Summary of MHRA preparations for Brexit

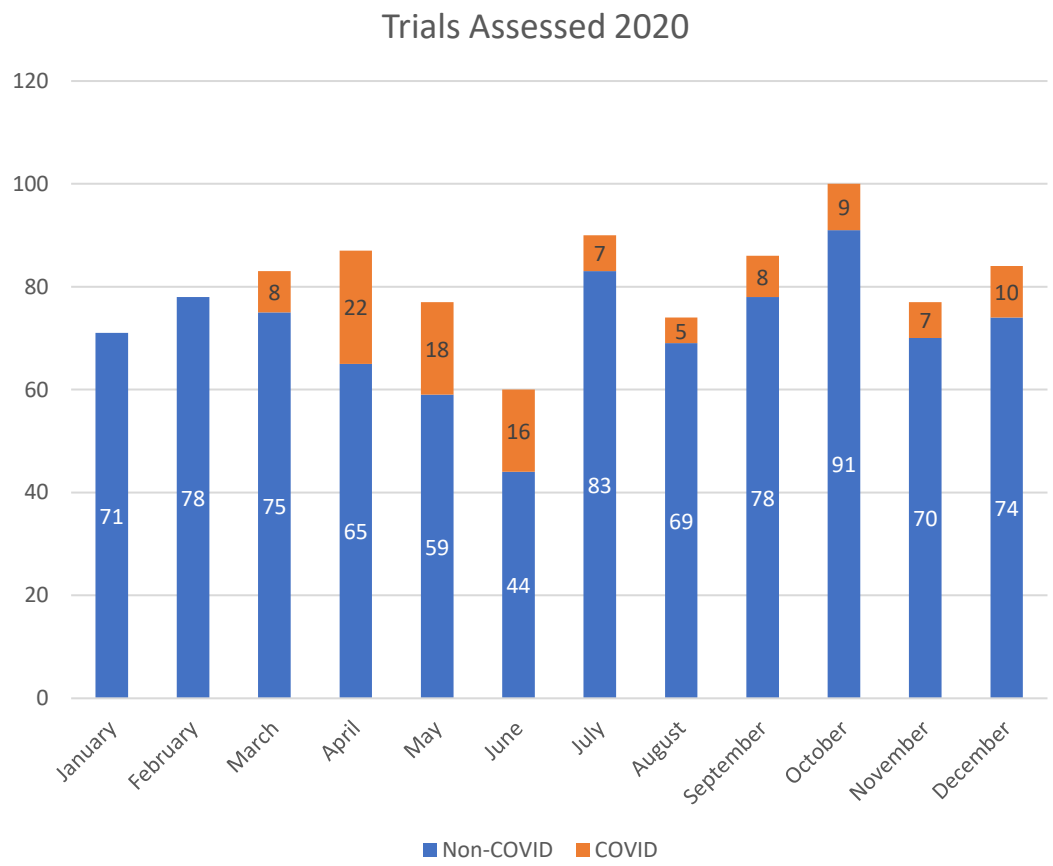
Presented by Dr Kirsty Wydenbach
Expert Clinical Assessor / Deputy Unit Manager CTU

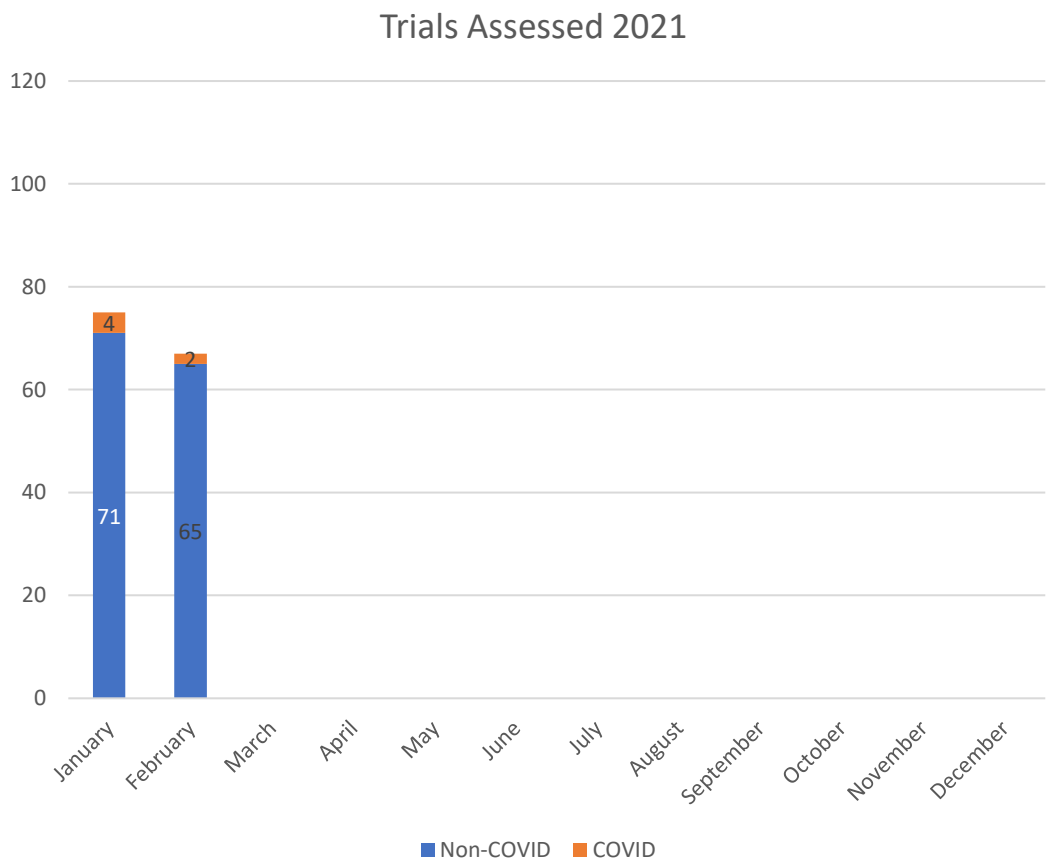
Agenda

- Metrics
- EU Exit transition guidance
- Novel trial design
- COVID-19
- Innovative Licensing and Access Pathway (ILAP)

