First lessons learnt about the regulatory aspects of human research related to COVID-19: Perspectives from the SCTO's Regulatory Affairs Platform

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This article summarises the findings of an internal survey, which was conducted at the end of the first wave of the COVID-19 pandemic by the Swiss Clinical Trial Organisation's (SCTO's) Regulatory Affairs Platform (RA Platform). The survey showed that the Clinical Trial Units (CTUs) and Swiss Group for Clinical Cancer Research (SAKK) centres received many requests to support academic human research on COVID-19 during the first wave of the pandemic. Local strategies to prioritise research projects had to be adopted, new practices were implemented, and ways of working from home were successfully developed. The established RA Platform network was considered helpful for sharing information and

effective practices. Synergies among research projects were initially missing, and better coordination should be encouraged. At the same time, services provided by and interactions with Swissmedic, swissethics, and the cantonal ethics committees (ECs) were much appreciated. Swissmedic and ECs focused their resources on projects related to COVID-19 and adapted their procedures to allow studies to start quickly. Some practices have been effective and should continue. The pandemic has shown that Switzerland can be considered a competitive place to launch studies in an emergency situation.

Introduction

The SCTO's CTUs and SAKK centres provide services to clinical research units at university and cantonal hospitals in Switzerland. During the first wave of the COVID-19 pandemic, an avalanche of human research projects linked to COVID-19 arose. They were crucial to try to identify strategies to fight the SARS-CoV-2 virus by understanding its epidemiology, its pathophysiology, and its mechanisms of actions and by testing the first strategies of care and potential therapeutic products. The multiplicity of research questions and the urgency to start the studies put pressure on the individual CTUs/SAKK centres as well as on every link in the implementation chain. As a consequence, many studies were able to start in less than one month, compared to the average preparation time of 9 to 12 months for different steps: writing the study protocol and other documentation, securing funding, preparing investigation sites, and making submissions to the authorities (ECs and Swissmedic). Sharing how this was accomplished and the lessons learnt along the way should be of benefit to the human research community as a whole.

Internal survey and follow-up workshop

After the first pandemic wave, a calmer period followed before the start of the second wave. This allowed the SCTO's RA Platform, which includes regulatory representatives from the different CTUs/SAKK centres, to share their experiences and lessons learnt from the first wave (from March to the beginning of July 2020). A 21-question survey was sent to seven CTUs/SAKK centres in June 2020, and answers were provided in July 2020. Survey feedback was analysed and discussed during a half-day, in-person workshop held in September 2020. There were two main objectives of the questionnaire and workshop. The first objective was to understand the situation for each CTU/SAKK centre and share eventual best practices: the number of requests for support each CTU/SAKK centre received, internal organisational policies and practices put in place, and the advantages of participating in the CTU/SAKK network. The second objective was to share the experiences of the CTUs/SAKK centres when interacting with local ECs, swissethics, Swissmedic, and the Swiss National Science Foundation (SNSF) and to make recommendations for the future.

An avalanche of requests made to the CTUs/SAKK centres to support projects linked to COVID-19

The CTUs/SAKK centres received 124 requests to support human research projects (all types) linked to COVID-19: 67 for observational studies, 36 for clinical trials, and 21 for registries (collections of health-related data for future research purposes) (**Figure 1**). One-third (41) of the projects asked for regulatory support mainly solicited for clinical trials (preparing documentation and making submissions for study authorisation to ECs and Swissmedic, participating in meetings with authorities, and entering information in study registries) (**Figure 2**). The most requests were received by the CTUs in Lausanne, Basel, and Geneva (**Figure 3**).

