Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Ethics & GCP Forum – MHRA Update

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Disclosure

A general election has been called and we have entered a pre-election period until a government is formed.

Essential business continues, but during an election period there are specific restrictions on UK civil servants and the way we interact with external audiences.

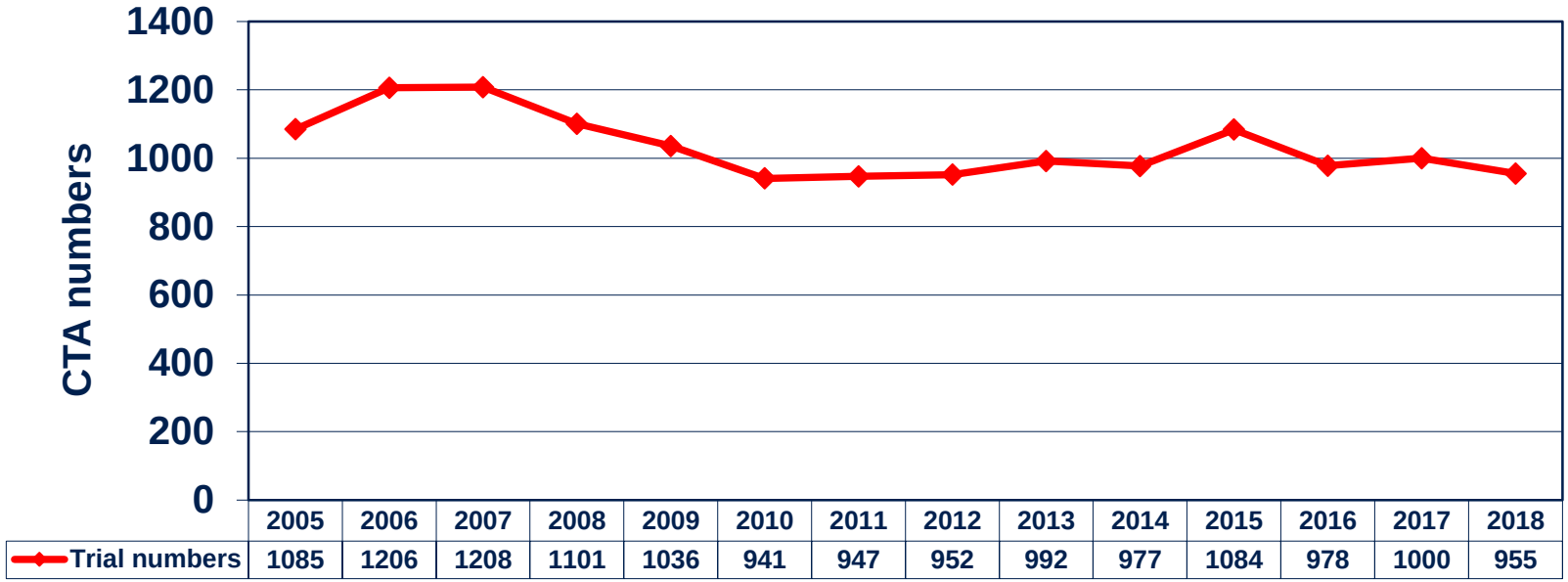
More discretion is shown on discussions of future policy and we must ensure that nothing we do competes with the election campaign for public attention.

These restrictions stem from the need to maintain, and be seen to maintain, the impartiality of the Civil Service

