ECMC Report: An Adapted Costing Process for Complex Commercial Clinical Trials

Executive Summary

The Experimental Cancer Medicine Centre (ECMC) Network (in partnership with the Health Research Authority [HRA]) has continued with delivery of our project to improve and speed up the set-up of commercially sponsored early-phase oncology trials within the UK as part of the UK Clinical Research Delivery (UKCRD) Programme. This is a key priority area for the UK, as outlined within Lord O'Shaughnessy's review into commercial clinical trials in the UK, which the new Government has committed to continuing the implementation of.

This paper focuses specifically on Costings, one of several themes for this project (alongside Pharmacy, Imaging, Contracting, and Best-Practice for Site Set-up). The paper provides the findings of an ECMC Network Pilot of a revised costing process for Phase 1 and 2a (early-phase) and Advanced Therapy Medicinal Product (ATMP) commercial cancer trials.

The National Contract Value Review (NCVR) process is a "standardised, national approach to costing for commercial contract research using standardised pricing and contract terms for commercial research across the whole of the NHS – providing transparent and predictable research delivery prices". NCVR is underpinned by the NHS Standard Contract and the National directive on commercial research studies.

NCVR was implemented in phases from the 1st of April 2022, with the stage 2 implementation from October 2023 making the process mandatory for all late phase commercial trials (phase 2b and above) within the NHS.

In October 2023, NHS England (NHSE) initiated a pilot program for the NCVR to develop and refine costing processes for early phase and ATMP trials. Based on the pilot's findings, NHSE and partners expanded NCVR to incorporate these trial types from 14th October 2024.

As a highly experienced and collaborative stakeholder group, the ECMC Network was asked to develop and pilot a process in parallel to inform the development of the expanded NCVR process ahead of the implementation, and to contribute longer-term as the process is embedded fully within the system. Through co-creation with ECMC stakeholders and the broader clinical research community, an adapted process was developed that moved the initial costing responsibility from the Company to the Lead Site. Additionally, a Network Site Review process was introduced, enabling all participating sites to contribute to the initial costings, further enhancing collaboration and efficiency.

The ECMC Programme Office (PO) played a pivotal role in shaping the adapted NCVR process by both coordinating pilot delivery and working to align national

strategy with site-level operational realities. The project's focus on co-creation ensured that stakeholder insights were embedded directly into process design, enabling a scalable and sustainable model for future implementation.

This report details the findings from the three trials that proceeded through the ECMC Pilot Process and the next steps that will be taken. The pilot has demonstrated that there is significant potential to improve the accuracy and completeness of costing early-phase and ATMP trials when enabling the lead site to initiate the costing process. With increased familiarity with the revised process and better system functionality to facilitate ATMP and early-phase costings, there could also clearly be improvements in the time taken to complete costings.

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List of Abbreviations

ATMP	Advanced Therapy Medicinal Product
CI	Chief Investigator
CPMS	Central Portfolio Management System
CRF	Clinical Research Facility
CRO	Contract Research Organisation
DA	Devolved Administration
DHSC	Department of Health and Social Care
ECMC	Experimental Cancer Medicine Centres
ECMC PO	Experimental Cancer Medicine Centres Programme Office
HCRW	Health & Care Research Wales
HRA	Health Research Authority
iCT	interactive Costing Tool
MFF	Market Forces Factor
NIHR	National Institute for Health and Care Research
NCVR	National Contract Value Review
NDA	Non-Disclosure Agreement
NHSE	NHS England
RDN	Research Delivery Network
RRDN	Regional Research Delivery Network
RDNCC	Research Delivery Network Coordinating Centre
SOP	Standard Operating Procedure
UKCRD	UK Clinical Research Delivery programme
WFC	Wendy Fisher Consulting

Background

The Experimental Cancer Medicine Centre (ECMC) Network (in partnership with the Health Research Authority [HRA]) has continued with delivery of our project to improve and speed up the set-up of commercially sponsored early-phase oncology trials within the UK as part of the UK Clinical Research Delivery (UKCRD) programme (Formerly the UK Clinical Research Recovery, Resilience, and Growth [RRG] Programme). This is a key priority area for the UK, as outlined within Lord O'Shaughnessy's review into commercial clinical trials in the UK, which the new Government has committed to continuing the implementation of.

This paper focuses specifically on Costings, one of several themes for this project (alongside Pharmacy, Imaging, Contracting, and Best-Practice for Site Set-up). The paper provides the findings of an ECMC Network Pilot of a revised costing process for Phase 1 and 2a (early-phase) and Advanced Therapy Medicinal Product (ATMP) commercial cancer trials.

In October 2023, NHS England (NHSE) initiated a pilot program for the National Contract Value Review (NCVR) process to develop and refine costing processes for early phase and ATMP trials. Based on the pilot's findings, NHSE and partners (see below) expanded NCVR to incorporate these trial types from the 14th of October 2024. An NCVR ATMP and Early Phase Studies Working Group was established to oversee the expansion of the process, with core membership from NHSE, the Research Delivery Network (RDN) Coordinating Centre (CC), the HRA, the Department of Health and Social Care (DHSC), and the Devolved Administrations (DAs). The ECMC Network, Cancer Innovation Pathway, and UK Clinical Research Facility (CRF) Network are also represented at the Working Group meetings, as are other key stakeholders including site representatives.

As a highly experienced and collaborative stakeholder group, the ECMC Network was asked to develop and pilot a process in parallel to inform the development of the expanded NCVR process ahead of the implementation, and to contribute longer-term as the process is embedded fully within the system. This is also in line with the ECMC Network Strategic Objectives to streamline and improve study set-up across the Network.

The National setting: National contract value review (NCVR)

The NCVR is a "standardised, national approach to costing for commercial contract research using standardised pricing and contract terms for commercial research across the whole of the NHS – providing transparent and predictable research delivery prices".

NCVR is underpinned by the NHS Standard Contract and the National directive on commercial research studies.

NCVR focuses on agreeing the resources and price needed to set up commercial research studies within NHS providers. This work forms part of a broader common goal to ensure clinical research continues to thrive in the UK, for the benefit of patients and the public.

