Completion and publication of clinical trials in a cooperative group: a cohort study of trials of the Swiss Group for Clinical Cancer Research (SAKK)

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ABSTRACT

Background Premature trial discontinuation and non-publication of trial results are still major issues negatively affecting reliable evidence generation. Objectives To investigate trial completion and publication rate of cancer trials conducted within the Swiss Group for Clinical Cancer Research (SAKK). Design Cohort study of clinical trials. Setting Cohort of interventional cancer trials conducted in Switzerland with accrual closure between 1986 and 2021 identified from the SAKK trial management system. Outcomes Premature trial discontinuation and publication in peer-reviewed journal. Results We included 261 trials; median number of recruited patients was 150.5 (range 1–8028). Most trials (67.0%) were randomised. Overall, 76 of 261 (29.1%) trials were prematurely closed for accrual. The three main reasons for premature closure were insufficient accrual in 28 trials, followed by stopping for futility in 17 or efficacy in 8 trials. We included 240 trials for the publication status (21 excluded, because 8 still in follow-up, for 10 the primary completion date was less than a year ago and for 3 the manuscript was submitted, but not accepted yet). 216 of 240 (90.0%) were published as a full article, 14 were published in other formats, leading to an overall publication rate of 95.8%. The rate of premature discontinuation declined over time, with 34.2%, 27.8% and 23.5% in trials activated before 2000, between 2000 and 2009, and since 2010, respectively. We observed an increasing publication rate in peer-reviewed journals over time: 79.2% (closed before 2000), 95.7% (closed between 2000 and 2009) and 93.2% (closed after 2010). Conclusion Insufficient patient recruitment is still the major reason for premature trial discontinuation. SAKK has continuously improved its quality management of trial conduct over time leading to increased successful trial completion and publication. However, there is still room for improvement to increase the number of trials reaching their target sample size.

INTRODUCTION

Cancer is one of the biggest medical burdens for western societies, both in the number of life years lost as well as in terms of direct and indirect costs.1-3 Clinical trials are essential to investigate and establish new treatment options and to improve care and outcome for patients with cancer. However, clinical trials are very resource demanding in terms of planning, setup, conduct, analysis and publication. Previous works have shown that poor patient recruitment is the predominant reason for premature trial closure.4 This is an important issue, because not reaching the planned number of patients is likely to render the research question unanswered because of insufficient power. Although reasons for poor patient recruitment are preventable, a recently updated analysis has revealed that the average rate of trial discontinuation is 30% and has not changed over time.5 Still, if results of discontinued trials are published, they can be very useful for meta-analysis. However, although laws have been set in place to enforce trial registration and dissemination of results,6 many discontinued trials remain unpublished and are not available for evidence generation.5 In summary, trial discontinuation and non-publication of clinical trials constitute a substantial waste of precious resources,7 especially because in most cases the discontinuation is preventable.8 Moreover, these shortcomings may increase distrust in clinical research, above all from patients and families. Some evidence suggests that cancer trials were more likely
to be completed as planned and results more often published compared with trials enrolling patients without cancer.\(^4\)

The Swiss Group for Clinical Cancer Research (SAKK) is a non-profit organisation organised as an academic research association consisting of 22 major hospitals in Switzerland. The SAKK receives funding from the Swiss Federation through the state secretary of Education, Research and Innovation. Other funding bodies include the Swiss Cancer League, Cancer Research Switzerland and private foundations. To realise clinical trials, additional project specific-funding is raised by the respective trial groups. The SAKK performs investigator-initiated trials including cooperative trials with other academic research groups ranging from phase I to phase III trials in university and non-university cancer centres in Switzerland. It is an area of public interest that state-funded research organisations use their resources well and efficiently. Thus, in this manuscript, we aim to analyse trial completion and publication from all SAKK trials over time.

