A scoping review showed that several non-validated budget planning tools for randomised trials are available

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Abstract

Objectives: We aimed to provide a systematic overview of freely available tools which may help to plan or monitor costs for randomised clinical trials (RCTs).

Study Design and Setting: We systematically searched MEDLINE, EMBASE and EconLit and conducted internet searches via Google (last search October 2018). We included all freely available tools and determined their specific purpose, which parts of clinical trial projects and which types of costs they covered, and if they were user tested or validated in any form.

Results: We identified 25 available tools. Most tools were downloadable on websites from institutions related to clinical research. Seven tools were developed to plan the budget for an entire RCT, 17 tools for calculating budgets of an individual trial centre, and one tool for monitoring costs of ongoing RCTs. 18 tools considered fixed, variable, and indirect costs. Only two tools were clearly user tested or validated.

Conclusion: Several freely available tools aim to support investigators in planning costs of an entire trial or in planning the budget for a clinical trial site. How valid and useful they are remains to be shown for most of them. Future tools should be openly shared, user tested, and validated.

What is new?

Key Findings

- Several freely available tools aim to support investigators in planning costs of an entire randomised clinical trial or in planning the budget for an individual trial centre.
- Only one tool aimed to support investigators in monitoring costs during trial conduct.
- The vast majority of trial planning tools were not validated or user tested.
- The tools were mostly produced for intra-institutional use and, based on our search, we did not have the impression that any tool was widely picked up by other researchers.

What this adds to what was known?

- Freely available, user-tested, and validated cost budgeting and monitoring tools for randomized clinical trials are lacking.

What is the implication and what should change now?

- Cost budgeting and monitoring tools should be openly shared, user tested, and validated using empirical resource use and cost data from clinical trials.

1. Introduction

Randomised clinical trials (RCTs) are the gold standard to assess benefits and harms of medical interventions [1, 2]. However, the planning and conduct of an RCT is usually administratively burdensome, complex and costly [1, 3, 4]. Already during the set up phase, experts from several disciplines are involved (e.g. clinical researchers, physicians, statisticians, data managers, regulatory experts, trial monitors) and a number of relevant cost items have to be considered such as protocol writing, communication, staff training, site management and set up of a database [5]. The conduct itself has then usually more cost-relevant components, some of which may be easily overlooked (e.g. fees for clinical facilities, data entry, time to respond to data queries, investigator meetings) [6].

While RCTs often require substantial resources, access to sufficient resources is typically challenging. Especially in academic research it seems common that clinical studies are underfinanced [7]. Additionally, the compensations paid to study centres participating in multicentre trials do often not cover the actual costs [7]. Consequently, insufficient resources may put RCTs at risk for early discontinuation [8]. Poor recruitment, which is also closely related to limited or running out of resources, was the main reason why about 30% of RCTs were discontinued [9]. Interviews with investigators from discontinued RCTs suggested that factors related to funding (e.g. errors in budget planning) were among the main reasons for insufficient recruitment and trial discontinuation [8]. Therefore, tools to support investigators in careful planning and monitoring trial costs are essential for the successful conduct of trials and to avoid research waste. We recently assessed costs of RCTs retrospectively and created a comprehensive cost item list based on a systematic review and stakeholder interviews [5, 10]. When we analysed the cost structures of these clinical trials, we noticed that

specific tools or evidence-based approaches to cost planning, budgeting, or monitoring of clinical trials were hardly ever mentioned in the trial literature. In this scoping review we aimed to give a broad overview of the publicly available budget planning tools that may assist clinical researchers in their preparation of a clinical trial.

2. Methods

2.1. Review type and reporting

This study used common methodology of a scoping review [11] and the manuscript adheres to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) reporting guidelines (see Appendix) [12]. No written protocol exists for this scoping review.

2.2. Literature search, internet search and eligibility criteria

A medical librarian (HE) systematically searched MEDLINE and EMBASE via Ovid, and EconLit. All databases were searched from inception until May 2018 without any language restrictions (see Appendix for detailed search strategy). We searched MEDLINE and EMBASE as typical medical literature databases, which clinical scientists or economists would probably search when looking for a clinical trial budget planning tool. We included EconLit as this widely available database contains health economic reports.