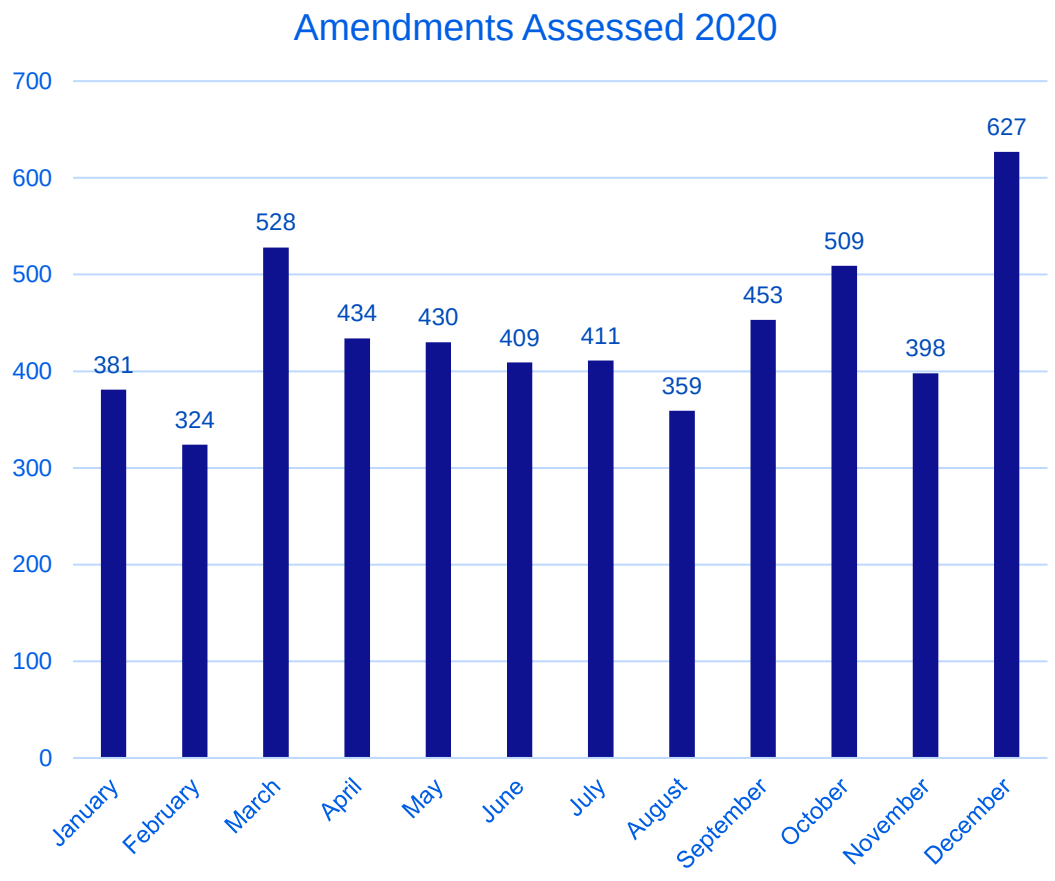
Metrics

Initial applications





Amendments


Amendments Assessed 2020
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600
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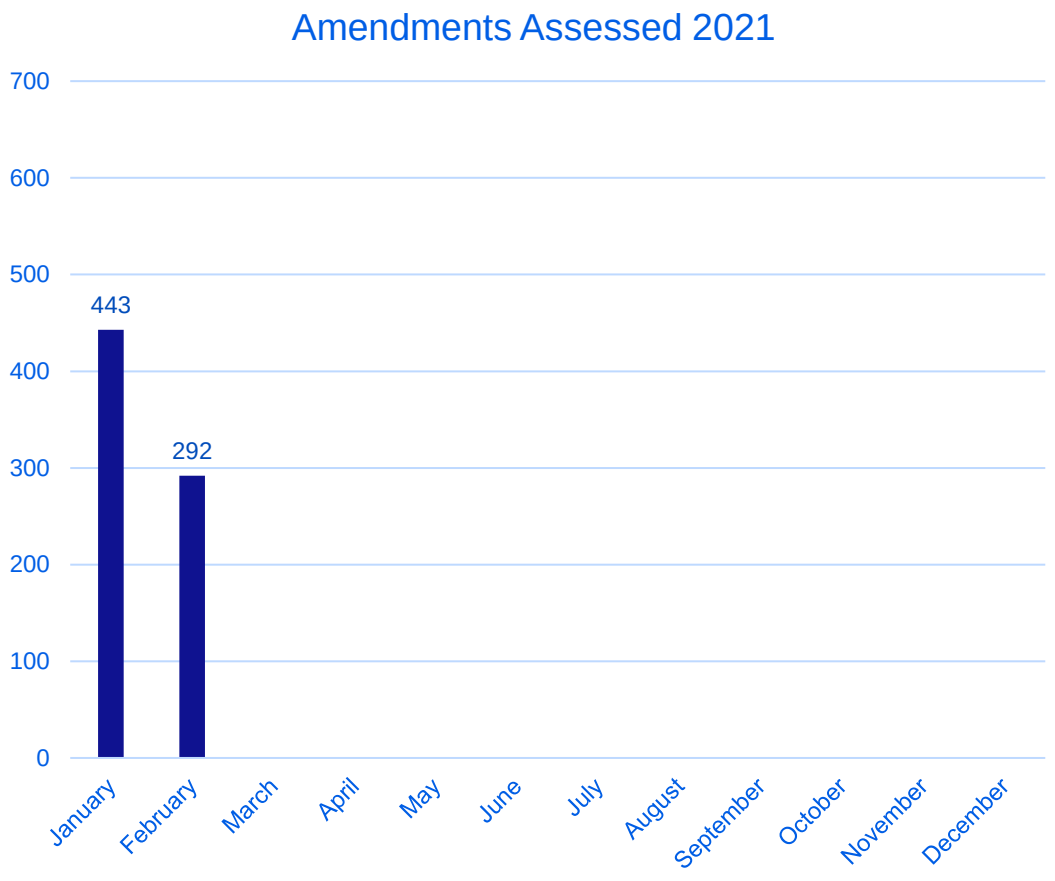
Amendments Assessed 2021
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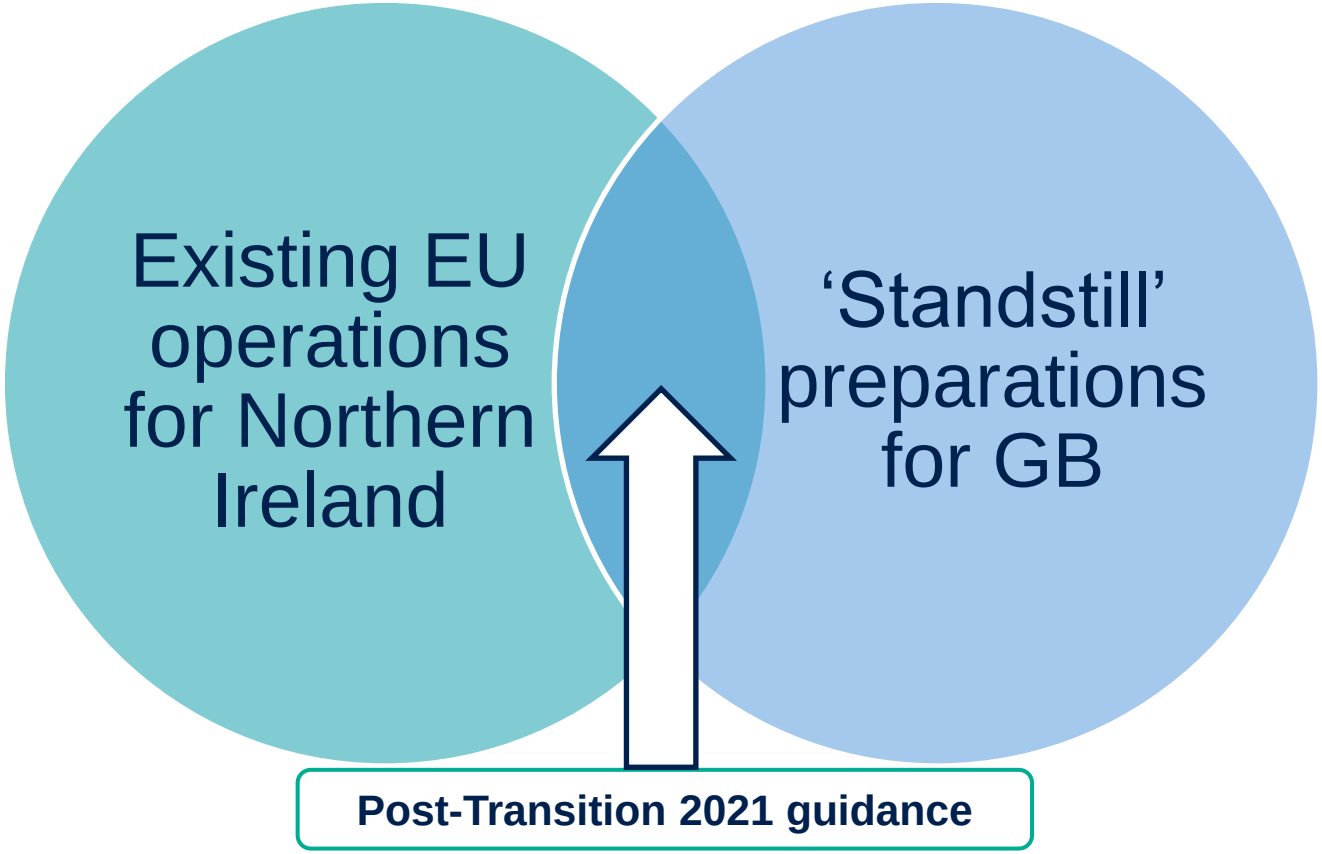
EU Exit Transition Guidance

