Session 2: Clinical Trials Post-Pandemic – Positive Disruption to Established Ways of Working?

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Post-Pandemic - Positive Disruption to Established Ways of Working?

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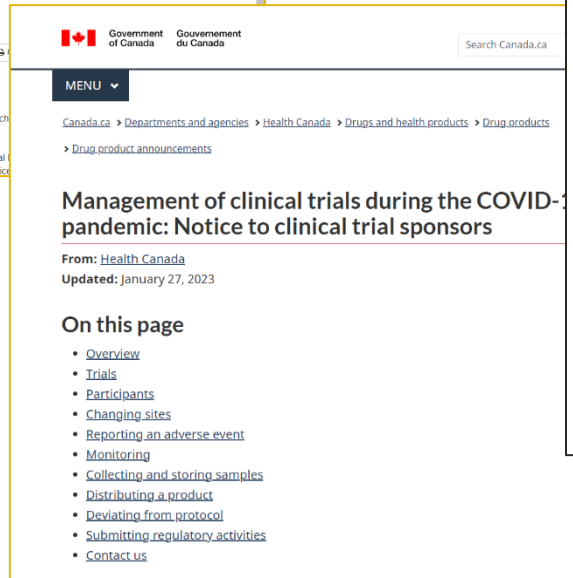
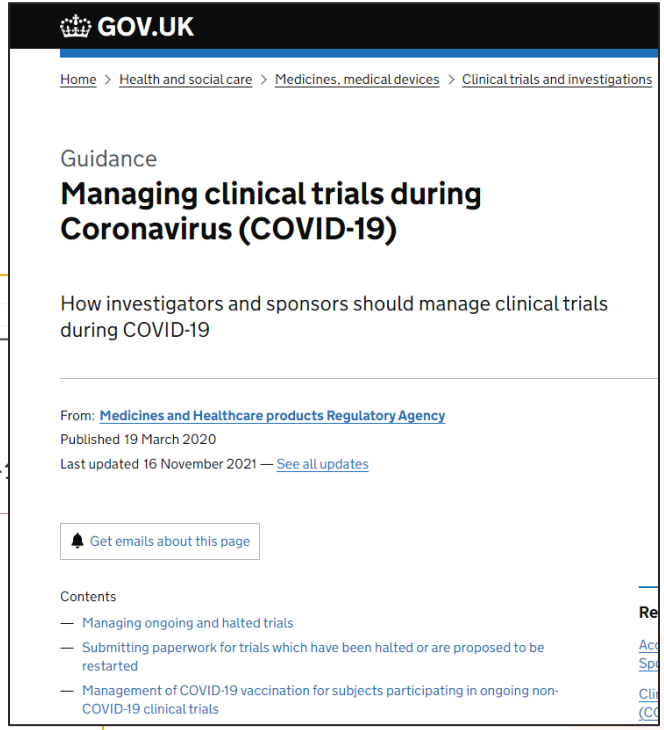
Overview

- Pandemic ‘regulatory flexes’
- Forced changes to ways of working
- Pre-pandemic activities

Pandemic Guidance





Examples of Regulatory Flexes

- Trial adaptations:
  - Changes to visit schedule
  - Use of remote visits
  - Informed consent
  - Delivery of IMP to participant's home
- Remote monitoring
- SAE reporting changes
- 'Acknowledgement' of protocol deviations

Prior Enablers (UK)

- Existing broad legislative requirements
- Previous pandemic legislation (limited)
- Technology changes industry wide:
  - eSystems
  - Remote access technologies
  - eConsent

But what did the Pandemic do for us?

- Required targeted trials
- Required prioritisation of trials
- Required risk adaption
- Required adoption of new ways of working
- Required continued evolution
- Stress tested some trial components!

What did the Pandemic do for us?

- Increased public/staff awareness of clinical trials
- Forced widespread implementation of ways of working which had previously been ’under consideration’
- Change of Regulator/Applicant relationship

Post-Pandemic?

