A STUDY SPONSORED BY THE SWISS FEDERAL OFFICE OF PUBLIC HEALTH

Effect of the Swiss human research legislation on the costs associated with randomised clinical trials in Switzerland

Final Report: Objectives I-IV

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List of abbreviations

AE	Adverse events
ASPIRE	Adherence to SPIrit REcommendations (study acronym)
BASEC	Business Administration System for Ethics Committees
CHF	Swiss Franc
CTU	Clinical Trial Unit
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
ICREL	Impact on Clinical Research of the European Legislation
IIT	Investigator-initiated Trial
IQR	Interquartile range (25th and 75th percentile)
LHR	(Swiss) Legislation on Human Research
max	Maximum
min	Minimum
n	Sample size
R&D	Research and development of new drugs
RCT	Randomised controlled trial
REC	Research ethics committees
SAE	Serious adverse events
SAKK	Swiss Group for Clinical Cancer Research (Schweizerische Arbeits-gemeinschaft für Klinische Krebsforschung)
SCTO	Swiss Clinical Trial Organisation
SFOPH	Swiss Federal Office of Public Health
SNSF	Swiss National Science Foundation
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SwAPP	Swiss Association of Pharmaceutical Professionals
Swissmedic	Swiss Agency for Therapeutic Products
Swiss TPH	Swiss Tropical and Public Health Institute
U.S.	United States of America
USD	United States Dollars

1. Executive summary

Key points

- Detailed data on the costs of randomised controlled trials are not routinely collected in a systematic way, at least not in the academic setting.
- It proved to be impossible to retrieve a satisfactory amount of valid cost information for randomised controlled trials, despite massive efforts. In particular, information on industry-sponsored trials was close to inaccessible.
- Results did not indicate any substantial change in the costs of the preparation phase of randomised controlled trials between 2012 (before enactment of the Swiss Legislation on Human Research) and 2016 (after the Legislation on Human Research). However, it is a relevant possibility that the observed lack of a cost difference is a distorted result influenced by selection, recall and chance effects.
- Approval times for randomised controlled trials may have relevant implications for preparation phase costs. Based on the available data, combined Swissmedic and research ethics committee approval times could not be assessed. This would have been of key interest given related changes introduced by the Legislation on Human Research (i.e. until 2013, Swissmedic and research ethics committee submissions had to be made sequentially while they can be made in parallel since 2014).
- Taken by themselves, median Swissmedic and research ethics committee approval times (including and excluding sponsor reaction times in the case of Swissmedic while only the former could be assessed for the research ethics committees) appeared to be longer in 2016 than in 2012. Longer Swissmedic approval times in 2016 may have been a consequence of the exemption of low risk randomised controlled trials from Swissmedic approval, since the introduction of the Legislation on Human Research.

Background

In January 2014, the Swiss regulatory framework for clinical research has considerably changed by the enactment of the new law on research with human beings (Human Research Act) and its ordinances, jointly abbreviated in this report as Swiss Legislation on Human Research (LHR) [1, 2]. The LHR regulates the requirements for the conduct of clinical trials, related authorisation and notification procedures, related duties and responsibilities of research ethics committees (RECs), the Swiss Agency for Therapeutic Products (Swissmedic) and the Federal Office of Public Health, and the registration of clinical research projects. Purposes of introducing the LHR were to improve the protection of involved subjects, to increase quality and transparency in clinical research and to create a solid framework with the necessary degree of regulation but no over-regulation [3].

One important element was the introduction of a regulatory system proportionate to the relative risk of each individual clinical research project, intending to reduce the administrative burden to a necessary minimum [2, 3]. Based on three risk categories, different administrative obligations relating to submission of documents, compulsory insurance and reporting of adverse events came into effect [2, 3]. A related element of the LHR was the introduction of a simplified and accelerated as well as more efficient approval procedure. Only one submission to a lead REC is now required for multicentre studies [2, 3]. Approvals can be submitted in parallel to Swissmedic and the competent REC since the roles of these institutions are clearly distinguished. Low risk randomised controlled trials (RCTs) do no longer require Swissmedic approval. Previously, Swissmedic had to approve all RCTs and approval was only possible if the RECs in charge had previously decided in favour of the study. There were also relevant changes to approval timelines. Before the introduction of the LHR, the RECs had 30 days from receipt of a study protocol to decide whether the study should be approved, revised or rejected. Swissmedic also had 30 days to request revisions, and both authorities were able to restart the deadline if revisions were necessary. Since the implementation of the new LHR, both institutions have, in parallel in case of simultaneous submission, a first phase of seven days to check if all formal requirements are met, and then an additional 30 days to decide if a study is approved or if amendments are required. Of note, for multicentre studies which are submitted simultaneously to lead- and non-lead RECs, this deadline is 45 instead of 30 days (i.e. 15 days for non-lead RECs to give feedback to the lead REC and then 30 days for the lead REC to come up with the final decision) [4]. The new law also highlights the importance of good clinical practice, scientific integrity and quality [1, 2]

The role of clinical research and, specifically, RCTs is central to determining the effectiveness and safety of medical interventions. While RCTs have a potential to provide reliable evidence for decision-making in clinical practice and health policy, they are complex to implement, require intensive quality assurance activities (both scientific and administrative), and are costly [5-9].

The overall aim of this project funded by the Swiss Federal Office of Public Health (SFOPH) was to study a possible impact of the implementation of the LHR on RCT-associated costs and efforts. We followed an empirical and quantitative approach. Qualitative methods (e.g. expert interviews investigating expected effects and underlying mechanisms using qualitative methods of content analysis) were not considered. Four specific objectives were defined to approach the topic.

Objectives and approach

1. To create a comprehensive standardised list of direct and indirect cost items associated with RCTs
2. To determine the unit costs for listed cost items and to evaluate the mean total costs of completed RCTs in Switzerland

3. To compare the preparation costs of RCTs in Switzerland before (2012) and after (2016) the introduction of the Swiss LHR
4. To analyse the association of the introduction of the LHR with time from submission to approval of RCTs by RECs and Swissmedic

The inclusion of Objective 1 was required because there was little information on the cost components of RCTs. In order to approach the topic of a potential impact of the LHR on RCT costs and efforts, a structured framework needed to be established. (The term 'direct cost items' associated with RCTs refers to those costs that are required to complete the work outlined in the RCT protocol. Direct costs may or may not be directly influenced by the number of centres or participants [10, 11]. The term 'indirect costs' refers to costs of the underlying infrastructures [11, 12].)

Within Objective 2, we aimed to gain an understanding of typical unit costs to be expected for the cost items defined in Objective 1. To generate reference points for Objective 3, we further intended to assess the costs of the RCT preparation phase before the introduction of the Swiss LHR and the relative contribution of the preparation phase to overall RCT costs. We were finally interested in overall costs of completed RCTs in Switzerland as a by-product, given a clear lack of related knowledge nationally and internationally. We did not intend, however, to acquire overall costs of RCTs initiated after the implementation of the LHR, since most of these RCTs would not be completed by the time of our evaluation. Thus, it was not the intention of this intermediate step to directly compare the situation before and after the introduction of the new LHR.

For the core before-after comparison in Objective 3, the costs of the RCT preparation phase (covering all efforts until enrolment of the first patient) were targeted. We expected that the most immediate impact of the LHR on RCT costs, if any, would occur in this phase, due to the new rules regarding administrative authorisation and ethical approval that have to be fulfilled to start an RCT. The costs of the conduct and post-conduct phases might also be affected by the LHR but in a more indirect way with additional influencing factors that could complicate the interpretation of any data. RCTs approved in the years 2012 (2 years before the enactment of the LHR) and 2016 (2 years after the enactment of the LHR) were studied to achieve synergies with the parallel, ongoing *Adherence to SPIrit REcommendations* (ASPIRE) project also funded by the SFOPH. ASPIRE evaluated the reporting quality of RCT protocols approved by a Swiss REC in these years, according to the SPIRIT guideline [13, 14]. It was assumed that two years around the LHR would be a sufficient time period to observe first effects of the new legislation.

Approval times for randomised trials may have relevant implications for RCT working time requirements and preparation phase costs. In Objective 4, we intended to compare approval times before and after the enactment of the new legislation, which aimed to accelerate these. To

facilitate comparison with effects on RCT preparation phase costs and working time efforts, we considered RCTs that entered their approval process in 2012 and 2016.

Overview of main findings and related issues

Objective 1 was achieved as planned, providing a tool for the documentation and potentially for the planning of RCT costs. Objectives 2 and 3 could not be achieved as planned as they were massively affected by difficulties to retrieve a sufficient amount of RCT cost data. Main reasons included non-response by clinical investigators and refusal to provide information due to a perception of too much effort required to estimate working times. The latter may hint at an absence of efficient documentation. In the case of RCTs approved before the enactment of the new LHR, some responsible persons could no longer be contacted (e.g. due to change of workplace with no new contact data available) and lack of recall played a relevant role. Additionally, legal and privacy issues were mentioned for industry-sponsored RCTs. Objective 4 was partially compromised by the fact that the information provided by Swissmedic did not allow us to distinguish RCTs from other clinical trials. More importantly, the Swissmedic data did not include an identification code that would have enabled a matching of Swissmedic and REC approval time data at the RCT level. In consequence, we had no means of assessing combined Swissmedic and REC approval times. This would have been of key interest given related changes introduced by the LHR (i.e. until 2013, Swissmedic and REC submissions had to be made sequentially while they can be made in parallel since 2014).

Due to the above-mentioned limitations, our numerical findings for Objectives 3 and 4 are of limited value only. In the context of Objective 3, complete data were available for 18 RCTs approved in 2012 and for 35 RCTs approved in 2016. Results did not indicate any substantial change in the costs of the preparation phase of RCTs between 2012 and 2016. Item-level cost comparisons indicated that selection effects may have been relatively limited despite the small numbers of RCTs with data available. This may provide an indication that there were no clear-cut, strong effects of the LHR on RCT preparation costs. However, a distortion of the observed (lack of a) cost difference by selection, recall and chance effects remains a very relevant possibility. For Objective 4, we assessed Swissmedic and REC approval times in 2012 (Swissmedic, n=213 and REC, n=183) and 2016 (Swissmedic, n=179 and REC, n=217). With respect to REC approval times, valid comparison was only possible for single centre studies (n=40 in 2012; n=68 in 2016), due to the development of the lead REC approach between 2012 and 2016. Median Swissmedic approval times were only available for 'any clinical trials' (including e.g. non-randomised or single arm trials). The vast majority of these trials were actual RCTs, according to Swissmedic, but they could not be formally distinguished based on the data we received. Taken by themselves, Swissmedic and REC approval times (including and excluding sponsor reaction times in the case of Swissmedic while only the former could be assessed for the

RECs) appeared to be longer in 2016 than in 2012. The smaller number of applications to Swissmedic and the longer Swissmedic approval times in 2016 may have been a consequence of the exemption of low risk RCTs from Swissmedic approval. Combined Swissmedic and REC approval times could not be assessed for reasons stated above. Thus, combined approval times may have been shorter in 2016 than in 2012 due to the possibility of parallel submission under the new LHR.

Additional information on methods and results by objective is provided in the next sections.

Objective 1

A comprehensive list of cost items was compiled by means of a systematic literature review, an internet search and materials provided by clinical trial experts. RCT cost items could mainly be extracted from budget templates provided by the clinical trial experts, eight articles identified by the literature review, and nine websites identified by the internet search. The resulting initial list of items was further adapted and expanded by nine clinical trial experts from pharmaceutical industry and academia. In a next step, pilot testing occurred in the frame of a case study in which resource use and costs of two RCTs carried out by fellow researchers were retrieved [15]. We noted during the conduct of semi-structured interviews that the item list was comprehensive but highly specific and difficult to use. It was subsequently improved towards a more user-friendly tool to retrospectively collect resource and cost data for RCTs, and to help investigators plan and monitor RCT costs. The final version was structured into the following three phases of RCT conduct: (i) preparation phase (from the start of planning until the enrolment of the first patient); (ii) conduct phase (from the enrolment of the first patient until the last follow-up visit of the last patient); and (iii) post-conduct phase (from after the last follow-up visit of the last patient until main results of study are published).

Objective 2

In order to determine typical unit costs for the cost items defined in Objective 1 and to understand the magnitude of the costs associated with the preparation, conduct and post-conduct phases of RCTs, we contacted experts from academia, industry, clinical trial units, contract research organisations, and clinical research organisations involved in the cost aspects of RCTs conducted in Switzerland. We also asked the principal investigators of RCTs approved by a Swiss REC in 2012 who provided us with preparation phase costs as part of Objective 3, to provide full cost data for their RCTs. Use of the list of cost items provided by us was encouraged but not obligatory. In addition, we conducted a systematic review to gain an overview of the available, published evidence on the resource use and costs for RCTs, with an international focus.

Overall, the RCT cost data we could gain access to remained very sparse, for reasons already stated above, i.e.

- inability to contact responsible persons (outdated contact information),
- non-response,
- perceived high effort to provide information (i.e. potential respondents expected the burden to be too high),
- lack of recall,
- legal and privacy issues in the case of industry-sponsored RCTs.

We managed to collect resource use and cost data for 20 investigator-initiated RCTs (in 10 cases with detailed cost data) but did not receive any detailed cost information for industry-sponsored RCTs. Due to the small sample size even for investigator-initiated RCTs, we judge the risk of selection bias to be high. Firm conclusions cannot be drawn from the results. Our accompanying systematic review indicated that despite the broadly shared opinion that RCTs are expensive and that their costs are increasing [6, 8, 9, 16], the published evidence on RCT costs is sparse internationally and the usefulness of the available data is highly limited [17]. The underlying methodology of gathering these data and translate them into estimates remained unclear. Furthermore, no detailed overview of all cost aspects of RCTs was provided in any of the published studies [17].

Given the sparseness of evidence at the international level, we performed a detailed retrospective assessment of our data despite the above-described limitations. The assessment is the first to address the resource use and costs of investigator-initiated RCTs fully conducted or at least initiated in Switzerland. In all of the ten RCTs with detailed full costs, the conduct phase accounted for the largest proportion of costs (median of 54% of total costs; 25th to 75th percentile range [IQR]: 40.4%-72.0%). The preparation phase ranged second (median: 26.1%; IQR: 18.9%-41.4%) and the post-conduct phase third (median 16.3%; IQR: 5.3%-24.1%). Total costs differed widely, ranging from CHF 0.1-5.0 million per RCT (see Table 2 and detailed cost listings in the Appendix, Tables S1 and S2). We also identified large differences in costs per patient, ranging from CHF 148 to CHF 20’301. For comparison, the literature review identified reports of RCT costs ranging from USD 0.2-611.5 million per RCT and from USD 43-103’254 per patient [17].

Objective 3

We aimed to compare costs and working time efforts for the RCT preparation phase, between RCTs approved by Swiss RECs in 2012 (before the LHR) and in 2016 (after the LHR). Contact details of principal investigators from all RCTs approved in 2012 and 2016 were retrieved via the ASPIRE-project. All investigators were contacted and informed by letter on the purpose of the data collection. A few days after the letter, we sent an email re-explaining the purpose. Together

with this email, the investigators received an abridged version of our cost item list developed in the context of Objective 1, covering general information and preparation phase cost items. We offered all principal investigators to assist them by phone or in person if they wished so. For RCTs approved in 2012, letters and first emails were sent during March and May 2017, and for RCTs approved in 2016, during September 2017. In case we received no reply, we sent two reminders, each approximately three weeks after the previous attempt. The principal investigators were asked to retrospectively estimate per-item working time efforts for all involved staff members during the preparation phase of their RCTs. Additionally, information on salary levels and fixed costs was requested. Due to the time lag of about five years between the approval of 2012 RCTs and our survey, recall issues were expected to be more of a problem here than in the case of the RCTs approved in 2016.

For very similar reasons as listed above in the section on Objective 2, we had difficulties to retrieve a sufficient amount of data. We received complete working time and cost data covering the preparation phase of 18 RCTs approved by Swiss RECs in 2012 and of 35 RCTs approved in 2016.

In this sample, the median working time for the preparation phase of RCTs was 113 days (IQR: 51-190 days) in 2012 and 133 days (IQR: 79-240 days) in 2016. The median estimated costs to plan and prepare an RCT were very similar: CHF 71’100 (IQR: CHF 58’400-86’100) in 2012 and CHF 71’300 (IQR: CHF 41’800-166’500) in 2016. While the results for the working time outcome appeared to indicate an increase of the required effort, the cost results did not indicate any substantial change between 2012 and 2016, for the preparation phase of RCTs. Consistent with this, ranges of costs were similar for 2012 and 2016, also at the item level (Table 9 and Table 10). Thus, selection effects may have been relatively limited despite the small numbers of RCTs for which we had data available. Still, a distortion of the observed (lack of a) cost difference by selection effects and recall problems remains a very relevant possibility, and chance effects may have influence the results substantially. RCT characteristics were partially different (Table 4). As many as 83% of the 2016 RCTs with complete preparation phase data were classified as risk category A (i.e., low risk), while there was no equivalent information for the 2012 RCTs.

Objective 4

We collected and assessed Swissmedic and REC approval times for 2012 and 2016. For RCTs approved in 2012, REC approval times were extracted directly from the REC records for each RCT. Under the new LHR, corresponding data for 2016 were directly provided through the newly introduced Business Administration System for Ethics Committees (BASEC). For multicentre RCTs, it was planned to collect approval times from all Swiss RECs, together with an identification of lead REC and non-lead RECs. However, in 2012 we could not distinguish between lead RECs

and non-lead RECs while in 2016 we received approval times from all lead RECs. We also contacted Swissmedic and requested approval times for all RCTs submitted in 2012 and 2016. Swissmedic provided us with lists covering clinical trials submitted for approval in 2012 and in 2016. The lists contained the dates of receipt of a dossier, of acknowledgement of receipt, and of the Swissmedic decision. Primarily, we calculated times from submission to approval that included the response time of the respective authority as well as any time the sponsor needed to respond to the authority's questions and additional requests. Reaction times of sponsors were available from the Swissmedic data and from the REC data for 2016 extracted from BASEC, but not from the REC data for 2012. Hence, approval times excluding sponsor reaction times could be calculated for Swissmedic but not for the RECs.

Across all eligible RCTs, median REC approval time was 72 days (n=183) in 2012 and 109 days (n=217) in 2016. However, these results are not directly comparable due to different use of lead REC procedures in 2012 and 2016 and lack of related, detailed information for 2012. A more valid comparison was possible at the level of single centre RCTs. Here, observed approval times were also shorter in 2012 (median: 82 days; IQR: 49-107 days; n=38) than in 2016 (median: 92 days; IQR: 65-131 days; n=63), although the difference was less pronounced than for all eligible RCTs. For all considered subgroups of trials, the difference went into the same direction (i.e. higher approval times in 2016) and was also visible in the times until first REC response (see Tables 12-14). As stated above, these observed approval times included any time the sponsors needed to respond to questions and requests.

Median Swissmedic approval times from for 'any clinical trials' (of which, according to Swissmedic, the vast majority were RCTs; there may have been, e.g., some non-randomised or single arm trials) were 27 days (IQR: 19.0-50.5 days; n=213) in 2012 and 49 days (IQR: 36.0-67.0 days; n=179) in 2016. When the times which sponsors needed for requested amendments were subtracted from the Swissmedic approval times, the median duration was 25.0 days (IQR: 33.0-38.0 days) in 2012 and 36.0 days (IQR: 33.0-38.0 days) in 2016. Of note, under the new LHR, RCTs falling in the lowest risk category A do not require Swissmedic approval. For the year 2012, before the enactment of the LHR, no such risk categorisation was available. Hence, the Swissmedic approval times for 2012 and 2016 cannot be assumed to apply to the same 'population' of RCTs, limiting comparability. The smaller number of applications to Swissmedic and the longer Swissmedic approval times in 2016 may both be a consequence of the exemption of low risk RCTs from Swissmedic approval. The remaining, higher risk RCTs may require more time than was required earlier, on average. More generally, changes in approval times may also have occurred due to general differences in approved studies (e.g. the proportion of industry funded RCTs was higher in 2016 compared to 2012; Table 12).

Combined Swissmedic and REC approval times could not be assessed, as the information from Swissmedic did not allow us to distinguish RCTs from other clinical trials and match Swissmedic and REC approval time data at the RCT level. Thus, we have no means to tell if combined approval times in 2016 may have been shorter than in 2012, due to the possibility of parallel submission under the new LHR. The number of Swissmedic approvals was lower in 2016, which may be due to the fact that low risk clinical trials do no longer require Swissmedic approval, as stated above. The number of RCTs approved by Swiss RECs was slightly higher in 2016 (345 RCTs) than in 2012 (324 RCTs). The approval of 149 multicentre trials in 2016 involved 2.4 RECs on average.

Issues affecting the collection of cost information for RCTs

Some additional details on the issues affecting the collection of cost information for RCTs may be of interest for future research and evaluation projects.

- None of the addressed companies provided full cost data for Objective 2. For example, after several inquiries with legal departments, access to costing data was denied by one company for reasons of confidentiality, while resource limitations and the complexity of internal costing structures were the stated reason for denial at a second company. Interpharma stated that the accounting structures at large pharmaceutical companies may not allow for the collection of unit costs per study. The data we received from industry respondents in the context of Objective 3 were also often incomplete. It was stated that not all required resources could be estimated retrospectively.
- For investigator-initiated RCTs it became evident that costs of RCTs are not routinely collected by academic investigators. Furthermore, many investigators abstained from contributing data due to the time efforts they feared. As academic CTUs are not involved in the costing of entire RCTs, but rather cover single aspects with their services, actual costs of entire RCTs could not be obtained from CTUs either. Another reason were outdated contact information (especially for RCTs approved 2012) as email addresses and letters could not be delivered in a number of cases, or we received responses that the main responsible person had left, retired or deceased. In some cases, we received messages that a study was never initiated or that the preparation phase was still ongoing.
- Furthermore, the cost data that we received were in heterogeneous formats, despite the cost item list that we provided to the addressed investigators and institutions.

Concluding remarks

We aimed to approach the question of a cost impact of the new LHR on RCT costs in four steps. In the first preparatory step, we created a comprehensive list of standard cost items for RCTs that can be used as a tool to assess and collect resource use and cost data for RCTs.

The second and third step involved the collection of RCT cost data. It proved to be impossible to retrieve a satisfactory amount of valid cost information for RCTs, despite massive efforts. Clearly, cost data for RCTs are not routinely collected. Therefore, working efforts had to be estimated retrospectively which was time consuming and most likely highly imprecise. This as well as problems of availability, recall problems and confidentiality issues were reasons for the overall low participation of principle investigators. Ultimately, we only received a relatively small sample of sets of full RCT cost data, which were all from non-industry RCTs. In addition, the sample of sets of preparation costs for RCTs collected for Objective 3 was also much smaller than anticipated and stemmed mainly from non-industry RCTs. A systematic review indicated that empirical and publicly available resource use and cost data for RCTs are also very sparse internationally.

The data gave no indication of a substantial change of RCT preparation costs between 2012 and 2016. However, due to the limited sample size and related risks of bias and chance effects, the data should be interpreted with caution. In the empirical approach taken and given the sparseness of data, there was no means of validly subdividing preparation costs further into elements where the LHR may have had a stronger *versus* weaker (or no) impact. A cost impact of the LHR on the costs of the other trial phases could not be excluded either.

Accessible data on REC and Swissmedic approval times for RCTs were substantially limited. The lack of risk categorisation in clinical trials submitted for approval in 2012 affected the comparability of Swissmedic approval times between 2012 and 2016. In addition, RECs and Swissmedic did not use a joint study identifier. This made it impossible to consistently assess approval history at the combined REC and Swissmedic levels. This issue might be overcome in the future, e.g. if Swissmedic also used the study identification numbers assigned in BASEC. REC and Swissmedic approval times appeared to be longer in 2016 compared to 2012. However, due to the described limitations, the situation at Swissmedic could not be judged in a valid way. Combined approval times, which the data did not allow us to assess, may still have been shorter due to the possibility of parallel submission under the new LHR.

