An SME perspective on the implementation of the EU Clinical Trials Regulation

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Trio Medicines / HMR

Trio Medicines

- Registered SME, established 2005
- 6 full-time staff
- Developing compounds in gastroenterology, inflammation & rare cancers
- Subsidiary of HMR:
  - MHRA-accredited CRO, specialising in early phase clinical trials
  - >700 trials, 230 staff
- Trio shares premises with HMR
- Trio benefits from QA/Regulatory support

Change management experience

- ISO 9001, 1999
- Accredited laboratory, 2002
- EU Clinical Trials Directive 2001/20/EC, 2004
- MIA(IMP)-licensed pharmacy, 2004
- MHRA accreditation scheme, 2008 (revised 2013 & 2015)
- Move of HMR's wards, laboratory, pharmacy and offices to new premises, 2009
- Move to ISO 17025 laboratory accreditation, 2017

HMR/Trio's experience in implementing the EU Clinical Trials Regulation

Implementation of EU Regulation: first steps

- Review Regulation
- Attend EMA stakeholder meetings on database and portal
- Feedback on EC consultations
- UAT of database and portal

Draft EU CT Regulation

EUROPEAN COMMISSION

Brussels, 17.7.2012
COM(2012) 369 final

2012/0192 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Review of Draft EU CT Regulation

Important changes documented in the proposed EU Regulation

The Regulation seems to replace the EU Clinical Trials Directive **and** its associated guidance documents.

An EU Regulation needs no additional national legislation to transpose it into national law. That means that the law will be the same in all EU Member States (MS). The aim is to harmonise the process across the EU.

The EU Clinical Trials Directive will be repealed. But old and new systems will run in parallel for a time (5 years is suggested).

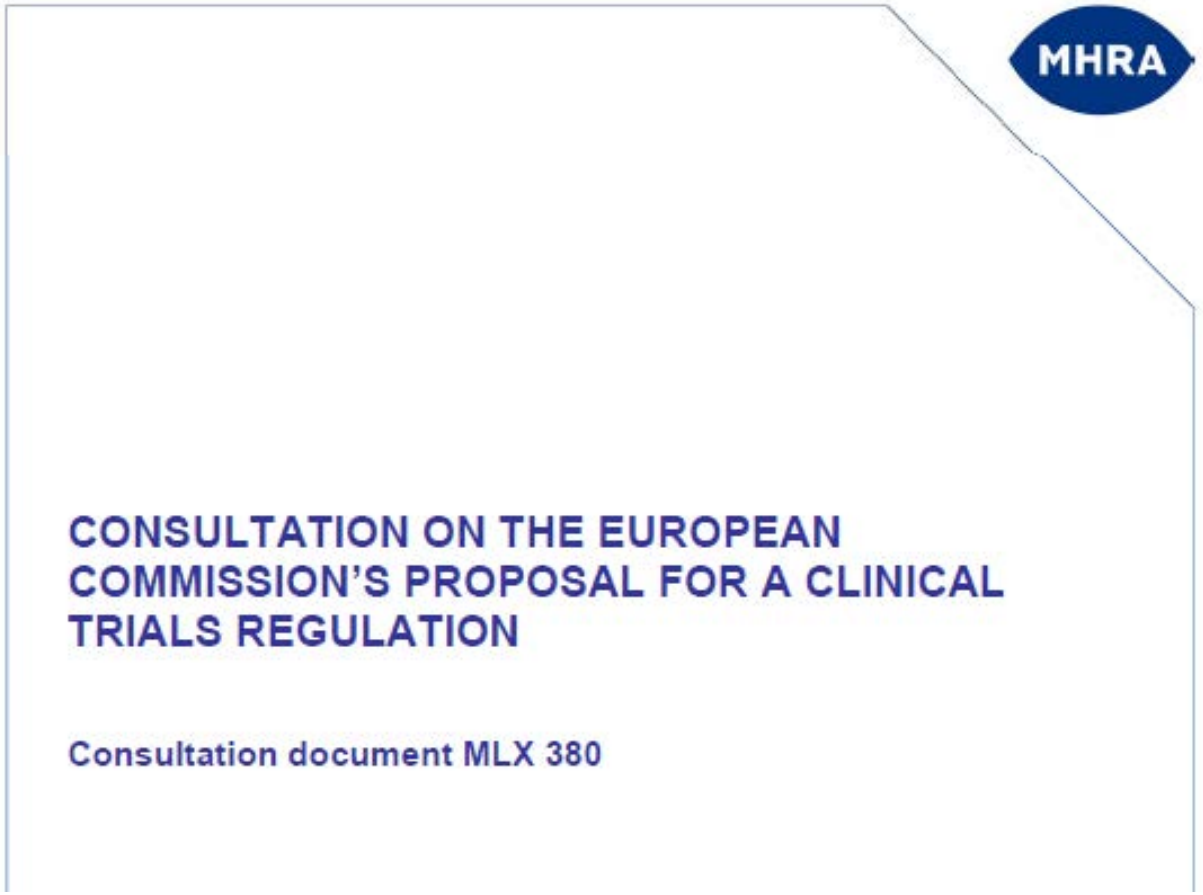
Brief and detailed summaries of the important changes are below. They're followed by speculation on what it could mean for HMR and Trio.

