**Systematic review on costs and resource use of randomised clinical trials
shows a lack of transparent and comprehensive data**

Benjamin Speich^{a,†}, Belinda von Niederhäusern^{b,†}, Nadine Schur^c, Lars G. Hemkens^a,
Thomas Fürst^{d,e}, Neera Bhatnagar^f, Reem Alturki^g, Arnav Agarwal^{f,h}, Benjamin Kasenda^{a,i},
Christiane Pauli-Magnus^b, Matthias Schwenkglenks^{c,j*}, Matthias Briel^{a,f*} for the MAKing
Randomized Trials Affordable (MARTA) Group

^a*Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research,
University of Basel and University Hospital Basel, Switzerland*

^b*Clinical Trial Unit, Department of Clinical Research, University of Basel and University
Hospital Basel, Switzerland*

^c*Institute of Pharmaceutical Medicine, University of Basel, Basel, Switzerland*

^d*Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute,
University of Basel, Basel, Switzerland*

^e*School of Public Health, Imperial College London, London, United Kingdom*

^f*Department of Health Research Methods, Evidence, and Impact, McMaster University,
Hamilton, ON, Canada*

^g*Multi Organ Transplant Center, King Fahad Specialist Hospital Dammam, P.O. Box 15215,
Dammam 31444, Saudi Arabia*

^h*School of Medicine, University of Toronto, Toronto, Ontario, Canada*

ⁱ*Department of Medical Oncology, University of Basel and University Hospital Basel,
Switzerland*

^j*Epidemiology, Biostatistics and Prevention Institute, University of Zürich, Zürich, Switzerland*

[†] These authors contributed equally to the work reported here and share first authorship.

* These authors contributed equally to the work reported here and share last authorship.

Corresponding author:

Matthias Briel, MD, MSc

Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research,

University of Basel and University Hospital Basel,

Spitalstrasse 12

4031 Basel

Switzerland

E-mail addresses of all co-authors

37 Benjamin Speich <benjamin.speich@usb.ch>
38 Belinda von Niederhäusern <belinda.vonniederhausern@usb.ch>
39 Nadine Schur <nadine.schur@unibas.ch>
40 Lars Hemkens <lars.hemkens@usb.ch>
41 Thomas Fürst <thomas.fuerst@unibas.ch>
42 Neera Bhatnagar <bhatnag@mcmaster.ca>
43 Reem ALTurki <alturkirk@gmail.com>
44 Arnav Agarwal <arnav.agarwal@mail.utoronto.ca>
45 Benjamin Kasenda <benjamin.kasenda@usb.ch>
46 Christiane Pauli-Magnus <christiane.pauli-magnus@usb.ch>
47 Matthias Schwenkglenks <m.schwenkglenks@unibas.ch>
48 Matthias Briel <matthias.briel@usb.ch>

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Abstract

Objectives: Randomised clinical trials (RCTs) are costly. We aimed to provide a systematic overview of the available evidence on resource use and costs for RCTs to support budget planning.

Study Design and Setting: We systematically searched MEDLINE, EMBASE and HealthSTAR from inception until November 30, 2016 without language restrictions. We included any publication reporting empirical data on resource use and costs of RCTs and categorised them depending on whether they reported (i) resource and costs of all aspects at all study stages of an RCT (including conception, planning, preparation, conduct, and all tasks after the last patient has completed the RCT); (ii) on several aspects, (iii) on a single aspect (e.g. recruitment); or (iv) on overall costs for RCTs. Median costs of different recruitment strategies were calculated. Other results (e.g. overall costs) were listed descriptively. All cost data were converted into USD 2017.

Results: A total of 56 articles that reported on cost or resource use of RCTs were included. None of the articles provided empirical resource use and cost data for all aspects of an entire RCT. Eight articles presented resource use and cost data on several aspects (e.g. aggregated cost data of different drug development phases, site specific costs, selected cost components). Thirty-five articles assessed costs of one specific aspect of an RCT (i.e. 30 on recruitment; 5 others). The median costs per recruited patient were USD 409 (range: USD 41-6,990). Overall costs of an RCT, as provided in 16 articles, ranged from USD 43-103,254 per patient, and USD 0.2-611.5 Mio per RCT but the methodology of gathering these overall estimates remained unclear in 12 out of 16 articles (75%).

Conclusion: The usefulness of the available empirical evidence on resource use and costs of RCTs is limited. Transparent and comprehensive resource use and cost data are urgently needed to support budget planning for RCTs and help improve sustainability.