We screened all titles and abstracts of our search results in duplicate (BS and VG). Titles and abstracts of articles, which were potentially relevant according to at least one reviewer, were independently screened at full text level by two authors (BS and

VG). We retrieved the full text of all articles that mentioned a tool for planning or monitoring costs of RCTs in the title or abstract.

We included any publication that described details of a tool to (i) plan a budget for an entire RCT or (ii) to plan a budget for an individual trial centre, or (iii) to monitor costs during the conduct of an RCT. We excluded (i) documents which described narratively how a budget should be calculated instead of providing details of a tool, (ii) tools (or descriptions thereof) which were generic for any research projects or research grants and were not tailored to (randomised) clinical trials, and (iii) tools which listed insufficient details (meaning less than 3 cost items) for more than one of the three relevant study phases of an entire RCT (i.e. pre-conduct phase, conduct phase, and post-conduct phase; Figure 1). For tools specifically focusing on trial conduct costs at individual centres, we expected no details for the pre-conduct or post-conduct phase.

In addition to the systematic literature search, two authors (BS and NS) individually searched for cost tools via Google.com between June and October 2018. Specific combinations of search terms were pre-specified by two authors (BS and HE; see Appendix) which could then be individually adapted by the authors who conducted the Google search. Separate combinations of terms were searched until the authors felt that saturation was reached (i.e. the last 20 hits did not reveal any new relevant information). Additionally, we specifically considered in the internet search national ministries of health from 13 countries (Australia, Austria, Canada, France, Germany, Italy, Japan, Norway, Spain, Sweden, Switzerland, USA, UK [13]; details in the appendix) . Potentially eligible tools were marked and downloaded. One author (BS) checked potentially relevant tools for eligibility and a second author (VG) crosschecked eligibility; if in doubt, a third author (MB) was consulted.

2.3. Data extraction

From the included tools we extracted the following: name of the institution that provided the tool, country of origin, whether the developers provided a manual explaining how the tool should be used, purpose of the tool as stated by the developers (e.g. monitoring costs of an entire RCT), and whether the tool provided examples for typical costs or plausible cost ranges for specific items. Furthermore we extracted information on evidence for any user testing (at least description of changes of the tool over time, indicating that the tool was used and adapted based on user experience) or validation of the tool. By validation we mean whether the accuracy of the tool was tested by comparing estimates from the tool for individual cost items or cost sections to a reference standard, e.g. retrospectively or prospectively collected actual cost data from RCTs.

We also determined if any underlying empirical evidence was provided indicating what information or sources the developers of the tools used to make sure that all relevant cost aspects and cost items are covered. In particular these sources could consist of resource use or cost examples from previous RCTs, identified cost item lists for RCTs, but also of expert discussions.

Next to the direct costs (i.e. costs that were related to the work as described in the study protocol), we further assessed, whether these costs were split into variable costs (i.e. costs which are directly related to the number of patients) and fixed costs (i.e. costs which are paid for the entire study independent of the number of enrolled patients [e.g. fee for approval from ethical committee]). Additionally, we assessed whether the tool considered indirect costs (e.g. infrastructure, overhead). Finally, a short narrative explanation of the tool which intends to give a broad idea of the tool was provided by

our author group. Data extraction was done by one author (BS) and checked by another (VG or MB).

2.4. Analysis

Results were descriptively summarised to provide an overview. Included tools were categorised (i) to plan a budget for an entire RCT, or (ii) to plan a budget for an individual trial centre, or (iii) to monitor costs during the conduct of an RCT. Planning tools for specific study sites would usually focus on items that are relevant for the conduct phase (including patient recruitment, treatment, and follow-up; Figure 1). However, they also might include, to a limited extent, items from the pre-conduct phase (e.g. getting familiar with the study protocol, ethical approval). Figure 1 illustrates the different study phases as well as examples of cost items which are commonly considered when planning an RCT.

Tools that do not consider all three relevant cost aspects (i.e. variable, fixed, and indirect costs) might be prone to underestimating the overall trial costs. Hence, we highlighted those which considered all relevant costs (direct costs, including fixed and variable costs, as well as indirect costs). The categorization and the assessment of tool characteristics was done by one author (BS) and crosschecked by another (VG or MB).