The discrepancy between reports of high RCTs costs, often used in discussions on healthcare costs and pricing, and the lack of transparent and valid evidence on the topic remains striking. Tools to budget and manage costs in the academic setting are urgently needed, and we believe that without budgeting and tracking costs efficiently, clinical research will risk to stay unsustainable [16] and prone to failure [18]. Stakeholders who are able to influence the planning and the design of academic RCTs, such as for example national funding agencies, should consider more emphasis on well-planned *a priori* feasibility assessments and well thought-through budgets. Further tools to monitor costs of RCTs prospectively are needed to acquire more data with higher accuracy.

2. Introduction

2.1 Background

Randomised controlled trials (RCTs) represent the current gold standard for the evaluation of healthcare interventions. Funding sources vary from country to country, but in developed countries funding opportunities exist at several levels: national/federal (non-profit/public), regional (private and non-profit/public), and international. In 2000, nearly 75% of all RCTs in the U.S. were funded by industry sponsors [19].

Over the last decades, the complexity of RCTs and regulatory requirements for their conduct have increased internationally. Related initiatives have been designed to protect research participants and improve research quality. Reportedly, they have also led to increased administrative burden, delays in time to approval and higher costs associated with conducting RCTs [5-7, 9]. In parallel to increased funding expenditure for RCTs, a 7.5% annual increase in study costs has been recorded above the rate of inflation [9]. The RCT-associated costs for non-clinical activities were estimated to amount to approximately USD 2'000 per subject in 2002, for an industry-sponsored RCT (oncology) in the U.S. [20]. For similar RCTs at academic and cancer centres or group practices, non-clinical costs were estimated at USD 4'000 or USD 1'400 per subject, respectively [20]. In the clinically and economically important area of drug development, the clinical phase is supposed to account for the highest proportion of expenses [8, 21], with specifically high costs for RCTs [16].

A European Union-wide study of the *Impact on Clinical Research of the European Legislation* (ICREL) in 2009 concluded that simplification and harmonisation of the clinical trial authorisation process by the competent authorities would facilitate and reduce the administrative burden, save time, expertise, and especially costs in multinational trials [22]. Further critical factors known to affect the costs of clinical studies include personnel costs (e.g. study nurses, investigator, monitoring) which in turn are dependent on and influenced by the duration of the study (e.g. affected by slow recruitment). Practices identified to dampen the costs of RCTs include streamlining clinical trial operations, using computer systems to improve site management, and improving the efficiency of patient recruitment [7, 11]. Furthermore, optimising the efficiency and cost of data monitoring was considered, by focusing on the most critical aspects of a clinical trial [23-25]. Regulatory authorities such as the U.S. Food and Drug Administration (FDA) [26] or the European Medicines Agency (EMA) [27], analysed the need for risk-based approaches and released guidance documents for industry.

2.2 The Swiss Human Research Legislation

The regulatory framework for clinical research in Switzerland has considerably changed. In January 2014, the enactment of the new law on research with human beings (Human Research Act, HRA) and its ordinances (Swiss Legislation on Human Research, LHR) was conceived as a major step forward to create favourable research conditions in Switzerland. The purpose of this Act is not only to protect the dignity, privacy and health of human beings involved in research, but should also help to ensure the quality of research and create transparency [1, 2]. Furthermore, it is designed to create favourable conditions for clinical research in Switzerland by introducing a regulatory system proportionate to the relative risk of each individual project. There is agreement that with the introduction of the LHR, additional administrative expenses may occur for some types or parts of clinical studies (e.g. study registration, insurance liability, or clarification of study risk category). At the same time, improvements for research conduct may have been achieved by introducing the parallel submission process to research ethics committees (RECs) and competent authorities as well as the lead ethics committee process which should reduce approval time for new study protocols and alleviate inter-regional differences between RECs. Furthermore, the newly introduced risk categorization should allow the differentiation of low (category A) and intermediate to high risk (categories B & C) trials, with significant facilitations for the conduct of low risk studies. For example, low risk trials do no longer require Swissmedic approval. As the low risk situation often applies to academic clinical research it is expected to improve the research environment at academic institutions in a relevant way. There are also relevant changes to approval timelines. Before the introduction of the LHR, RECs had 30 days from receipt of a study protocol to decide whether the study should be approved, revised or rejected. Swissmedic also had 30 days to request revisions, and both authorities were able to restart the deadline if revisions were necessary. Since the implementation of the new LHR, both institutions have, in parallel in case of simultaneous submission, a first phase of seven days to check if all formal requirements are met, and then an additional 30 days to decide if a study can be approved or if amendments are required. Of note, for multicentre studies which are submitted simultaneously to lead REC and non-lead RECs, this deadline is 45 instead of 30 days (i.e. 15 days for non-lead RECs to give feedback to the lead REC and then 30 days for the lead REC to come up with the final decision) [4]. Finally, the introduction of a national study registry is a major step forward in creating transparency and should increase the trust of the different stakeholders in clinical research. Key aspects around the new LHR are summarised in the following references: [1-3].

The new Swiss legislation foresees that its impact on clinical research in Switzerland should be scientifically assessed (Article 61 Humanforschungsgesetz), which makes the present study instrumental and timely. The research reported has been commissioned by the Swiss Federal Office of Public Health (SFOPH), as part of this impact assessment.

2.3 Objectives

Changes in regulatory and administrative requirements may influence the costs of RCTs. Our study intended to approach the impact of the introduction of the LHR on RCT costs in Switzerland. We aimed to approach this topic in several steps. Our specific objectives were the following:

1. To create a comprehensive standardised list of direct and indirect cost items associated with RCTs in industry and academic settings (items relevant for the preparation phase served to systematically collect cost data from selected RCTs in Objective 3).
2. To determine the unit costs for listed cost items and to evaluate the mean total costs of completed RCTs in Switzerland, stratified by sponsor (industry vs. non-industry)
3. To compare the preparation phase costs of RCTs in Switzerland before (2012) and after (2016) the introduction of the Swiss LHR, stratified by:
    - Type of sponsor (industry vs. non-industry (public/not-for-profit))
    - Type of cost (Direct vs. indirect)
    - Single-centre vs. multicentre RCTs
    - National vs. international RCTs
    - Site of RCT initiation (Switzerland vs. other)
    - LHR risk category
    - CTU involvement
4. To analyse the association of the introduction of the LHR with:
    - the time from submission to approval in individual RECs (single & multicentre RCTs)
    - the time from submission to first Swiss REC until approval for all Swiss centres (multicentre RCTs)
    - the time from submission to Swissmedic approval (LHR risk category B&C)
    - the combined approval time for Swiss REC and Swissmedic
    - the number of RCTs recruiting in Switzerland
    - the number of recruiting sites in Switzerland
    - the number of RCTs needing Swissmedic approval

The inclusion of Objective 1 was required because there is little clear information on the cost components of RCTs. In order to approach the topic of a potential impact of the LHR on RCT costs and efforts, a structured framework needed to be established. (The term 'direct cost items' associated with RCTs refers to those costs that are required to complete the work outlined in the study protocol. Direct costs may or may not be directly influenced by the number of centres or participants [10, 11]. The term 'indirect costs' refers to costs of the underlying infrastructures [11, 12].)

Within Objective 2, we aimed to gain an understanding of typical unit costs to be expected for the cost items defined in Objective 1. To generate reference points for Objective 3, we further intended to assess the costs of the RCT preparation phase before the introduction of the Swiss LHR and the relative contribution of the preparation phase to overall RCT costs. We were finally interested in overall RCT costs as a by-product, given the lack of knowledge in the field. It was not intended, however, to acquire overall costs of trials initiated after the implementation of the LHR, since most of these RCTs would not be completed by the time of our evaluation. It was not the intention of this step to directly evaluate the impact of the new LHR.

For the core before-after comparison in Objective 3, the costs of the RCT preparation phase (covering all efforts until enrolment of the first patient) were targeted. We expected that the most immediate impact of the LHR on RCT costs, if any, would occur in this phase, due to the new rules regarding administrative authorisation and ethical approval. The costs of the conduct and post-conduct phases might also be affected by the LHR but in a more indirect way with additional influencing factors that could complicate the interpretation of any data. Trials approved in the years 2012 (2 years before the enactment of the LHR) and 2016 (2 years after the enactment of the LHR) were studied to achieve synergies with the parallel, ongoing *Adherence to SPIrit REcommendations* (ASPIRE) project. ASPIRE evaluated the reporting quality of RCT protocols according to the SPIRIT guideline [13, 14]. The ASPIRE project included protocols of RCTs that were approved by a Swiss RECs in 2012 or 2016. It was assumed that two years around the LHR would be a sufficient time period to observe first effects of the new legislation.

Approval times for randomised trials may have relevant implications for RCT working time requirements and preparation phase costs. In Objective 4, we intended to compare approval times as the new legislation aimed to accelerate these. To facilitate comparison with effects on RCT preparation costs, RCTs were studied if they entered the approval process in 2012 and 2016.

3. Methods

The relationship of our objectives and corresponding methodological approaches are graphically summarised in Figure 1. In short, in Objective 1 we produced a standardised list of RCT cost items by conducting a systematic literature and internet search and by including experts from industry and academia. This list was then used to assess the costs of Swiss RCTs (Objective 2) and the planning and preparation costs of RCTs that were approved by Swiss RECs in 2012 and 2016 (Objective 3). Where we received planning and preparation cost data, we also asked for full RCT costs to receive more data for Objective 2 (only applicable to RCTs that were approved in 2012). In Objective 4, we compared approval times received from RECs, Swissmedic and, as an additional source included at a later stage of study conduct, Interpharma. Methodological details per objective are described in the next sections.

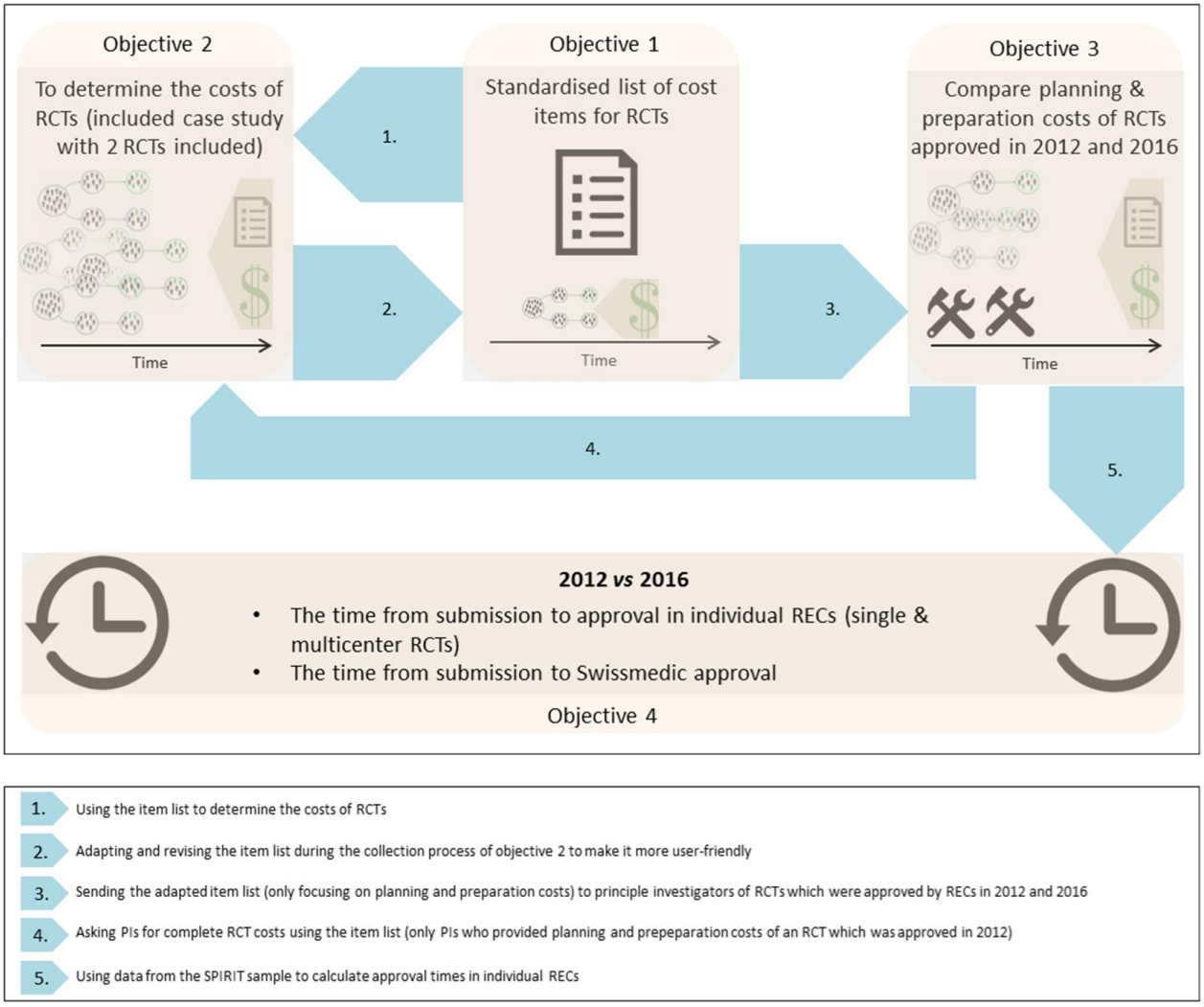

Figure 1. Overview of Objectives I-IV and corresponding methodological approaches.
Abbreviations: RCT= randomised controlled trial; REC= research ethics committee.

3.1 Approach for Objective 1

The types of costs associated with an RCT can be divided into direct and indirect costs. Direct study costs include those required to complete the work outlined in the protocol. These can be further subdivided into fixed costs related to the cost of supporting the study and variable costs related directly to the sample size of the study [10, 11]. Variable costs are commonly underestimated as only one-third of patients screened for a study actually enrol [28, 29]. The indirect costs associated with an RCT are related to the infrastructure and are calculated as a percentage of the total direct costs [11, 12].

Based on a systematic literature review (MEDLINE / EMBASE / EconLit), a systematic search of the internet (websites and linked information), and templates from two institutions conducting clinical research in Switzerland (one industry, one not-for-profit), a comprehensive, standardised list of direct and indirect cost items associated with RCTs was compiled.

Whilst collecting data for the standardised cost items list, potential expert names for the validation of the list and the completion of Objective 2 were recorded.

For validation, this list was circulated among six experts from the pharmaceutical industry and five experts from academia. We received input, adaptations and additions to our list from four and three experts, respectively. The suggestions were discussed amongst the study team and adaptations to the item list were made where applicable. After compilation of the final item list, the aim was to create an adaptable tool (template) which may be used for various types and settings of clinical research studies. Therefore, all cost items were structured through iterative discussions amongst the investigators, and functionalities (e.g. automatic calculation of staff rates x hours in costing sheets etc.) were introduced. For completeness, a short instruction manual as well as a glossary for important template terminology were developed.

3.1.1 Systematic literature review

A systematic literature search of MEDLINE and EMBASE via the Ovid interface and EconLit was designed and conducted on Tuesday 3rd November 2015. Our search was not restricted in terms of language, publication type, or publication date. Before starting the systematic literature review, we thoroughly discussed the search strategy, tested the results based on a subset of hits and improved the search criteria in order to obtain more relevant and less irrelevant hits. The final search strategy is described in Appendix A. On this basis, the above-listed databases were searched.

During the initial review of titles and abstract level, we included any articles

a. Indicating the stratification of costs related to RCTs into different costing groups and/or specific cost items.

b. Describing the development and implementation of RCT budget templates and budgeting tools.

c. Discussing a single RCT-related costing group (e.g. study development, study implementation), as long as this was the overall *topic* of the article according to the abstract/title and this costing group was considered an integral part of the overall study costs.

At full text level, we considered all articles providing specific cost items of RCTs.

We excluded any articles that focused on i) animal research, ii) hospital / health care costs and iii) cost-benefit analyses.

Whenever studies mentioned websites and/or additional documents provided via the internet, we flagged the articles and checked the information during the systematic internet search process.

All relevant cost items related to RCTs based on the systematic literature review were gathered and incorporated in an electronic shared database (googledocs.com).

3.1.2 Systematic internet search

In addition to the systematic literature review, we systematically searched for direct and indirect cost items associated with all phases of an RCT (i.e. planning and preparation, conduct, analysis, reporting) by systematically screening websites (and any linked information) of various stakeholders involved in clinical research. Stakeholders mostly included governmental bodies, academic research organizations, and funding agencies. Websites were identified through search engines using the keywords “clinical trial”, “randomised controlled trial”, “RCT”, or “clinical research” and “cost”, “costing“, “cost items”, “budget”, “budget template”.

Cost items associated with RCTs were extracted and compiled in an electronic, shared database (googledocs.com) together with the findings from the literature review. All websites / documents were searched for cost items until no additional items emerged, following the principle of saturation. A list of all relevant websites is provided in Appendix B.

3.1.3 Templates used by Swiss institutions

In addition to the systematic searches, two of the interviewed experts provided RCT budget templates from institutions involved in clinical research in Switzerland (one industry / one not-for-profit). Cost items were extracted and added until no new items emerged.

3.1.4 Adapting the standardised cost item list

In a case study conducted as part of Objective 2 [15] (i.e. collecting cost data from completed RCTs), the standardised cost item list was applied to assess the resource use and costs of two RCTs from our close network. We noted during the conduct of semi-structured interviews that the item list was comprehensive, but not very user-friendly. Therefore, we adapted the item list, omitting some highly specific items and structuring it into three parts reflecting three phases of RCT conduct: the *trial conception, planning and preparation phase* (preparation phase), the *patient enrolment, treatment and follow-up* phase (conduct phase), and the *data analysis, interpretation, and reporting* phase (post-conduct phase).

The preparation phase includes items that are required from the initial idea and planning of the RCT until enrolment of the first patient. This refers to items that are related to (i) the development of protocols and forms (e.g. preparation of the research protocol or grant proposals, ethics committee applications, development of the investigational brochure and case report forms, statistical analysis and data management plan), (ii) budgeting, (iii) communication tasks (e.g. with funders, authorities, study sites, stakeholders), (iv) staff training, (v) study site set-up and management (e.g. initiation visit, set-up of trial master and investigator site files, coordination, preparation), (vi) database set-up (e.g. development and testing of data entry system), and (vii) biobank set-up.

The conduct phase starts with the enrolment of the first patient and lasts until the last follow-up visit of the last patient. Typical cost items that fall in this phase are (i) (pre-)screening activities (e.g. identification of eligible patients, screening, time for clinical services with the purpose of screening), (ii) preparation of patient-specific documents, (iii) informed consent process, (iv) randomisation, (v) obtaining baseline characteristics, (vi) application of intervention, (vii) application of control, (viii) outcome assessment, (ix) source data completion and transfer, (x) patient follow-up, (xi) assessment, treatment and reporting of adverse events, and (xii) specimen collection, processing and analysis.

The post-conduct phase follows after the last follow-up visit of the last patient and continues until the main results of the study are reported, published and presented. This phase includes (i) data cleaning and management, (ii) statistical analysis, (iii) presentation of results (e.g. abstract writing

and submission, preparation of presentations, time spend at conferences/meetings), (iv) publication (e.g. manuscript preparation, submission, revision, proof reading), (v) biospecimen storage or destruction, and (vi) reporting to sites, funding agencies and authorities.

3.2. Approach for Objective 2

3.2.1 Overview

In order to determine the range of *unit costs and staff costs* associated with the individual cost items and the *average costs* associated with the preparation, conduct, and analysis of RCTs, we contacted and aimed to perform surveys of experts from academia, industry, clinical trial units, contract research organisations, clinical research organisations involved in the cost aspects of RCTs conducted in Switzerland (including Roche Pharma Schweiz, Roche International, Novartis Pharma Schweiz, Novartis International, Department of Medicines Research and CRO at the Swiss Tropical and Public Health Institute (Swiss TPH), clinical research consulting firms, the Swiss Association of Pharmaceutical Professionals (SwAPP), the Swiss Clinical Trial Organisation (SCTO), Interpharma, the Swiss Group for Clinical Cancer Research (Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung, SAKK), the Clinical Trial Units Basel, Bern, and Zurich, and investigators at the respective institutions). Moreover, we re-contacted investigators who provided us with preparation phase costs (see Objective 3) and were in charge of an RCT approved by a Swiss REC in 2012, two years before the new LHR came into force. We asked if they would provide their complete RCT cost data (including conduct phase and post-conduct phase costs) in order to broaden our data basis. For RCTs approved in 2016, we did not ask for complete RCT costs because the vast majority of these trials were still ongoing.

Additionally, we conducted a systematic review to provide an overview of the published available evidence on the resource use and costs for RCTs. This systematic review was not pre-specified within our study protocol for this project. However, in our opinion this work complements our assessment of overall RCT costs and is therefore included in the reporting on Objective 2.

3.2.2 Resource and associated cost estimations

In a preparatory step, we developed a detailed item list of all resources (e.g. human resources, materials, infrastructure) associated with RCTs which was reviewed by experts from academia as described in section *"3.1 Approach for Objective 1"*. We then stratified all items by study phases, i.e. preparation phase, conduct phase or post-conduct phase. *Additional costs* were

considered separately. In all categories, we divided costs into (i) costs associated with human resources ("salary costs") based on the hours worked multiplied by the respective staff salary per hour; and (ii) "other costs" including fixed priced items such as laboratory materials, approval fees, etc. In the work on Objective 2, only cost items that were applicable to a particular study (based on study protocol, flow chart, and semi-structured interviews) were collected. Figure 2 exemplifies the employed items of a cost and resource use evaluation based on two studies (the Prednisone and the Oxantel Trial) as reported in Speich et al. [15].

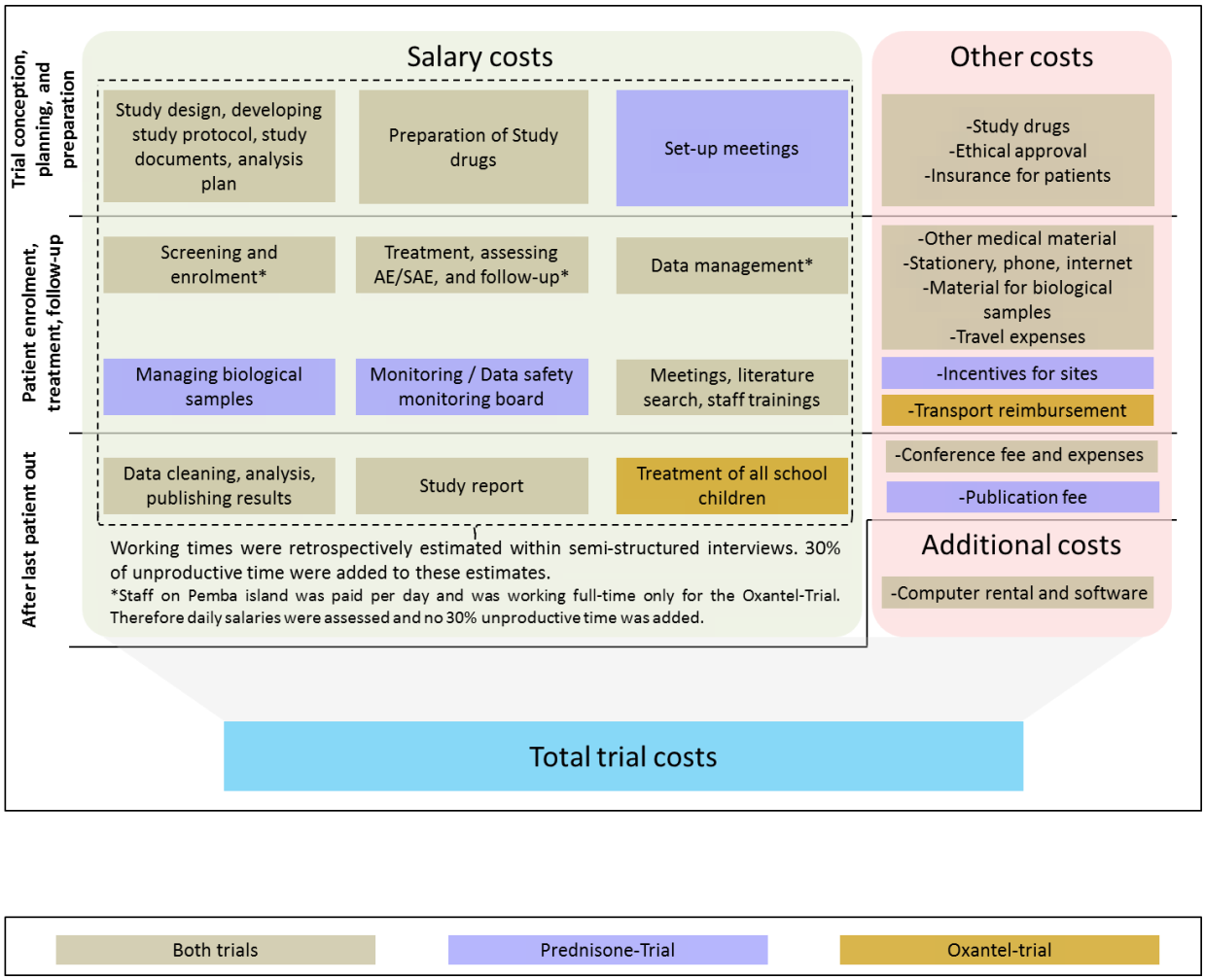

Figure 2. Example of categories of cost and resource use evaluation used with two randomised clinical trials, the Prednisone* and the Oxantel Trial*.

