Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Ethics & GCP Forum – MHRA Update

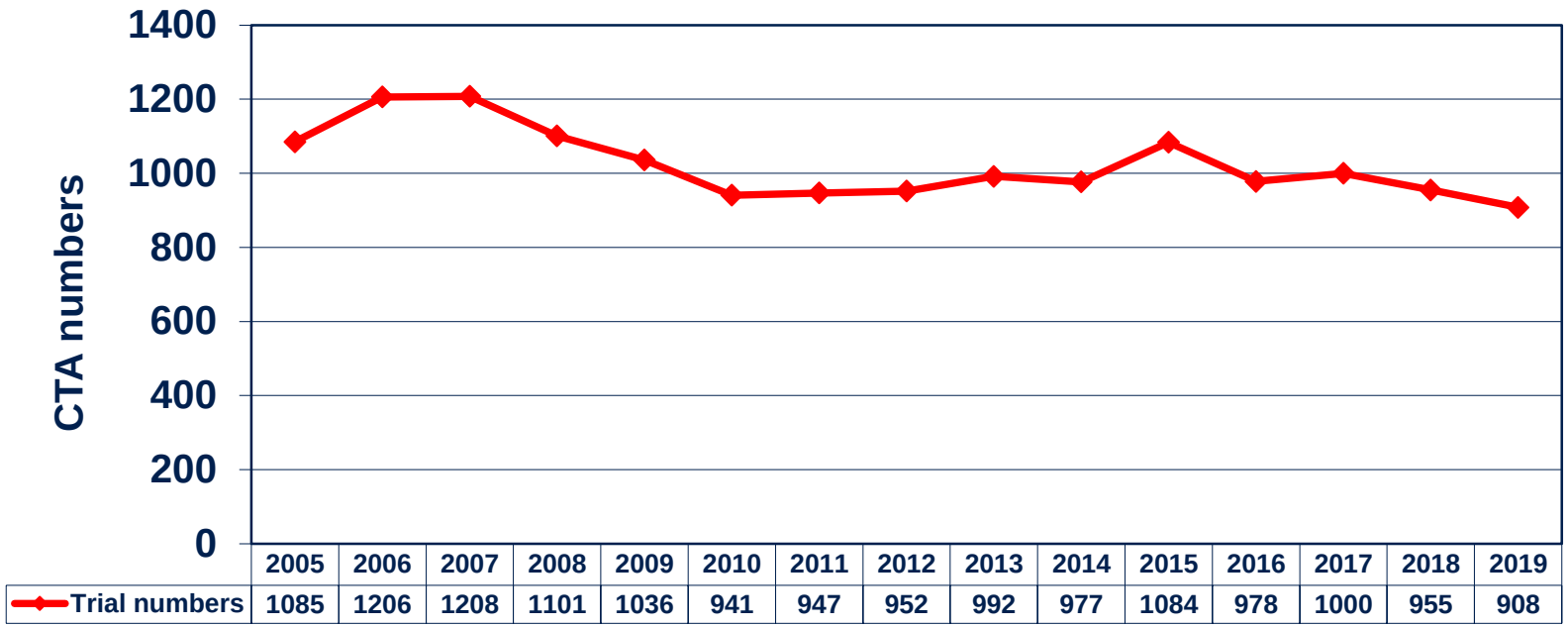
Dr Kirsty Wydenbach
Senior Clinical Assessor / Deputy Unit Manager CTU

Agenda

- Metrics
- CT Regulation Update
  - Including MHRA-HRA pilot
- Innovative trial designs
- COVID-19