87 **What is new?**

88

89 **Key Findings**

- 90 • Despite frequent claims that clinical research costs are on constant rise, empirical
91 evidence on resource use and associated costs for randomised clinical trials (RCTs)
92 is limited.
- 93 • Current estimates of overall RCT costs cover a wide range, but the underlying
94 methodology of gathering these estimates often remains unclear.
- 95 • Most articles focus on the comparison of different recruitment strategies, but none
96 provide a detailed overview of all aspects of resource use and associated costs of an
97 RCT.

98 **What this adds to what was known?**

- 99 • To our knowledge this is the first systematic overview of published estimates on trial
100 costs. There is a lack of transparent and comprehensive empirical data on RCT costs.

101 **What is the implication and what should change now?**

- 102 • Empirical evidence on cost items for RCTs, specifically in the academic setting, is
103 urgently needed so that budget planning and feasibility of RCTs can be improved.
104 Investigators should make resource use and cost data of RCTs publicly available.

1. Introduction

A growing body of evidence documents substantial scientific and monetary waste in biomedical research, including clinical research [1-6]. Sources of waste include problematic research question selection, poor study design and execution, as well as non-publication and selective reporting [1-5]. Financial estimates for research and development (R&D) for new drugs in 2009 were reported to range from USD 92 million to USD 884 million per compound [7, 8]. The currently highest estimates, published in 2016 by DiMasi et al., are as high as USD 1.4 billion. These high estimates are controversially discussed in the scientific communities. A number of institutions and scientists have criticized them as intransparent and expressed scepticism about whether reported high R&D costs always reflect reality, or might be overestimated to justify high drug prices [9-11].

In contrast to the debate about R&D cost estimates, there is agreement that randomised clinical trials (RCTs) produce the most reliable evidence about the benefits and harms of clinical interventions (including also non-drug interventions), ultimately leading to better care for patients [12, 13]. At the same time, the clinical phases seem to account for the highest expenses in R&D [14, 15], with particularly high costs of RCTs [16]. During the last decades a number of initiatives and regulations aiming to improve research quality and to increase participant protection were implemented [17]. Some argued that due to these measures the complexity, administrative burden, and overall costs of RCTs increased, too, which could compromise the motivation of investigators to initiate new trials [12, 18-20]. In addition, a substantial proportion of initiated RCTs that are prematurely discontinued due to organisational and recruitment problems [21] risk that more uncertainties about medical treatments will remain unaddressed. Thus, efforts to improve the planning of RCTs and to make them more affordable and sustainable are urgently needed.

The authors of the 2014 article series on “how to increase value and reduce waste” in biomedical research provided stakeholders with 17 recommendations on how to increase value [1-5]. Without empirical cost data and evidence on potential cost-drivers, such an optimisation process remains challenging at best [22]. Not only researchers involved in planning the cost of their studies, but also funding agencies, regulators, and academic institutions would benefit from a transparent reporting of the resource use and costs of RCTs, and from the identification of potential key factors that could make them more sustainable. For example, while the overall allocation of research funds might primarily require estimates of overall costs, more specific details on costing of particular tasks is reasonable or could be done more efficiently. To reduce waste, research funders might provide specific instructions for grant applications [23]. Furthermore, a detailed overview of what is known on resource use and costs would provide a reference for trial budgeting and an orientation for assessing the relative value of individual trial components. Therefore, the aim of this study was to systematically review the currently available evidence on resource use and associated cost data for RCTs.

2. Methods

2.1. Literature search and eligibility criteria

An experienced medical librarian (NB) systematically searched Medline, EMBASE and HealthSTAR via Ovid from their inception until November 30 2016 without any language restriction. We used MeSH terms like “Clinical Trials as Topic” and “Cost Analysis” and text words such as “costs” in combination with “clinical trials” (see Online Appendix for the detailed search strategy). We searched Medline and EMBASE through OVID as typical databases which clinical scientists might search when looking for empirical data to support budget planning for an RCT. In addition, we included HealthSTAR as this database is widely available and contains additional health care, health economics, and technical reports. At title

and abstract level, we included any publication that mentioned the assessment of empirical data on resource use and costs of RCTs or provided cost or resource data (covering totals or specific aspects) in the abstract. At full text level, we included any publication that provided empirical data on single, several, or all aspects of resource use and/or associated costs of one or multiple RCTs, or total costs of at least one RCT. We excluded articles that assessed the costs or the cost-effectiveness of the intervention only and studies that analysed the cost of R&D in general without giving any specific cost or resource data for RCTs.