Agenda

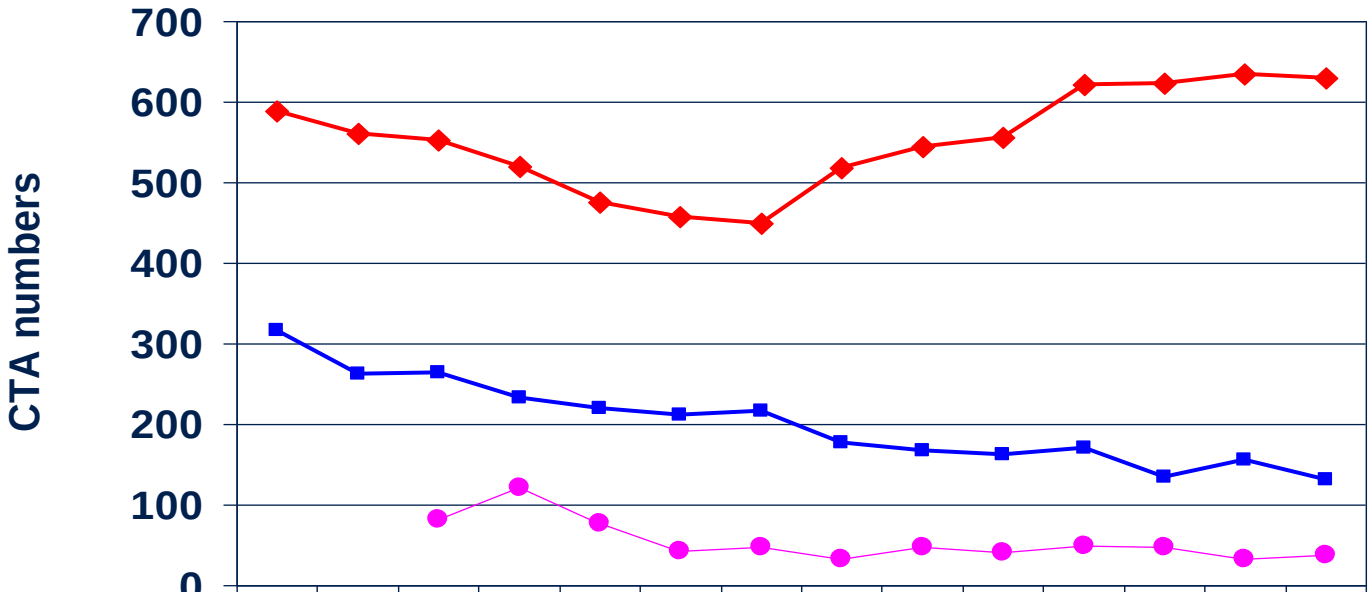
- Metrics
  - Trends in CTA applications
  - Assessment performance
  - Rejection rates
- CT Regulation Update
  - Including MHRA-HRA (CWOW) pilot
- Common Grounds for Non Acceptance Reference Safety Information (RSI)
- Innovative trial designs
- Blogs
- Seeking advice

UK Clinical Trial numbers



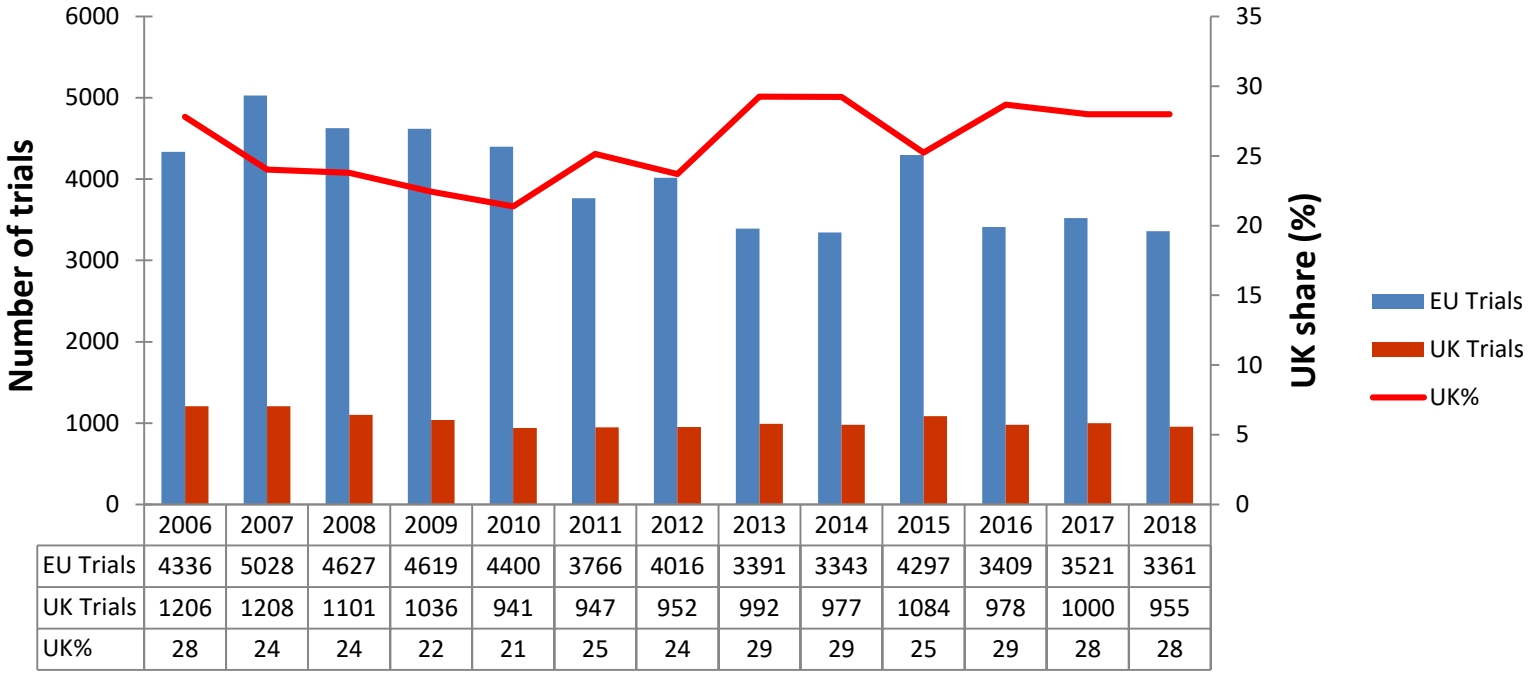
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Trial numbers	1085	1206	1208	1101	1036	941	947	952	992	977	1084	978	1000	955