Our approach for 1 January 2021



Guidance

- MHRA Guidance Published 1 September 2020 (updated 7 December 2020)
  - https://www.gov.uk/government/collections/mhra-post-transition-period-information
- 34 items of guidance relating to regulation of medicines and medical devices in GB from 1 January 2021
- 6 relate directly/indirectly to Clinical Trials
  - Registering to make submissions to the MHRA from 1 January 2021
  - Webinars: preparing to make submissions to the MHRA from 1 January 2021
  - Guidance on substantial amendments to a clinical trial from 1 January 2021
  - Registration of clinical trials for investigational medicinal products and publication of summary results from 1 January 2021
  - Importing investigational medicinal products into Great Britain from approved countries from 1 January 2021
  - Approved countries for definition of ‘marketing authorisation’

Sponsor / Legal Representative

- The sponsor or legal representative of a UK clinical trial must be in UK or a country on an approved country list which would initially include EU/European Economic Area (EEA) countries.
  - Approved country list reviewed every 3 years
  - Legislation to determine considerations for adding/removing countries

- After the end of the transition period, a sponsor established in UK and conducting a clinical trial in the EU must ensure that a sponsor or a legal representative is established in the EU.

- An amendment to MHRA will not be needed if a UK sponsor is adding an EU legal representative to cover EU/EEA sites.

Submitting a CTA application to MHRA

- Up until 31 December 2020, users were able to submit applications for CTAs (including Initial Applications, Substantial Amendments, End of Trial Notifications and Developmental Safety Update Reports (DSURs)) via CESP.
  - UK no longer has access to CESP

- From 1 January 2021, users will need to submit their applications via MHRA Submissions.

- All users requiring access to clinical trials submissions will need to register for access to MHRA Submissions.

- You will still be required to obtain and use a EudraCT number as your trial reference number.

Submission process

Current Process

- Get EudraCT#
- Complete application form in EudraCT or IRAS

- Download application form and XML
- Submit via CESP

- MHRA validates application
- MHRA communicates any RFI / decision directly to applicant

Process from 1 January 2021

- Get EudraCT#
- Complete application form in IRAS

- Download application form and XML
- Submit via MHRA Submissions

- MHRA validates application
- MHRA communicates any RFI / decision directly to applicant

Registration and results reporting

Registration:

- Any favourable opinion given by a UK Research Ethics Committee is subject to the clinical trial being registered on a publicly accessible database
- The HRA has made a commitment in its Make It Public research transparency strategy, in the long term, to register clinical trials on behalf of sponsors and researchers
- Until the HRA system is place, from 1 January 2021, sponsors should register UK clinical trials on an established international register such as ISRCTN registry, or ClinicalTrials.gov, to ensure the public is aware of your trial.
- Registration should occur before the first participant is recruited and no later than six weeks after recruitment of the first participant.
- Deferrals/exemptions: as per current guidelines (eg adult phase 1 studies) contact the Health Research Authority (HRA) at study.registration@hra.nhs.uk

Registration and results reporting

Summary of results:

- Sponsors of ongoing trials conducted in UK will be able to submit results to EudraCT after the end of the transition period (note that MHRA will not have access to EudraCT to update trial status)
- For new trials you should publish in the public register where your study is registered.
- As per current expectations, you should inform MHRA when this has been done and provide HRA with final study report (for trials exempt from publication provide the summary results to MHRA)

Safety Reporting: Reference Safety Information (RSI) clarification

- Currently, where an IMP has a marketing authorisation and the product is to be used in accordance with the terms of that authorisation, the summary of product characteristics (SmPC), relating to that product would be accepted as an alternative to the investigator's brochure in a clinical trial application.
- From January 2021, this will apply for IMPs that have a marketing authorisation in a listed country which would initially include EU/EEA countries.
- To harmonise RSI implementation date, in a trial with UK and EU sites the implementation date can be the date when approval has been granted in all member states and UK. To facilitate multinational trials it is recommended that amendments for changes to the RSI are submitted to UK and EU at the same time.
- As per current expectations, for trials conducted in UK the RSI cannot be used for expectedness until it has approval from MHRA

Safety reporting

- Currently SUSARs are reported via the Eudravigilance system using EVWEB or the Eudravigilance Gateway routes. The eSUSAR web reporting tool is an additional reporting route.
- From 1 January 2021, sponsors and CROs will have to submit SUSARs via the ICSR Submissions Portal or the MHRA Gateway. The eSUSAR portal will continue to be available to submit SUSARs.
- Please note: Users intending to submit SUSARs via MHRA Gateway will first need to gain access to MHRA Submissions as this is where the Gateway registration steps are performed.
- From 1 January 2021 DSURs will be submitted via MHRA Submissions portal using the Human Medicines Tile where it can be selected as an ‘Original Submission’ under the Regulatory Activity.