- Tightening back up of Covid-19 flexibilities
- Continuation and expansion of ways of working
  - Decentralised and virtual trials
  - Innovative trial designs
  - Remote monitoring

Post-Pandemic (2)

- New approaches to Applicant/Regulator ways of working e.g. rolling review
- What else can we do?
- How else can we run this trial?

ICH E6 R3

- Update to modernise the guidance
  - New trial designs
  - Technological innovations
  - Proportionate risk based approach
  - Risk mitigation
- Includes pandemic learning/experience

Summary

- Many processes and approaches already existed
- The pandemic forced further evolution of trial processes and designs
- Risk based trial design and conduct needs further expansion

Resources

- https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19
- https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/management-clinical-trials-during-covid-19-pandemic.html
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency
- https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/hra-mhra-econsent-statement-sept-18.pdf
- https://www.gov.uk/guidance/on-site-access-to-electronic-health-records-by-sponsor-representatives-in-clinical-trials

Closing Thought

We all should ensure that we have learnt from our Covid-19 clinical trial experiences, evolving our practices and conduct, by the development of innovative, effective and risk proportionate clinical trials

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Clinical Trials Post-Pandemic – Positive Disruption to Established Ways of Working?

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U.S. FOOD & DRUG ADMINISTRATION

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Overview

- Inspection Changes During Pandemic
- Introducing Compliance Readiness Inspections (CRIs)
- Inspection Changes Post Pandemic
- Case Studies of CRIs

Clinical Trial Compliance Program (CTCP)

- Mandate: promote and verify compliance of drug clinical trials against *Food and Drugs Act* and associated Regulations
- How?
  -Inspections,
  -Guidance Development,
  -Compliance Promotion, etc.

Inspection Changes During Pandemic

- On-site inspections halted
- Need to ensure regulated party's compliance
- Switched methodology to remote and hybrid inspections
- New stakeholders conducting clinical trials
- New temporary regulatory measures developed
- Remote Compliance Readiness Inspections start

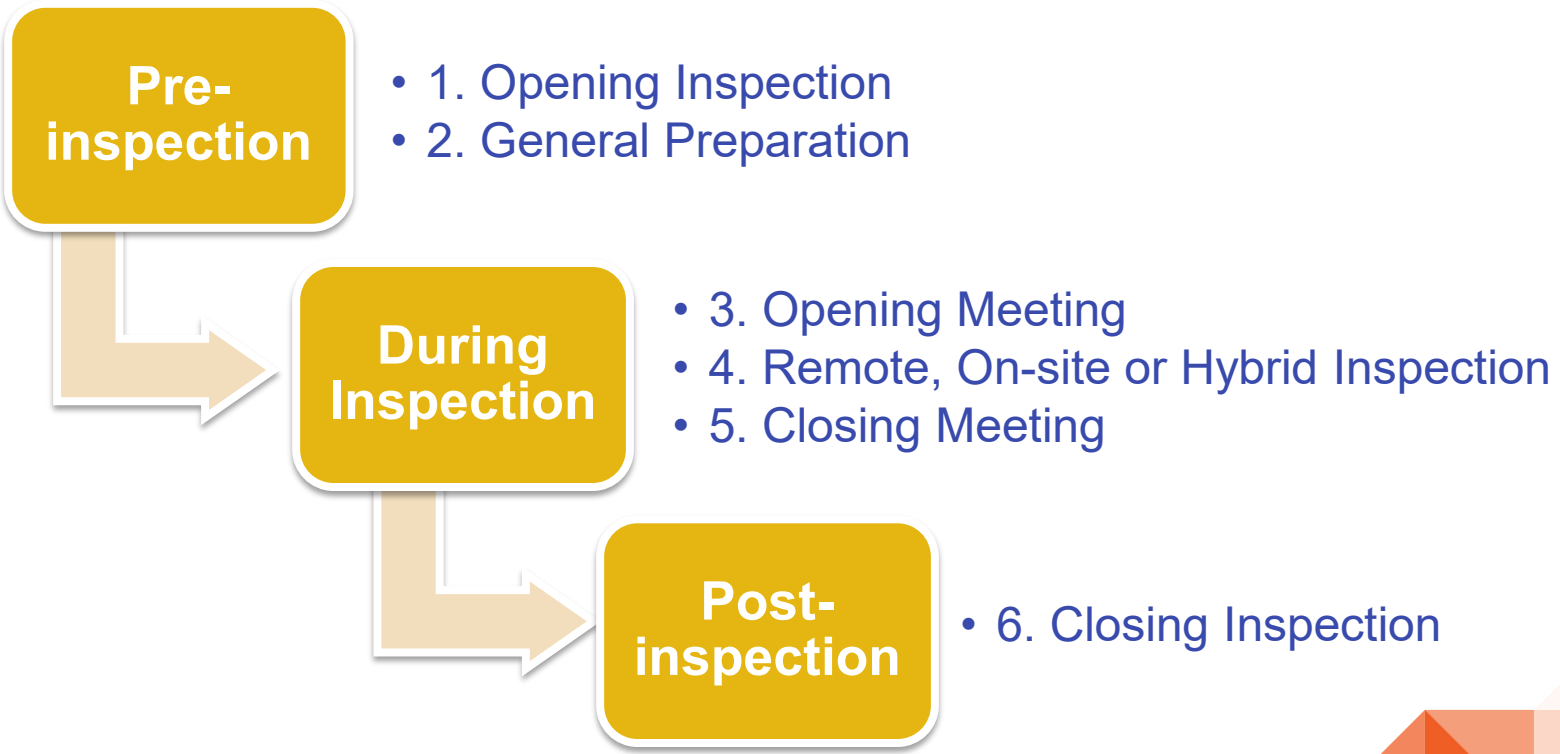
Compliance Readiness Inspection (CRI)

