



Streamlining MHRA Inspection Preparation and Execution in CROs

SA03 - Submissions & Agencies (SA)

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The Clinical Data
Science Conference

EU 2024

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*"Can you share your screen and show me the execution of all the steps required to produce **this** summary table, starting with the EDC datasets locked by the data management team?"*

"Please also give me the evidence and the reference of the standard procedures used for each step."

MHRA Lead Inspector

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MHRA inspections

General Information



Regulatory Framework

MHRA Powers and Responsibilities

The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK has a range of powers and responsibilities to ensure the safety, quality, and efficacy of medicines and medical devices, as well as the protection of public health.

- **Statutory authority to conduct routine and triggered GCP inspections** of sponsors and other organizations involved in clinical trials of investigational medicinal products (CTIMPs).

Inspection Authority



- The regulations require sponsors and other entities to take preventive and **corrective actions if non-compliances are identified during inspections**. Failure to do so can result in further enforcement actions.

Corrective Actions



- The MHRA can take enforcement actions, including issuing **warnings**, suspending or **terminating trials**, and imposing **penalties**, if significant departures from legislative requirements or GCP guidelines are found.

Enforcement Actions



Regulatory Framework

Types of MHRA inspections

Among the 2 main MHRA inspections types, Cytel experienced a Statutory GCP inspection in Sept. 2023.

MHRA Risk-Based Compliance Programme Statutory GCP Inspection ('Routine' inspection)

- **Purpose**
 - Demonstrate regulatory compliance with current requirements for clinical trials.
 - These can be either systems-based or trial specific.
- **Risks considered**
 - internal information about previous inspection history
 - organizational changes
 - intelligence from external sources
- **Notification**
 - Typically notified by email titled '*Advance Notice of MHRA Statutory GCP Inspection*'.

Triggered Inspection

- Triggered inspections are initiated **when the MHRA receives concerns** about the conduct of a clinical trial that warrants expedited on-site follow-up.
- The nature of the information, which may come from sources such as serious breach notifications, whistleblowers, other MHRA departments, or other organizations, determines whether the MHRA gives **short notice or no notice** of the triggered inspection.

Regulatory Framework

Grading of inspection findings

Inspections deficiencies are categorized into three levels: critical, major, and other.

Critical

- Evidence of significant departures from legal requirements
- Inadequate Corrective Action
- Non-compliance with TMF requirements

Major

- **Significant departures from legal requirements:**
 - Non-critical findings that have the potential to become critical if not addressed.
- **Multiple departures within a single area:**
 - systematic quality assurance failure.

