Revision of the Clinical Trials Regulation and Transparency
Revision of the CT Directive

• Draft Regulation published in July 2012
• Submitted to the European Parliament and Council
• Parliament’s rapporteur (MEP Glenis Willmott) discussed with political groups—proposed amendments agreed by Parliament May 2013.
• In parallel the Council Working Group (Pharmaceuticals and Medical Devices) discussing and proposing changes to the draft Regulation.
  – MHRA represented by Martyn Ward and Sandor Beukers
  – Aim to reach agreement by end of October
UK Approach

- UK Government position agreed across Government (through European Affairs Committee and Devolved Administrations)
- Stakeholder engagement:
  - Public consultation
  - Stakeholder Reference Group
- Governance of the negotiation: Clinical Trials Steering Group (MHRA, DH, BIS, Devolved nations)
- Day-to-day business: close collaboration Policy, Licensing, IE&S and HRA
Next Steps

• Following agreement in Council, Trialogues (Commission, Parliament and Council) begin to negotiate the final text of the Regulation.
• Co-decision hoped for before European elections in May 2014.
• If the negotiations are finalised in 2014, the legislation will apply from 2016 (2 years after publication)
Main Discussion Points

- Authorisation Process (portal functionality, opt-out)
- Reference to Ethics Committees
- Timelines
- National Indemnity Scheme
- Transparency
- Proportionate approach (low interventional trials)
- Emergency Clinical Trials – consent
- Commission inspection powers
Transparency

• Key aspect of the proposed Regulation – strongly supported by Parliament (who also propose a lay summary and that CSRs published within a month of the regulatory decision)

• Media attention – AllTrials, Ben Goldacre

• The Science and Technology Committee has published its report (17 September 2013) and has a number of recommendations for greater transparency in the area of clinical trials

• The European Medicines Agency (EMA) has consulted on a proposed policy for publication and access to clinical trial data (to apply from 1 January 2014).

• HRA have stipulated that favorable opinion will be conditional on clinical trials being registered on a publically accessible database (from 30 September 2013)
Key Issues

• There is a significant amount of data held by competent authorities and the EMA in relation to clinical trials (some of which will be duplicated).

• Who would be responsible for release? Sponsor/applicant, EMA, MHRA?

• What and when to release – summaries/CSRs/patient-level data

• When – post marketing approval, post trial?

• Patient confidentiality issues – would patient listings allow the identity of a patient to be determined?

• Commercial confidentiality
MHRA Activities

- Cross-Agency Transparency Working Group has been established to:
  - take stock of the current position in relation to information the Agency receives;
  - form a position in line with DH and wider Government objectives on future and retrospective release of information; and
  - contribute to a work programme feeding into the development of the EMA’s policy of transparency.
QUESTIONS
Voluntary Phase I Accreditation Scheme Update

(Jennifer Martin, 25 October 2013)
Phase I Accreditation Scheme

Background

• One of the Expert Scientific Group on Phase I Clinical trials recommendations as a result of the TGN1412 incident in March 2006
• Implemented in April 2008
• Voluntary scheme
• Gave MHRA; RECs; Sponsors assurance that units exceeded basic regulatory requirements, thereby making significant contributions to enhancing the safety of volunteers
• Two types (standard and supplementary accreditation)
Scheme Changes agreed via Phase I Stakeholder Group:

- Single classification
- Expanded to include units that function differently to traditional commercial units (non-commerical)
  - Use of a Phase I review committee where PI may not meet the requirements of the scheme
- Expand to encompass more types of phase I trials run in accredited units
  - First time in patient trials and patient volunteers included
- Expand to encompass need for
  - Quality systems
  - Robust resourcing and training of staff
Phase I Accreditation Scheme

Guidance
• Updated to expand on expectation surrounding the scheme requirements

Launch of updated scheme and guidance
• 31 October 13

Future
• Investigating possibility of accredited units being granted authorisation to use of MHRA logo with specific wording as a mechanism for easy identification of accredited units
• Review of certification time in line with the RBI for risk based scheduling
Questions
MHRA Inspections using E-TMF

MHRA Stakeholder Engagement Meeting: 25 Oct 2013
Need to know

- Given the drive for global companies to have a global eTMF what is it reasonable for the MHRA to expect?

- Especially where there is an overlap between good practices between GMP and GCP, and GCP and GPvP.
Talking Point (1)

• TMF review is intrinsic to MHRA inspections

• e-TMF, widely used, presents specific challenges
  – Training for the inspectors pre-inspection and remote – problems with firewalls and their availability
  – Access provision to the inspectors not part of the standard set up for Pharma companies
  – E-TMF documents may reside in several different systems each requiring own training and access
Talking Point (2)

• Essential documents (E6 section 8) can reside on a single system, but the MHRA extended expectations include access to material residing on different systems:
  – GMP data (e.g. batch records) not needed by clinical staff
  – Regulatory documentation (e.g. applications to MHRA)

• Occasional use, e.g. by the MHRA requires additional help/indexes to improve clarity of document locations

• User guide is more suited to staff filing documents than MHRA retrieving them due to study specific requirements.
Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials Feb 2013 refers to:

• The inspectors must have direct access to the entire TMF (Directive 2005/28/EC Article 16 and 258 Recommendations on the content of the trial master file and archiving Section 2), which means reviewing the TMF as used by the staff conducting the trial. A copy or artificial construction of it is unlikely to be accepted for trials currently in the live phase and puts an additional QC requirement on the sponsor. (line 261)

In cases where the sponsor company will not give direct access to the eTMF or/and where other electronic repositories feed into the eTMF, will the MHRA accept an artificial construction of the eTMF?