Metrics

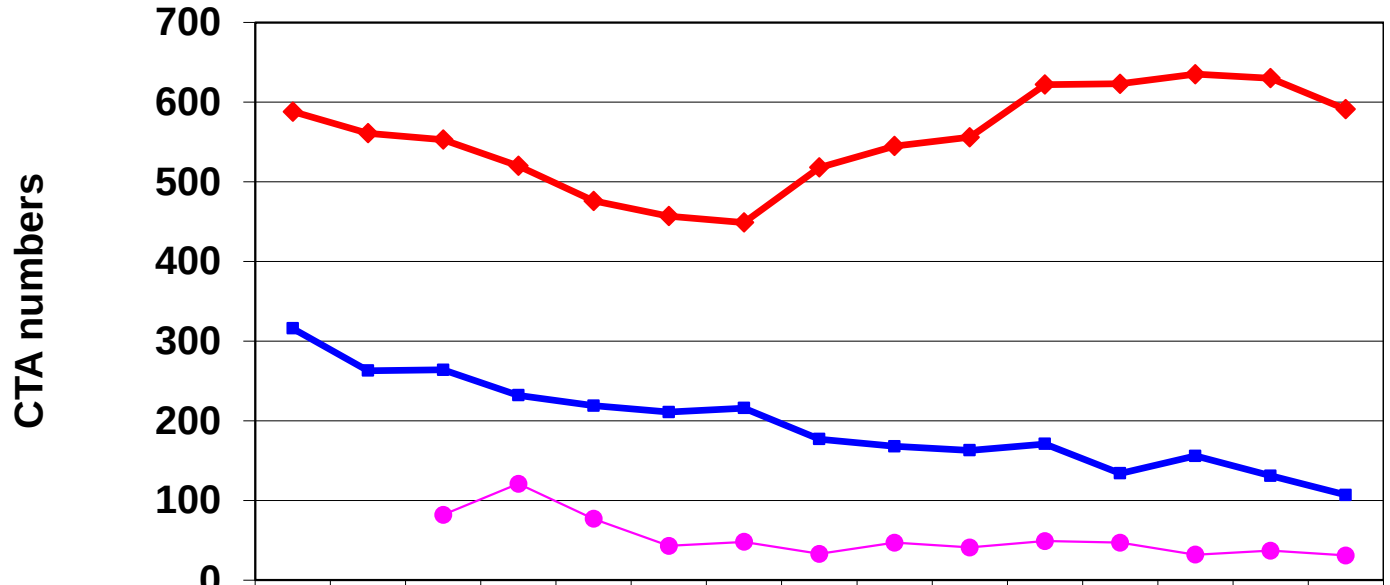
Total trial applications assessed



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Trial numbers	1085	1206	1208	1101	1036	941	947	952	992	977	1084	978	1000	955	908