UK Commercial applications received



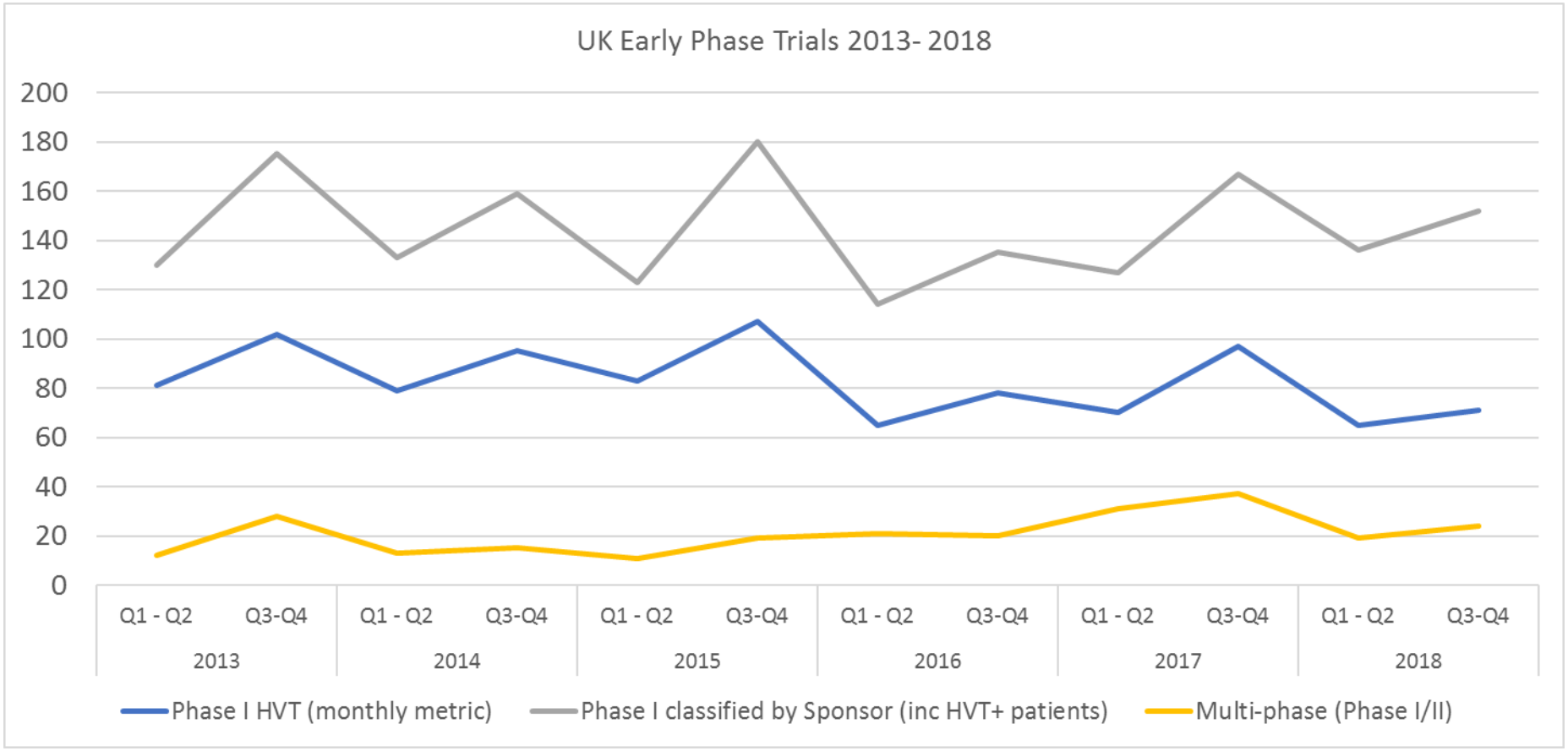
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Commercial Phase 2-3	588	561	553	520	476	457	449	518	545	556	622	623	635	630
Commercial Phase 4			82	121	77	43	48	33	47	41	49	47	32	37
Commercial Phase 1	316	263	264	232	219	211	216	177	168	163	171	134	156	131