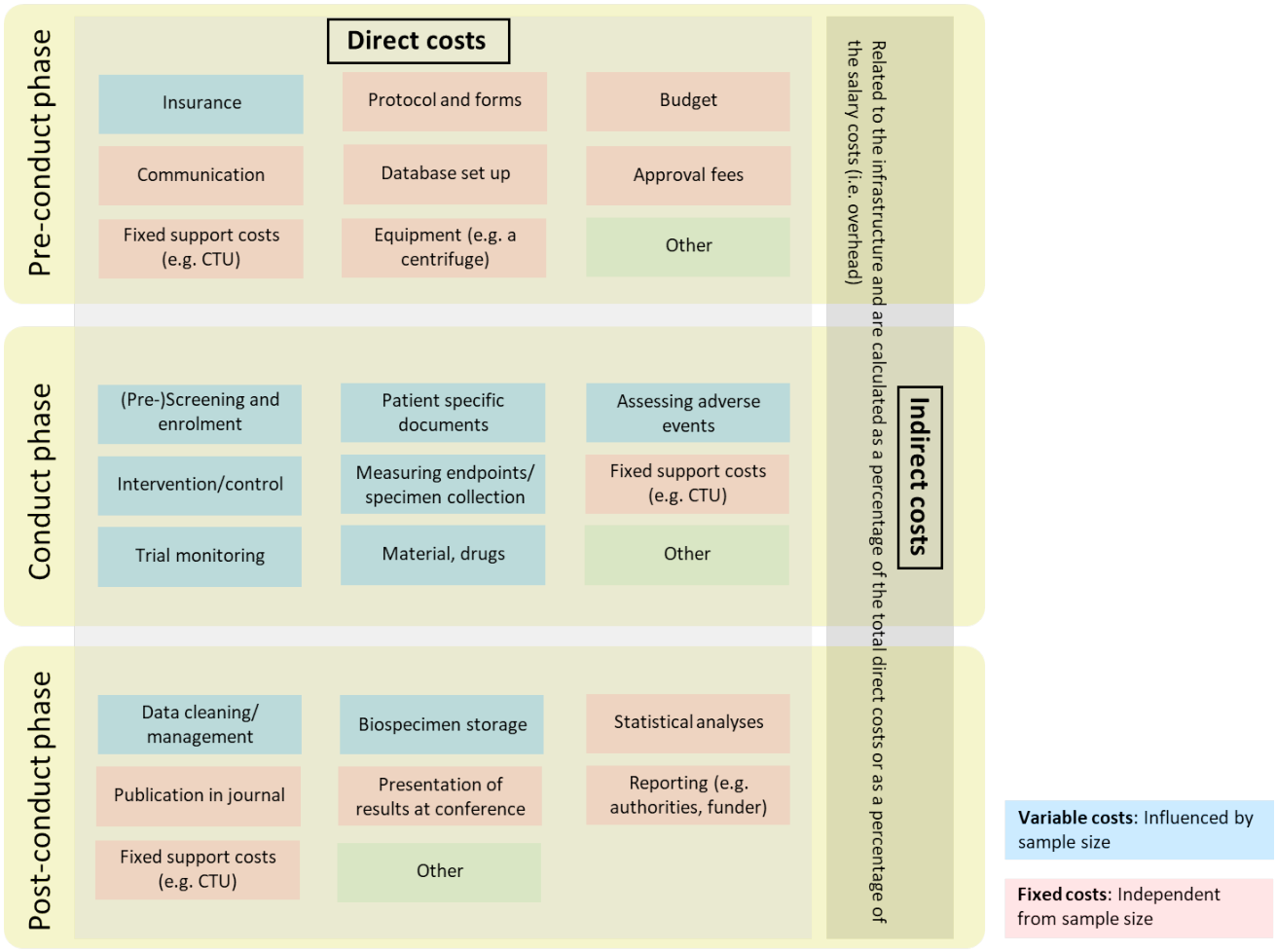

Figure 1: An example of typical costs which should be considered when planning a randomised clinical trial.
Abbreviations: CTU = Clinical Trial Unit

3. Results

Search results

Our search of MEDLINE, EMBASE and EconLit resulted in a total of 1914 hits after deduplication (Figure 2). We excluded 1850 articles based on title and abstract and assessed 62 full texts. We tried to contact the authors of five publications, to ask for access to their tools and to clarify eligibility (see appendix for detailed process). One

study group provided their eligible budgeting tool upon request [14]. We included two tools based on searching scientific databases [14, 15].

