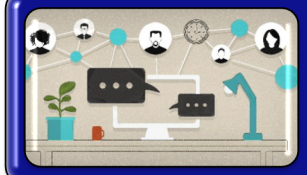
MHRA regulatory update for Non-commercial Sponsors

Jennifer Martin, GCP Operations Manager & Lead Senior GCP Inspector

Medicines & Healthcare products Regulatory Agency

Overview

EU Transition – clinical trials



Remote Inspections

Sponsor oversight during COVID-19

Other Activites

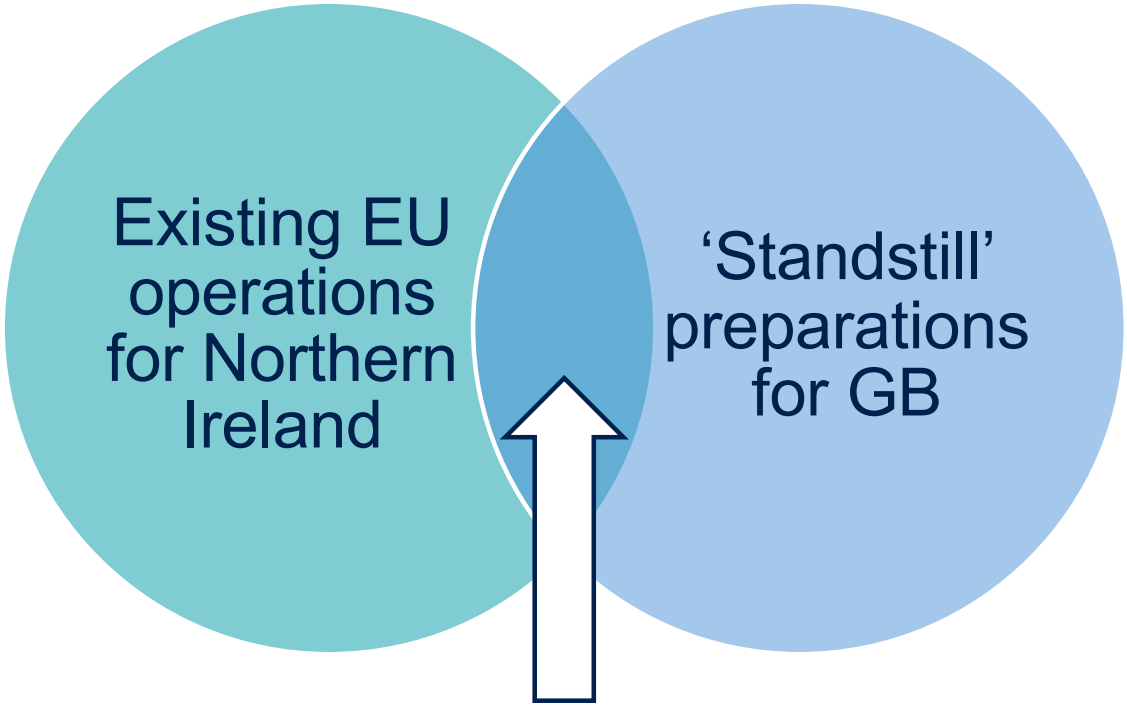
EU Transition – clinical trials

From 1 January 2021, the MHRA will be the UK's standalone medicines and medical devices regulator.

- UK will offer fully independent regulatory decisions for both devices and pharmaceuticals (nationally and jointly with other international regulators)
- Guidance now published which will apply following the end of the transition period.

The Northern Ireland Protocol (NIP) was signed by the EU and UK as part of the Brexit Withdrawal Agreement to avoid a hard border on the island of Ireland in the event of a no-deal Brexit.

MHRA approach for 1 January 2021



Post-Transition 2021 guidance

Clinical Trials

MHRA CTU will assess/authorise CTA applications for UK (NI and GB)

Sponsor / Legal Representative

- The sponsor or legal representative of a clinical trial must be in UK or a country on an approved country list which would initially include EU/EEA countries
- A sponsor established in UK and conducting a clinical trial in the EU must ensure that a sponsor or a legal representative is established in the EU

Submitting a CTA application to MHRA

- Preparation of a CTA application will be via IRAS (as is currently possible)
- Submission of a CTA application will be via the new MHRA Submissions system

Safety reports

- Submissions for safety reports will also be via MHRA Submissions and relevant portal

Clinical Trials

Trial registration, transparency and reporting of results

- Sponsors should continue to use existing and established international registers, so the public is aware of the trial and results