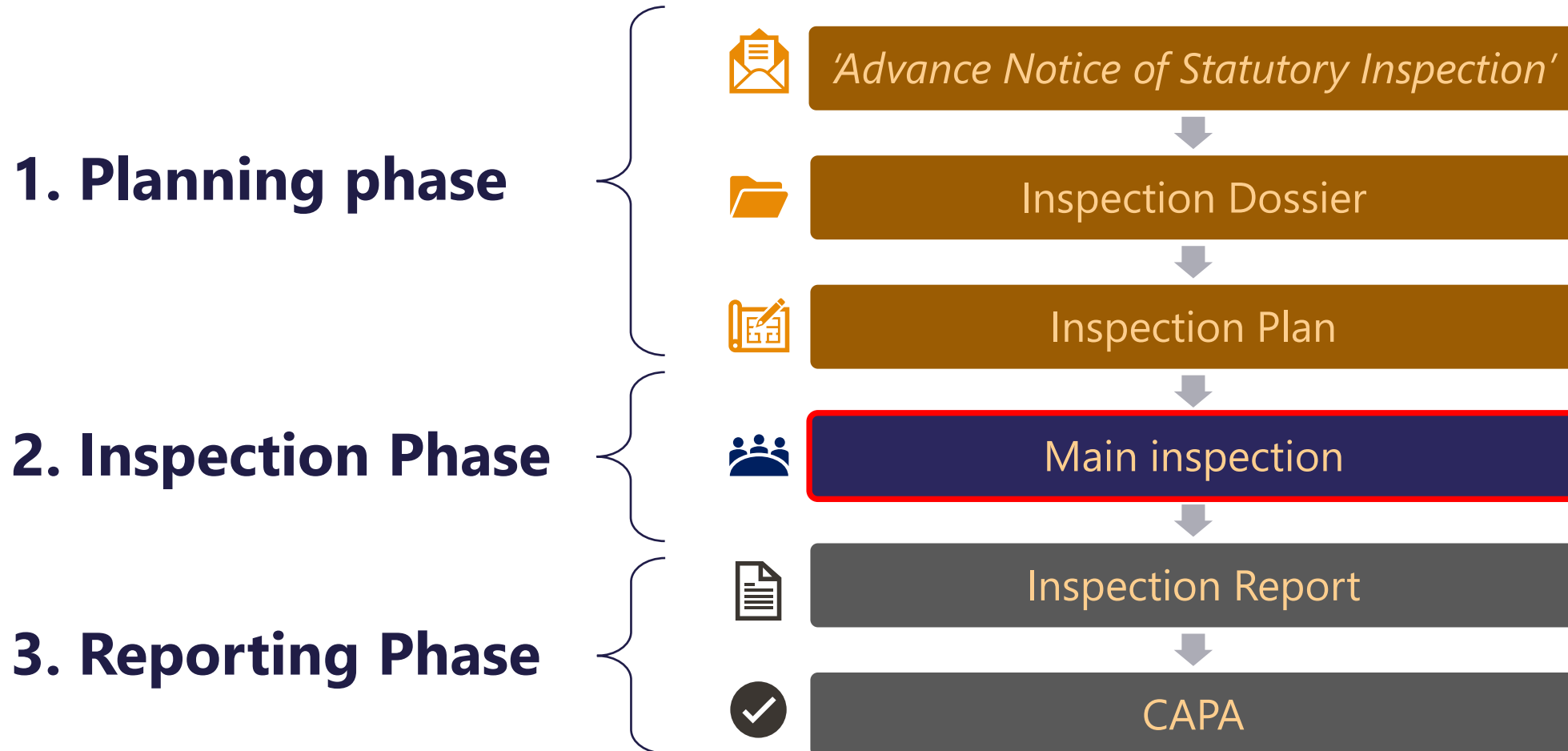
Other

- Minor departures



MHRA Statutory GCP Inspection Process

Essential Steps and Documents



02

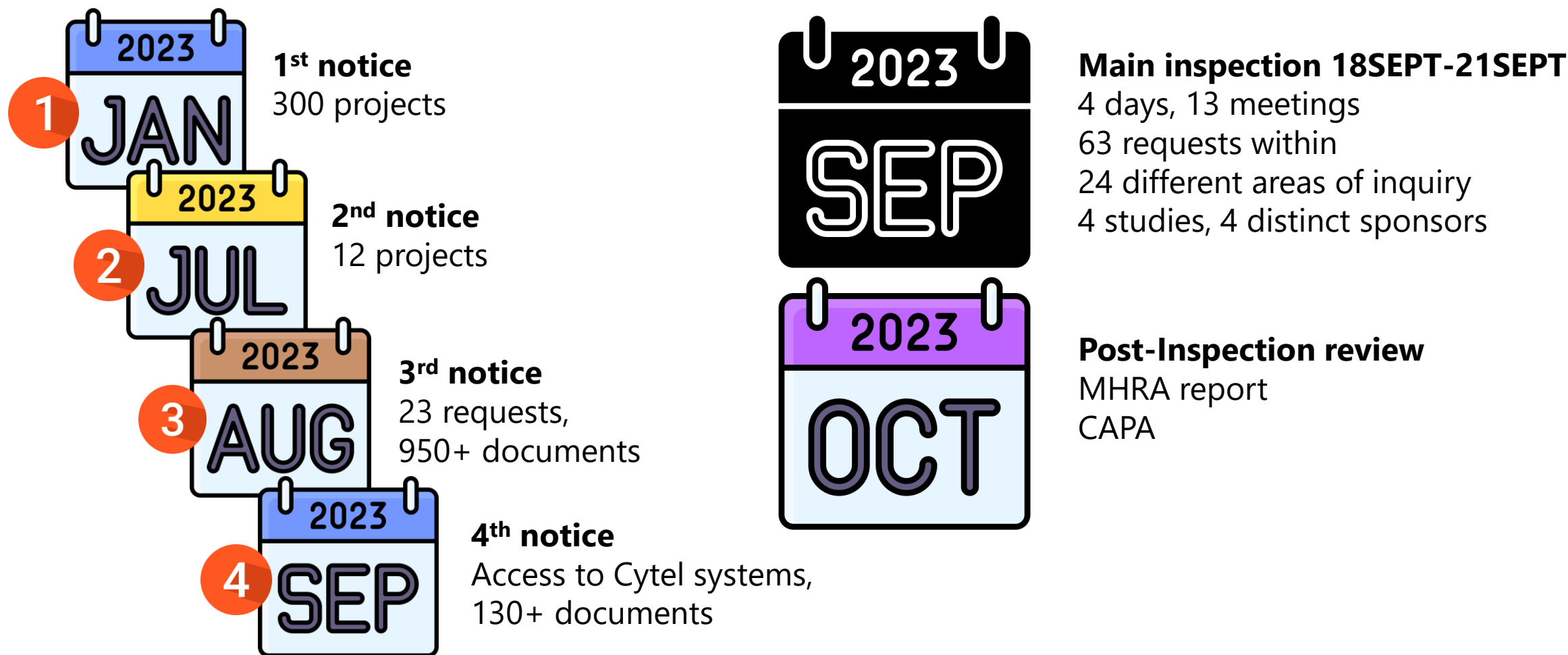
MHRA inspection at Cytel

Preparation and Conduct



Chronology of events

The main inspection spanned four days in September 2023, but the entire MHRA inspection process was initiated nine months earlier.



Logistics

Managing the inspection information flow

3000+ documents requested/provided



e-mails

MHRA <> Cytel

Exchange of main inspections documents, e.g.:

- **Inspection plan**
- **Inspection report**

Notifications for documents requests, review, transfers



Cytel Clinical Data repository

- Preparation of **pre-inspection dossier** (compile information to requests of notices 1 through 4)
 - **uploaded to MHRA servers**
- preparation of main inspection (internal audit, gap analysis)
- **Support Main inspection requests** (studies 1 to 4)
- Setup a **dedicated areas for 'show and tell' sessions** to demonstrate processes.
- Access granted to "clean/light" copy of projects folder



Secured Access granted to Cytel infrastructure

DMS :

- SOPs, Wis and related tools
- GCP trainings



Secured shared area

Cytel Internal use

(real time editing, single source of truth, access control, powerful search)

- **Trackers**, e.g.
 - **Internal and Inspections Requests** (owners, Req. Id, description, assignments, status, pathnames, etc.)
 - No trials data, only path within the SCE
- Copy of **main inspection documents** (=augmented versions): Inspection plan and reports
- Inspection notes
- **Supportive presentations**, e.g.
 - data integrity framework,
 - critical processes,
 - trials overview and focus on key topics

Workforce

Main Inspection (18-21 Sept. 2023)

Less than 1/10th of the staff directly involved in the inspection session was visible.



**MHRA Inspectors
(2 to 3 people)**

1 Senior Lead inspector
2 inspectors



**Cytel Inspection Sessions Attendees
(~5 people in the closed room)**

1 Inspection Lead (Cytel QA) hosting the meeting
~2-4 Presenters/Interviewees.



**Pool of
Interviewees
(20+ people)**



**Scribes (QA)
(~2 people)**

Real-Time Note-Taking



**Documents
Tracker (QA)
(~1 person)**



**Runners (QA)
(~2 people)**

Answer expected
within 30 mn.