* More details regarding the Prednison and the Oxantel Trial are provided in 3.2.6, the Appendix (Tables S1 and S2) and [8].

Abbreviations: AE=Adverse events; SAE=Serious adverse events.

Reprinted from the Journal of Clinical Epidemiology; 2017 Dec 29. pii: S0895-4356(17)30883-1; Speich B, von Niederhäusern B, Blum CA, Keiser J, Schur N, Fürst T, Kasenda B, Christ-Crain M, Hemkens LG, Pauli-Magnus C, Schwenkglenks M, Briel M; MAking Randomised Trials Affordable (MARTA) Group. Retrospective assessment of resource use and costs in two investigator-initiated randomised trials exemplified a comprehensive cost item list. Epub ahead of print, with permission from Elsevier.

3.2.3 Human resources

Whenever possible, human resource use was retrospectively estimated based on available time log sheets and by conducting structured interviews with study staff. Within the structured

interviews, we used our pre-specified cost item list to cover all relevant working steps and asked the involved persons what time effort (hours, working days) they had spent on each step of their study (e.g. preparation of specific documents, meeting time, organising patient insurance, screening patient, enrolling patient, data management, statistical analysis, publishing results). Moreover, the interviewed persons explained all their tasks within the study to assess if additional working time from other, none listed tasks, had to be considered. To account for non-included time, unforeseen tasks (e.g. walking between patients or buildings, discussing study) and unproductive phases, we added 30% of non-pre-specified time to each item which was retrospectively estimated [30].

Of note, we expected that it would not be possible to assess the use of human resources in an identical way for all RCTs. For example, depending on the documentation quality of logged hours and number of centres and staff involved, data had to be estimated for co-investigating centres based on the resource use at main coordinating centre, or central study staff had to estimate resource use for staff at collaborating sites.

Furthermore, the cost data provided by the SAKK were exported from an internal cost and resource management system, and are therefore not in the same format as our cost item list. While the hours worked by central SAKK staff were individually listed, costs associated with the clinical sites are only depicted as “fees per patient” or lump sums. These data are reported in this report as provided by the SAKK.

3.2.4 Human resources translated into salary costs

Salary tables from the relevant institutions, for the time periods when the RCTs were conducted, were used to calculate total salary costs (including social benefits) based on human resource estimates. In detail, we used (i) daily salaries or (ii) hourly salary rates, taking into account varying target hours per day depending on position of medical staff for all resource use in Switzerland, and other countries. In the standardised cost data collection an overall 20% overhead was added independent where the study was conducted. For our case study [15], overhead rates of 25% for the University Hospital Basel, 20% for the Public Health Laboratory on Pemba Island, and 15% for the Swiss Tropical and Public Health Institute were applied. Resources (staff times) and costs were tabulated as working days and associated costs.

3.2.5 Other resources and costs

To evaluate other costs, we listed all expenditures which were explicitly made for the RCTs under study, including fees (e.g. for ethical approval, trial registration, publication), expenses (e.g. for study drugs), reimbursements for participants, infrastructure costs (e.g. for car, freezer), service costs (e.g. for tests performed by the hospital laboratory) and material costs (e.g. for medical material, laboratory material, stationery). The vast majority of these costs could easily be assessed from bills or financial reports (e.g. to a public funding agency).

3.2.6 Analyses

The overall costs and costs per patient were presented for all RCTs separately. Furthermore, mean and median costs (including 25^{th} to 75^{th} percentile range [IQR], minimum [min] and maximum [max]), costs per patient as well as costs per site were calculated for all RCTs with completed patient recruitment. In a number of additional analyses we calculated the RCT costs (i) excluding the most expensive and the cheapest RCT to capture the impact of mature outliers; (ii) excluding the RCTs for which we had not received salary information; and (iii) including only RCTs with completed recruitment. Two subgroups of (iv) only RCTs that were entirely conducted at Swiss sites and of (v) RCTs in oncology (data provided by the SAKK) were also analysed separately. We listed, for all RCTs separately, how high proportional expenditures were for the three pre-defined main phases of RCT conduct (preparation phase, conduct phase, and post-conduct phase). The resource use and specific per-item-costs of two RCTs (the Prednisone and the Oxantel Trial) with full details available were listed and categorised (see Appendix, Tables S1 and S2 and [15]). For those two RCTs we presented associated costs and proportional contributions to the total costs (to the extent data quality allowed for this).

3.2.7 Systematic review

For the systematic review, Medline, EMBASE and HealthSTAR were systematically searched for studies which included empirical resource use data or cost data for RCTs. Eligible articles were assigned to one of four categories: (i) articles presenting resource and cost data for all aspects of an entire RCT (including preparation phase, conduct phase, and post-conduct phase; (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). For the overall costs of RCTs we decided to present

the published cost data as well as costs converted into USD 2017. Further details are reported in Speich et al. [17].

3.3 Approach for Objective 3

3.3.1 Sample

The parallel, ongoing ASPIRE project evaluated the reporting quality of study protocols for RCTs according to the SPIRIT guideline [13, 14]. The ASPIRE project included protocols of RCTs that were approved in 2012 or 2016, two years before and after the introduction of the LHR, by a Swiss REC. RCTs were defined as a prospective study in which patients, or groups of patients, were assigned to one or more interventions to evaluate their effects on health outcomes. Only clinical trials that allocated participants prospectively and concurrently to comparison groups using truly random allocation were included. Eligible RCTs had to evaluate an Investigational Medicinal Product (IMP) and to compare it with placebo, a sham intervention, another active intervention or no intervention or combinations thereof.

ASPIRE excluded studies primarily evaluating pharmacokinetics or physiology (e.g. studies with healthy volunteers), or health economics, as well as animal studies, tissue banking, observational studies, studies involving only qualitative methods, and studies using a quasi-random method of allocation (such as alternation, date of birth, or case record number). Pilot studies, dose finding studies and studies with healthy volunteers were excluded as well. These exclusion criteria were chosen to achieve a sufficient degree of comparability among included RCTs.

For each RCT, ASPIRE recorded information on the general trial characteristics including investigator names, sponsor, funding source, medical specialty field, type of intervention, type of patients, number of patients, number of study centres, number of involved countries, site of study initiation (Switzerland vs. other) and the LHR risk category (available only for study protocols approved in 2016). The LHR risk categories (A, B and C) were newly introduced with the LHR in January 2014 taking into account the risk for the patients and RCT complexity (A: lowest risk; C: highest risk) [31]

Based on ASPIRE, we planned to receive cost data for 54 RCTs approved in 2012 and for another 54 approved in 2016. In a first step, we first contacted 54 investigators of RCTs approved in 2012. Our planning was to contact, in a next round, as many investigators as RCTs with cost data would be missing, and to repeat the procedure until the sample size of 54 would be reached. However, as the participation of investigators was smaller than anticipated, we contacted all investigators from all approved RCTs in 2012 and 2016, as identified within the ASPIRE project.

3.3.2 Collecting preparation costs of RCTs

All investigators of the above mentioned sample were contacted and informed by letter about the purpose of the cost collection. A few days after receiving our letter, we sent all investigators an email, explaining again the purpose of the RCT cost data collection. Together with this email, they received the current version of our pre-specified item list to assess RCT costs, as developed in the frame of Objective 1. In this first step, we only sent the parts of the pre-specified item list focusing on general study information and costs associated with the preparation phase. We proposed all investigators to support in the completion of the pre-specified item list by walking them through all necessary steps over the telephone or in a personal meeting. For 2012, letters and first emails were send during March and May 2017 and for 2016, during September 2017. In case we received no answer, we send two reminders, each approximately three weeks after the previous attempt.

3.3.3 Data cleaning and data preparation

All received cost item lists filled in by investigators were checked for accuracy and completeness. The cost templates were allocated to one of the following categories:

- Complete (sponsor site)
- Incomplete (industry sponsor)
- Incomplete (non-sponsor site in a multicentre study)
- Incomplete (other reasons)

In case forms were incomplete (i.e. contained missing data which could potentially be provided by the investigators; e.g. missing fixed costs), we contacted the investigators again and asked whether the missing data could be provided. We did not re-contact investigators if only salaries were missing as these requested data was labelled as “optional”. From the forms that contained salary information the median salaries for each type of position (e.g. coordinating principal investigator, investigator, research nurse, medical staff (senior), medical staff (junior), information technology support) were calculated. Missing salaries were then imputed using the calculated median salaries. For each working time effort item in the RCT preparation phase cost item list, the total time effort was calculated (considering all included individuals contributing to the same item). To account for non-included time, unforeseen tasks (e.g. walking between patients or buildings, discussing study) and for unproductive phases, we increased the calculated working time by 30% (“non-pre-specified time”) [30]. Based on our experience from the case study [15], 20% were added to the salaries for overhead costs. If investigators reported working time efforts

and/or costs that were not part of the planning and preparation phase of RCTs or infrastructure costs, we excluded these items.

The total time expenditures and total costs for each cost item were then transferred, together with the obtained fixed costs, into a master file containing all data from all included RCTs. Additionally, the "Study info" from the cost-template as well as general study characteristics as recorded in the ASPIRE database (i.e. population, intervention, control group, primary outcome, sponsor, if the RCT is industry or investigator initiated, single centre or multicentre, national or international, CTU involvement, site of initiation [Switzerland or other], and LHR risk category [only for 2016]) were added to the masterfile. We also included the information which of the above mentioned categories the RCT was allocated to and if salaries were provided or if calculated medians were imputed.

3.3.4 Analysis

Total working time and costs (median, mean, IQR, minimum and maximum) to plan and prepare an RCT in 2012 and 2016 were calculated and presented descriptively. For this main analysis we only included completely filled in cost item lists (minor missing items which could be imputed, e.g. ethical fee, were acceptable, as well as missing salary information).

We further investigated whether there were differences in total costs and working time estimates with respect to the following characteristics:

- Type of sponsor (industry vs. non-industry (public/not-for-profit))
- Single-centre vs. multicentre RCTs
- National (Swiss) multicentre vs. international multicentre RCTs
- CTU involvement
- LHR risk category

Furthermore, we estimated the total costs for retrospectively estimated working efforts and fixed cost items separately. Additionally, the total working time and costs (median, mean, IQR, minimum and maximum) were calculated for each specified main category during the preparation phase (e.g. *Protocol and forms*, *Budget*, *Communication*). For these analyses we also included incomplete forms whenever possible (i.e. when they reported time efforts and costs for a given main category).

We intended to statistically compare the working time and costs to plan and prepare an RCT in Switzerland, in total and for key RCT characteristics, between 2012 and 2016. Specifically, we planned to perform statistical tests if at least two thirds of the anticipated number of complete

datasets for each year would be available (36/54), and/or if the number of datasets for a given key RCT characteristic (industry sponsored single centre, national multicentre and international multicentre as well as non-industry sponsored single centre, national multicentre and international multicentre) would reach nine complete datasets per time point. Given an anticipated non-normal distribution of working time and cost outcomes, it was planned to perform non-parametric two-sided Wilcoxon rank-sum tests for unpaired samples.

In sensitivity analyses, we (i) calculated results without adding 30% of non-pre-specified time; (ii) calculated results without adding 30% of non-pre-specified time and without adding 20% overhead for salaries; and (iii) excluded all studies where we needed to impute the salaries of the study personnel.

3.4 Approach for Objective 4

We planned to assess the approval times by Swiss RECs (lead RECs and non-lead RECs) and by Swissmedic in 2012 as well as in 2016. Data from RECs were collected within the frame of the ASPIRE project (for 2016: from the newly introduced Business Administration System for Ethics Committees (BASEC) system). Swissmedic data were directly requested from the authority. The next sections address the methods for the different endpoints we intended to address here. Given the sparseness of data that could be retrieved for the project, we decided to also consider Swissmedic and REC approval time information provided by Interpharma, as addressed in Section 3.4.6.

3.4.1 Time from submission to approval in individual RECs

In the above-mentioned ASPIRE project, we recorded the following information for each protocol in 2012: (i) date of submission; (ii) date of first response from REC; and (iii) date of approval by the REC. In 2016, these data were provided directly through BASEC. Pilot studies and RCTs including healthy volunteers were excluded from the analysis. For 2012 and 2016, we present mean, median, IQR, minimum and maximum for the following durations: i) time from submission until approval by the REC; (ii) time from submission until first response by REC; and (iii) time from first response until date of approval by the REC. For the studies approved in 2016 we also report the duration from receipt of the complete document pack by the REC until date of approval, excluding sponsor response times. This information was not available for 2012 studies. Additionally, we assessed if there were differences in approval times with respect to the following characteristics.

- Tertile within the year
- Type of sponsor (industry vs. non-industry (public/not-for-profit))
- Single-centre vs. multicentre RCTs
- National (Swiss) multicentre vs. international multicentre RCTs
- Risk category (A; B; C; only for RCTs approved in 2016)

Within the sample of RCTs approved in 2012, we gathered information on approval times from lead RECs and non-lead RECs, but there was unfortunately no basis to distinguish these. Therefore, the overall approval times in 2012 were not directly comparable to the overall approval times in 2016. However, for the subsample of single-centre studies each REC was necessarily the lead REC. Therefore, within this subsample, a direct comparison was possible. Times from application to approval in the subset of single centre studies were hence compared statistically using a two-sided Wilcoxon rank-sum test for unpaired samples, as the data were not normally distributed before or after the exclusion of outliers. Outliers were identified by visual inspection of boxplots.

3.4.2 Time from submission to first Swiss REC until approval for all Swiss centres (multicentre RCTs)

For multicentre RCTs, it was planned to collect approval times from all Swiss RECs, together with the identification of lead- and non-lead RECs. We planned to collect this data directly from the RECs for 2012, and to extract the same data directly from BASEC for 2016.

3.4.3 Numbers of RCTs needing Swissmedic approval, time from Swissmedic submission to approval

We contacted Swissmedic and asked for a pseudonymised list including all RCTs that were submitted for approval to Swissmedic in 2012 and 2016. We requested information on the date when an RCT was submitted for approval, duration in days until the final decision, duration in days during the decision process in which the sponsor had to answer requests from Swissmedic, type of sponsor (i.e. industry, investigator initiated RCT), single centre or multicentre RCT, and risk category (only for RCTs submitted in 2016). We excluded RCTs that had to be submitted to the Federal Office of Public Health for further evaluation.

From the provided data by Swissmedic, we calculated the median and mean time (and IQR, minimum and maximum) from submission until approval. In one scenario the time in which the sponsor had to react to specific requests by the Swissmedic was included while in another

scenario this time was excluded. Subgroup analyses by type of sponsor, single versus multicentre RCT and risk category were conducted whenever feasible.

Under the new LHR, RCTs falling in the lowest risk category A do not require Swissmedic approval. For the year 2012, before the enactment of the LHR, no such risk categorisation was available. Hence, the Swissmedic approval times for 2012 and 2016 could not be assumed to apply to the same 'population' of RCTs, limiting comparability. For this reason, no statistical testing was planned.

3.4.4 Time from submission to first Swiss REC or Swissmedic until all competent authorities (Swiss REC and Swissmedic) have approved the RCT

We aimed at matching Swissmedic and REC approval time data at the RCT level, on the basis of a joint identifier. For each RCT, the date of the first submission (either to a Swiss REC or to Swissmedic) and the date when both competent authorities approved the RCT were to be identified as a basis for the calculation and descriptive statistical analysis of joint Swissmedic and REC approval time.

3.4.5 Number of RCTs recruiting in Switzerland and number of recruiting sites in Switzerland

In the absence of reliable data on ongoing RCTs in Switzerland, we decided to use the number of approved RCTs as proxy information. In parallel, as there was no reliable information on the number of recruiting sites available, we used the number of RECs that had to approve each multicentre study as a basis for estimating the number of recruiting sites in Switzerland.

3.4.6 Approval times for RCTs collected by Interpharma

Interpharma is the association of pharmaceutical companies with research activities in Switzerland (for further information see www.interpharma.ch). To be as comprehensive as possible we also asked Interpharma to provide the above-mentioned data (i.e. time from submission to approval in individual RECs and time from submission until approval for swissmedic) for RCTs approved in 2012 and 2016, with an industry sponsor. We intended to calculate median and mean duration in days (and IQR, minimum and maximum) from submission to REC until final approval as well as median duration from submission to Swissmedic until final approval.

4. Results

4.1 Results for Objective 1

The RCT budget templates retrieved from the expert survey provided the most detailed cost item information to create the final list. Additional budget templates from industry and academia were found based on the systematic literature and internet search. The systematic literature review resulted in eight included articles which could be used to extract cost items (Figure 3). References of the articles included at full-text level as well as a list of all relevant websites are provided in Appendix B. Both the systematic internet search and literature review resulted in some supplementary cost items to complete the final list. After iterative discussions and adaptations, the final item list was structured into a costing template which should serve both a detailed, but also a coarse if applicable, costing of clinical research studies (see separate Microsoft Excel® files "*Cost item list template.xlsx*" and "*Cost item list template - simplified.xlsx*").

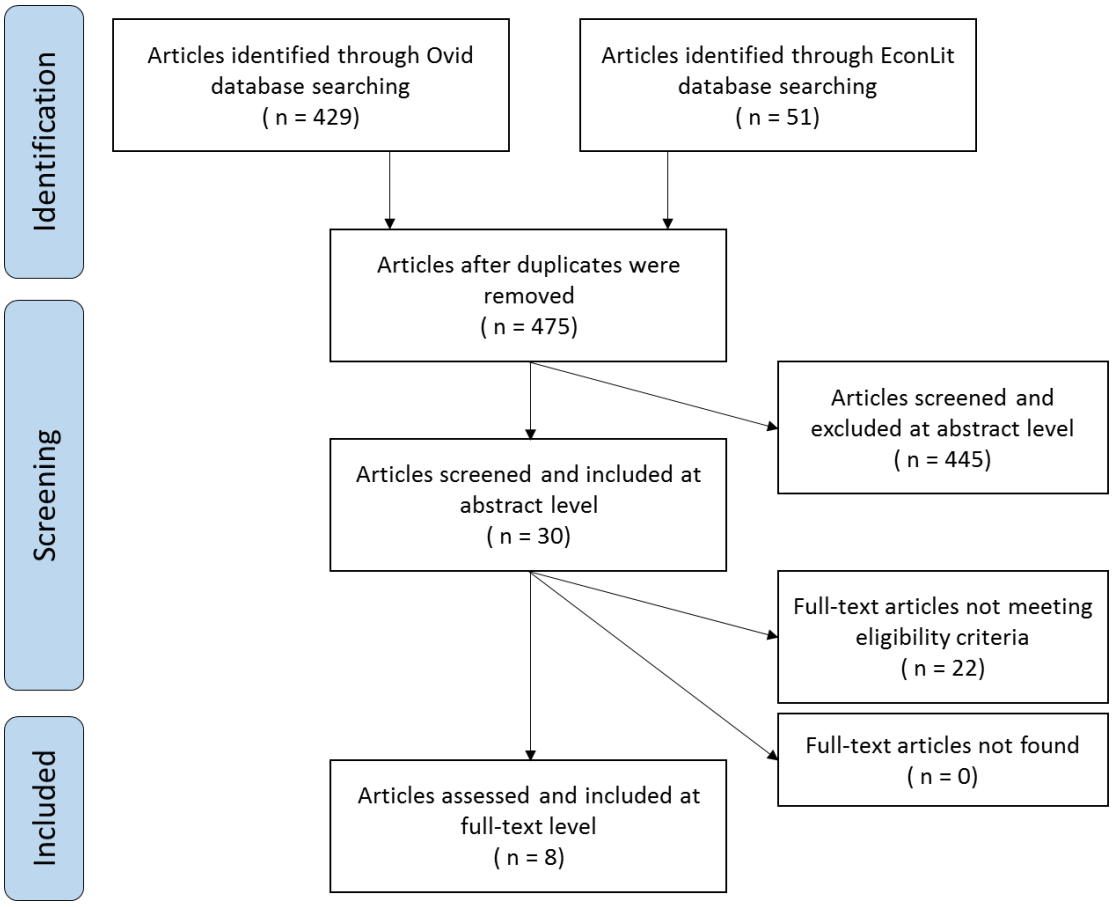

Figure 3. Overview of the systematic literature review process to identify RCT cost items.

In the comprehensive template, all collected cost items were compiled and stratified by direct costs versus indirect costs. Within the direct costs items, categories were applied as following:

- Study phase related costs
- Participant related costs
- Administrative & Training related costs
- Biospecimen related costs (e.g. storage costs)

Within the indirect cost items, users can choose between two options: 1) allowing to itemize the indirect cost items (e.g. running utilities, medical record set up etc.), 2) allowing to add a fixed percentage on top of all staff unit costs. In addition, users may choose to add a capacity building element, or to apply an inflation rate for long-lasting studies at their discretion.

The comprehensive template further contains an adaptable section on specific study information, a section for study-specific staff rates which are linked with all cost items that are costed on an hourly basis, an instruction manual, and a glossary of economic terms for simplified use.

For each cost item or work package, users can choose a responsible institution, designate the hours worked by the involved personnel, choose an item unit (e.g. hours, items, patients recruited, etc.), determine the cost per unit (in a pre-specified currency), and the total quantity of items. All total costs are calculated automatically and summarised in a final “Summary of costs”.

After adapting and revising the list during the data collection process for Objective 2, we achieved a second version that can be used by researchers to assess cost data or by clinical investigators to plan and monitor study costs.

This adapted, more user friendly version of the standardised cost item list includes most of the items from the original standardised list but contains 5 sections. In the first, as in the original item list, general study characteristics are entered. Section 2 to 4 cover the following phases of an RCT: preparation phase (section 2); conduct phase (section 3); and post-conduct phase (section 4). Within these sections, staff times for different professional groups are entered for each item and fixed costs can be entered. In section 2 and 4 working times are estimated in days while in section 3 working efforts are estimated in minutes per patient. Additionally, information about the number of patients needs to be entered in section 3 (stratified by pre-screening, screening, randomised, treated, undergoing follow-up). In the last section, staff unit costs can be entered so that time efforts from sections 2 to 4 can be translated into cost data automatically. This adapted template was used to collect planning and preparation costs of RCTs in Switzerland (Objective 3) and was partially used to collect mean total costs of RCTs conducted in Switzerland (Objective 2).

4.2 Results for Objective 2

4.2.1 Costs of completed RCTs in Switzerland

We could analyse the resource use and costs of a total of 20 investigator-initiated RCTs that were predominantly conducted in Switzerland and submitted to RECs before the new LHR (Table 1). We did not receive RCT costs data for any industry-sponsored RCTs. For eight of the 20 RCTs, data were provided by the SAKK that was the sponsor of these RCTs (oncology). The University (Hospital) Basel contributed four RCTs (1 infectiology in general practice, 1 surgery, 1 cardiology, 1 endocrinology); the Inselspital Bern contributed two (1 urology/infectiology in general practice, 1 dermatology); the Swiss Tropical and Public Health Institute (infectiology in Africa), the Kantonsspital Aarau (nutrition), and the Lausanne University Hospital (HIV vaccine) contributed one RCT each. The investigators of three RCTs requested strictly anonymised treatment of the information provided; therefore, no place of origin is presented. In another three RCTs, there was no salary information provided. Therefore, salaries were imputed based on the median salaries for equivalent positions as they were calculated from salary information provided in the context of Objective 3.