2.2. Selection of articles and data extraction

In teams of two, we examined all identified titles and abstracts independently and in duplicate (BS, BvN, NS, LGH, TF, RA, AA, CPM, MS, MB). For titles and abstracts that were considered potentially relevant by at least one reviewer, we obtained corresponding full texts that were independently reviewed by two authors (BS, BvN). In case of disagreement, a third reviewer (MB) was consulted and the respective article discussed until agreement was reached. Each eligible articles was assigned to one of the following four categories: (i) articles presenting resource and cost data for all aspects of an entire RCT (including conception, planning, and preparation, conduct (including patient enrollment, treatment, and follow-up), and all tasks after last patient out (including data analysis, interpretation, and reporting)); (ii) articles presenting resource use or cost data for several aspects of an RCT (e.g. including costs or resource use of different individual trial components); (iii) articles presenting resource use or cost data for only one aspect of an RCT (e.g. recruitment); and (iv) articles that reported overall costs (i.e. cost per patient or cost per RCT). The first three categories were mutually exclusive, but not the fourth (overall costs).

From all included articles the following information was extracted by one reviewer and cross-checked by a second reviewer (BS, BvN): Year of publication, time of conduct, and cost data (including costs for single trial aspects such as recruitment and overall costs). We

183 additionally extracted information on population, experimental intervention, control
184 intervention, and primary outcome (PICO) to descriptively characterise the RCTs. If an article
185 reported on multiple RCTs we extracted ranges for year of publication, time of conduct and
186 overall costs. Furthermore, we extracted the overall therapeutic area of the multiple RCTs
187 (e.g. HIV). If no overall topic was given we categorized them as `multiple` and extracted the
188 therapeutic areas of the individual RCTs if they could be identified. From articles reporting
189 overall costs, we extracted, to the extent available, why the authors published cost figures as
190 well as what they felt could be learned from them.

192 2.3. Analysis

193 Articles presenting resource use or cost data for several aspects were descriptively
194 summarised. For articles covering one aspect of costs, (e.g. cost of recruitment of
195 participants), median and range of the costs for this specific aspect were calculated. Overall
196 costs of RCTs and costs per patient for a complete RCT were descriptively listed per article.
197 If more than two RCTs from the same therapeutic area presented overall costs we calculated
198 and presented medians and ranges for the sample size, overall costs and costs per patient.
199 In case an article described the costs of several RCTs, we presented the range of those
200 costs. All cost data were converted into USD 2017 using the annual inflation listed by the
201 OECD (Organisation for Economic Co-operation and Development) [24]. For the overall
202 costs of RCTs we present the published cost data as well as costs converted into USD 2017.
203 We converted currencies into USD [25] using the start date of the RCT, or, if unknown, the
204 date of the publication. If reported, we used the following date in this order of priority to adjust
205 for inflation: (i) date of currency listed in the publication (e.g. USD 2011); (ii) date when the
206 RCT was started; (iii) date of publication.

3. Results

3.1. Search results

Our systematic search yielded 6650 articles after removing duplicates. We excluded 6326 articles based on titles and abstracts, and 268 based on the full text (Figure 1). We included 56 articles (Table 1): (i) there were no articles that presented detailed empirical resource and cost data for all aspects of one or more RCTs; (ii) eight articles presented resource or cost data on several aspects of an RCT (three out of these 8 articles also presented overall RCT costs); (iii) 35 articles presented only one specific resource or cost aspect of RCTs (i.e. 30 recruitment costs, 2 costs of protocol development, 1 adverse event costs, 1 pharmacy costs, 1 costs of Good Clinical practice [GCP] compliance); and (iv) 16 articles presented overall costs.

Figure 1: Selection of articles

221 **Table 1:** Characteristics of the 56 included articles.

