ECMC Centre Business Leads Restart Considerations Guidance

ECMC Programme Office

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Content

Latest update April 2020: DHSC Central portfolio prioritisation exercise

NIHR Managed Recovery

The DHSC has asked NIHR to work with research funders and partners across the research system to develop and implement a plan to manage the recovery of multi-site studies over the next 6-12 months.

The plan aims to support interventional, multi-site clinical research studies that are both urgent and should benefit from the support of NIHR CRN and its Devolved Administration equivalents to enable them to fully recruit and/or close in the next year.

NIHR CRN will establish a partnership through which studies can be collated, prioritised and collectively supported to deliver as fast as possible.

Both commercial ad non-commercial funders have been asked to identify a list of specific studies deemed as most urgent to NIHR CRNs.

NIHR CRN, working with the LCRNs, Devolved Administrations (DAs) and R&D teams, will provide an assessment of the deliverability of studies identified by the funders and subject to a positive outcome of this, will direct research delivery support to the studies. Studies for which challenges in deliverability are identified, will be highlighted to funders and options for their management presented.

Guidance for Funders on managed recovery prioritisation avaible on Centre Business leads Forum Teams channel

Government's new vision for the Future of UK Clinical Research Delivery: https://www.gov.uk/government/publications/the-future-of-uk-clinical-research-delivery/saving-and-improving-lives-the-future-of-uk-clinical-research-delivery#where-we-go-from-here

Purpose & Background

This guidance is for members of the ECMC network and identifies key points for consideration when planning to restart local experimental medicine clinical trials

Purpose

The Experimental Cancer Medicine Centre (ECMC) network is made up of 18 adult centres and 11 paediatric centres across the UK. The Centre business leads from these centres and their operational teams worked collaboratively to produce this guidance. This document contains information that centres may find helpful to consider when reviewing and making improvements to local restart frameworks for set up (where applicable) and to open early phase oncology trials that were either paused or closed during the Covid-19 pandemic and to keep them open and recruiting during subsequent waves of lockdown.

The contents of this document are not intended as definitive Network guidance on what a restart prioritisation framework should be but as suggested guidance based on experiences and approaches across the Experimental Cancer Medicine Centre (ECMC) Network and in line with guidance from the NIHR and NHSE. This guidance should be used in conjunction with relevant Trust policies and regulatory guidance.

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Background: The impact of Covid-19 on Experimental Cancer research at centres

Trusts research teams were redeployed to support the Covid-19 research and front-line clinical services

Research trials were paused, closed or suspended by sponsors, funders, investigators and sites

The NIHR Restart Framework was introduced May 2020

- **Level 1:** Essential studies providing evidence for pandemic management, i.e. nationally prioritised COVID-19 Urgent Public Health (UPH) Research studies.
- **Level 2:** Studies where the research protocol includes an urgent treatment or intervention without which patients could come to harm. These might be studies that provide access to potentially life preserving or life-extending treatment not otherwise available to the patient. Experimental Cancer early phase studies fell into this category.
- **Level 3:** All other studies (including new COVID-19 studies not in Level 1).

ECMCs planned a phased restart of experimental cancer studies, prioritising the safety of patients and staff and aligning with the NIHR Restart Prioritisation categorisation

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Background: The impact of Covid-19 on Experimental Cancer research at centres

The ECMC Programme convened Centre Business Leads from across the adult and paediatric networks to discuss current challenges and mitigation plans from an operational perspective. A sub group was tasked with identifying the impact of the pandemic on early phase oncology trials at ECMC's and a survey was conducted in July 2020 during the first wave to understand the impact on trial restart, monitoring and operational practicalities.

20 of the 18 adult and 11 paediatric ECMCs responded to the survey.

For restart, oncology trials that were paused was a primary focus for the ECMCs. 100% of ECMCs either successfully reopened some of their early phase oncology portfolio or never closed their active studies.

Prioritisation of which trials were reopened first varied by location.

The most common barrier to restart was due to reduced support service capacity, Covid-related safety measures, and negotiating changing monitoring methods with trial sponsors, which are covered in this guidance.

Principal Investigators (PIs) worked in consultation with local NHS R&D to assess pharmacy and radiology service capacity, departmental capacity, and risk to patients in order to prioritise trial restart.

While resource was diverted to restart trials that were paused and to make the necessary changes, most Centres were able to continue with elements of setup activity. However, R&D capacity was a limiting factor to progressing studies that were in setup. New studies in setup were assigned different priorities within the Centre portfolio depending on local capacity and approach to restart, with a large tranche of centres prioritising restart over new trials.

