1. **Title of Project**

**Costing Adaptive Trials (CAT): developing best practice costing guidance for CTUs supporting adaptive trials**

1. **Abstract**

Background

There is an ongoing drive towards developing trial methods that increase efficiency. The use of adaptive designs has recently increased, although their use in practice still remains relatively low. One important barrier is understanding the resources and costs needed; we investigated these for adaptive compared to non-adaptive trial designs.

Methods

We developed five trial scenarios representing commonly used adaptive designs. A non-adaptive version of the trial was also provided, alongside further details about the trial. Staff resource and non-staff costs were requested for the non-adaptive and adaptive version of each example scenario from colleagues in seven UKCRC Registered Clinical Trials Units (CTUs). Each scenario had costings from at least five CTUs; three CTUs completed all scenarios. Qualitative interviews were also conducted with 10 staff across participating CTUs to understand the rationale for differences in resources.

Results

There was variability in how much additional resource was requested for adaptive designs between CTUs, category of costs and type of design.

On average, across all scenarios and all CTUs, statistical resource was increased more than data management and trial management resource. For data management, all CTUs increased resource for three of the designs but not for the other two. There was agreement on increasing trial management resource for sample size re-estimation (which has a potentially longer trial duration) but disagreement amongst the other designs. Qualitative interview findings highlighted reasons for variability, including CTU experience, approaches to costing, and trials.

Conclusions

Adaptive designs can provide substantial benefits in many scenarios but require (generally small to moderately) higher required resources to support high-quality delivery. CTUs (especially those that are new to delivering adaptive designs) should consider what extra resources might be required; we are developing guidance to inform these decisions. Further research weighing when the benefits of adaptive designs outweigh the extra resource required is warranted.

1. **Introduction**

There is a growing focus on increasing the efficiency of clinical trials, which are key tools for improving global healthcare. A key driver of efficiency is to ensure each trial provides as much robust information as possible in a timely manner; it is also important that patients are not subjected to harmful treatments. Adaptive Designs (ADs) can achieve both of these objectives. An AD allows the opportunity for patient outcome information gathered during the trial to be used to make prespecified modifications, in a statistically robust way, to the trial.

ADs represent a wide range of potential approaches, including group sequential, sample-size re-estimation, multi-arm multi-stage (MAMS), and adaptive enrichment designs. ADs can: 1) improve statistical power; 2) reduce average sample size and/or trial length for a target level of power; 3) improve robustness when information is lacking at the design stage; or 4) improve how trial patients are treated. Each type of AD provides one or more of these advantages compared to non-adaptive alternatives.

ADs are now being increasingly used, including examples funded by NIHR and supported by UKCRC Regsistered Clinical Trials Units (CTUs); they have been successfully used in several trials of COVID prevention and treatment(1), which will likely lead to further demand for their use in the future.

Guidance on ADs is available, including how to implement and report them (2,3). A key outstanding issue is understanding what funding and personnel resources (i.e. staff time) are required to successfully conduct a high-quality adaptive trial and how these compare to more traditional trial designs. When implemented with insufficient resources, adaptive trial delivery is likely to be compromised and some potential benefits may not be realised.

Better understanding of the costs involved may also inform decision making about the situations in which ADs are worth using(4).

The objectives of the Costing Adaptive Trials (CAT) project were:

1) to estimate any additional (financial and staffing) resources required to support adaptive trials compared to non-adaptive trials, through conducting a mock costing exercise of several scenarios;

2) to investigate reasons for differences in costs between non-adaptive and adaptive trials through qualitative research, thereby understanding the factors that drive the costing of adaptive trials;

3) to provide best-practice guidance on what resources should be included in funding applications for trials using ADs.

1. **Methods**

*Development of mock scenarios*

A subgroup of the CAT team developed five trial scenarios based on real trials. Each scenario, detailed in Appendix 1, represented the potential use of a different AD: group-sequential design, model-based dose-finding trial, MAMS, adaptive umbrella trial, and sample size re-assessment.