**Documents
QC reviewers
(QA/SMEs)
(~2 people)**



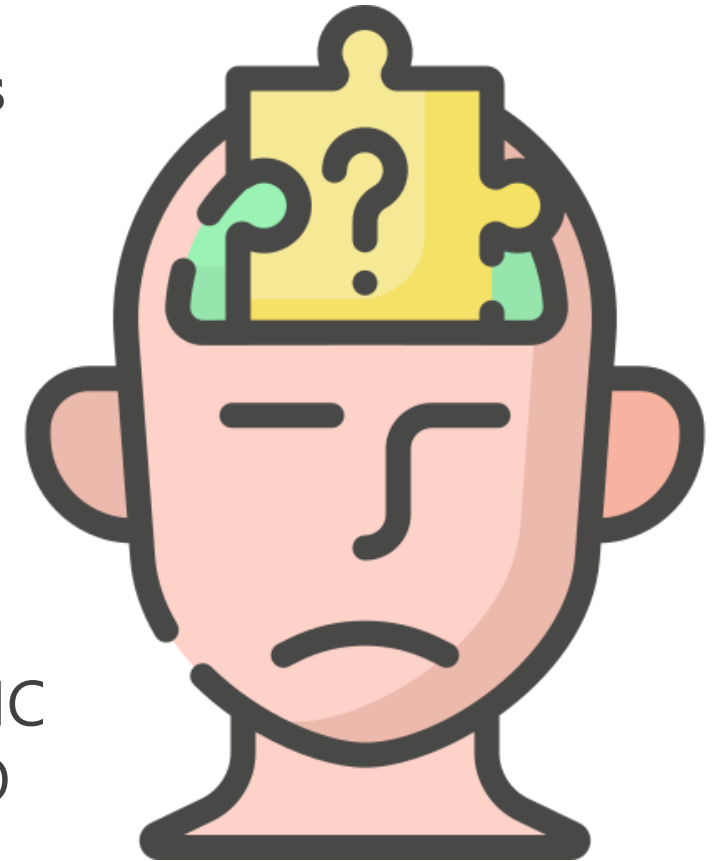
**Support
(80+ people)**

Complexities

Additional factors to consider

4 inspected studies (among 4 distinct sponsors) spanning a wide time range, from 2016 to recent studies.

- Different versions of Standard Operating Procedures
- Key staff turnover
- Significant internal changes including:
 - Infrastructure & Systems upgrades
 - e-signatures...
 - Organizational restructuring: Creation of the Cytel DMC Center of Excellence, following the acquisition of AXIO



03

Strategies



Framework for Engagement

We have crafted a targeted engagement framework that defines clear duties and responsibilities, emphasizes collaboration, and fosters productive dialogue. Applied with discipline, the approach based on simple principles enhanced our readiness and clarity when interacting with MHRA inspectorate.

Steering Group and Communication

- Form a Steering Group led by Quality Assurance (QA)
- Designate a Single point of contact with the Authorities: the Cytel MHRA Inspection Lead

Resource Management and Flexibility

- Inspection training and coaching program with consultants being former MHRA lead inspectors.
- Limit number of personnel interacting with inspectors
- Allow flexibility in interviews. Adapt to any agenda changes

Documentation and Support

- Prepare supportive documents
- Conduct gap analysis. Prioritize the Trial Master File (TMF)

Preparation and Strategic Anticipation

- Anticipate interview directions by identifying patterns in selected studies and requests.



Preparation of Supportive Documents

- Quick access to information in high-pressure situations,
- Thorough understanding of the procedures and trial materials under scrutiny,
- Developing tools and well-defined responses for expected critical discussion points.

Also, within our engagement framework, we want to demonstrate our commitment to transparency with inspectors by highlighting sub-optimal areas we have identified and are addressing.



Cheat sheets

Single-page printed memos

- E.g. **QA docs (procedures)**
 - Linkage SOPs/WIs/RTs
 - Versions dates



Slide decks

Processes

- **Overview**
- Focus on **Key processes**



Slide decks

Inspected Studies

- **'Story Board'**
- **Critical points**



Gap-analysis reports

Identified deviations,
proposed corrections

- **deviations and corrected documents** from the **internal audit**

Personnel Training



Training on QA documents

- SOPs, WIs, and related tools: mandatory trainings on current versions, plus on the historical versions as used in the inspected studies.
- Being mindful of the differences between current processes and those implemented during the inspected studies.

