Ethics & GCP Forum – MHRA Update

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Agenda

• CTIMP numbers
• CT Regulation Update
  • Including MHRA-HRA pilot
• Reference Safety Information (RSI)
• Innovative trial designs
• Blogs
• Seeking advice
Numbers
UK Clinical Trial numbers

![Graph showing UK Clinical Trial numbers from 2005 to 2018 with trial numbers from 1085 to 955]
UK Commercial applications received

<table>
<thead>
<tr>
<th>Year</th>
<th>Commercial Phase 2-3</th>
<th>Commercial Phase 4</th>
<th>Commercial Phase 1</th>
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<td>2018</td>
<td>630</td>
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UK vs EU New Trials by Year – All Phases

<table>
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<th>Year</th>
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<th>UK%</th>
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UK First in Human (FTIH) totals by year
CTR update
• General update
  • Awaiting an update to take account of contract restructuring and iterative way of working
  • Impact on timetable not yet known.

• Still proposed to come into force late 2020
After March April 2019

• Expected to apply in 2020 during the time-limited implementation period (IP):
  • It will therefore apply to the UK
  • Includes access to networks, information systems and databases
  • Unknown if UK can act as a lead assessor under the CTR during the IP (due to ‘leading authority’ clause)
  • MHRA (UK) well-placed to implement and influenced many of the provisions of the CTR

• Regarding future relationship, UK Government is clear that preferred outcome is continued close cooperation with the EU (across all aspects of medicines regulation), but we are preparing for all scenarios.
No matter what the outcome of negotiations, the UK is committed to offering a competitive service for clinical trial assessment.

Promoting increased collaboration between MHRA and the Health Research Authority to ensure balanced and risk based regulation of clinical trials
Exploring Combined Ways of Working (cWOW)
Exploring Combined Ways of Working

Aim to run a scheme that will test:

- a new process that will result in a single UK decision on a clinical trial (consisting of the current ethics opinion and MHRA clinical trial authorisation).
- a single clinical trial application route that incorporates both the Research Ethics Service and the MHRA regulatory centre
- The pilot is currently open to applications by prior agreement only, with the expectation that it will be opened up to all CTIMP applications as it develops.

Ultimately, we hope to discover, evidence and refine a combined way of working and the processes needed to enable this.
1. Submission

• Submission package is submitted by the Sponsor via IRAS
• Package is retrieved by the CTU Support team and confirmation of receipt is sent
• Package is extracted to CTU SharePoint Team Site
• Submission is validated
1. Submission

1. Cover letter
2. EudraCT form PDF and XML file
3. Protocol
4. Investigator’s Brochure (IB)
5. Documents relating to compliance with Good Manufacturing Practice (GMP) for the IMP
6. Investigational Medicinal Product Dossier (IMPD)
7. Auxiliary (i.e. non-IMP) Medicinal Product Dossier
8. Scientific Advice and Paediatric Investigation Plan
9. Content of the labelling of the Investigational Medicinal Product
10. Recruitment arrangements
11. Subject information, informed consent form and informed consent procedure
12. Suitability of the investigator
13. Suitability of the facilities (For non NHS sites the SSI form to be submitted via IRAS)
14. Proof of insurance cover or indemnification
15. Financial and other arrangements
16. Proof that data will be processed in compliance with current data protection legislation.
2. Allocation & Assessment

- Allocation to assessors with a 30 day initial assessment timeline (But assessment team have 14 days to assess)
- By Day 14, medical assessor uploads DAR to the Hub
- By Day 21, DAR will include REC input
- DAR consolidated by assessor
- By Day 28 – HRA will upload the Part 2 assessment and ethics opinion letter (approval/RFI) to the Hub
3. RFI

- By Day 30
  - If no RFI 2x approval letters sent to sponsor.
  - If RFI, CTU Support team will combine the RFI from MHRA and HRA for Part 1 assessment into a common letter.
- Email Part 1 and Part 2 RFI letters to named contact

- Sponsor has 14 days to respond to the list of RFI

- By Day 58, MHRA medic and REC agree position
  - MHRA Medic to upload FAR to case folder
  - HRA upload Part 2 decision to the Hub
4. Finalisation

- By Day 60 – CTU support team will email 2 decision letters (MHRA + HRA) to named contact

  cWOW tracking spreadsheet updated throughout process to monitor performance
MHRA/HRA Interaction in UK: Status

- Ongoing meetings with HRA/DAs on developing policy, processes and responsibilities.
- Agreement on which organisation assesses which aspects of joint assessment.
- Agreed process maps for new process.
- Building new IT including electronic workflow.
- Recognise stakeholder value of expedited review for phase 1 studies. Aim is to maintain competitive timelines.
New IRAS

- New application system aligned with EU Portal
- Electronic interfaces with UK REC and MHRA systems
- Roll out with user input during 2019
- In future – extend platform to other study types
Status of pilot