The benefits of NCVR include:

- A streamlined research process to speed up access to research – getting life-changing treatment to patients faster.
- NCVR works as a system-wide tool and process enabling individual NHS organisations taking part in a study to operate as one.
- The nationwide approach for price calculation and contracting terms provides assurance to the NHS, its patients, and life science partners that appropriate resources and legal provisions are in place for each study, while avoiding duplication across multiple NHS organisations.
- Removing competition through collaboration increases access to research across the UK. Research is for everyone, everywhere.
- There is a sense of collective responsibility emerging in bringing together the 400+ NHS based costing experts into a visible community.

NCVR was implemented in phases from the 1st of April 2022, with the stage 2 implementation from October 2023 making the process mandatory for all late phase commercial trials (phase 2b and above) within the NHS. Within England, NCVR is being delivered by NHSE, the National Institute for Health and Care Research (NIHR), the HRA, and the DHSC. Aligned processes are also in place across Scotland, Wales, and Northern Ireland, and there is a reciprocal recognition of contract value reviews conducted by NHS organisations across the whole of the UK. The stage 2 implementation also amended the process for site-specific costings, with all NHS organisations required to accept the national review outcome and iCT generated site prices for all studies, with no negotiation permitted.

NCVR aims to reduce duplication and delays within the costing process for sites and industry by having a single costing produced for each trial, increasing budget accuracy while also reducing the set-up time for clinical trials. The outline process is as follows:

1. **Preparation by company representative**: Prior to application for HRA/Health and Care Research Wales [HCRW] Approval. The company representative populates the interactive Costing Tool (iCT).
2. **Assignment to study resource reviewer:** The populated iCT is sent to the appropriate Regional Research Delivery Network (RRDN), which assigns it to a Study Resource Reviewer..
3. **Study Resource Review:** In partnership with the Chief Investigator (CI) and the company representative, the Study Resource Reviewer undertakes the Study Resource Review. The Study Resource Reviewer will assess the iCT and confirm that the activities, visits, and occurrences entered, and the corresponding resources allocated, accurately reflect the study activities listed in the study documentation.
4. **Site Specific Assignments**: The company representative then assigns Site Representatives for all NHS organisations participating in the trial and site specific iCTs are created. An escalation process for site representatives is in place for potential issues or errors with the national Study Resource Review, with the relevant RRDN or equivalent DA managing the process.

This unified approach ensures consistency and efficiency across all trials conducted under the NCVR principles.

To accommodate for price variations between NHS organisations, several updates were made to the iCT tariff and workings, including a change to the Research Market Forces Factor (MFF) for NHS organisations in England to incorporate broader site-specific multipliers (multipliers were already in place within the iCT for sites within the DAs). The Research MFF is used to ensure the trial costings reflect the location and setting requirements of an NHS organisation, as well as any dedicated infrastructure, local provisions, and equity of access. For example, the revised Research MFF includes a 2% uplift of an organisation's MFF for those that host an ECMC and/or a CRF. The intention of the increases to Research MFF within England is to incorporate any of the site-specific multipliers automatically within the iCT, therefore removing the need for any local negotiations.

In addition to the pilot processes being tested, additional workstreams were delivered in parallel, including:

1. Development of the iCT to ensure ATMP and early-phase functionality.
2. Development and review of Standard Operating Procedures (SOPs) for the NCVR ATMP process.
3. A review of the existing guidance for costing ATMP and early-phase trials.

4. Development of the process for Unmodified Clinical Trial Agreements for ATMP trials.

ECMC representatives contributed to all of these workstreams in addition to the work delivered for the ECMC pilot.

ECMC Network Pilot for Early-phase and ATMP Trials

Development

An ECMC ATMP Costings Working Group was established early in the project delivery to ensure that any proposed solution(s) for costing early-phase and ATMP trials were truly co-created by the stakeholders directly involved with the delivery of the process. The Working Group's focus was to bring together a network of specialists with practical experience of the financial management and delivery of early-phase and ATMP trials in both adult and paediatric ECMC locations from across the UK, embedding co-creation into the development of an improved process. A Sub-Group of Working Group members was also established to meet on an ad-hoc basis when specific, detailed process decisions were required at pace and a full Working Group meeting was not practical. Membership of the Working Group and Sub-Group included Centre Business Leads (CBLs), Trial Managers, Pharmacists, and Investigators, from across the ECMC Network.

Through meetings with the Working Group, Sub-Group, industry stakeholders, and other members of the early-phase and ATMP community, a process was developed for pilot. The process development used the existing NCVR process as a starting point before considering what amendments were required to ensure that early-phase and ATMP trials could be effectively and promptly costed, and that the challenges identified within the non-NCVR costing system would be addressed.

It was important that where possible and practical, the revised process remained in-line with the standard NCVR methodology; this would help to avoid creating a two-tier system that can be confusing for industry and require additional guidance and management for users. However, the initial pilot process developed through the stakeholder groups had several significant distinctions from the standard NCVR process:

- **A 'single, lead-site costing':** The focus of the process development was to ensure that the experience of those delivering and managing early-phase and ATMP trials at site-level was fully utilised during costings. This level of experience is not always available within sponsor organisations

and Contract Research Organisations (CROs), where there are also often high levels of staff turnover. The motivation for this was to ensure that the initial costing of a trial accurately reflects the complexities of early-phase and ATMP delivery with the NHS. This should in turn lead to more complete initial costings that require less negotiation and processing and are therefore more efficient overall. The proposed process required that either the company allocates the iCT to the lead study site to undertake the first costing directly) or the company can partially complete some information within an iCT and the lead site representative can then be added as a company representative to complete the full costing (Both of these options require direct input from the CRN to facilitate). To support the lead site with completing the iCT a mandatory call between the company and the lead site was implemented ahead of the initial draft iCT being completed. The call is an opportunity for the lead site to identify and request any supporting information required to undertake the costing, and for the company and lead site to discuss the detail of the trial and any other pertinent information. It is crucial for the lead site that all information required is provided in a timely manner; ideally, the study manuals would be available to support the costing process, however in practice they are rarely accessible at this stage. The completed draft iCT is subsequently returned to the company for their initial review (after the Network Sites Review process described below, if applicable). The company can then make any adjustments they feel are required, or raise queries for the lead site, and submit these back to the lead site for review. If further discussion is required at this stage of the process, a second call between the company and the lead site is scheduled so that any outstanding issues can be resolved. Through the implementation of the mandatory calls and a staged review process, the common practices of both extensive negotiation periods and the creation of numerous comments within the iCT can be avoided.