UK vs EU New Trials by Year – All Phases

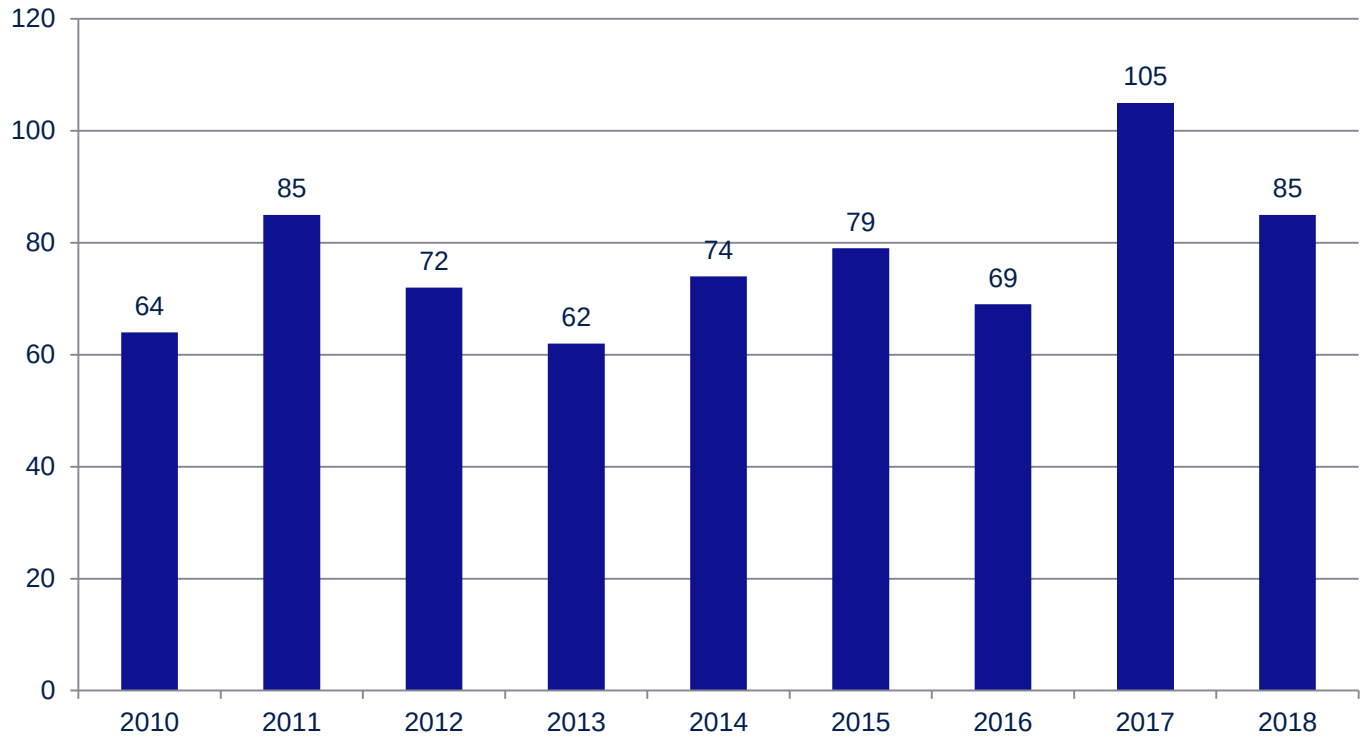


	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
EU Trials	4336	5028	4627	4619	4400	3766	4016	3391	3343	4297	3409	3521	3361
UK Trials	1206	1208	1101	1036	941	947	952	992	977	1084	978	1000	955
UK%	28	24	24	22	21	25	24	29	29	25	29	28	28