In our internet search, we visited 352 websites, identified 41 tools as potentially relevant during the internet search, and finally included 23 after closer eligibility assessment [16-38].

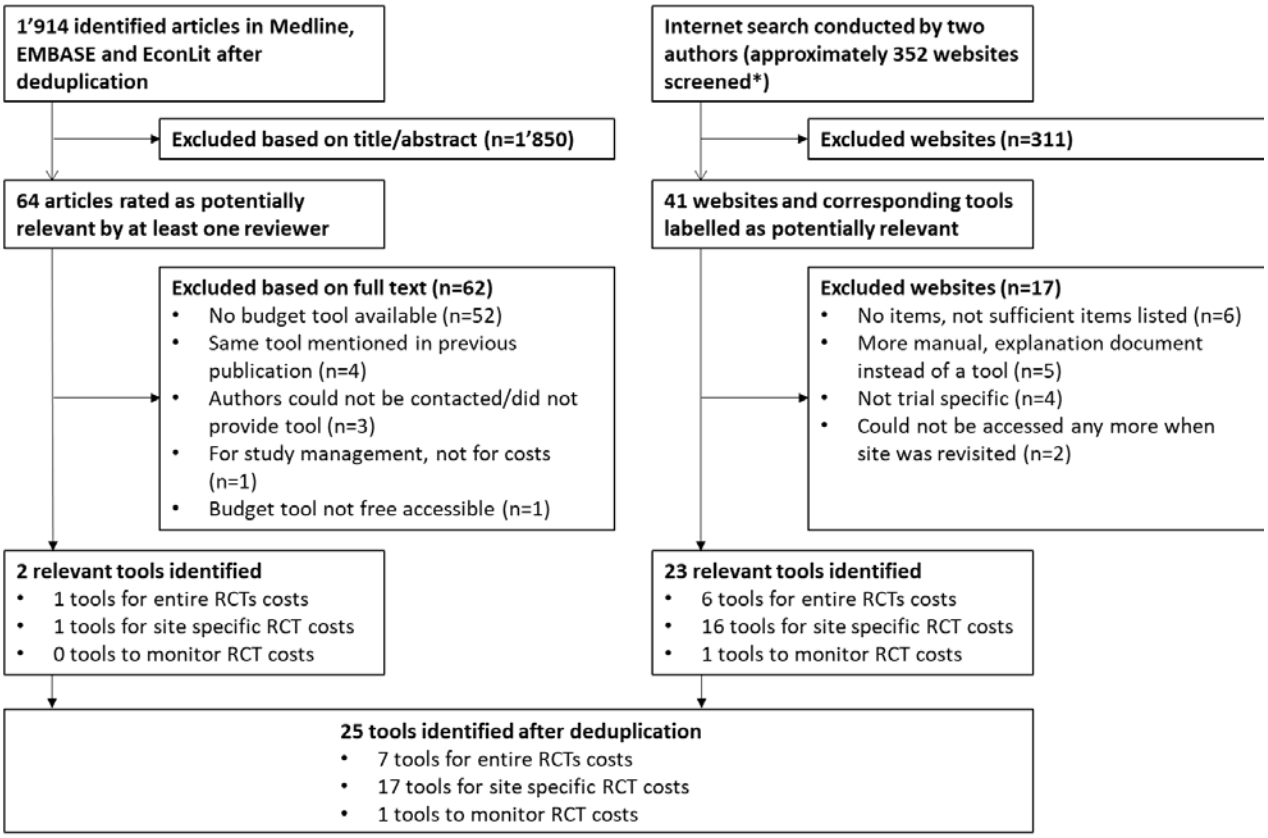

Figure 2: Selection of budgeting tools

Types of tools

Of the 25 tools there were (i) seven tools for planning the budget for an entire RCT; (ii) 17 tools for planning the budget of an individual trial centre; and (iii) one tool for monitoring costs of ongoing RCTs. Details and download links for all these tools are

provided in the Appendix (Table S1). The majority of tools were adapted MS Excel® spreadsheets (n=23), while one used a web-based tool, and another one was a detailed item list in Portable Document Format (PDF; Appendix; Table S2).

