPDs provided to patients for duration of trial.

Inspection findings

- Several hundred changes made to subject-reported data across six trials;
- Changes requested by sponsor's data management and investigator site staff;
- Changes accepted in the study databases without adequate support from source data i.e. no contemporaneous source record of the discussion between the investigator site staff and the subject/ caregiver documenting the reason for the change.
- Graded **Critical** due to systematic issue and impact on Data Integrity.

Inspection continued

- Identified via the **audit trail** of the EPD system.
- Other issues:
  - Lack of UAT (and evidence of UAT) of EPD system prior to release;
  - Issues with user access e.g. trial coordinators approving changes requiring investigator approval;
  - Missed injections = protocol deviations, but these were not captured in CSR from EPD data (relevant to MAA).

Relevant Regulations

All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified.

SI 2004/1031, Schedule 1, Part 2 (9)

The necessary procedures to secure the quality of every aspect of the trial shall be complied with.

SI 2004/1031, Schedule 1, Part 2 (4)

The sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to.

SI 2004/1031, Part 4, 28(2)

Impact of lack of source data

- The procedural data clarification process had been followed;
- Data queries generated, sent to sites and verified prior to changes to implementation of patient data changes;
- However no source data to support either why these changes were needed or confirming patient approval of changes;
- Also patients asked to agree data changes months after the event to ensure ‘best-fit’ of IMP administration vs. planned administration schedule;
- Conclusion: significant lack of data integrity (Sponsor responses agreed)

Impact of lack of UAT

- Issues in design of system resulted in a proportion of required EPD data changes;
- For example forced patient entry of bleeding event details every time IMP administered (even if related to follow-up of same event);
- Had sufficient UAT been performed, less data changes would have been required;
- Impact of issues would have been less (to a certain degree!)

Inspection outcome

Sponsor Perspective:

- Significant CAPA required (some with urgent implementation requirements);
- Notification to EMA as data submitted as part of MAA application.

MHRA Perspective:

- Early re-inspection conducted;
- New area for inspectors too;
- Blog planned!

Thoughts/ Discussion