In each scenario, a non-adaptive version of the trial was created, with a protocol synopsis containing a summary of the trial’s PICO (Participants, Intervention(s), Comparator, Outcomes). The last section of the scenario outlined a summary of the AD proposed, with the rationale and implications on the design.

*Cost and resource data requested*

A spreadsheet was provided which asked for information on the resources required to undertake each trial scenario. This was split into: 1) pre-award, the resources needed to develop the application to the point of the grant starting; 2) post-award staff resources that would be required to deliver the trial; 3) post-award non-staff costs required to deliver the trial once the grant had started.

For staff resource, information was requested on: role; co-applicant status; grade; contract type; whether the post was underpinned by central (core) funding; the percentage of full-time equivalent (FTE) the staff member would be working on the trial; total number of months on trial; total salary cost (including national insurance and superannuation); any indirect costs charged and any additional employment-related costs. For non-staff resource, suggested cost items were listed including: stationery; travel (for trial oversight committees, site initiation visits, monitoring, closedown of centres); project meeting costs (launch and investigator meetings); teleconferencing fees; clinical data management and randomisation system fees; Medicines and Healthcare products Regulatory Agency (MHRA) fees (including amendments); computing costs (including specialist statistical software); staff training; Patient and Public Involvement (PPI); dissemination (including open-access publication costs); data sharing and post project costs (e.g. data archiving and anonymisation). There was provision for CTUs to add any additional costs not listed.

Staff resource and non-staff costs were collected for the non-adaptive and adaptive version of each scenario from each CTU. Guidance was given to each CTU as comments within the spreadsheet and in a separate guidance document. If CTU staff had queries, they were offered the opportunity to send any queries to the core CAT team.

After receiving the completed costings, any queries in the costing exercise were sent to CTUs. The majority of these queries were resolved; for the very few minor queries that remained unresolved, assumptions were made based on the other information provided by that CTU.

*Participating Clinical Trials Units*

In the initial grant application, some of the co-applicants were associated with participating CTUs. Additional CTUs were invited through an email sent to directors of all UKCRC-registered CTUs describing the project in November 2019. All CTUs who confirmed their willingness to take part were included. All materials required for conducting the costing were sent out in January 2020, with a request to send back completed costings by March 2020.

*Analysis methods*

In the presentation of results, CTUs are anonymised. Due to the large variation in how different institutions dealt with indirect staff costs, we summarise requested staff resource using the number of ‘FTE-years’. For example, a staff member funded at 50% FTE for four years of a grant would contribute 2 FTE-years.

FTEs were summarised by total, as well as by category (statistics, data management and trial management). Other categories included programming, administration, quality assurance, senior management/operations, data entry, and researcher; however, these were inconsistently used across CTUs and so are not separately reported, but contribute to the overall total. Non-staff costs were considered as a total.

Staff FTE-years and non-staff costs are presented as a percentage change between the non-adaptive and AD and as a relative change for the AD compared to the median non-adaptive design figure for each scenario and CTU. Statistical analysis was descriptive and the percentage change data was summarised as a median and range.

*Qualitative methods*

Participants who undertook the costing exercise were invited to attend an interview; all were interviewed via Videoconference. A semi-structured topic guide was used to explore local costing procedures and reasons for differences in costs between the adaptive and non-adaptive scenarios.

Qualitative interviews were transcribed verbatim and coded in Nvivo. The National Centre for Social Research ‘Framework’ approach(5) (familiarisation; identifying a thematic framework; indexing; charting; and, mapping and interpretation) was used for analysis. Themes were derived inductively from reading the transcripts.

The results were presented and discussed at an investigator meeting in January 2021.

*Ethical approval*

The project received an ethical waiver by Newcastle University’s ethics committee due to it not involving patients.

