

ORIGINAL RESEARCH**Resource use and costs of investigator-sponsored randomized clinical trials in Switzerland, Germany, and the United Kingdom: a meta-research study**

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Abstract

Background and Objectives: Conducting high-quality randomized clinical trials (RCTs) is challenging and resource intensive. Funders and academic investigators depend on limited financial resources and, therefore, need empirical data for optimal budget planning. However, current literature lacks detailed empirical data on resource use and costs of investigator-sponsored RCTs. The aim of this study is to systematically collect cost data from investigator-sponsored RCTs from Switzerland, Germany, and the United Kingdom (UK).

Methods: Principal investigators were asked to share their RCT cost and resource use data and enter it into an online case report form. We assessed cost patterns, cost drivers, and specific cost items, examined costs by study phase (planning-, conduct-, and finalization phase), compared planned with actual RCT costs, and explored differences in cost patterns across countries, medical fields, and intervention types.

Results: We included 93 RCTs which were initiated in Switzerland ($n = 53$; including eight conducted in low- and lower middle-income countries), Germany ($n = 22$), and the UK ($n = 18$). The median total trial cost in our RCT sample was \$645,824 [interquartile range (IQR), \$269,846–\$1,577,924]. The median proportion of the total costs spent for planning phase was 27.5% [IQR, 20.6%–39.7%], for conduct phase 57.3% [IQR, 44.4%–66.3%], and for finalization phase 12.7% [IQR, 8.5%–19.3%] with little variation across countries. The items that contributed most to the total costs were protocol writing (7.2%; IQR 3.8%–10.6%), data management (5.0%; IQR 2.2%–8.1%) and follow-up (4.5%; IQR 2.3%–8.4%). Of the 66 RCTs with an available original budget, 46 (69.7%) exceeded the budget by over 50%. Use of routinely collected data to assess primary outcomes was independently associated with lower per patient- and lower total trial costs.

Conclusion: Over a quarter of total trial costs were incurred in the planning phase, which is typically not fully funded. Two-thirds of RCTs exceeded their budget by more than 50%. Investigators and funders should consider empirical cost data to improve budgeting and

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1. Background

Randomized clinical trials (RCTs) are time consuming and resource demanding [1,2]. RCT costs have continuously risen over time due to increasing trial complexity, higher administrative burden [3–7], and smaller beneficial effects of treatments requiring larger sample sizes [8–12]. As a consequence the number of independent investigator-sponsored RCTs has decreased in the last decade leaving many research questions unanswered [3,13,14].

Empirical data on resource use and costs for investigator-sponsored RCTs are scarce [15–18]. A health technology assessment report on 125 National Institute for Health Research (NIHR) supported clinical trials, for instance, assessed total trial costs and determined that actual costs exceeded the planned costs in 78% of trials; in multivariable regression analyses, a greater number of trial sites and longer trial duration were independently associated with higher trial costs [15]. Based on simulation studies, experts repeatedly criticized extensive on-site monitoring, which has accounted for 15%–30% of total costs in industry-sponsored RCTs [9,19–21]. In contrast, utilizing routinely collected data to assess trial outcomes has been reported to decrease trial costs [22]. A study with a detailed breakdown of empirical RCT costs into specific cost items from a sample of RCTs including different countries and medical fields is to date not available [16].

A better understanding of cost patterns and cost drivers would be important for investigators, funders, and policy makers to ensure sufficient funding for investigator-sponsored RCTs and their cost-considerate conduct [16,23]. Therefore, we investigated detailed resource use and costs of investigator-sponsored RCTs initiated in Switzerland, Germany, and the United Kingdom (UK). Specifically, we aimed to, i) examine RCT cost patterns on an absolute and relative scale (costs in USD and % of total costs), including the largest cost items in the planning, conduct, and finalization phase; ii) determine cost drivers and cost savers; iii) explore differences in RCT costs across countries, medical fields, and intervention types; iv) compare planned with actual costs and to identify factors associated with excess costs; and v) investigate monitoring costs in investigator-sponsored RCTs.