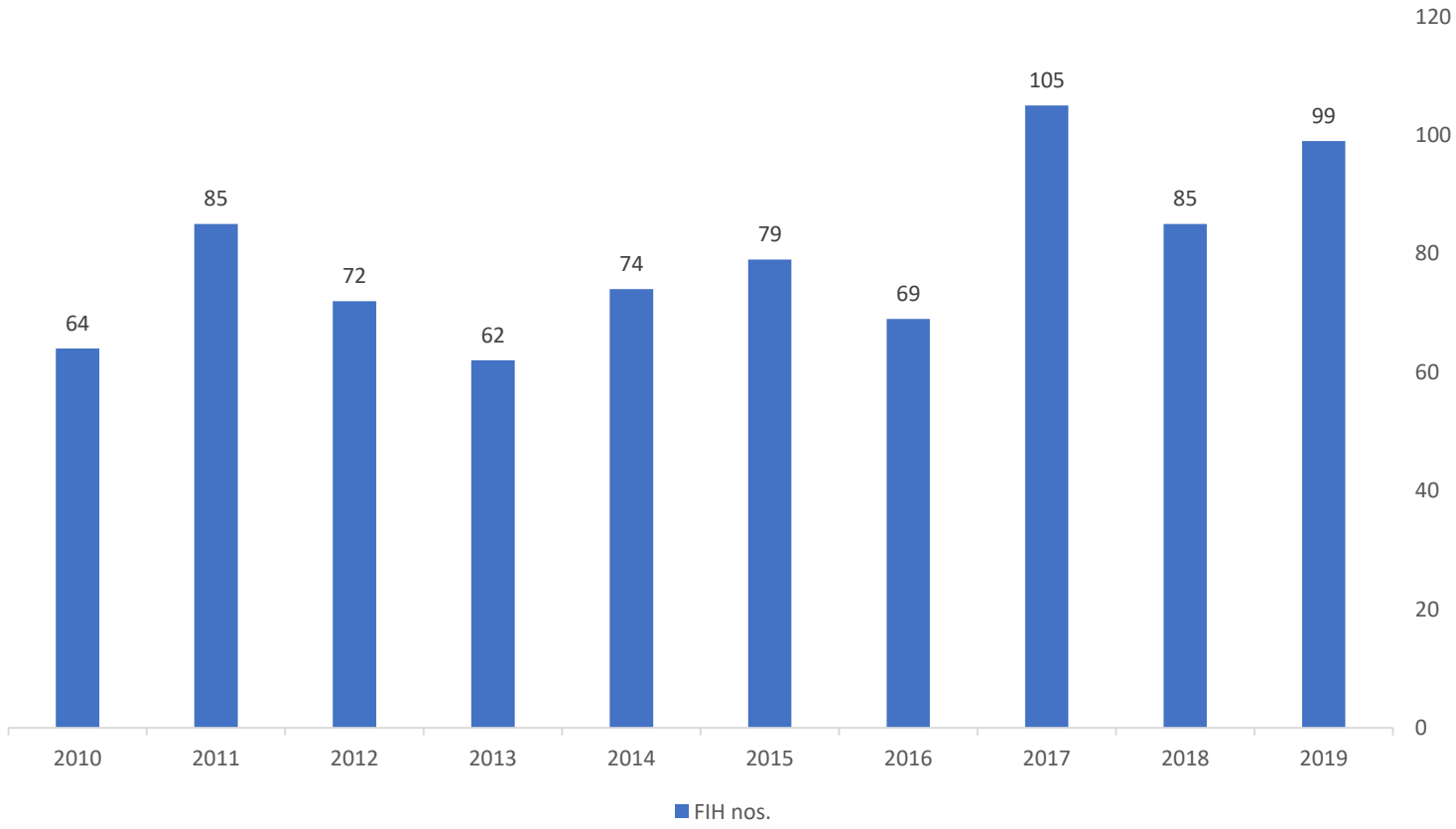
Note! Data from the European database shows that UK workload as a % of total EU/EEA trials has remained **constant.**

UK Commercial applications received



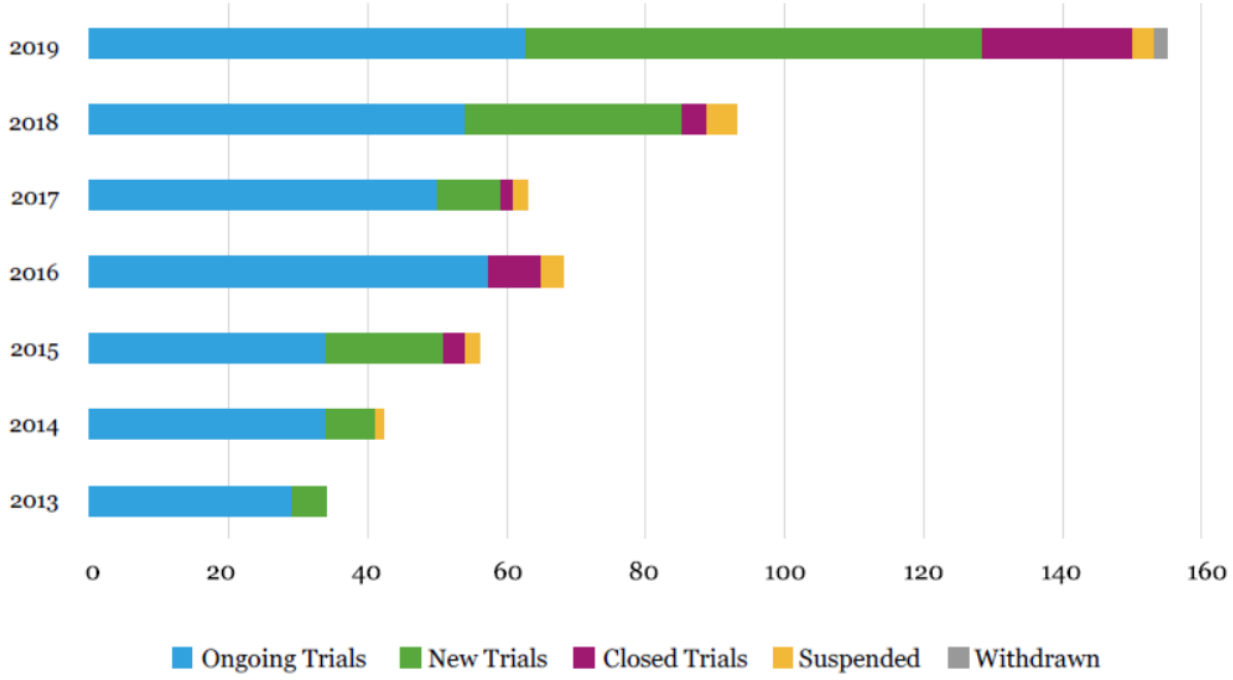
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Commercial Phase 2-3	588	561	553	520	476	457	449	518	545	556	622	623	635	630	591
Commercial Phase 4			82	121	77	43	48	33	47	41	49	47	32	37	31
Commercial Phase 1	316	263	264	232	219	211	216	177	168	163	171	134	156	131	107