- **Network Sites Review:** An additional step for multicentre trials was added to the process prior to the initial draft iCT being returned to the company to enable costing experts from other participating sites to support their colleagues and to suggest any adjustments that they feel are necessary. The Network Sites Review proactively embeds quality assurance into the process for multicentre trials, helping to minimise the chance that a local site may need to escalate costings at a later stage. It also provides an opportunity for local sites to potentially influence the

costings ahead of the receipt of the local iCT, at which point no local negotiation is allowed within NCVR. Throughout the process development work, the ECMC site leads were keen to ensure that a collaborative approach could be taken where possible, referring to a 'buddy system' to incorporate their colleagues from other ECMC locations. This was important to make sure that experience from across the community could be utilised effectively, but also to provide support for any potential lead sites that have less experience of costing these trial types, recognising that there are sites within the Network that deliver ATMPs much less frequently than some other organisations and may not be as confident undertaking the initial costing on behalf of the company. The Network Sites Review ensures that the broad experience of the ECMC sites can input into costings while also maintaining the lead site's ownership of the budget; any changes to the costings are made at the lead site's discretion.

The intention to implement the lead-site costing was presented at several forums and stakeholder events, including the ECMC Network Meeting (May 2023), and an industry survey was also conducted. Responses to the survey were split evenly on the proposal, with concerns noted that the lead site may not have sufficient resource to meet the turnaround times required by the company, and that the company is ultimately responsible for the protocol and subsequent funding and therefore should make the initial decisions. However, all but one of the companies surveyed expressed interest in piloting the process. The Project Team also felt that the concerns raised by the companies could be mitigated through ensuring that the company was involved throughout the costing process, and via the Network Sites Review to provide additional support to the lead site.

A key driver behind the implementation of NCVR, and of this ECMC Project, is the reduction of avoidable delays within the costing process for commercial trials. It was essential that any adjustments made for the pilot process would meet this criterion. The Working Group felt strongly that the potential for a slower initial turnaround when creating the initial draft (if comparing the lead-site to the company) would be outweighed by the time saved during a reduced negotiation period and a more structured process of information gathering early-on in the trial costing, resulting in a more accurate final draft iCT.

To further embed speed into the process, ambitious timelines were selected for the key stages of the iCT completion. Initially, a maximum of 10 working days was assigned for the lead site to produce the initial draft (from the receipt of all required

information from the company), including the Network Sites Review stage for multicentre trials. A further 10 working days was assigned for the company to undertake their review of the initial draft iCT, complete any negotiations with the lead site, and mark the study resource review as complete. These timelines were amended to 15-working days later in the pilot to streamline the pilot process with standard NCVR (See Trial 3, below).

A flowchart of the ECMC pilot process accompanies this report.

Pilot structure

The primary objectives of the project pilot were to:

- Promote open and effective communication between the lead site and the company
- Ensure an accurate initial costing was created by the lead site
- Ensure that essential information was available to the lead site when it was needed
- Minimise negotiations required between the lead site and company, including the need to provide local site adjustments later in the process
- Demonstrate that clinical trials can be set up more efficiently utilising the revised pilot process

The roles and responsibilities for the pilot process were:

Role/ organisation	**Responsibilities**
ECMC Programme Office (PO)	– To oversee the pilot process, ensuring adherence to established guidelines. – To serve as the primary point of contact for all stakeholders involved in the pilot. – To proactively identify and address potential issues or risks. – To foster clear and consistent communication throughout the costing pilot. – To share outcomes from the pilot with the NHSE and NIHR Strategic Group.
Lead site	– To manage and negotiate the study budget with the company. – If applicable, to collaborate with participating sites via the Network Sites Review process and incorporate local requirements into the study costings as appropriate.

	– To consult with support departments and other applicable stakeholders from within their site to ensure accuracy.
Company (sponsor and/or CRO)	– To ensure timely provision of the study information/documentation to the lead site. – To provide active participation in productive and efficient negotiations with the lead site. – To make timely decisions and respond promptly to queries from the lead site and other stakeholders. – (For the Sponsor, if applicable) To agree and manage the CRO's roles and responsibilities to ensure the timely execution and management of the study costs.
Participating sites	– To review the draft costs created by the lead site. – To participate in the Network Sites Review process to contribute to the costing accuracy, and to provide any site-specific costing requirements. – To agree the final study costs aligned with NCVR principles, as agreed upon by the lead CI site and sponsor.
NIHR RDN	– To proactively manage the functionality of the CPMS system to accommodate the nuances of the ECMC pilot process. – To attend meetings, as required and appropriate. – Consider the outputs of the pilot project and apply these to the implementation phase of the NCVR.

Trials 1 and 2: Pilot delivery

The initial two trials that were selected for the pilot both had the same sponsor/company. One trial was a single centre study, the other multicentre. Both trials were of CAR-T therapies. The schedule of activities for both trials was identical, with each trial using a different therapy, meaning that the costings could be completed in parallel. The company and lead site were experienced with trials of this type. The company also had prior experience of the NCVR process for late-phase trials.

For both trials, the study manuals and other supporting documentation were available from the early stages of the costing process, which is not the case for most trials.

Trial 1 – Single centre trial

- Lead site completed the initial draft iCT within 12 working days
- The company completed their iCT review within 49 working days
- Total time: 61 working days