Most tools originated from North America (United States n=9, Canada n=3) and Australasia (Australia n=4, New Zealand n=2; Appendix Figure S1). The other tools were developed in Europe (United Kingdom n=2, Germany n=1, Ireland n=1, collaboration between Belgium and the Netherlands n=1; Table 1). For 13 of the 25 tools, developers provided clear instructions in a manual, on how the tool should be used (Table 1).

244 **Table 1:** Characteristics of the identified tools.

Source	Country	Explanation how to fill out the tool	Description of any (i) experience based changes of tool, (ii) user testing, or (iii) validation	Examples for cost-values provided	Evidence-base (i.e. the was the tool based on resource use or costs from previous RCTs)	Direct costs[1]: Variable costs	Direct costs[1]: Fixed costs	Indirect costs (e.g. infrastructure, overhead costs)	Possibility to assess variable costs, fixed costs and indirect costs (all 3)
Tools to plan costs of an entire randomised clinical trial									
Belgian Health Care Knowledge Centre [16]	Belgium and Netherlands	Yes	No	Yes, costs per items and hourly rates. "For general tasks a fixed price (FX) has been determined". Unclear how these fixed prices were established	NR	Yes	Yes	No	No
California Institute for Regenerative Medicine [23]	Canada	Yes	No	No	NR	No	Yes	Yes	No
Clinical trial podcast [19]	USA	No	No	Yes, costs per unit. Unclear how example costs were established.	NR	Yes	Yes	No	No
Health Research Board Clinical Research Coordination Ireland [20]	Ireland	No	No	No	NR	No	Yes	No	No
Murdoch children's research institute [17]	Australia	No	No	No	NR	Yes	Yes	Yes	Yes
University of Birmingham; Clinical research compliance team [18]	UK	Yes	No	No	Yes	No	Yes	No	No
University of Texas at San Antonio [14]	USA	No	Yes, user testing with data from a clinical trial [14]	No	NR	Yes	Yes	Yes	Yes
Tools to plan a budget for an individual trial centre									
Advocate Health Care [21]	USA	Yes	No	Yes, non-refundable start-up costs and fees. Costs are shortly explained within the Budget Justification Template.	NR[4]	Can be entered, but none listed	Yes	Yes	Yes
Auckland District Health Board [22]	New Zealand	Partially, some comments in the template	No	No	NR	Yes	Yes	No	No
Government of Western Australia. Department of Health [35]	Australia	Yes	No	No	NR	Yes	Yes	Yes	Yes
National Institute for Health Research (NHS) [24][3]	UK	Yes	Yes, changes summarised based on previous experience	Yes, costs examples for fees and a few tasks (pharmacy time, set-up management and close-down costs). Fees explained within document.	NR	Yes	Yes	Yes	Yes