- New inspection developed during pandemic
- Conduct prior to participant enrollment
- Purpose: Verify site/organization readiness to enroll/dose participants
- Goal: Reduce clinical trial non-compliances

Methodology for CRIs

- Focus on compliance readiness targeting human drug trials (Canada)
- Conduct remotely (on-site or hybrid option)
- Regulated party(ies) inspected: Sponsor, CRO and/or QI (if Sponsor-QI)
- Document review: 2-3 days with 1-2 inspectors

Stages of CRIs



CRI Process: Pre-Inspection

- Inspector selects regulated party/study to inspect from risk-based list of recommended studies
- Inspector contacts inspected party
- Inspector sends notification letter and CRI checklist
- Inspector obtains study information from Health Canada records
- Inspector prepares inspection plan and presentation

Inspection Plan/Checklist for CRI

- Status of clinical trial (dates, sites, participants)
- Organizational charts
- Clinical trial related procedures and plans
- Protocol, Informed Consent Form, Investigator's Brochure
- Training records
- Contracts/agreements
- Investigational product label
- Electronic systems

CRI Process: During Inspection

- Opening meeting with introductions and Inspector requests
- Inspector reviews clinical trial documents, conducts interviews and additional requests
- Closing meeting with Inspector's verbal inspection findings summary
  (no compliance/risk rating, no written inspection report and no CAPA required)

CRI Process: Post-Inspection

- Inspector sends inspected party closing letter
- Inspector completes inspection summary and saves relevant documents
- No inspection report issued
- No posting on Health Canada website
- For significant findings noted, recommend regular inspection

Summary of CRIs

- Ensure regulated party better prepared to meet ICH GCP and Canadian regulatory requirements
- Goal: reduce likelihood of non-compliances
- Expanded post pandemic to other areas:
  → emerging with non-compliance
  → new sponsors and qualified investigators

Inspection Changes Post-Pandemic

- On-site, remote and hybrid inspections
- Continue (and expand areas) for new inspection options
- Canadian Regulations provide alternate optional pathway for conducting clinical trials
- Compliance Readiness Inspections continue

Case Studies

Case Study A

- Sponsor new to clinical trials and not previously inspected by Health Canada
- COVID-related clinical trial
- CRI conducted remotely during pandemic
- Regular sponsor inspection conducted on-site post-pandemic