Brief summary:

Authorisation of a clinical trial and amendments

A single application will be made by the sponsor and a single opinion will be given by each MS in which the trial will run. Currently, sponsors submit REC and CTA applications separately in each MS in which they plan to run the study.

MHRA consultation



Submitted feedback to MHRA 9-week consultation, ending Dec 2012

EU Regulation published

Official Journal of the European Union

L 158

English edition

Legislation

Volume 57

27 May 2014

Contents

I *Legislative acts*

REGULATIONS

★ **Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC** (1) 1

Impact assessment, June 2014

Important changes documented in EU Regulation 536/2014

Summary

EU Regulation 536/2014, on clinical trials on medicinal products for human use, was published on 27 May 2014. The Regulation will replace the EU Clinical Trials Directive **and** its associated guidance documents. It will be implemented no earlier than 28 May 2016. Some of the main changes are summarised below.

Authorisation of a clinical trial: There will not be separate REC and CTA applications in each MS in which the trial will run: the sponsor will make ONE application, and each concerned MS will give a single opinion.

The contents of the application will be similar to the combined contents of the CTA and REC applications, but we'll need extra documents, and extra information in the protocol.

The assessment will be in 2 parts, done in parallel: Part I (similar to the CTA application); and Part II (similar to the REC application).

The Regulation allows 60 days for review of an application. But, if further information is needed from the sponsor, maximum timelines could range from 60–106 days:

- 10 days for validation, with a possible extension of up to 15 days
- 45 days for assessment, with a possible extension of up to 31 days
- 5 days for notification

The 'reporting' MS (RMS) will do an initial review of Part I, and produce a final assessment report (after feedback from all concerned MS, if the study will run in more than one MS). Each concerned MS will assess Part II separately. For studies in the UK only, the MHRA will be the RMS and there will be no other concerned MS.

If the RMS authorises Part I, any other concerned MS can't come to a different conclusion on Part I, but they can opt out of authorisation under certain defined circumstances, with detailed justification.

Amendments: Amendments will be renamed 'modifications'. Timelines for review of substantial modifications are longer than the current 35-day clock:

- 6 days for validation, with a possible extension of up to 15 days
- 38 days for assessment, with a possible extension of up to 31 days
- 5 days for notification

So, maximum timelines could range from 49 to 95 days

Impact assessment

1-page executive summary:

- ***Authorisation of a clinical trial***
- ***Amendments (modifications)***
- ***Start of the trial***
- ***Notifications***
- ***Non-IMPs (auxiliary medicinal products)***
- ***Transparency***
- ***Reporting***
- ***Archiving***

16-page summary & assessment of impact

Circulated to key staff

EMA stakeholder meetings

- EMA, regulators and industry stakeholders
- 1-day meetings; initially every 3 months, now every 6 months
- Updates on status & design of EU database and portal
- Opportunity to comment/raise concerns