2. Methods

2.1. Study design and eligibility

The design and rationale for this study has been published [24]. In short, we aimed to retrospectively collect detailed empirical cost and resource use data from 100 investigator-sponsored RCTs from Switzerland ($n = 60$),

Germany ($n = 20$), and the UK ($n = 20$). RCTs were eligible if they were investigator-sponsored (nonindustry) and if they were completed or close to completion (ie, last patient visit for primary outcome completed). Prematurely discontinued RCT were eligible if at least 70% of the sample size was reached or the planned trial duration was exceeded. Trials were excluded if they were dose-finding RCTs, RCTs primarily evaluating pharmacokinetics or physiology, included healthy volunteers, or RCTs that published results more than 10 years prior to the start of this investigation. To improve comparability across countries, we aimed to include 10–15 RCTs from cardiovascular, oncology, surgical and miscellaneous fields (irrespective of country). Due to early challenges reaching our planned sample size, we broadened the eligibility criteria and included a small sample of pilot RCTs and RCTs initiated in Switzerland but conducted in low or lower-middle income countries.

RCTs were identified using two approaches: Firstly, we contacted Clinical Trial Units, trial networks, and individual principal investigators known to the authors, and asked them about eligible RCTs. Secondly, we screened trial registries for completed RCTs and invited principal investigators to participate in our study (see list of registries screened in supplementary material, section A).

2.2. Data collection and data management

The survey was designed using a previously developed and tested cost item list that follows the principle of activity-based costing [17,25]. This cost item list was adapted into a REDCap case report form (CRF) [26,27]. Participating trial teams entered their cost and resource use data directly into the CRF. This was followed by a cost report detailing all trial costs and an interview with AG (in person or online) to clarify unclear values and missing data. The CRF and an overview of all cost variables (cost items) and their associated phase (planning, conduct, finalization), can be found in the supplementary material ([Supplementary Material, section B](#)). An example of the cost report sent to investigators can be found in the supplementary material ([STROBE Checklist](#)).

In short, the following two types of cost data were collected: Firstly, *fixed costs*, which are independent of staff salary, such as ethical approval fees, insurance fees, travel costs, or material fees, were collected ([supplementary material Fig S1](#)). Secondly, we collected *variable costs*, which arose from a predefined list of study tasks, dependent on human resources (staff salary), such as days needed to write the protocol, minutes needed for informed consent

What is new?**Key findings**

- This article presents the first systematic analysis of randomized controlled trial (RCT) costs across multiple medical fields and countries.

What this adds to what is known?

- Unlike previous studies, we offer a detailed breakdown of total costs, including the costs for recruitment, data management, protocol development, statistical analysis, follow-up, and project management, amongst others.

What is the implication and what should change?

- Our analysis provides valuable insights into the cost landscape of RCTs, offering a comprehensive resource for researchers, sponsors, and policy-makers to better understand and optimize trial-related expenditures.

procedures, and minutes needed for patient treatment (excluding routine medical care). The variable costs were calculated for each trial team member by estimating the time needed for each study task and multiplying the total days with their gross yearly income to calculate billable days. We considered the standardized number of working-days and hours for each country, and the variable costs were adjusted for employer contributions, the overhead of the sponsor institution and for unaccounted time (30%) [28]. Costs were converted into USD (2022) and adjusted for inflation (for more details on employer contributions, work-days, unaccounted time, exchange rate and inflation, see supplementary C).

2.3. Analysis

We calculated the proportional contributions to total costs for individual cost items and for the three predefined study phases (planning, conduct, and finalization phase; Fig S1). Proportions across RCTs were summarized with descriptive statistics (median and interquartile ranges [IQRs]). We summarized the total resource use and costs, as well as for individual cost items (Fig S1), and costs per patient using descriptive statistics, overall and stratified by country. In sensitivity analyses, we calculated total costs of the trials without adding 30% of unaccounted time, overhead costs, or employer contributions. To assess the heterogeneity of costs, we stratified the analyses by medical field, intervention type, and country.

To investigate the potential influence of different RCT characteristics on trial costs and per patient costs, we conducted linear multivariable regression analyses with total

trial costs and costs per patient as dependent variables. In our protocol, we had prespecified medical field, intervention type, country, number of trial sites, achieved sample size, actual trial duration, and use of routinely collected data for primary outcome assessment as independent variables (excluding achieved sample size in per patient cost analysis). In response to peer reviewer comments, we conducted two post hoc regression analyses, in which we added placebo use as independent variable to the preplanned models. In a further multivariable regression analysis, we examined the influence of trial characteristics on RCT excess costs. We calculated excess costs (dependent variable) for each RCT with an available budget (actual total trial costs minus planned trial costs). Independent variables were achieved sample size, actual number of trial sites, country, medical field, and the delta in recruitment duration (actual recruitment duration minus planned recruitment duration) as independent variables. Furthermore, RCTs were categorized into being within or below budget, exceeding the initial budget by more than 10% and more than 50%. Reasons for exceeding the budget and reasons for prolongation of recruitment, as reported by trial investigators, were recorded and categorized.