Registration

- The HRA has made a commitment, in the long term, to register clinical trials on behalf of sponsors and researchers
- Until the HRA system is place, from 1 January 2021 sponsors will need to register UK trials on an established international register (e.g. ISRCTN registry, or ClinicalTrials.gov)

Summary results

- Post transition, results from ongoing trials can continue to be submitted to EudraCT
- For new trials, results should be published in the public register where the study is registered

Clinical Trials

Manufacture and supply of Investigational Medicinal Product

- No changes to manufacturing authorisation requirements for manufacture / packaging of IMPs in UK or import from third (non-listed) countries (QPs etc)
- IMPs may be supplied direct to CT sites in GB, if QP certified in a listed country
  - UK MIA(IMP) oversight of supply chain; 12 month period to implement
  - No UK re-certification required
  - QP may be resident in UK or a listed country (for oversight of supply chain only)
- Importing QP certified NIMPs or unmodified comparators from ‘listed countries’
  - Wholesale dealer licence required
  - Existing WDA(H) holders: 6 month period for notification; 2 year period to name Responsible Person (Import)
  - New WDA(H) applicants after 1 January 21: RPI required at time of application

Clinical Trials

GCP Challenges

- UK CT Legislation based on EU Directives, CT guidance in Volume 10 EudraLex
- UK Exit SI removes references to EU Directives and makes provisions for the UK to publish guidance
- EU guidance is still helpful as our legislation is based on the EU Directives. Therefore it is our expectation that they are followed as this is our interpretation as to *how* the legislative requirements can be met (and this will help in terms of harmonisation and running global trials).
- However, we will be changing our legislation next year, so new guidance also needs to align with that too
- No impact of EU Exit or NIP on GCP Inspections (GB and NI)

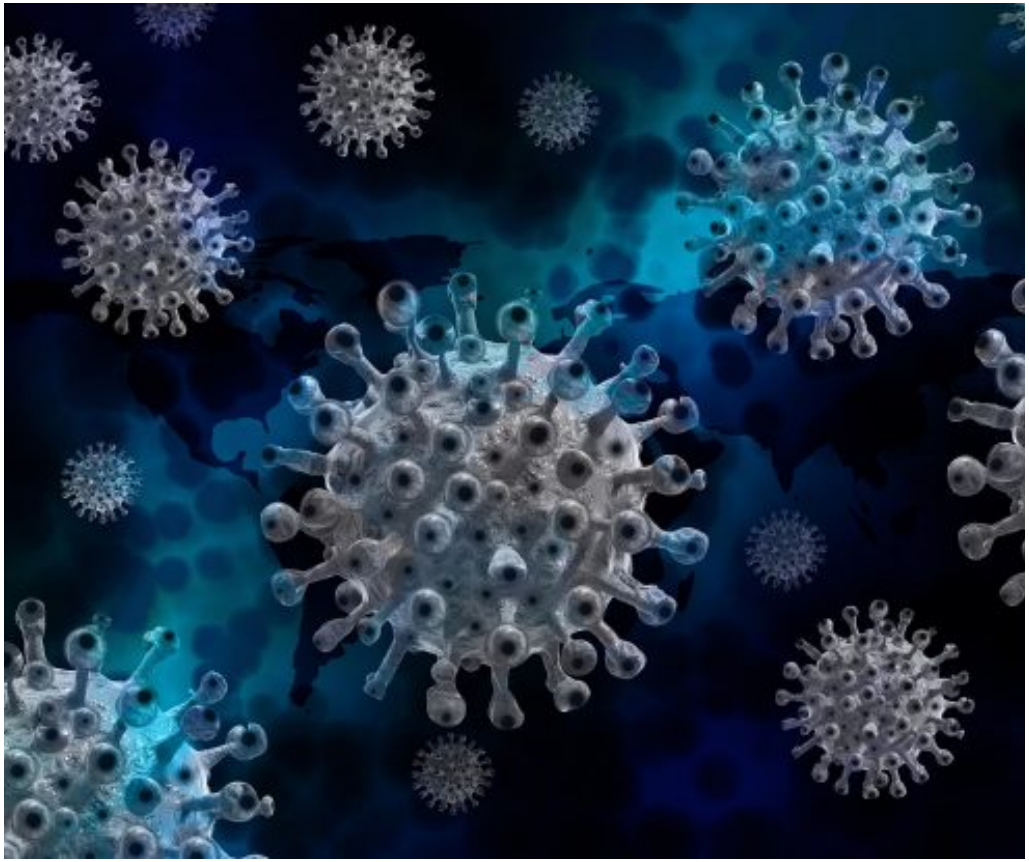
Remote Inspections (key hot spots/logistics)

Why Office-based Inspections?