New South Wales Government [26][3]	Australia	Yes	No	No	NR	Yes	Yes	Yes	Yes
New Zealand Association of Clinical Research [25]	New Zealand	Yes	Yes, summary of changes document	No	NR[4]	Yes	Yes	Yes	Yes
OHSU Oregon Clinical and translational research institute [27]	USA	Yes	No	No	NR	Yes	Yes	No	No
St Vincent's Hospital Sydney Research Office [28]	Australia	Yes	No	No	NR	Yes	Yes	Yes	Yes
The Alberta Clinical Research Consortium [36]	Canada	Yes	No	No	NR	Yes	Yes	Yes	Yes
The Global Health Network [29]	NR/NA	No	No	No	NR	Yes	Yes	Yes	Yes
The Johns Hopkins Institute for Clinical and Translational Research [30]	USA	No	No	No	NR	Yes	Yes	Yes	Yes
The University of Texas Health Science Center at Houston [31][2]	USA	Yes	No	No	NR	Yes	Yes	Yes	Yes
UC Davis Medical Center [32][2]	Canada	No	No	Yes, suggested range of time efforts and costs. Unclear how example costs were established.	NR	Yes	Yes	Yes	Yes
University of Arizona Health Sciences, College of Medicine [37]	USA	No	No	Yes, separate MS Excel® sheet with a completely filled out sample. Unclear how example costs were established	NR	Yes	Yes	Yes	Yes
University of Cologne, Clinical Trials Center Cologne [15]	Germany	No	Yes, validation paper [15]	Yes, examples for time efforts and (variable costs and fixed costs) are already entered. Salaries can be defined. Cost next to the are shown next to the time effort. Unclear how example costs were established.	NR	Yes	Yes	Yes	Yes
University of Tennessee Health Science Center [33]	USA	No	No	Yes, form is completely filled out as an example. Unclear how example costs were established.	NR	Yes	Yes	Yes	Yes
Virginia Commonwealth University [34]	USA	Yes	No	No	NR	Yes	Yes	Yes	Yes
Tools to monitor ongoing costs of a randomised clinical trial									
The Global Health Network [38]	NR/NA	No	No	Yes, completely filled out form. Unclear how example costs were established.	NR	No	Yes	Yes	No

[1]Direct costs, meaning costs that were related to the work as described in the study protocol.
[2]These institution stated that the tool is for internal use only.

[3]Nearly identical tool
[4]Described that a group of experts was involved in the development (i.e. “a task group of experienced investigators and study coordinators” [15] and “Working group of Research Management and Finance staff” [25])
Abbreviations: NR=Not reported; NA=Not applicable

Reported purpose

The developers of eleven tools gave a rather general statement, i.e. that the tool had been designed to help investigators with budget planning (n=6) [18-20, 25, 26, 31] or that templates were provided to support investigators (n=5) [28-30, 34, 38] (Table 2). For six tools [15, 21, 24, 32, 35, 36], all belonging to the category “tools to plan a budget for an individual trial centre”, it was mentioned that they were intended to support budget negotiation for industry-sponsored RCTs. Two stated that the tool could be used to apply for a specific grant [16, 23], two others stated that the tool could help to implement “good financial practice” [14, 17], while the completion of one tool was mandatory to conduct a project at the corresponding institution [22]. For three tools, no explicit explanation of the intended use was found [27, 33, 37] (Table 2).

Considered cost types and example costs

All 25 tools considered fixed costs, 21 considered variable costs, and 19 considered indirect costs. Overall, 18 tools considered all three cost types. Examples of costs (or work load) were provided for 9 tools. However, it remained unclear in all cases how these examples were chosen or from where they originated. The New Zealand Association of Clinical Research [25] clearly mentions that they did not provide standards costs, as each site has its own cost structures.

Validation and user testing

A validation study or user testing was described for two tools [14, 15]. Holler and colleagues (University of Texas, San Antonio, USA) developed a tool for the budget planning of an entire RCT [14]. The tool was provided directly from the authors. The STUDGET tool is intended to plan the costs for a specific trial site (Arenz et al.,

University of Cologne, Clinical Trials Center Cologne, Germany [15]). For two other tools (from the National Institute for Health Research in the UK [24] as well as from the New Zealand Association of Clinical Research [25]) a separate document was identified which summarised how the tool changed over time (Table 1).

Evidence-base for tool development

We found for only one tool [14] an explicit mentioning of any underlying empirical evidence, i.e. that cost data or resource use from previous clinical trials were used to develop the tool. However, the specific source remained unclear. For two tools [15, 25] it was mentioned that an expert group was involved in the development (Table 1).