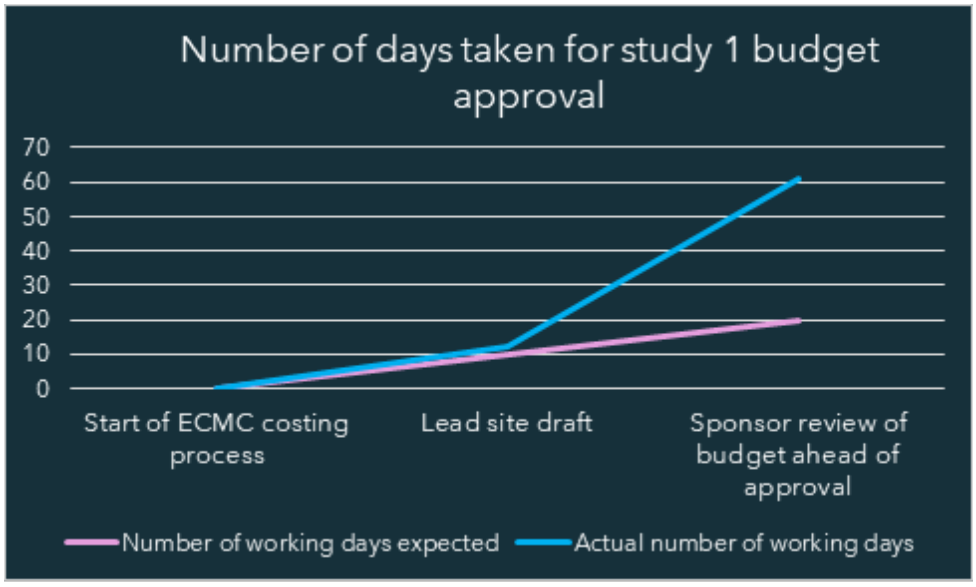

Figure 1: Number of days taken for Trial 1 budget approval

Trial 2 – Multicentre trial

- Lead site completed the initial iCT within 12 working days
- Network Sites Review was completed within 9 working days
- The company completed their iCT review within 49 working days
- Total time: 70 working days

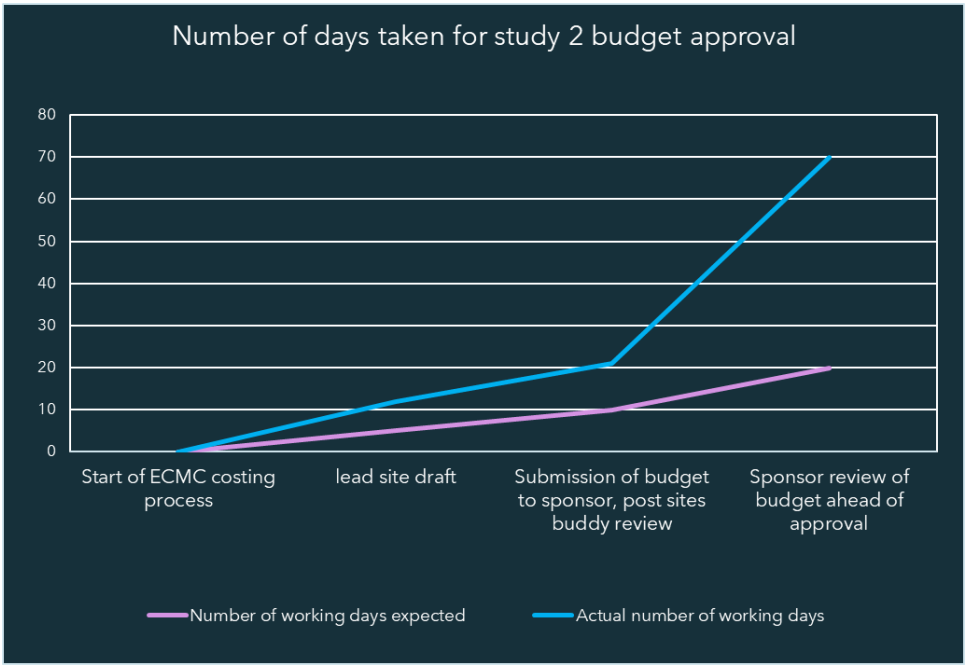

Figure 2: Number of days taken for Trial 2 budget approval

Trials 1 and 2: Findings

<u>iCT costings:</u>

Because the company did not know initially that both trials would be utilising the pilot process, a draft iCT had already been completed by the company ahead of the iCT being allocated to the lead site. This has enabled a comparison to be drawn between the initial versions created by the company and the lead site, the subsequent total value of the budget following the Network Sites Review call, and the final approved budget.

As shown in Figure 3 below, the initial lead site costing was substantially higher than the proposed costing created by the company. Although the figures rose sharply, this was not unexpected; during the development process it was raised regularly by members of the Working Group that site costings are routinely higher than those created by the company, and discussions with those stakeholders with direct experience of the NCVR process had noted that study costings were generally higher than they would be outside of NCVR.

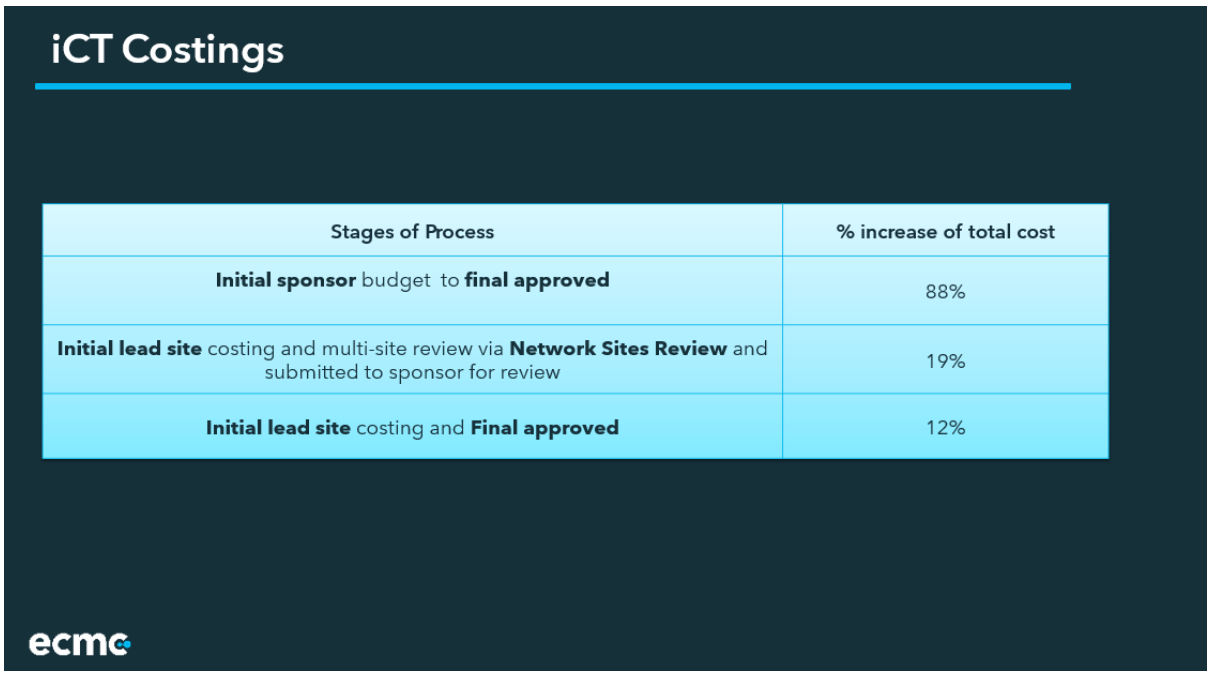

Figure 3: iCT Costings chart

It can be shown by comparing the two initial iCTs for the trials (company and lead site drafts) that the increase in costs within the lead site version is because multiple additional activities were added to the iCT by the site. The company subsequently accepted most of these additional lines, strongly suggesting that the additions were justifiable delivery costs that were omitted from the company's first draft.