1. **Results and Conclusion**

*Costing exercise*

A total of 10 CTUs expressed willingness to take part in the mock exercise. Three subsequently dropped out due to workload issues. Seven went on to contribute at least one costing scenario, with three providing a costing for all scenarios. In all scenarios that CTUs provided a costing for, they provided a costing for both the non-adaptive and adaptive versions of the scenario. Each scenario had costings from at least five CTUs.

Percentage increases in total FTE years, median (range) across designs were as follows: Group-sequential design: 3.9% (2.7%, 27.7%) n=6; Phase IIb dose-response: 2.2% (0.7%, 17.5%) n=6; MAMS: 3.0% (1.3%, 7.9%) n=5; Umbrella trial: 3.0% (1.0%, 34.2%) n=5; Sample size re-estimation: 26.5% (0.8%, 38.9%) n=5. Sample size re-estimation increased FTE and non-staff costs more on average than other scenarios, which was due to a longer maximum project length.

Resources were consistently increased for the statisticians across every scenario. This reflected the additional work required at the development stage, with more complex protocols, statistical analysis plans, and training, alongside the time needed to undertake the interim analyses. There was wider variability in the need for additional staff resource beyond statistics. The data and trial management time was not increased for the Phase IIb dose-response design, and likewise trial management time was not increased for the MAMS or Umbrella trials, however the wide ranges indicate that this is not consistent between units.

*Qualitative research*

All seven CTUs took part in an interview, with staff interviewed either individually or in pairs where they had worked together on the costing exercise. Eight interviews took place with 10 individuals (mean 40 minutes; range 33-55 minutes). Interviewees were experienced in costing trials, with variation in their experience of costing ADs. Individuals with more experience in ADs tended to work on oncology trials.

Interviewees used a similar process for costing non-adaptive and ADs, with some differences in who was consulted or was involved in the costing. In cases where the trial design would have a variable duration, all interviewees costed for the maximum duration, or so called ‘worst-case scenario’, to ensure the CTUs could deliver the whole trial.

Statistics resource (i.e. FTE) was always increased to undertake the interim analyses, and sometimes increased due to a higher workload during the development of the protocol and the statistical analysis plan.

CTUs increased data management or related resource to account for changes to the randomisation system or the database during the trial, or for increased intensity of activity around interim analyses, e.g. for data cleaning. CTUs that did not increase data management resource (or increased it by a small amount) tended to be those that were more experienced in making adaptations during their trials and therefore had systems set up to accommodate these changes, such as units experienced in oncology trials.

CTUs that increased trial management time, usually by increasing the FTE across the trial, did so to cover increased complexity of the design, the potential for increased protocol amendments, data cleaning and other activity around interim analyses. In some scenarios, some CTUs did not increase this as it was thought the trial manager could undertake the additional tasks required for the AD within the FTE that they had been allocated for the non-adaptive design.

Reasons for differences in cost increases between scenarios within a CTU were related to the complexity of the non-adaptive design in the scenario, or the consequence of the interim analysis/es.

*Discussion and Limitations*

This research has provided useful information to inform how CTUs should consider the appropriate resources required for delivering adaptive trials. Nevertheless, there are several limitations of this work.

The results are derived from seven CTUs, however the extensive discussions, including two workshops with a larger range of CTUs nationally, involved a wider group of nine CTUs. The conclusions and discussion detailed might therefore be more representative than the sample size indicates.

Theoretical scenarios were provided without the wider context of the full application, and without opportunity for refinement of resource needs, which would typically occur outside the artificial construct of this exercise. There was recognition that final resource request would typically involve discussion and refinement during and following the application. Without repeating the exercise or engaging in re-running the exercise including a discussion element, it will not be known what impact this may have had on the resources included.

The scenarios were of differing length, with the baseline (non-adaptive) scenarios varying in complexity. This made it difficult to draw direct comparisons across scenarios and accounting for differences in how much the adaptive version increased estimated required resources.

There was variation in the experience of designing, gaining funding, running and completing adaptive trials. Those who had experience of working with ADs in oncology, were likely to be those with the most experience of the design, development and delivery of adaptive trials.

