Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Ethics & GCP Forum – MHRA Update

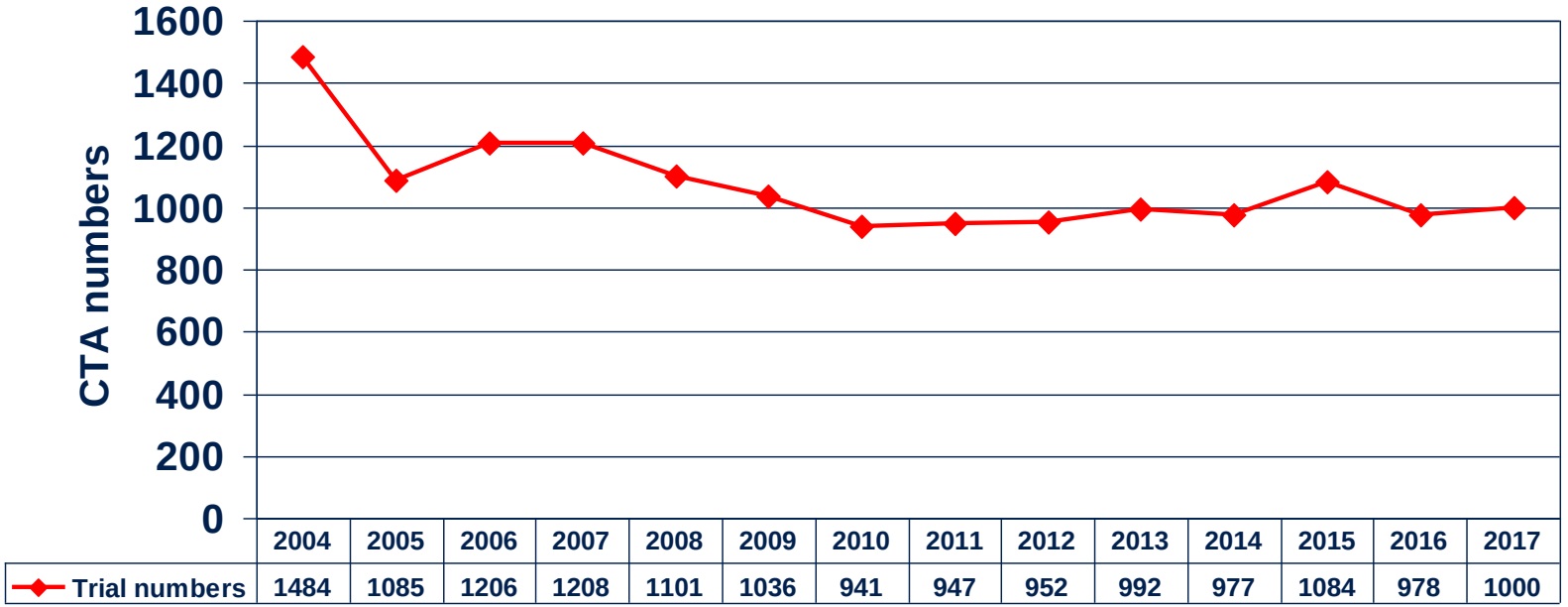
Dr Kirsty Wydenbach
Senior Clinical Assessor / Deputy Unit Manager CTU

Agenda

- CTIMP numbers
- Common GNA document
- CT Regulation Update
  - Including MHRA-HRA pilot
- Reference Safety Information (RSI)
- Innovative trial designs
- Seeking advice