• 49 Initials consisting of:
• 15 Phase 1 HVTs
• 34 Phase 2-4
(35 approved, 8 are still under assessment, 4 is awaiting a response to questions raised, 1 was rejected and 1 was withdrawn)

• 32 Amendments consisting of:
• 9 Phase 1 HVTs
• 23 Phase 2-4

• 4 End of Trials
Timelines for approved pilot applications

Validation: 0-3 days

Initial applications: quickest 20 days, average 51 days

Amendments: quickest 2 days, average 10 days
Some reflections

- At this stage a resource-heavy process! Need to develop national IT further to support scale-up (submission/integration with ethics)
- Mix of phases and sponsors (many CROs)
- Seeing value-added already
- Fortnightly support call with stakeholders
- Very good relationship with ethics coordinator body (HRA)
- “Journey” required for EC to move from ‘conversation’ with sponsors to GNA. Clear concise questions, review of responses with decision.
- Delay in receiving EC considerations after the meeting (writing minutes, sign-off etc)
- Good sponsor feedback so far
Next steps

• Development of ‘new IRAS’ to support scale-up of the pilot
  – Will remain ‘by invitation’ until scale-up possible
• Implementation of new MHRA case management system
• Development of interface between MHRA and HRA case management systems to facilitate co-assessment
• ‘Live’ guidance document updated based on discussion in support calls
• Ongoing formal feedback gathering from applicants
Reference Safety Information
Reference Safety Information (RSI)

• Reference safety Information (RSI) is addressed in a recently updated guideline

• Q&A from Clinical Trials Facilitation Group (CTFG):

• This is still a common GNA (and GCP inspection topic!) but we can provide assistance prior to an application or at any time during development
RSI enforcement


The national competent authorities represented at CTFG plan to implement the guidance more strictly from 1/1/2019, and submission of an application and/or substantial amendment with an RSI that does not comply with the guidelines outlined in the Q&A risks being rejected.
Innovative Trial Design
What do we mean by innovative design?

- Basket
- Umbrella
- Matrix
- Platform
- Pick-a-winner
- Adaptive.....
Guidance

• We are seeing all types and increasing our experience about what is acceptable and where the current limits may lie. Most approved.

• Received feedback that a publication from MHRA on these designs would be very welcome.
  • MHRA contributing to a consensus paper – other contribution from ECMC, BIA, ABPI, HRA, MRC…..
• CTFG Stakeholder workshop on ‘complex trial designs’ held 22 March 2018.

• “Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials” published February 2019
Supporting innovative trial designs

• Key message!

• Don’t let anyone tell you “the MHRA will never accept that”!
  • We are open to innovative approaches eg
    – Protocol design
    – Design space for manufacture
  • We encourage researchers to discuss their proposals with us prior to submission.
Blogs

https://mhrainspectorate.blog.gov.uk/category/good-clinical-practice/

https://medregs.blog.gov.uk/

**MHRA Inspectorate**

**Good clinical practice**

Risk Adapted Approach – Neonatal Pharmacokinetic Clinical Trial of Ciprofloxacin in Critical Care. Part 2

**About the MHRA Inspectorate Blog**

This blog shares the work of the Medicines and Healthcare products Regulatory Agency (MHRA) Inspectorate, by inspectors and those the Inspectorate works with.

**Categories**

- Good clinical practice (96)

**MHRA Inspectorate & Process Licensing**

**Organogram**

**We are hiring**

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- MHRA's company page

**MedRegs**

**Spread the word – clinical trial regulators don’t bite!**

The rumours are still out there about not talking to regulators: they will “just say no”. It’s such a shame we are still hearing this, particularly about the use of complex innovative trial designs, such as basket and umbrella trials.

**Faster approvals for clinical trial applications - what our robots have taught us so far**

Art Feb, 22 October 2018 - Improving Our Services

DID YOU KNOW?

Around 50% of applications fail automation due to abbreviated company names

Here at the MHRA’s Information Processing Unit we are getting to know our newest colleagues - five robots called Alpha, Bravo, Charlie, Delta and Echo. While our robots don’t need tea breaks or have a social life outside of work, we...

**Categories**

- Behind the Scenes
- Biological Medicines
- Conferences and events
- eCTD
Finally…..
The biggest barrier to innovation and research from our perspective is not coming to ask our advice early enough (or at all !)

We can offer

- Scientific advice
- Broader scope meetings
- Regulatory advice
- Innovation office meetings
  - https://www.gov.uk/government/groups/mhra-innovation-office
  - innovationoffice@mhra.gov.uk
- SCOPE advice – is a study a CTIMP or not
- Email advice – clintrialhelpline@mhra.gov.uk
- Telephone assistance – 020 3080 6456
Questions?
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