	All articles (n=56)	Articles assessing several aspects (n=8*)	Articles assessing only one aspect (n=35)	Articles reporting overall costs (n=16*)
Year of Publication				
Median	2009	2008	2009	2013
Interquartile range	2002-2014	1995-2015	2002-2013	1997-2014
Range	1985-2016	1992-2016	1993-2016	1985-2016
Number of trials				
One specific trial	35 (62.5%)	3 (37.5%)	26 (74.3%)	8 (50.0%)
More than one trial	21 (37.5%)	5 (62.5%)	9 (25.7%)	8 (50.0%)
Origin of trials				
North America	33 (58.9%)	4 (50.0%)	25 (71.4%)	6 (37.5%)
Europe	7 (12.5%)	1 (12.5%)	5 (14.3%)	1 (6.3%)
Other	3 (5.4%)	0	3 (8.6%)	0
Unknown	2 (3.6%)	0	0	2 (12.5%)
Multiple	11 (19.6%)	3 (37.5%)	2 (5.7%)	7 (43.8%)
Type of Article				
Original article	51 (91.1%)	7 (87.5%)	34 (97.1%)	13 (81.3%)
Short communication, Editorial/Comment	4 (7.1%)	0	1 (2.9%)	3 (18.8%)
HTA Report	1 (1.8%)	1 (12.5%)	0	0
Medical field				
Medical	18 (32.1%)	2 (25.0%)	10 (28.6%)	7 (43.8%)
Surgery	1 (1.8%)	0	0	1 (6.3%)
Other (e.g. behavioral, physical therapy, psychological therapy, dental treatment)	26 (46.4%)	2 (25.0%)	18 (51.4%)	5 (31.3%)
Multiple trials/unclear	11 (19.6%)	4 (50.0%)	7 (20.0%)	3 (18.8%)
Population				
Adults	32 (57.1%)	4 (50.0%)	20 (57.1%)	10 (62.5%)
Adults and children	3 (5.4%)	0	3 (8.6%)	0
Children	5 (10.7%)	0	3 (8.6%)	2 (12.5%)
Elderly	3 (5.4%)	0	3 (8.6%)	0
Multiple trials	13 (23.2%)	4 (50.0%)	6 (17.1%)	3 (18.8%)

*3 articles reporting overall costs also presented cost data on several aspects.

225

226 3.2. Articles presenting resource and cost data for all aspects of RCTs

227 We did not find any article that empirically assessed resource use and associated costs for
228 all aspects of an entire RCT at all study stages (*conception and planning* (including project
229 development and preparation), *conduct* (including patient recruitment, treatment, and follow
230 up), and *after last patient out* (including data analysis, interpretation, and reporting)).

231

232 3.3. Articles presenting resource or cost data for several aspects of RCTs

233 Eight articles presented resource or cost data on several aspects for RCTs (Table 2) [26-33].
234 In short, two studies assessed the overall costs of several industry-sponsored clinical trials
235 stratified by different clinical trial phases [26, 33]. While Sertkaya and colleagues presented
236 “costs per patient”, “per site cost” and “pre study costs” with additional stratification per
237 medical field, Getz et al. presented costs stratified into “core” and “noncore” procedures. One
238 article from Raftery and colleagues retrospectively assessed the mean costs per patient and
239 other cost components (e.g. costs of statistical input) from studies supported by the British
240 National Health Service (NHS) between 1995 and 2005 [27]. One article authored by Zhu
241 and colleagues [28] listed the overall costs of a large oncology screening RCT and stratified
242 the costs for further screening centres, coordinating centre and for collecting biological
243 samples. Another article assessed time efforts for 41 cancer-trial tasks from 83 Clinical
244 Research Associates in 1996 [29]. Thornquist and colleagues estimated the resource use and
245 costs of a large academic prevention trial that was conducted between 1988 and 1991 [31].
246 While cost components for specific items are listed (e.g. follow up of an active participant for
247 1 year), resource data (i.e. time efforts) are missing. Two studies published in the 1990s
248 assessed site-specific resources and costs [30, 32].

249 **Table 2:** Summary of the 8 articles presenting resource use or cost data on several aspects for randomised clinical trials.