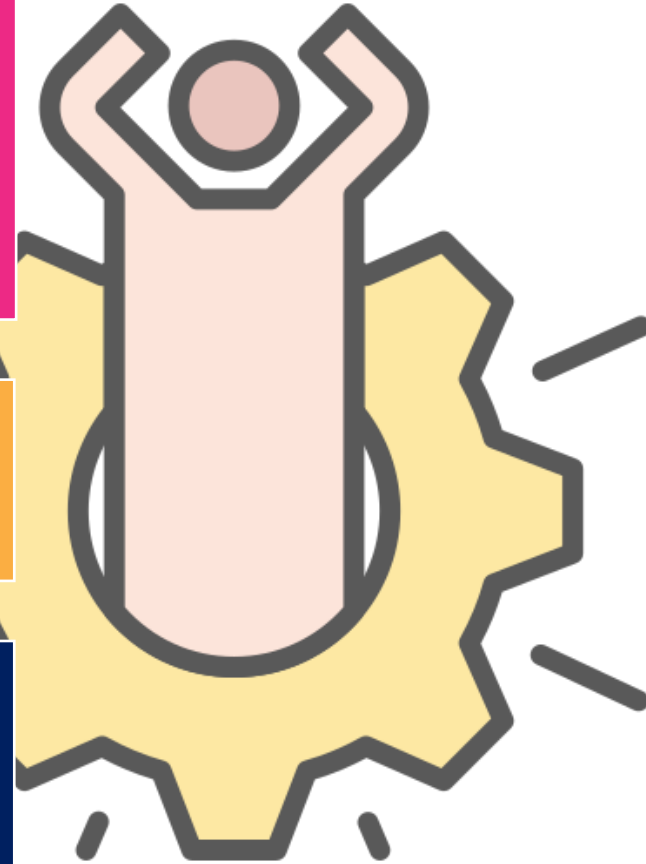


Coaching by former MHRA Lead Inspectors

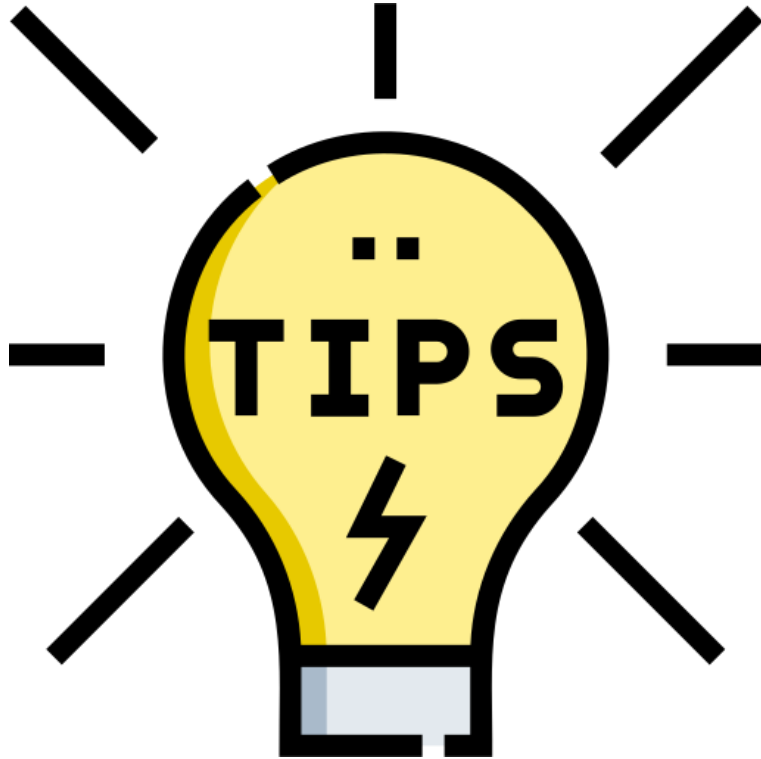


Interview Preparation

- Mock interviews, incl. individuals' interviews by former MHRA Lead Inspectors
- Role-playing scenarios (typically between functional leads)
- Mock live-demos



Personnel Training



Quick Tips: Preparing Interviews

Prepare your 1 mn bio, including:

- your role in the inspection team
- And that you are trained on GCP practices.

It is appropriate to seek clarification to accurately define the scope of the question. Better to ask than assume wrongly.

Anticipate FAQs and appropriate responses, e.g.

- *"Can you describe how ..." and then "Can you show me the evidence?"*
- *"Are you aware of any discrepancies between the documented procedures and the practices employed on the projects within the scope of this inspection?"*
- *"Would you like to add anything?"*

Preparation of Supportive Documents

Live Demos



Preparation phase

- **Coaching program**
- **Dedicated and Restricted area within our SCE:**
 - The study materials from the inspected studies are copied, enabling the on-the-fly recreation of any necessary output (SDTM, ADaM, TLFs).
- **Mock demos**
- **Opportunity for introspection**
 - e.g. Risks at the intersections of multiple functions.

