Collated experiences of paediatric oncology REC review

This document summarises the results from a recent project conducted by the Experimental Cancer Medicine Centre (ECMC) Paediatric Network to identify specific challenges faced in the ethics review of paediatric early phase oncology trials in the UK. These findings are to be shared with the Health Research Authority (HRA) to support a discussion on potential solutions and collaborations, and to feed into their broader piece of work reviewing the research ethics service.

Executive Summary

The ECMC Network supports the delivery of early phase oncology trials in the UK, including complex innovative design and paediatric studies. Preliminary analysis of the ECMC trial portfolio showed that the set-up of paediatric studies in the UK takes on average 41 days longer than adult studies, whilst anecdotal reports from academic and commercial sponsors cite trials opening in the UK up to 12 months after their European counterparts. The Network set out to investigate challenges in early phase trial set-up in the UK, with regulatory processes identified as a key theme[1]. Following initial discussions, the HRA invited the Network to share collated feedback on paediatric REC review to support their ongoing review of the research ethics service.

Project Aims

- To generate an evidence base to better understand the challenges in REC review of paediatric oncology trials.
- To share insight gathered from the ECMC Network with the HRA in order to support its ongoing review of ethics processes and inform recommendations related to REC review and training.

Recommendations for discussion:

Minimising timeline-extending follow-up queries:

- Educational resources to improve REC awareness of paediatric oncology research setting, or more broadly to include early phase and complex innovative design trials, e.g. case studies demonstrating impact of early phase trials, or a follow-up ECMC-HRA podcast series[2]
- Improving patient/parent involvement in the development of key documents.
- Showcasing patient/parent involvement in the approvals application and presentation of study at RECs.
- Review guidance for applicants to ensuring sponsors request RECs that are flagged with the appropriate expertise e.g. 'Research involving children' and 'Phase I'.

Expediting specialist review:

- Address queries in REC meeting as much as possible e.g. for complex or priority studies:
- Ensure there is sufficient expertise in the REC to prompt specialist queries.
- Arrange for external specialist review and submission of queries in advance of the REC.

[1] Investigating Paediatric Clinical Trial Set Up – ECMC Report (May, 2020)

[2] https://www.hra.nhs.uk/about-us/news-updates/podcast-series-on-complex-innovative-design-trials/

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1. Background

The ECMC Paediatric Network set out to investigate challenges in early phase trial set-up in the UK. An initial consultation identified six key themes which were explored at a workshop[3] in November 2019 and summarised in a report published in May 2020[4]. One of the themes explored was 'regulatory processes', with workshop participants citing particular issues faced by paediatric early phase studies in Research Ethics Committee (REC) review.

Gathering structured feedback on paediatric REC review was prioritised as a workstream to take forward, in order to identify common challenges and opportunities to accelerate patient access to innovative treatments in the UK. Following initial discussions, the HRA invited the Network to share collated feedback on paediatric REC review to support their ongoing review of the research ethics service.

2. Approach

Table 1

Feedback gathered	• Dates of submission, date of meeting, date of approval • Whether a REC for 'Research involving children' and 'Phase I' were requested • Who presented the study at the REC meeting • Detail on any issues faced and outcome
Academic Sponsors	• Discussion at ECMC Paediatric Strategy Group meeting • Timeline data from CRUK Clinical Research Team – academic funder • Survey feedback from CRUK Birmingham Cancer Research Clinical Trials Unit – the major academic sponsor of paediatric oncology trials in the UK
Commercial Sponsors	• Survey distributed to ABPI Cancer Project Group • Survey distributed to ECMC industry contacts

3. Results

3.1 REC approval timeline data

Table 1

Measure	Academic	Commercial
Mean days from submission to REC meeting	41	39
Mean days from submission to approval	152	97

The timeline data gathered (Table 2) shows that whilst paediatric oncology trials are consistently reviewed by a REC within the target of 60 days, they largely do not receive a favourable opinion at the committee meeting. Follow-up queries and specialist consultations routinely extend approval timelines to an average of 97 and 152 days for commercial and academic studies, respectively, contributing to a slower set-up time for the study in the UK.