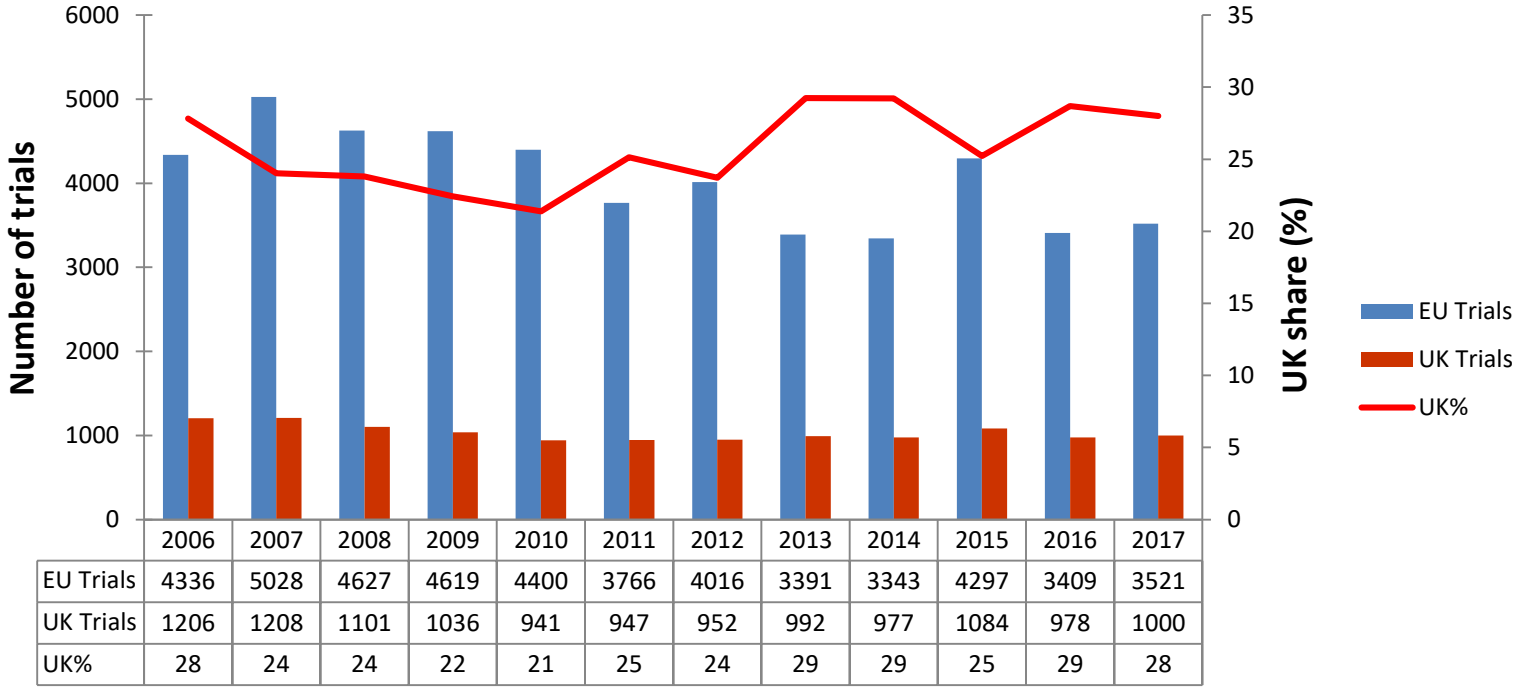
Numbers

UK Clinical Trial numbers



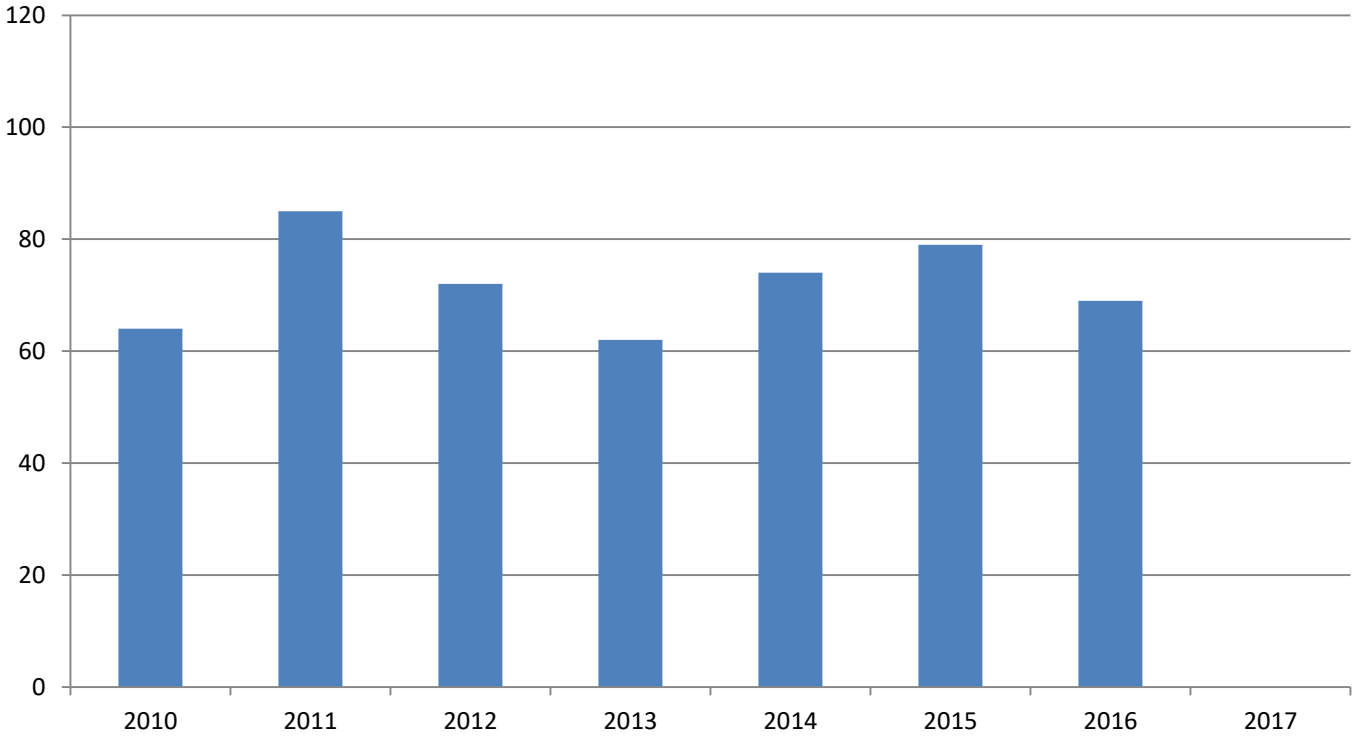
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Trial numbers	1484	1085	1206	1208	1101	1036	941	947	952	992	977	1084	978	1000

