Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

# MHRA GCP Inspections: Shifting focus and current trends

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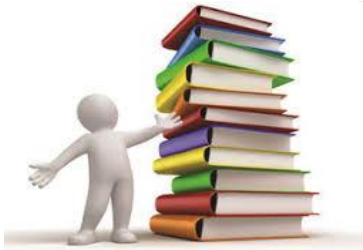
# Agenda


## Overview of the MHRA GCP Inspectorate

- Types of inspections
- Organisations and areas inspected

## Current trends in inspection findings

- eSystems
- Reference safety information



## Recent publications and further reference information

# MHRA GCP Inspectorate

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**Hayley Dixey**

Inspector
**Emma Whale ****
**Jason Wakelin-Smith*****

Inspectors
**Catharine Raitt******

* Head GLPMA
** GCP/Labs Inspector
*** GCP/GLP Inspector
****GCP/PV Inspector

# Types of Inspections

Risk-based and triggered: systems or trial-specific

Voluntary Phase 1 Accreditation Scheme

Marketing Authorisation Application Related

centralised (co-ordinated by EMA)

- national (requested by MHRA Assessors)

# Organisations Inspected

- Commercial sponsors
- Non-commercial sponsors
- Investigator sites
- Contract Research Organisations (CROs)
- Niche providers
- Laboratories
- Phase 1 units

# Areas Inspected

| | |
|---|---|
| Contract management | Regulatory submissions |
| Project management | Report writing |
| Monitoring | Computer systems |
| IMP management | Quality assurance |
| Pharmacovigilance | Quality systems |
| Medical expertise | Training |
| Data management | Archiving |
| Statistical analysis | Laboratories |
| Trial Master File (TMF) management for selected clinical trial(s) | |
| Visits to selected investigational sites | |

# Shifting focus / current trends in inspection findings

# Electronic systems and computer systems validation

# eSystems

Electronic source data - Electronic Health Records (EHRs), including:

- Consultation notes
- Nursing notes
- Medication Chart / e-prescribing (e.g. chemocare, HEPMA, ePMA)
- Laboratory and imaging (MRI/X-ray/CT Scan etc.) results
- Dictaphone transcriptions / letters

eCRF

ePRO (study specific hand held devices to mobile phone apps)

IRT (interactive response technology)

**Intentionally left out the eTMF!**

# eSystems

- Potential eSystem positives:
  - Easy to read/legible
  - Automated date/time stamp
  - Audit trail recording who did what and when
  - Back-ups to prevent data being lost
  - Environmentally friendly

- **Consideration needs to be given to how electronic systems are designed, built, tested, maintained and controlled to be effective and compliant tools for conducting for clinical trials.**

- **As assessment of electronic systems should be performed to determine their suitability for use in clinical trials and establish what additional controls are required, i.e. for the protection of source data.**

# eSystems inspection findings - EHRs

- The monitor was given incomplete EHR printouts so was not aware of all information or the discrepancies between the EHR and additional paper source data - there was no direct access to the EHR

- The printed EHRs given to the monitor were destroyed after the monitoring visit so there was no record of what monitors reviewed - there was no direct access to the EHR

- Vital Signs were recorded using Vitopacx – the actual values were only available whilst subjects were inpatients. Following discharge, the results were converted to a PDF document which only contained a pictorial summary. Therefore, it was only possible to estimate the results rather than review the actual readings.

# eSystems inspection findings – EHRs cont.

- The laboratory results for the screening visit for patient B were not signed off until 16 days after the PI had stated that eligibility criteria had been met and 12 days after the subject had been dosed. The PI stated the results were authorised electronically, but there was no audit trail to support this.

- All study visit entries had been entered by the research nurse in the EHR, including activities delegated to the medical staff. Therefore, the medical staff were unable to demonstrate involvement despite being present during the visit.

- The EHR audit trail was not comprehensive – it did not record who made the entry or if the data had been changed.

# eSystems inspection findings – EHRs cont.

- When “notes” were created, they remained editable, there was no audit trail to show the reason for the edit/deletion.

- There was no on-screen audit trail. Staff had to hand type initials and hand select the date of who was entering at the time. Therefore the records were not fully traceable as you could type in other staff member’s initials on their behalf.

# eSystems inspection findings - ePRO

- The ePRO device had been designed such that no changes could be made to the source data, even when the PI contacted the helpdesk to advise the subject had confirmed the entry needed to be updated. As a result the data used for analysis was incorrect.