MHRA expedited review P1 Vs Sponsor defined P1



UK First in Human (FTIH) totals by year

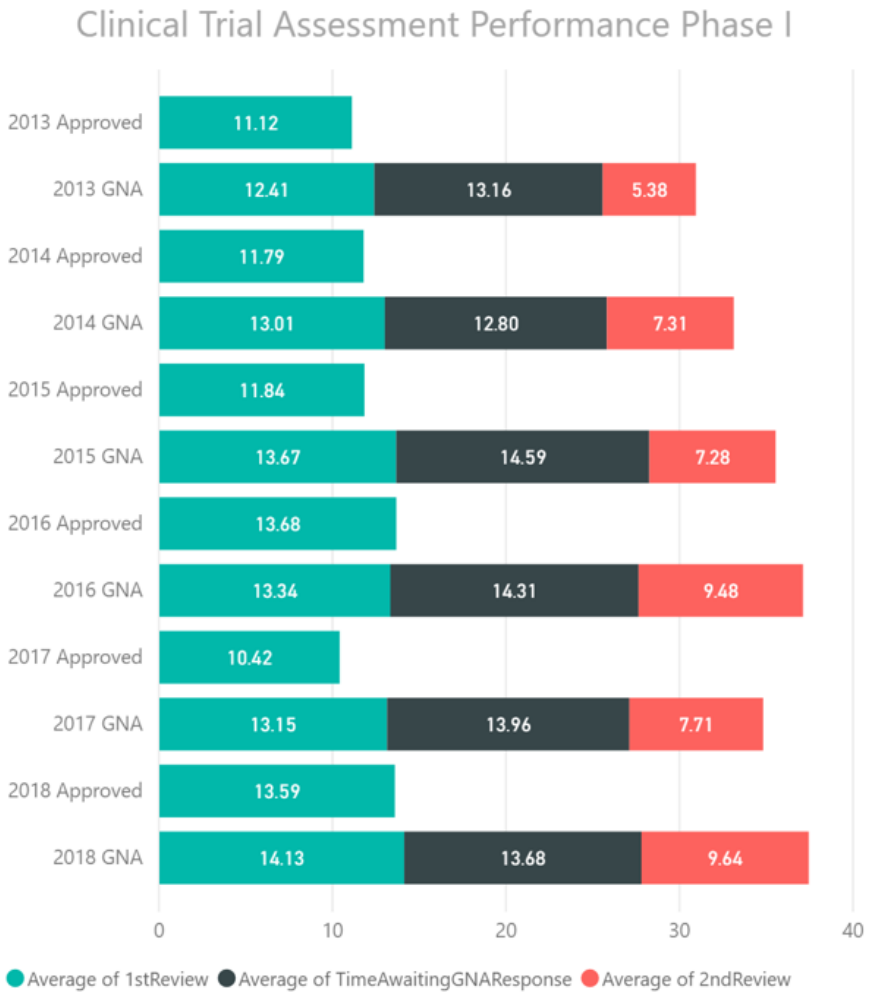


2017 FTIH trials

- In 2017 and 2018, First-in-human trial numbers have **increased by ~50% and ~23% respectively,** compared with the same period in 2016.
- The ratio of healthy volunteer: patient, FTIH studies remained similar at ~40:60.
- The ratio of EU/EEA: Non-EU Sponsor's (~2/3:1/3) and the number of UK: USA Sponsor, seem fairly similar over time, with a slight increase in EU sponsors and a slight decrease in UK and US sponsors in 2018.

- The number of Phase I advanced therapy trials in UK increased ~5 fold from 2016 to 2017, and increased by a further ~10% from 2017 to 2018.
  - In 2018, ~50% of the Sponsors of these trials were UK based, ~35% were EU/EEA (excluding UK) based Sponsors, and the remainder non-EU (USA only) Sponsors ~15%.

Clinical Trial Assessment Performance Phase 1



April to October 2019 average time for initial review was 11.91 days

Clinical Trial Assessment Performance Phases 2-4

April to October 2019 average time for initial review was 26.05 days

