Inspections: an academic perspective

Patricia Henley
Quality and Governance Manager
Head, Research Governance & Integrity Office
London School of Hygiene & Tropical Medicine
Email: patricia.henley@lshtm.ac.uk

Outline

- Background
- How to approach inspections
  - Interviews
- Inspection process
  - What are they looking for?
  - What will they ask for?
- Common findings

I have survived!

- 4 MHRA inspections
  - 3 at LSHTM
    - 2 routine
    - 1 triggered
- 2 HTA inspections
  - 1 at LSHTM

Types of Inspections

- Routine
  - Scheduled inspections performed periodically based on risk rating
  - Advanced notice
  - Systems-based
  - Reviews trials to determine sponsor oversight
- Triggered
  - Suspected violations
- Requested
  - MAA-related, pre-licensing

Risk-based approach

- Based on results from compliance reports
  - But no longer required
  - Approximate schedule:
    - High risk = every 1-2 years
    - Medium risk = every 3 years
    - Low risk = every 4-5 years
- Factors that may affect schedule:
  - Number of trials sponsored, hosted or managed
  - Number of UK participants
  - IMP characteristics
  - Outcome of previous inspections
  - Non-compliance reports

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

MHRA

GCP Inspection Process

Version 2 (22 Nov 2012)

What do they inspect?

- Contract Management
- Project Management
- Monitoring
- Pharmacovigilance
- Data management
- Statistical analysis
- IMP management
- TMF management
- Insurance
- Regulatory submissions
- Quality assurance
- Training
- Computer systems
- Report writing
- Archives
- Laboratories
- Medical Advice

Investigator site inspections

Interviews

- PI
- Sub-investigator
- Pharmacists and pharmacy technician
- Research Nurses

Documentation

- CRFs
- Source data
- Investigator site file
- Consent forms
- IMP accountability

Tours

- Pharmacy
- Clinic
- Support sites
- Archives
- Laboratory

What happens during the visit?

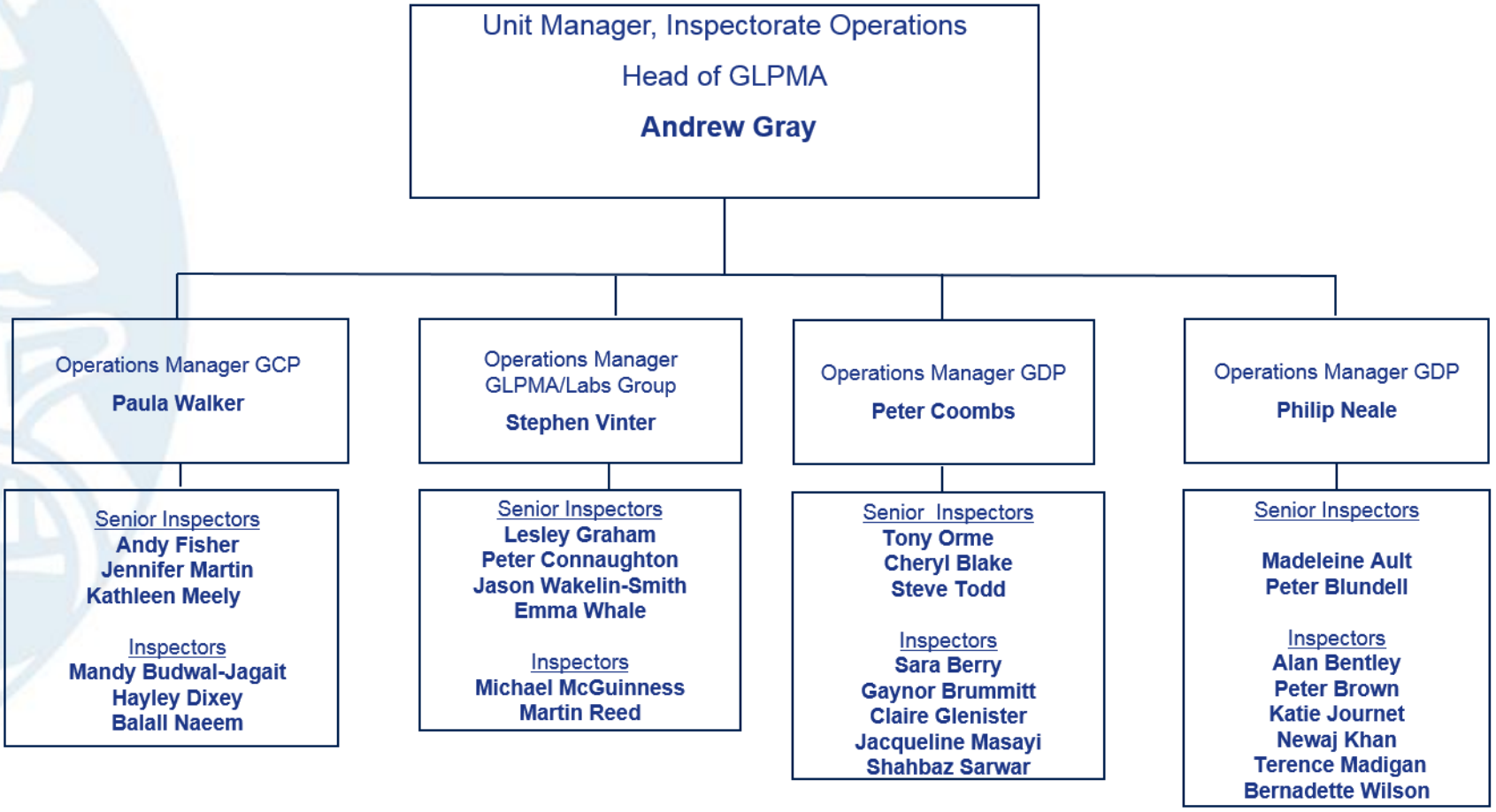
- Typically 2-3 day inspection by 2 inspectors
- Review of policies and SOPs
- Detailed inspection of 3-4 trials to test systems
- Interview with key personnel, eg:
  - Sponsor representative
  - Trial teams
  - QA
  - Contracts
  - Archives