- Treatment compliance data for 2 trials had been changed in the ePRO data (232 and 110 changes respectively) by the vendor based on a request from the sponsor. However, there was insufficient source data to confirm the accuracy of these changes and the PIs were not aware of the changes.

- The ePRO device could not scan the IMP barcodes for 4 trials so subjects manually entered IMP batch numbers which led to a large number of errors, affecting integrity of primary endpoint data – the ePRO had not undergone user acceptance testing.

# eSystems inspection findings – ePRO cont.

- There was insufficient UAT documentation for electronic patient diaries - their UAT plan had not been internally approved, there was no documentation to confirm that the UAT plan steps had been followed and by whom.

- Reviews of edited EPD data on a monthly basis (required by study-specific plans as part of sponsor oversight) had not taken place.

- There was a failure to detect and monitor user assignments to the database that contained patient reported data, for example, inappropriate staff had been given PI user rights.

# eSystems inspection findings – eCRF

- Subjects recorded a daily fatigue score in a paper diary but there were insufficient boxes in the eCRF to capture a score for every day of the month. Hundreds of data points were not captured across a large phase 3 pivot trial.

- A CD containing eCRF data had been provided to the investigator site, however the CD was not checked for completeness on receipt. During the inspection it was identified that some of the data headings in the disk were in French and the audit trail had not been included.

# General eSystems inspection findings

- Inadequate documentation to demonstrate design, testing and release of eSystems.

- Inadequate change control processes to manage update to eSystems, i.e. following protocol amendment of SOP change.

- No impact assessment of the integrity of data held in the database following system upgrade(s).

- No review of audit trail(s) to assess integrity of data by the Sponsor.

**Pre-inspection prep**: organisation should be prepared to discuss and demonstrate electronic systems which support your work, **including access controls, audit trails, change control processes.**

# References & Guidance

**eSystems**

- MHRA GXP Data Integrity Guidance
  https://www.gov.uk/government/publications/guidance-on-gxp-data-integrity

- MHRA GCP Guide (grey guide), chapter 11

- MHRA EHR position statement:
  http://forums.mhra.gov.uk/showthread.php?1885-Electronic-Health-Records-MHRA-Position-Statement

- MHRA Blog: ePRO – an inspectors perspective
  https://mhrainspectorate.blog.gov.uk/?s=ePRO

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

# References & Guidance

**eSystems cont..**

- Guidance for data integrity has finished public consultation and comments are being addressed, this will be released in due course.

- ICH GCP E6 R2: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

- EMA reflection paper on electronic source data: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf

- EMA Q&As for how and where source data should be defined (Q3) pitfalls regarding contractual arrangements with e-vendors (Q8) :

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000016.jsp&mid=WC0b01ac05800296c5

# Reference safety information (RSI)

# RSI – purpose and content

- The RSI is a list of **expected serious adverse reactions**, which are classified using Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA).

- It is used for **the assessment of the expectedness** of all 'suspected' serious adverse reactions (SARs) that occur in clinical trials.

# RSI inspection findings

- No clearly defined or controlled RSI
- Incorrect RSI being used to assess expectedness of SARs
- UK relevant SARs being assessed against RSI from a different region
- Insufficient processes for informing MHRA of updated RSI as a substantial amendment and documentation of decision if non-substantial:
  - The RSI, a Summary of Product Characteristics (SmPCs) was being updated without an amendment being sent to the MHRA or any assessment of new expected terms being carried out.

# RSI inspection findings cont.

- Implementation of an updated RSI prior to receiving MHRA approval.
- Use of updated RSI for SUSAR case follow up information and downgrading of SUSARs. RSI in place at time of occurrence should be used as per CT-3 guidance.
- Not using the RSI in place at start of reporting period for DSUR SAR listing.
- Same event being assessed as both expected and unexpected in single DSUR period

# RSI Case Study

All issues seen at one organisation:

- Implementation of RSI changes before amendments have been approved by the MHRA.
- Actual RSI used by case processers was a separate document with additional terms, to that sent to MHRA.
- Latest versions of SmPCs being used as the comparator RSI - not the version sent to MHRA.
- Separate measure of suitability for SUSAR submission to REC compared to MHRA (large number of SUSARs not sent to REC)