METHODS

Study design and definitions

In this retrospective cohort study, we included all trials with patient accrual closure (irrespective of whether planned sample size was achieved) between 1986 and 2021 for which the sponsor of the study was either SAKK or another collaborative group with SAKK as sponsor representative in Switzerland. Trials still ongoing, completed or stopped prematurely after 2021 were excluded for this analysis. Type of trials included all interventional clinical trials (phases I, II and III). We excluded cohort studies, registries and other research projects (eg, translational studies), because recruitment mechanisms are assumed to be different from interventional clinical trials. We prespecified study characteristics to be collected for each study including information on year of study activation and closure (the date when the trial was closed for patient accrual for whatever reason), sponsor of the study, type of study, patient population, whether the study was randomised, and planned and actual number of recruited patients. A trial was considered prematurely discontinued if accrual was closed before recruiting the planned sample size. The recruited sample size was recorded together with the discontinuation status and the reason for premature discontinuation, if applicable. The reasons were categorised into insufficient accrual, early stopping for futility, efficacy or toxicity/harm based on an interim analysis, external evidence, competing study, lack of funding or other reasons. We categorised the publication status as follows: published as a full article (defined as a peer-reviewed journal publication), published, but not as a full article and not published at all. For the analysis of publication status, we excluded all trials: (1) that were still in follow-up, (2) for which the primary completion date was less than a year ago at the data cut-off date (31 December 2022) (because 12 months is not enough time for statistical analysis, manuscript preparation, revision and submission) and (3) were recently presented at congresses and for which the manuscript was submitted to a journal, but not accepted yet (N=3). The planned and recruited sample size was categorised into four groups (<50, 50–99, 100–499, ≥500).

Data collection

We identified all trials with accrual closure between 1986 and 2021 from the SAKK project management system and exported the list into an Excel file. Authors who extracted the data are all SAKK employees and thus have direct access to the SAKK project management system. Additional information not available in the project management system was extracted from publications, clinical study reports and annual reports from the SAKK server and the SAKK archive. If no publication was found in either of these databases, we searched the following data sources: electronic publication databases (eg, PubMed, Google Scholar), online trial registries (eg, ClinicalTrials.gov, clinicaltrialsregister.eu), libraries (eg, Nationalbibliothek, Unibibliothek Bern, Schweizer Bibliothekskatalog Swissbib), journal websites, conference archives and collaborative groups. If the discontinuation or publication status or reason for premature discontinuation or non-publication of the trial remained unclear, we contacted the coordinating investigator, other investigators involved in the study, SAKK personnel and persons at collaborative groups by email or telephone to request the missing information.

One investigator (SH) extracted the data that were cross-checked by another reviewer (ALS, CK or SS). Unclear cases were checked by a third reviewer.

Statistical analysis

We summarised continuous variables using median and range. Categorical variables were summarised using frequency counts and percentages. We used univariable and multivariable logistic regression models to investigate the association between prespecified study-level characteristics and the two outcomes: discontinuation of the study (yes vs no) and non-publication (non-publication vs peer-reviewed journal publication). For these models, all trials that were not published in a peer-reviewed journal were classified as not published. The prespecified criteria included the following variables: study activation year and closure for accrual year (both as continuous variables), randomised (yes vs no), planned and recruited sample size (both as continuous variables) and for modelling non-publication also premature closure (yes vs no). We investigated correlation between covariates before running the multivariable logistic regression models. For highly correlated variables always the one with the higher p value in the univariable logistic regression was excluded from the multivariable model to avoid collinearity. We used the Akaike information criterion for final model selection. For the multivariable models, only complete
We included 261 trials with accrual closure between 1986 and 2021 that were either led by SAKK as sponsor or led by a collaborative group with SAKK as sponsor or sponsor representative in Switzerland.

The trial characteristics of all 261 trials are shown in table 1. All trials were multicentre trials, and the most common disease group was breast cancer, followed by lymphoma, leukaemia, gastrointestinal cancer, lung cancer and urogenital cancer. The activation year was between 1981 and 2021 and the closure for accrual year between 1986 and 2021. The median planned sample size was 240 (range 18–5180), whereas the median number of recruited patients was 150.5 (range 1–8028). Most trials (67.0%) were randomised.

At the time of this analysis, 8 trials were still in follow-up, for 10 trials the primary completion date was less than a year ago at the time of data cut-off, and 3 trials were recently presented at congresses and the manuscript was submitted to a journal, but not accepted yet. Thus, these 21 trials were excluded for the analysis of publication status and we finally included 240 trials into the analyses regarding publication status.