3. Results

Between January 2021 and January 2024, we contacted 775 principal investigators, of whom 93 (12.0%) agreed to participate and shared their RCT cost data (Fig S2; nonparticipating RCTs listed in supplementary material Table S1). Our sample included RCTs conducted in Switzerland (45/93, 48.4%), Germany (22/93, 23.7%), the UK (18/93, 19.4%), and low- and lower middle-income countries with Swiss principal investigators (8/93, 8.6%). They covered various medical fields, including infectious diseases (12/93, 12.9%), cardiology (11/93, 11.8%), anaesthesiology (10/93, 10.8%), oncology (8/93, 8.6%), neurology, (8/93, 8.6%), psychiatry (8/93, 8.6%), and other fields (Table 1). The majority of RCTs were drug trials (35/93, 37.6%), had noncommercial funders (84/93, 90.3%), were single center trials (50/93, 53.8%) and recruited a median of 167 patients (IQR: 93–438). The sample also included nine (9/93, 9.7%) pilot trials.

The median total RCT cost in our sample was \$645,824 (IQR: \$269,846–\$1,577,924), and the median per patient cost was \$3,999 (IQR: \$1,638–\$6,658; Table 2). Per patient costs were comparable across Switzerland, Germany, and the UK, but approximately 25% lower for RCTs conducted in low- and lower-middle-income countries (\$3,001 per patient; IQR: \$1,175–\$3,358). The sensitivity analysis of the total trial costs excluding employer contribution, overhead and unaccounted time is available in the supplementary Table S2. More study centers, more patients, and longer trial duration were independently associated with higher total RCT costs (Table S3). Per patient costs