There were also several costs that were revised by the site to incorporate a more complex activity. For example, the lead site amended the pharmacy cost to 'Pharmacy D', the highest banded pharmacy charge within the iCT. This was to ensure that the technical pharmacy activities required for delivery of an ATMP were all included. Once the lead site had provided a detailed explanation to the company for why this higher cost was required (see below) the company accepted the inclusion within the final iCT.

Timelines:

As outlined above, for the pilot process a target timeline of 10 working days was chosen for the completion of the initial draft iCT by the lead site (including the mandatory call with the company and the Network Sites Review process, if applicable), with a second 10 working days allowed for the company to then undertake their review of the initial draft iCT, complete any

negotiations/clarifications with the lead site, and mark the study resource review as complete.

For both trials, the lead site completed the initial draft iCT in 12 working days, slightly outside of the 10-working day target. For Trial 2, there was a slight delay with incorporating the other trial site via the Network Sites Review process, though the review was still completed promptly (within 9 days of the information being provided to the other trial site).

However, for both studies the company and lead site required a longer period to complete the second stage of the process (review of the lead site draft iCT, completion of negotiations, and release of the final draft iCT). There are several reasons identified for why the company and lead site were not able to complete these steps of the process more promptly:

- Although the UK-based division of the company was responsible for the practical tasks of completing the costing templates and UK contracts, ultimately the budget for UK sites had to be reviewed and agreed by the global office of the company. This is a common working practice for global industry. It has been identified through this project that this can cause delays within the process, sometimes because the decision-making process between the UK and global branches of the company can be time-consuming, but also because there may not be a clear understanding at a global level of the requirements of NHS delivery. There is no straightforward solution to this; ultimately, companies have complete autonomy about how they operate, and it is not within the remit of the ECMC Network to influence a company's financial decision-making processes. Although delays could potentially be mitigated through clearer guidance for companies, it is likely that instead a longer period would need to be allowed for companies to complete their internal processes. It would also be preferable for companies to make global milestones known to other stakeholders upfront in the process to ensure that every party is able to work to the same criteria.
- Timelines were impacted by individuals from all organisations involved being away from the office (either due to annual leave, other work projects, or unexpected absences). There is only a small team from each organisation that would be directly involved with a trial costing, therefore the impact of one person being away from work can be significant as the trial may be unable to proceed further through the process. As above, this is likely something that can be mitigated to an extent (for e.g. via advance notice of stakeholder absence and where possible delegation of tasks to another team member)

however the complexity of costing these types of trials requires a specific skillset and there will almost certainly be instances where delays because someone is unavailable are unavoidable.

- The pilot process is a substantial change in process for the company, and it is reasonable to expect that a change in approach would impact on timelines initially. As outlined above, the initial draft iCT created by the lead site resulted in a much larger budget than the company would have proposed to the lead site if the standard NCVR process had been followed. Even if the lead site iCT was ultimately more of a complete costing that reflects the complexities of trial delivery, the company was required to undertake an extensive review of the iCT and seek feedback from both the lead site and their global team. Post-pilot feedback from the company confirmed that although this stage of the process was more extensive than the target timeline, they found the initial costing process with the lead site to be favourable to the standard process (with the caveat that the lead site in this case was highly-experienced) and it is reasonable to expect that the company review could be streamlined once they are more familiar with the process and the costing implications.
- The inclusion of Pharmacy D costs by the lead site was challenged by the company during negotiations because the increase in charges from Pharmacy C within the iCT tariff is substantial. The company had initiated similar trials previously with the lead site which had not included Pharmacy D costs, and the global budget had therefore not accounted for this charge. The baseline cost of Pharmacy C is £1,800, whereas Pharmacy D is £23,100, not including the further increase from site-specific Research MFF and other overheads which ultimately inflated the Pharmacy D figure to over £40k. An additional meeting with the trial pharmacist from the lead site was required to provide justifications to the company for why Pharmacy D was applicable for these trials, following which the company agreed on including the higher charge. This suggests that it would be valuable to have representation from support departments within the mandatory calls to provide the required technical information to the company directly. More detailed company guidance to accompany the iCT tariff could also simplify negotiations and mitigate against delays like this, including further information on which studies require which grade of Pharmacy cost.

Trial 3: Pilot Delivery

The third study selected for the pilot was a multicentre CAR-T trial involving a vaccine. The trial is sponsored by a company with prior experience of the NHSE NCVR pilot and is also managed by a CRO (NB: The term 'company' below refers to the sponsor and/or CRO collectively unless otherwise specified). The 6 participating sites are located in England and Scotland, meaning this trial was the first pilot project to involve a site within a DA.

Ahead of piloting Trial 3, the timelines were amended to 15-working days for the lead site to complete the initial draft (including the Network Sites Review stage), and a further 15-working days for the company to complete their review, undertake any negotiations with the lead site, and mark the study resource review as complete. These changes were made to ensure that the pilot matched the standard NCVR timelines. However, following discussions with the company and the lead site, it was agreed that due to the very complex nature of the trial 15-working days was unrealistic to complete all the necessary costings processes. Therefore, the timeline was revised from 30- to 45-working days for completion of the whole process.

For Trial 3:

- The lead site completed the initial draft iCT within 14 working days. The costing was completed in the absence of the laboratory manual.
- The Network Sites Review process was completed within 13 working days. The total timeline of 27 working days to provide an agreed draft iCT to the company was longer than the intended 15-day timeline, however this reflected the complexity of the trial (see below).
- The company completed their iCT review within 5 working days and provided some requested adjustments to the lead site for review.

The lead site and company were unable to reach a resolution following further negotiations. The study was subsequently escalated to NIHR and NHSE via the NCVR escalation process in December 2024.