Safety reporting

- New guidance published in September 2020 covers procedures for registering and submitting SUSARs to MHRA using the new reporting routes.

- Short video demos and reference guides documenting registration and submission processes for MHRA Gateway, ICSR Submissions and MHRA Submissions portals

  Registering to make submissions to the MHRA from 1 January 2021

  Webinars: preparing to make submissions to the MHRA from 1 January 2021

- Registration has been open since March 2019 to enable reporters to be ready to use the new reporting routes from 01 January 2021.

Further manufacturing information

Importing and exporting

- To check the suitability of your qualifications/professional body membership: GDP.Inspectorate@mhra.gov.uk
- Queries on importing of investigational medical products (IMPs) from approval countries: gmpinspectorate@mhra.gov.uk
- Queries on exporting active substances manufactured in the UK: gmpinspectorate@mhra.gov.uk

Importing and exporting

Supplying medicines to Northern Ireland from 1 January 2021
20 October 2020 Guidance

Sourcing medicines for the Great Britain market from an approved country for import or Northern Ireland from 1 January 2021
20 October 2020 Guidance

Exporting active substances manufactured in Great Britain for use in EEA and Northern Ireland from 1 January 2021
30 November 2020 Guidance

Importing investigational medicinal products into Great Britain from approved countries from 1 January 2021
20 October 2020 Guidance

List of approved countries for authorised human medicines from 1 January 2021
25 September 2020 Guidance

Acting as a Responsible Person (import) from 1 January 2021
20 October 2020 Guidance

Register for submissions / Contact us

Register: www.gov.uk/guidance/registering-to-make-submissions-to-the-mhra-from-1-january-2021

Seek further information at: www.gov.uk/government/publications/webinars-preparing-to-make-submissions-to-the-mhra-from-1-january-2021

For enquiries relating to the Agency's planning and procedures from 1 January 2021: https://www.gov.uk/guidance/contact-mhra#enquiries-about-the-period-from-1-january-2021

(list of email addresses)

Novel trial design

MHRA continues to support novel trials

Clinical Trial Transformation Initiative (CTTI)

https://www.ctti-clinicaltrials.org/projects/master-protocol-studies

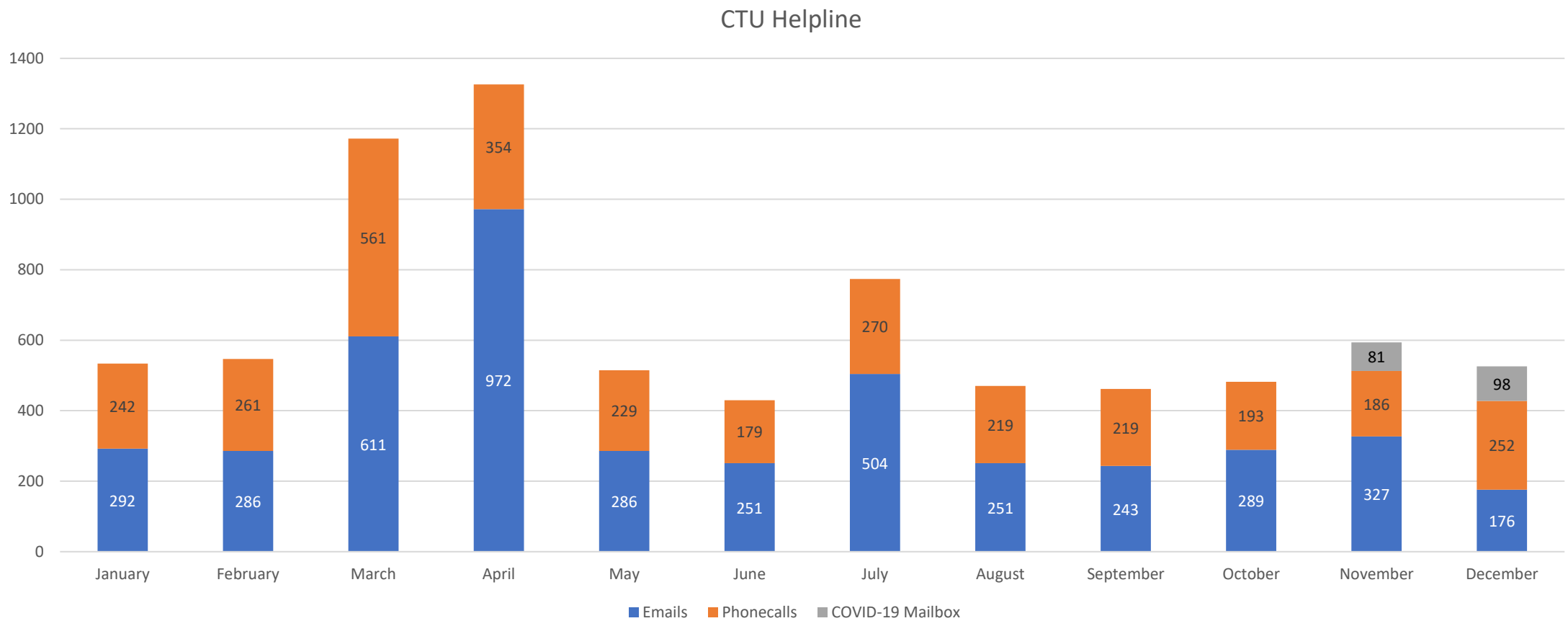
- Regulators (FDA, MHRA), academia, industry, consultants developed a guide to Master Protocol trials
- Set of tools to guide appropriate use of master protocols
- Launched: 13th of October 2020
- Pre-planning tools, as well as planning and implementation, study simulation tool and protocol development map

MHRA implementation plan for novel trials as part of LSIS

- Key outcome: Strengthened UK environment for clinical research that provides support for innovative trial design
- Included
  - Engagement with stakeholders on novel trials and our advice services
  - Workshop – October 2020
  - Internal training
  - Report