**Discontinuation of trials**

Overall, 76 of 261 (29.1%) trials were fully or partly (only one arm or cohort) prematurely closed for accrual (figure 1A); for 182 (69.7%) trials, the accrual was completed as planned and for three trials completion status was unknown. The main reason for premature closure was insufficient accrual in 28 of 76 trials (36.8%), followed by stopping for futility (17/76 trials (22.4%)) or efficacy (8/76 trials (10.5%)) after an interim analysis. The reason was unknown in 5/76 trials (6.6%) (figure 1B).

The rate of premature discontinuation declined over time (figure 2A,C), with 34.2%, 27.8% and 23.5% in trials activated before 2000, between 2000 and 2009, and since 2010, respectively. In univariable logistic regression models, the only variables that were found to be significantly associated with premature discontinuation of accrual were the year of trial activation (OR 0.85 (95% CI 0.74 to 0.98)) and year of trial closure (OR 0.82 (95% CI 0.70 to 0.96)), respectively. This means that the likelihood for premature discontinuation decreases over time (table 2).
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Publication of trials
Of all 240 trials considered for analysis of publication status, 216 (90.0%) were published as a full article in a peer-reviewed journal. Eighteen trials (7.5%) were published as conference presentations, brief reports, letters, thesis or in meta-analysis, resulting in an overall publication rate of 95.0%. All 167 trials that recruited the planned sample size were published, of which 161/167 (96.4%) were published as a full article in a peer-reviewed journal. Seventy of 240 (29.2%) trials were prematurely discontinued; of these, 54/70 (77.1%) were published in a peer-reviewed journal (figure 3A). Overall, 10/240 trials (4.2%) were not published at all and the reason for non-publication was insufficient data due to premature closure of accrual in 9 trials (median recruited sample size 15, range 1–97) (table 3) and the manuscript was still in preparation for 1 trial.

We observed a positive association between the sample size and publication rate (figure 3B). Trials that recruited less than 50 patients were not published in a peer-reviewed journal in 19.4%, but the rate of non-publication clearly decreased with rising sample size: 9.7%, 7.8% and 3.1% for trials with 50–99 patients, 100–499 patients and more than 500 patients. The publication rate in peer-reviewed journals was similar in randomised trials (90.0%) compared with non-randomised trials (90.0%) (figure 3D) and similar for the type of study with 92.3%, 88.9% and 90.5%, for phases I, II and III trials, respectively.

A clear improvement of the rate of publication can be observed over time (figure 2B,D), with publication rates in a peer-reviewed journal of 79.2% (closed before 2000), 95.7% (closed between 2000 and 2009) and 93.2% (closed after 2010). This is also reflected in the univariable logistic regression models, where year of trial activation (OR 0.78 (95% CI 0.61 to 0.99)) and year of trial closure (OR 0.69 (95% CI 0.53 to 0.91)) are both significantly associated with non-publication in a peer-reviewed journal; meaning that the likelihood for non-publication is decreasing over time (table 4). Prematurely closed trials and trials with lower recruited sample size both increased the likelihood for non-publication. Type of study, randomisation and planned sample size did not show a significant association (table 4). Because the variables year of trial activation, year of trial closure, accrual target and actual accrual as well as type of study and randomised were highly correlated, the variables year of trial activation, accrual target and randomisation status were excluded from the multivariable model. In the resulting multivariable logistic regression model, only premature trial closure remained significantly associated (tables 2 and 4). However, as mentioned above, year of trial closure was significantly associated with premature trial closure, which might be the reason that it is not significant anymore in the multivariable model.

DISCUSSION
Summary of findings
In this cohort study of investigator-initiated clinical cancer trials, we found that successful completion of SAKK trials was high and importantly, increased over time reaching a level of about 75% for the last 15 years. Insufficient recruitment was the predominant reason for premature trial closure, but this affected only 11% of all trials. The great majority of trials (90%) was published.