Table 1. Baseline characteristics of included investigator-sponsored RCTs

Trial characteristics	Switzerland (<i>n</i> = 45)	Germany (<i>n</i> = 22)	UK (<i>n</i> = 18)	Low- and lower middle-income countries ^a (<i>n</i> = 8)	Overall ^a (<i>n</i> = 93)
Medical field (%)					
Infectious diseases	6 (13.3%)	0 (0.0%)	0 (0.0%)	6 (75.0%)	12 (12.9%)
Cardiology	2 (4.4%)	2 (9.1%)	6 (33.3%)	1 (12.5%)	11 (11.8%)
Anesthesia	6 (13.3%)	2 (9.1%)	2 (11.1%)	0 (0.0%)	10 (10.8%)
Oncology	4 (8.9%)	2 (9.1%)	2 (11.1%)	0 (0.0%)	8 (8.6%)
Neurology	4 (8.9%)	4 (18.2%)	0 (0.0%)	0 (0.0%)	8 (8.6%)
Psychiatry	3 (6.7%)	2 (9.1%)	2 (11.1%)	1 (12.5%)	8 (8.6%)
Other ^b	20 (44.4%)	10 (45.5%)	6 (33.3%)	0 (0.0%)	36 (38.7%)
Type of intervention (%)					
Drug	23 (51.1%)	2 (9.1%)	7 (38.9%)	3 (37.5%)	35 (37.6%)
Behavioral	8 (17.8%)	10 (45.5%)	5 (27.8%)	3 (37.5%)	26 (28.0%)
Medical device	5 (11.1%)	8 (36.4%)	1 (5.6%)	0 (0.0%)	14 (15.1%)
Other ^c	9 (20.0%)	2 (9.1%)	5 (27.8%)	2 (25.0%)	18 (19.4%)
Placebo control (%)	14 (31.1%)	1 (5.0%)	3 (16.7%)	0 (0.0%)	18 (20.0%)
Design (%)					
Parallel	40 (88.9%)	20 (90.9%)	17 (94.4%)	4 (50.0%)	81 (87.1%)
Cross-over	4 (8.9%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	5 (5.4%)
Cluster	1 (2.2%)	2 (9.1%)	0 (0.0%)	4 (50.0%)	7 (7.5%)
Trial purpose (%)					
Superiority	37 (84.1%)	19 (90.5%)	12 (66.7%)	7 (87.5%)	75 (82.4%)
Noninferiority	6 (13.6%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	7 (7.7%)
Pilot trial	1 (2.3%)	2 (9.5%)	5 (27.8%)	1 (12.5%)	9 (9.9%)
Planned target sample size median (IQR)	200 (96–500)	156 (100–491)	98 (81–220)	288 (215–875)	186 (90–500)
Number of participants recruited median (IQR)	200 (96–480)	151.5 (100–472)	102 (76–176)	281 (207–547)	167 (93–438)
Number of trial arms median (IQR)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2,–2)
Number of follow-up visits median (IQR)	4 (2–6)	5 (4–6)	5 (3–7)	5 (5–6)	4 (3–6)
Planned recruitment duration in months	24. (15–36)	24 (16–35)	20 (10–29)	16 (13–18)	23 (12–33)
Actual recruitment duration in months	28.0 (17.0–42.0)	23.0 (15.0–39.8)	14.5 (9.3–24.0)	20.5 (15.5–24.0)	24.0 (14.0–35.0)
Trial duration in months ^d median (IQR)	29.0 (21.0–43.0)	26.5 (19.5–42.3)	21.0 (13.0–31.0)	24.0 (17.5–30.5)	27.0 (18.0–40.3)
Funder (%)					
Commercial	0 (0.0%)	2 (9.1%)	3 (16.7%)	0 (0.0%)	5 (5.4%)
Noncommercial	41 (91.1%)	20 (90.9%)	15 (83.3%)	8 (100.0%)	84 (90.3%)
Both	4 (8.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (4.3%)
Multicenter or single center (%)					
Single center	24 (53.3%)	13 (59.1%)	10 (55.6%)	3 (37.5%)	50 (53.8%)
Multicentre- national	15 (33.3%)	9 (40.9%)	7 (38.9%)	2 (25.0%)	33 (35.5%)
Multicentre- international	6 (13.3%)	0 (0.0%)	1 (5.6%)	3 (37.5%)	10 (10.8%)
Number of centers median (IQR)	1.0 (1.0–5.0)	1.0 (1.0–4.8)	1.0 (1.0–2.3)	2.5 (1.0–8.5)	1.0 (1.0–5.0)
Monitoring method (%)					
100% source data verification	1 (2.2%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	3 (3.2%)
None/internal monitoring	19 (42.2%)	17 (77.3%)	9 (50.0%)	3 (37.5%)	48 (51.6%)

(Continued)

Table 1. Continued

Trial characteristics	Switzerland (<i>n</i> = 45)	Germany (<i>n</i> = 22)	UK (<i>n</i> = 18)	Low- and lower middle-income countries ^a (<i>n</i> = 8)	Overall ^a (<i>n</i> = 93)
Risk based monitoring with partial source data verification	20 (44.4%)	2 (9.1%)	4 (22.2%)	5 (62.5%)	31 (33.3%)
Targeted with centralized monitoring	2 (4.4%)	1 (4.5%)	5 (27.8%)	0 (0.0%)	8 (8.6%)
Missing	3 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.2%)
Use of routinely collected data to assess primary outcomes (%)	5 (11.1%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	7 (7.5%)

RCT, randomized clinical trial; UK, United Kingdom; IQR, interquartile range.

^a *n* = 92 reached at least 70% of planned sample size and *n* = 1 reached planned trial duration.

^b Primary care (*n* = 5), endocrinology (*n* = 5), pneumology (*n* = 5), general surgery (*n* = 5), gastrointestinal (*n* = 4), nephrology (*n* = 2), ophthalmology (*n* = 2), orthopedics (*n* = 2), urology (*n* = 2), hematology (*n* = 1), dermatology (*n* = 1), rheumatology (*n* = 1), neonatal care (*n* = 1).

^c Diagnostic (*n* = 4), physical therapy/exercise (*n* = 4), surgical (*n* = 4), dietary (*n* = 3), vaccine/biological (*n* = 3).

^d Defined as date from first patient first visit to last patient last visit.

^e Trials conducted in low- and lower middle-income countries but initiated (sponsorship) in Switzerland.

were similar across medical fields, with the exception of oncological trials, which were more expensive (\$8,142 per patient; IQR: \$5,730–\$11,357; Table S4, Fig S3). Per patient costs were also higher in drug trials as compared to nondrug trials, independent of medical field (Table S4, Fig S4). The use of routinely collected data for the primary outcome reduced total trial costs and per patient costs (Tables S3, and S4). In post hoc analyses including placebo use as an additional independent variable, the findings with respect to total trial costs remained unchanged (Table S5), however with respect to associations with per patient costs, only the use of placebo was significantly associated with increased per patient costs (Table S6).