UK FIH totals by year



Advanced therapies:

Figure 1. Number of ongoing, new and completed ATMP clinical trials in the UK from 2013-2019



Source: Cell and Gene Therapy Catapult (Jan '20)

- 127 ongoing trials observed in December 2019, with a majority employing viral vector mediated gene transfer. This represents approximately 12% of all ongoing global trials

CTR update

- General update
  - UK will no longer be part of the Clinical Trial Regulation since we will have exited the EU by the time it comes into force
  - UK specific legislation will be followed from 1st January 2021
    - For clinical trials this will not look much different as it has always been a national competency

  - Monitor MHRA website as updates will be posted later this year
  - No matter what the outcome of current 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

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.

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- 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. ATIMPs have now been included

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

New IRAS

- New application system
- Electronic interfaces with UK REC and MHRA systems
- The first part of this new technical process went live on 2 March for a small number of sponsors involved in the CWoW pilot following user testing in February 2020. This initial release provides those sponsors already on the pilot with basic functionality that we will continue to refine during 2020.

Status of pilot

- 177 Initials consisting of:
- 29 Phase 1 HVTs
- 148 Phase 2-4

(152 approved, 14 are still under assessment, 7 is awaiting a response to questions raised, 1 was rejected and 1 was withdrawn, 2 removed from the pilot as responses to the list of questions raised weren't submitted within the timeframe)

- 271 Amendments consisting of:
- 33 Phase 1 HVTs
- 238 Phase 2-4

- 18 End of Trials

Timelines for approved pilot applications

Validation:	average of 3.5 days
Initial applications:	quickest 17 days
	average 53 days
Amendments:	quickest 0 days
	average 27 days