The NIHR prioritisation framework was used in most English ECMCs, others used their own framework or a combination of their own and the NIHR framework

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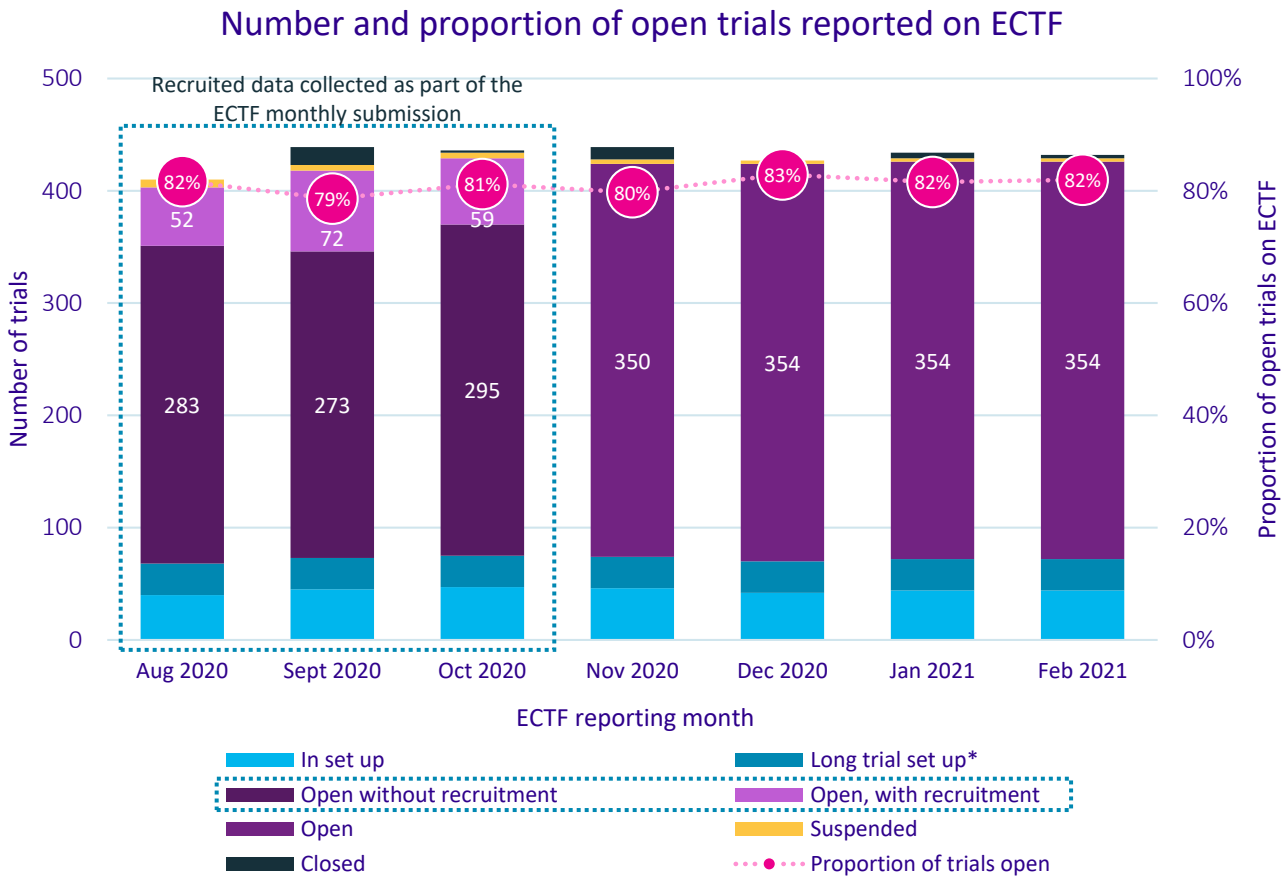
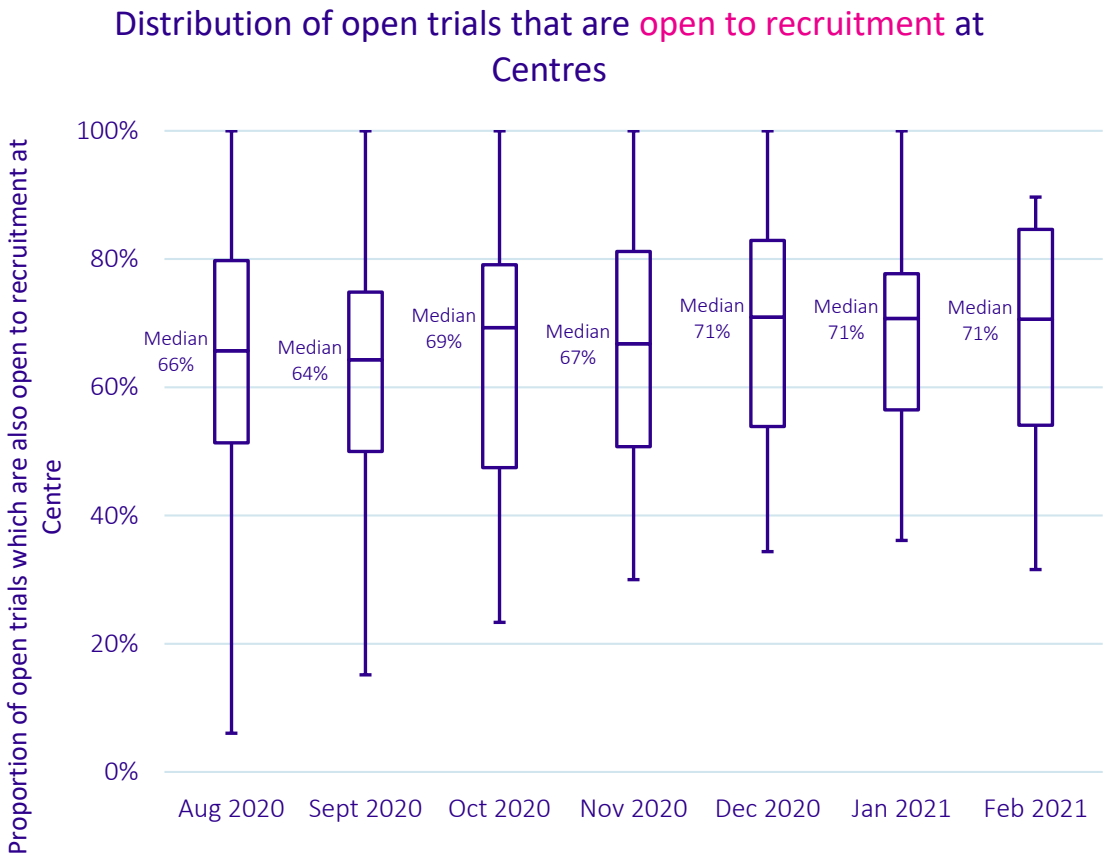
Open trials reported on ECTF Aug 20 – Feb 21