COVID-19

Helpline


CTU Helpline
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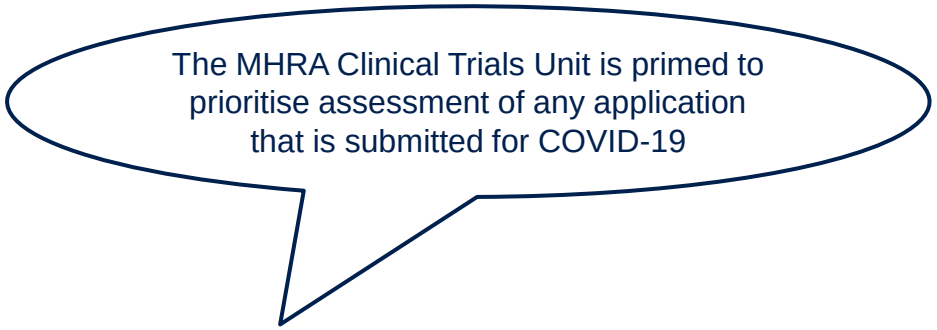
Emails
Phonecalls
COVID-19 Mailbox

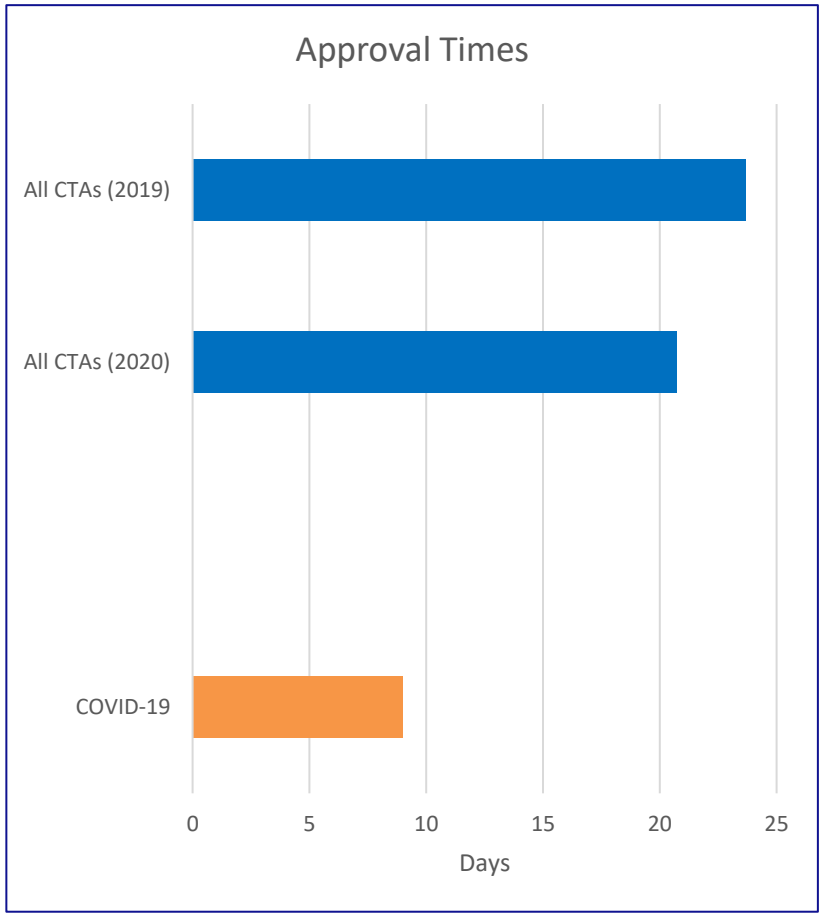
Early COVID-19

- Expedited clinical trial review (with an optional informal pre-assessment process prior to the formal submission) became key
- Dedicated assessment team for COVID-19 trials, others overseeing non-COVID-19 work
- Established that all Clinical Trial Authorisation applications for COVID-19 required Expert Advisory Group review
- Close liaison with HRA already in place – continued to work for COVID-19 trials



Approval times: Jan-Aug

- “All CTA” times are time to first review
- COVID-19 times are time to approval (first and second review)

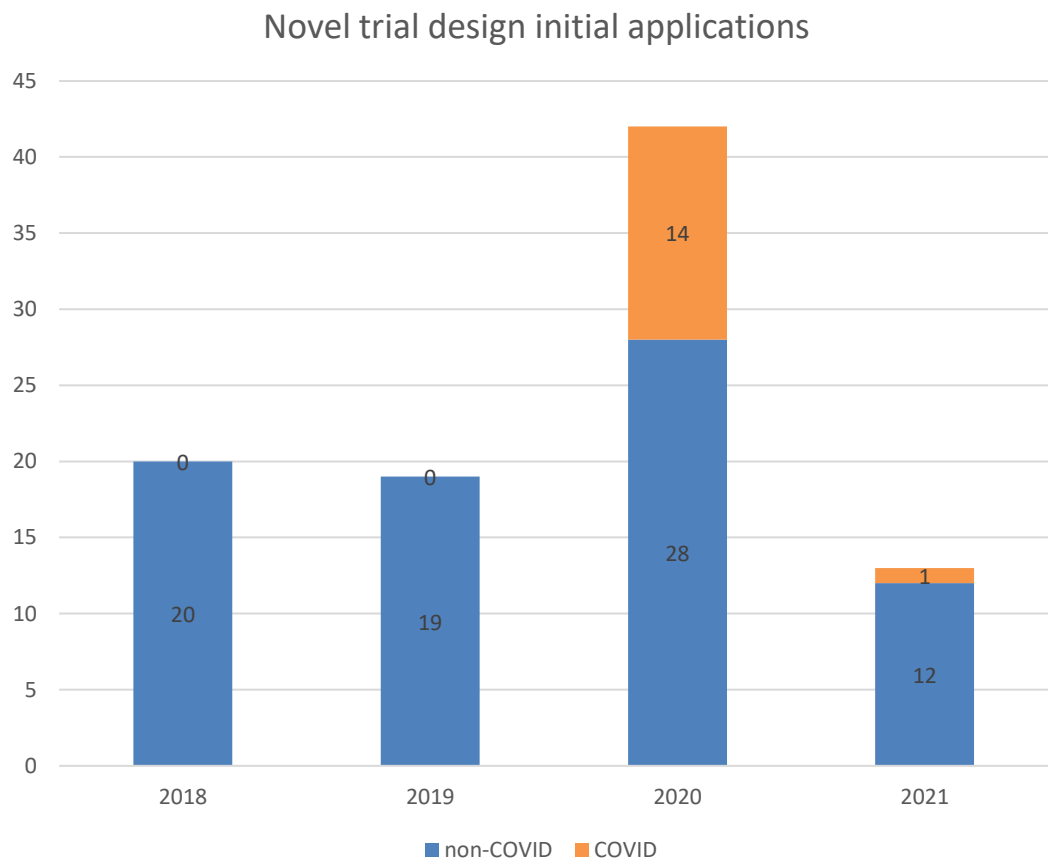


Novel trial designs

MHRA CTU has been tracking these trials since January 2018.