• Remote access to eTMF without the inspector visiting the site. What is the MHRA position on this?
Inspection of Trial Master Files

MHRA Stakeholder Engagement Meeting (StEM)
25th October 2013

Andy Fisher
Senior GCP Inspector
Access to the Trial Master File

GCP Directive 2005/38/EC: Chapter 4 Article 16

The trial master file shall provide the basis for the audit by the sponsor’s independent auditor and for the inspection by the competent authority.

UK Statutory Instrument 2004/1031 Regulation 31A.

(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.
Access to the Trial Master File

The Human Medicines Regulations 2012 (SI 21012/1916) (Regulation 325, 327 and Schedule 34, Part 4, (64) Schedule 9)

Rights of Entry (325) [summarised]

An inspector may at any reasonable time enter premises in order to verify any statement contained in an application or request for an authorisation under the Clinical Trials Regulations.

Powers of inspection, sampling and seizure (327) [summarised]

An inspector may inspect and if the inspector reasonably believes that it may be required as evidence in proceedings, seize and retain any information and documents relating to clinical trials as part of verifying any statement contained in an application or request for an authorisation under the Clinical Trials Regulations.

The inspector may require a person associated with a clinical trial to produce information or documents relating to the clinical trial which are in the person’s possession or under the person’s control (lists: sponsor, any person who carries out functions of the sponsor, any person, including the investigator, who conducts a clinical trial or occupies premises at which a clinical trial is being conducted; or any person who, in the course of employment with any of these undertakes activities in connection with a clinical trial.)
Inspectors have a right of **direct access** to the TMF.
The Content of the TMF

GCP Directive 2005/38/EC: Chapter 4 Article 16

…the trial master file shall consist of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated. Those documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice.

UK Statutory Instrument 2004/1031 Regulation 31A.

(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
(b) show whether the trial is, or has been, conducted in accordance with the applicable requirements of Directive 2001/83/EC, the Directive, the GCP Directive and Commission Directive 2003/94/EC.

(6) The sponsor shall ensure that any alteration to a document contained, or which has been contained, in the trial master file shall be traceable.

(7) The sponsor and the chief investigator shall ensure that the documents contained, or which have been contained, in the trial master file are retained for at least 5 years after the conclusion of the trial and that during that period are—
(a) readily available to the licensing authority on request; and
(b) complete and legible.
Essential Documents

Documents required to reconstruct the trial conduct

ICH/volume 10 essential documents

Documents not applicable or not required for the trial

ICH - International Conference for Harmonisation
EU Guidance (TMF\textsubscript{1}, GCP\textsubscript{2}) covers filing in a timely manner, indexing, use of electronic media etc.

Essentially, during the trial and afterwards, the TMF should be up to date or complete, well structured, date-ordered, indexed and documents in it should be complete, signed and dated (where applicable) and legible.

1. Recommendation on the content of the trial master file and archiving July 2006
2. CPMP/ICH/135/95: “Note for Guidance on Good Clinical Practice” (ICH E6)
Provision of the TMF for inspection

For UK inspections of UK trials, inspectors may require you to provide for inspection:

- Sponsor TMF relating to UK investigator site (site Level), files with UK relevant documentation (country level and trial level)

- Specific sections of the TMF or all of it (dependent upon the scope of the inspection)

- For contracted out trials (where TMF is managed by the CRO), the sponsor’s “oversight files” would be required instead of/in addition to the CRO’s TMF dependent on scope of inspection and trial status
Direct Access is an inspector’s right, however, issues with “Hybrid TMF” (paper/eTMF (formal eTMF plus one or more electronic systems))

• Direct Access to primary eTMF system or Paper Files is expected (this is often the organisation’s perception of what the TMF is). Access to a certified copy (sponsor would have to demonstrate that this is an accurate and reliable copy) may be acceptable to the inspector.

• Direct Access to other systems that contain TMF documents (often the organisation is unaware that these are part of the TMF) is expected. Access via a system user, access to a certified copy (sponsor would have to demonstrate that this is an accurate and reliable copy), or by specific document request may be acceptable to the inspector.
Provision of TMF for inspection

The organisation should discuss the provision of the TMF (or specific sections) with the Lead Inspector when the inspection is being planned:

- Organisation should know what the TMF is and where all of its documents are located
- Should have formal processes to define, manage and control the TMF
- Should decide how the TMF will be provided to the inspector in accordance with the regulatory requirements

- Failure to meet the requirements agreed during the planning is NOT acceptable
Globalisation of Trial Functions

Activities outside of UK, but involving UK Patient data (e.g. Data Management, Pharmacovigilance).

Rights to see documentation, but scope of inspection may determine what is acceptable to the inspector:

- Actual TMF documents (direct access)
- Certified Copy of TMF documents
- Access to particular documents via document requests
Inspection of TMF

- As part of the planning process the inspector will now ask for indices and SOPs/Plans for the TMF for the selected trials.
- Inspection plans already have statements regarding the TMF provision
- Training in an electronic system should not be more than 1 hour (could happen prior to inspection)
- MHRA Inspectors will not sign any document (aside from site/facility access badges/sign in) at the inspection
- MHRA Inspectors are not required to follow organisation’s SOPs/Policies relating to accessing the TMF
- Currently not inspecting TMF remotely – no plans to change this
Summary

- Organisation’s responsibility to meet regulatory requirements for provision of the TMF, failure to do so is likely to result in:
  - Major/Critical Findings
  - Termination of inspection and revisit
  - Additional days fees

- Whilst we appreciate there is a change from paper to electronic systems in clinical trials, compliance with regulatory requirements is still necessary at all times

- Inspectors aim to clarify and agree with organisation prior to the inspection, how and what will be required for the TMF inspection, however, during the inspection it may be necessary to change this dependent upon what is found.

- The commissioning of new eTMF systems by an organisation should include regulatory requirements as part of the specification of the functional/user requirements.