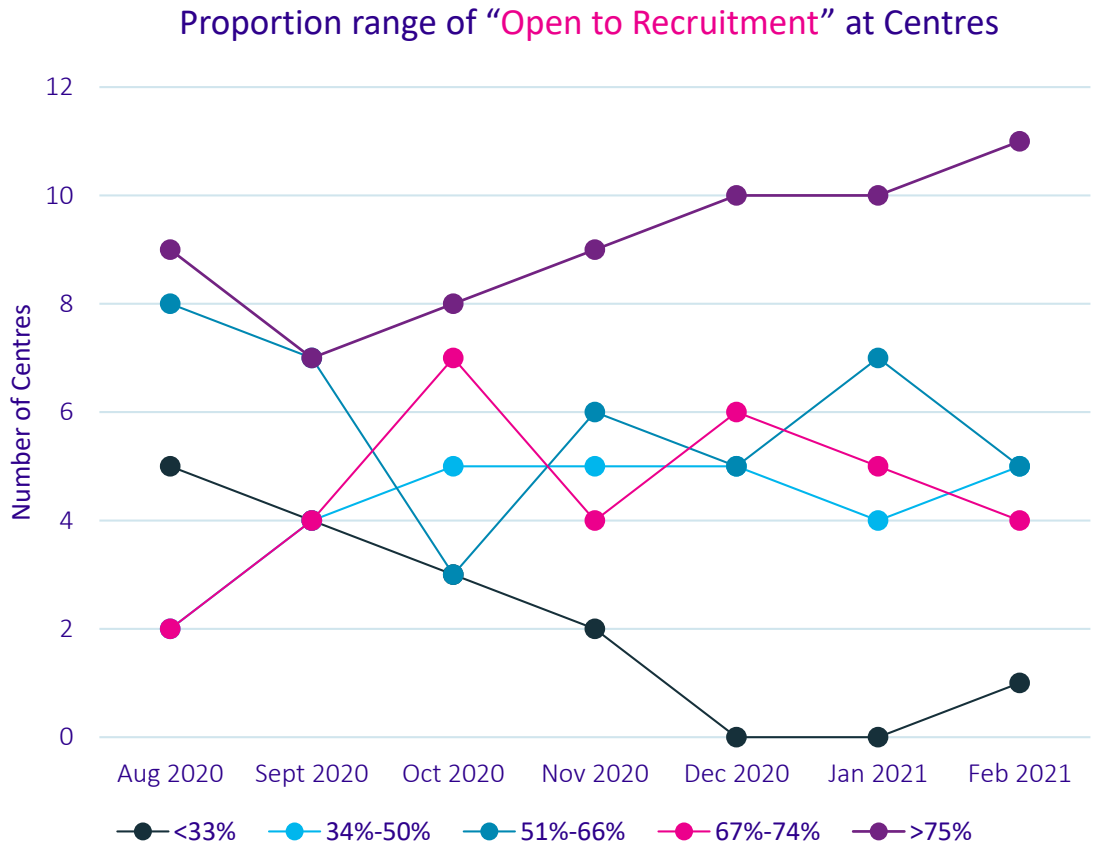


- The number of trials open has remained fairly stable pre and during the current COVID wave
- The open trials in the first 3 months includes number of trials where centres reported at least 1 patient recruited vs open with no recruitment
- There were 28 trials which remained in set up during the reporting period

* Long trial set up: where trials have remained in setup throughout the presented timeframe