Author and year	Publication content in terms of empirical trial costs and resource use	Primary results regarding resource and cost data (based on abstract; in USD 2017)
Sertkaya et al., 2016 [33]	Aggregate cost data of different phases (I-III) from three proprietary data bases (Medidata solutions). Cost per RCT across therapeutic areas with aggregated cost details (per patient and per site) from the pharmaceutical industry (2004-2012). No resource data available.	Phase 2: USD 9.1 Mio (cardiovascular) – 25.4 Mio (hematology). Phase 3: USD 14.9 Mio (dermatology) – 68.5 Mio (pain and anesthesia)
Getz et al., 2015 [26]	Tufts Center for the Study of Drug Development study among working group of 15 pharmaceutical companies, looked between 2011 and 2012 at study reports and analysis plans, identified and assessed costs of “core” and “noncore” procedures per phase II/III protocol. No resource data available.	Phase 2: USD 300,000 (13.1%) is spent in direct costs of noncore procedures Phase 3: USD 1.8 Mio (18.5%) is spent in direct costs of noncore procedures
Raftery et al., 2015 NHS HTA Report [27]	Questionnaire used to assess planned and actual costs of RCTs funded by the NHS HTA programme (1995-2005). Provides mean cost per patient per year and other cost components (e.g. costs of “statistician input”). “Research cost, as funded by the HTA programme, accounted for some 70% of the total cost...” No resource data available.	No abstract. Mean annual cost per patient: USD 3,062 – 9561
Zhu et al., 2013 [28]	A large trial (n=154,901) assessing different screening strategies for prostate, lung, colorectal and ovarian cancer. The trial was funded by the National Cancer Institute Division of Cancer Prevention. Besides overall costs, costs are separately listed for screening centers, coordinating center and collection of biological samples. No resource data are listed.	The overall costs over 20 years were USD 494 Mio with approximately USD 40.3 Mio for the collection, processing and storage of biospecimens.
Roche et al., 2002 [29]	In 1996 Clinical Research Associates (n=83) collected timing observations of 41 cancer-trial tasks (156 subtasks) over 30 consecutive days. Time efforts for all trial stages were obtained. No cost data available.	“Industry-sponsored studies had significantly higher overall mean times than did local and cooperative group studies. Early-phase studies required more time than did phase III trials.”
Evans et al., 2000 [30]	Retrospective estimate of resource use and cost of two phase II trials in lung cancer. Only site specific costs available in 1993 Canadian dollars. Resource and cost data for the project development phase (e.g. development of study protocol) and the phase “after last patient out” not available.	Taxotere trial: USD 1,755 per patient Gemcitabine trial: USD 2,973 per patient
Thornquist et al., 1993 [31]	Costs and resource use of a large academic prevention trial (i.e. of β -carotene and vitamin A in decreasing the incidence of lung cancer in two populations at high risk) conducted between 1988 and 1991. Resource use (i.e. time effort) not presented in results.	The total direct costs over 13 years was approximately USD 80 Mio
Eri et al., 1992	Cost and extra time needed for patient recruitment and on site trial tasks in one academic	The costs for the hospital to carry out a trial with

[32] hospital conducted between 1989 and 1991.

65 evaluable is approximately USD 127,000

250 Abbreviations: RCT= Randomised clinical trial; NHS= National Health Service; HTA= Health Technology Assessment

3.4. Articles presenting resource or cost data for one specific aspect of RCTs

A total of 30 articles [34-63] described the costs of recruitment for an RCT (Table 3). Print advertisement (described in 14 articles), mail-based invitation (11 articles), and radio advertisement (6 articles) were the most commonly assessed recruitment methods. Phone screening was the cheapest recruitment method (USD 116, range USD 98-1,146 per recruited patient) and combining different media the most expensive (USD 2,058; range USD 91-16,399 per recruited patient). Cost ranges within categories were large. Fifteen articles reported the overall costs for recruitment independent of any recruitment strategy. The median costs for recruiting a patient were USD 409 (range: USD 41-6,990).

Table 3: Summary of the 30 articles presenting costs to recruit one patient into a randomised controlled trial according to different recruitment strategies.

Recruitment strategy	Number of studies (total n=30)	Median number of recruited patients (range)	Median costs per recruited patient in USD 2017 (range)	References
Print advertisement	14	19 (4-141)	580 (43-2,254)	[35, 37, 38, 43, 45-49, 51-54, 58]*
Mail invitation	11	82 (4-337)	228 (15-1,116)	[36, 40, 44, 46, 48, 49, 51-53, 61, 63]*
Radio advertisement	6	5 (3-38)	627 (204-5,243)	[35, 37, 43, 46, 51, 58]*
General practitioner referral	5	18 (4-107)	541 (9-2716)	[40, 45, 48, 58, 63]
Billboard/posters	5	15 (2-36)	1,134 (64-12,538)	[35, 45, 53, 58, 63]
Community workers (Church, social service)	5	5 (1-152)	642 (22-1938)	[43, 45, 48, 49, 52]
Internet advertisement	4	11 (2-37)	198 (155-2,621)	[35, 37, 48, 51]*
Phone screening	4	192 (87-347)	116 (98-1146)	[44, 59-61]
Public transport advertisement	3	2 (2-26)	1,295 (1,252-7,750)	[35, 37, 40]
Combination of different media (i.e. radio, newspaper, posters)	3	27 (1-75)	2,058 (91-16,399)	[39, 40, 63]
TV advertisement	2	24 (5-174)	440 (69-3,548)	[51, 64]*
Manual chart screening and algorithm search	1**	16 (11-20)	297 (227-366)	[42]
Overall costs of recruitment	15	164 (15-4249)	409 (41-6,990)	[34, 38, 41, 46, 48, 50-58, 62]*

* One article [51] reports on two separate datasets from two RCTs.