EC consultations

- 4-week consultation on transparency, ending Feb 2015

Press release

21/01/2015

Public consultation on application of transparency rules of EU Clinical Trial Regulation

Stakeholders to submit their comments by 18 February

- Trio's recent patent application could have been compromised if results had been prematurely disclosed

Consultations

- Prepared consortium position paper & lobbied ministers, MHRA, HRA
- Participated in EMA consultation
- Attended EMA meeting & submitted supporting information
- Final policy: deferral options


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 October 2015
EMA/228383/2015 Endorsed

Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014"

EC consultations

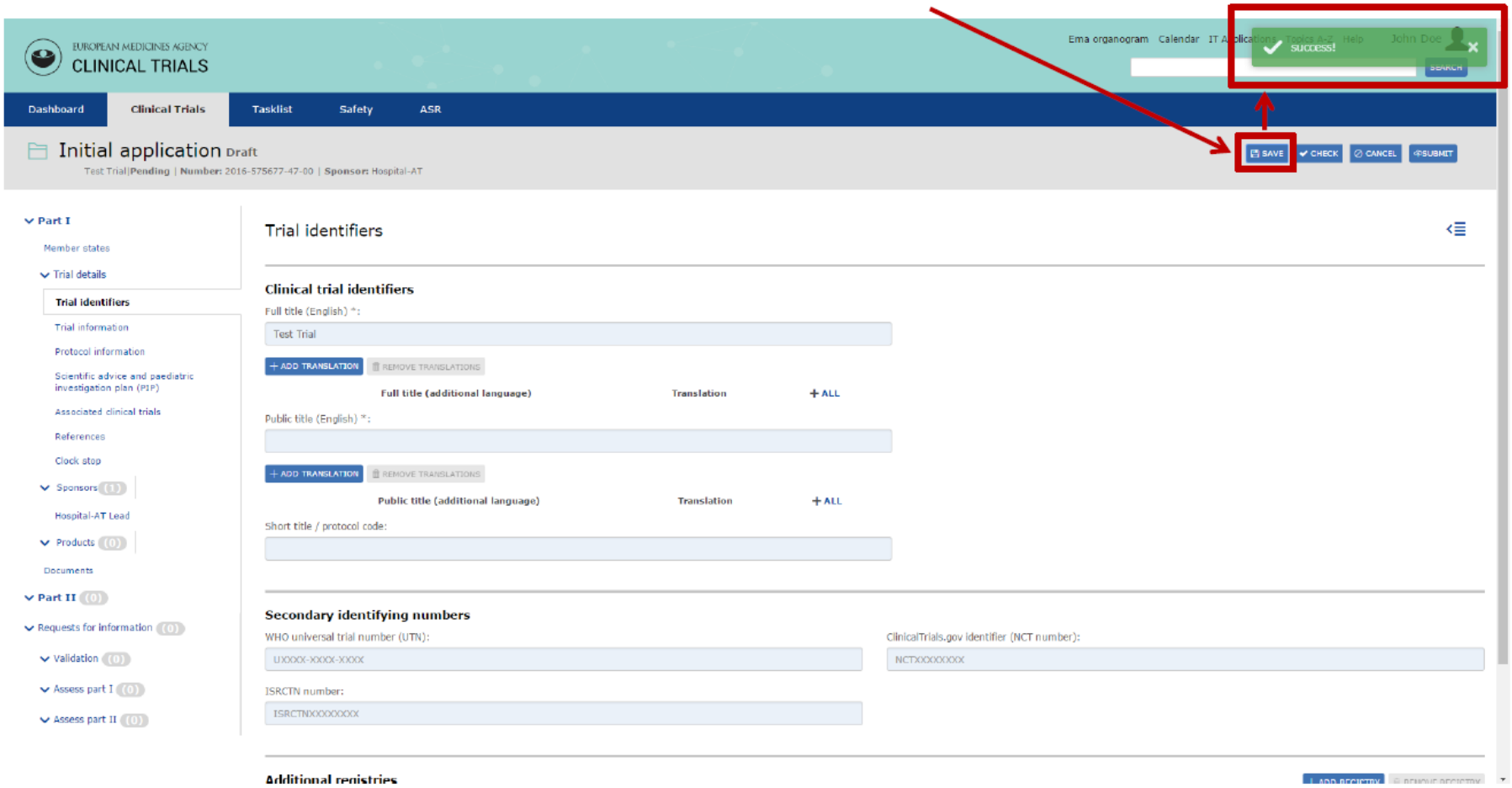
- 9-week consultation on 4 guidance documents:
  - Summary of clinical trial results for laypersons:
    previously submitted feedback to HRA
  - Definition of investigational medicinal products and use of auxiliary medicinal products
    submitted feedback
  - Ethical considerations for clinical trials on medicinal products conducted with minors
  - Risk proportionate approaches in clinical trials
- Forthcoming consultations (eg guidance on serious breaches and the trial master file)