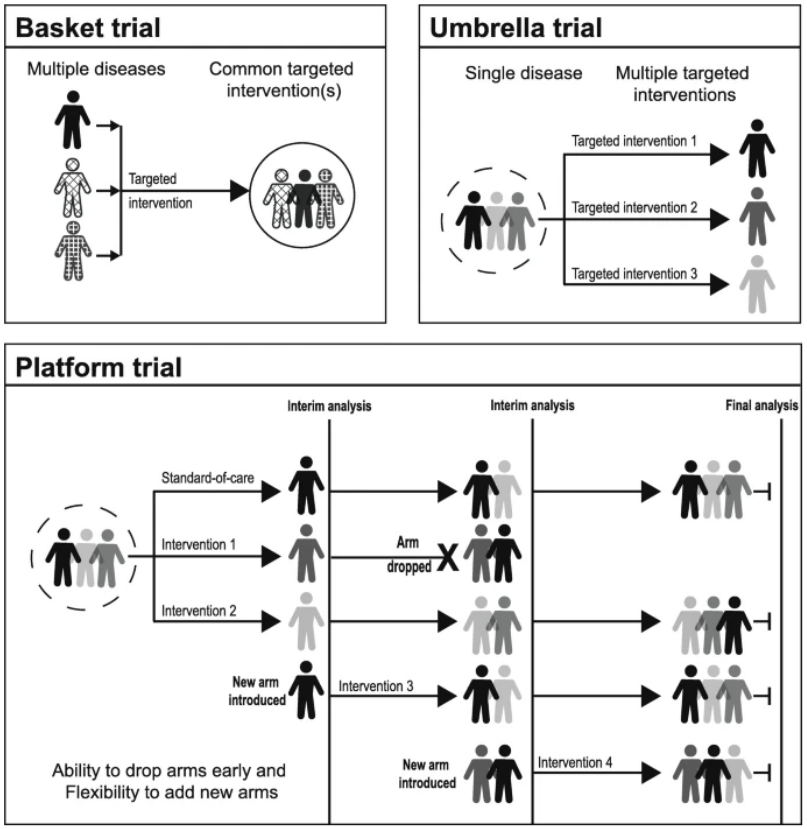
Next steps

- Continued 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

Innovative Trial Design

What do we mean by innovative design?

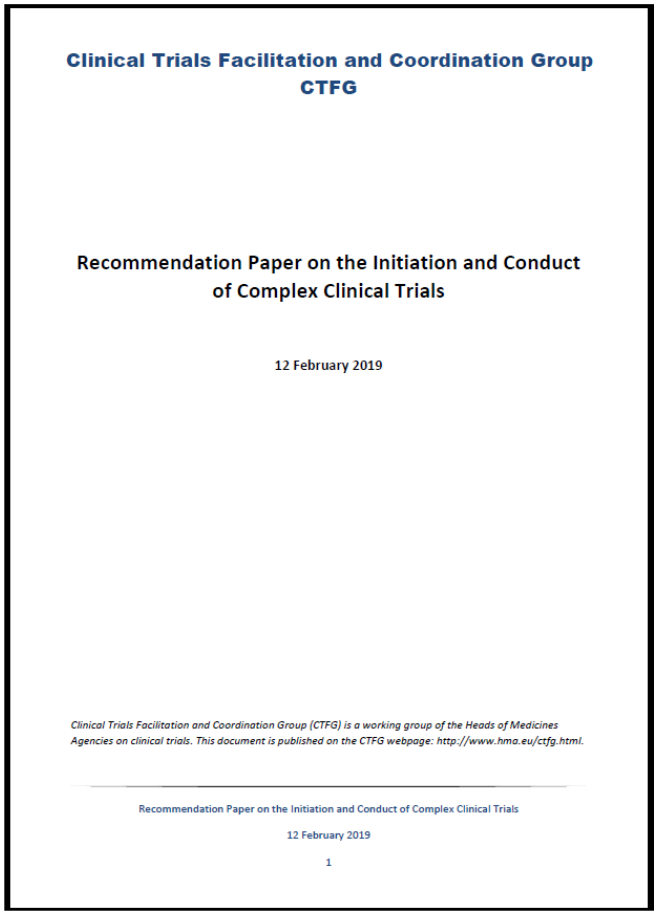
- Basket
- Umbrella
- Matrix
- Platform
- Pick-a-winner
- Adaptive…..



Trials **volume 20**, Article number: 572 (2019)