288 **Table 2:** Statement from the developers about the intended use of each tool
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Source	Statement from developer
Tools to plan costs of an entire randomised clinical trial	
Belgian health care knowledge centre [16]	Template for the BeneFIT call, a research grant from Belgium and the Netherlands ("The first BeNeFIT call focuses on comparative effectiveness trials which show clear value for money and have the potential for return on investment"). “If you wish to use this budget tool outside the KCE Trials Programme or the BeNeFit call, you should contact trials@kce.fgov.be”
California Institute for Regenerative Medicine [23]	Form is part of the application for the California Institute for Regenerative Medicine Targeted Clinical Development Awards Application
Clinical trial podcast [19]	"Clinical trial budgets are often put together in haste. […] This post covers the key cost drivers for medical device clinical trials."
Health Research Board Clinical Research Coordination Ireland [20]	"The HRB CRCI have published a guide document on clinical trial costs. The purpose of the guide is to outline the potential costs associated with running a clinical trial and can be used by investigators or sponsors when compiling the clinical trial budget."
Murdoch children’s research institute [17]	"All campus staff planning to undertake a research project have a responsibility to ensure that good financial management practices are in place. This guideline on setting up a research budget and the budget template will help you cost your project, with useful tips and tricks to ensure you include everything you need. The template is best suited to clinical trials, but can be adapted for other research."
University of Birmingham; Clinical research compliance team [18]	"The aim of this document is to provide a template for clinical trial costings"
University of Texas at San Antonio [14]	"[...] an interactive clinical trial decision support system provides clarity and an increased level of certainty to the decision-making process. Investing the time to assimilate and input the data will pay off in terms off in terms of better resource allocation and better decisions."
Tools to plan a budget for an individual trial centre	
Advocate Health Care [21]	"The Department of Research can assist with budget development and contract negotiations for sponsored research"
Auckland District Health Board [22]	Budget needs to be used for all projects which incur costs to the Auckland District Health Board
Government of Western Australia. Department of Health [35]	"The form can be used to (a) negotiate funding, (b) complete the Research Governance Service (RGS) Budget Form."
National Institute for Health Research (NHS) [24]	“The Industry Costing Templates provide a framework for transparent cost display and calculation to support swift local site budget negotiations when performing commercial trials in the NHS"
New South Wales Government [26]	"The costing tool is a spreadsheet developed to facilitate the process of study costing for research being conducted by NSW Public Health Organisations."
New Zealand Association of Clinical Research [25]	"The tool was developed to cost site participation in interventional commercial clinical trials, however it can be adapted by the user for non-commercial clinical trials"
OHSU Oregon Clinical and translational research institute [27]	-
St Vincent's Hospital Sydney Research Office [28]	"This template is only a guide, not mandatory "
The Alberta Clinical Research Consortium [36]	"The Internal Cost Template is a simple planning tool to assist researchers in estimating more accurate expenses in budget preparation and in negotiation of industry-sponsored and grant funded trial"
The Global Health Network [29]	Partially. "The templates [listed] have been shared by other groups, and are free to use and adapt for your research studies" "Improving Health by Improving Research"
The Johns Hopkins Institute for Clinical and Translational Research [30]	"This page contains helpful resources on various research related topics"

The University of Texas Health Science Centre at Houston [31]	"Development of a clinical trial coverage analysis grid and budget. It contains internal price lists and formulas for effort calculations." "For internal use only."
UC Davis Medical Centre [32]	"The Unified Budget Template is used to prepare budgets for industry sponsored clinical trials." "For internal use only"
University of Arizona Health Sciences, College of Medicine [37]	-
University of Cologne, Clinical Trials Centre Cologne [15]	"Efforts to estimate fees are currently limited by a general lack of reliable and transparent references for calculation [...]. To overcome this shortcoming, the 'STudy site bUDGEting Tool' (STUDGET) was developed, allowing calculation of trial related staff costs."
University of Tennessee Health Science Centre [33]	-
Virginia Commonwealth University [34]	"This template is provided as guidance and not meant to cover all scenarios"
Tools to monitor ongoing costs of a randomised clinical trial	
The Global Health Network [38]	Partially. "The templates [listed] have been shared by other groups, and are free to use and adapt for your research studies" "Improving Health by Improving Research"

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4. Discussion

We identified a total of 25 freely accessible tools which can be used to plan or monitor the costs of RCTs. The majority were designed to assess the costs of an individual trial centre within a multicentre RCT while some were made for planning costs of an entire RCT. Only one tool for monitoring costs during the conduct was found. Almost all tools were developed using Microsoft Excel®. Being based on standard office software has the advantage of allowing wide use of the tools. The spread sheets were typically not protected, allowing researchers to make adaptations. On the other hand, this might increase the risk of unrecognised errors.