A protocol amendment was submitted in February 2025; however, the study was ultimately withdrawn entirely in June 2025 following safety concerns and did not complete set-up.

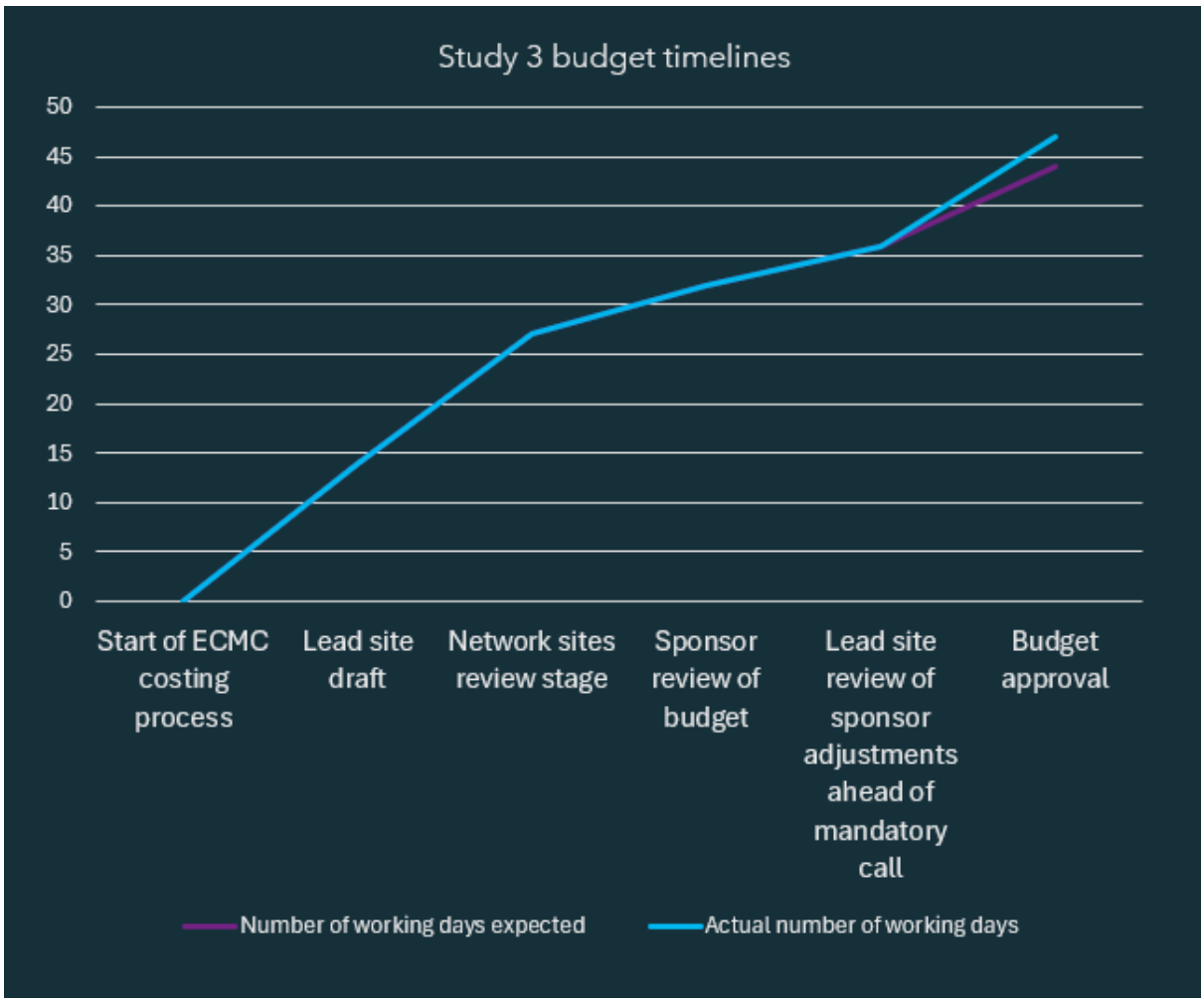

Figure 4: Number of days taken for Trial 3 budget negotiations (45-working day target)

Trial 3: Findings

Lead site costing and Network Sites Review process:

The lead site was able to complete the initial costing within 14 working days, without the laboratory manual. The company provided the lead site with milestones and a base budget to guide the lead site through their initial costing.

The Network Sites Review process was subsequently completed within a further 13 working days, meaning the total time for producing the initial draft for sponsor review was 27 days. Although this is longer than the NCVR 15-working day timeline, this study is particularly complex and required extensive review to ensure the costings were complete and accurate. Several additional costs were identified by participating sites during the Network Sites Review that the lead site agreed should be incorporated into the budget, which increased as a result of the amendments.

The company and lead site both agreed during the costing process that for highly complex trials like this 15-working days is unlikely to be sufficient given the need to involve a broader group of stakeholders and also the challenge of ensuring all possible activities are considered and included if applicable.

The Network Sites Review process highlighted that there were variations in operating processes across the sites involved in the trial that would impact on local delivery of the trial. This in turn led to multiple requests from individual sites to include costs that were related to their site-specific processes only. In accordance with the principles of NCVR, local price variations should be covered by the MFF and overheads, and the lead site has the final ownership of the budget; the Network Sites Review is to identify any adjustments to the budget that are required for all sites, not to enable sites to request price adjustments to cover local variations in delivery. The participating sites were reminded of this by the ECMC PO during the Network Sites Review meetings, and most of these requests were not included within the final budget unless there was a justification that they could apply to all sites equally.

The sites found it challenging to agree to a consistent position on how to cost for some support services, including apheresis services, Cell Therapy Laboratories, and Infusion Wards. For instance, several sites raised that their apheresis process is undertaken within the Cellular Therapy Team and not within pharmacy, and it was therefore requested that additional pharmacy-related charges should be included within the budget to cover this additional activity (Pharmacy D and E). Questions were also raised by those sites that outsource some of their support services (including apheresis) concerning how these costs should be covered fully. This is particularly relevant to sites within Scotland where apheresis is outsourced to the Scottish National Blood Transfusion Service (SNBTS); in this instance, the company and the Scottish site conducted specific negotiations to ensure that the costs were fully covered to reflect this. The guidance available through NCVR and the iCT tariff did not contain sufficient detail to instruct the sites on what the correct process should be.