The 20 RCTs had mean total costs of CHF 1’527’890 (median: CHF 1’222’112; Table 2). Total costs ranged from CHF 93’987 for the Oxantel trial, conducted in Tanzania, to CHF 4’991‘884 for the SAKK 1 trial. Overall, the studies that had completed patient recruitment at the time of report writing included a mean total sample size of 660 patients (median: 208) and were conducted at a mean number of 18 sites (median: 15). This resulted in mean costs of CHF 221’492 (median: CHF 93’527, range: CHF 31’065-1’222’122) per site and CHF 8’367 (median: CHF 5’864, range: CHF 148-20’301) per patient.

Oncology RCTs generally had higher per patient costs than the other RCTs, independent of whether study drug costs were born by a company (n=4) or covered by the SAKK directly (n=2; Table 1). The two oncology RCTs that had the lowest costs were non-drug RCTs (SAKK 3 and SAKK 6). Considering only trials that were entirely conducted at Swiss sites, 13 RCTs had mean total costs of CHF 1'175'233 (median: CHF 612’875, range: CHF 133’925-4’991’884). The ten Swiss RCTs that had completed recruitment resulted in mean costs per site of CHF 312'594 (median: CHF 148’247, range: CHF 31’065-1’222’122) and CHF 7’482 (median: CHF 5’587, range: CHF148-19’053) per patient, respectively.

Table 1. Study characteristics and overall cost of included RCTs.

Trial Acronym	SAKK 1	SAKK 2	SAKK 3	SAKK 4
Year study conducted (first patient in to last follow-up, unless specified)	Oct. 2007 – May 2012	Dec. 2009 – Feb. 2013	Sep. 2009 – Aug. 2011	April 2010 – Dec 2013, follow up ongoing
Year study published	2015	2016	2014	Not yet published
Setting	26 centres in Switzerland	15 centres (13 in Switzerland, 1 in Hungary, 1 in Austria)	15 centres in Switzerland	57 centres (21 in Switzerland, 7 in Austria, 16 in France, 12 in Germany, 1 in Hungary)
Sample size	262	106	90	297
Population and disease	Patients with metastatic colorectal cancer	Patients with hepatocellular carcinoma	Women with metastatic breast cancer	Patients with adenocarcinoma of the Gastroesophageal Junction or esophageal cancer
Intervention and control	1) No bevacizumab continuation after completing first-line chemotherapy 2) Bevacizumab continuation after first-line chemotherapy	1) Sorafenib 2x400mg daily plus everolimus 5 mg daily 2) Sorafenib 2x400mg daily	1) Low-lipid oil-in-water cream containing aluminium chlorohydrate 2) Cream without aluminium chlorohydrate	1) Standard treatment with cetuximab 2) Standard treatment without cetuximab
Primary outcome	Time to progression	Progression-free survival at 12 weeks	First occurrence of grade 2 or 3 palmar-plantar erythrodysesthesia	Progression-free survival
Total cost in CHF without drugs (cost per patient)	**2'126'266 (8’116)**	**1’402'898 (13’235)**	**527'728 (5’864)**	**3'745'417 (12’361)**
Total cost in CHF with drugs (cost per patient)	4’991’884 (19’429)	-	-	4’372’056 (14’429)
Comments	In-kind contributions not considered*	Drug cost not coved by SAKK In-kind contributions not considered*	In-kind contributions not considered*	Follow-up ongoing In-kind contributions not considered*

Table 1 (continued)

Trial Acronym	SAKK 5	SAKK 6	SAKK 7	SAKK 8
Year study conducted	Sep. 2010 – Dec. 2012	Feb. 2011 – Apr. 2014, follow-up ongoing	Feb. 2011 – Oct. 2013, follow-up ongoing	July 2013 – Nov 2017, follow-up ongoing
Year study published	2016	Primary outcome expected 2018/2019; early adverse events 2015	Not yet published	Not yet published
Setting	22 Centres in Switzerland	24 Centres (14 in Switzerland, 8 in Germany, 2 in Belgium)	33 Centres (18 in Switzerland, 9 in Sweden, 6 in Norway)	71 Study Centres (21 in Switzerland, 37 in France, 13 in Netherlands, 1 in Germany)
Sample size	147	350	152	208 Recruitment complete, follow-up ongoing.
Population and disease	Women with metastatic or locally recurrent inoperable HER2-negative breast cancer	Men with biochemical failure after radical prostatectomy (lymph node-negative adenocarcinoma of the prostate treated with radical prostatectomy)	Patients with follicular lymphoma (stage III or IV disease OR stage II disease not suitable for radiotherapy; Grades 1, 2, or 3a disease)	Patients with breast cancer with distant metastases
Intervention and control	1) Bevacizumab every 2 weeks with i.v. paclitaxel (day 1/8/15 of a 4 week cycle) 2) Bevacizumab every 2 weeks with daily oral cyclophosphamide and capecitabine	1) 64 Gy in 32 daily fractions of 2 Gy 2) 70 Gy in 35 daily fractions of 2 Gy	1) Rituximab plus Lenalidomide 2) Rituximab	1) Chemotherapy-free dual HER2-inhibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) 2) Chemotherapy-containing dual HER2-inhibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line)
Primary outcome	Incidence of selected grade 3-5 adverse events	Freedom from biochemical progression	Complete response at week 23	Overall survival at 24 months
Total cost in CHF without drugs (cost per patient)	**1'672'934 (11'381)**	**1'550'115 (4'429)**	**2'083'987 (13'710)**	**4'222'659**
Comments	Drug cost not coved by SAKK In-kind contributions not considered*	In-kind contributions not considered*	Drug cost not coved by SAKK Follow-up ongoing In-kind contributions not considered*	Drug cost not coved by SAKK Follow-up ongoing In-kind contributions not considered*

Table 1 (continued)

Trial Acronym	Prednisone trial	Oxantel trial	Stenting trial
Year study conducted	2009 – 2014	2012	Apr. 2010 – 2012
Year study published	2015	2014	2015
Setting	Seven hospitals across Switzerland	Two schools on Pemba Island, Tanzania	8 Centres (5 in Switzerland, 1 in Germany, 1 in Austria, 1 in Denmark)
Sample size	802	480	2291
Population and disease	Adults with community-acquired pneumonia	Children 6 to 14 years of age, infected with soil-transmitted helminths (i.e. *Trichuris trichiura* and hookworm)	Unselected series of patients in need of large (>3mm) stents only in native vessels irrespective of clinical indication
Intervention and control	Prednisone Placebo	Oxantel pamoate and albendazole Oxantel pamoate Albendazole Mebendazole	Newest-generation thin-strut BMS coated with a biocompatible silicone-carbide layer (ProKinetik, Biotronik) Second-generation biolimus-A9–eluting biodegradable-polymer stainless-steel DES (Nobori, Terumo) Second-generation everolimus-eluting durable-polymer cobalt-chromium DES (Xience Prime, Abbott Vascular)
Primary outcome	Time to clinical stability (in days)	Cure rate and egg reduction rate three weeks after treatment	Freedom of combination of cardiac death (all death not clearly of extra cardiac origin and documented non-fatal MI)after 24 months
Total cost in CHF (cost per patient)	**2'181'880 (2'720)**	**93'987 (196)**	**1'879'826 (821)**
Comments	Very detailed analysis, incl. 30% non-pre-specified time for hours that were not logged Published as a case study [15]	Very detailed analysis, incl. 30% non-pre-specified time for hours that were not logged Published as a case study [15]	Large parts of costs of conduct are based on fee per patient payments, and not actual resource use. Same fee per patient for all centres (also non-Swiss). Costs for insurance could not be determined.

Table 1 (continued)

Trial Acronym	Nutrition trial	Antibiotics in urinary tract infection trial	Bullous pemphigoid trial
Year study conducted	2014 – Dec. 2017	Feb. 2012 – Feb. 2014	Feb. 2013 – Jan. 2017
Year study published	Not yet	2017	Not yet
Setting	8 hospitals in Switzerland with dieticians	17 general practices in Switzerland	3 Centres in Switzerland
Sample size	2000-3000 planned	254	32
Population and disease	Unselected adult medical inpatients at risk of undernutrition and an expected hospital stay of ≥ 5 days	Women presenting with uncomplicated lower urinary tract infections in general practice	Active Bullous Pemphigoid
Intervention and control	1) Nutritional therapy (counselling) 2) standard hospital nutrition	1) Olfen®-75 duo release (Mepha Pharma) 2x75mg for 3 days 2) Norfloxacin-Teva® 400mg (Teva) 2x400mg for 3 days as described in the product information	1) Mepolizumab 750 mg four times one month apart 2) Placebo (saline) four times one month apart
Primary outcome	Combined adverse outcome within 30 days defined as (a) all-cause mortality, (b) admission to the intensive care unit from the medical ward, (c) major complications, (d) unplanned hospital readmissions and (d) decline in functional outcome from admission to day 30 assessed by Barthel`s index (-10%)	Proportion of patients with resolution of symptoms 72 hours after initiation of treatment	Time period (in days) from start of therapy until relapse
Total cost in CHF (cost per patient)	**1'853'660**	**528'106 (2'079)**	**411'499 (15'984)**
Comments	Still ongoing, but full cost estimated based on yearly salary rates for dieticians at hospital until end of trial Costs for secondary projects not included	Including 30% non-pre-specified time for hours that were not logged	Salaries imputed from median salaries of other studies (Objective 3). Conference and publication fees unknown. Detailed analysis, incl. 30% non-pre-specified time for hours that were not logged

Table 1 (continued)

Trial Acronym	Pharmacist-led medication review in ambulatory care	HIV vaccine trial	Timing of antimicrobial prophylaxis trial	Other RCTs, anonymised (n=3)
Year study conducted	July 2012 – Apr. 2014	Aug. 2012 – Apr. 2013	Feb. 2013 – Aug 2015	2012-2017
Year study published	2016	2017	2017	-
Setting	54 Pharmacies in Switzerland	Lausanne University Hospital	University Hospital Basel and Hospital of Aarau	2 multicentre; 1 single centre
Sample size	780 planned; 450 achieved	96	5580	<100
Population and disease	Patients using at least 4 prescribed medications for longer than 3 months	Healthy volunteers (age 18-50 years) in good general health	Patients undergoing surgery with surgical antimicrobial prophylaxis indicated	-
Intervention and control	1) A pharmacist-led medication review at study start and at 28 weeks. 2) A pharmacist-led medication review at 28 weeks.	Four preventive HIV vaccine regimens	1) Early surgical antimicrobial prophylaxis (30-75 min before incision) 2) Late surgical antimicrobial prophylaxis (0-30 min before incision)	-
Primary outcome	"Change in patients' objective adherence, calculated as Medication Possession Ratio (MPR) and Daily Polypharmacy Possession Ratio (DPPR), using refill data from the pharmacies and patient information of dosing"	Safety and tolerability	Occurrence of surgical site infection within 30 days of surgery	-
Total cost in CHF (cost per patient)	**612'875 (1'362)**	**1'222'112 (12'730)**	**827'429 (148)**	**Range: 133'925-159'328** **(Range: 2'679-25'778)**
Comments	Detailed analysis, incl. 30% non-pre-specified time for hours that were not logged Study most likely discontinued (not explicitly stated)	Detailed analysis, incl. 30% non-pre-specified time for hours that were not logged Healthy, HIV uninfected individuals-	Salaries imputed from median salaries of other studies (Objective 3). Detailed analysis, incl. 30% non-pre-specified time for hours that were not logged	One out of the three trials was discontinued

* Cost data provided by the SAKK (sponsor of the RCTs) include only the funds that were provided by the SAKK. Additional in-kind contributions by the SAKK network and the investigators are not covered in these calculations. Therefore effective costs may have been higher.
Abbreviations: CHF=Swiss Francs; RCT=randomised controlled trial.

Table 2. Description of analysed randomised clinical trial costs.

Trial costs	n	Mean	Median	IQR	Min-Max*
Total trial cost (all trials)	20	1'527'890	1'222'112	411'499-2'083'987	93'987[1]-4'991'884[2]
Total trial cost (without min and max trial)[2]	18	1'408'472	1'222'112	469'614-1'981'906	133'925-4'327'056[3]
Total trial cost (excluding trials without salary information)	17	1'698'631	1'476'507	251'428-2'157'407	93'987-4'991'884[2]
Total patients enrolled (only trials with completed recruitment[4])	17	660	208	93-415	32-5580
Total sites (only trials with completed recruitment[4])	17	18	15	1.5-25	1-71
Cost per site (only trials with completed recruitment[4])	17	221'492	93'527	61'313-213'487	31'065-1'222'122
Cost per patient (only trials with completed recruitment[4])	17	8'367	5'864	2'379-13'473	148-20'301
Subgroup of RCTs that were only conducted at Swiss sites					
	n	**Mean**	**Median**	**IQR**	**Min-Max**
Total trial cost (only Swiss trials)	13	1'175'233	612'875	285'414-1'763'297	133'925-4'991'884[2]
Cost per site (only Swiss trials with completed recruitment)	10	312'594	148'247	65'827-440'630	31'065-1'222'122
Cost per patient (only Swiss trials with completed recruitment)	10	7'482	5'587	2'529-12'763	148-19'053
Subgroup of oncology trials (sponsored by SAKK)[5]					
	n	**Mean**	**Median**	**IQR**	**Min-Max**
Total trial cost (all SAKK trials)[5]	8	2'603'033	1'878'461	1'439'702-4'334'708	527'728-4'991'884[2]
Total trial costs without oncology drugs (all SAKK trials)	8	2'166'501	1'878'461	1'439'702-3'340'629	527'728-4'222'659
Cost per site (SAKK trials with completed recruitment)	8	82'583	70'315	60'393-89'321	35'182-191'996
Cost per patient (SAKK trials with completed recruitment)	8	12'837	13'473	7'243-17'970	4'429-20'301
Cost/patient without oncology drugs (SAKK trials with completed recruitment)	8	11'206	11'996	6'427-13'592	4'429-20'301

[1] Oxantel Trial, conducted in Tanzania (Table S2, Appendix)

[2] SAKK 1 trial with total costs of CHF 4'991'884, including drug costs of CHF 2'839'168 (56.9% of total cost).

[3] SAKK 4 trial with total costs of CHF 4'327'056, including drug costs of CHF 578'579 (13.3% of total cost).

[4] Target sample size reached and study completed for primary outcome measure, but follow up may still be ongoing.

[5] Two RCTs sponsored by the SAKK included drug costs, for five trials oncology drug costs were borne by a company and therefore not included in total costs. One RCT sponsored by the SAKK tested a non-drug intervention.

* Based only on RCTs where investigators did not request anonymization.

Abbreviations: IQR=Interquartile range; Max=maximum; Min=minimum; n=sample size; RCT=randomised controlled trial; SAKK=Swiss Group for Clinical Cancer Research.

As oncology RCTs are conducted in a particular setting, often including expensive drugs, and the cost data provided by the sponsor (SAKK) did not fully conform to the structure of our cost item list format, we additionally analysed this subgroup separately (Table 2). Mean total RCT costs for all SAKK trials were CHF 2'603'033 (median: CHF 1'878'461, range: CHF 527'728-4'991'884), corresponding to a mean cost per site of CHF 82'583 (median: CHF 70'315, range: CHF 35'182-191'996) and mean cost per patient of CHF 12'837 (median: CHF 13'473, range: CHF 4'429-20'301). For five RCTs sponsored by the SAKK, drug cost was completely borne by the marketing authorisation holder (SAKK 2, 3, 5, 7, 8), whereas for two, the SAKK had to purchase drugs at regular prices (SAKK 1, 4). For SAKK 4, this applied to only part of standard treatment (docetaxel). One oncology RCT assessed the effect of a supportive cream which was available at low costs (SAKK 3) while another was a radiooncology RCT comparing different radiation regimens (SAKK 6). We therefore additionally calculated total RCT costs and cost per patient for all SAKK trials without treatment costs (Table 3). Mean total RCT costs without oncology drugs resulted in CHF 2'166'501 (median: CHF 1'878'461, range: CHF 527'728-4'222'659) and mean cost per patients in CHF 11'206 (median: CHF 11'996, range: CHF 4'429-20'301). The cost data provided by the SAKK included only the funds that were provided by the SAKK. Additional in-kind contributions by the SAKK network and the investigators were not covered in these calculations. Therefore, costs may have been higher.

Table 3. Components of total costs (in %) per trial, considering ten randomised clinical trials that provided the most detailed cost data.

Trial	Components of total costs (in %) of different phases of RCTs		
	Preparation phase	Conduct phase	Post-conduct phase
Prednisone	10.1	84.2	5.6
Oxantel	26.3	44.8	28.4
Antibiotics in Urinary Tract Infection	25.9	57.7	16.4
Bullous pemphigoid	21.9	69.4	8.7
Medication review*	20.1	51.4	28.6
HIV Vaccine	15.1	79.8	5.0
Timing of antimicrobial prophylaxis	32.2	64.4	3.3
Mean anonymised 1 and anonymised 3‡	42.3	39.0	18.7

* Discontinued; recruited more than 50% or anticipated patients.
‡ Anonymised 2 was discontinued and recruited less than 20% of anticipated patients. Therefore, Anonymised 2 was excluded from the analysis.
Abbreviations: RCT= randomised controlled trial.

A total of ten RCTs provided detailed data on the different phases of RCT conduct (Table 3). Two of these RCTs were discontinued and one was excluded from the analysis because less

than 20% of the anticipated patients were recruited. The conduct phase, (i.e. *Patient enrolment, treatment, and follow-up*) was the most expensive phase in seven out of nine RCTs. The two RCTs which are only presented in an anonymised form had proportionally higher project development and preparation costs (mean of anonymised 1 and anonymised 3: 42.3%) than the other RCTs.

The cost listings of the SAKK-sponsored RCTs did not allow us to group costs into the three temporal phases that were used for the analysis of the other trials.

4.2.2 Systematic Review

A systematic review was additionally conducted with the aim to gain on understanding of the currently available evidence on resource use data and associated cost data for RCTs [17]. The results of this review are presented in detail in Speich et al. [17]. In brief, a total of 6650 identified articles were screened in duplicate. The search identified no articles which evaluated the resource use and associated costs for all aspects on an RCT (including trial conception, planning, and preparation; patient enrolment, treatment, follow up; and after last patient out). A total of 16 articles reported overall costs or costs per patient for one or multiple RCTs. The costs ranged from USD 43-103'254 per patient and USD 0.2-611.5 million per RCT. However, in twelve out of 16 articles it remained unclear how the costs data were assembled. The systematic review clearly indicated that, despite a general consensus that RCTs are expensive, published evidence is sparse and the usefulness of the currently available data is limited [17].

4.3 Results for Objective 3

4.3.1 Available data

Based on the full ASPIRE sample, investigators of a total of 228 and 285 RCTs approved in 2012 and 2016, respectively, were contacted and asked to provide us with planning and preparation costs from their RCTs (Figure 4). From the sample of RCTs initiated two years before the implementation of the LHR (2012), we received preparation and planning costs for 19 RCTs that were incomplete in one case (where all estimates of working time effort were missing). From the RCTs that were approved in 2016 (two years after implementation of the LHR), we received a total of 47 sets of preparation and planning cost data. However, of these 47 datasets, twelve were incomplete and could only be used for the evaluation of costs of

specific items. The following data were missing (multiple reasons possible): fixed costs (n=3), part of the working time effort estimates (n=9), all working time effort estimates (n=3).

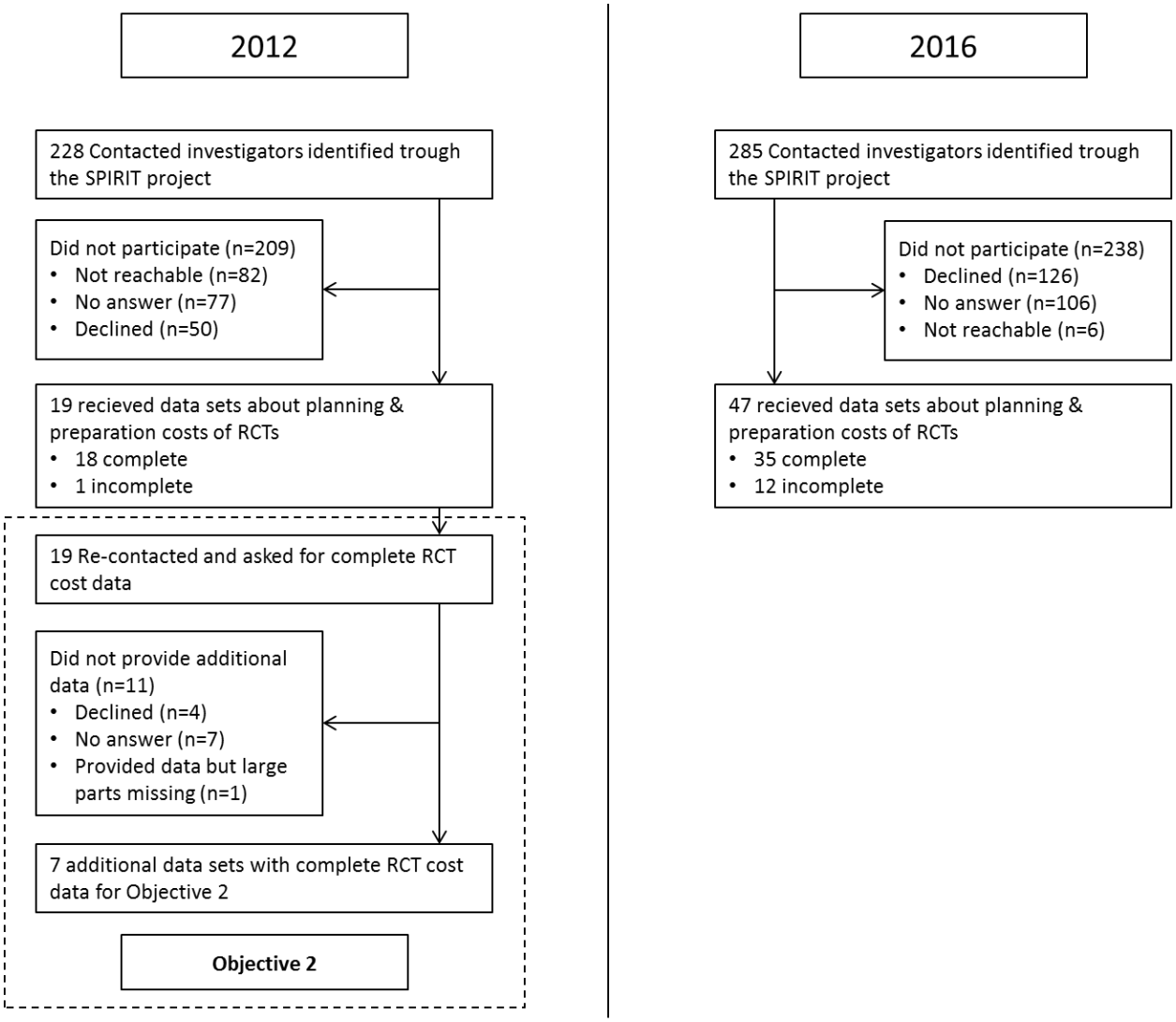

Figure 4. Flow chart summarising the collection of RCT planning and preparation costs for Objective 3 and additional full cost data for Objective 2.
Abbreviations: RCT=randomised controlled trial.

We had planned to include appropriate statistical tests to compare the situation in 2012 and 2016 if at least two thirds of the anticipated total sample size would have been reached for each year, and/or nine datasets each for a given RCT characteristic of interest. However, as the number of complete datasets was smaller (especially for the year 2012, for which we obtained only 33% of the anticipated data) and as for some RCT characteristics (such as industry sponsor and international multicentre RCTs), we did not even receive five datasets, we only prepared descriptive statistics. Given the small number of trials we received data for, any observed differences may be due to chance and selection effects (due to non-representative samples), which needs to be considered in the interpretation of the results.