[3] 50 attendees including representatives from CTUs, Industry, NIHR, HRA, patient and public involvement, Research Nurses, NHS Research & Development

[4] Investigating Paediatric Clinical Trial Set Up – ECMC Report (May, 2020)

Time limit extension criteria outlined in the REC Standard Operating Procedures [5] are likely to disproportionately affect Phase I oncology trials due to the growing complexity of cancer treatments, such as CAR T cell immunotherapy for haematological cancers.

These delays are particularly critical for phase I oncology trials, which grant patients access to potentially life-extending treatments that are otherwise unavailable through standard of care pathways. Demonstrating efficient study set-up timelines is also key for securing access to future innovative treatments, by maintaining the UK's position as an efficient place to deliver early phase trials for commercial sponsors.

3.2 Cited causes of delay in REC approval

Feedback gathered from academic and commercial sponsors of paediatric oncology trials, as outlined in Table 1, cited two key causes of delay in REC approval:

3.2.i Follow up queries

Most of the trials required sponsors to submit updated versions or further supporting documents addressing issues raised in order to receive a final approval. Investigators reported that queries around Patient Information Sheets and consent are common in paediatric trials due to the young age of participants and the role of parents/family members in their care. It was suggested that some of the issues arise due to a lack of understanding of the paediatric oncology research setting, i.e. what is considered acceptable to patients and their families in the context of an early phase trial, where experimental medicine can provide access to treatments that are otherwise unavailable.

Opportunities to explore:

- Educational resources to improve REC awareness of paediatric oncology research setting, or more broadly to include early phase and complex innovative design trials, e.g. case studies demonstrating impact of early phase trials, or a follow-up ECMC-HRA podcast series[6]
- Improving patient/parent involvement in the development of key documents.
- Showcasing patient/parent involvement in the approvals application and presentation of study at RECs.
- Review guidance for applicants to ensuring sponsors request RECs that are flagged with the appropriate expertise e.g. 'Research involving children' and 'Phase I'.

3.2.ii Specialist reviews

Several respondents commented that their studies were referred for additional review following the REC meeting, which significantly extended the approval timeline. As referenced above, phase I oncology trials are likely to be disproportionately impacted in this way due to the growing complexity of experimental treatments and trial design.
It was strongly felt by members of the ECMC Paediatric Strategy Group that the queries raised by specialist review could easily be addressed by the Chief Investigator and/or study representative present at the REC meeting, if this could be facilitated.

[5] UK Health Departments Research Ethics Service, Standard Operating Procedures for Research Ethics Committees, Section 3.1. p78. Version 7.4. *Accessed 18.12.2020.*
[6] https://www.hra.nhs.uk/about-us/news-updates/podcast-series-on-complex-innovative-design-trials/

Opportunities to explore:

Address queries in REC meeting as much as possible e.g. for complex or priority studies:

- Ensure there is sufficient expertise in the REC to prompt expert queries.
- Arrange for necessary specialist review and submission of queries in advance of the REC.

About the ECMC Network

The Experimental Cancer Medicine Centre (ECMC) Network aims to advance experimental cancer research and ensure UK patients have access to innovative treatment[7]. More than 2,100 early phase oncology trials have been delivered through the network over the last 10 years.

The network regularly convenes strategic forums which include clinical, scientific, and operational leads from the 18 adult and 11 paediatric ECMC sites. These meetings provide opportunities to distribute information, facilitate engagement, and collate feedback from clinicians, research nurses, scientists, and patient representatives in the network. In addition to facilitating network initiatives, the ECMC Programme Office supports commercial sponsors and contract research organisations in placing their trials within the UK.

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[7] https://www.ecmcnetwork.org.uk