Following extensive discussion between the sites it was agreed not to duplicate the pharmacy costs to cover activities conducted by cellular therapy teams because it would substantially inflate the overall budget and not all sites agreed that it was necessary due to the differing operating models in place locally. Some additional costs were included for the receipt, storage, and dispensing of the CAR-T cells by the cellular therapy lab on behalf of pharmacy; this additional time added to the tariff was to cover the pharmacy time required to confirm that the CAR-T cells could

be dispensed for treatment, and that the dispensing procedures within the cell therapy laboratory were appropriate.

Following feedback from the participants in the Network Sites Review, and a review of the process by the ECMC PO, it was agreed that a more concise group of stakeholders might have made the process more straightforward to manage. The meetings were large groups, with numerous attendees from some of the participating sites. Instead, a single representative from each organisation could attend the meetings, and in turn take any discussion points back to their teams to collate any responses. A centralised feedback document could also be implemented to simplify the collection of participating site comments by the lead site. These amendments would help to further streamline the Network Sites Review and ensure it remains constructive within the overall process without becoming an administrative challenge for the lead site to manage.

Company and lead site final budget negotiations:

Although Trial 3 was able to proceed through the earlier stages of the costing process within the agreed pilot timelines, ultimately it was not possible for the company and the lead site to agree a final budget and the decision was taken for the study to be escalated to NHSE and NIHR. Similarly to Trials 1 and 2, pharmacy-related costs became a particular sticking point during the negotiations. As outlined above, the specifics of which activities to include to ensure that all pharmacy and cell therapy costs were sufficiently covered was discussed extensively during the Network Sites Review meetings, and some additional pharmacy costs were subsequently added to the budget (however, not the full duplication of set-up fees requested by some sites). The company sought input from the NIHR prior to continuing negotiations with the lead site, however there was still no consensus reached between the negotiating organisations concerning which activities are included within the pharmacy set-up fees within the iCT tariff and which aren't, and also what the appropriate pharmacy training fees should be for a trial of this type. The company felt mostly that the costs related to the cell therapy processes should be paid for internally using the Pharmacy D set-up fee, however the lead site (and many of the participating sites) disagreed that these costs are included within the standard tariff item.

Concerns were also raised during the Network Sites Review process that mechanisms for internal financial distribution of costs at site-level continues to be a challenge. Although NHSE and NIHR have published guidance concerning commercial funding distribution, including good practice examples, feedback from participating sites within this pilot, and more broadly from the ECMC Network, is

clear that for many sites there is an absence of established process in place to ensure fair recovery of costs for research departments.

As encountered during the negotiations for Trials 1 and 2, the tariff guidance is insufficiently detailed to confirm one way or the other, and the costs involved are substantial enough that the company position was that the additional charges could not be justified within the global budget. From the lead site perspective, it was clear that the team felt unable to proceed with the trial without these specific costs being covered. Reflecting on the negotiations and the subsequent choice to escalate the study through the established NCVR process, this decision could have potentially been made at an earlier stage when it became clear to both parties that the tariff guidance was insufficient to confirm which position was correct. As noted above, the company had sought input from the NIHR outside of the escalation process ahead of this point, although the ECMC Network was not involved in these discussions.

iCT and Central Portfolio Management System (CPMS) functionality

Delivery of the pilot required the lead site to undertake the initial costing of each trial. However, within CPMS the iCT is created by and assigned to the company initially. For all trials piloted, the RRDN were required to manually assign the initial iCT to the lead site reviewer. Although the RRDN was able to complete this for the trials in the pilot without complications, the requirement to implement this additional process for CPMS coupled with the administrative burden this creates for the RRDN and other study stakeholders would be inadequate longer-term as part of a streamlined solution.

During the Network Sites Review process for the multicentre trials, and during the company review of the initial iCT, it became clear to the Project Team that different stakeholders interpret activities within the tariff very differently. For example, sites have different assumptions of what is and isn't included in line items such as virology (Hep B, HIV etc.) and tissue handling (stem cells). As outlined above, this is especially true for pharmacy-related costs. This can lead to variation in site-level costings; sites might assume that costs for certain activities are already included within existing line items, or sites might inadvertently duplicate costs by adding additional charges to cover activities they assume are not already included. The impact of poorly defined tariff items is that costs can be undervalued, overvalued, or both. This can then be exacerbated further if the company has a different interpretation of what an activity within the tariff does or doesn't include. This lack of clarity among users was observed in all three trials in the pilot and caused extended negotiations both at the

Network Site Review stage and during the company review. As explained above, for Trial 3 the differences between company and lead site positions were substantial enough to require escalation.

It was also found that for trials involving ATMPs, and early-phase trials more broadly, there are line items within the tariff that are insufficient to cover the full cost of an activity. There are also some line items that are 'missing' from the tariff completely, such as an option for higher fees for ATMP-specific amendments which are usually more resource intensive to implement. This corresponds with data gathered from costing experts during other parts of this project and is evidenced above through the extensive negotiations required for costs related to pharmacy, cellular therapies, training, and other activities.

The accuracy of the costing process could be substantially increased, and negotiations minimised, if the tariff fully reflected the activities that constitute a ATMP and/or early-phase trial, and if the corresponding guidance had sufficient clarity concerning what each line item does and doesn't cover.

Feedback from pilot stakeholders

Following completion of the pilot for each trial, feedback was gathered from key stakeholders from the lead site and company on their experiences of the process via a survey and interviews. The feedback received was very positive overall, although some concerns were raised over specific parts of the process.

All pilot participants were supportive of the lead-site undertaking the initial costing of the trial. The company involved in Trials 1 and 2 felt that this approach made the process quicker overall as they would only have to review and then negotiate a single costing. They also noted that the costing was of a high quality (although there was concern that not all sites may have the same level of expertise as the lead site for these trials) and that this process was suited to early-phase and ATMP trials due to the additional complexity of these study types.

The lead site for Trials 1 and 2 did not feel that the process was quicker overall currently as they were responsible for producing the full initial draft costing; however, the lead site did feedback that reviewing the sponsor's initial draft during the standard process is generally very labour intensive, and that the adapted process was therefore more time efficient after the initial stage because the first costing was more accurate (i.e., less time spent reviewing the company costing).

