# Investigating Paediatric Clinical Trial Set Up

ECMC Project Report and Proposed Actions

## Introduction

The Experimental Cancer Medicine Centre (ECMC) Paediatric Network[1] aims to improve the availability of novel therapies for children with cancer in the UK by supporting a scientifically advanced and operationally efficient clinical research landscape to conduct early phase trials.

Building on national measures taken in recent years to enhance clinical research delivery in the UK, the Network is keen to understand additional steps that could be taken to improve study set up times for both academic and commercial studies. Within this context, the ECMC Paediatric Network has explored the factors that influence the set up of paediatric trials within the NHS, in order to identify potential efficiencies that could be made.

This document summarises the outputs of a three-phase project to support this work, beginning with an overview of the actions the ECMC Network proposes to take forward to drive progress. Further detail on the project background, including a multi-stakeholder workshop held in November 2019, can be found later in the report.

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## 1. Proposed Actions

Following workshop discussions and subsequent scoping exercises, the ECMC Network has identified two approaches to take forward in order to achieve sustainable improvements in UK study set up:

**A. Review and improve the current system:** by refining our own processes, supporting existing initiatives (including those not specific to paediatrics) and developing resources.

**B. Support a strategic shift:** addressing larger scale and complex challenges which require a shift in the future clinical research landscape.

As a network of adult and paediatric early-phase trial centres comprising partnerships between National Health Service (NHS) Trusts, Health Boards, and Universities, the ECMC Network holds a unique position to shape the clinical research environment in the UK.

We will continue to utilise this network to establish a UK clinical trial delivery forum with representation from key stakeholders and develop an implementation roadmap addressing the six themes below:

[1] ECMC Paediatric Network (https://www.ecmcnetwork.org.uk/paediatric-network)

| | Activity | 1. Contracting with sites | 2. Commercial costing | 3. Academic funding | 4. Regulatory processes | 5. Site initiation / governance | 6. Site-level resourcing |
|---|---|---|---|---|---|---|---|
| Review and Improve | Support development of guidance and training for trial costing*† | | | | | | |
| | Investigate challenges with REC & IRMER Review*† | | | | | | |
| | Pilot the development of Standard of care guidance for relapsed paediatric patients† | | | | | | |
| | Simplify contracting processes* | | | | | | |
| | Develop guidance for industry to navigate placing trials in UK* | | | | | | |
| Future Landscape | Strategic development of ECMC Network models* | | | | | | |
| | Establish a UK clinical trial delivery forum*† | | | | | | |
| | Engage with Europe-wide initiatives investigating challenges in early phase paediatric trials† | | | | | | |

*Activities will benefit both adult and paediatric ECMC Networks.

†Activities depend on collaboration with external organisations.

## A. Next steps to review and improve the current system

➢ **Support development of guidance and training for commercial trial costing.**

Anticipating the launch of updated costing and contracting methodology for commercial trials, as outlined in the National Directive on Commercial Contract Research Studies[2], we plan to work with the NIHR to deliver guidance on these new resources for the ECMC Network. The proposed training would address difficulties faced when costing for paediatric and complex design trials, and provide an opportunity for the Network to feedback their challenges. We will also explore opportunities to establish an ongoing dialogue between the Network and NIHR, with the ECMC Programme Office acting as broker, in order to support the development and refinement of future resources.

➢ **Investigate challenges with Research Ethics Committees and IRMER review.**

In order to address the variety of challenges faced by the Network during regulatory review of paediatric trials, the Programme Office will collect specific feedback and case studies to share with the Health Research Authority (HRA). By gathering this evidence, we aim to help identify the major causes of delay in radiation review, encourage a review of current processes, and support the development of training for Research Ethics Committee (REC) members longer term.

[2] https://www.england.nhs.uk/wp-content/uploads/2018/09/national-directive-on-commercial-contract-research-studies-v2.pdf

- **Pilot the development of Standard of Care guidance for relapsed paediatric patients.**

The Paediatric Network will explore the suggestion to develop consensus guidance on the minimum standard of care for relapsed paediatric patients, in order to support accurate and consistent costing of paediatric trials using the SoECAT form. This will be piloted first in one cancer type in collaboration with the European Society for Paediatric Oncology (SIOPE).