**One article with the two mentioned recruitment strategies (i.e. manual chart screening and algorithm search)

Five articles assessed other specific cost aspects of RCTs. Two articles evaluated the costs of protocol procedures including protocol amendments [65, 66], one article estimated the costs of adverse event procedures in an HIV trial [67], one calculated the average costs of a hospital pharmacy among all trials where the pharmacy has been involved [68], and one article assessed the costs of “GCP-related activities” in an RCT [69]. A comprehensive overview of these studies is listed in Appendix Table S1.

3.5. Articles presenting overall costs of RCTs

Sixteen articles presented overall costs for one or several RCTs [23, 28, 31, 33, 70-81] (Table 4, Appendix Table S2). The methods to estimate these cost data were not reported at all in 7 articles (38%), or little detailed and intangible in 5 articles (31%; e.g. personal communication; estimated based on final study reports). Three out of these 16 articles were published editorials or comments. The cost of the cheapest RCT was listed by Detsky [80], for a trial published in 1983 and assessing the efficacy of propranolol in 48 patients with esophagael varices (overall costs USD 209,202) [82]. The most expensive RCT (overall costs USD 611.5 Mio) was the MR-FIT (“Multiple Risk Factor Intervention Trial”) enrolling 12,866 men with high risk for coronary heart diseases. The enrollment started more than 40 years ago in 1973 and the intervention consisted of “stepped-care treatment for hypertension, counseling for cigarette smoking, and dietary advice for lowering blood cholesterol levels” [83]. The second most expensive RCT was a cancer screening trial starting in 1993 enrolling 154,901 patients over a period of eight years and conducted a follow-up of 13 years (overall costs USD 494 Mio) [28]. The data from this trial were used

and presented in a total of 335 publications. The lowest costs per patient (USD 43) were reported in 2014 for a trial using routinely collected data as registry embedded trial (TASTE trial) that assessed thrombus aspiration during myocardial infarction in 7244 patients [73]. Here, endpoints were completely assessed through national registries. The highest costs per patient (USD 103,254) were reported for a lipid research trial conducted in 1983 [80]. The trial randomised 3,806 men with primary hypercholesterolemia to bile acid sequestrant cholestyramine resin or placebo. Median follow-up was 7.4 years and participants visited the clinics every two months. Four articles reported overall costs for a total of 9 specific cardiovascular RCTs (n=5 [80]; n=2 [81]; n=1 [73]; n=1 [75]). These RCTs included a median of 1,741 patients (range: 48-12,800) and had median overall costs of USD 22.9 Mio (range: USD 0.209-611.5 Mio). The median costs per patient among these 9 studies was USD 17,020 (range: USD 43-103,262). For all other therapeutic areas, no more than 2 RCTs presenting overall costs were identified.

The most common reasons stated by the authors why they published overall costs were to “gain [...] a better understanding of the key cost drivers” [84] or to compare the costs of the RCT with the resulted benefit or profit (Appendix Table S3). Authors comparing costs with benefit or profit concluded that the RCTs resulted in a substantial return on investment. One RCT which was conducted over a mobile phone application [70] and one RCT using routinely collected data to measure endpoints [73] highlighted that pragmatic RCTs (i.e. “providing evidence on the relative effectiveness of a treatment strategy in routine clinical practice” [85]) might result in high cost savings (Appendix Table S3).