The lead site for Trial 3 fed back that they would like to see more suitable formal training resources and guidance made available by NIHR for costing these types of complex trials. The company agreed that there is a need to have this in place and that there must be a consensus between sponsors, CROs, and sites relating to the tariff items for activities. Feedback from participating sites highlighted that they found companies often do not fully understand the complexities of delivering early-phase and ATMP trials within the NHS, and by extension therefore do not reflect this fully within the allocated global budgets (this is true for all 3 trials piloted). For Trial 3, which involved a sponsor and CRO, there were also times when the organisations took different approaches to which costs were appropriate or not during negotiations, which the lead site found challenging to navigate; for trials involving both a sponsor and CRO there must either be clear delegation put in place during negotiations so that one organisation is making the decisions, or a consensus agreed between the two parties prior to starting the costing process.

The Network Site Review process was viewed as a helpful addition to standard NCVR, particularly for the participating sites who found there was significantly less work to do overall, and there was increased transparency, which should help to proactively minimise the potential for future escalations.

Negotiations between site and company were complex and therefore time-consuming; however, the lead sites and the companies involved in all three trials reported that the mandatory calls were very beneficial in aiding negotiations, setting clear timelines and expectations, and in ensuring information was shared appropriately. Good communication was maintained between all organisations throughout. Stakeholders were confident that the burden of negotiations would reduce in time, especially if the guidance and iCT were updated accordingly. For Trials 1 and 2, the company reported that contracting with the lead site was executed swiftly following completion of the costing process.

Next steps

The pilot has demonstrated that there is significant potential to improve the accuracy and completeness when costing early-phase and ATMP trials when enabling the lead site to initiate the costing process. With increased familiarity with the revised process and better system functionality to facilitate ATMP and early-phase costings, there could also clearly be improvements in the time taken to complete costings. Although all three trials experienced delays when compared with the target timelines, the overall turnaround time was still good considering the complexity of the trials and also that this was a new process for stakeholders to navigate.

Following consultation with NHSE, NIHR, and the RDN, the ECMC-adapted NCVR process followed for the pilot was not mandated as part of the October 2024 expansion of NCVR. This was due to the CPMS functionality limitations outlined above, and because there was not sufficient evidence to justify the change to the standard process. However, although the ECMC adapted process will not be mandated, companies and sites who prefer the process will be able to utilise it by contacting the applicable RRDN.

Following the extended roll-out of NCVR to ATMP and early-phase trials, there are several broader considerations that should be highlighted:

Considerations	**Details**	**Suggestions**
Insufficient iCT Tariff Items and Descriptions	iCT tariff lacks items for complete costing of ATMP and early-phase trials; existing line items lack sufficient descriptions. Guidance options are incomplete or outdated.	Update iCT to incorporate all common ATMP and early-phase specific activities (or variations of standard activities that are routinely substantially different for these trial types). The explanations accompanying line items should be expanded to provide more detailed information, including for all Pharmacy setup fees. The current guidance options are incomplete and/or outdated and require revision. A permanent training program and/or resources focused on ATMP and early-phase trials to accompany the iCT would be of huge benefit to many users, particularly those stakeholders with less experience of these types of studies (for e.g., junior staff within a CRO).
Amendment to the Network Site Review process	Feedback of the Network Site Review process was positive; however, as outlined above for Trial 3, when incorporating a larger group of stakeholders the process became more difficult to manage for the lead site.	Each participating site should nominate 1-2 key stakeholders to attend the Network Sites Review meeting. These members can then collate the information and responses within their own sites

		and feed back to lead on behalf of their organisation. A centralised feedback document could also be implemented to simplify the collection of participating site comments by the lead site.
Higher Final Contract Values	For both Trial 1 and 2 the final contract values were significantly higher than initial drafts, providing a more accurate cost breakdown for ATMP trials. Although Trial 3 did not reach the contracting stage, the final draft budget was higher than the initial expectations of the company. This should be viewed as a success; the final iCTs were a more accurate breakdown of what the delivery of an ATMP trial will cost, the expertise of the site teams was utilised effectively, and the company accepted the final costs as accurate and complete. There is a concern that for these trials, and for NCVR more broadly, commercial costs will be much higher than pre-NCVR, and this must be managed with companies to ensure that the UK does not lose any competitive edge with other markets.	It is important for the long-term sustainability of UK clinical research that trials are accurately costed in a timely manner as part of a streamlined process; if this results in companies having to pay more to deliver trials then the advantages of the new system must be communicated effectively so that sponsors are not put off working within the UK.
Availability of Study Manuals	Study manuals were available during initial costing for Trials 1 and 2, which is rare for early-phase and ATMP trials. Manuals are often not able to be shared by the company until just prior to the first site opening. Feedback from the lead site suggests	Encourage earlier sharing of study manuals or where manuals are not available to the lead site at the onset of the costing process then prepare for a more extensive period of information sharing with the company.

	that the availability of manuals in this instance made the initial costing process more straightforward. For Trial 3, the laboratory manual was not available for the initial costing which made the process more challenging for the lead site.	
CPMS Limitations in Delivering Pilot Process	CPMS is not currently able to deliver the ECMC pilot process without direct input from the RRDN to manually assign the iCT to the lead site from the company. The totals within the draft iCT that the company reviews initially are also exclusive of Research MFF and other overheads and therefore do not provide the company with the complete information about the projected costs.	Update CPMS to address manual assignment issues *Note – A formal process was agreed with the RDN CC following completion of the initial 2 trials through the pilot.* Include complete cost information in initial draft iCTs reviewed by company.
Handling of Protocol Amendments	Protocol amendments that are received after the iCT has been shared with participating sites are not processed within NCVR, and sites must each negotiate directly with the company to agree any study resource changes. Early-phase and ATMP trials often involve multiple amendments to the protocol, including within the very early stages of set-up.	Incorporate protocol amendments into the NCVR process to ensure uniformity across all organisations and to simplify the process for the company. The Network Site Review process could be utilised to simplify amendment costings and reduce variation between sites.
NIHR Escalation Pathway	The escalation process for Trial 3 was slow and did not follow a clear process.	The escalation process should be formalised, with clearer guidance and accompanying timelines to ensure disputes are swiftly resolved.

Site-level internal financial management	The NHSE and NIHR guidance on commercial funding distribution has not been fully implemented at many sites which limits access to fair recovery of costs of research delivery.	Ensure full implementation of NHSE and NIHR guidance on commercial funding distribution at sites to support equitable recovery of research delivery costs within all internal departments.

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- NHS England » NHS Standard Contract
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