Only two tools, made to plan costs of an entire RCT, covered all three relevant cost aspects (i.e. variable, fixed, and indirect costs) [14, 17]. For one of those (tool by Holler and colleagues) it was described that previous trials were used as information source during the development and that the tool was user tested [14]. Therefore, this tool by Holler et al., which could only be accessed by contacting the authors, currently seems to be the most promising to plan a budget for an entire RCT. Since the other five tools that were developed to plan an entire RCT did not cover all three relevant cost aspects, it is possible that a budget calculated with those tools would underestimate the true costs. However, a valid comparison of the usefulness of all tools was beyond the scope of this review as it would require extensive user testing.

While 15 tools to plan individual trial site costs included all three relevant cost types, only one was validated [15]; for two tools the changes and adaptations over time were reported, indicating possible user testing. The only tool explicitly intended to monitor costs and resources of an ongoing RCT did not cover all three cost types and was not validated. Some of the other tools have the possibility to plan or list cost by time periods

(e.g. by month or year). Hence, we believe that some of these tools could also be used to monitor ongoing RCT costs.

Overall, our search indicated that cost tools were developed individually by several different institutions across different countries and jurisdictions. The development process remained usually unclear and did not include user testing. Only two exceptions were found, both identified in the literature and not through the internet search. For the STUDGET-tool it was described how trial activities were identified, how the tool was created and validated [15]. Similarly, Holler and colleagues described that they reviewed other trial tools and RCTs, analysed their key features and then developed their own spreadsheet [14]. Our own study group followed a similar approach. To create a comprehensive cost item list we conducted a systematic search followed by an adaptation phase including clinical trial costing experts from pharmaceutical companies and from academia [10]. Based on this comprehensive item list, a freely available tool was generated which was used to retrospectively calculate costs of RCTs [5]. The tool can also be used to prospectively estimate RCT costs, but specific functions, e.g. regarding the inclusion of indirect costs, are currently missing and need to be entered manually (e.g. to adapt salary levels).

Our study has several limitations. First, it is possible that we may have missed some relevant tools despite searching three large electronic databases. We addressed this by adding an internet search, which can be very powerful to supplement systematic literature searches [39], in particular in situations as ours, where we had to rely on websites and online publications of research institutions. Inherent risks of searching the internet are selection bias (bubble effect) and the issue of limited reproducibility due to the non-transparent and non-consistent search algorithm by Google.com [40]. These limitations, however, are hardly relevant for our conclusion that user tested and

validated budgeting tools are lacking; but adding the internet search may have limited the representativeness of the included tools. Additionally, our search was conducted using English search terms, which further limits generalisability of our findings. Nevertheless, we think that our search allowed us to identify the available tools that an investigator would find, who probably conducts less extensive searches of the internet or literature databases. We are convinced that many more cost planning tools exist (used by pharmaceutical companies or trial support organisations such as clinical trial units) that were not considered in our scoping review because they are not freely available.

Second, a detailed description of advantages and disadvantages of the different tools would require comprehensive user testing, ideally using RCTs as examples that are currently in the planning phase. Still, our overview indicates that currently a variety of tools exist, which were mostly developed by different organisations or by specific funders. They seem to be mostly used internally; during our search we did not come across any indication that the identified tools were externally assessed or discussed by other researchers (e.g. using the related articles function in PubMed). Hence, we gained the impression that existing tools were hardly taken up and used in the wider scientific community.

In conclusion, our scoping review showed that a variety of freely accessible budget planning tools for RCTs exist, but they typically do not cover all major cost items and little is known about their validity, applicability and uptake in research reality.

However, since many research organisations put effort in developing budgeting tools, the need for an accurate planning of RCT budgets has been recognised at many levels. Developing a tool with demonstrated validity and applicability and that can be broadly used across a wide range of RCTs and settings should therefore be a research priority.

This would allow to have valid cost estimates for an efficient planning of clinical trials, increasing chances for successful trial conduct, avoiding the risk of discontinuation due to limited resources, and thus increasing the value of research investments. This may lead to fewer funded RCTs but would manifest the statement of the REduce research Waste And Reward Diligence (REWARD) campaign that we need less but better research [41-43].

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