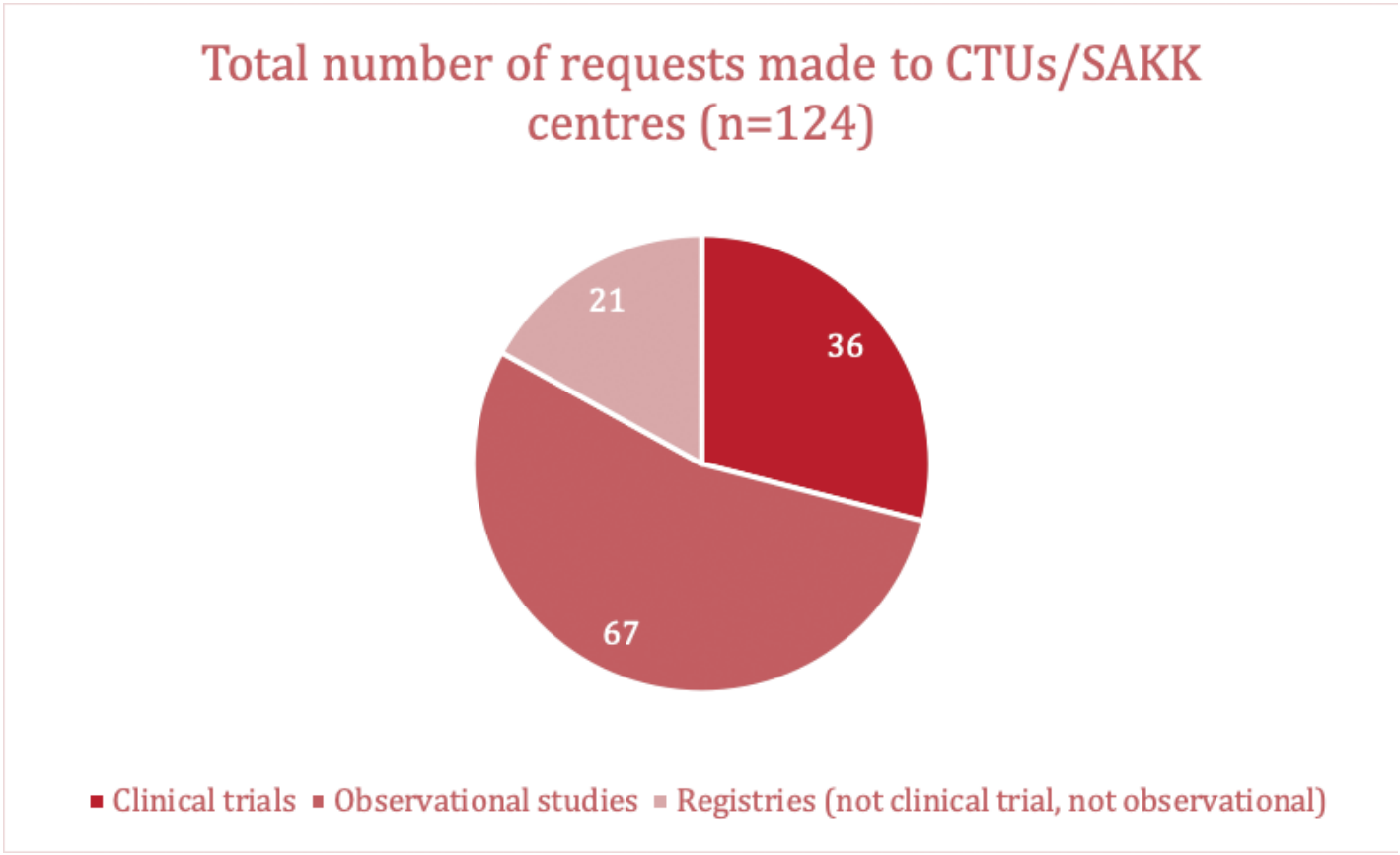

Figure 1: Number of requests made to CTUs/SAKK centres by human research project types on COVID-19 (from March to 10 July 2020)