The planning phase of the RCTs accounted for 27.5% (IQR: 20.6%–39.7%; median \$176,433; IQR: \$92,596–\$424,916) of the total RCT costs. The conduct phase constituted 57.3% (IQR: 44.4%–66.3%; median \$313,234; IQR: \$103,990–\$912,818) of the total costs and the finalization phase 12.7% (IQR: 8.5%, 19.3%; median \$82,536; IQR: \$45,385–\$167,744) of the total trial costs. The total cost proportions for the planning, conduct and finalization phases were similar across countries (Table 2). Data on the time (days) invested into each study phase (planning, conduct and finalization), and the proportions to the total time invested into the RCT are presented in Table S10.

Of the RCTs with an available original budget calculation (66/93, 71.0%) the median planned budget was \$480,122 (IQR: \$214,116–\$1,181,661). In contrast the actual total RCT costs were, on average, 57.5% higher with a median of \$835,606 (IQR: \$340,084, \$1,862,009). As such, 86.4% of RCTs (57/66) exceeded their original budget by more than 10%, and 69.7% (46/66) exceeded the budget by over 50% (Table 3). Only 13.6% RCTs (9/66) were within (± 10) or below the original budget. Drug trials were independently associated with increased excess

cost (Table S11). Although longer recruitment was not independently associated with increased excess costs (Table S11), the most common self-reported reason given by principal investigators explaining the causes for the excess costs, was slow recruitment (17/35, 48.6%) (Table S12). In addition, many principal investigators (46/93, 49.5%) reported that their RCT experienced recruitment problems. The major cause for slow recruitment was difficulty finding eligible patients (37/46, 80.4%) (Table S13).

When considering the planning phase, writing the research protocol and preparing patient-related forms (eg, consent form, questionnaires, diaries) accounted for the highest proportion of total RCT costs (median 7.3%; IQR: 3.8%–10.9%). In the conduct phase, screening and recruitment of patients (median proportion of total costs: 3.8%; IQR: 1.6%–7.3%), follow-up and source data entry (median proportion of total costs: 4.5%; IQR: 2.3%–8.4%), in addition to ongoing communication and project management (median proportion of total costs: 3.2%; IQR: 1.6%–5.5%), constituted the greatest proportions of total RCT costs. For the finalization phase, writing the manuscript contributed the highest proportion to total costs (median 3.2%; IQR: 1.7%–5.5%, Table S14, Fig S6). With respect to fixed costs, a median of 3.6% (IQR: 1.1%–11.3%) of the total costs were designated to additional procedures or materials needed during RCTs (eg, images, lab materials, tests, PET Scans), excluding routinely available procedures and care (Table S15, Fig S7). Data management, specimen analyses, statistics and monitoring accounted for medians of 5.0% (IQR: 2.2%–8.1%), 4.1% (IQR: 1.3%–5.5%), 3.9% (IQR: 2.2%–6.1%), and 2.2% (IQR: 0.9%–5.0%) of the total RCT costs, respectively (Table S16). For all cost items (USD), cost proportions (%), the time needed for specific study tasks (days), and costs for trial committees, see supplementary Tables S13,

Table 2. Overview of total costs and cost proportions in investigator-sponsored RCTs