# End Result

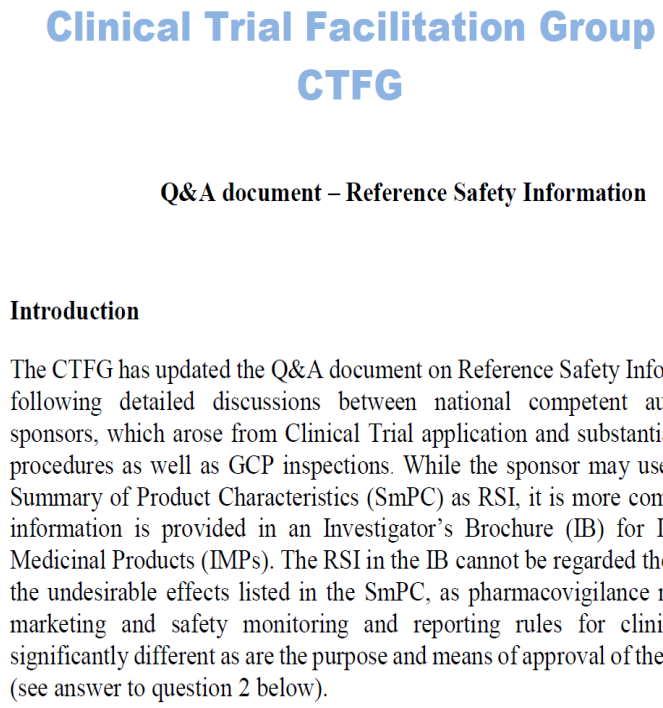
- Unreported SUSARs
- SUSARs incorrectly downgraded
- Substantial amendments not submitted for approval
- DSUR line listings incorrect
- Line listings provided to investigators incorrect

**The MHRA has not had the opportunity to assess new information that may impact on the risk benefit ratio of the trial and to determine if the IMP and its dosing regimen are still appropriate for the trial population.**

# References & Guidance

**Reference safety information:**

- CTFG RSI Q&A (November 2017): http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf



Clinical Trial Facilitation Group

CTFG

**Q&A document – Reference Safety Information**

**Introduction**

The CTFG has updated the Q&A document on Reference Safety Information (RSI) following detailed discussions between national competent authorities and sponsors, which arose from Clinical Trial application and substantial amendment procedures as well as GCP inspections. While the sponsor may use an approved Summary of Product Characteristics (SmPC) as RSI, it is more common that this information is provided in an Investigator's Brochure (IB) for Investigational Medicinal Products (IMPs). The RSI in the IB cannot be regarded the same way as the undesirable effects listed in the SmPC, as pharmacovigilance rules for post-marketing and safety monitoring and reporting rules for clinical trials are significantly different as are the purpose and means of approval of the IB and SmPC (see answer to question 2 below).

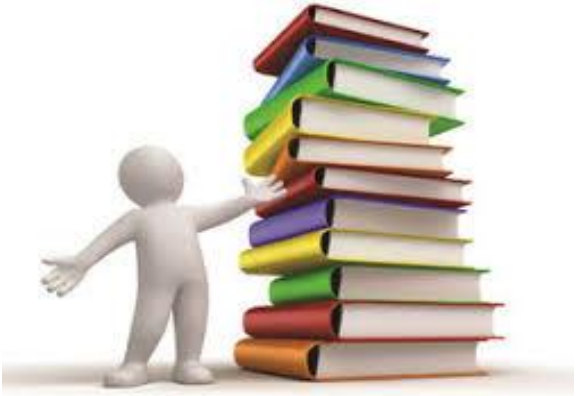
# References & Guidance cont..

- MHRA Inspectorate Blog
  - https://mhrainspectorate.blog.gov.uk/2016/03/02/reference-safety-information-for-clinical-trials/
  - https://mhrainspectorate.blog.gov.uk/2017/01/18/reference-safety-information-ii/

- Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’)

- Statutory Instrument 2004/ 1031(as amended) The Medicines for Human Use (Clinical Trials) Regulations

# Recent publications and further reference information



# ICH E6 Addendum

- ICH E6 in place since 1996; clinical trials have moved on considerably

- An addendum has been developed to address:
- Risk management – critical aspects of the trial
- New technologies – eTMF, eCRF, ePRO
- Complexity of clinical trials
- Overall efficiency of clinical trials

# Glossary

- **Certified Copy**

A paper or electronic copy of the original record that has been verified (e.g. by a dated signature) or has been generated through a validated process to produce an exact copy having all of the same attributes and information as the original

- **Monitoring Plan**

A description of the methods, responsibilities and requirement for monitoring the trial

- Outcomes of any centralized monitoring should also be reported

# Glossary

- **Validation of computerized systems**

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled. Validation should ensure accuracy, reliability and consistent intended performance, from design until decommissioning of the system or transition to a new system.