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 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

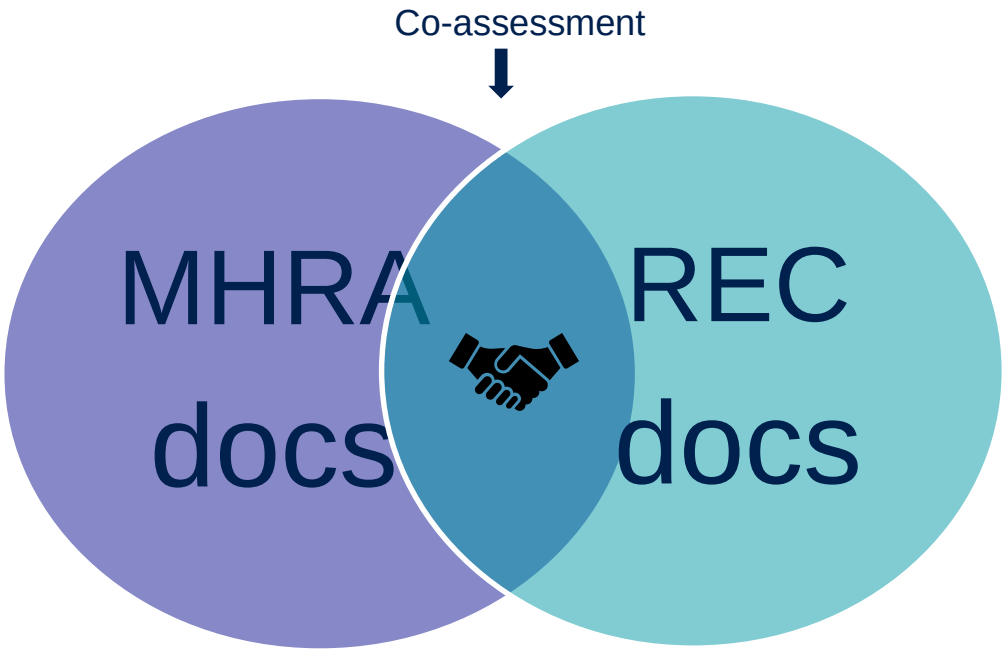
- Regarding future relationship, UK Government is clear that preferred outcome is continued close cooperation with the EU (across all aspects of medicines regulation), but we are preparing for all scenarios.

No matter what the outcome of negotiations, the UK is committed to offering a competitive service for clinical trial assessment.

https://www.gov.uk/government/publications/further-guidance-note-on-the-regulation-of-medicines-medical-devices-and-clinical-trials-if-theres-no-brexit-deal

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)



We have been exploring opportunities to improve our service to sponsors for some time; we see increased integration as beneficial irrespective of the future regulatory landscape.

MHRA 5-year corporate plan includes exploring opportunities to develop a joined up clinical trials authorisation process with other health sector partners.

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) to ensure balanced and risk based regulation of clinical trials
- 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.