4.3.2 Preparation costs of RCTs

In 2012, nine out of the 18 RCTs with complete datasets were multicentre RCTs with a median of 3 and a maximum of 70 centres (interquartile range: 2-3 centres). None of these RCTs was international (Table 4). Two RCTs were initiated by industry sponsors and 16 by non-industry sponsors. CTU involvement was reported for seven RCTs. A median planned sample size of 78 individuals was anticipated, with an interquartile range from seven to 5'000 individuals. The majority of RCTs were medical trials focussing on adult populations (aged 16 years and above), with only two trials on children (aged below 18 years) and two from the surgical area. The types of interventions were diverse and sometimes combinations of interventions were studied. Five RCTs used medical devices, four drugs, three dietary supplements, three behavioural or lifestyle interventions, education or counselling and two rehabilitation activities. Some RCTs addressed other types of interventions (e.g. surgeries, vaccines). The one RCT with incomplete data was a national multicentre RCT in children initiated by a non-industry sponsor and without CTU involvement.

For 2016, we received complete datasets for nine multicentre and 26 single centre RCTs. Multicentre RCTs, including two international RCTs, showed a median of 3 and a maximum of 7 centres (interquartile range: 2-6 centres). Four RCTs were initiated by industry sponsors and eight had CTU involvement. Most of the trials were labelled as risk category A (29 out of 35), while three RCTs each belonged to risk categories B and C (Table 4). The median sample size was 70 individuals (interquartile range: 20-496 individuals). Twenty-eight of a subset of 33 RCTs (some characteristics of three RCTs could not be obtained as these studies were excluded from the ASPIRE project) were based on adult populations, four on elderly populations and one on children. Only three RCTs were reported to be surgical trials, while 23 were medical trials. The most common types of interventions were (in descending order) drugs, behavioural interventions, devices, rehabilitation activities, and dietary supplements. Most RCTs with incomplete datasets were multicentre RCTs (ten out of twelve) and mainly initiated by industrial companies at the international level (seven RCTs). The median planned sample size was 251 individuals (interquartile range: 45-8'000 individuals). Only three of the incomplete RCTs had CTU involvement. The numbers of incomplete RCTs by risk category were similarly spread between LHR risk categories A, B and C. The majority of these RCTs focussed on adults (eight out of eleven RCTs), stemmed from the medical area (nine out of eleven RCTs) and used drugs as their intervention (seven out of eleven RCTs).

Table 4. Number of datasets received by year, completeness and categorisation.

	2012			2016		
	All data sets	**Complete datasets**	**Incomplete datasets**	**All data sets**	**Complete datasets**	**Incomplete datasets**
Total	**19**	**18**	**1**	**47**	**35**	**12**
Multicentre	10 (53%)	9 (50%)	1 (100%)	19 (40%)	9 (26%)	10 (83%)
International multicentre	1 (5%)	0 (0%)	1 (100%)	9 (19%)	2 (6%)	7 (58%)
Industry initiated	2 (11%)	2 (11%)	0 (0%)	11 (23%)	4 (11%)	7 (58%)
CTU involvement	7 (37%)	7 (39%)	0 (0%)	11 (23%)	8 (23%)	3 (25%)
Risk category A	NA	NA	NA	33 (70%)	29 (83%)	4 (33%)
Risk category B	NA	NA	NA	8 (17%)	3 (9%)	5 (42%)
Risk category C	NA	NA	NA	6 (13%)	3 (9%)	3 (25%)
Median planned sample size (IQR)	80 (7-5'000)	77.5 (7-5'000)	115 (NA)	120 (20-6'800)	70 (20-496)	251 (45-8'000)
Total*	**19**	**18**	**1**	**44**	**33**	**11**
Age: Adults (≥ 16 years)	16 (84%)	16 (89%)	0 (0%)	36 (82%)	28 (85%)	8 (73%)
Elderly (≥ 60 years)	0 (0%)	0 (0%)	0 (0%)	6 (14%)	4 (12%)	2 (18%)
Children (< 18 years)	3 (16%)	2 (11%)	1 (100%)	2 (5%)	1 (3%)	1 (9%)
Clinical area: medical	14 (74%)	14 (78%)	0 (0%)	32 (73%)	23 (70%)	9 (82%)
surgical	2 (11%)	2 (11%)	0 (0%)	3 (7%)	3 (9%)	0 (0%)
paediatrics	3 (16%)	2 (11%)	1 (100%)	1 (2%)	0 (0%)	1 (9%)
Intervention: drug	5 (26%)	4 (22%)	1 (100%)	15 (34%)	8 (24%)	7 (64%)
device	5 (26%)	5 (28%)	0 (0%)	7 (16%)	6 (18%)	1 (9%)
behavioural§	3 (16%)	3 (17%)	0 (0%)	7 (16%)	7 (21%)	0 (0%)
rehabilitation	2 (11%)	2 (11%)	0 (0%)	5 (11%)	5 (15%)	0 (0%)
dietary	3 (16%)	3 (17%)	0 (0%)	4 (9%)	4 (12%)	0 (0%)

* The RCT characteristics in the lower part of the table were retrieved from the ASPIRE project. However, three RCTs were excluded from ASPIRE data as they were not approved; hence there were no RCT characteristics available.
§ Behavioural, lifestyle, educational and/or counselling interventions.
Abbreviations: CTU=Clinical Trial Unit; IQR=inter quartile range; NA=not applicable.

The median costs of the preparation phase of RCTs in 2016 were almost the same as in 2012 (2012: CHF 71'100; 2016: CHF 71'300; Table 5) while the mean costs were 45% higher (2012: CHF 75'800; 2016: CHF 109'600; Table 5). The interquartile range based on complete RCT datasets was more than four times as wide in 2016 (CHF 124'600) than in 2012 (CHF 27'700) indicating a higher amount of variation.

The total working time effort for the preparation phase of RCTs was, in the median, 113 days in 2012 (mean: 122 days), with a minimum of 21 days, a maximum of more than 240 days and an interquartile range of 139 days (Table 6). In 2016, the preparation phase of RCTs required, in the median, 133 days (mean: 190 days), with a minimum of 38 days, a maximum of almost 1'000 days and an interquartile range of 160 days (Table 6).

Histograms presenting the distribution of costs and working time (Figure 5) of the preparation phase show that the distributions of cost and time are wider and less peaked for 2016 than for 2012.

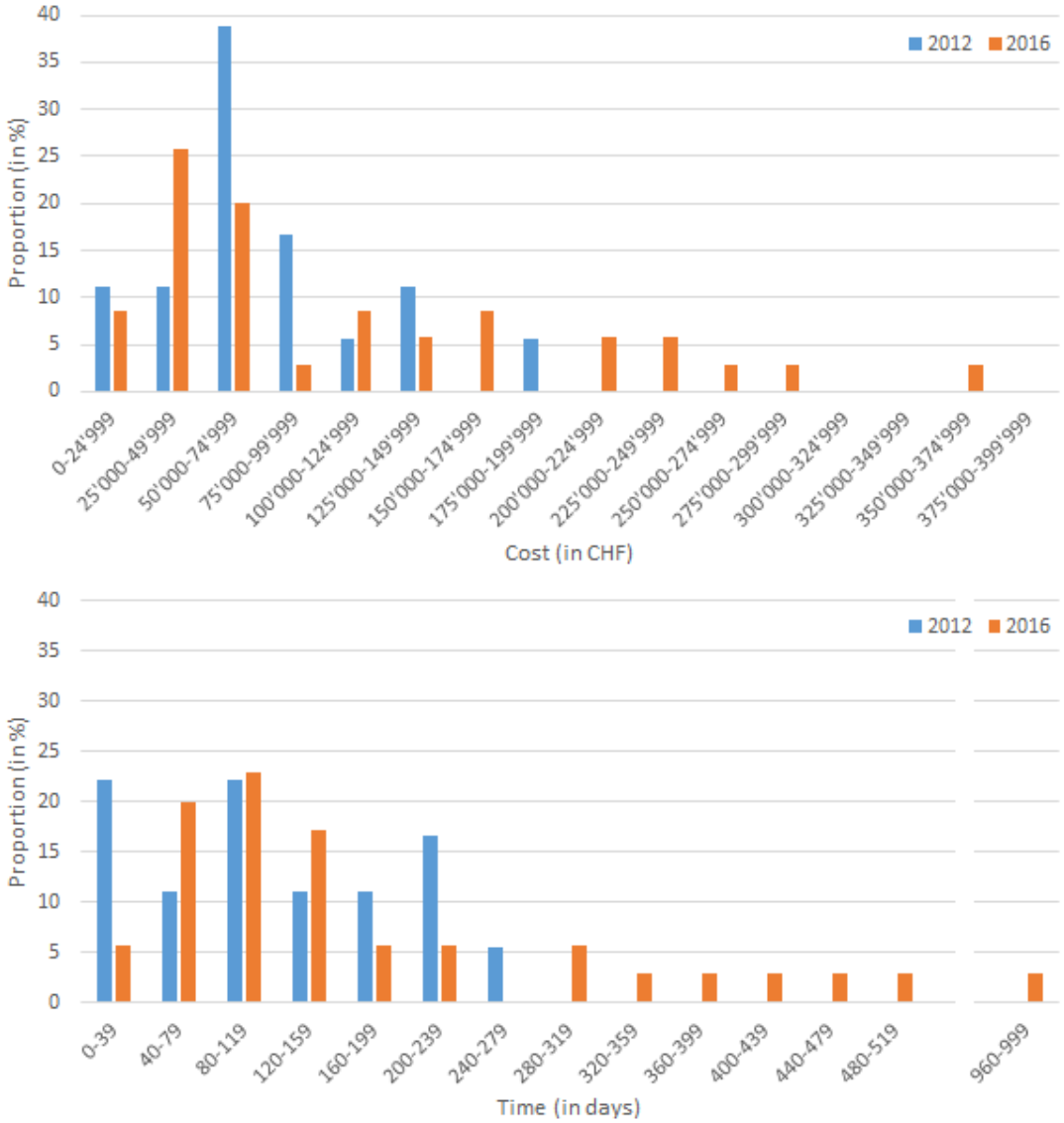

Figure 5. Histograms of costs and working time efforts of the preparation phase in 2012 and 2016, including 30% non-pre-specified working time and 20% overhead, based on complete datasets.
Abbreviations: RCT=randomised controlled trial.

Table 5. Retrospectively estimated costs prepare an RCT in 2012 and 2016, including 30% non-pre-specified working time and 20% overhead, based on complete datasets.

Costs (in CHF)	2012			2016		
	n	Median (mean)	IQR (min-max)	n	Median (mean)	IQR (min-max)
Total	18	71'129 (75'794)	58'366-86'062 (13'726-177'558)	35	71'325 (109'595)	41'845-166'492 (11'693-360'061)
Single centre	9	72'953 (77'147)	58'366-86'062 (13'726-177'558)	26	61'134 (89'749)	36'149-149'199 (11'693-255'775)
Multicentre	9	69'973 (74'441)	59'302-75'598 (37'271-132'267)	9	137'957 (166'927)	85'969-217'056 (60'961-360'061)
National	9	69'973 (74'441)	59'302-75'598 (37'271-132'267)	7	137'957 (164'454)	85'969-217'056 (71'325-360'061)
International	0	-	-	2	175'582 (175'582)	60'961-290'202 (60'961-290'202)
Non-industry	16	66'487 (75'330)	49'238-99'231 (13'726-177'558)	31	71'325 (115'610)	43'266-173'360 (11'693-360'061)
Industry	2	79'507 (79'507)	72'953-86'062 (72'953-86'062)	4	56'546 (62'977)	35'965-89'989 (31'096-107'720)
No CTU involvement	11	78'297 (86'675)	58'366-126'528 (13'726-177'558)	20	71'792 (99'272)	43'397-138'383 (28'095-255'775)
With CTU involvement	7	59'302 (58'695)	40'110-72'285 (37'271-72'953)	8	51'698 (112'072)	26'447-184'264 (11'693-360'061)
Risk category A	NA	-	-	29	72'259 (109'791)	43'266-166'492 (11'693-290'202)
Risk category B	NA	-	-	3	69'639 (150'500)	21'799-360'061 (21'799-360'061)
Risk category C	NA	-	-	3	61'552 (66'789)	31'096-107'720 (31'096-107'720)

Abbreviations: CHF=Swiss Francs; CTU=clinical trial unit; IQR=inter quartile range; max=maximum; min=minimum; NA=not applicable.

Table 6. Retrospectively estimated working time to prepare an RCT in 2012 and 2016, including 30% non-pre-specified working time and 20% overhead, based on complete datasets.

	2012			2016		
Working time (in days)	**n**	**Median (mean)**	**IQR (min-max)**	**n**	**Median (mean)**	**IQR (min-max)**
Total	18	113.1 (121.7)	51.3-189.8 (20.8-241.8)	35	132.6 (189.6)	79.3-239.2 (37.7-971.1)
Single centre	9	143.0 (132.6)	82.6-189.8 (24.1-211.9)	26	106.0 (155.7)	58.5-217.6 (37.7-458.9)
Multicentre	9	106.6 (110.7)	51.3-126.1 (20.8-241.8)	9	156.7 (287.4)	132.6-288.6 (92.3-971.1)
National	9	106.6 (110.7)	51.3-126.1 (20.8-241.8)	7	156.7 (328.6)	132.6-500.5 (107.9-971.1)
International	0	-	-	2	143.0 (143.0)	92.3-193.7 (92.3-193.7)
Non-industry	16	107.9 (112.3)	45.2-164.5 (20.8-241.8)	31	135.2 (202.7)	80.6-288.6 (39.7-971.1)
Industry	2	196.3 (196.3)	189.8-202.8 (189.8-202.8)	4	72.5 (87.9)	39.4-136.5 (37.7-169.0)
No CTU involvement	11	143.0 (143.4)	68.9-211.9 (24.1-241.8)	20	133.9 (177.8)	89.4-228.8 (41.0-500.5)
With CTU involvement	7	82.6 (87.5)	39.0-109.2 (20.8-202.8)	8	76.1 (235.0)	49.4-310.3 (37.7-971.1)
Risk category A	NA	-	-	29	135.2 (180.3)	86.5-239.2 (39.7-500.5)
Risk category B	NA	-	-	3	79.3 (368.8)	55.9-971.1 (55.9-971.1)
Risk category C	NA	-	-	3	93.6 (100.1)	37.7-169.0 (37.7-169.0)

Abbreviations: IQR=inter quartile range; min=minimum; max=maximum; CTU=clinical trial unit.

The preparation phase for a single centre RCT in 2012 required about 36 working days more to complete and cost about CHF 3'000 more than for a multicentre RCT, based on medians (single centre: CHF 73'000, 143 days; multicentre: CHF 70'000, 107 days; Table 5 and Table 6). However, in 2016, the situation was reversed. The working time for a multicentre RCT was much higher (50 days more) and the cost was more than twice as high as for a single centre RCT (single centre: CHF 61'100, 106 days; multicentre: CHF 138'000, 157 days; Table 5 and Table 6).

The costs reported for the preparation phase for Swiss multicentre RCTs in 2016 were lower than the costs for international RCTs (CHF 138'000 vs. CHF 175'600), while the working time effort for the preparation phase was 14 days longer based on the median (157 days vs. 143 days). No data on international multicentre RCTs were received for 2012.

Industry initiated RCTs required about 80% more working time than non-industry initiated RCTs in 2012 (196 days vs. 108 days) but the costs of the preparation phase were only 20% higher (CHF 79'500 vs. CHF 66'500). Similar to the single centre RCT results presented above, the situation in 2016 was different. Now, industry initiated RCTs took only half as long as non-industry initiated RCTs (73 days vs. 135 days) and costs were CHF 14'800 lower (CHF 56'500 vs. CHF 71'300). However, the number of complete datasets from industry sponsors in both years was below five and the results are prone to chance effects and potential biases.

RCTs with CTU involvement showed lower costs and working times in the preparation phase in 2012 as well as 2016 compared to RCTs without CTU involvement.

The highest costs and longest working time of the three LHR risk categories based on the median was observed for category A. The lowest median working time and second lowest costs were associated with category B even though this category had the widest interquartile range resulting in the highest mean costs and longest mean working time. Due to the low number of complete datasets, especially in category B and C trials, may well be due to chance.

The median costs of the retrospectively estimated working time efforts for single centre and industry-initiated RCTs were lower in 2016 than in 2012 (single centre: 2012: CHF 71'400, 2016: CHF 53'100; industry-initiated: 2012: CHF 77'500, 2016: CHF 45'200; Table 7), while the median costs of the working efforts for multicentre RCTs were much higher (2012: CHF 59'000, 2016: CHF 103'500). Median costs of working time efforts in 2012 and 2016 for non-industry initiated RCTs as well as RCTs with and without CTU involvement were rather similar (non-industry initiated: 2012: CHF 58'200, 2016: CHF 65'800; with CTU involvement: 2012: CHF 49'200, 2016: CHF 50'500; without CTU involvement: 2012: CHF 77'800, 2016: CHF 65'500).

The costs of all fixed cost items accounted for about 5% of the median preparation costs in 2012 (total fixed costs: CHF 3’500, Table 8; total preparation costs: CHF 71’100, Table 5). The median of the total fixed costs was almost twice as high for multicentre trials than for single centre trials (CHF 4’600 vs. CHF 2’500), as well as for non-industry initiated RCTs compared to industry initiated ones (CHF 4’200 vs. CHF 2’100; Table 8). Fixed costs for RCTs with CTU involvement were higher than for RCTs without CTU involvement (CHF 9’800 vs. CHF 3’200) since CTU-related costs were often reported as part of the fixed costs. One international multicentre RCT in 2016 falling in risk category A reported extremely high fixed costs of CHF 187’000. This was almost entirely due to a very high amount of training costs as part of the fixed costs.

The relative contribution of fixed costs to the total preparation costs was less than 3% in 2016 (total fixed costs: CHF 2’000, Table 8; total preparation costs: CHF 71’300, Table 5). Single centre RCTs had median fixed costs of CHF 1’100 only while the fixed costs for multicentre RCTs summed up to CHF 3’900 (Table 8). International multicentre RCTs had fixed costs of more than twenty times the amount of Swiss multicentre RCTs (CHF 95’200 vs. CHF 3’900); however, this was based on two international RCTs only. Industry-initiated RCTs accounted for four to five times higher fixed costs than non-industry initiated RCTs (CHF 6’500 vs. CHF 1’500), reversing the direction seen in 2012. Fixed costs in RCTs with CTU involvement were a bit lower than in RCTs without CTU involvement (CHF 1’500 vs. CHF 2’300) also reversing the direction seen in 2012. The highest fixed costs of the LHR categories was observed for category B RCTs (CHF 7’800), followed by category C RCTs (CHF 6’000) and category A RCTs (CHF 1’500).

Table 7. Retrospectively estimated costs of working time efforts to plan and prepare an RCT in 2012 and 2016, including 30% non-pre-specified working time and 20% overhead, based on complete datasets.

	2012			2016		
Costs of working time efforts (in CHF)	**n**	**Median (mean)**	**IQR (min-max)**	**n**	**Median (mean)**	**IQR (min-max)**
Total	18	59'379 (66'606)	37'350-83'562 (13'226-143'596)	35	65'259 (100'520)	41'445-162'376 (11'293-352'231)
Single centre	9	71'353 (69'189)	49'174-83'562 (13'226-143'596)	26	53'142 (86'339)	29'829-148'199 (11'293-254'975)
Multicentre	9	58'973 (64'022)	37'350-72'398 (15'442-127'717)	9	103'502 (141'489)	83'969-169'660 (57'211-352'231)
National	9	58'973 (64'022)	37'350-72'398 (15'442-127'717)	7	124'957 (158'956)	83'969-213'176 (65'829-352'231)
International	0	-	-	2	80'357 (80'357)	57'211-103'502 (57'211-103'502)
Non-industry	16	58'245 (65'249)	36'435-92'707 (13'226-143'596)	31	65'825 (106'558)	42'466-165'492 (11'293-352'231)
Industry	2	77'457 (77'457)	71'353-83'562 (71'353-83'562)	4	45'177 (53'727)	23'965-83'489 (22'834-101'720)
No CTU involvement	11	77'797 (79'209)	52'701-116'316 (13'226-143'596)	20	65'542 (95'879)	42'857-137'483 (22'834-254'975)
With CTU involvement	7	49'174 (46'800)	35'521-59'785 (15'442-71'353)	8	50'498 (109'268)	23'047-181'764 (11'293-352'231)
Risk category A	NA	-	-	29	65'825 (100'413)	42'466-162'376 (11'293-254'975)
Risk category B	NA	-	-	3	46'639 (139'957)	20'999-352'231 (20'999-352'231)
Risk category C	NA	-	-	3	59'552 (62'122)	25'096-101'720 (25'096-101'720)

Abbreviations: CHF=Swiss Francs; CTU=clinical trial unit; IQR=inter quartile range; max=maximum; min=minimum; NA=not applicable.

Table 8. Retrospectively estimated fixed costs to plan and prepare an RCT in 2012 and 2016, including 30% non-pre-specified working time and 20% overhead, based on complete datasets.

	2012			2016		
Fixed costs (in CHF)	**n**	**Median (mean)**	**IQR (min-max)**	**n**	**Median (mean)**	**IQR (min-max)**
Total	18	3'525 (9'188)	1'750-11'000 (500-43'860)	35	2'000 (9'074)	800-5'500 (280-186'700)
Single centre	9	2'500 (7'958)	850-9'800 (500-33'962)	26	1'100 (5'425)	800-4'000 (280-23'000)
Multicentre	9	4'550 (10'419)	3'200-11'000 (1'750-43'860)	9	3'880 (25'438)	3'700-7'830 (2'000-186'700)
National	9	4'550 (10'419)	3'200-11'000 (1'750-43'860)	7	3'880 (5'499)	2'580-7'830 (2'000-13'000)
International	0	-	-	2	95'225 (95'225)	3'750-186'700 (3'750-186'700)
Non-industry	16	4'200 (10'081)	2'255-11'750 (500-43'860)	31	1'500 (9'052)	800-3'880 (280-186'700)
Industry	2	2'050 (2'050)	1'600-2'500 (1'600-2'500)	4	6'500 (9'250)	6'000-12'500 (6'000-18'000)
No CTU involvement	11	3'200 (7'466)	850-10'300 (500-33'962)	20	2'290 (3'393)	900-4'120 (280-18'000)
With CTU involvement	7	9'800 (11'896)	1'750-12'500 (1'600-43'860)	8	1'500 (2'804)	600-5'000 (400-7'830)
Risk category A	NA	-	-	29	1'500 (9'378)	800-3'880 (280-186'700)
Risk category B	NA	-	-	3	7'830 (10'543)	800-23'000 (800-23'000)
Risk category C	NA	-	-	3	6'000 (4'667)	2'000-6'000 (2'000-6'000)

Abbreviations: CHF=Swiss Francs; CTU=clinical trial unit; IQR=inter quartile range; max=maximum; min=minimum; NA=not applicable.

4.3.3 Preparation costs at the level of specific items

Item-specific median costs in 2016 were more than 25% higher than in 2012, for the items of budgeting (2012: CHF 1'400, 2016: CHF 1'900; Table 9), site management (2012: CHF 3'700, 2016: CHF 6'100), biobank setup (2012: CHF 500, 2016: CHF 1'600), support (2012: CHF 2'000, 2016: CHF 3'300) and other fixed costs (2012: CHF 6'200, 2016: CHF 15'000). They

were more than 25% lower for the items of insurance (2012: CHF 7'300, 2016: CHF 600). The three RCTs reporting insurance costs in 2016 were risk category A trials, while risk categories in 2012 were not yet recorded. The largest absolute change of more than CHF 8'000 was observed for other fixed costs, but based on only two datasets providing information for 2012.

We expected that we would find the most obvious cost impact of the LHR, if any, in the protocol writing and form preparations item as the new law has changed some important aspects of the submission process to RECs and Swissmedic. The introduction of a regulatory system proportionate to the relative risk of each individual clinical research project might have changed the effort required for the preparation of forms related to the submission process. Even though it was intended to reduce the administrative burden to a necessary minimum, there is a potential that the process may have become more time consuming. On the other hand, protocol writing and form preparation may have become easier under the new law as only one submission to the lead REC is required for multicentre studies, the roles of the RECs and Swissmedics are now clearly distinguished, and low risk RCTs do no longer require Swissmedic approval. An impact of the LHR on other preparation-phase items, such as budgeting or site management, is possible but presumably less obvious and more biased by other influencing factors.