Breakdown of open to recruitment centre status for open trials

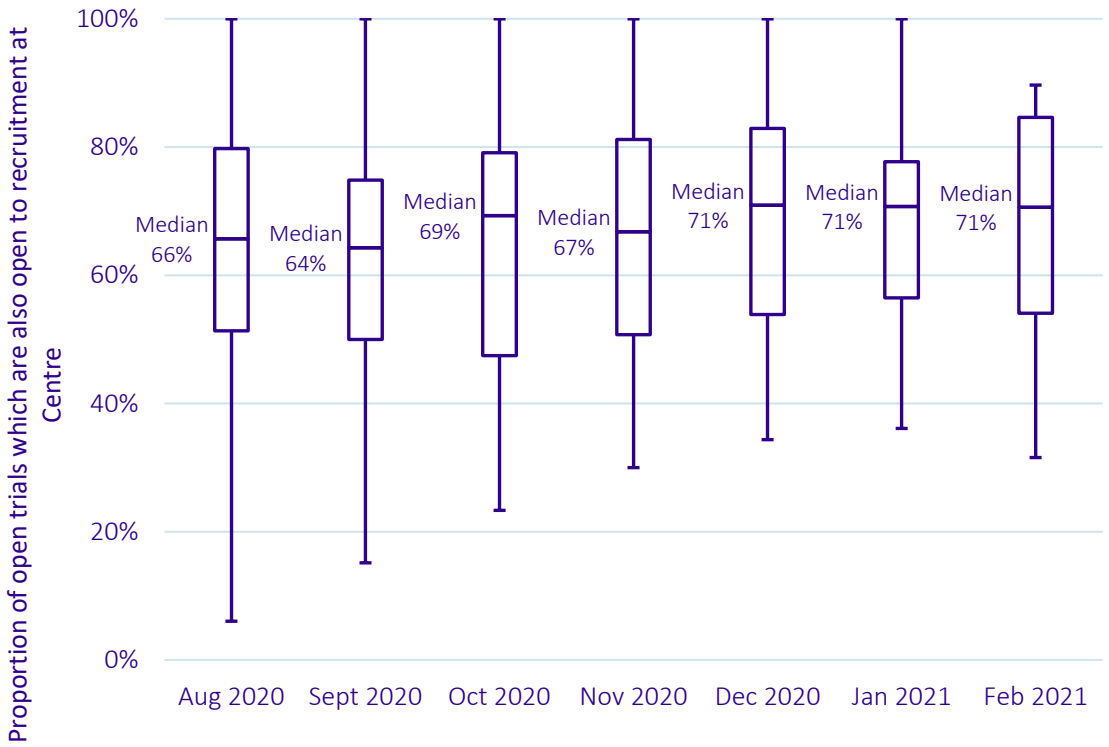




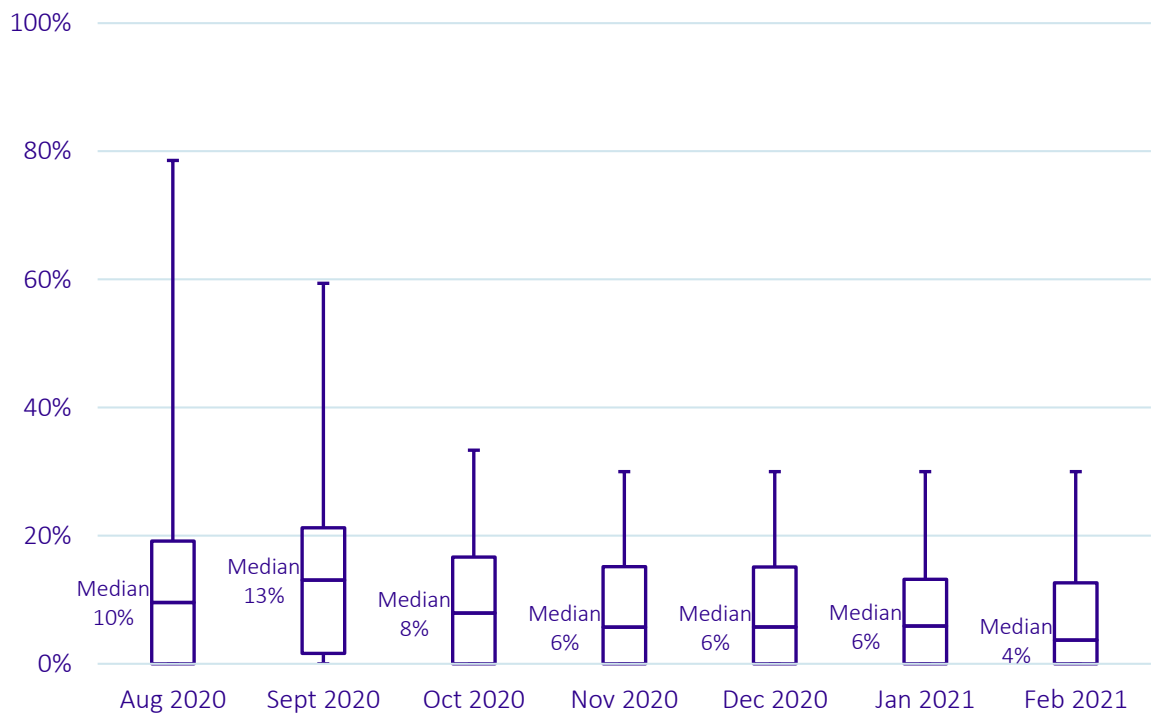
1 Centre had 100% trials open to recruitment except for Feb 2021
There are 26 Centres listed on ECTF as some paediatric centres report via the adult centre