UAT

- Volunteered to participate in testing of sponsor-related functionality of EU database & portal
- 2 testers for each round of UAT (UAT 5 just completed)
- So far, testing has included:
  - Part 1 application (similar to CTA)
  - Part 2 application (similar to ethics)
  - Addition of new Member State(s)
  - Substantial and non-substantial modifications

UAT

A successful save leads to a success notification.



UAT

- Benefits:
  - Early look at new system requirements
  - Possibility to influence design and scope of portal (eg suitability for early phase studies)
  - Updates on progress of system implementation
- Drawbacks:
  - Time consuming (pre-meetings, testing, reports)
  - Difficult to fully test database & portal in allotted time (1 week)
  - Not working with ‘real’ clinical trial data, so testing limited

Strategy for EU Clinical Trials Regulation

Activities to date:

- Regulatory lead, update management
- Review information – drafts, EMA stakeholder meetings, regulators, UAT
- Feedback to EC consultations

Strategy for EU Clinical Trials Regulation : next steps

1. Continue to gather information
   - EMA stakeholder meetings
   - EC consultations
   - UAT
   - Pilot database and portal

2. Detailed gap analysis (Oct 2017)
   - Identify gaps in processes & stakeholders

Strategy for EU Clinical Trials Regulation : next steps

3. Assemble team
   - Stakeholder representatives – Trio & HMR
   - QA & regulatory

4. Implementation plan
   - Agree strategy to fill gaps
   - Identify procedures to update
   - Map tasks to individuals with timelines
   - Regular meetings to track progress
   - Review in light of new information

Strategy for EU EU Clinical Trials Regulation : next steps

5. SOP strategy
   - Incorporate into current system or parallel system?
   - 2 x Eudralex Volume 10

6. Clinical trial strategy
   - Transition period
     - 1st year, can still apply under Directive
     - Trials can run under Directive for 1st 3 years
   - Consider:
     do ongoing trials need to transition from Directive to Regulation?
     new trials - run under Directive or Regulation?

Strategy for EU Clinical Trials Regulation : next steps

7. Training
   - update whole organisation on essentials
   - train specific staff in new procedures
   - train specific staff in use of database and portal
     (make use of EMA training provision)

Challenges

Resources!

- 11 EMA stakeholders' meetings
- UAT: 2 staff, 5 rounds completed; ≥2 planned
- Review of draft and final Regulation
- EC consultations: review drafts, prepare feedback, transparency position paper, engage with stakeholders, regulator & HRA
- Increased resource requirement from October 2017

Challenges

- Implementation of Regulation within an evolving regulatory environment, eg:
  - EMA consultation on mitigating risk in first in human clinical trials
  - GCP R2 implementation 14 June 2017
  - MHRA consultation on GXP data integrity
  - HRA new system for ethics/management approval of patient studies involving NHS
- Day-to-day needs of the business

Thank you

Abbreviations

EC	European Commission
CTA	Clinical trial authorisation
CRO	Contract research organisation
MHRA	Medicines and Healthcare products Regulatory Agency
HRA	Health Research Authority
HMR	Hammersmith Medicines Research
GCP R2	Good clinical practice revision 2
MIA(IMP)	Manufacturer's and importer's license for investigational medicinal products
UAT	User acceptance testing
QA	Quality assurance