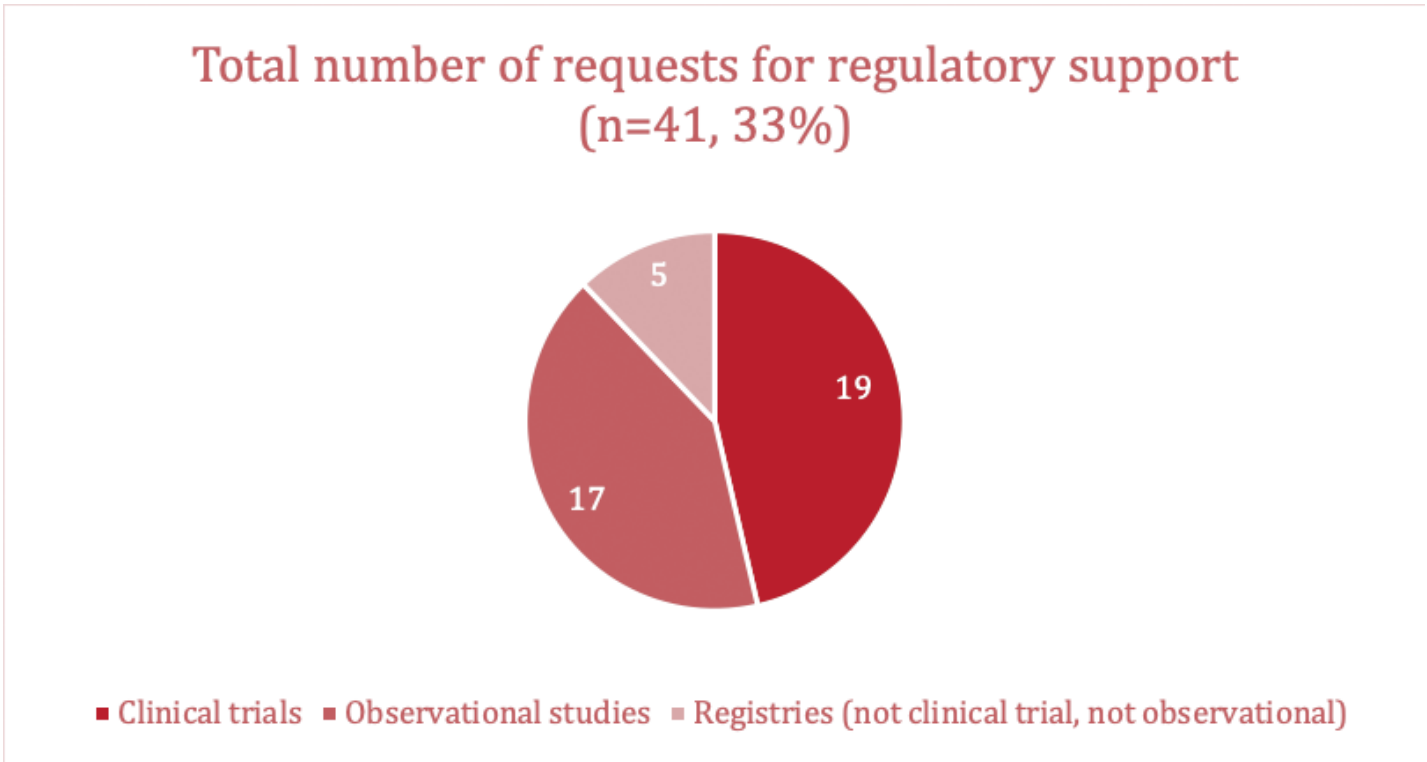

Figure 2: Number of requests for regulatory support made by human research projects on COVID-19