Guidance

- “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

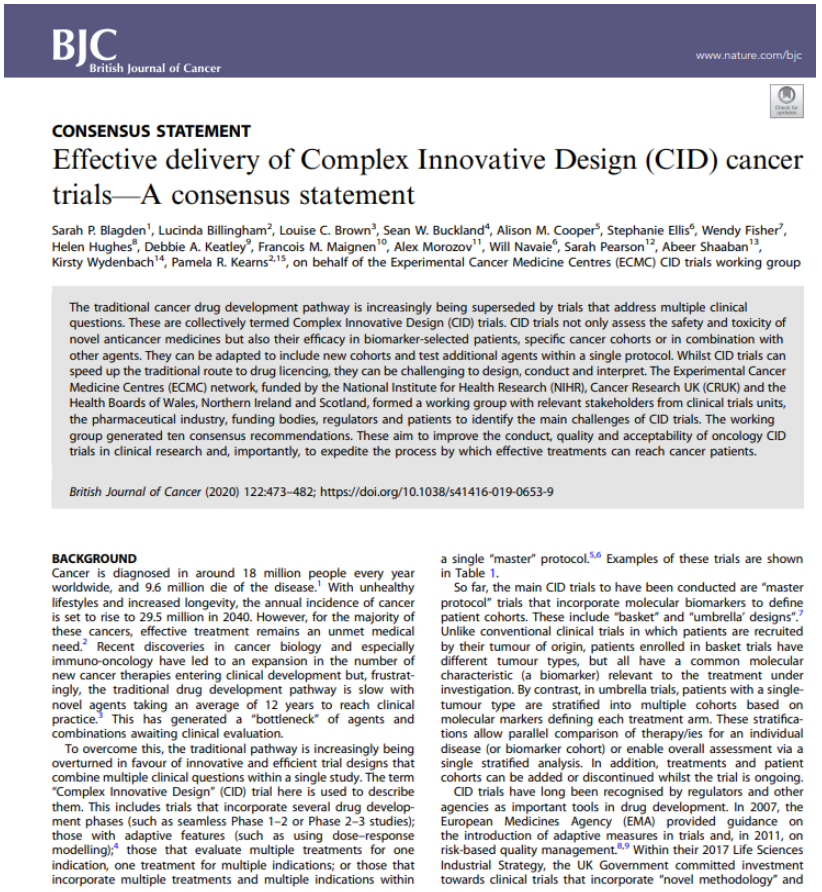
Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

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

- Effective delivery of Complex Innovative Design (CID) cancer trials—A consensus statement
  - https://www.nature.com/articles/s41416-019-0653-9
  - *British Journal of Cancer volume* **122**, pages 473–482(2020)



BJC British Journal of Cancer www.nature.com/bjc

CONSENSUS STATEMENT

Effective delivery of Complex Innovative Design (CID) cancer trials—A consensus statement

Sarah P. Blagden[1], Lucinda Billingham[2], Louise C. Brown[3], Sean W. Buckland[4], Alison M. Cooper[5], Stephanie Ellis[6], Wendy Fisher[7], Helen Hughes[8], Debbie A. Keatley[9], Francois M. Maignen[10], Alex Morozov[11], Will Navaie[6], Sarah Pearson[12], Abeer Shaaban[13], Kirsty Wydenbach[14], Pamela R. Kearns[2,15], on behalf of the Experimental Cancer Medicine Centres (ECMC) CID trials working group

The traditional cancer drug development pathway is increasingly being superseded by trials that address multiple clinical questions. These are collectively termed Complex Innovative Design (CID) trials. CID trials not only assess the safety and toxicity of novel anticancer medicines but also their efficacy in biomarker-selected patients, specific cancer cohorts or in combination with other agents. They can be adapted to include new cohorts and test additional agents within a single protocol. Whilst CID trials can speed up the traditional route to drug licencing, they can be challenging to design, conduct and interpret. The Experimental Cancer Medicine Centres (ECMC) network, funded by the National Institute for Health Research (NIHR), Cancer Research UK (CRUK) and the Health Boards of Wales, Northern Ireland and Scotland, formed a working group with relevant stakeholders from clinical trials units, the pharmaceutical industry, funding bodies, regulators and patients to identify the main challenges of CID trials. The working group generated ten consensus recommendations. These aim to improve the conduct, quality and acceptability of oncology CID trials in clinical research and, importantly, to expedite the process by which effective treatments can reach cancer patients.

British Journal of Cancer (2020) 122:473–482; https://doi.org/10.1038/s41416-019-0653-9

BACKGROUND

Cancer is diagnosed in around 18 million people every year worldwide, and 9.6 million die of the disease.[1] With unhealthy lifestyles and increased longevity, the annual incidence of cancer is set to rise to 29.5 million in 2040. However, for the majority of these cancers, effective treatment remains an unmet medical need.[2] Recent discoveries in cancer biology and especially immuno-oncology have led to an expansion in the number of new cancer therapies entering clinical development but, frustratingly, the traditional drug development pathway is slow with novel agents taking an average of 12 years to reach clinical practice.[3] This has generated a "bottleneck" of agents and combinations awaiting clinical evaluation.