Compared with other studies
A Swiss study looking at randomised controlled trials (RCTs) supported by the Swiss National Science Foundation between 1986 and 20159 reported that 26% of RCTs were prematurely discontinued. A similar rate was

Table 1 Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N=261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruited sample size</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>71 (27.2)</td>
</tr>
<tr>
<td>50–99</td>
<td>36 (13.8)</td>
</tr>
<tr>
<td>100–499</td>
<td>85 (32.6)</td>
</tr>
<tr>
<td>≥500</td>
<td>69 (26.4)</td>
</tr>
</tbody>
</table>

This table summarises the key trial characteristics of all included multicentre trials.

Figure 1 Premature closure of accrual (A) and reasons for premature closure of accrual (B).
reported in a study of RCTs approved by research ethics committees Switzerland, Germany and Canada between 2000 and 2003 reporting 28% of RCTs as discontinued. These findings are very similar to our overall discontinuation rate of 29%. Another Swiss study of RCTs submitted to research ethics committees in Switzerland between 1988 and 1998 reports a lower number of only 11% discontinued trials, however, this discrepancy is most likely explained by the study design, because this study used a survey with 29% non-responders, which likely lead to an underestimation of the discontinuation rate.

Our findings are also in line with other studies highlighting that insufficient patient recruitment is still the main reason for discontinuation, followed by futility as the second most reason. However, in contrast to the findings by Amstutz et al, our discontinuation rate has decreased over time. There may be different factors driving this positive development. One of them may be stricter selection criteria for trials conducted by SAKK and implementation of quality management introduced in 2005 which includes checking feasibility of recruitment and asking for recruitment estimates and to monitor accrual during conduct more closely including implementation of measures to address and improve accrual issues early on.

Overall, 90% of trials sponsored by SAKK were published as a full article in a peer-reviewed journal. This is substantially higher than previously reported from other trial cohorts. Trials that were prematurely discontinued were less likely to be published. However, even for these prematurely closed trials, the publication rate was around 77%, which is higher than reported in other studies of 30%,9 67%5 and 45%.4 One of the main reasons for this continuous improvement could be the cooperative group setting and its continuous development of professionalisation. For example, SAKK has implemented and steadily improved its publication guidelines included in the contract between SAKK and the chief investigator of the respective trial. Furthermore, the SAKK project group presidents are responsible for the publication of all closed trials within due time. Finally, by the regulations of SAKK, the statistics team is responsible to monitor the publication activity and regularly reports to the SAKK director’s committee. An additional explanation for the higher publication rate than reported in the literature could be that all our trials were multicentre trials, which are known to be more likely to be published than single-centre trials. A study evaluating publication rates among abstracts presented at American Society of Clinical Oncology (ASCO) in 2009–2011 identified cooperative group sponsorship as an important predictor for publication. However,

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Factors associated with discontinuation (univariable logistic regression model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Study activation year (per 5 years more)</td>
<td>0.76 (0.57 to 1.00)</td>
</tr>
<tr>
<td>Study closure year (per 5 years more)</td>
<td>0.69 (0.50 to 0.94)</td>
</tr>
<tr>
<td>Type of study (phase II vs phase I)</td>
<td>1.76 (0.47 to 6.60)</td>
</tr>
<tr>
<td>Type of study (phase III vs phase I)</td>
<td>1.53 (0.86 to 2.75)</td>
</tr>
<tr>
<td>Randomised (yes vs no)</td>
<td>0.99 (0.96 to 1.03)</td>
</tr>
<tr>
<td>Planned sample size (per 100 more)</td>
<td>1.76 (0.47 to 6.60)</td>
</tr>
</tbody>
</table>
they also identified industry sponsorship as an important predictor, which is controversially reported in the literature: some analyses showed that industry-sponsored trials were less likely to be published,\textsuperscript{4,10} whereas others found no difference between different sponsor types.\textsuperscript{11,12}

**Strengths and limitations**

Our study has limitations. We only focused on multicentre cancer trials conducted within the network of SAKK in Switzerland. Thus, generalisability of our findings to other indications, healthcare systems and countries is certainly limited. This study includes all clinical trials run by SAKK as sponsor or sponsor representative since 1986 and information on trial characteristics and their structured documentation has changed over time. Thus, in some cases we had to gather information from other sources than the trial management system including some investigator surveys which may have impacted on data quality.