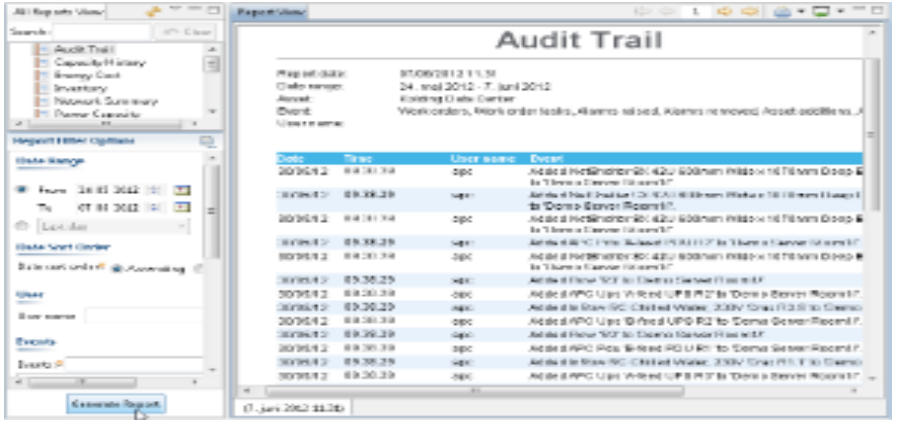
- **The Principles of GCP**

All clinical trials information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification

<u>This principle applies to all records (paper or electronic) referenced in this guideline</u>

# Investigator responsibilities

- Supervision of delegated tasks
- Ensure qualification of any party conducting delegated tasks; implement procedures to ensure integrity of tasks and data generated
- Source documents and trial records
  - ALCOA – attributable, legible, contemporaneous, original, accurate and complete
  - Audit trial




# Quality management

- Sponsor to implement systems to manage quality throughout the trial, focussing on trial activities in relation to subject safety and reliability of trial results
- Methods used proportionate to the risks
- Operationally feasible and avoid unnecessary complexity, procedures and data collection
- Operational documents should be clear, concise and consistent

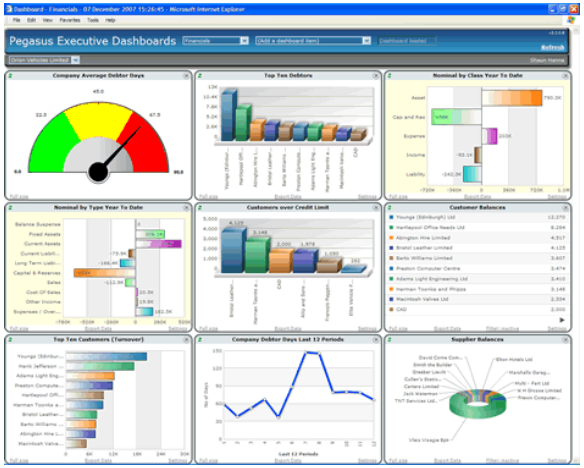
# Risk-based approach

- Critical Process and Data Identification – data and processes critical for subject safety and data integrity

- Risk
  - Identification – risks at system and trial level
  - Evaluation – likelihood, extent, impact
  - Control – mitigation (or acceptance), tolerance levels and detection
  - Communication – stakeholder involvement
  - Review – effectiveness, any changes
  - Reporting – any deviations in the CSR


# Monitoring

- Risk-based approach, flexible approach to permit varied approaches to improve efficacy/efficiency
- A combination of on-site and centralised monitoring may be appropriate
- Approach documented in the monitoring plan
- Centralised monitoring – remote evaluation of ongoing an/or cumulative data:
  - Missing/inconsistent data
  - Data outliers
  - Protocol deviations
  - Data trends
  - Performance metrics




# Other……

- Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan
- Significant non-compliance – a root cause analysis should be conducted, CAPA and if required report serious breach to regulatory authorities
- TMF
  - May require additional documents not mentioned in the list (section 8)
  - Investigator has control of and continuous access to the CRF – sponsor should not have exclusive control
  - Investigator should have control of all essential documents they generate before, during and after the trial

# Further information

**Recent publications:**

- MHRA Blog: risk adaptation in clinical trials of IMP https://mhrainspectorate.blog.gov.uk/2017/11/16/risk-adaption-in-clinical-trials-of-investigational-medicinal-products-ctimps/

- Joint statement on GCP training for researchers https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/

**Other useful resources:**

- GCP Inspections https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

- Inspection metrics https://www.gov.uk/government/statistics/good-clinical-practice-inspection-metrics-2007-to-present

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