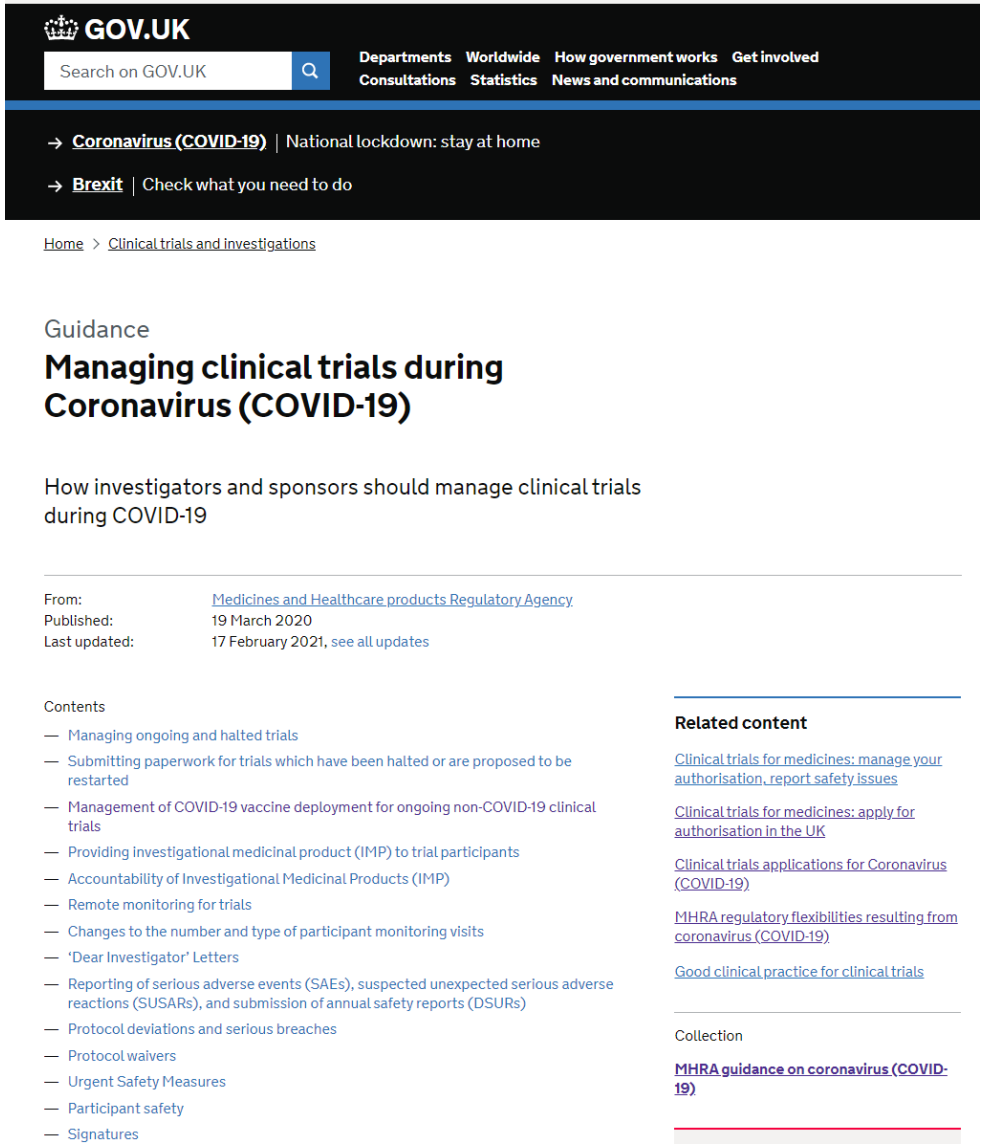
COVID-19 saw a rise in submissions – supported by NIHR and Chief Medical Officer

- Recovery
- Principle
- REMAP-CAP
- Others…..



Lots of information…

[Managing clinical trials during Coronavirus (COVID-19) - GOV.UK (www.gov.uk)]



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→ Coronavirus (COVID-19) | National lockdown: stay at home

→ Brexit | Check what you need to do

Home > Clinical trials and investigations

Guidance

Managing clinical trials during Coronavirus (COVID-19)

How investigators and sponsors should manage clinical trials during COVID-19

From: Medicines and Healthcare products Regulatory Agency
Published: 19 March 2020
Last updated: 17 February 2021, see all updates

Contents

Related content

Clinical trials for medicines: manage your authorisation, report safety issues

Clinical trials for medicines: apply for authorisation in the UK

Clinical trials applications for Coronavirus (COVID-19)

MHRA regulatory flexibilities resulting from coronavirus (COVID-19)