Overview

- Pilot launched in April 2018
- First application 29th May 2018
- Mix of phases and sponsors (many CROs)
- Only certain RECs are involved in this pilot (training dependent), although the number involved continues to increase.
- The most up-to-date information about which RECs are taking part in the pilot and when they meet is published on the HRA website.

Status of pilot

- 97 Initials consisting of:
  - 15 Phase 1 HVTs
  - 34 Phase 2-4

(85 approved, 4 are still under assessment, 5 are awaiting a response to questions raised, 1 was rejected, 1 was withdrawn, 1 was removed)

- 104 Amendments
- 12 End of Trials

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; MHRA Part 1 Medical Assessment Report is shared with the REC prior to their REC meeting
- 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)

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

For applications that had Grounds for Non-Acceptance (GNAs) issued, timelines for the combined MHRA and ethics initial assessment range from 17 to 36 days (target 30 days) with final approvals being issued between 23 and 78 days (target 60 days).

Two of the applications surpassed the 60 day decision target as the Sponsor requested an extension to the GNA response deadline.

Four applications had no Grounds for Non-Acceptance (GNAs) issued and therefore final approvals were issued. Timelines for the combined MHRA and ethics initial assessment range from 17 to 29 days (target 30 days) for these applications.

Time taken for a Phase 1 initial assessment was between 20-33 days when a RFI was issued and 17-29 days if no questions were raised. Time for a final decision after RFI assessment was 28-54 days from receipt of the valid application.

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

- A new IRAS form is being developed and training workshops taking place at the HRA for those part of the CWoW pilot
- 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.

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

Common GNA document

- MHRA has launched a “Common issues” (and how to avoid) document: https://www.gov.uk/government/publications/common-issues-identified-during-clinical-trial-applications

- Common GNAs:
  - Validation – failure to provide documents
  - Non-clinical – OECD GLP compliance, analytical methods
  - Clinical – SAE reporting, unblinding, contraception, RSI (new CTFG Guidance issued Dec 2017, 1 yr transition)
  - Quality – shelf life/retest period, MIA(IMP), batch analysis

16,504 unique page views since March 2017

- There is no current way to benchmark the UK against the EU or globally.
- The % of commercial trials that receive GNAs has remained relatively constant over the last 6 years (around 65-70%)

- However, MHRA CTU will be reviewing the GNAs in more depth in order to understand if common issues underpin them, will engage with sponsors to prevent them, and update the common GNA document appropriately.
- Other methods will be used to publicise the common GNAs seen

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): http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf

- 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

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2018_03_CTFG_RSI_Q_A_Covernote.pdf

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…..

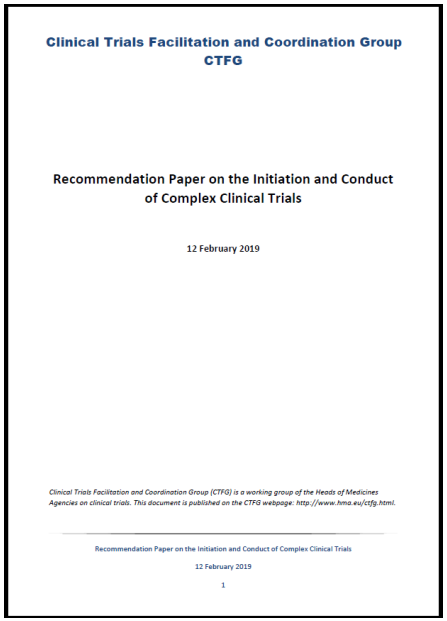
Guidance

- 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 Guidance document on these designs is to be published very soon: http://www.hma.eu/ctfg.html

- 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
  - http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf



Clinical Trials Facilitation and Coordination Group
CTFG

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

12 February 2019

Clinical Trials Facilitation and Coordination Group (CTFG) is a working group of the Heads of Medicines Agencies on clinical trials. This document is published on the CTFG webpage: http://www.hma.eu/ctfg.html.