Costs	Switzerland (<i>n</i> = 45)	Germany (<i>n</i> = 22)	UK (<i>n</i> = 18)	Low- and middle-income countries ^a (<i>n</i> = 8)	Overall (<i>n</i> = 93)
Total costs (adjusted for employer contributions, unaccounted time and overhead)	962,260	469,470	448,334	775,712	645,824
Costs in USD, median (IQR)	(376,349–1,792,765)	(184,481–1,861,895)	(227,428–868,349)	(235,256–950,052)	(269,846–1,577,924)
Cost per patient in USD, median (IQR)	4325 (2337–8566)	3,892 (1563–5634)	4,608 (2209–9245)	3,001 (1175–3358)	3999 (1638–6658)
Costs by phases					
Planning					
Costs in USD, median (IQR)	248,176	119,627	133,556	187,780	176,433
	(116,310–470,955)	(56,626–279,907)	(67,841–257,402)	(83,556–254,634)	(92,596–424,916)
Cost per patient in USD, median (IQR)	980 (379–1469)	616 (226–1652)	807 (438–2936)	577 (234–801)	779 (306–1535)
Proportion of total costs, median % (IQR)	26.8 (18.9–39.7)	26.6 (19.2–42.2)	30.4 (24.0–39.7)	31.6 (28.7–34.2)	27.5 (20.6–39.7)
Conduct					
Costs in USD, median (IQR)	462,838	165,978	180,027	435,944	313,234
	(146,748–1,073,906)	(75,783–974,607)	(69,025–594,878)	(74,698–487,364)	(103,990–912,818)
Cost per patient in USD, median (IQR)	1518 (746–3478)	1286 (527–2405)	1697 (532–2,972)	989 (527–1544)	1476 (579–2564)
Proportion of total costs, median % (IQR)	57.3 (44.4–68.9)	52.0 (35.8–69.1)	59.9 (45.4–64.3)	55.3 (49.4–63.6)	57.3 (44.4–66.3)
Finalization					
Costs in USD, median (IQR)	103,863	81,719	41,721	87,144	82,536
	(53,725–202,893)	(47,964–171,123)	(20,752–66,447)	(48,088–102,179)	(45,385–167,744)
Cost per patient in USD, median (IQR)	399 (193–722)	426 (154–643)	417 (198–625)	134 (97–268)	374 (143–654)
Proportion of total costs, median % (IQR)	12.4 (7.3–19.9)	15.6 (11.7–9.6)	11.8 (8.7–14.2)	12.1 (9.6–16.4)	12.7 (8.5–19.3)

UK, United Kingdom; IQR, interquartile range.

^a Trials conducted in low- and lower middle-income countries but initiated (sponsorship) in Switzerland.

S15, S16 and S17. Data monitoring was performed by 75.3% (70/93) of the RCTs. Monitoring in form of 100% source data verification (3/70, 4.3%), accounted for a median of 2.8% (IQR: 2.6%–15.4%) of the total trial costs. Internal monitoring (28/70, 40.0%) accounted for a median of 0.4% (IQR: 0%–2.6%) of the total trial costs (Table 4).

The median total treatment costs (costs for intervention group and control group, excluding routine medical care) were \$25,830 (IQR: \$6,809–\$76,114), contributing 4.2% (IQR: 1.1%, 9.4%)—the total trial costs (see supplementary Table S18). Per patient treatment costs were \$159 (IQR: \$35–\$397) and were highest in medical device trials (\$258 per patient, IQR: \$39–\$355; median contribution to total patient costs: 6.6%; IQR 1.4, 12.3%; Table S19).

The subsample of pilot trials (9/93, 9.7%) included four cardiology trials (50.0%), three (37.5%) oncological trials, and one psychiatry RCT (1/86, 12.5%) and one other (supplementary Table S20). The median total cost of pilot trials was \$161,168 (IQR: \$102,689–\$534,052), that is, less expensive than full-scale RCTs (\$787,813; IQR: \$287,864–\$1,651,060). However, median per patient costs for pilot trials were \$3,998 (IQR \$1,239–\$10,270), comparable to nonpilot trials (\$4,036, IQR: \$1,919–\$6,556). The proportional costs for the planning phase of a pilot trial (46.9%, IQR: 30.5%–52.9%) were larger compared to full-scale RCTs (26.7%; IQR: 19.8%, 36.9%). The proportional costs for the conduct phase were smaller (pilot trial: 34.0%; IQR: 21.9%–50.9% vs full-scale RCT trial: 58.2%; IQR: 44.9%–68.9%; Table S21).

4. Discussion

This meta-research study on retrospectively collected resource use and costs from 93 investigator-sponsored RCTs found that writing of the protocol was responsible for the largest single proportion of total RCT costs (7.2%). Subsequent key contributors included data management (5.0%), participant follow-up (4.5%), and treatment costs (4.2% for control and intervention groups). Of particular interest were relatively low monitoring costs (2.2%), compared to what had previously been reported for industry sponsored trials (15%–30%) [9,19–21]. Nevertheless, costs could be reduced by using low-intensity monitoring methods, which were found to offer similar study oversight as compared to full on-site monitoring [29]. Number of trial centers and longer trial duration were associated with increased total trial costs (independent of sample size), aligning with prior research [15]. Drug and oncological trials were independently associated with increased per patient costs [18]. RCTs which collected their primary outcome using routinely collected data had lower per patient- and total trial costs, which had previously been suggested based on five case studies by Mc Cord et al [22]. In a post hoc analysis, however,