309 **Table 4:** Summary of the 16 articles presenting overall costs for RCTs

Reference	Therapeutic area	Year RCTs conducted	Sample size	Overall costs in USD 2017 (published costs)	Costs per patient in USD 2017 (published costs per patient in USD if not indicated differently)
Larson et al., 2016 [71]	HIV	2002-2016	4,150 - 5,472	101.7 Mio-151.6 Mio (71.9 Mio – 111.9 Mio)	24,512-27,702 (17,313-20,441)
Sertkaya et al., 2016 [33]	Multiple pharmaceutical RCTs from different medical fields	2004-2012	NR	Phase II: 9.0 Mio – 25.4 Mio (7.0 Mio- 19.6 Mio) Phase III: 14.9 Mio – 68.5 Mio (11.5 Mio – 52.9 Mio)	NA
Anguera et al., 2015 [70]	Depression	2014-2015	1,098	323,624 (314,264)	295 (286)
Roth et al., 2014 [72]	Gynaecology	1997-2002; (costs in USD 2012)	16,608	276.1 Mio (260 Mio)	16,624 (15,655)
Chit et al., 2013 [74]	Multiple influenza vaccine RCTs	2000-2012	Phase II: 517 Phase III: 4,461	Phase II: 2.3 Mio (CAD 2.3 Mio) Phase III: 15.1 Mio (CAD 15.4 Mio)	Phase II: 4,354 (CAD 4,505) Phase III: 3,379 (CAD 3,457)
Zhu et al., 2013 [28]	Oncology	1993-2001 (costs in USD 2011)	154,901	494 Mio (454 Mio)	3,189 (2,931)
Light et al., 2009 [76]	Multiple rotavirus vaccines RCTs	1987-2003; (costs in USD 2008)	Phase II: 184-2,464 Phase III: 63,225 – 68,083	Phase II: 1.5 Mio-3.3 Mio (1.3 Mio – 2.9 Mio) Phase III: 167.6 Mio-280.9 Mio (148.0 Mio – 248.1 Mio)	Phase II: NA Phase III: 2,651-4,129 (2,340 – 3,646)
Baker-Smith et al., 2008 [77]	Multiple RCTs on Antihypertensive drugs	NR (submitted to FDA: 1997 – 2004)	110 - 441	1.8 Mio-17.5* Mio (1.3 Mio – 12.9* Mio)	10,475-49,412 (7,605 – 37,291)
Li et al., 2007 [78]	Multiple paediatric trials from different therapeutic areas	NR (costs in USD 2005)	25 - 404	2.1 Mio-16.2 Mio (1.7 Mio – 12.9* Mio)	17,532-94,482 (14,044 – 75,686)
Thornquist et al., 1993 [31]	Dietary Supplement	1988-1991 (costs in USD 1989)	17,000	80.7 Mio (40.9 Mio)	4,747 (2,406)
Drummond et al., 1992 [79]	Diabetic	1972-1975	1732	61.2 Mio (10.5 Mio)	35,359 (6,062)
Detsky 1989 [80]	Multiple RCTs from different therapeutic areas	1981-1983 (Published: 1982-1986)	24 – 6,400	209,202-611.5Mio (78,000 – 110 Mio)	4,359-103,254 (1,625 – 42,182))

Detsky 1985 [81]	Two cardiovascular RCTs	1975-1979	1,629 - 4,524	22.7 Mio- 77.0 Mio (5 Mio – 17 Mio)	13,909-17,029 (3,069 - 3,758)
Editorials/Comments:					
Muennig, 2015 (Commentary) [23]	Behaviour	NR (costs in USD 2014)	NR	283,207 (275,000)	-
Lauer et al., 2014 (Editorial) [73]	Cardiovascular	NR	7,244	313,964 (300,000)	43 (41)
Callaway, 2012 (NATURE-News) [75]	Cardiovascular	2003-2011	1,708	41.9 Mio (31.6 Mio)	24,514 (18,501)

310 * Trial costs of one RCT are presented both in the publication by Baker-Smith and colleagues [77] and the publication by Li et al [78].

311 Abbreviations: RCT= randomised clinical trial; NIH=National Institutes of Health; FDA=US Food and Drug Administration; NR=not reported; NA=not assessable

4. Discussion

Our systematic literature search of over 6000 titles and abstracts identified 56 articles that presented some cost or resource use data of RCTs in any form but we found no article assessing resource use and associated cost data for all aspects of an RCT (including detailed empirical resource use during the planning, conduct, and reporting of an RCT, and the associated costs). The data we found had only limited usefulness for all the different stakeholders in clinical research due to their insufficient comprehensiveness and lack of standardized methodology of assessment.

A large proportion of the included articles assessed the costs to recruit one participant into an RCT. Presumably this reflects the fact that recruitment of a sufficiently large number of patients is considered one of the biggest challenges by many investigators [21, 86], but also the fact that evaluating the costs of patient recruitment is probably a relatively simple study-within-a-trial (SWAT; 29 out of 30 articles). SWATs can make use of an ongoing funded RCT (host-trial) to practically test and evaluate different concepts or interventions within the trial (e.g., by randomizing study centres to different recruitment strategies) and produce trustworthy evidence that can inform the planning and conduct of future trials. Embedding methodology research in clinical trials can increase value for minimal extra costs [87]. Our pooled results from 15 articles indicate a large range of recruitment costs per patient (USD 41 – 6,990), also within specific recruitment strategies (e.g. mail invitation, radio advertisement, phone screening), which reflects a large diversity of RCTs recruiting various patient populations (e.g. patients with chronic depression; diabetic patients; rainwater drinkers) and allocating them to a large variety of interventions. This diversity can also be seen in the RCTs that presented overall costs. Besides nine cardiovascular RCTs which had a large range of overall costs (range: USD 0.2-611.5 Mio) and cost per patient (range: USD 48-12,800), no further therapeutic area was represented by more than two RCTs presenting overall costs. Due to the high diversity of medical fields, interventions, measurement tools

and follow-up times it is difficult to generalize trial costs. One observation in our study was that some of the oldest RCTs were very costly (i.e. USD 61 Mio [79], USD 77 Mio [81], USD 367 Mio and USD 611 Mio [80]; Table 4), which is in contrast to the existing opinion that RCT costs are on constant rise [12, 14, 16, 88]. However, one has to be aware that all findings of this systematic review could be substantially affected by publication bias (i.e. “more extreme data” representing very low or very high costs might be published more often) and other issues of selective reporting bias.