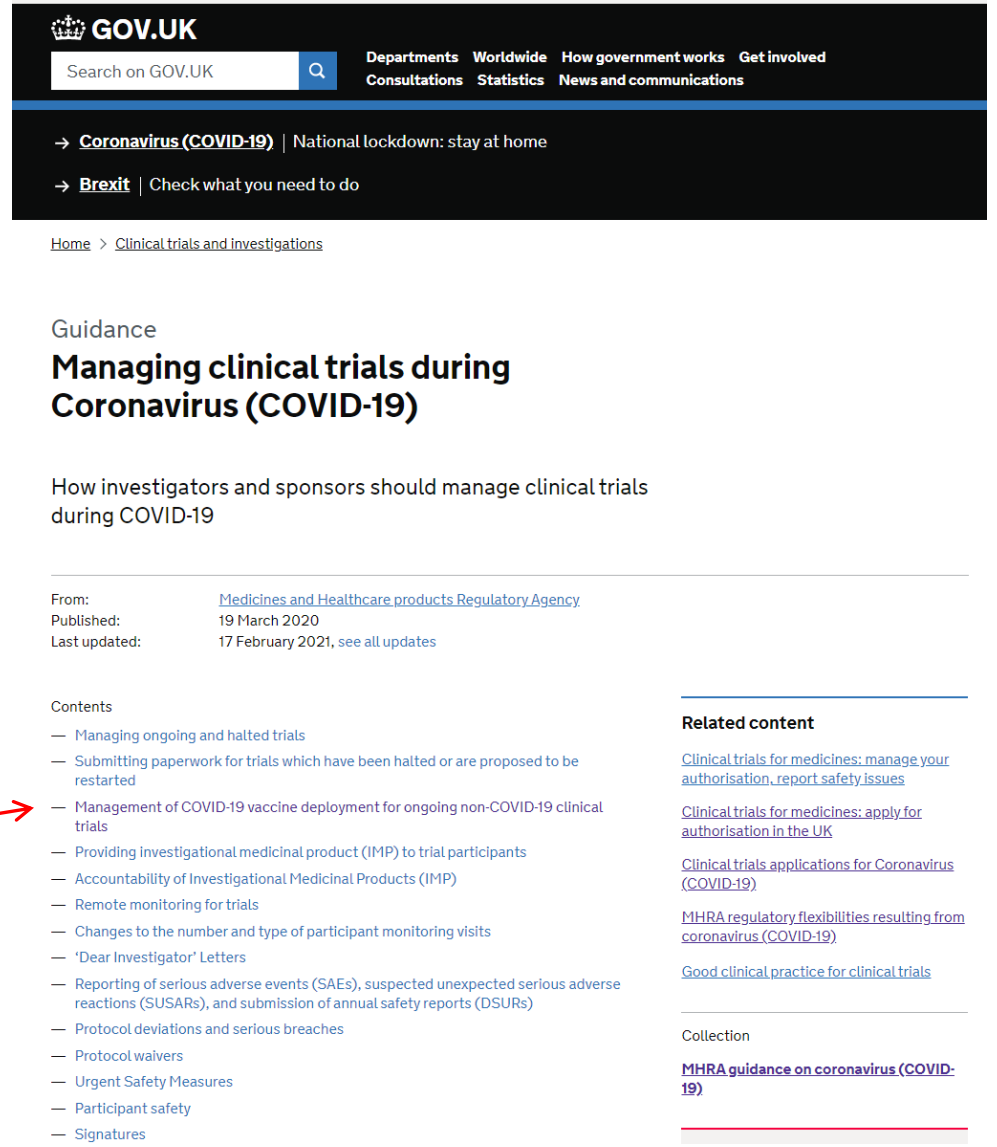
Good clinical practice for clinical trials

Collection

MHRA guidance on coronavirus (COVID-19)

Lots of information…

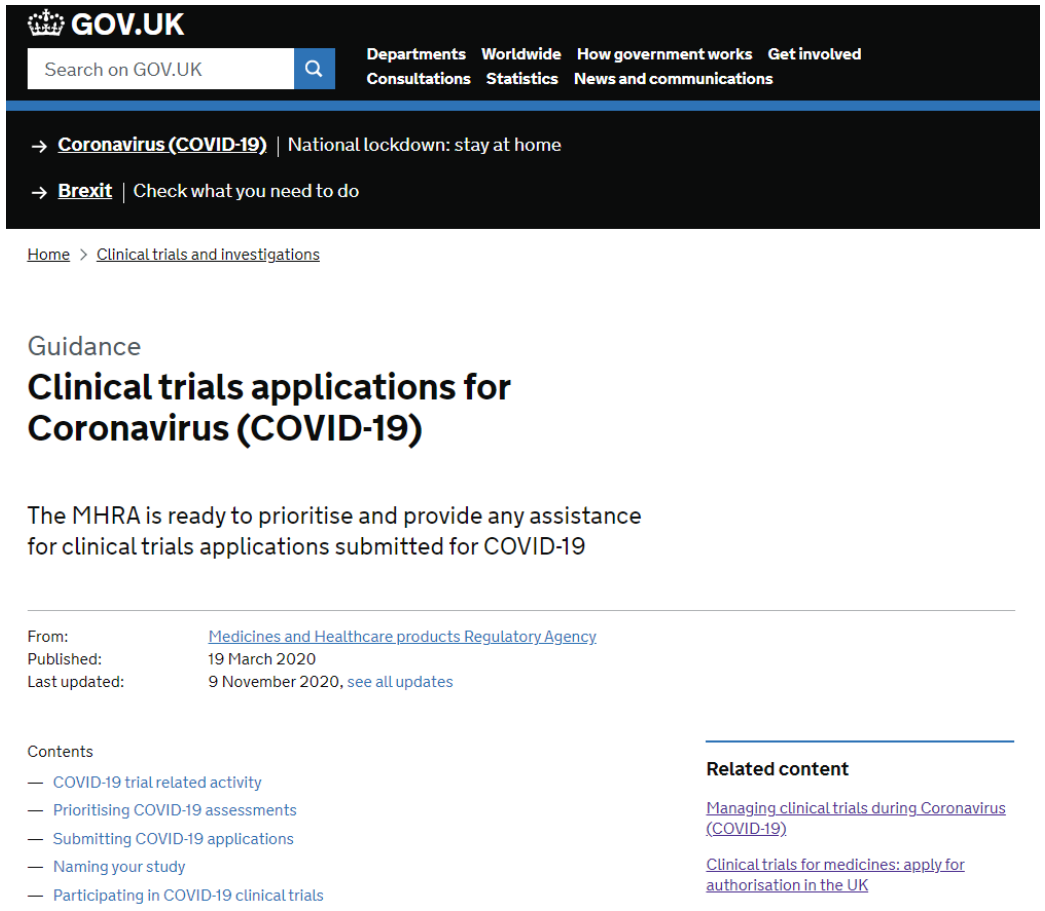
[Managing clinical trials during Coronavirus (COVID-19) - GOV.UK (www.gov.uk)]



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

COVID trial applications



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Guidance

Clinical trials applications for Coronavirus (COVID-19)

The MHRA is ready to prioritise and provide any assistance for clinical trials applications submitted for COVID-19

From: Medicines and Healthcare products Regulatory Agency
Published: 19 March 2020
Last updated: 9 November 2020, see all updates

Contents

— COVID-19 trial related activity
— Prioritising COVID-19 assessments
— Submitting COVID-19 applications
— Naming your study
— Participating in COVID-19 clinical trials

Related content

Managing clinical trials during Coronavirus (COVID-19)

Clinical trials for medicines: apply for authorisation in the UK

The clinical trials unit have set up a specific mailbox for COVID-19 related trial activity;

Covid.clinicaltrials@mhra.gov.uk

This must be used instead of the previously used clinical trial helpline email.

So how does the COVID-19 work and lessons learnt combine with our experience with novel trial design to inform on the ambitions for the future?