placebo use was the only variable significantly associated with increased per patient costs; this can at least partly be explained by the fact that the group of 18 RCTs with placebos and the group of seven RCTs with routinely collected outcome data were mutually exclusive. Furthermore, there is substantial confounding between drug trials, oncology trials, and trials using placebos in association with increased per patient costs. Another interpretation is that RCTs without placebo (ie, unblinded or open trials) are significantly associated with decreased per patient costs, open trials, nondrug trials, are often more pragmatic, closer to clinical practice, and more likely to use routinely collected data [22].

The cost proportions for the planning, conduct and finalization phase of an RCT were similar across countries suggesting a degree of uniformity in how resources and expenses are allocated across various trial phases and cost items, regardless of the specific geographical location. The high proportion of total costs associated with the planning phase (median 27%) are particularly noteworthy, since the costs of planning an RCT are often underestimated, not accounted for in the initial trial budget, and typically not externally funded [30,31]. Investigators may improve the budgeting and costing of their clinical trials by conducting pilot studies as well as using publicly available budgeting tools to estimate the costs for the planning, conduct, and finalization phase [32].

Over 85% of RCTs exceeded their original budget by more than 10%, which is comparable to the 78% previously reported by Raftery et al in NIHR supported trials [15]. Moreover, 70% of RCTs exceeded their original budget by more than 50%. Investigator-sponsored RCTs are at least partly considered an altruistic activity in academia, and it is commonly expected that clinical and research staff invest some of their time without receiving any financial compensation. Nevertheless, these figures underline the necessity for optimisation of current budgeting and funding practices for investigator-sponsored RCTs [31]. The most common reason given by principal investigators for exceeding their budget was slow recruitment of trial participants (48.6%). Although, our regression analyses did not show an association between extended recruitment duration and excess costs.

4.1. Strengths and limitations

Our study has several strengths. Firstly, using a systematic methodology, we collected the largest and most detailed sample of RCT costs in the literature thus far. Secondly, our sample included RCTs from diverse medical fields, intervention types, and countries which has previously not been investigated. Thirdly, final cost and resource use data from each included RCT were summarized into a structured cost report with relevant categories and then reviewed and approved by the principal investigator. Lastly,

Table 3. Comparison of planned vs. actual costs in investigator-sponsored RCTs

Planned and actual costs	Switzerland (<i>n</i> = 30)	Germany (<i>n</i> = 15)	UK (<i>n</i> = 16)	Low- and middle-income countries ^a (<i>n</i> = 5)	Overall (<i>n</i> = 66)
Planned budget, median (IQR)	540,528 (282,336–1,309,482)	252,278 (98,554–832,368)	416,867 (290,076–673,475)	914,099 (379,129–1,00,6312)	480,122 (214,116–1,181,661)
Funding received, median (IQR)	648,514 (265,733–1,597,715)	328,111 (79,650–748,921)	396,578 (274,510–687,672)	784,241 (379,129–1,00,6312)	475,480 (215,655–1,223,144)
Total costs (adjusted for employer contributions, unaccounted time and overhead)	225,357 (391,046–2,061,996)	586,990 (255,223–2,149,812)	494,354 (284,620–1,039,783)	947,857 (908,567–956,634)	835,606 (340,084–1,862,009)
Costs in USD, median (IQR)					
Cost per patient in USD, median (IQR)	3904 (1775–6084)	3438 (1680–5428)	4925 (4186–11879)	1295 (814–3497)	3967 (1528–6082)
Excess costs					
Within (±10%) budget	1 (3.3%)	3 (20.0%)	1 (6.2%)	0 (0.0%)	5 (7.6%)
Below budget (> 10%)	1 (3.3%)	0 (0.0%)	2 (12.5%)	1 (20.0%)	4 (6.1%)
Exceeding budget by more than 10%	28 (93.3%)	12 (80.0%)	13 (81.3%)	4 (80.0%)	57 (86.4%)
Exceeding budget by more than 50%	22 (73.3%)	11 (73.3%)	10 (62.5%)	3 (60.0%)	46 (69.7%)

UK, United Kingdom; IQR, interquartile range.