Who are the inspectors?

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Inspection, Enforcement & Standards Division

Inspectorate



Logistics

Documents

- The following essential documents should be made available:
  - TMF (ie ICH GCP section 8)
  - CVs, job descriptions and training records for interviewees
  - SOPs, working instructions
  - SAE and deviation listings
  - Standard training material and presentations
  - Contracts and agreements templates
  - Evidence of CAPA from previous inspections
  - Audit schedules
- Documents are requested throughout the inspection so have someone on hand to help

Before the big day…

- Re-read SOPs, GCP and the regulations
- Re-test systems
  - 24 hour telephone numbers, helpline
  - Unblinding
- Check training files
  - All CVs up to date
- Check TMFs and ensure essential documents are available
- Don’t write any new SOPs, guidelines etc!!

The dreaded interview…

Points to remember

- Not answering is not an option
  - But you can say “I don’t know and will check that for you”
- Do not speculate, assume, guess, or offer personal opinion
- Do not blame, do not argue
- Honesty best policy
  - Tell them how it really is – not what you think they want to hear
- Know your area of responsibility and answer questions relating to this

Top tips

- Stay calm
  - They expect you to be nervous, it's ok
- It's not a memory test
  - If it's in the SOP, then say it's there and you can look it up
- Don't just quote the regulations
  - Explain how you deal with them
- Be prepared for last-minute deviations from their plan

Typical questions (1)

- Training
  - How are you qualified to undertake your role in the trial?
  - Provide overview of qualifications and how many studies you are currently working on
  - GCP training and when undertaken (may check training records)
  - Co-investigator training

- Trial set-up
  - How do you know what is and isn't required in reports to MHRA, ethics etc?
  - Risk assessment at study planning stage

Typical questions (2)

- Study Conduct
  - Give overview of study
  - What steps do you use to ensure protocol compliance?
  - Who maintains the TMF?
  - How is the TMF maintained, eg electronic or hard copy?
  - Take me through the informed consent procedure
  - Where are consent forms stored?
  - Trial steering committee? DMC? Independent?
  - Discussion of roles and responsibilities in study or within organisation
  - How is monitoring performed?

Typical questions (3)

- IMP management
  - Does IMP have a marketing authorisation?
  - How is drug accountability performed?
  - Pharmacy issues
    - Eg where is IMP stored at site

- Data Management & Statistics
  - Data storage – where held? Identifiable information? Back up?
  - Database development, testing and validation
  - Who did / is doing data analysis?
  - Statistical plans
  - Data security – how?

Typical questions (4)

- Pharmacovigilance
  - Can you talk me through how Adverse Events are managed in your study?
  - Who do you report SAEs to?
  - Timelines of SUSAR reporting etc
  - What if you disagreed with the local PI's causality assessment
  - When/how RSI updated
  - How do you know if an event is expected?
  - How do you unblind, if requested?

Typical questions (5)

- Protocol deviations/violations
  - What do you class as a deviation?
  - Have there been any deviations from the protocol?
  - Have there been any breaches of GCP?
  - How do you assess whether the breach is serious?
  - Have there been any persistent deviations of GCP or the protocol?

Typical questions (6)

- Sponsor
  - How often do you talk to the Sponsor?
  - Do they contact you to ask how the study is progressing?
  - What type of insurance does the study have?
  - Do you know what the Sponsor delegated to you as investigator?
  - How do you know which SOPs apply to you?
  - Have you been audited?