- **Streamline contracting processes.**

To address delays caused by contract negotiations in trial set up, the Network will investigate opportunities to simplify contracting across sites. Approaches to be explored include mandating the use of model agreements at ECMC sites, limiting the number of modifications allowed, and introducing deadlines for finalisation.

- **Develop guidance for industry to navigate placing trials in UK.**

By providing a single-entry point to the Network, the ECMC Programme Office works to streamline and facilitate site selection and feasibility in the UK. Commercial sponsors can face additional challenges implementing international trial protocols in the UK, often due to a lack of input from UK and European clinicians during protocol development. To address this, the Programme Office will work with the Association of the British Pharmaceutical Industry (ABPI) to encourage sponsors to engage with UK clinicians and the Innovative Therapies for Children with Cancer (ITCC) consortium early in study development, in order to mitigate challenges in contracting and site initiation further down the line.

## B. Supporting a strategic shift in the future clinical research landscape

The consultations and workshop discussions highlighted several challenges which require larger scale change across the clinical research landscape to address. The Network intends to work with the appropriate national and international bodies, such as the NIHR, HRA, ITCC, and ABPI, to better understand what is needed and support long-term sustainable improvement in early phase trial set up across the UK.

- **Strategic development of ECMC Paediatric Network model.**

The Paediatric Network will use the insight generated from this project to consider how its infrastructure can evolve to support faster set up of early phase trials in the UK. Future discussions will focus on how strategic development of the network, in terms of its structure and capabilities, could address site-level resource challenges longer term.

- **Establish a UK clinical trial delivery forum.**

Many of the themes identified in this project are common to all early phase cancer trials. To ensure we maximise the impact of future activity, we want to ensure we align with other key initiatives working in this area. The ECMC Programme Office will establish a regular forum with other key groups, such as CRUK Clinical Research Funding, CRUK Policy, and the National Cancer Research Institute to share knowledge and align on our next steps.

- **Engage with Europe-wide initiatives investigating challenges in early phase paediatric trials.**

We will look to engage with European organisations such as the ITCC and ACCELERATE consortia to address larger scale issues in paediatric early phase trials. For example, the Network will support the UK's participation in a survey of resource challenges in paediatric trial delivery, which is due to form part of the ITCC's next strategic review.

## 2. Project Background


### Phase 1 - Consultation

**Identifying issues at site** – Six paediatric and two adult early phase trials were shortlisted from the ECMC Network portfolio as case studies, with equal representation of commercial and academic studies. In order to survey examples of both fast and slow set up, the shortlisted trial set up times ranged from 53 to 668 days (calculated from site selection to first patient recruited). Semi-structured interviews were then conducted with 30 people involved in these trials' set up across 12 sites, including Clinical Investigators, NHS Research and Development managers, Trial Coordinators and Research Nurses, to gather qualitative data and identify both key barriers and enablers in their set up.

**Surveying Industry** - A questionnaire was also distributed to a sample of commercial sponsors in order to survey their perspectives on early phase cancer trial start up in the UK, receiving 19 company responses.

This qualitative data was analysed by Wendy Fisher Consulting (WFC), leading to the identification of six major themes that can cause delays in trial set up:

| 1. Contracting with sites | 2. Commercial costing | 3. Academic funding | 4. Regulatory processes | 5. Site initiation/ governance | 6. Site-level resourcing |
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### Phase 2 – Stakeholder Workshop

These six themes were discussed at a multi-stakeholder workshop, held on 20th November 2019, which was attended by 50 people from a range of representative groups involved in early phase trials, detailed in the next section. Following the workshop, WFC collated and prioritised key outputs from the discussions into an independent report.

### Phase 3 – Workstream Development

Recommendations from the WFC report were presented and discussed at the ECMC Paediatric Strategy Group meeting in January 2020. The ECMC Programme Office then worked with key stakeholders to map other existing initiatives focussing on improving trial set up at a national and international level, in order to identify representatives to engage with going forward and maximise the impact of any follow up activity.

The outcomes of this scoping and prioritisation phase are outlined in Section 1 of this document. Our next steps will involve reconvening with the appropriate organisations to develop implementation roadmaps for these workstreams.