Inspection phase

- **Perfect understanding and Detailed exploration**
 - Inspectors visualize and understand our processes perfectly.
 - They delve into the intricate details of our practices.
- **Open dialogue**
 - very engaging interactions
 - Inspectors quickly formulate relevant questions, leading to dynamic and insightful discussions.
- **Strategy to Limit Number of Speakers**
 - No disconnect between task performers and process experts.
 - To be acknowledged: Increased pressure on demonstrators.

Post-Inspection Activities

Innovative solutions for ongoing enhancement

- Following the main inspection, the **MHRA inspector's report**, issued 25 days later, formally kicks off the **CAPA** preparation process.
- Beyond the inspection process, **Continuous quality enhancement** involves gap analysis, internal audits, expert consultations, and cross-functional dialogues.
- Focus on **streamlining processes rather than adding steps**, to prevent complexity and non-compliance.
 - As an example, implementation of tools like checksum algorithms for data integrity, replacing manual steps and reducing errors, enhancing effectiveness and compliance.



04

Conclusions



Conclusions

- **Insightful engagement**
 - Inspectors analyze far beyond surface-level documents.
- **CROs: Risk alerts!**
 - Holistic perspective is essential: excuses like '*the client didn't inform us*' are unacceptable.
 - Gaps in infrastructure or sole reliance on external QA contractors would jeopardizes inspection success... and ultimately the sponsors interests!

Solid infrastructure and strategies are required to decrease unpredictability during inspections and increase the chance of success.

Oh! By the way, don't forget to **pay the fees** for your inspection!
Cf. <https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees>



Thank you!

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Back-up slides

PHUSE EU Connect conference – Strasbourg (France) 10-13 NOV 2024

MHRA Guidances and Templates

The MHRA publishes guidance documents and templates to help the inspected organizations to understand and comply with the regulatory requirements.

- **MHRA Guidance 'Good clinical practice for clinical trials'** (22JUL2024), how to show MHRA you're meeting good clinical practice (GCP) standards and what to expect from an inspection.
 - <https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials>
- MHRA "GXP' Data Integrity Guidance and Definitions'
 - [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA GxP data integrity guide March edited Final.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf)
- MHRA Guidance on responding to a GMP/GDP post inspection letter
 - <https://www.gov.uk/guidance/guidance-on-responding-to-a-gmpgdp-post-inspection-letter>
- When the MHRA notifies an organization of an upcoming inspection, it also requests specific information which must be provided in the form of a GCP inspection dossier and a clinical trials spreadsheet, which need to be submitted within 30 days. The MHRA provides templates for these documents, including a dossier checklist. These **templates are available on the MHRA website**:
 - [GCP inspection dossier template](#) (MS Word Document, 147 KB)
 - [GCP inspection dossier clinical trial spreadsheet](#) (MS Excel Spreadsheet, 83.9 KB)
 - Check List [GCP inspection dossier checklist](#) (MS Word Document, 182 KB)
- Other resources, like the **MHRA Inspectorate Blog**
 - This blog shares the work of the MHRA Inspectorate, by inspectors and those the Inspectorate works with: <https://mhrainspectorate.blog.gov.uk/>



Regulatory Framework

Regulation 31A: TMF requirements

- To be noted, the ‘Regulations’ are specifying notably the Trial Master File (TMF) Requirements:
- regulation 31A of the principal Regulations: the Trial Master File (TMF) must be readily available at all time and accessible for inspection. The TMF must be complete and form the basis for verifying compliance with the regulations.
- Source: <https://www.legislation.gov.uk/uksi/2006/1928/regulation/18/made#:~:text=31A.,the%20arrangements%20for%20the%20trial.>

The screenshot displays the UK Legislation website interface. At the top, the Royal Coat of Arms and the URL 'legislation.gov.uk' are visible. Navigation links include 'Home', 'Explore our Collections', 'New Legislation', 'Help and Guidance', and 'Changes to Legislation'. A search bar is present with fields for Title, Year, Number, and Type, and a dropdown menu set to 'All UK Legislation (excluding originating from the EU)'. The main content area is titled 'The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006' and 'UK Statutory Instruments > 2006 No. 1928 > Regulation 18'. The 'Content' tab is selected, showing a table of contents and navigation buttons. The 'What Version' section shows 'Original (As made)' as the selected version. The 'Status' box indicates this is the original version. The main text of Regulation 18 is displayed, with Regulation 31A highlighted in a pink box. Regulation 31A states: (1) The sponsor shall keep a trial master file for a clinical trial. (2) The sponsor shall ensure that the trial master file is readily available at all reasonable times for inspection by the licensing authority or any person appointed by the sponsor to audit the arrangements for the trial. (3) The master file shall at all times contain the essential documents relating to that clinical trial. (4) The essential documents relating to a clinical trial are those which— (a) enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and