### Table 3 Publication status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Completed (N=167)</th>
<th>Prematurely discontinued (N=70)</th>
<th>Unknown (N=3)</th>
<th>Total (N=240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Published</td>
<td>167 (100.0)</td>
<td>60 (85.7)</td>
<td>3 (100.0)</td>
<td>230 (95.0)</td>
</tr>
<tr>
<td>Full journal article</td>
<td>161 (96.4)</td>
<td>54 (77.1)</td>
<td>1 (33.3)</td>
<td>216 (90.0)</td>
</tr>
<tr>
<td>Not published as full journal</td>
<td>6 (3.8)</td>
<td>16 (22.9)</td>
<td>2 (66.7)</td>
<td>24 (10.0)</td>
</tr>
<tr>
<td>Brief report, letter or thesis</td>
<td>2 (1.2)</td>
<td>2 (2.9)</td>
<td>0 (0.0)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>3 (1.8)</td>
<td>2 (2.9)</td>
<td>1 (33.3)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Conference presentation only</td>
<td>1 (0.6)</td>
<td>2 (2.9)</td>
<td>1 (33.3)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Not published at all</td>
<td>0 (0.0)</td>
<td>10 (14.3)</td>
<td>0 (0.0)</td>
<td>10 (4.2)</td>
</tr>
</tbody>
</table>

For the analysis of publication status, we only included 241 trials. This is because at the time of this analysis, 8 trials were still in follow-up, for 10 the primary completion date was less than a year ago at the time of data cut-off allowing not enough time for statistical analysis and manuscript preparation and three trials were recently presented at congresses and the manuscript was submitted to a journal, but not accepted yet. Thus, these 21 trials were excluded for the analysis of publication status.
This has led to a high proportion of trial results being published and of around 70% of trials reaching the planned sample size. However, there is still room for improvement to increase the number that reach their target sample size.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request.

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**Implications**
Proper planning, professional conduct and dissemination of results are pivotal for the research community. Not only for advancing the research field, but also to build and maintain trust of patients, payers and policy-makers. This is of particular need in the field of oncology where most patients with advanced disease still carry a very limited prognosis. Federally funded research organisations such as SAKK play an important role to support academically driven and cooperative research endeavours to improve patient care and outcome. Adequate funding allowing to generate reliable evidence especially for patient populations that are usually excluded from pivotal registration trials should be one of the major goals.

**CONCLUSIONS**
SAKK has continuously improved its operational infrastructure and quality management of trial conduct over time.

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**Table 4** Factors associated with non-publication in a peer-reviewed Journal

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study activation year (per 5 years more)</td>
<td>0.78 (0.61 to 0.999)</td>
<td>0.0499</td>
</tr>
<tr>
<td>Study closure year (per 5 years more)</td>
<td>0.69 (0.53 to 0.91)</td>
<td>0.009</td>
</tr>
<tr>
<td>Premature closure (yes vs no)*</td>
<td>7.95 (2.96 to 21.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of study (phase II vs phase I)</td>
<td>1.50 (0.18 to 12.79)</td>
<td>0.711</td>
</tr>
<tr>
<td>Type of study (phase III vs phase I)</td>
<td>1.26 (0.15 to 10.47)</td>
<td>0.832</td>
</tr>
<tr>
<td>Randomised (yes vs no)</td>
<td>1.00 (0.41 to 2.45)</td>
<td>1.000</td>
</tr>
<tr>
<td>Planned sample size (per 100 more)</td>
<td>0.98 (0.89 to 1.07)</td>
<td>0.620</td>
</tr>
<tr>
<td>Recruited sample size (per 100 more)</td>
<td>0.82 (0.68 to 0.99)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

* trials with unknown premature closure status excluded due to the low sample size in this group.
† complete-case multivariable logistic regression analysis (n=236), 4 trials were excluded due to missing values in covariables. Of collinear variables, always the one with the higher p value in the univariable logistic regression was excluded from the multivariable analysis. Model selection was performed based on the AIC. AIC, Akaike information criterion.

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