To the best of our knowledge this is the first systematic review addressing the existing evidence on RCT resource use and associated costs. Although we consider our search approach comprehensive from the perspective of an applied clinical researcher (3 electronic databases: Medline, EMBASE, and HealthSTAR) we might have overlooked articles in journals not indexed in these electronic search databases. We aimed for a systematic approach and we may have overlooked sporadic cost information in main texts or Discussion sections of studies, with no related hint in the title, abstract, or keywords. Further, we did not screen reference lists or searched other economic databases. However, we believe that some more cost estimates or selective descriptions of partial cost details in trials would most likely not change our overall conclusion. We explicitly refrained from assessing and using funding databases as they often do not reflect actual trial costs, but may only cover a part of the funds required to plan, conduct, and complete an entire RCT. Detailed costs and resource use for individual trial-related tasks are, in our experience, not available on the websites of funding institutions. Furthermore, funders` databases are not necessarily the first resource clinical researchers would use as a tool to estimate costs when planning a trial. We acknowledge that our survey mostly portrays costs of RCTs in high income nations that may not necessarily overlap with those of low- or middle-income countries. We tried to make the available data comparable by translating all cost data into USD 2017. We had originally planned to use purchasing power parities to translate costs of studies that were conducted outside of the United States, into USD. However, due to the fact that many studies were

conducted in several countries and some of the RCTs did not state where they were conducted, this would have introduced a relevant amount of inconsistency, and was therefore omitted.

To date, as far as we know, no similar systematic review exists to which we could compare our results. A short report published in 2017 by Martin et al. [89] identified similar gaps in the evidence base of RCTs. The authors undertook an analysis of cost data from 726 pharmaceutical interventional trials, resulting in a median cost of USD 8.6 million for phase II trials and USD 21.4 million for phase III trials. However, again, the report lacks a transparent methodology and presents overall cost numbers only.

Based on our systematic review, cost data for industry funded RCTs are little detailed and often not transparent in terms of the methods used to collect the cost data. For RCTs funded by academic sponsors there seems to be no comprehensive analysis of the costs available to date. Therefore, we composed a detailed list of costing items applicable to RCTs, collected empirical data on resource use and associated costs for two RCTs conducted within our network of collaborators, and summarised the results in a case report (*Speich et al., submitted together with this manuscript to the JCE*). With this we meant to set an example for a transparent and comprehensive reporting of actual resource use and costs of RCTs. Transparently published resource use and costs may support researchers and funders alike to prospectively plan and monitor the costs associated with the conduct of RCTs in the future.

Conclusion

While the present systematic review revealed several studies on costs or resource use for specific aspects of RCTs or articles providing estimates for total costs of individual RCTs, we could not identify any article reporting detailed empirical data on resource use and costs for all aspects of a RCT. Therefore the usefulness of the currently available data is limited.

391 Accessible empirical resource use and cost data are urgently needed to optimise the value
392 for money of RCTs and ultimately make the current research environment more sustainable.

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394 **The MARTA Group**

395 Benjamin Speich¹, Belinda von Niederhäusern², Nadine Schur³, Lars G. Hemkens¹, Benjamin
396 Kasenda^{1,4}, Christiane Pauli-Magnus², Matthias Schwenkglenks^{3,5}, Matthias Briel^{1,6}

397 ¹ Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research,
398 University of Basel and University Hospital Basel, Switzerland

399 ² Clinical Trial Unit, Department of Clinical Research, University of Basel and University
400 Hospital Basel, Switzerland

401 ³ Institute of Pharmaceutical Medicine, University of Basel, Basel, Switzerland

402 ⁴ Department of Medical Oncology, University of Basel and University Hospital Basel,
403 Switzerland

404 ⁵ Epidemiology, Biostatistics and Prevention Institute, University of Zürich, Zürich,
405 Switzerland

406 ⁶ Department of Health Research Methods, Evidence, and Impact, McMaster University,
407 Hamilton, ON, Canada

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