- GCP inspections ‘Day 1’ office-based assessments for years
- Office based assessments for IAG cases

- Pandemic halted routine on-site inspections
- Transformation of inspection model
- High-risk or COVID-19 support inspections prioritized

https://www.gov.uk/guidance/guidance-for-industry-on-mhras-expectations-for-return-to-uk-on-site-inspections



Risk-Based Approach

Continued

- Prioritised inspections for Critical finding follow-up, licensing need or COVID-19 support
- Refined inspection scope to ensure risk-based need met:
  - Cross-divisional support from CTU and Licensing

Paused

- Overseas inspections halted
- NHS-sites were not inspected unless critical, to enable essential COVID-19 work to continue
- Routine investigator sites were stopped; but now being incorporated into remote working

What Have We Been Doing?

- Routine GxP inspections moved completely remote:
  - Q1/2 remote model refined, defined, quality system'd!

- Only triggered/ critical on-site inspections
- Pragmatic approach implemented, reducing burden wherever possible
- Accommodation of 'inspectees' working remotely as well as inspectors!

Some inspection elements considered impossible remotely, however challenging that moving forwards…

- One remote BE inspection trialled in October

Approaches used in GCP Inspections

Common logistical approaches used

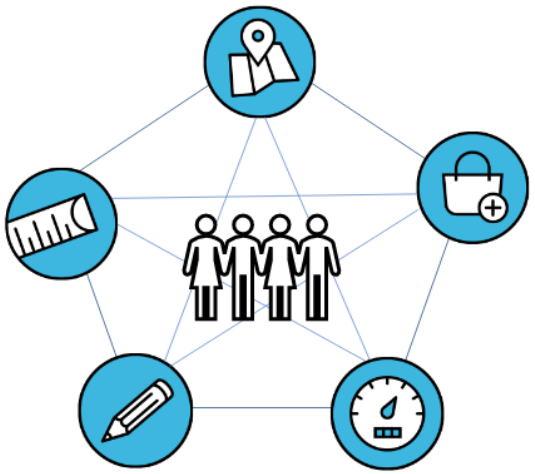
Prior to the inspection:

- Organisations notified as normal (unless triggered short-notice)
- Modified GCP Dossiers were requested initially ensuring needs of inspection scope & practicalities
- An email is sent to the inspection site to explain the virtual inspection process.
- A second meeting is held to discuss the logistics of the upcoming inspection.
- Additional meetings for training on different electronic systems used by the site.

Approaches used GCP Inspections

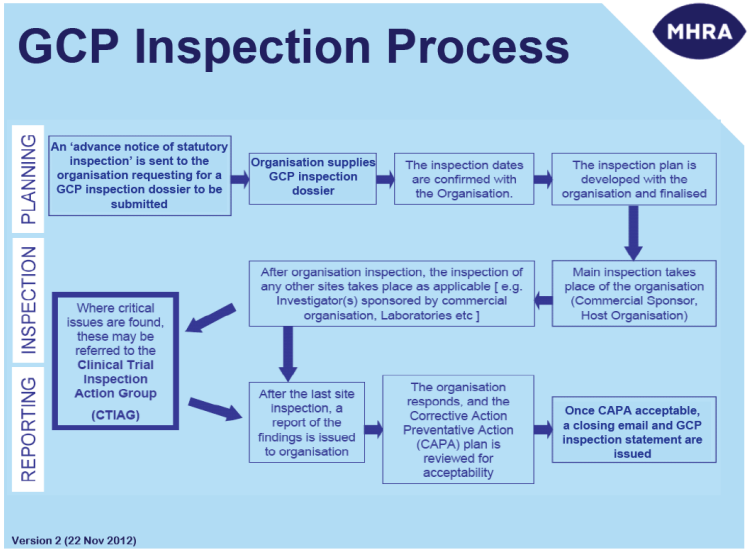
Common approaches used

- Tele/Video conference for opening and closing meetings, as well as interviews and demonstrations via screen share.
- Documents requested & reviewed as normal
- Use of file sharing platforms (e.g. Teams, SharePoint)
- Email
- Livestreaming of documents
- Access to electronic systems remotely such as eTMF, eCRF via internet (unless eTMF not available - for critical inspections substantial document requests



Differences between traditional & remote inspections

Inspection process (traditional)



file:///C:/Users/martinj/OneDrive%20-%20MHRA/Regs%20&%20Guidance/GCP-flowchart.pdf