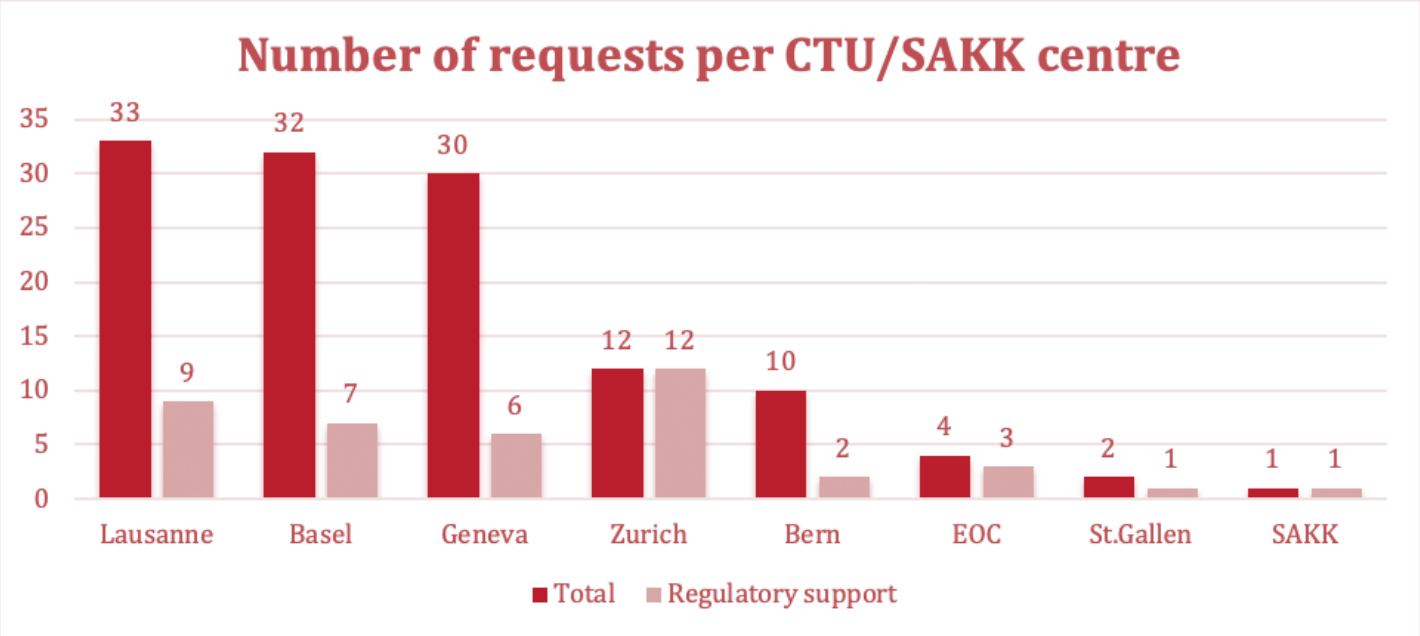

Figure 3: Number of requests made by human research projects on COVID-19 per CTU/SAKK centre

Local strategies at CTUs/SAKK centres and hospitals to perform human research activities

The incidence of infection was not homogenous in the different regions of the country. In order to manage research projects in view of the number of COVID-19 research requests, CTUs/SAKK centres and the institutions to which they belong followed different internal strategies (**Table 1**). The CTUs in Lausanne, Zurich, and Ticino decided to put the management of non-COVID-19 research projects on hold (with some exceptions) in order to focus on COVID-19 projects. The CTUs in Geneva, Bern, and St.Gallen prioritised COVID-19 projects but tried to continue with ongoing projects as much as possible. SAKK centres and the CTU Basel analysed non-COVID-19 projects case by case to determine if they could be put on hold. One illustration of a local strategy is the prioritisation committee put in place at Lausanne University Hospital (CHUV) to select COVID-19 projects to run at the institution (such committees were also put in place in other CTUs). Each COVID-19 project was evaluated in order to avoid harassing patients and staff with multiplicity and fragmented research initiatives and to consider ethical and practical issues – for example avoiding the enrolment of the same patient in many studies, reducing the use of multiple consent forms, and limiting blood spoliation with cumulated research-related samples. Such approaches were also taken to protect healthcare providers from an additional workload burden for research purposes and to indirectly limit the number of premature or infeasible projects submitted to ECs. Non-COVID-19 clinical trials projects were also affected by federal hygiene measures for protecting the public, such as limiting the visits of trial participants, delivering the investigational medical product to a patient's home, doing remote monitoring, etc. At the CTU Basel, a clinical research advisory board evaluated all studies to decide case by case if they could be continued or not; the evaluation was based on a justification prepared by each researcher.

Table 1: Local strategies for managing research projects in view of COVID-19 research requests made to the CTUs and SAKK centres during the first wave of the pandemic

Lausanne, Zurich, Ticino	COVID-19 studies prioritised, and other studies put on hold (with some exceptions)
Geneva, Bern, St.Gallen	COVID-19 studies prioritised, but other studies still continued
SAKK, Basel	Case-by-case analysis of whether to stop non-COVID-19 studies

Learning to work from home

During the first wave of the pandemic, federal measures recommended working from home until the end of June. This applied to the regulatory teams as well as the rest of the centres' teams. A few people were allowed to go into the offices for specific reasons, for example to do filing or get signatures. There were initial fears that working from home could be a problem because it involved managing an increased workload – sometimes with children staying at home as well (until the beginning of May) – with inadequate equipment, and it required defining new ways to communicate within teams and with investigators (e.g. teleconferences, e-learning, a hotline, and online Q&A). But in the end, it turned out well, and teams were able to manage work demands in a very short amount of time while maintaining a high level of quality.