## 3. Workshop Outputs

### Attendees

The workshop was attended by 50 people from a range of roles and representative groups, including:

- ECMC Programme Office
- Charitable funders of paediatric cancer trials:
  - Cancer Research UK Clinical Research Team
  - Solving Kids Cancer
  - Childhood Cancer and Leukaemia Group
- Cancer Research UK Centre for Drug Development
- ECMC Paediatric Network Centre Leads
- NHS Research & Development
- Commercial Sponsors
- Contract Research Organisations
- Clinical Trial Operations
- Health Research Authority
- NIHR Clinical Research Network
- Research Nurses
- Patient and Public Involvement (PPI) representatives

### Themes Discussed

During the workshop sessions, all groups were given the opportunity to discuss the following themes in turn. Participants considered their own experiences of these challenges and worked together to identify potential solutions that could be implemented. Brief summaries of the discussions and actionable suggestions are outlined below.

1. **Contracting with sites** – despite the implementation of model agreements for commercial trials and progress made to standardise the process, contracting between trial sponsor and sites can still be extremely time-consuming. Contract negotiation came out as the top cause for delay for industry.

   Whilst model trial agreements have been mandated for commercial studies in the UK[4], participants were concerned that contracting is still an issue. Key recommendations for this theme related to simplifying the contracting process, enforcing the use of model agreements across the ECMC network, and exploring opportunities to limit the number of modifications allowed and/or introduce hard deadlines for finalisation. It was recognised that commercial sponsors refusing to accept these templates will continue to present a major barrier.

2. **Commercial costing** – Whilst all commercial studies are fully funded by the sponsor, costings often do not accurately reflect the resource required to deliver trials in a paediatric setting. These challenges relate to inconsistent practice and confusion when applying the Industry Costing Template[5] to paediatric studies.

   With a new interactive tool for contract research costing due to launch in April 2020[6], the recommendations for this theme set out to ensure there is sufficient guidance and training so that sites are equipped to accurately cost for paediatric and complex studies using this new process.

3. **Academic funding** – Paediatric trials are often under-costed by Sponsors/CTUs in their grant applications, in part due to considerable uncertainty around the use of SoECAT[7] and AcoRD[8] processes for paediatric indications.

[4] https://www.nihr.ac.uk/documents/model-site-agreements-model-contracts-standard-research-agreements/11612
[5] https://www.nihr.ac.uk/documents/the-excel-industry-costing-template-getting-started/12177
[6] https://www.nihr.ac.uk/partners-and-industry/industry/run-your-study-in-the-nhs/faster-costing-and-contracting.htm
[7] Schedule of Events Cost Attribution Template (SoECAT) https://www.nihr.ac.uk/researchers/collaborations-services-and-support-for-your-research/run-your-study/excess-treatment-costs.htm
[8] Attribution of Costs for Research and Development (AcoRD)

Discussions on this theme highlighted a need for coordinated guidance on what minimum standard of care looks like for relapsed patients, in order to support more accurate and consistent identification of excess treatment costs in early phase paediatric trials.

4. **Regulatory processes** – Clinical Investigators cite highly variable and inconsistent quality of review by Research Ethics Committees. The process for Ionising radiation review (IRMER)[9] was also referenced as a common cause of delay.

   The key solutions proposed for this theme involved collecting and sharing detailed feedback on these experiences with the Health Research Authority (HRA). This will support the development of training or support materials to address current gaps, and help identify where additional resource may be required.

5. **Site initiation and governance** – Centres across the UK have variable and complex processes for site initiation and governance. This high variation limits the potential for intervention on a network level.

   Timely sharing of key materials, such as lab manuals, would allow sites to conduct feasibility earlier and help support faster set up times. However, it was recognised that the core challenges with this theme link to capacity and resource levels at site, which were addressed in Theme 6.

6. **Site-level resourcing** – Resource challenges in delivery teams and support services such as pharmacy and radiology were reported across all sites as a key cause of delay, as well as a lack of support for investigator time and capacity in job plans. Funding channels at sites are also complex, with multiple funding sources being pooled and re-distributed to support infrastructure and specific studies in various ways.

   Whilst strategic placement of trials in the network may help to mitigate this, a more thorough review of capacity and capability is needed at an individual site level to understand where the gaps are and how to address them.

## 4. Acknowledgements

On behalf of the ECMC Paediatric Network we would like to thank all those who participated and contributed towards this project. As we move forward with the actions above, there may be opportunities for future consultations or involvement. If you would be interested in supporting future activities relating to this project, please do get in touch with Tara McKay, ECMC Paediatric Network Manager: Tara.McKay@cancer.org.uk

[9] https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/ionising-radiation/