Resource needs in the exercise were included at the ‘worst case’ scenario, which included resourcing for multiple amendments, multiple database changes, more frequent monitoring visits based on classifying all centres as potentially risky, and the uncertainty generated from the limited information provided. The aim was to avoid, where possible, the requirement to return to the funder for additional funding, or the need for an academic unit to underwrite trial resource needs, though one unit described providing funders with multiple costs. It was not possible to assess management of resource where the adaptation was implemented caused the ‘worst case’ not to be realised.

*Conclusions*

This study used both quantitative and qualitative methods to explore the resource needs for a range of adaptive trial designs with academic CTUs in the UK. It is the first study to systematically gather and analyse prospective data on resourcing trials utilising an AD. Whilst we have seen large variation within our sample, we have also identified a consistent and clear need for additional resource, most notably in statistical support. Findings indicate that adaptive trials may require more staff and non-staff resources than non-adaptive trials, at least in the ‘worst case scenario’.

ADs provide convincing advantages in many situations. Further research to examine how to weigh-up the advantages against the additional resource would help ensure that ADs are used when they are likely to provide benefit. Additional research that could help reduce the gap in resources required between non-adaptive and adaptive trials would help increase the number of situations that the latter provide benefit.

1. **Dissemination**

We are drafting two papers to submit for publication. The first will be a full report of the research methods and results. The second will be aiming to provide guidance on how to estimate the resources needed for an adaptive trial, using the themes identified from the research. These will be made open-access.

The results will be presented at relevant clinical trials conferences. We have an oral presentation at the 2021 Society of Clinical Trials conference and will submit an abstract to the 2022 International Clinical Trials Methodology Conference.

The two papers will be disseminated throughout the UKCRC CTU network, with a summary presentation offered to the UKCRC Directors, Trial Manager Network and Statistics Operational Group. We will also send this to NIHR Programmes to share with funding panels as well as other funders of clinical trials (e.g. BHF, CRUK, MRC, Wellcome Trust). Several co-investigators have prominent roles in these networks and will help with dissemination.

We will work closely with the MRC-NIHR Trials Methodology Research Partnership (TMRP) Adaptive Designs Working Group to disseminate the results (e.g. through a TMRP webinar) and plan future research. Longer term outputs will come from methodology research motivated from this work. The first will be to investigate formally evaluating the cost-effectiveness of adaptive designs in different scenarios. We have identified aspects of supporting trials that require higher resources for adaptive trials. We will develop methodological improvements that could mitigate these costs. For these we will propose Studies Within A Trial (SWAT) that could investigate the effect of implementing the improvement within a trial.

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1. **Acknowledgements**

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1. **References**

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1. **Appendices**

Appendix 1 – trial scenarios

Below is an overview of each scenario used in the mock costing exercise; it is worth noting that group-sequential designs are not always considered an example of an adaptive design but were included in the definition within this project

*Scenarios*

* Group-sequential design: Two-arm randomised controlled trial assessing addition of biomarker-testing to an existing early warning score in the management of patients with suspected sepsis in the emergency department
* Design that updates dose allocation in second stage based on optimal design fitted to stage 1 patients: A randomised dose-finding study of JAK1 inhibitor for patients with active rheumatoid arthritis
* Multi-arm multi-stage design with early stopping for lack of benefit: A multi-arm open-label phase 3 trial comparing regimens for treating intermediate and high-risk oropharyngeal cancer
* Adaptive umbrella trial, allowing early stopping of arms within patient subgroups: A randomised controlled trial assessing clinical and cost-effectiveness of earlier treatment of ovarian hyper-stimulation syndrome
* Sample size re-assessment: Randomised double-blinded placebo-controlled trial of the efficacy of nicotinic acid derivative (NAD) for treatment of fatigue in mitochondrial disease
1. **Conflict of interest declaration**

There were no competing interests relevant to this work.