Centre recruitment status distribution for open trials

Distribution of open trials open to recruitment trials at Centres

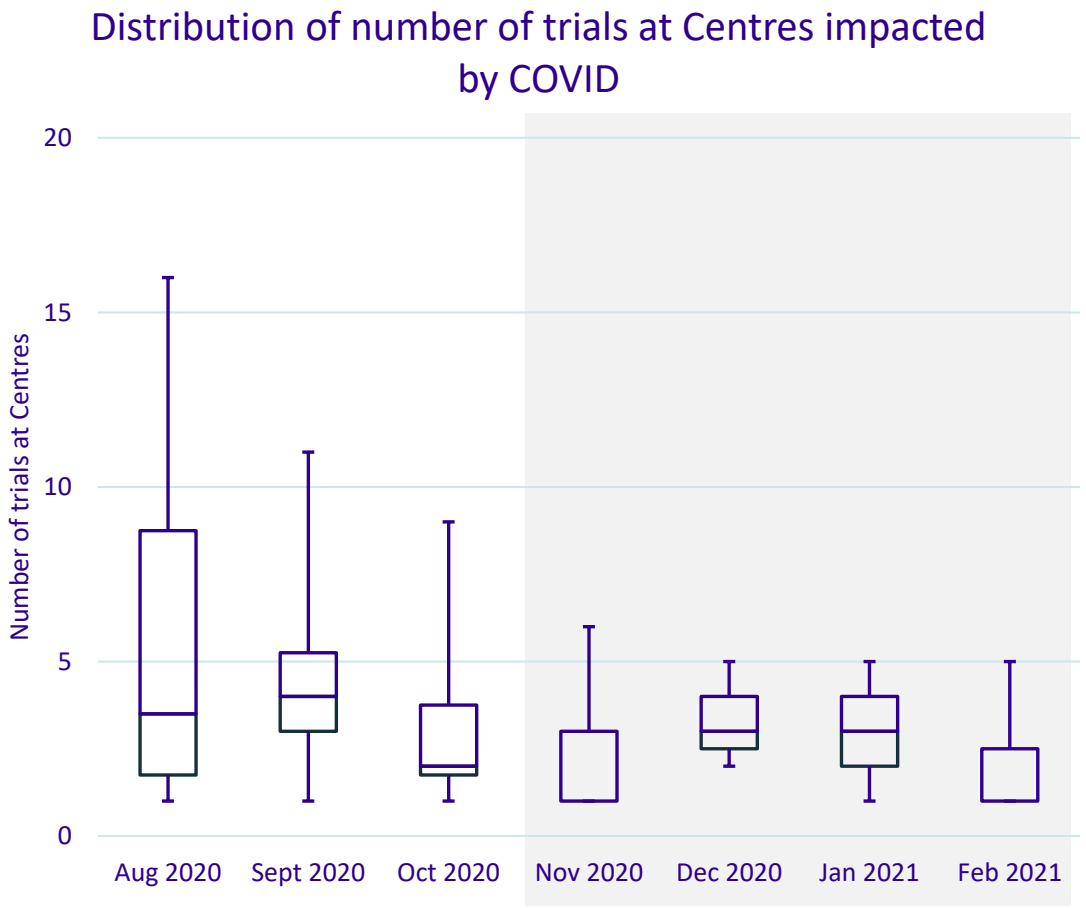


Distribution of proportion of PAUSED trials at sites



There is a slight decline in the number of trials being paused at Centres over the current wave.
This includes all paused trials, including those due to COVID

COVID impact at Centres



- This graph looks at the distribution of the number of trials reported as being impacted by COVID by Centres
- Includes all trials regardless of Trial status
- There is a slight increase at the start of the current wave but this soon tailed off.
- From Nov 2020 onwards, the completeness of the cause for the pause/ early closure is more variable as not all of the data was completed

COVID impact on trials by cancer type

- A total of 72 trials reported specific COVID impact on recruitment/early closure
- 18/72 are investigating at least 1 Haematological Cancer type
- 15/72 trials are investigating more than 1 ECTF Cancer Type*

* In ECTF terms, All Solid counts as 1 cancer type as does All Haematological

Top 5 common cancer types included in trials impacted by COVID

ECTF Cancer Type	No. of trials
All-Solid	12
Breast	12
Small Cell Lung Cancer	11
Non-Small Cell Lung Cancer	8
Hepatocellular Carcinoma	6

There were no clear differentiators in terms of cancer type and treatment modality linked to impacted trials to make any robust conclusions

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COVID impact on recruitment status variability across multi-site trials

- There weren't many trials where there was a sizable difference between number of Centres open to recruitment vs centres paused to recruitment
- There were 3 trials with a noteworthy difference between open and paused
  - A First-in-human, Multi-center, Open-label, Phase I Clinical Study with RNA Oligonucleotide Drug MTL-CEBPA to Investigate Its Safety and Tolerability in Patients with Advanced Liver Cancer (OUTREACH)
    - 7 Centres reported this trial – average 1.6 Centres are open to recruitment each month that leaves 3.7 Centres paused each month
    - lead site is reporting it as open to recruitment each month
  - A Phase I/IIA Study to Assess Safety, Tolerability and Preliminary Activity of the Combination of FAK (Defactinib) and PD-1 (Pembrolizumab) Inhibition in Patients with Advanced Solid Malignancies (FAK-PD1)
    - 4 Centres reported this trial – average 1.3 Centres reported open to recruitment each month with average of 2.7 centres paused
    - lead site is reporting it as open to recruitment each month
  - Phase II Trial of Pembrolizumab and Radiotherapy in Cutaneous T cell lymphoma
    - 4 Centres reported this trial – 50% split between Centres open to recruitment vs paused

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Restart Considerations

General Restart Considerations

- A flexible restart framework to manage increased waves of infection
- Adapting research facilities to keep staff and patients safe
- Research staff not to be redeployed unless unprecedented clinical demand is met.
- Feasibility for a flexible workforce that covers 7 days per week to manage operational practicalities and trial delivery
- Research staff working from home have secure IT access to Trust systems. Follow Trust Information Governance policy introduced during pandemic
- Aim to retain skill mix in early phase unit when considering redeployment

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General Restart Considerations Contd.