The median costs for protocol writing and form preparations were CHF 34'100 in 2012 and CHF 38'800 in 2016 (Table 9), i.e. slightly higher. This resulted in a portion of more than 54% of the total planning and preparation costs in 2016 (CHF 71'300; Table 5) instead of 48% in 2012 (CHF 71'100; Table 5). A difference of about CHF 2'500 between the 2012 and 2016 medians of the corresponding sub-items was seen with respect to preparatory steps (e.g. literature review, development of idea, writing, meeting time with external experts, etc.) and development of the research protocol (results not shown). Another difference of CHF 2'500 was observed for the development of grant proposals and related documents (e.g. for applications from grants from the Swiss National Science Foundation [SNSF]) and a difference of about CHF 2'200 to preparatory steps of applications to ethics committee, authorities, insurance (e.g. writing of informed consent and other specific documents; but not fees).

The median working time spent on protocol writing and form preparations in 2012 and 2016 were 53 days and 65 days, respectively (Table 10). Nine additional days were required for the preparatory steps of the research protocol sub-item. The median amount of days spent on the preparatory steps of the grant proposal and related documents as well as preparatory steps required for approvals from ethics committees, authorities and insurances were almost the same but more time of better trained personnel was required.

Table 9. Item-specific costs to prepare an RCT, including 30% non-pre-specified time and 20% overhead, based on all datasets with available information.

		2012			2016	
Item-specific costs (in CHF)	**n**	**Median (mean)**	**IQR (min-max)**	**n**	**Median (mean)**	**IQR (min-max)**
Protocol/Forms	18	34'149 (40'712)	24'167-62'926 (6'816-75'391)	43	38'793 (60'088)	20'190-86'681 (4'042-306'397)
Budget	16	1'436 (1'826)	665-1'989 (250-5'847)	35	1'933 (3'933)	1'000-4'958 (312-20'009)
Communication	18	7'190 (11'904)	4'538-14'854 ('678-33'101)	40	6'389 (12'247)	2'993-14'979 ('682-64'667)
Staff training	15	3'256 (5'012)	1'119-8'139 (712-14'841)	34	2'861 (5'979)	1'357-4'473 (136-45'850)
Site management	14	3'719 (5'343)	1'750-5'426 (250-16'322)	35	6'064 (7'849)	3'451-10'611 (434-39'214)
Database	16	2'086 (4'506)	1'424-4'476 (987-17'635)	35	2'442 (4'756)	1'085-4'531 (268-32'557)
Biobank setup	1	509 (509)	509-509 (509-509)	7	1'628 (1'604)	868-2'001 (570-3'151)
Fees	19	1'750 (2'858)	800-4'000 (500-12'600)	44	1'500 (3'068)	800-3'000 (280-19'000)
Insurance costs	4	7'318 (10'924)	3'813-18'036 (3'500-25'562)	3*	600 (867)	500-1'500 (500-1'500)
Support	7	2'000 (9’551)	800-14'400 (160-40’000)	10	3'250 (6'065)	500-6’000 (200-25'000)
Travel expenses	8	2'500 (2'663)	650-4'400 (200-6'000)	12	2'000 (2'372)	740-4'000 (20-6'000)
Other fixed costs	2	6’180 (6’180)	3’360-9’000 (3’360-9’000)	4	15’000 (52’625)	5’250-100'000 (500-180'000)

* These three RCTs were classified as risk category A.
Abbreviations: CHF=Swiss Francs; IQR=inter quartile range; max=maximum; min=minimum.

Table 10. Item-specific working time to prepare an RCT, including 30% non-pre-specified time, based on all datasets with available information.

		2012			2016	
Item-specific time (in days)	**n**	**Median (mean)**	**IQR (min-max)**	**n**	**Median (mean)**	**IQR (min-max)**
Protocol/Forms	18	52.7 (74.9)	30.6-122.2 (10.4-198.9)	44	65.0 (108.2)	39.7-123.4 (8.5-808.6)
Budget	16	2.6 (3.1)	1.3-3.9 (.3-11.7)	36	3.3 (7.8)	1.3-7.2 (0.7-49.4)
Communication	18	13.0 (20.1)	7.2-31.2 (1.3-53.3)	40	13.0 (22.8)	4.6-26.0 (1.3-136.5)
Staff training	15	5.2 (9.6)	2.6-19.5 (1.3-26.0)	34	5.2 (11.9)	2.6-10.4 (0.3-88.4)
Site management	14	7.8 (9.8)	3.9-11.7 (.3-26.0)	35	13.0 (15.5)	6.5-20.8 (1.3-74.1)
Database	16	3.9 (9.3)	2.6-9.8 (1.3-39.0)	35	3.9 (10.9)	2.6-13.0 (0.7-78.0)
Biobank setup	1	1.3 (1.3)	1.3-1.3 (1.3-1.3)	7	2.6 (2.9)	2.6-2.6 (0.7-6.5)

Abbreviations: IQR=inter quartile range; max=maximum; min=minimum.

4.3.4 Sensitivity analyses

Scenario 1 (repetition of the main analysis but without adding 30% non-pre-specified time to the working time data) resulted in median working time estimates compared to the main analysis which were reduced by 26 days for 2012 (87 days vs. 113 days; Table 11) and 31 days for 2016 (102 days vs. 133 days). The median total costs for the preparation of RCTs were reduced by about CHF 14'000 for both years (2012: CHF 56'400 vs. CHF 71'100; 2016: CHF 57'200 vs. CHF 71'300). The median total costs in the second scenario (repetition of main analysis but without adding 30% non-pre-specified time and 20% overhead for salaries) were CHF 49'200 for 2012 and CHF 48'800 for 2016, which is around 31% lower than the estimated median total costs in the main analysis.

An additional scenario tested how our results would change when only considering datasets where the salaries of the study personnel were actually provided and did not require imputation. We found that the number of days spent on the preparation phase in 2012 would be 22 days longer than in the main analysis (135 days vs. 113 days) and 40 days less in 2016

(93 days vs. 133 days). The median costs would slightly increase by CHF 3'100 to a total of CHF 74'300 in 2012 and decrease by CHF 16'700 to a total of CHF 54'600 in 2016.

Table 11. Results of the sensitivity analyses.

	2012			2016		
	n	**Median (mean)**	**IQR (min-max)**	**n**	**Median (mean)**	**IQR (min-max)**
Total working time (in days)						
Main analysis	18	113.1 (121.7)	51.3-189.8 (20.8-241.8)	35	132.6 (189.6)	79.3-239.2 (37.7-971.1)
Scenario 1	18	87.0 (93.6)	39.5-146.0 (16.0-186.0)	35	102.0 (145.8)	61.0-184.0 (29.0-747.0)
Scenario 2	18	87.0 (93.6)	39.5-146.0 (16.0-186.0)	35	102.0 (145.8)	61.0-184.0 (29.0-747.0)
Scenario 3	12	134.6 (135.3)	75.7-196.3 (24.1-232.7)	14	93.0 (122.6)	57.4-135.2 (37.7-500.5)
Total costs (in CHF)						
Main analysis	18	71'129 (75'794)	58'366-86'062 (13'726-177'558)	35	71'325 (109'595)	41'845-166'492 (11'693-360'061)
Scenario 1	18	56'425 (60'424)	45'093-66'778 (10'674-144'420)	35	57'199 (86'398)	33'466-128'302 (9'087-278'777)
Scenario 2	18	49'206 (51'884)	37'719-56'065 (8'978-126'011)	35	48'832 (73'510)	28'004-107'085 (7'639-253'048)
Scenario 3	12	74'275 (81'717)	58'670-106'295 (13'726-177'558)	14	54'597 (69'280)	31'096-85'969 (21'799- 217'056)

Main analysis: +30% non-pre-specified time, +20% overhead on salaries, complete datasets but including imputed salaries.
Scenario 1: +0% non-pre-specified time, +20% overhead on salaries, complete datasets but including imputed salaries.
Scenario 2: +0% non-pre-specified time, +0% overhead on salaries, complete datasets but including imputed salaries.
Scenario 3: +30% non-pre-specified time, +20% overhead on salaries, complete datasets without imputed salaries.
Abbreviations: CHF=Swiss Francs; IQR=inter quartile range, max=maximum; min=minimum.

4.4 Results for Objective 4

4.4.1 Time from submission to approval in individual RECs

A total of 183 and 217 REC approval times were analysed for 2012 and 2016, respectively. The number of industry-initiated studies was 94 (51.4%) in 2012 and 88 (40.6%) in 2016 (Table 12). There were 89 (48.6%) and 129 (59.4%) non-industry initiated studies for 2012 and 2016, respectively. Single centre studies were represented by 40 (21.9%) studies in the sample for 2012 and 68 (31.3%) in 2016. Out of the 143 (78.1%) multicentre studies in 2012, 120 (83.9%)

were international and 23 (16.1%) studies were conducted in Switzerland only. In 2016 149 (68.7%) were multicentre studies, out of which 116 (77.9%) international and 33 (22.1%) conducted in Switzerland. In 2016 there were 99 (45.62%) risk category A, 50 (23.04%) risk category B and 68 (31.34%) risk category C studies.

The median time from REC submission to approval was 72 days (IQR: 41-107) in 2012 and 109 (IQR: 79-154) days in 2016 (Table 12). The duration from submission until first response from the REC was 25 days (IQR: 17.5-41.5) in 2012 (information missing for 20 studies) and 36 (IQR: 27-49) days in 2016 (Table 13). The duration from first response from the REC until final approval was 42 days (IQR: 15.5-75.5) in 2012 (information missing for 20 studies) and 63 (IQR: 41-106) days in 2016 (Table 14). In addition, Table 15 shows the time from completion of the information provided to the REC by the responsible investigator, to approval. This information was only available for RCTs approved in 2016.

Table 12. Time (in days) from submission to REC approval by study characteristic and year.

	2012			2016		
	n (%)	Median (mean)	IQR (min-max)	n (%)	Median (mean)	IQR (min-max)
Total	183 (100.0)	72 (85.0)	41-107 (1-329)	217 (100.0)	109 (128.6)	79-154 (20-467)
1st tertile	70 (38.3)	78 (88.4)	42-109.5 (5-320)	76 (35.0)	109 (139.9)	83.5-161 (36-467)
2nd tertile	66 (36.1)	69.5 (88.9)	48.2-112.5 (1-329)	79 (36.4)	115 (130.1)	78-154.5 (20-369)
3rd tertile	47 (25.7)	72 (74.6)	33-94 (4-243)	62 (28.6)	95 (113.0)	77-143.5 (22-262)
Single centre	40 (21.9)	87 (91.4)	51-113.5 (14-329)	68 (31.3)	97 (121.0)	71.2-141 (29-393)
Multicentre	143 (78.1)	70 (83.2)	38-105 (1-320)	149 (68.7)	114 (132.1)	85-155 (20-467)
National	23 (16.1)*	76 (96.3)	45-115 (1-320)	33 (22.1)*	103 (123.2)	75-135 (20-467)
International	120 (83.9)*	70 (80.7)	37.5-104 (5-301)	116 (77.9)*	120 (134.6)	87-161 (21-322)
Not applicable	40	87 (91.4)	51-113.5 (14-329)	68 (31.3)	97 (121.0)	71.2-141 (29-393)
Non-industry	89 (48.6)	67 (85.5)	35-107 (1-329)	129 (59.4)	99 (124.7)	74-145 (20-467)
Industry	94 (51.4)	81.5 (84.6)	46-106 (5-292)	88 (40.6)	117.5 (134.4)	87-162.5 (21-322)
Risk category A	-	-	-	99 (45.)	97 (114.6)	70-136.5 (20-467)
Risk category B	-	-	-	50 (32.0)	110 (138.0)	85.2-158 (38-393)
Risk category C	-	-	-	68 (31.3)	134.5 (142.1)	88-175 (50-322)

* Proportion based on multicentre randomised controlled trials.
Abbreviations: IQR=inter quartile range; max=maximum; min=minimum; REC=research ethics committee.

Table 13. Time (in days) from submission to first REC response by study characteristic and year.

	2012			2016		
	n (%)§	Median (mean)	IQR (min-max)	n (%)	Median (mean)	IQR (min-max)
Total	163 (100.0)	25 (33.3)	17.5-41.5 (1-165)	217 (100.0)	36 (45.2)	27-49 (10-247)
1st tertile	55 (33.7)	26 (36.1)	18-46 (1-165)	76 (35.0)	41 (50.6)	29-50 (15-240)
2nd tertile	63 (38.7)	26 (35.1)	17-44.5 (1-131)	79 (36.4)	35 (47.3)	26-53.5 (16-274)
3rd tertile	45 (27.6)	23 (27.3)	17-32 (4-85)	62 (28.6)	31 (36.1)	25-44 (10-127)
Single centre	35 (21.5)	30 (41.3)	21-51.5 (4-157)	68 (31.3)	34 (47.5)	27-46.5 (16-240)
Multicentre	128 (78.5)	24 (31.1)	17-37 (1-165)	149 (68.7)	38 (44.2)	26-49 (10-274)
National	20 (15.6)*	21.5 (32.0)	13.8-37 (1-165)	33 (22.1)*	29 (38.8)	21-41 (10-193)
International	108 (84.4)*	24 (31.0)	17-37 (1-131)	116 (77.9)*	41.5 (45.8)	28-50 (15-274)
Not applicable	35 (21.5)	30 (41.3)	21-51.5 (4-157)	68 (31.3)	34 (47.5)	27-46.5 (16-240)
Non-industry	78 (47.9)	25 (34.9)	17-40 (1-165)	129 (59.4)	34 (48.2)	26-50 (10-274)
Industry	85 (52.1)	25 (31.8)	18-42 (2-120)	88 (40.6)	40 (40.9)	27-48 (15-99)
Risk category A	-	-	-	99 (45.0)	34 (50.8)	22.5-51.5 (10-274)
Risk category B	-	-	-	50 (32.0)	35.5 (37.7)	27-44 (14-76)
Risk category C	-	-	-	68 (31.3)	41 (42.8)	29.8-49 (15-125)

* Proportion based on multicentre randomised controlled trials.
§ Number of missing trials: 20 (10.9%).
Abbreviations: IQR=inter quartile range; max=maximum; min=minimum; REC=research ethics committee.

Table 14. Time (in days) from first REC response to approval by study characteristic and year.

	2012			2016		
	n (%)§	Median (mean)	IQR (min-max)	n (%)	Median (mean)	IQR (min-max)
Total	163 (100.0)	42 (54.8)	15.5-75.5 (0-281)	217 (100.0)	63 (83.4)	41-106 (0-357)
1st tertile	55 (33.7)	42 (59.3)	19-83 (0-269)	76 (35.0)	61 (89.2)	42-112 (0-357)
2nd tertile	63 (38.7)	38 (54.5)	19-64.5 (0-281)	79 (36.4)	70 (82.8)	39-104.5 (0-348)
3rd tertile	45 (27.6)	47 (49.7)	14-65 (0-220)	62 (28.6)	60 (76.9)	40-106 (6-218)
Single centre	35 (21.5)	47 (55.0)	22.5-68 (0-281)	68 (31.3)	47.5 (73.5)	29-103 (0-357)
Multicentre	128 (78.5)	41.5 (54.7)	12-78 (0-271)	149 (68.7)	72 (87.8)	44-110 (0-348)
National	20 (15.6)*	53.5 (66.8)	30-87 (0-241)	33 (22.1)*	70 (84.4)	35-99 (0-348)
International	108 (84.4)*	39.5 (52.5)	5-70.5 (0-271)	116 (77.9)*	76.5 (88.8)	49-114 (0-268)
Not applicable	35 (21.5)	47 (55.0)	22.5-68 (0-281)	68 (31.3)	47.5 (73.5)	29-103 (0-357)
Non-industry	78 (47.9)	37 (53.0)	14-65.2 (0-281)	129 (59.4)	53 (76.5)	33-102 (0-357)
Industry	85 (52.1)	47 (56.4)	23-84 (0-271)	88 (40.6)	79.5 (93.5)	50-119 (0-268)
Risk category A	-	-	-	99 (45.0)	48 (63.8)	30-84 (0-274)
Risk category B	-	-	-	50 (32.0)	75 (100.4)	46.5-111 (9-357)
Risk category C	-	-	-	68 (31.3)	90.5 (99.4)	49-124 (12-268)

*: Proportion based on multicentre randomised controlled trials.
§: number of missing trials: 20 (10.9%).
Abbreviations: IQR=inter quartile range; max=maximum; min=minimum; REC=research ethics committee.

Table 15. Time (in days) from completion of information submitted to REC to approval by study characteristic and year.

	2012			2016		
	n (%)§	Median (mean)	IQR (min-max)	n (%)	Median (mean)	IQR (min-max)
Total	-	-	-	217 (100.0)	91 (109.1)	63-136 (15-391)
1st tertile	-	-	-	76 (35.0)	87 (112.9)	62.5-142 (15-391)
2nd tertile	-	-	-	79 (36.4)	97 (112.8)	63-137.5 (15-386)
3rd tertile	-	-	-	62 (28.6)	84.5 (99.7)	61-128 (21-238)
Single centre	-	-	-	68 (31.3)	65 (93.5)	50-120 (15-391)
Multicentre	-	-	-	149 (68.7)	101 (116.2)	70-139 (15-386)
National	-	-	-	33 (22.1)*	93 (117.8)	68-114 (28-386)
International	-	-	-	116 (77.9)*	104.5 (115.8)	70-141 (15-314)
Not applicable	-	-	-	68 (31.3)	65 (93.5)	50-120 (15-391)
Non-industry	-	-	-	129 (59.4)	81 (102.1)	55-121 (15-391)
Industry	-	-	-	88 (40.6)	107 (119.4)	73-148 (15-314)
Risk category A	-	-	-	99 (45.)	72 (87.4)	50.5-110 (15-386)
Risk category B	-	-	-	50 (32.0)	99.5 (127.7)	80-145 (16-391)
Risk category C	-	-	-	68 (31.3)	114.5 (127.0)	76-157 (44-314)

*: Proportion based on multicentre randomised controlled trials.
§: number of missing trials: 20 (10.9%).
Abbreviations: IQR=inter quartile range; max=maximum; min=minimum; REC=research ethics committee.

A visual comparison of the time from submission to REC approval by year and tertile based on boxplots is provided in Figure 6. The duration to approval seems to be longer in 2016 than in

2012. However, we did not perform a statistical comparison since we could not distinguish between lead RECs and non-lead RECs as described in the methods section. Only a direct, statistical comparison for single centre studies was performed as here, by definition all RECs were lead RECs.

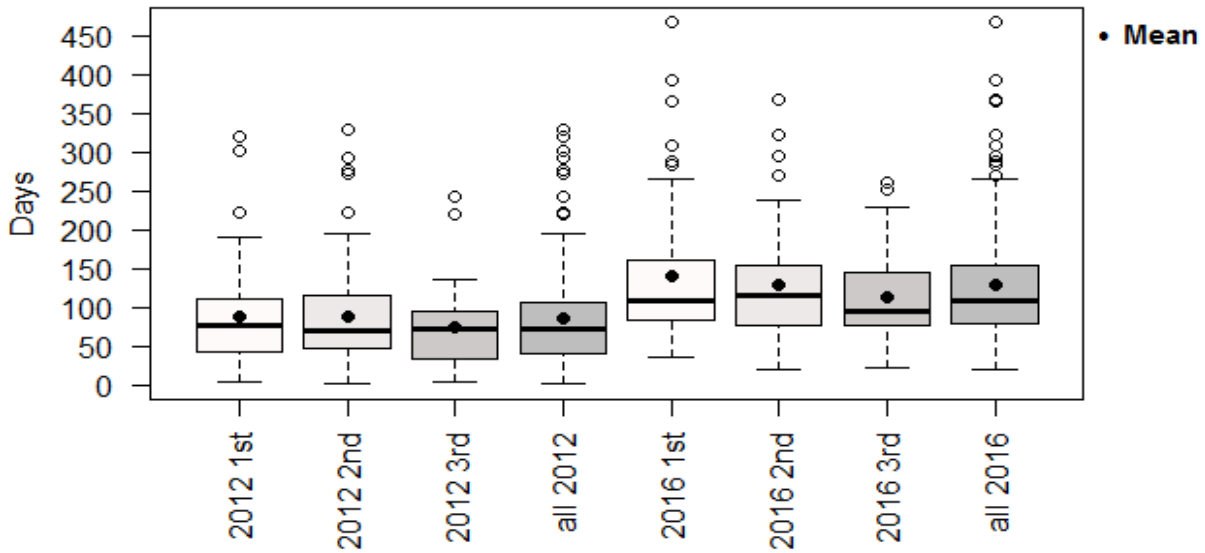

Figure 6. Boxplot of time from REC application to approval in days by year and tertile.
Abbreviations: REC=research ethics committee.

The median time from submission to REC approval for single centre studies was 87 days (mean: 91.4, IQR: 51-113.5) in 2012 and 97 (mean: 121.0, IQR: 71.25-141) days in 2016, before the removal of outliers (Table 16). There were two outliers in the 2012 subset (243 and 329 days) and five in 2016 (265, 365, 366, 368 and 393 days), as visible from Figure 7. Without the outliers, the median time from submission to approval was 82 days (mean: 81.2, IQR: 49-106.8) in 2012 and 92 (mean: 102.7, IQR: 65-131) days in 2016.

Table 16. Time (in days) from application to REC approval for single centre studies by year.

	2012			2016		
	n (%)[§]	Median (mean)	IQR (min-max)	n (%)	Median (mean)	IQR (min-max)
Including outliers	40	87 (91.4)	51-113.5 (14-329)	68	97 (121.0)	71-141 (29-393)
Without outliers*	38	82 (81.2)	49-107 (14-167)	63	92 (102.7)	65-131 (29-219)

*: Outliers identified by visual inspection of boxplots.

Abbreviations: IQR=inter quartile range; max=maximum; min=minimum; n=sample size; REC=research ethics committee.

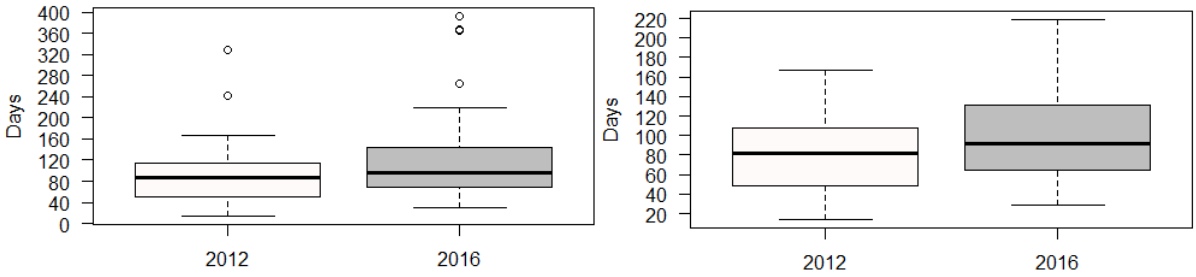

Figure 7. Boxplots of time from application to approval by the REC before (left) and after (right) elimination of outliers, for single centre studies.

Abbreviations: REC=research ethics committee.

We performed a two-sided Wilcoxon rank-sum test for unpaired samples, as the data were not normally distributed (Figure 8 and Figure 9).This test used a null hypothesis of no difference in the distributions representing times from application to approval, for 2012 and 2016. Before the removal of outliers the resulting p value was p=0.043; after the removal of outliers, it was p=0.048. The results provide some evidence that there may be a difference in the times from submission to approval for single centre RCTs between 2012 and 2016.

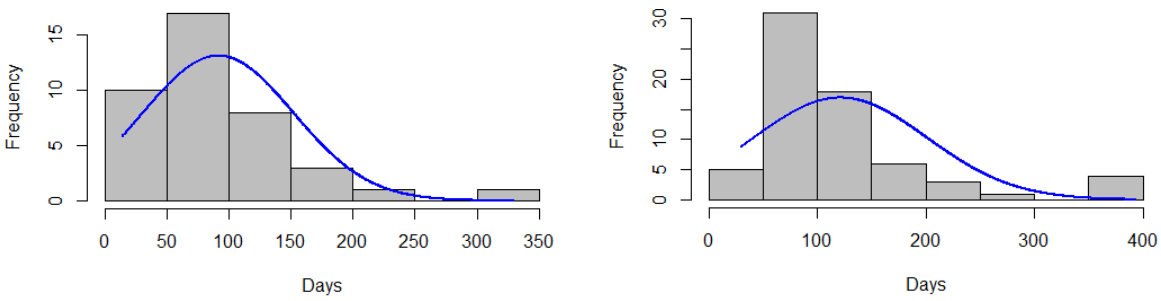

Figure 8. Histograms of time from application to approval by the REC in 2012 (left) and 2016 (right), for single centre studies.