^a Trials conducted in low- and lower middle-income countries but initiated (sponsorship) in Switzerland.

Table 4. Total monitoring costs by type of monitoring in investigator-sponsored RCTs ($n = 90^a$)

Monitoring type	n (%)	Costs in USD, median (IQR)	Proportion of total costs, median (IQR)
Internal monitoring	28 (30.1)	2085 (0–11,092)	0.4 (0–2.6)
100% source data verification	3 (3.2)	60,097 (39,823–79,005)	2.8 (2.6–15.4)
Risk based monitoring with partial source data verification	31 (33.3)	16,889 (8,724–74,075)	1.6 (0.6–6.0)
Centralized monitoring with targeted data verification	8 (8.6)	28,974 (6,353–65,717)	1.4 (0.9–5.1)
None	20 (21.5)	0 (0–0)	0 (0–0)

UK, United Kingdom; IQR, interquartile range.

^a For three randomized clinical trials the monitoring type was not clear.

the applied cost items list had previously been tested and developed involving relevant stakeholders [17].

Nevertheless, we note the following limitations: Firstly, we cannot exclude recall bias when retrospectively inquiring trial investigators about their detailed resource use and costs of their RCTs. Secondly, only 12% of the 775 contacted investigators agreed to share their cost data. As such, our sample may be biased toward more successful and more low-cost RCTs since cost data may be simpler to record and investigators may be more likely to share cost data, so costs may be higher in a more representative sample. To explore potential selection bias, we additionally collected characteristics of RCTs, for which principal investigators declined participation, and found that UK and German RCTs, single center trials, and other miscellaneous medical fields were underrepresented in our sample. Lastly, there is high variability in absolute costs between countries, medical fields, and intervention types and our sample is too small to provide precise estimates for small subgroups (medical fields, low- and lower middle-income countries, pilot trials, trials with routinely collected data). More empirical evidence on trial costs is needed to determine cost estimates for such subgroups.

4.2. Implications

We provide empirical cost estimates for investigators supporting future budget planning, in addition to funders, who often do not have adequate data to base their costing on [31]. Our data suggest common cost patterns across countries and may help ensure sustainable funding of RCTs in the future and reduce research waste. The costs of the planning phase are often underestimated and only partially accounted for in grant applications. The financial burden of the planning phase should be considered carefully, since cutting cost here may have dire consequences, for example poorly planned recruitment and retention strategies. Lastly, we observed a wide spectrum of applied monitoring methods in our RCT sample and over 20% of RCTs without monitoring. Monitoring costs for investigator-sponsored RCTs appear considerably lower than for industry-sponsored RCTs with a median of 1.5% of total trial costs for risk-based monitoring with partial source data verification or centralized

monitoring with targeted data verification. These findings may help inform trial investigators about affordable monitoring strategies to ensure adequate data quality in their RCTs.

5. Conclusion

This study provides a detailed overview of the costs and resources required to plan, conduct, and finalise investigator-sponsored RCTs. Over a quarter of total trial costs were incurred in the planning phase, which is typically not fully funded. Two-thirds of RCTs exceeded their budget by more than 50%. Use of routinely collected data can lower total trial and per patient costs. Investigators and funders should consider empirical cost data to improve funding and budgeting.

Ethics statement

Ethical approval was not required for this project and this was confirmed by the ethics committee, Ethikkommission Nordwest-und Zentralschweiz (EKNZ, project-ID: Req-202400581).

Patient and public involvement statement

No patient and public involvement was considered for this project.

Dissemination to participants and related patient and public communities

This project has been presented at the Clinical Research Day, University Hospital Basel, 2024.

CRedit authorship contribution statement

Alexandra Griessbach: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology,

Investigation, Formal analysis, Conceptualization. **Benjamin Speich:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Alain Amstutz:** Writing – review & editing, Data curation, Conceptualization. **Lena Hausheer:** Data curation. **Manuela Covino:** Data curation. **Hillary Wnfried Ramirez:** Data curation. **Stefan Schandelmaier:** Writing – review & editing, Methodology, Data curation. **Ala Taji Heravi:** Writing – review & editing, Data curation. **Shaun Treweek:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Matthias Schwenkglenks:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Matthias Briel:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

B.S. and M.B. report an unrestricted grant from Moderna for a study outside of the submitted work. There are no competing interests for any other author.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jclinepi.2024.111536>.

Data availability

The data that has been used is confidential.

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