To overcome this, the traditional pathway is increasingly being overturned in favour of innovative and efficient trial designs that combine multiple clinical questions within a single study. The term "Complex Innovative Design" (CID) trial here is used to describe them. This includes trials that incorporate several drug development phases (such as seamless Phase 1–2 or Phase 2–3 studies); those with adaptive features (such as using dose–response modelling);[4] those that evaluate multiple treatments for one indication, one treatment for multiple indications; or those that incorporate multiple treatments and multiple indications within a single "master" protocol.[5,6] Examples of these trials are shown in Table 1.

So far, the main CID trials to have been conducted are "master protocol" trials that incorporate molecular biomarkers to define patient cohorts. These include "basket" and "umbrella' designs".[7] Unlike conventional clinical trials in which patients are recruited by their tumour of origin, patients enrolled in basket trials have different tumour types, but all have a common molecular characteristic (a biomarker) relevant to the treatment under investigation. By contrast, in umbrella trials, patients with a single-tumour type are stratified into multiple cohorts based on molecular markers defining each treatment arm. These stratifications allow parallel comparison of therapy/ies for an individual disease (or biomarker cohort) or enable overall assessment via a single stratified analysis. In addition, treatments and patient cohorts can be added or discontinued whilst the trial is ongoing.

CID trials have long been recognised by regulators and other agencies as important tools in drug development. In 2007, the European Medicines Agency (EMA) provided guidance on the introduction of adaptive measures in trials and, in 2011, on risk-based quality management.[8,9] Within their 2017 Life Sciences Industrial Strategy, the UK Government committed investment towards clinical trials that incorporate "novel methodology" and

Supporting innovative trial designs

Enabling access to advice that supports innovative trial design

https://www.surveymonkey.co.uk/r/InnovativeTrialDesign

Workshop planned for Mid-2020 following analysis of survey results

GOV.UK

Blog

MedRegs

Organisations: Medicines and Healthcare products Regulatory Agency

Survey on novel trials and MHRA advice services – tell us what you think

Kirsty Wydenbach, 23 December 2019 - Improving Our Services

Innovation and supporting the research environment in the UK is a key priority for MHRA. But we know we can do more and be even better.

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https://www.surveymonkey.co.uk/r/InnovativeTrialDesign NOW CLOSED

Workshop planned for Mid-2020 following analysis of survey results

- 2 afternoon webinars – October 12th and October 13th
- Open to all – sign up will be available soon