Activity	Traditional	Remote
Dossier request	Approx. 3 months in advance (unless triggered)	No change
Inspection planning	4-8 weeks in advance	No change
Main inspection	1 pre-inspection day week before on-site (if required) then consecutive on-site inspection over X no. days	planned over a couple of weeks (giving time for request/receipt of documents & staff availability
Investigator site (IS) inspection	6 weeks after main sponsor inspection	originally no IS inspection, now remote if possible ~6 weeks after main sponsor inspection
Report	25 working days	No change
Responses	25 working days	No change
Closure	acceptance of responses	No change

Remote Inspections: Logistical challenges

- Resource availability / staff support.
- Sites conducting COVID-19-related studies – disruption to key work.
- Inspections take longer.
- Delays in receipt of requested documents.
- Inability to ask impromptu real-time questions to subject matter experts.
- Inability to see facial expressions and body language.
- Inability to assess the state of premises, equipment and utilities.
- Rapport building: lack of personal interaction doesn't foster development of trust between the regulator and company or allow sharing of best practise.
- Ensuring clarity of emails.
- Access to all electronic systems (management of accounts/permissions/passwords, training).
- Hybrid Systems.

Remote Inspections: Technological challenges

- Web-based/digital interactions can have connection issues/black spots (an inspection cancelled due to this).
- Remote interactions and document sharing impacted by site's technological capabilities.
- Not all inspections conducted using same file transfer systems.
- Permitted portals/transfer systems.
- Data privacy considerations & undisclosed recordings.
- Audio troubles frequently occurred.
- The size of the electronic files shared and the time/ability to download the file.
- Scheduling can sometimes be an issue as not all sponsors are capable of participating in a virtual inspection as they are not always fully electronic (eTMF, eCRF, etc).

GCP Specific Challenges

- Complexity of the study protocol
- The availability of study data
- The TMF may be electronic, but often other documents are filed elsewhere such as contracts, regulatory, safety – it's difficult to ascertain if we have been given access to everything when we are remote.
- Inspection of Investigator sites
- Access to paper based medical records

Hybrid Inspections & the Future

- For the foreseeable…MHRA operating ‘Critical’ and ‘Covid-19 support’ required inspections on-site only
- Hybrid approaches will continue to be used in the future
- Continued development of remote approaches

Sponsor oversight during COVID-19

At start guidance was issued on clinical trial during the COVID pandemic:

MHRA:

https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19

Specifically for clinical trials:

https://www.gov.uk/guidance/clinical-trials-applications-for-coronavirus-covid-19
https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19
https://www.gov.uk/guidance/approval-of-gxp-documents-when-working-from-home-during-the-coronavirus-covid-19-outbreak
https://mhrainspectorate.blog.gov.uk/2020/03/12/advice-for-management-of-clinical-trials-in-relation-to-coronavirus/

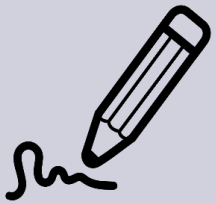
HRA:

https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/covid-19-guidance-sponsors-sites-and-researchers/

NIHR

https://www.nihr.ac.uk/covid-19/
https://www.nihr.ac.uk/researchers/collaborations-services-and-support-for-your-research/run-your-study/government-support-for-research-related-to-covid-19.htmRA

Challenges with Home working

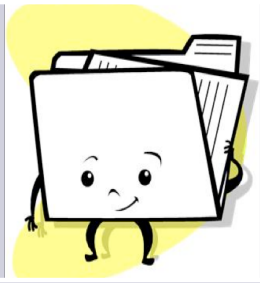


Approvals of clinical trial documents

- MHRA guidance on approving GxP documents when working from home

Home set-up Do you have the?

- space
- privacy
- tech



Paper TMF

- Can you access it?
- What's happened to it during the pandemic?
- How much of it is there?
- Supporting docs?

Small person invasion (for some)

- explain up-front
- mute / switch off video
- All impacted

Other Activities Ongoing at MHRA

- Joint EHR access for monitors position statement published with HRA (& input from ICO)
  https://www.gov.uk/guidance/on-site-access-to-electronic-health-records-by-sponsor-representatives-in-clinical-trials
- Joint site types guidance with HRA (including home care nursing & vaccine trials
- Working with stakeholders on the EHRs guidance
- Innovative Licensing & Access Pathway
- ICMRA Digital Transformation
- Input into update of ICH GCP E6
- Building resilience into clinical trials
  https://www.gov.uk/guidance/guidance-on-minimising-disruptions-to-the-conduct-and-integrity-of-clinical-trials-of-medicines-during-covid-19

© Crown Copyright 2020