UK vs EU New Trials by Year – All Phases



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

UK First in Human (FTIH) totals by year



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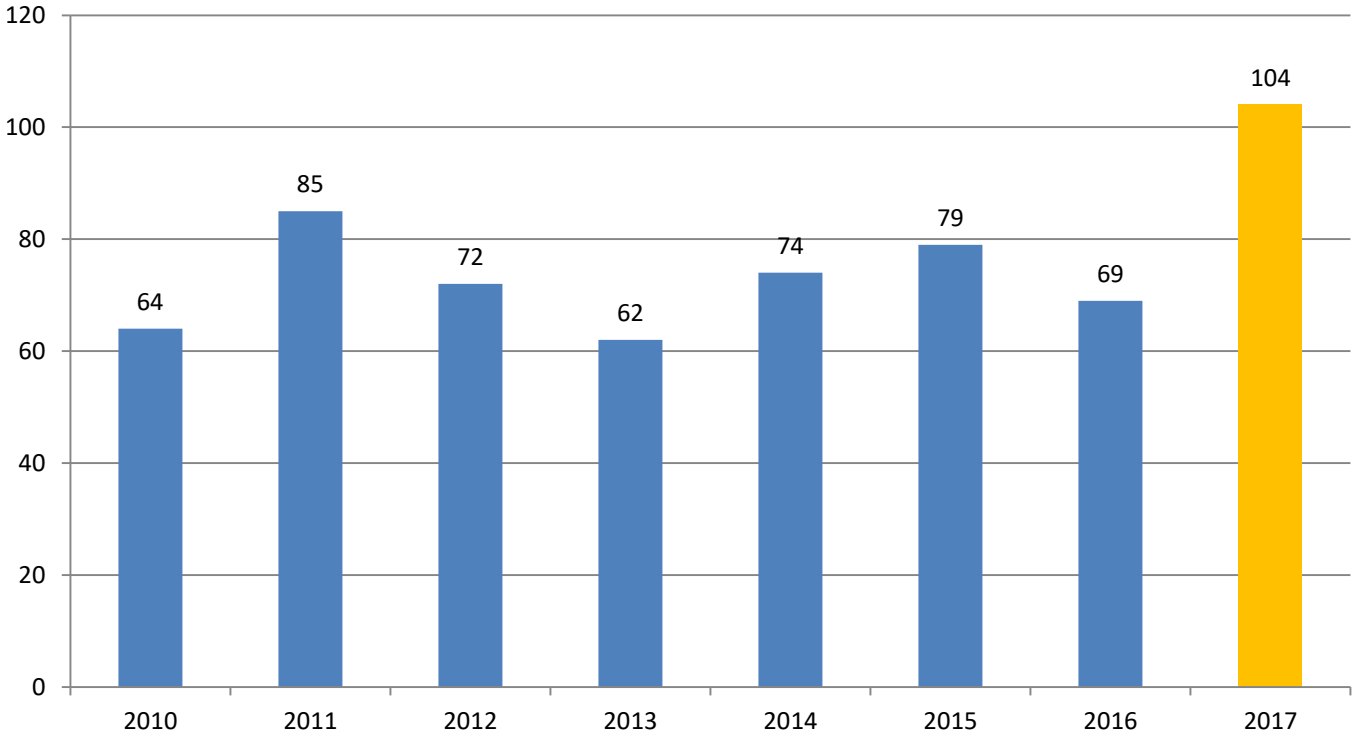
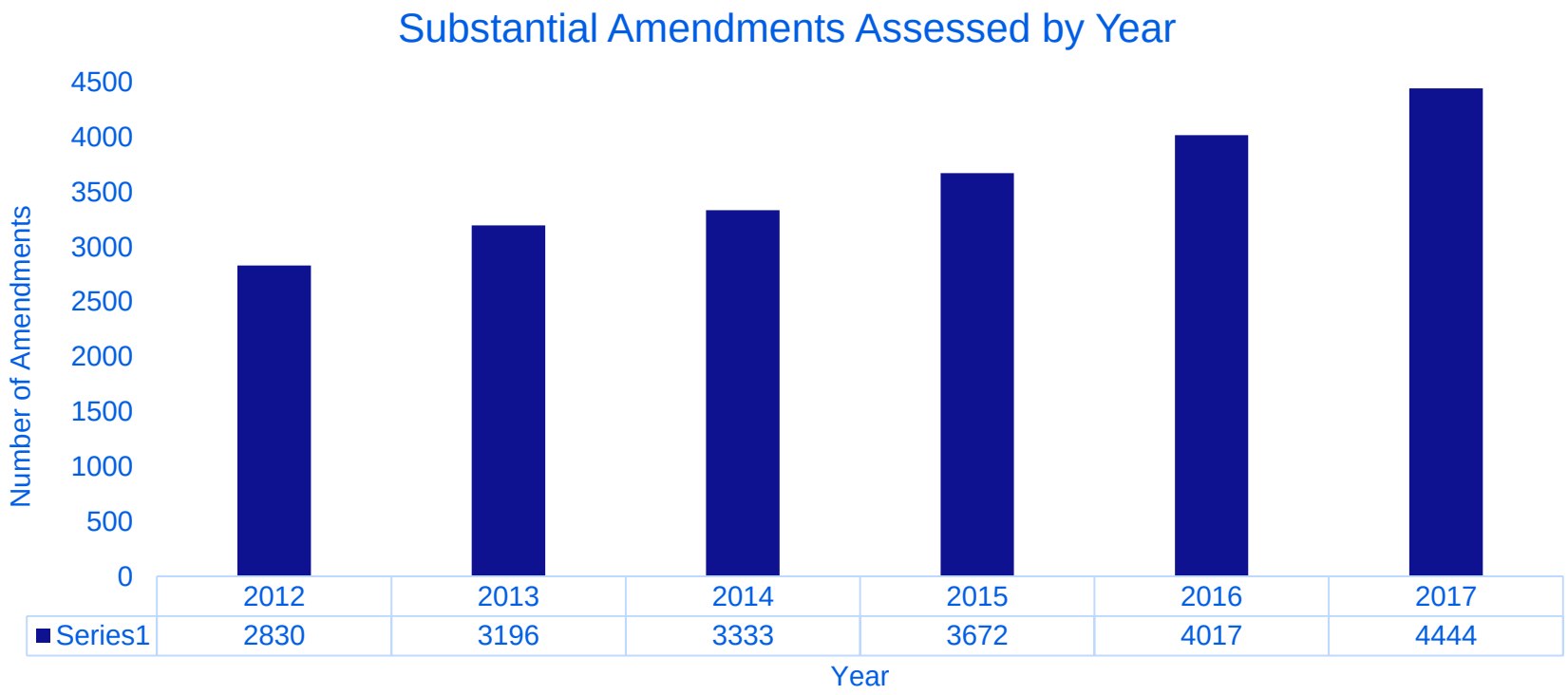