Case Study A

CRI Findings:

- SOPs, Plans and other documents mostly in place
- Miscellaneous issues with procedures (version control, approvals, missing elements such as remote monitoring)
- Document quality issues (drug accountability, delegation log, training record)
- No study team training on Canadian Regulations related to Interim Order and Pharmacy Manual

Case Study A

Sponsor Inspection:

- CRO involved remotely
- Observations (deficiencies related to):
  - Documents and safety data reviews
  - Clinical trial plans (monitoring, safety management) and associated documentation
  - Electronic system access, traceability
  - Training and associated records
- No critical observations

Case Study B

- Sponsor-QI new to clinical trials and not previously inspected by Health Canada
- COVID-related clinical trial
- No CRI conducted
- Referred to CTCP for compliance verification

Case Study B

- Sponsor clinical trial issues:
  - Implementation of protocol amendments without HC approval
  - Submissions/notifications to HC not within regulatory timelines
  - Multiple other deficiencies from Canadian (Clinical Trial) Regulations
    (systems and procedures, delegation/training, informed consent, protocol adherence, monitoring, investigator oversight, records management, etc.)
- Sponsor may have benefitted from CRI

Case Study C

- Sponsor-QI new to clinical trials and not previously inspected by Health Canada
- Non-COVID clinical trial
- CRI conducted remotely post-pandemic

Case Study C

CRI Findings:

- Several documents (SOPs, Plans) not yet finalized or approved, missing aspects
- Not all personnel selected/delegated/under contract
- No ICH GCP or Canadian (Clinical Trial) Regulations training
- Study drug documents with unclear/wrong/missing info
- Recommendation for future inspection

Case Study Take Aways

- CRIs are finding non-compliances
- Learning experience for regulated party and identifying improvements to make
- Lack of regulatory knowledge and clinical trial preparation
  → increased number and risk level of inspection findings and non-compliance
  → risk to participant safety and data integrity

Overall Summary

- More flexible inspection strategy for HC's CTCP:
  → remote and hybrid inspections now also conducted
  → CRI flexible option in regulator's compliance toolbox
- Electronic documentation and systems more commonplace
  → easier, faster and more efficient communication, document sharing, record retention, etc.

Questions?

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Overview

- Innovations to assessments of clinical trials during the pandemic
- A field investigator's ground level observations of the result of post-pandemic clinical research.
  - Applies across sponsor, clinical investigator, and clinical bioequivalence inspections.
- Modern approach of FDA

Disclaimer

- The information provided in this presentation is reflective of the personal experiences and opinions of the presenter and is not the official perspective of FDA

Remote Regulatory Assessments

Remote Regulatory Assessments

- On-site inspections not feasible during the pandemic
- Provided a way to conduct targeted review of critical information

Remote Regulatory Assessments

- FDA had to develop policies and procedures in real time
- Bioresearch Monitoring had different needs than other areas
- Used by CDER & ORA
- Continuing to evolve in scope and functionality

Investigator Perspective

Pre-Pandemic Inspections

- Typically highly centralized
- Data usually created/kept at investigator site
- Subjects typically seen exclusively at study site

Post-Pandemic Inspections

- Increase in decentralization of clinical trials
  - Remote informed consent
  - Remote telehealth visits
  - Home healthcare evaluations
  - Numerous vendors responsible for data evaluation

Post-Pandemic Inspections

- Increased digital health technology monitoring
  - Electronic Patient Reported Outcomes
  - Standalone devices for recording subject source data

Summary

- Decentralization of clinical trials is here to stay
- Remote Regulatory Assessments are a new tool in the assessment arena & continue to evolve
- Careful planning is needed to conduct efficient inspections of clinical sites

Closing Thought

The pandemic presented numerous challenges, but as long as we keep subject safety and rights at the forefront, innovation can only improve the output of clinical research as long as regulatory review practices adapt accordingly

Questions?

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Resources

- FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency
- Draft Guidance: Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities
- Draft Guidance: Decentralized Clinical Trials for Drugs, Biological Products, and Devices