- Increased demands due to sickness and staff redeployment
- Staff track and trace procedures. Additional resources required in team if not managed by Trust Occupational Health department
- Important to include support services representatives on restart panels to advise on general capacity
- Early phase team and support services should keep measuring capacity against reopening of portfolio.
- Can support service departments pre-assign capacity (monthly) for research trial patients i.e. number of scan slots, biopsy slots. Will also help avoid protocol deviations
- Utilise private sector and academic links where possible to minimise impact on NHS support services

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Prioritisation Considerations

Prioritisation Considerations - General

- Aligning with the NIHR Restart Prioritisation categorisation. *Scotland and the other devolved administrations have been fully involved in the development of this restart framework and are supportive of the guiding principles and prioritisation criteria*.
- Health and safety of staff and patients, adapting research facilities in line with local and national policy. Follow govt and Trust guidance on social distancing, use of PPE and travel
- Making the restart framework flexible to manage increased waves of infection
- Scientific integrity of the study is compromised with data return, safety reporting and oversight of amendments. E.g. dose escalation
- Where patient assessments and monitoring are likely to be impacted by site staff availability or social distancing rules can a trial's assessments be minimised to essential information only
- Generating a risk assessment & mitigation plan for all studies. This is consideration for prioritisation as high risk trials are more likely to be a low priority, medium risk trials with mitigation plan can become a higher priority. *Risk assessment checklist available on slide 16*

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Prioritisation Considerations – Trial Management

- New training requirements for trial to continue
- Sponsor requirements:
  - confirmation to restart,
  - Covid-19 related amendments,
- Have protocol amendments been implemented by sponsors to reduce risks and number of visits for participants
- Where possible can remote trial management be done i.e. SIVs and monitoring visits
- Remaining number of patients to recruit pre-COVID?
- Is drug available via compassionate use or licensed
- Volume of trial data to be entered per visit/patient

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Prioritisation Considerations – Patient Management

- Covid-19 testing and PPE requirements
- Patient demographics and specific care needs
- Can any patients visits be done remotely to avoid risk of Covid-19
- Does the patient population have any other factors and conditions which could increase risk for patients to COVID-19 due to participation (e.g. diabetics, elderly)?
- Does benefit of participation offset the magnitude of risk?
- Face to Face visits kept to a minimum e.g. Clinical Trial Medication: patients keep their returns and bring remaining medication back at a later visit, remote consent
- Increased risk of complications of Covid-19 posed by intervention (immunosuppression)
- Risk that cancer patients become unwell if they do not have access to treatment as part of a research trial as it's the only option available for their care
- Estimated recruitment for next XX months
- How many patients are left to recruit?
- Where possible, can trial be delivered remotely i.e. pre-screening, follow up visits by telephone or video conferencing
- Where a trial can continue, routine follow-up and monitoring activities are likely to be impacted by investigator site staff availability or social distancing rules. Care should be taken to ensure that these are minimised to essential information only (e.g. primary endpoint data and safety reporting) until normal capacity resumes.

Patient & Public Involvement

Update local PPI groups on restart strategy and ask their advice

Prioritisation Consideration – Workforce

- Staff available to cover remote or onsite delivery of trial including Dr, RN, pharmacy and radiology. Also factoring in staff for reporting SAE's and documentation.
- What role/type of staff needed to support trial delivery

Prioritisation Considerations - Capacity

- Clinical pathway changes impacting on ability to recruit patients to trials
- Access to intensive care for early phase trial patients required for trial
- Restricted facility space available due to social distancing measures that are in place and required space for trial
- Sponsor requirements for monitoring (e.g. number of monitoring visits)
- Existing backlog of data and/or queries to be resolved

Prioritisation criteria – Capacity: Support Services

- Volume of Imaging for trial patients; increased cleaning in-between procedures
- Can delivery of trial medication to patient by courier be considered or is it a requirement (cost and organisational implications.)