Amendments

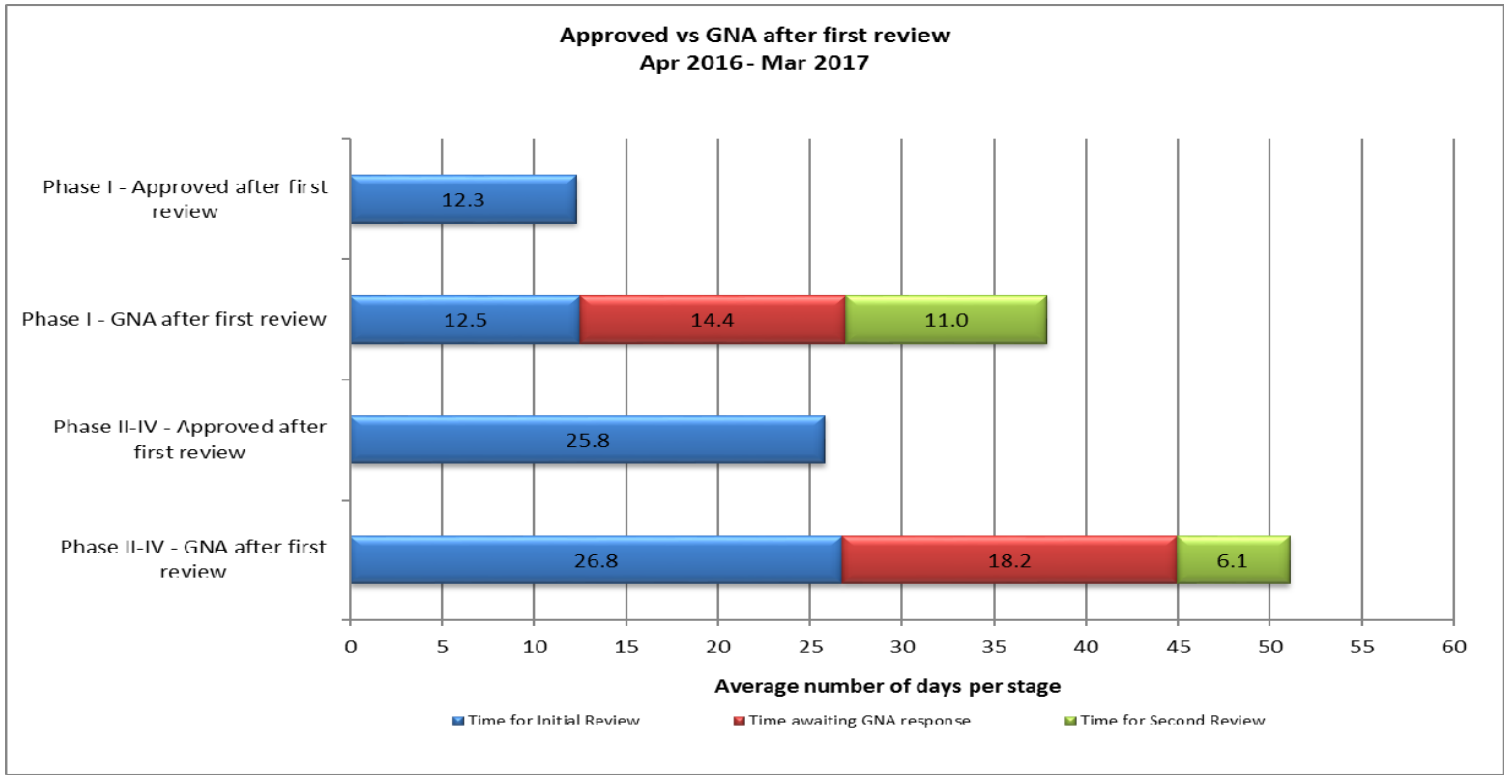

Substantial Amendments Assessed by Year
Number of Amendments
4500
4000
3500
3000
2500
2000
1500
1000
500
0
2012
2013
2014
2015
2016
2017
Series1
2830
3196
3333
3672
4017
4444
Year

Summary: General clinical trials environment

- MHRA largest single regulator in EU (since 2013) and is (joint) largest authority for advanced therapy trials
- Clinical trials numbers have been generally increasing since 2011 (approx. 1000 trials per year; ~5000 amendments)
- Overall trial numbers have increased (22 applications) on the same period last year.
- Phase 1 trials increased by 24 applications on same period last year
- First-in-human trial numbers have **increased by** ~**50%** compared with the same period last year.

Common GNA Document

Timelines: Clinical Trial Assessment Performance



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

CTR update

Overview of the Regulation

New simplified approval procedure

- Single EU Portal & Database
- Single dossier and single submission
- Sponsor nominated Reporting MS
- Coordinated assessment for multi-state clinical trials
  - Part I – joint assessment by all concerned MS
  - Part II – National assessment only (R&D offices and Ethics Committee)
- Clear timelines, concept of tacit approval

Overview of the Regulation

- Risk-based approach to trial authorisation and management.
- Simplified safety reporting, new EU safety databases
- Introduction of rules for emergency clinical trials, co-sponsorship and serious breaches.
- Increased transparency (registry, results; dbase publically accessible)
- Commission inspection powers

Coordinated assessment

- Major change will be movement from national only assessment to coordinated assessment of multi-state trials (and joint ethics/NCA assessment of part 1).

- Actively involved in Voluntary Harmonisation Procedure (VHP) for past few years to prepare for coordinated working
  - MHRA acts as RMS in about 40% of the VHP we take part in

- Trials will still be approved on a national basis (decision based on part 1 and part 2 assessment reports).

CTD→CTR

Dec 2008: Commission announces that an assessment would be made of the application of the Clinical Trials Directive

Oct 2009: Public consultation on the functioning of the Directive

Feb 2011: Public consultation on revision of the Directive

Jul 2012: Proposal for a Regulation and repeal of Directive

Dec 2013: Informal agreement on text by EU co-Legislators

Apr 2014: EU Parliament and EU Council approve

May 2014: Published in Official Journal by Commission

Jun 2014: Entered into force

May 2016: will apply “no earlier than…”

Dec 2017: Proposed application date

Oct 2018: Revised application date

??? 2019: Revised application date

EU Portal & Database

Key Time points:

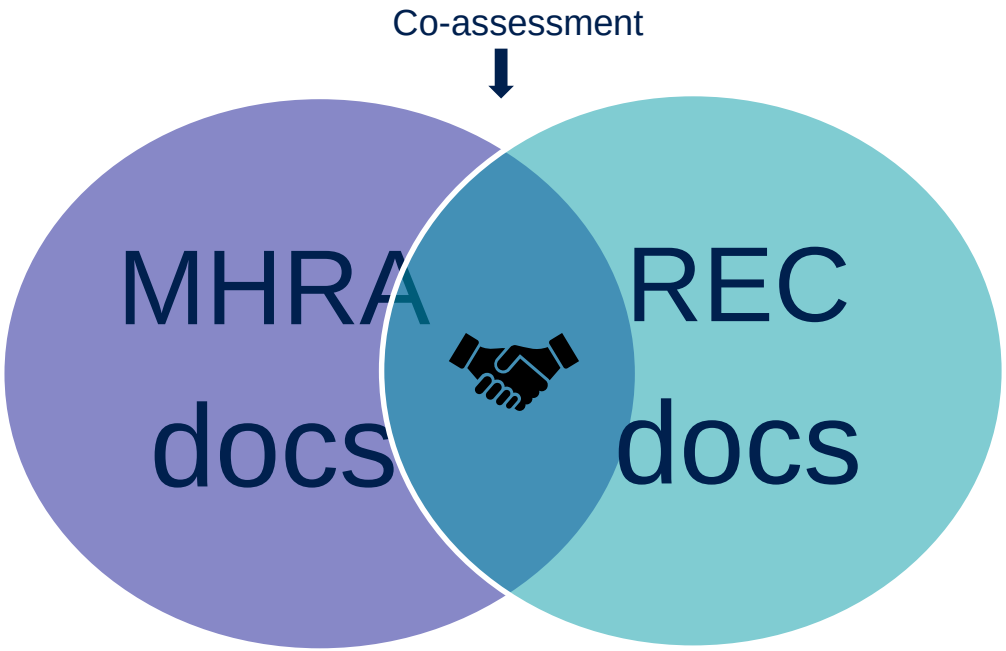
- Release 0.6 – UAT dates: 6 Nov - 27 Nov 2017
- Release 0.7 – UAT dates: end of Q1 2018 tbc
- Audit of the EU Portal and Database: Q2 2018 tbc
  - **The purpose of the audit is to confirm that the EU Portal and Database have achieved full functionality and the system meets the functional specifications which are defined**
- Release 0.8 – UAT dates: Q3 2018 tbc
- EMA MB to endorse the results of the audit
- EU Portal and database launch: 2019 (actual date to be six months after the notice referred to in Article 82(3) of the CT Regulation No.536/2014 is published)

Summary

- CTA numbers remain healthy, particularly in the innovative areas such as FTIH and ATMPs
- MHRA are working with colleagues to facilitate innovative trial designs across EU
- We are developing closer working relationships with HRA and Devolved Nations to improve our service to sponsors for some time.
- MHRA remain fully engaged with the EMA and European Commission groups involved in implementing the CTR

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



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

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

Key Impacts for RECs

- No IRAS form for CTIMPs – ‘application dossier’
- Consolidation with MHRA of Part 1 assessment
  - single UK request for further information and output
- Completion of structure assessment forms
  - Forms agreed EU wide
- Timelines
  - Less flexibility as always require consolidation with MHRA and may require consolidation with other MS’

- **HRA supporting committees with the change**

MHRA/HRA Interaction in UK: Status

- Ongoing meetings with HRA/DAs on developing policy, processes and responsibilities.
- High level agreement on which organisation assesses which aspects of Part 1 assessment.
- High level agreement on which organisation interacts with EU portal.
- Engagement of IT teams to explore solutions for UK part 1 co-assessment.
- Further discussions on detailed process mapping required.
- Recognise stakeholder value of MHRA expedited review for phase 1 studies. Aim is to maintain competitive timelines.
- Developing a pilot co-assessment using Part 1 template.

Reference Safety Information

Reasons the guidance needed updating

- RSI serves 3 purposes:
  - Information for the investigator
  - Basis for expectedness for SUSAR reporting
  - Basis for annual safety report

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- Clarification was given in 2013 but needed updating
- There was inconsistency among sponsors, member states, and there were findings in GCP inspections

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

Aim and content

- ✓ CTFG Q&A document includes 18 questions
- ✓ EMA SmPC guidance, ICH E2A, Dir. 2001/20/EC, CT-1, CT-3 as well as Reg 536/2014

For Sponsors:

- To provide updated details on RSI requirements based on shared experiences since 2013
- To reduce complexity & confusion in relation to RSI generation
- To ensure consistent approach by sponsors to allow for supervision of CTs, e.g. valuable interrogation of EV database by NCAs

For NCAs: To support and ensure harmonised requirements & decisions from NCAs

Q1 – purpose and content

- The RSI is a list of **expected serious adverse reactions**, which are classified using Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA).