Typical questions (7)

- Amendments
  - What is the difference between a substantial and non-substantial amendment?
  - Any amendments to the study and how dealt with?

- End of study
  - Where will final data be stored?
  - Who is responsible for archiving?
  - End of study unblinding

Then it's all over?

Not yet!!

- Site inspections will be selected during the inspection
- Typically 4-6 weeks after sponsor inspection
- Report follows the site inspection
- CAPA plan
- Critical findings are referred to CTIAG/IAG2
  - Also shared with NRES

Findings

Definition of Findings 1

Critical

a) Where evidence exists that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that:

   i. the safety or well-being of trial subjects either have been or have significant potential to be jeopardised, and/or

   ii. the clinical trial data are unreliable and/or

   iii. there are a number of major non-compliances (defined in d and e) across areas of responsibility, indicating a systematic quality assurance failure, and/or

b) Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances (defined in d and e)

Definition of Findings 2

Critical (new)

c) Where provision of the Trial Master File (TMF) does not comply with Regulation 31A 1-3, as the TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the Regulations

Definition of Findings 3

Major

d) A non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that may not have developed into a critical issue, but may have the potential to do so unless addressed, and/or

e) Where evidence exists that a number of departures from applicable legislative requirements and/or established GCP guidelines have occurred within a single area of responsibility, indicating a systematic quality assurance failure.

Other

f) Where evidence exists that a departure from applicable legislative requirements and/or established GCP guidelines and/or procedural requirement and/or good clinical practice has occurred, but it is neither Critical nor Major

Common findings (1)

- TMF management
  - Unable to access TMF or documents within TMF
  - Difficulty in accessing and manoeuvring around eTMF system
    - eTMF includes the metadata
  - 82% commercial sponsor inspections (n=11) had TMF findings in 2014-2015
    - 22% of those critical
    - 67% major

** note: increased number of inspection days due to eTMF issues **

Common Findings (2)

- Protocol deviations
  - Lack of procedures to capture non-compliances
  - Lack of consistency in definition:
    - deviation vs violation vs serious breach
  - No demonstration of why SB or not SB
  - File notes with no further action

Common Findings (3)

- Decision of Eligibility
  - No documented review and assessment of eligibility
  - Must be completed by clinician
  - Two-step process:
    - Medical history and recent results
    - Review of further screening results

Common Findings (4)

- Safety reporting processes
  - Reference Safety Information (RSI)
    - Contained in the Investigator Brochure or Summary of Product Characteristics
    - Most inspections have major or critical findings with this!
    - Note: changing the RSI is usually a substantial amendment
  - Inadequate systems to monitor safety
  - Not reporting SAEs, SUSARs
  - DSURs not completed
  - SUSARs not reported within timelines
  - Unblinding arrangements

Common Findings (5)

- Non-CTU clinical trials
  - CTU trials demonstrated good compliance
  - Stand alone Investigators had more findings
  - Sponsor oversight and experience of CTIMPs
  - Ensure processes in place to identify and oversee all CTIMPs
  - Duplication of Quality System

Common findings (6)

- Change control
  - Electronic systems
  - Amendments
  - SOPs
  - Reference Safety Information (RSI)
  - No documentation of further risk assessment
  - No documentation of why substantial or non-substantial
  - No assessment of further impacts of change on other systems

And the MOST Common Finding

- Sponsor Oversight
  - Contracts, Agreements, Insurance
  - Quality System
  - Inadequate investigator participation – excessive and/or inappropriate delegation of duty
  - Failure to inform MHRA and/or REC of issues within trial
  - Training documentation and requirements
  - IT systems not fit for purpose

MHRA vs HTA

- MHRA
  - Inspection results confidential (until 2017!)
  - Usually 2-3 days, unless at site
  - Review CAPA plan

- HTA
  - Inspection results public
  - Usually 1 day
  - Review evidence that CAPA plan completed

Questions?

Useful Guidance

- SI 2004:1031: www.opsi.gov.uk/si/si2004/20041031.htm
- SI 2006:1928: http://www.opsi.gov.uk/si/si2006/20061928.htm
- SI2006:2984: http://www.opsi.gov.uk/SI/si2006/20062984.htm
- Clinical Trials Tool-kit http://www.ct-toolkit.ac.uk/
- ICH GCP (Topic E6) http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Essential Reading

- MHRA GCP inspection process
  - https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials
- EudraLex Volume 10: Clinical trials guidelines (Chpater IV: Inspections)
  - http://ec.europa.eu/health/documents/eudralex/vol-10/
- NHS R&D Guide to GCP Inspections
  - http://www.rdforum.nhs.uk/content/wp-content/uploads/2014/05/RDFguidance-MHRA.pdf