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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# 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; $25^{th}$ to $75^{th}$ 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 **Fehler! Verweisquelle konnte nicht gefunden werden.** 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.