- It is used for **the assessment of the expectedness** of all 'suspected' serious adverse reactions (SARs) that occur in clinical trials.

Q3,4,5 - format

Table 1.0 Serious Adverse Reactions for the IMP considered expected for safety reporting purposes.

preferred terms (PTs)

calculated on an aggregated level; based 'suspected' SARs to the IMP

body system organ class

SOC	SARs	Number of subjects exposed (N) = 328		
		All SARs	Frequency of fatal SARs	Frequency of life-threatening SARs
		n (%)	n (%)	n (%)
Gastro-intestinal disorders	Diarrhoea	25 (7.6)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	ALT increase	12 (3.6)	0 (0.0)	0 (0.0)
	AST increase	9 (2.7)	0 (0.0)	0 (0.0)
Cardio vascular disorders	Myocarditis	33 (10.0)	0 (0.0)	2 (0.6)

expected expected

8

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expected expected

8

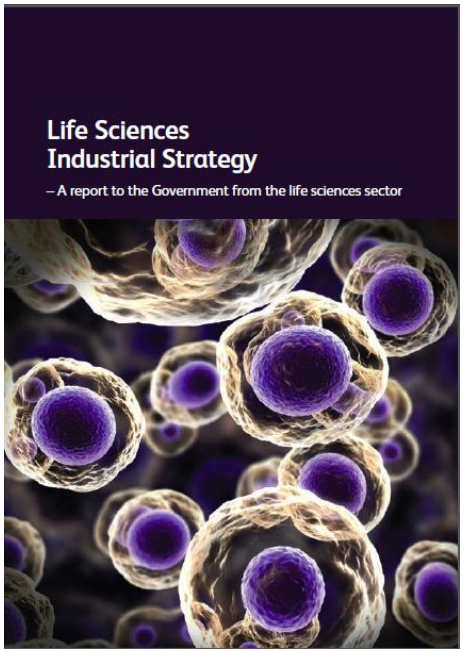
Innovative Trial Design

Life Sciences Industrial Strategy 2017 report to the UK Government:

Our goal

"As the UK seeks to do more **complex and innovative trials**, MHRA needs to continue engaging with sponsors to **assist with innovative protocol designs** and should facilitate efficient approval of complex trials and amendments to such trials, for example, to add new arms.

The **UK should attempt to lead the innovation** in clinical trial methodology, such as basket trials, and should also attempt to embed routine genomic analysis to make trials more targeted, smaller and more likely to deliver high efficacy."



What do we mean by innovative design?

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

Guidance

- We are starting to see all types and gain experience ourselves 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. Will be written-up and published as a reflection paper

Potential issues

- Adapting such trials via an amendment is not always justified; best if the proposed ‘adaptations’ are clearly discussed in the **initial CTA** application in order to allow thorough assessment.

- If a combination/additional IMP is discussed in the initial protocol and there is adequate rationale/safety measures:
  - The use of the IMP in future is acceptable (provided that there is no new information that prevents the safe use of the IMP/IMP combination at the time of the implementation)

- If a combination/additional IMP is added at the time of a substantial amendment: this *may* be acceptable.
  - If the changes are not in line with the original research hypothesis / there has been significant ‘drift’, – new trial?
  - Assessed on a case by case level

- **In case the Sponsor proposes to have a ‘Core protocol’ plus additional IMP-specific ‘parts’:**
  - MHRA accepts that a core protocol could be common and used for several trials (the core protocol could contain: background, available treatment for the disease under investigation, safety reporting requirements, publication policy, data policy, unblinding, compliance assessment etc).
  - Combination of the core protocol plus each IMP-specific part can be submitted as a separate trial.

- **An initial protocol with the potential for “n” potential combinations is becoming the concern.**
  - What is the real trial hypothesis and when will the trial be over?
  - “n” potential combinations are possible, the trial can run forever. How do we ensure safety and scientific rigour? (and transparency)
  - **Best to discuss these designs with us!**

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.

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
- Email advice – clintrialhelpline@mhra.gov.uk
- Telephone assistance – 020 3080 6456

Questions?

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