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials
12 February 2019
1

Supporting innovative trial designs

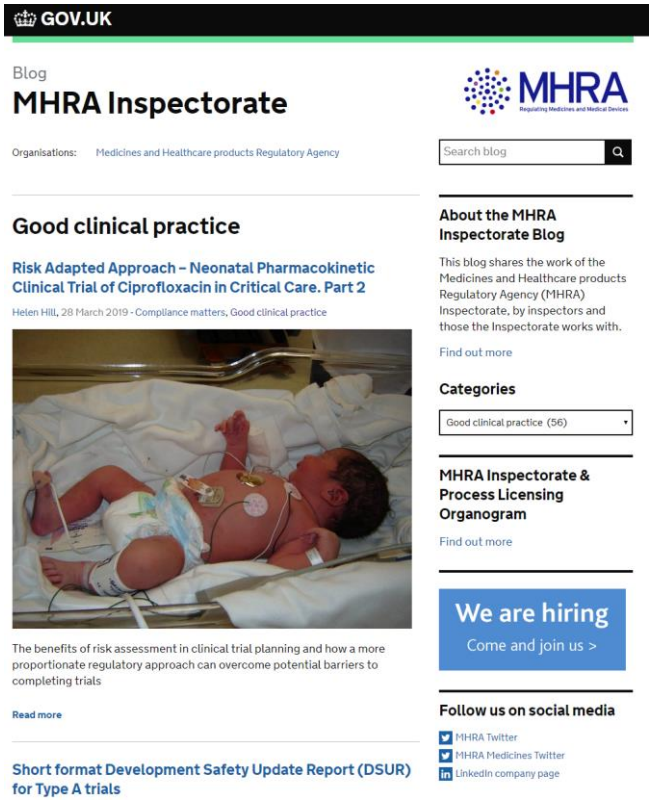
- Key message!

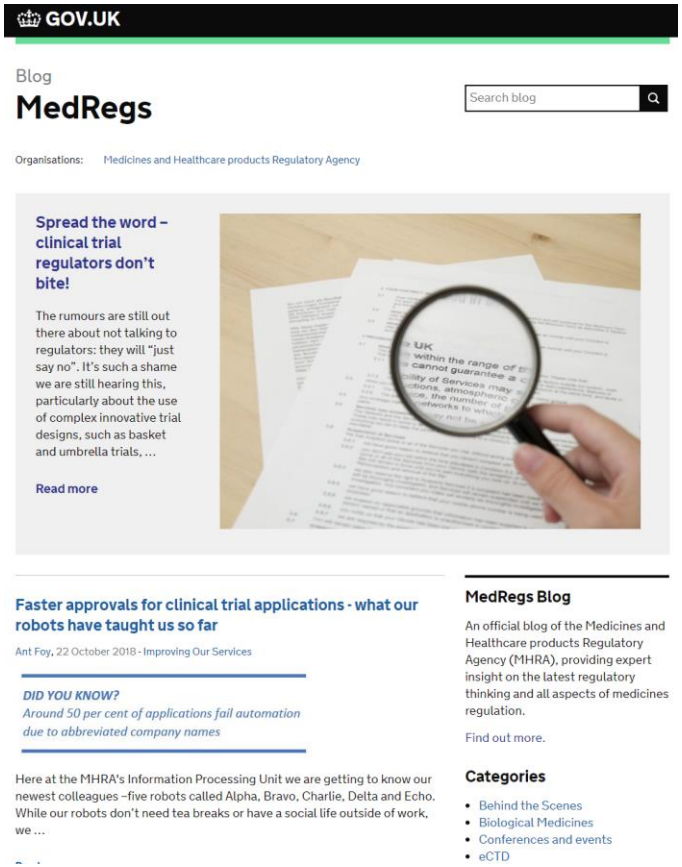
- Don’t let anyone tell you “the MHRA will never accept that”!
  - We are open to innovative approaches eg
    - Protocol design
    - Design space for manufacture
  - We encourage researchers to discuss their proposals with us prior to submission.

Blogs

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

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





Finally…..

Summary: General clinical trials environment

- MHRA continues to be a key regulator in Europe
- Overall trial numbers no significant change – small decrease in line with EU-wide changes
- FTIH continue to show an increasing trend
- CWoW has had positive feedback and is working well to date

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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