Abbreviations: REC=research ethics committee.

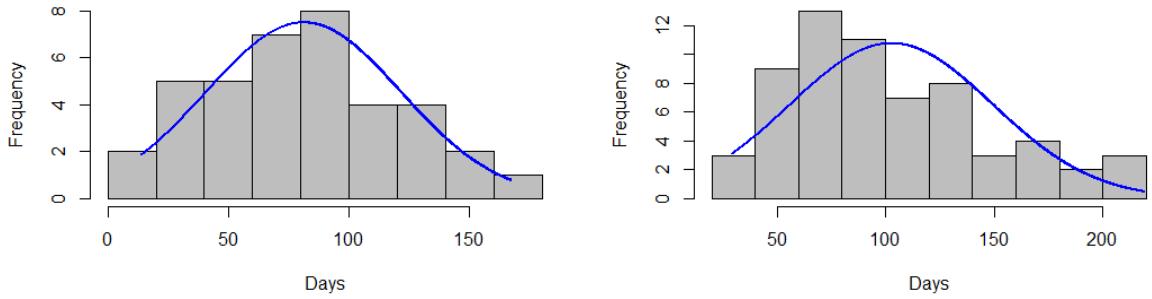

Figure 9. Histograms of time from application to approval by the REC in 2012 (left) and 2016 (right), after elimination of outliers, for single centre studies.
Abbreviations: REC=research ethics committee.

4.4.2 Time from submission to first Swiss REC until approval for all Swiss centres in multicentre RCTs

In the ASPIRE data collection for 2012, data were only extracted when the study team first got in contact with a specific RCT. For example, when data were extracted for a specific RCT at the REC in Basel, data were not re-extracted if the same study protocol was re-identified at another REC. As a consequence of this approach, there is no clear identification available which RECs were the lead RECs for specific trials in 2012. For the sample of RCTs submitted to RECs in 2016, we received the data from BASEC. Here, the time to approval data were only recorded for the lead REC. Times to approval for the other RECs were not available.

For these reasons, the question of total approval time for all Swiss centres in multicentre RCTs cannot be answered directly, based on the data sources available to us. However, Interpharma provided some data discriminating between approval times of lead RECs and non-lead RECs. This data is presented in section 4.4.5.

4.4.3 Number of RCTs recruiting in Switzerland and number of recruiting sites in Switzerland

As described in section 2.4.4., we used the number of approved RCTs by RECs as a proxy for the number of recruiting RCTs in Switzerland. In 2012, 324 RCTs were approved, while in 2016 345 RCTs were approved. There were eight RECs in 2012 and seven in 2016. No data for number of RECs involved in the approval process per multicentre RCT could be collected for 2012. For 2016, these data could be retrieved from BASEC. In 2016, 149 multicentre RCTs were approved by a mean of 2.4 RECs (median: 2; min-max: 1-7, IQR 1-3). The number of approving RECs per multicentre RCT is presented in Table 17. Of note, it is possible that only one REC approved a multicentre RCT. Examples are multinational studies with only one centre in Switzerland or RCTs with multiple centres within the catchment area of a single REC.

Table 17. Number of RECs which approved the same multicentre RCT.

Number of RECs approving a protocol in 2016	Number of multicentre RCTs	%
1*	54	36%
2	36	24%
3	31	21%
4	13	9%
5	4	3%
6	5	3%
7	6	4%

* For example multinational studies with only one centre in Switzerland or RCTs with multiple centres within the catchment area of a single REC.
Abbreviations: RCT=randomised controlled trial; REC=research ethics committee.

4.4.4 Numbers of RCTs needing Swissmedic approval plus time from submission until approval

Swissmedic kindly provided us with two lists (one for clinical trials submitted for approval in 2012 trials and one for clinical trials submitted in 2016) including the dates of receipt of a dossier, of acknowledgement of receipt, and of Swissmedic decision. There was also information on how many days the sponsor required to provide amendments requested by Swissmedic. These two lists included clinical trials in general and were not specific for RCTs. However, according to Swissmedic, the vast majority of the clinical trials were RCTs. As RCTs could not be retrospectively identified, we calculated time from submission until approval for all clinical trials as a proxy.

For 2012 we received data for 213 clinical trials and the median duration from receiving a dossier until the final decision by Swissmedic, without counting the time which the sponsor used to provide requested amendments, was 25 days (IQR: 18-33 days) (Table 18). In 2016 a total of 179 clinical trials were evaluated, with a median time to Swissmedic decision of 36 days (IQR: 33-38 days). Of note, for a few clinical trials submitted to Swissmedic in 2012 the date when the dossier was sent back to the sponsor was not noted, hence the durations for 2012 might be overestimated. The total duration from receiving a dossier until the final decision (not subtracting the days a sponsor used to implement requested amendments) was, in the median, 27 days (IQR: 19-51) in 2012 and 49 days (IQR: 36-67) in 2016. Swissmedic divided trial sponsors into the following three groups: (i) industry; (ii) investigator-initiated trial (IIT), hospital; and (iii) research group (“Forschungsgruppe”). The specific approval times for the different sponsor types are presented in Table 19.

Table 18. Swissmedic approval times by year.

	2012		2016	
	Median (mean)	**IQR (min-max)**	**Median (mean)**	**IQR (min-max)**
Approval time (in days) Swissmedic (excluding time sponsor used to implement requested amendments)	25.0 (27.2)	17.8-33.0 (4-177)	36.0 (37.9)	33.0-38.0 (1-72)
Approval time (in days) Swissmedic (including time sponsor used to implement requested amendments)	27.0 (48.0)	19.0-50.5 (8-315)	49.0 (55.1)	36.0-67.0 (1-224)

Abbreviations: IQR=inter quartile range; max=maximum; min=minimum.

Of note, under the new LHR, RCTs falling in the lowest risk category A do not require Swissmedic approval. For the year 2012, before the enactment of the LHR, no such risk categorisation was available. Hence, the Swissmedic approval times for 2012 and 2016 cannot be assumed to apply to the same 'population' of RCTs, limiting comparability. The smaller number of applications to Swissmedic and the longer Swissmedic approval times in 2016 may both be a consequence of the removal of the need for Swissmedic approval for low risk RCTs. The remaining, higher risk RCTs may require more time than was required earlier, on average.

Table 19. Swissmedic approval times by year and sponsor.

	Sponsor	n	Median (mean)	IQR
2012				
Approval time (in days) Swissmedic (excluding time sponsor used to implement requested amendments)	All	213	25.0 (27.2)	17.8-33.0
	Industry	143	22.5 (24.3)	16.0-33.0
	IIT, hospital	52	28.0 (34.5)	20.5-43.0
	Research group	18	27.0 (27.3)	17.8-36.3
Approval time (in days) Swissmedic (including time sponsor used to implement requested amendments)	All	213	27.0 (48.0)	19.0-50.5
	Industry	143	23.0 (34.1)	16.0-50.0
	IIT, hospital	52	44.5 (85.4)	25.0-134.0
	Research group	18	28.5 (56.9)	21.0-86.5
2016				
Approval time (in days) Swissmedic (excluding time sponsor used to implement requested amendments)	All	179	36.0 (37.9)	33.0-38.0
	Industry	120	36.0 (38.0)	34.0-37.0
	IIT, hospital	42	36.0 (36.0)	32.0-38.3
	Research group	17	37.0 (41.8)	33.0-53.0
Approval time (in days) Swissmedic (including time sponsor used to implement requested amendments)	All	179	49.0 (55.1)	36.0-67.0
	Industry	120	42.0 (50.4)	36.0-62.0
	IIT, hospital	42	56.5 (62.0)	40.5-79.0
	Research group	17	72.0 (70.9)	48.0-88.0

Abbreviations: IIT=investigator-initiated trial; IQR=inter quartile range; max=maximum; min=minimum; n=sample size.

4.4.5 Time from submission to first Swiss REC or Swissmedic until all competent authorities (Swiss REC and Swissmedic) have approved the RCT

Since under the new LHR research projects can be submitted in parallel to Swiss RECs and Swissmedic, it would be highly relevant to assess total approval times (i.e. from first submission to first Swiss REC or Swissmedic until all competent authorities (Swiss REC(s) and Swissmedic) have approved the RCT). However, the information provided by Swissmedic did not allow us to distinguish RCTs from other clinical trials. More importantly, the Swissmedic data did not include an identification code that would have enabled us to match Swissmedic and REC approval time data at the RCT level. In consequence, we had no means of assessing combined Swissmedic and REC approval times.

4.4.6 Approval times for clinical trials collected by Interpharma

Interpharma supported our evaluation by providing approval times for clinical trials (not only RCTs) in an aggregated form, combined for 2012 and 2013 as well as separately for 2016. As we only received aggregate data, we present the data as provided and did not perform any calculations of our own. We do not exactly know how the numbers were generated. Results for 2012 and 2013 are based on 71 clinical trials conducted at more than 200 study sites by 14 pharmaceutical companies. The mean approval time (i.e. from first submission until final approval) at a lead REC was 72.6 days (median 64.0 days) and the approval time at a non-lead REC 23.0 days (median 31.0 days) (Table 20). The mean duration to obtain Swissmedic approval was 25.2 days (median 22.0 days) in 2012 and 2013. Results for 2016 considered 10 pharmaceutical companies, a total of 64 clinical trials conducted at approximately 178 study sites. The mean approval time in 2016 was 109.8 days (median 95.0 days) for a lead REC, 98.3 days (median 99.5 days) for a non-lead REC, and 75.5 days (median 75.5 days) for receiving approval from Swissmedic. Interpharma did not describe how the data were derived and if the data were collected in an identical way for the years 2012-2013 and 2016.

Table 20. Approval times, meaning time from first submission until final approval, provided by Interpharma.

	2012-2013			2016		
	n	**Mean**	**Median**	**n**	**Mean**	**Median**
Lead REC	111	72.6	64.0	55	109.8	95.0
Non-lead REC	143	23.0	31.0	20	98.3	99.5
Swissmedic	144	25.2	22.0	52	75.5	75.5

Abbreviations: n=sample size; REC=research ethics committees.

5. Discussion

Study background and setup

In January 2014, the Swiss regulatory framework for clinical research has considerably changed by the enactment of the new LHR [1, 2]. The LHR regulates the requirements for the conduct of clinical trials, related authorisation and notification procedures, related duties and responsibilities of RECs, Swissmedic and the Federal Office of Public Health, and the registration of clinical research projects. Purposes of introducing the LHR were to improve the protection of involved subjects, to increase quality and transparency in clinical research and to create a solid framework with the necessary degree of regulation but no over-regulation [3].

One important element was the introduction of a regulatory system proportionate to the relative risk of each individual clinical research project, intending to reduce the administrative burden to a necessary minimum [2, 3]. Based on three risk categories, different administrative obligations relating to submission of documents, compulsory insurance, approval procedures and reporting of adverse events came into effect [2, 3]. Another element of the LHR was the introduction of a simplified and accelerated as well as a more efficient approval procedure. Approvals can now be submitted in parallel to Swissmedic and the competent REC since the roles of these institutions are clearly distinguished. Only one submission to a lead REC is required for multicentre studies [2, 3]. The new law also highlights the importance of good clinical practice, scientific integrity and quality [1, 2].

The role of clinical research and, specifically, RCTs is central to determining the effectiveness and safety of medical interventions. While RCTs have a potential to provide reliable evidence for decision-making in clinical practice and health policy, they are complex to implement, administratively burdensome and costly [5-9].

This is the first study that aimed to evaluate the impact of this new legislation on RCT-associated costs and efforts. We followed an empirical and quantitative approach. Qualitative methods (e.g. experts interviews investigating expected effects and underlying mechanisms using qualitative methods of content analysis) were not considered. We approached the task by defining a stepwise approach with four objectives. In Objective 1, we planned to create a comprehensive standardised list of cost items associated with RCTs, as nothing of the kind was available. Objective 2 aimed to gain an understanding of typical unit costs to be expected for the cost items defined in Objective 1. To generate reference points for Objective 3, we further intended to assess the costs of RCT preparation phases before the introduction of the new LHR and the relative contribution of the preparation phase to overall RCT costs. We were finally interested in overall costs of completed RCTs in Switzerland as a by-product, given a

clear lack of related knowledge nationally and internationally. Other than in the case of Objectives 3 and 4, it was not the intention of this intermediary step to directly compare the situation before and after the introduction of the new LHR. In fact, many RCTs approved under the new LHR would not be completed by the time of our evaluation. Objective 3 aimed to compare costs of the RCT preparation phase (covering all efforts until enrolment of the first patient) before and after the introduction of LHR. We expected that the most immediate impact of the LHR on RCT costs, if any, would occur in this phase, due to the new rules regarding administrative authorisation and ethical approval. The costs of the conduct and post-conduct phases might also be affected by the LHR but in a more indirect way with additional influencing factors that could complicate the interpretation of any data. Trials approved in the years 2012 (2 years before the enactment of the LHR) and 2016 (2 years after the enactment of the LHR) were studied to achieve synergies with the parallel, ongoing ASPIRE project. ASPIRE evaluated the reporting quality of RCT protocols approved by a Swiss REC in these years, according to the SPIRIT guideline [13, 14]. It was assumed that two years around the LHR would be a sufficient time period to observe first effects of the new legislation. In Objective 4, we intended to compare approval times before and after the enactment of the new legislation, which aimed to accelerate these. To facilitate comparison with effects on RCT preparation phase costs and working time efforts, we considered RCTs that entered their approval process in 2012 and 2016.

Overview of main findings and related issues

Objective 1 was achieved as planned, providing a tool for the documentation and potentially for the planning of RCT costs. Objectives 2 and 3 could not be achieved as planned as they were massively affected by difficulties to retrieve a sufficient amount of RCT cost data. Main reasons included non-response by clinical investigators and refusal to provide information due to a perception of too much effort required to estimate working times. The latter may hint at an absence of efficient documentation. In the case of RCTs approved before the enactment of the new LHR, some responsible persons could no longer be contacted (e.g. due to change of workplace with no new contact data available) and lack of recall played a relevant role. Additionally, legal and privacy issues were mentioned for industry-sponsored RCTs. Objective 4 was partially compromised by the fact that the information provided by Swissmedic did not allow us to distinguish RCTs from other clinical trials. More importantly, the Swissmedic data did not include an identification code that would have enabled a matching of Swissmedic and REC approval time data at the RCT level. In consequence, we had no means of assessing combined Swissmedic and REC approval times. This would have been of key interest given related changes introduced by the LHR (i.e. until 2013, Swissmedic and REC submissions had to be made sequentially while they can be made in parallel since 2014).

Due to the above-mentioned limitations, our numerical findings for Objectives 3 and 4 are of limited value only. In the context of Objective 3, complete data were available for 18 RCTs approved in 2012 and for 35 RCTs approved in 2016. Results did not indicate any substantial change in the costs of the preparation phase of RCTs between 2012 and 2016. Item-level cost comparisons indicated that selection effects may have been relatively limited despite the small numbers of RCTs with data available. This may provide an indication that there were no clear-cut, strong effects of the LHR on RCT preparation costs. However, a distortion of the observed (lack of a) cost difference by selection, recall and chance effects remains a very relevant possibility. For Objective 4, we assessed Swissmedic and REC approval times in 2012 (Swissmedic, n=213 and REC, n=183) and 2016 (Swissmedic, n = 179 and REC, n=217). With respect to REC approval times, valid comparison was only possible for single centre studies (n=40 in 2012; n=68 in 2016), due to the development of the lead REC approach between 2012 and 2016. Median Swissmedic approval times were only available for 'any clinical trials' (including e.g. non-randomised or single arm trials); the vast majority were actual RCTs according to Swissmedic but they could not be formally distinguished based on the data we received. Taken by themselves, Swissmedic and REC approval times in 2016 appeared to be longer than in 2012. The smaller number of applications to Swissmedic and the longer Swissmedic approval times in 2016 may have been a consequence of the exemption of low risk RCTs from Swissmedic approval. Combined Swissmedic and REC approval times could not be assessed for reasons stated above. Thus, combined approval times may have been shorter in 2016 than in 2012 due to the possibility of parallel submission under the new LHR.

Considerations regarding Objective 1

The cost item list for RCTs resulting from the work on Objective 1 is, to our knowledge, the first comprehensive cost item list, developed using a consensus process, for clinical research studies in Switzerland. It was used to systematically collect cost data for Objective 2 and Objective 3 (see Figure 1). The item list may also serve as an actual costing template or a checklist during the planning phase of a RCT, in Switzerland and abroad. For the latest version of the cost item list, see separate Microsoft Excel® file "*Cost item list template - simplified.xlsx*".

Considerations regarding Objective 2

Objective 2 could not be achieved as planned as it was massively affected by difficulties to retrieve a sufficient amount of RCT cost data, despite our efforts to contact experts from academia, industry, clinical trial units, contract research organisations, clinical research organisations involved in the cost aspects of RCTs conducted in Switzerland, and investigators who provided us with preparation phase costs (as part of Objective 3) and were in charge of an RCT approved by a Swiss REC in 2012. Discernible reasons for the difficulties to collect

RCT cost data included inability to contact responsible persons (outdated contact information), non-response, perceived high effort to provide information (i.e. potential respondents expected the burden to be too high), lack of recall, and legal and privacy issues in the case of industry-sponsored RCTs.

We managed to collect resource use and cost data for 20 investigator-initiated RCTs (in 10 cases with detailed cost data) but did not receive any detailed cost information for industry-sponsored RCTs. Due to the small sample size even for investigator-initiated RCTs, we judge the risk of selection bias to be high. Firm conclusions cannot be drawn from the results. Our accompanying systematic review indicated that despite the broadly shared opinion that RCTs are expensive and that their costs are increasing [6, 8, 9, 16], the published evidence on RCT costs is sparse internationally and the usefulness of the available data is highly limited [17]. The underlying methodology of gathering these data and translate them into estimates remained unclear. Furthermore, no detailed overview of all cost aspects of RCTs was provided in any of the published studies [17].

Given the sparseness of evidence at the international level, we performed a detailed retrospective assessment of our data despite the above-described limitations. The assessment is the first to address the resource use and costs of investigator-initiated RCTs fully conducted or at least initiated in Switzerland. In all of the ten RCTs with detailed full costs, the conduct phase accounted for the largest proportion of costs (median of 54% of total costs; 25th to 75th percentile range [IQR]: 40.4%-72.0%). The preparation phase ranged second (median: 26.1%; IQR: 18.9%-41.4%) and the post-conduct phase third (median 16.3%; IQR: 5.3%-24.1%). Total costs differed widely, ranging from CHF 0.1-5.0 million per RCT (see Table 2 and detailed cost listings in the Appendix, Tables S1 and S2). We also identified large differences in costs per patient, ranging from CHF 148 to CHF 20’301. For comparison, the literature review identified reports of RCT costs ranging from USD 0.2-611.5 million per RCT and from USD 43-103’254 per patient [17].

Costs per site were higher for RCTs only conducted in Switzerland than for the oncology RCTs sponsored by the SAKK (with additional clinical centres outside Switzerland), or the sample including all RCTs. This difference may indicate that the per-site costs of RCTs are higher in Switzerland than in other countries. However the difference was driven to some extent by one large RCT, referred to in this report as the Prednisone trial [32], which was conducted at seven sites in Switzerland and for which we had the most detailed cost data. Therefore, the observation needs to be interpreted with caution.

In line with previous studies [33], personnel costs accounted for the majority of expenditures, mainly during the conduct phase. In line with this, salary costs were a main driver in time-

intense interventions (e.g. behavioural counselling, nutrition trial). Overhead expenditures were included in personnel costs on a pro-rate basis. Hence, some infrastructure, equipment and material (e.g. stationery) costs are contained in the estimates of personnel costs. Furthermore, drugs costs were found to be major cost components in some oncology trials (if not sponsored by a company; e.g. SAKK 1 and 4), while other RCTs used relatively cheap drugs (Appendix, Table S1 and S2).

The assessed cost data indicated that the conduct phase was the most expensive part of most RCTs. Differences in the relative weight of this phase could be explained by the duration of patient enrolment, treatment, and follow-up, the place where an RCT was conducted, drug costs, how many centres were involved, and to some extent, sample size. Sample size affected costs during all three main phases of trial conduct, i.e. during the conduct phase, but also during the preparation phase (e.g. insurance fee) and post-conduct phase (e.g. data cleaning). Very moderate costs compared to the included sample size were seen in an antibiotics prescription trial. This was mainly due to the partial use of routinely collected data, which allowed achieving a large target sample size at a low cost.

In order to gain a deeper understanding of reasons for the large range in total costs and costs per patient, we performed an in-depth analysis of two different trials, for which we had access to very detailed resource use and cost data, the Oxantel and the Prednisone trials [32, 34]. This case study, which also exemplified how RCT costs could be reported, has been published separately in the Journal of Clinical Epidemiology [15].

Considerations regarding Objective 3

Despite intensive efforts to contact the principal investigators of all RCTs approved by Swiss RECs in 2012 (before the LHR) and in 2016 (after the LHR) and offering assistance by phone or in person, the amount of available data remained non-satisfactory. For very similar reasons as listed above in the section on Objective 2, we had difficulties to retrieve a sufficient amount of data.

We received a total of 19 cost datasets (n=18 complete) for RCTs that were approved by Swiss RECs in 2012 and 47 datasets (n=35 complete) for RCTs approved in 2016. Based on the sample with complete data, the median working time for the preparation phase of RCTs was 113 days (IQR: 51-190 days) in 2012 and 133 days (IQR: 79-240 days) in 2016. The median estimated costs to plan and prepare an RCT were very similar: CHF 71’100 (IQR: CHF 58’400-86’100) in 2012 and CHF 71’300 (IQR: CHF 41’800-166’500) in 2016. While the results for the working time outcome appeared to indicate an increase of the required effort, the cost results did not indicate any substantial change between 2012 and 2016, for the preparation phase of RCTs. Consistent with this, ranges of costs were similar for 2012 and 2016, also at the item

level (Table 9 and Table 10). Thus, selection effects may have been relatively limited despite the small numbers of RCTs for which we had data available. Still, a distortion of the observed (lack of) cost differences by selection effects and recall problems remains a very relevant possibility, and chance effects may have influence the results substantially. RCT characteristics were partially different (Table 4). Most 2016 RCTs were classified as risk category A (n=29: 83%), the lowest LHR risk category. Only three RCTs each were classified as risk category B or risk category C. The six RCTs belonging to risk category B or risk category C seemed to be less time consuming and less expensive than category A trials (Table 5). Given the very small for risk categories B and C, chance and selection effects may be the likeliest explanation. There was no information on risk categories for the 2012 RCTs.

In general, fixed costs, which were paid via separate bills for specific fees (e.g. RECs) and services (e.g. sample size estimation), accounted for a relatively small proportion (i.e. less than 5%) of the overall preparation phase costs (Table 5 and Table 8). The only exception was seen in international multicentre RCTs in 2016, where fixed costs were extremely high. However, this observation was based on only two international RCTs and may be chance-driven.

Considerations regarding Objective 4

We collected and assessed Swissmedic and REC approval times for 2012 and 2016. REC and Swissmedic data did not share a common trial identification number that could have been used to match the information between the sources. Therefore, we could only study REC and Swissmedic approval times separately. It would have been important to estimate combined approval times (from first submission to either first REC or Swissmedic until last approval by REC or Swissmedic) given that submissions under the new LHR can be done in parallel to the lead REC and Swissmedic while they had to be sequential in 2012 [2]. This may allow for relevant time savings for researchers which could not be quantified within this study, as the structure and content of the available data did not allow us to assess combined approval times.

We calculated times from submission to approval that included the response time of the respective authority as well as any time the sponsor needed to respond to the authority's questions and additional requests. Reaction times of sponsors were available from the Swissmedic data and from the REC data for 2016 extracted from BASEC, but not from the REC data for 2012. Hence, approval times excluding sponsor reaction times could be calculated for Swissmedic but not for the RECs.