GOV.UK

Blog

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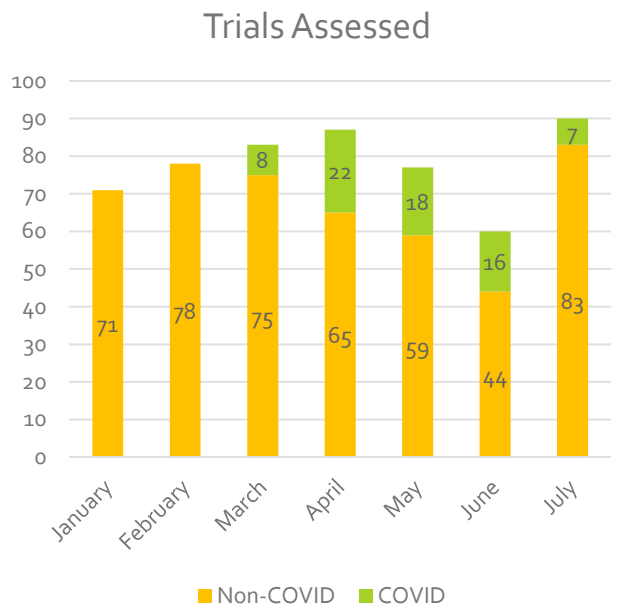
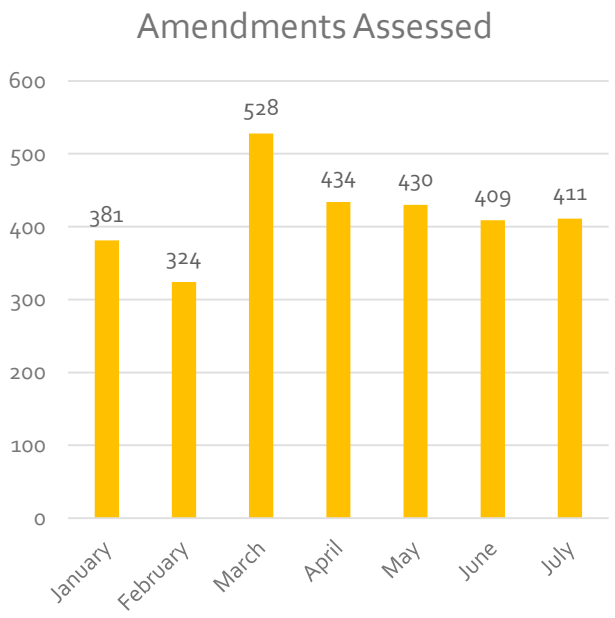
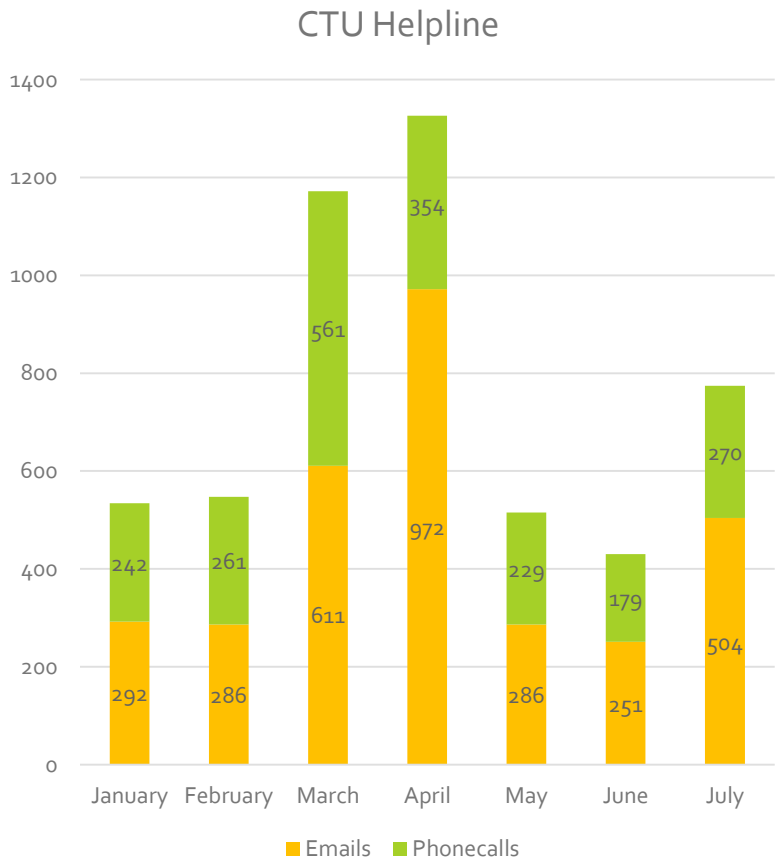
COVID-19

COVID-19 work





Helpline


CTU Helpline
1400
1200
1000
800
600
400
200
0
242
292
261
286
561
611
354
972
229
286
179
251
270
504
January
February
March
April
May
June
July
Emails
Phonecalls

Information updates

The MHRA Clinical Trials Unit is primed to prioritise assessment of any application that is submitted for COVID-19.

We would advise that COVID-19 applications are submitted directly to the clinical trial Helpline (clintrialhelpline@mhra.gov.uk) as well as via the normal route (CESP) so that our assessors can begin their work as soon as possible. We will liaise very closely with you to ensure your application is managed as efficiently as possible.

We would recommend you review our guidance on submission and management of COVID-19 trials here and here and regulatory flexibilities here. We also recommend that you comply with the NIHR process for prioritisation of COVID-19 research https://www.nihr.ac.uk/covid-19/

Documents to send with your application can be found here

Non-COVID trials

- Updates on flexibilities are available for GCP aspects that may be impacted by COVID-19 such as
  - Remote monitoring
  - Consent / signatures
  - How to manage protocol deviations
  - USMs
  - When to submit changes to MHRA
  - Halting trials

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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