Examples of prioritisation based on the considerations in previous slides

High

- Studies that can provide patients with a diagnosis e.g. new genetic disorder
- Studies where the only treatment option for patients is an early phase experimental cancer trial and other care options are not effective
- Studies where the protocol includes an urgent treatment or intervention without which patients could come to harm
- Trust sponsored studies where recruitment period is closest to ending.
- Low impact studies that require minimal support from support services to deliver

Medium

Studies where there is a safe and effective 'usual care' treatment option for patients not enrolled in the trial, e.g. a RCT of novel antihypertensive versus standard care, or a device study where an alternative device or treatment option exists

Low

Studies that will require significant support from support services facing reduced capacity due to COVID-19 e.g. requirement for intensive care pathway

Observational/phenotypic, tissue bio-bank, qualitative studies. *Not applicable to early phase oncology but will be considered as part of the bigger Trust R&D Portfolio*


Risk Assessment

Risk assessment of trials: RAG rating criteria

These criterion have been collated from the network centres and is not an exhaustive list

- Sponsor requirements for patient safety linked to risks of Covid-19.
- Availability of PI - clinical commitment / shielding etc
- Additional staff required to support study
- Level of immunosuppression from the IMP's
- Patients already enrolled on study: Number of visits to hospital required
- Length of stay for research visit
- Requirement for pre visit PCR swabs
- Can follow up continue with Telemedicine
- Potential ability to outsource trial to homecare nurses.
- Intensity of schedule of event
- Impact on service support departments heavily burdened by COVID (ie radiology, pharmacy, lung function etc)
- Mandatory biopsy requirements
- Patients required to attend site for safety reasons (e.g. blood tests for toxicity)
- Requirement for more than basic PPE (i.e. gowns/visors/FFP3 masks) based on Scenarios?
- Request to use additional onsite space or relocate service
- Staffing, Procurement or estates considerations which may impact on other Trust services or COVID surge plans

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Useful Links

Links to Guidance: NIHR and Government

A framework for restarting NIHR research activities which have been paused due to COVID-19:
https://www.nihr.ac.uk/documents/restart-framework/24886

NIHR Guidance on funding cost of redeployed research staff:
https://www.nihr.ac.uk/documents/guidance-on-funding-the-cost-of-research-staff-redeployed-to-the-nhs-during-the-covid-19-pandemic/25208

Guidance for the prioritisation of NIHR infrastructure resources (including NIHR Clinical Research Network resources) during a 'second wave' of high COVID-19 activity. The guidance applies to England, but has been developed in consultation with representatives of the devolved administrations, who may themselves publish analogous guidance in due course.
https://www.nihr.ac.uk/documents/nihr-guidance-for-a-second-wave-of-covid-19-activity/25837

Government guidance on safer travel:

https://www.gov.uk/guidance/coronavirus-covid-19-safer-travel-guidance-for-passengers

Government guidance for people who work in or run indoor labs and research facilities and similar environments:
https://www.gov.uk/guidance/working-safely-during-coronavirus-covid-19/labs-and-research-facilities

Government's new vision for the Future of UK Clinical Research Delivery

https://www.nihr.ac.uk/news/nihr-welcomes-new-vision-for-the-future-of-uk-clinical-research-delivery/27308

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Links to Guidance: Scotland

NHS Research Scotland Re-starting non-COVID-related clinical research

Approach across NHS Research Scotland
http://www.nhsresearchscotland.org.uk/coronavirus/arrangements-for-clinical-trials

CSO Statement on guidance to protect research during a second wave of COVID-19 activity

http://www.nhsresearchscotland.org.uk/news/cso-statement-on-guidance-to-protect-research-during-a-second-wave-of-covid-19-activity

Links to Guidance: CRUK

Coronavirus (COVID-19): information for grant applicants and grant holders:

https://www.cancerresearchuk.org/funding-for-researchers/applying-for-funding/policies-that-affect-your-grant/coronavirus-covid-19-information-for-grant-applicants-and-grantholders

CRUK: A 12-point plan for restoration, recovery and transformation of cancer services in England, developed in collaboration with other:
https://www.cancerresearchuk.org/sites/default/files/covid_and_cancer_12_point_plan_ocv_-_final.pdf

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Links to Guidance: Regulators and Industry

Regulators:

MHRA: Managing clinical trials during Coronavirus (COVID-19)
https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19

HRA: Making changes to a research study to manage the impact of COVID-19

https://www.hra.nhs.uk/covid-19-research/covid-19-guidance-sponsors-sites-and-researchers/

ABPI:

The UK has been leading the rest of Europe in early-stage clinical research according to new data published by the ABPI in its second annual report on the state of clinical trials in the UK.

https://www.abpi.org.uk/media-centre/news/2020/october/uk-leading-europe-in-clinical-trials-but-strategy-needed-to-restart-non-covid-research/

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