Among all RCTs the time to achieve approval from RECs seemed to be longer in 2016 compared to 2012 (Table 12). However, 2012 data were retrieved differently (directly from RECs) compared to 2016 data (from BASEC). Therefore, the 2012 sample included approval times from lead RECs as well as from non-lead RECs while the 2016 sample only included

approval times from lead RECs. We tried to retrieve information on which of the RECs was a lead REC in 2012 but we did not succeed with this. We were informed by swissethics, the organisation of the Swiss RECs, that the process of differentiating between lead and non-lead RECs was only partially implemented in 2012. (This information, however, is in contradiction with the fact that Interpharma reported approval times for lead and non-lead RECs already for 2012 and 2013. The data received from Interpharma for clinical trials (not only RCTs) also indicated that approval times were longer in 2016 (lead REC: 109.8 days; non-lead REC: 98.3 days) compared to 2012 (lead REC: 64.0 days; non-lead REC: 31.0 days). However, the approval times reported by Interpharma for 2016 appeared to be very high. As we do not know how these were generated, we cannot comment on this.)

Independent of the discussion about lead or non-lead RECs we feel that at least approval times for single centre RCTs could be compared without major limitations as in single centre RCTs each REC must have been the quasi-lead REC. While the size of the sample of single centre RCT was rather limited in size (n=40 in 2012 and n=68 in 2016), we also found some evidence that approval times in 2016 were longer (median: 92 days; IQR: 65-131) compared to 2012 (median: 82 days; IQR: 49-106.8). As explained above, these approval times included any time the sponsors needed to respond to questions and requests.

Median Swissmedic approval times from for 'any clinical trials' (of which, according to Swissmedic, the vast majority were RCTs) were 27 days (IQR: 19.0-50.5 days; n=213) in 2012 and 49 days (IQR: 36.0-67.0 days; n=179) in 2016. When the times which sponsors needed for requested amendments were subtracted from the Swissmedic approval times, the median duration was 25.0 days (IQR: 33.0-38.0 days) in 2012 and 36.0 days (IQR: 33.0-38.0 days) in 2016. Of note, under the new LHR, RCTs falling in the lowest risk category A do not require Swissmedic approval. For the year 2012, before the enactment of the LHR, no such risk categorisation was available. Hence, the Swissmedic approval times for 2012 and 2016 cannot be assumed to apply to the same 'population' of RCTs, limiting comparability. The smaller number of applications to Swissmedic and the longer Swissmedic approval times in 2016 may both be a consequence of the exemption of low risk RCTs from Swissmedic approval. The remaining, higher risk RCTs may require more time than was required earlier, on average. More generally, changes in approval times may also have occurred due to general differences in approved studies (e.g. the proportion of industry funded RCTs was higher in 2016 compared to 2012; Table 12). There seemed to be a tendency towards shorter approval times in industry-sponsored trials compared to trials initiated by hospitals or research groups as sponsors (according to the Swissmedic classification).

In summary, despite some uncertainties, the approval time data available to us appeared to indicate that REC and Swissmedic approval times, taken by themselves, increased after the

implementation of the LHR. In the case of Swissmedic, this may be explained by the new rule under which low risk trials do no longer require Swissmedic approval. Unfortunately, combined approval times could not be assessed within this study, due to the structure of the available data.

Strengths and limitations

According to our knowledge, this study is the first evaluating in detail costs, resource use and approval times of RCTs in Switzerland. While other studies of costs and resource use mainly focused on industry-sponsored studies, they did not offer the level of detail and transparency that we do [35]. Due to our detailed and transparent listing of resources used for two RCTs, it is for the first time possible to understand how RCT costs actually arose. Moreover, we assessed the working time effort for each step of RCT conduct, whenever possible. In our opinion, this approach is better suited to reflect true costs than taking lump sums, which are e.g. paid by funders per patient, because such payments may not adequately reflect the costs of RCT conduct. Reportedly, they are often beyond (or below) covering the actual expenses [36]. With respect to approval times by Swiss RECs and Swissmedic, we believe to have retrieved and analysed as much information as was possible at this point in time.

Our study has, however, major limitations: Above all, we were unable to retrieve a satisfactory amount of valid cost information for RCTs, despite massive efforts. In consequence, our samples sizes for Objective 2 but also for Objective 3 (particularly for RCTs submitted in 2012) remained small. There were different reasons for this. None of the addressed companies provided full cost data (Objective 2). For example, after several inquiries with legal departments, access to costing data was denied by one company for reasons of confidentiality, while resource limitations and the complexity of internal costing structures were the stated reason for denial at a second company. Interpharma stated that the accounting structures at large pharmaceutical companies may not allow for the collection of unit costs per study. The data we received from industry respondents in the context of Objective 3 were also often incomplete. It was stated that not all required resources could be estimated retrospectively. For investigator-initiated RCTs it became evident that costs of RCTs are not routinely collected by academic investigators. Furthermore, many investigators abstained from contributing data due to the time efforts they feared. As academic CTUs are not involved in the costing of entire RCTs, but rather cover single aspects with their services, actual costs of entire RCTs could not be obtained from CTUs either. Another reason were outdated contact information (especially for 2012) as email addresses and letters could not be delivered in a number of cases, or we received responses that the main responsible person had left, retired or deceased. In some cases, we received messages that a study was never initiated or that the preparation phase was still ongoing.

Furthermore, the cost data that we received were in heterogeneous formats, despite the cost item list that we provided to the addressed investigators and institutions. For some trials, we were able to obtain a very high level of detail (Oxantel and Prednisone trials, see section 4.2.1 [15, 32, 34]), while for others, there was much less granularity. The trial costs for oncology trials provided by the SAKK did not include “in-kind” contributions of the SAKK and its affiliated members and hospitals. The SAKK trials costs are therefore likely to be underestimated to a certain degree.

The majority of the time efforts spent on RCTs had to be estimated retrospectively within structured interviews, implying risks of lack of completeness and recall bias.

Overall, the cost data presented in this report can only be considered as rough estimates, except in a few cases where we had a high level of detail available. They give an indication of the magnitude of RCT costs, in a field where data are very sparse. The relevance of this is reflected in two publications in the Journal of Clinical Epidemiology that emerged from our work [15, 17]. Beyond this, it needs to be re-stated that only relatively few investigators and institutions responded positively to our data requests. This implies small sample sizes and a strong possibility of selection and chance effects. Hence, our results for Objective 2 cannot be regarded as precise or representative of all trials conducted or initiated in Switzerland. Our results for Objective 3 are potentially affected by similar problems, despite a few hints (namely similar item-level cost estimates for 2012 and 2016) that distorting selection effects may have been rather limited.

For Objective 3 we were able to collect more complete preparation phase datasets for RCTs submitted to RECs in 2016 (n=35) than in 2012 (n=18). This may be because retrospectively estimating working times, in general already difficult, is much more challenging after several years. It may also be easier to reconstruct working efforts in RCTs with a 'simpler' structure, which may have led to selection effects. It is important to note in this context that more than half of our cost data were from single centre RCTs, while approximately 78% (2012) and 69% (2016) of all RCTs approved by Swiss RECs were multicentre trials.

We assumed that the cost impact of the LHR, if any, would be strongest in RCT preparation costs because the newly implemented rules changed mainly the conditions that have to be fulfilled to start an RCT. In the empirical approach taken and given the sparseness of data, there was no means of validly subdividing preparation costs further into elements where the LHR may have had a stronger *versus* weaker (or no) impact. A cost impact of the LHR on the costs of the other trial phases could not be excluded either.

In Objective 4, the major limitation was that combined REC and Swissmedic approval times could not be assessed due to the structure of the data and that approval times from RECs

could only be directly compared for single centre RCTs (as discussed above). Furthermore, it was not possible to collect specific approval times for lead- and non-lead RECs, for multicentre RCTs. We received data from Interpharma which may give an impression of the differences between lead and non-lead RECs. However, we did not receive study-level data from Interpharma and no information on the underlying data collection process. We were therefore unable to interpret some of the information provided (e.g. very long approval times for non-lead RECs in 2016 compared to 2012 reported by Interpharma).

If any of the observed changes in approval times were caused to some extent by the new LHR, these effects may still be only temporary, until researchers are used to the new LHR and the associated new requirements.

Therefore, it would be interesting to collect more data on preparation costs as well as on approval times in the future, to see how these values develop over the next few years. In addition, data from more Swiss RCTs on total and detailed resource use and costs would be extremely useful to eventually create a sort of reference database that may support investigators and clinical trial units in the budget planning of RCTs as well as funding agencies or other stakeholders in the validation of RCT budgets. A comparison with empirical cost data from RCTs conducted outside of Switzerland would be of value too.

6. Conclusion

We aimed to approach the question of a cost impact of the new LHR on RCT costs in four steps. In the first preparatory step, we created a comprehensive list of standard cost items for RCTs that can be used as a tool to assess and collect resource use and cost data for RCTs.

The second and third step involved the collection of RCT cost data. It proved to be impossible to retrieve a satisfactory amount of valid cost information for RCTs. Clearly, cost data for RCTs are not routinely collected. Therefore, working efforts had to be estimated retrospectively which was time consuming and most likely highly imprecise. This as well as problems of availability, recall problems and confidentiality issues were reasons for the overall low participation of principle investigators. Ultimately, we only received a relatively small sample of sets of full RCT cost data, which were all from non-industry RCTs. In addition, the sample of sets of preparation costs for RCTs collected for Objective 3 was also much smaller than anticipated and derived also mainly from non-industry RCTs. A systematic review indicated that empirical and publicly available resource and cost data for RCTs are also very sparse internationally.

The data gave no indication that RCT preparation costs may have changed substantially between 2012 and 2016. However, due to the limited sample size and related risks of bias and chance effects, the data should be interpreted with caution.

Accessible data on REC and Swissmedic approval times for RCTs were substantially limited. The lack of risk categorisation in clinical trials submitted for approval in 2012 affected the comparability of Swissmedic approval times between 2012 and 2016. In addition, RECs and Swissmedic did not use a joint study identifier. This made it impossible to consistently assess approval history at the combined REC and Swissmedic levels. This issue might be overcome in the future, e.g. if Swissmedic also used the study identification numbers assigned in BASEC. REC and Swissmedic approval times appeared to be longer in 2016 compared to 2012. However, due to the described limitations, the situation at Swissmedic could not be judged in a valid way. Combined approval times, which the data did not allow us to assess, may still have been shorter due to the possibility of parallel submission under the new LHR.

The discrepancy between reports of high RCTs costs, often used in discussions on healthcare costs and pricing, and the lack of transparent and valid evidence on the topic remains striking. Tools to budget and manage costs in the academic setting are urgently needed, and we believe that without budgeting and tracking costs efficiently, clinical research will risk to stay unsustainable [16] and prone to failure [18]. Stakeholders who are able to influence the planning and the design of academic RCTs, such as for example national funding agencies, should consider more emphasis on well-planned *a priori* feasibility assessments and well

thought-through budgets. Further tools to monitor costs of RCTs prospectively are needed to acquire more data with higher accuracy.

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Appendix

A - Search Strategy for Objective 1

Ovid search strategy

1 Randomised Controlled Trial* as Topic.mp. or Randomised Controlled Trials as Topic/
2 clinical trial* as topic.mp. or Clinical Trials as Topic/
3 1 or 2
4 (cost* adj2 (component* or item*)).tw.
5 (budget* adj2 calc*).tw.
6 ((study or trial) adj2 budget*).tw.
7 cost* method*.tw.
8 (unit* adj2 cost*).tw.
9 4 or 5 or 6 or 7 or 8
10 3 and 9
11 remove duplicates from 10

EconLit search strategy

1st field: TX All Text:
(randomised control* trial*) or RCT* or (clinical trial*) or (clinical stud*)
AND
2nd field: TX All Text:
(cost* component*) or (cost* item*) or (budget* calc*) or (study budget*) or (trial budget*) or (cost* method*) or (unit* cost*)

B - References Systematic Internet Search & Literature Review

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Table S1. Detailed resources used and associated costs of the Prednisone Trial.

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs in 2012 USD	Fraction of total costs (%)
Preparation phase					
Salary costs:					
Study design, proposal, documents, analysis plan	Principal investigator	52		49'949	2.2
	Methodological expert	4		3'746	0.2
	Statistician	3		2'497	0.1
	External expert	1		2'755	0.1
	External expert	1		2'755	0.1
	External expert	1		2'755	0.1
	10 external experts	3		2'497	0.1
Source documents	Resident	14		8'142	0.4
Consultation of further experts	Clinical Trial Unit	6		6'329	0.3
After ethics votum: protocol/dossier rewriting	Resident	4		2'443	0.1
Dossier preparation for different ethics committees	Resident/study nurse	33		18'728	0.8
	Principal investigator	3		3'122	0.1
Swissmedic dossier preparation	Resident/study nurse	7		4'071	0.2
Protocol amendments	Resident	17		9'771	0.4
Communication with centres for set-up	Principal investigator	16		14'985	0.7

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs in 2012 USD	Fraction of total costs (%)
Set-up meeting with pharmacy	Resident/study nurse	3		1’628	0.1
	Principal investigator	1		1’249	0.1
Meeting with laboratories	Resident/study nurse	11		6’514	0.3
	Principal investigator	10		9’990	0.4
Set up of sites	Resident/study nurse	6		3’420	0.1
Other costs:					
Approval fees (4 ethics committees, Swissmedic)			5	5’433	0.2
Insurance			1	68’568	3.0
Subtotal: Trial conception, planning, and preparation		**196**		**231’347**	**10.1**
Conduct phase					
Salary costs:					
Study drug and matching placebo (production, analytics, packaging, labelling, and randomisation, concealment, etc.)	Pharmacy	Time missing	800	11’922	0.5
Coordinating site (2328 patients screened, 400 enrolled)					
· Screening	Resident/study nurse	99		57’160	2.5
· Informing participants	Resident/study nurse	164		94’778	4.1
· Enrolment	Resident/study nurse	85		48’855	2.1
Site 2 (458 screened, 40 enrolled)				0	0.0
· Screening	Resident/study nurse	18		10’585	0.5

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs in 2012 USD	Fraction of total costs (%)
· Informing participants	Resident/study nurse	32		18’646	0.8
· Enrolment	Resident/study nurse	8		4’885	0.2
Site 3 (96 screened, 33 enrolled)					
· Informing participants	Resident/study nurse	7		3’908	0.2
· Enrolment	Resident/study nurse	7		4’031	0.2
Site 4 (542 screened, 153 enrolled)					
· Screening	Resident/study nurse	46		26’463	1.1
· Informing participants	Resident/study nurse	38		22’066	1.0
· Enrolment	Resident/study nurse	32		18’687	0.8
Site 5 (185 screened, 148 enrolled)					
· Screening	Co-investigator	64		56’817	2.5
· Informing participants	Co-investigator	13		11’551	0.5
· Enrolment	Co-investigator	31		27’722	1.2
Site 6 (11 enrolled)					
· Informing participants	Co-investigator	1		687	0.0
· Enrolment	Co-investigator	2		2’060	0.1
Site 7 (15 enrolled)					
· Informing participants	Resident/study nurse	1		611	0.0

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs in 2012 USD	Fraction of total costs (%)
· Enrolment	Resident/study nurse	3		1’832	0.1
Additional time for 1/10 patients for which exclusion criteria was only noticed after informing the patient	Resident/study nurse	6		3’257	0.1
Additional time for 508 patients with immunosuppression which were assessed for eligibility	Resident/study nurse	7		4’071	0.2
Additional time for "no informed consent possible" assessed for eligibility	Resident/study nurse	7		3’925	0.2
Additional time for patients which did not consent	Resident/study nurse	43		24’631	1.1
Treatment / follow up / data entry at coordinating site	Study nurse	392		260’460	11.3
Site 2	Study nurse	53		27’684	1.2
Site 3	Study nurse	43		22’840	1.0
Site 4	Study nurse	201		105’892	4.6
Site 5	Study nurse	195		102’432	4.4
Site 6	Study nurse	14		7’613	0.3
Site 7		20		10’382	0.5
Determination of clinical stability	Resident	92		52’926	2.3
Patient discharge	Resident	37		21’496	0.9
Ongoing communication/coordination with participating sites	Resident/study nurse	204		107’350	4.7
Additional insulin therapy necessary in an additional 8 % (n=33) of treatment arm patients:					

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs in 2012 USD	Fraction of total costs (%)
Informing patients	Study nurse	3		1'344	0.1
	Resident	1		430	0.0
Insulin (covered by insurance)					
Ongoing data management	Data manager	17		18'144	0.8
Ongoing monitoring	Monitor	17		14'531	0.6
Ongoing sample management	Resident	59		34'153	1.5
Sample sorting (n=16'000)	Study nurse/student	38		25'317	1.1
Shipping: Admin time and fees	Resident/study nurse	20		18'217	0.8
Adverse events / severe adverse events documentation	Resident	13		7'287	0.3
Data safety & monitoring board	External expert	1		936	0.0
	External expert	1		2'755	0.1
Yearly safety report	Resident, study nurse	53		27'626	1.2
Ongoing meetings of principal investigator with staff, collaboratios, literature research related to project, etc.	PI	303		292'203	12.7
Ongoing training of staff at sites	Resident	14		8'142	0.4
	Study nurse	26		13'419	0.6
Other costs:					
Study drug compound			400	3'070	0.1
Biological samples (materials, analysis of biological samples)			16'000	218'624	9.5

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs in 2012 USD	Fraction of total costs (%)
Other medical material (freezer, blood pressure machine, etc.)			7	23'015	1.0
Other material (flyers, photocopies, folders etc.)				10'549	0.5
Incentives for sites (e.g. breakfasts, dinners, etc.)			38	14'294	0.6
Travel expenses				26'680	1.2
Subtotal: Patient enrolment, Treatment, Follow-up		**2'533**		**1'938'958**	**84.2**
Post-conduct phase					
Salary costs:					
Data cleaning	Resident	28		12'487	0.5
	Registrar	26		12'487	0.5
Statistical analysis	Methodological expert	13		16'285	0.7
	Statistician	13		18'712	0.8
Final study report	Principal investigator	1		499	0.0
	Resident	3		1'628	0.1
	Study nurse	3		1'384	0.1
Writing of main publication (Lancet)	Principal investigator	9		8'741	0.4
	Resident	14		8'142	0.4
	Registrar	7		4'678	0.2
	Methodological expert	3		2'497	0.1
	Statistician	3		2'497	0.1

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs in 2012 USD	Fraction of total costs (%)
Submission procedures	Resident	1		814	0.0
	Secretary	2		814	0.0
Review process	Principal investigator	8		8'991	0.4
	Resident	10		5'863	0.3
	Methodological expert	3		2'497	0.1
	Statistician	3		2'497	0.1
	Registrar	7		6'243	0.3
	External expert	1		1'377	0.1
Proofs	Principal investigator	3		2'497	0.1
	Resident	3		1'628	0.1
Other costs:					
Publication fee				1'315	0.1
Conference fee and expenses	Resident	7		4'940	0.2
Subtotal: post-conduct phase		**168**		**129'518**	**5.6**
Additional costs					
Computer rental and software				2'061	0.1
Total costs		**2'897**		**2'301'884**	**100.0**

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Table S2. Detailed resources used and associated costs of the Oxantel-Trial.

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs (in 2012 USD)	Fraction of total costs (in %)
Trial conception, planning, and preparation					
Salary costs:					
Preparation of research protocol (e.g. literature review, development of idea, writing-up, meeting time)	1 Principle Investigator	7.8		5'343	5.3
	1 PhD Student	15.6		3'637	3.6
	2 Statistician	1		844	0.8
	2 Consulted experts	1		1'055	1.1
	1 In house authority	0.5		527	0.5
Acquiring funding	1 Principle Investigator	6.5		4'453	4.4
Developing/updating investigational brochure, standard operating Procedures, case report form and patient related forms	1 Principle investigator	0.25		171	0.2
	1 PhD Student	7.2		1'679	1.7
	1 Co-Principle investigator	1		60	0.1
	1 In house authority	0.25		264	0.3
Applications to ethics committee, authorities, insurance (e.g. preparation, submission; but not fees)	1 Principle investigator	0.5		343	0.3
	1 PhD Student	3.4		793	0.8
Budgeting (study budget calculation and controlling)	1 PhD Student	1.3		303	0.3
Reporting to funders, managing clinical trial portals	1 Principle investigator	1		891	0.9
	1 PhD Student	1		233	0.2
Production of Oxantel Pamoate and matching placebos	1 Research Associate (Pharmaceutical Technology)	5		2'637	2.6

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs (in 2012 USD)	Fraction of total costs (in %)
Packaging and labelling of study drugs	1 Pharmacy PostDoc	1		356	0.4
	1 Pharmacy PhD student	1		249	0.3
Other costs:					
Ingredients Oxantel Pamoate			1	251	0.3
Ethical approval in Basel, Switzerland			1	317	0.3
Ethical approval on Pemba Island, Tanzania			1	240	0.2
Trial registration			1	310	0.3
Insurance for participants			1	1'482	1.5
Subtotal: Trial conception, planning, and preparation		**55.6**		**26'437**	**26.3**
Patient enrolment, Treatment, Follow-up					
Salary costs:					
Screening and enrolment	6 Field staff	120		2'880	2.9
	6 Laboratory staff	120		3'024	3.0
	1 Cleaner	21		252	0.3
	2 Co-Principle investigator	48		2'880	2.9
	2 Data entry staff	42		1'008	1.0
	1 PhD student	25		5'829	5.8

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs (in 2012 USD)	Fraction of total costs (in %)
Treatment, assessing AE/SAE, and follow-up	2 Local Physicians	30		1'800	1.8
	6 Field staff	66		1'584	1.6
	6 Laboratory Staff	66		1'584	1.6
	1 Cleaner	11		132	0.1
	2 Co-Principle investigator	32		1'920	1.9
	2 Data entry staff	28		672	0.7
	1 PhD student	23		5'363	5.3
	1 Principle investigator	7		4'795	4.8
Other costs:					
Material for stool collection (stool containers)			2'400	240	0.2
Material for stool analysis (Kato-Katz Kit, wire mesh)				1'072	1.1
Hired car (in days) including fuel and driver			40	1'920	1.9
Transport reimbursement for patients/guardians			600	720	0.7
Albendazole			300	90	0.1
Mebendazole			150	38	<0.1
Albendazole matching placebo			300	158	0.2
Mebendazole matching placebo			450	211	0.2
Materials for clinical examination and adverse event mitigation				370	0.4
Telephone, Fax, Internet, stationery				432	0.4

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs (in 2012 USD)	Fraction of total costs (in %)
Costs for 2 investigators from Switzerland (flights, bill of expenses, accommodation)	1 Principle investigator, 1 PhD student			5'994	6.0
Subtotal: Patient enrolment, Treatment, Follow-up		**645**		**44'968**	**44.8**
After last patient out					
Salary costs:					
Treatment of all school-children	6 Field staff	6		145	0.1
	1 PhD student	1		232	0.2
Data management, data cleaning	1 PhD student	4		933	0.9
Statistical analyses	1 PhD student	6.5		1'516	1.5
	1 Statistician	1		844	0.8
Output Tables and Figures plus interpretation of results	1 PhD student	13		3'031	3.0
	1 Principle investigator	0.5		343	0.3
Manuscript preparation and revision	1 PhD student	53		12'358	12.3
	1 Principle investigator	4.5		3'083	3.1
	1 Statistician	3		1'532	1.5
	2 Consulted experts	1		1'055	1.1
Conference (including abstract submission)	1 PhD student	3.5		816	0.8
Other costs:					
Albendazole for treatment of all school-children			2100	630	0.6
Hired car (in days) for treatment of all school children			1	48	0.1

Cost component	Persons involved	Total time estimation (in days)	Number of items	Costs (in 2012 USD)	Fraction of total costs (in %)
Conference fee and expenses (British Society for Parasitology)	1 PhD student		1	1'020	1.0
Publication fees (*New England Journal of Medicine*)	1		1	0	0.0
Subtotal: After last patient out		**97**		**28'585**	**28.5**
Additional costs					
Computer rental and software (STATA)	2			384	0.4
Total costs		**797.6**		**100'374**	**100.0**

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Supplementary File 1:

Comprehensive version of the RCT cost item list (submitted as an Excel file).

Supplementary File 2:

Simplified, easier to use version of the RCT cost item list (submitted as an Excel file).