MHRA Guidances and Templates

Useful information are available from the MHRA inspectorate website. Screenshot below shows information relative to dos and don'ts when hosting a GCP inspection. Please note *'Inspectors like to drink lots of tea'*



GCP Inspections: Expectations and the dos and don'ts for hosting

[Hayley Dixey](#), 10 March 2020 - [Compliance matters](#), [Good clinical practice](#)

DO: contact the Lead Inspector if you have any questions or concerns once you have received the report.

DO: ensure CAPA provided is proportionate, measurable, timely, fixes the root cause and is followed-up through implementation with effectiveness checks.

DON'T: provide non-committal responses and CAPA, 'the sponsor will consider...', 'this is acknowledged'. As these types of responses and CAPA are likely to not be accepted by the Lead Inspector and therefore closure of the inspection will take longer. If the organisation continually provide unacceptable CAPA further action may be taken and the inspection statement will be issued reflecting this.

DO: the responses should be clearly set-out and should state what the found root cause is for each finding.

A few final points to consider;

- MHRA GCP Inspectors like to drink lots of tea. 
- Please don't accompany us to the toilets, since I started as an Inspector, I have never understood why companies do this, we have better things to do on Inspection than to start wandering around aimlessly.
- If you think the Inspection would be better to be conducted outside of the UK contact the Lead Inspector about locations. It may be more cost effective for inspectors to travel to your HQ, rather than having a large number of your staff travel to the UK.
- Be transparent, if you know of problems it is best to let us know up front and present your CAPA plan rather than waiting for us to find the issues (or

MHRA Statutory GCP Inspection Process

Typical agenda of a Main Inspection

At Cytel, inspectors held 13 meetings within 4 days, typically lasting around two hours each, with the QA team and relevant stakeholders; a total of 63 requests were made across 24 different areas of inquiry, reflecting the depth of their evaluation.

Day x:

1. **Opening Meeting**
2. **Document Review and Interviews**
 - Interview sessions:
 - formal interviews to cover systems
 - The MHRA are likely to use study-specific examples to demonstrate the system
 - 'Show and Tell' sessions
 - ad hoc question sessions to clarify questions and queries as they arise from the document requests
 - Document Review sessions, e.g.
 - Trial Documentation
 - SOPs
 - Training files
3. **Reconciliation call**
 - The MHRA will provide feedback of general findings at a closing meeting and notify of any update in the agenda of the upcoming day.



MHRA Statutory GCP Inspection Process

Post-Inspection Activities

The full inspection report will be provided by the Lead Inspector within approximately 25 working days of the last date of the inspection. If there are any delays in providing the report the Lead inspector will let the organization know.

- The organization (CRO) then has 25 working days to provide a **written response and a Corrective and Preventive Actions (CAPA)** to all findings, this includes:
 - Confirming if the findings are accepted (!)
 - Assessing **risks and impacts**
 - Undertaking a **root cause analysis**
 - Develop and document a CAPA plan
 - **Corrective actions**
 - E.g., Creation of a new tool with targeted date of implementation in production.
 - **Preventative actions**
- The inspectors will review the responses provided and may request additional clarifications.
- Only after the organization and the Lead Inspector have agreed upon the CAPA can an inspection statement be issued to the organization, and the inspection will be closed by the Inspectorate.



Logistics

Physical organization of the inspection sessions (18-21 Sept. 2023)

As a global organization, Cytel sought to centralize part of its Core Inspection Team at a single location in the EU. This approach was intended to effectively prevent technical risks for remote/overseas key team members, optimize time zone coordination, enhance real-time responsiveness, and encourage direct engagement among team members overall. NB: Cytel anticipated managing to conduct parallel sessions in line with the Inspection Plan.