Innovative licensing and Access Pathway

Innovative Licensing and Access Pathway

- **Goal**: to deliver efficient and timely development of medicines and earlier patient access

- A new medicine designation links to the development of a roadmap to patient access – **Innovation Passport**

- **Target Development Profile** (TDP) creates a unique UK roadmap, utilising tools from a toolkit and providing a platform for sustained mutli-stakeholder collaboration

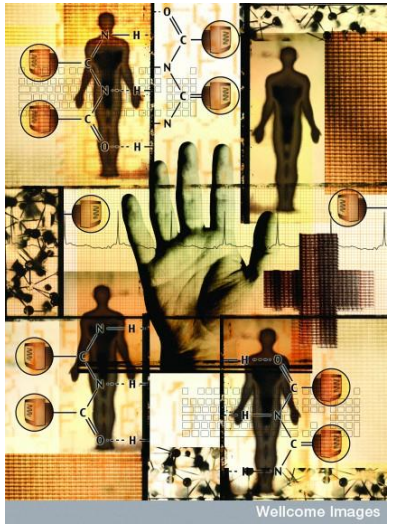
- The regulatory toolkit is intended to drive efficiencies in the development programme, supporting data generation and evidence requirements

- An integrated pathway will pull together expertise from across the MHRA and partners in the wider healthcare system including NICE and the SMC

- Built-in flexibility, with multiple entry points along the pathway (non-clinical data → clinical trials)

Some of the tools being developed in the Toolkit

- Adaptive inspections
- ATMP Centre accreditation*
- Novel CT methodology & design support
- Common medicine & device trial design
- Coordinated approvals process for co-developed medicines & IVDs
- CPRD assisted recruitment in clinical trials
- Rapid Clinical Trial Dossier pre-assessment service
- Certifications



- CPRD control groups
- Enhanced patient engagement
- Continuous benefit-risk assessments that integrate real word evidence
- New licensing procedures:
  - Rolling review
  - Accelerated timetables for marketing authorisation, flexibilities
  - International options
    - FDA Orbis
    - ACCESS

*contact GCP.inspectorate@mhra.gov.uk

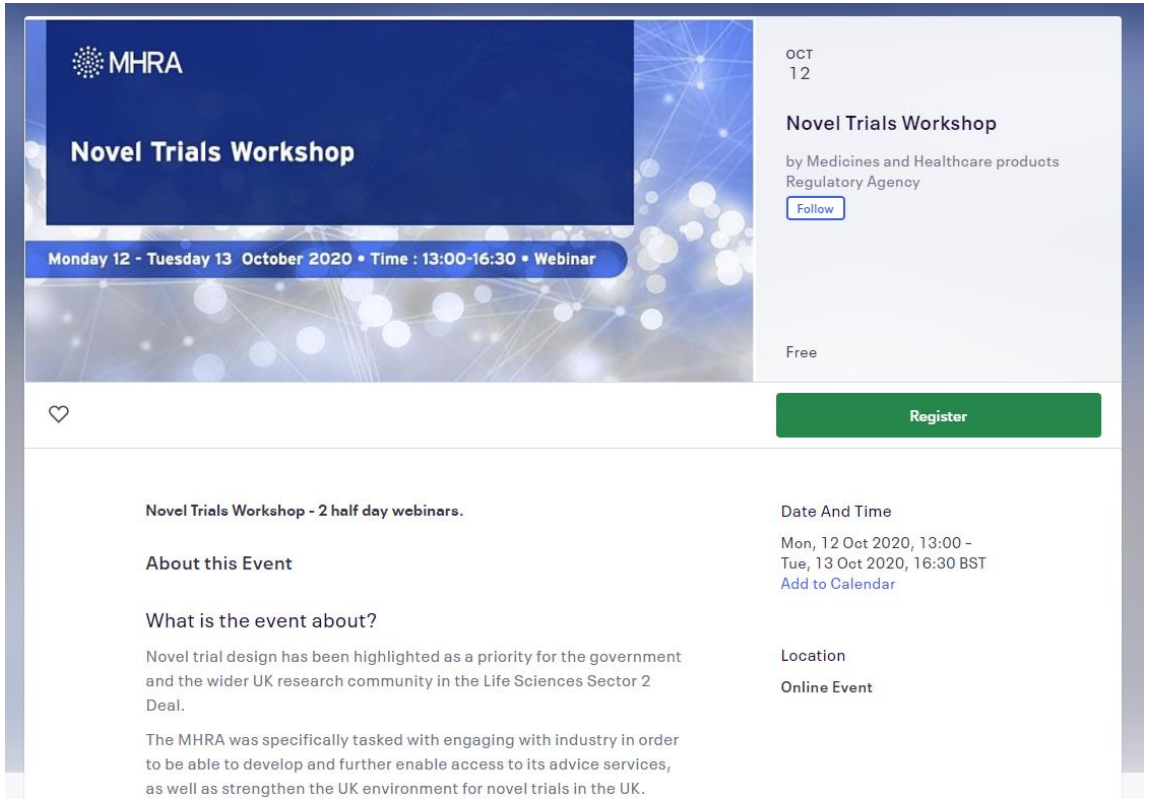
Pre-assessment service

MHRA will offer a service for sponsors of designated clinical trials to assist with finalisation of their key documentation (protocol, IB, IMPD) for application for a Clinical Trial Authorisation (CTA).

CTU assessment team will provide feedback on documentation in an expedited timeframe to facilitate document finalisation and internal sign offs prior to the project entering the critical path. This will greatly improve the chance of the application receiving a CTA without additional requests for further information at the time of the formal submission.

Regulatory support for novel CT methodology & design

- Guidance
- Events
- Publications



https://www.eventbrite.co.uk/e/novel-trials-workshop-registration-116984195879

Enhanced scientific support

Early engagement support and advice, joined-up with HRA, and others, where appropriate (via MHRA Innovation Office)

Promote early engagement throughout the development lifecycle, as part of a wider more flexible regulatory system

Continued streamlining of reviews/approvals with HRA – combined ways of working

Consideration for how the patient voice can be heard

Enhanced patient engagement

- Enable patients to add their perspective on benefits and risks of medicines, relevance of efficacy endpoints e.g. through contribution to guidance, specific product interactions

- Wider ambition which recognises patients as partners, transforming our activity, culture and reputation in the minds of patient groups

MHRA launches consultation on how to best engage patients and the public

The Medicines and Healthcare products Regulatory Agency (MHRA) has today launched a 12-week consultation on how to best engage and involve patients in the Agency's work.

Published 15 July 2019
From: Medicines and Healthcare products Regulatory Agency

The responses will help inform the MHRA's future engagement with patients and the public.

The MHRA wants to adopt a more systematic approach to listening to and involving patients. They want to make sure that the patient voice is more clearly heard when safety issues, concerning medicines or medical devices, are identified and in the licensing of new medicines.

Summary

Integrated approach to support innovation in design through continued engagement with industry, charities, patients and research bodies such as the ECMC.

Develop components of a regulatory toolkit composed of required components (tools that ensure regulatory compliance) as well as those that can be selected individually to support a bespoke development programme that reflects a lifecycle approach to evidence generation.

Questions?

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