SCTO's existing RA Platform was useful

The RA Platform's members appreciated the positive communication within the network during the first wave of the pandemic, especially the monthly conference calls with representatives from each of the CTUs/SAKK centres, the special internal *RA Watch* COVID-19 weekly updates on regulatory developments in Switzerland and abroad, and the opportunity as a trusted partner to comment early on the joint guidance document written by swissethics and Swissmedic. The workshop held in September was also a good opportunity to share local experiences and best practices among the CTU/SAKK network. Examples of local best practices include the flexible reallocation of staff to urgent tasks, the possibility to quickly recruit manpower, compulsory good clinical practice (GCP) courses for all physicians and research staff to facilitate setting up research teams, a hotline for consultation services, regularly updated online Q&A resources for researchers, a crisis management approach to operating, and the aggregated reporting of study interruption and continuation to ECs, Swissmedic, etc. A detailed example of work practices at the CTU Basel is provided here.

A trusted network, but upfront coordination needed

The feeling within the CTU/SAKK network was that the individual CTUs are reliable, service-oriented partners at the hospital institution level that help investigators to submit and run high-quality projects in a very short amount of time. The feedback received from researchers at individual CTUs was positive, especially the responses and advice received in such an unclear situation. An example of this appreciation (which can be listened to here) comes from the principal investigator of the CORON-ACT study, a multicentre trial that is being conducted at four Swiss hospitals. The CTU Bern provides support for CORON-ACT, and the CTU Zurich participates in the study as well. Another example of the CTU network's recognition is the involvement of both the CTU Lausanne and the CTU Bern in the World Health Organization's (WHO's) Solidarity trial in Switzerland (17 sites), which is one of the largest international randomised clinical trials for testing repurposed drugs for treating COVID-19. The lessons learnt so far from the Solidarity experience can be

read here.

One main lesson learnt by the network is that the multiplicity of the demands significantly increased the workload of all teams involved. And despite all the efforts made, studies were not launched until the end of the first wave, which was too late to get enough patients enrolled (however, ongoing studies are recruiting during the second wave). The network's members observed a redundancy of sometimes small projects and lack of synergies. In the future, a more pronounced global coordination would be appreciated, including upfront discussions with the SNSF regarding funding key priority projects at the national level. More multicentre and multinational initiatives favouring platform studies should also be encouraged (an article on the EU-RESPONSE initiative can be read here). In addition, the "covidisation" of research has an impact on other research areas and consequently on patients affected by those other therapeutic fields. This aspect should be considered and mitigation plans should be proposed if other pandemics arise in the future.

Interactions with swissethics, local ECs, Swissmedic, and the SNSF

The CTU/SAKK network appreciated the collaborative attitude and the initiatives of all stakeholders involved in the authorisation and conduct of human research projects during this crisis period. Survey respondents were highly satisfied with their interactions with Swissmedic, which received a mean score of 4.5 on a scale from 0 (not satisfied) to 5 (highly satisfied). There was also high satisfaction regarding interactions with local ECs (score of 4.2), with some local differences, and with swissethics (score of 4).The details of what was considered positive, what could have been better, and recommendations for the future were discussed during the workshop in September and are summarised in **Table 2**.

Experiences and recommendations			
Stakeholder	**Positive**	**Less positive/could be improved**	**Recommendations for the future**
ECs	• Helpful, available, supportive, fast, and pragmatic	• Sometimes some ECs insisted on unimportant questions; sometimes some ECs made inadequate/incomplete checks of studies • Initial unclear period with imprecise or contradicting information	• Harmonised work and improved communication among ECs • Possibility to implement fast-track authorisation during future crises
swissethics *Note: only half of the CTUs and SAKK centres were in contact with swissethics*	• Good and fast interactions • Joint guidance document: exchanges with the RA Platform allowed for an improved version • Online COVID-19 projects lists were helpful	• Guidance document: first version edited by swissethics was not aligned with Swissmedic and not as comprehensive as the EU guideline • Difficult management of the initial situation	• Possibility to reduce redundancy and loss of time and resources (for multicentre projects involving more than one EC) • Develop guidance for future crises
Swissmedic	• Very fast, helpful, available, informative • Joint guidance document: exchanges with the RA Platform allowed for an improved version • Electronic dossier submissions in advance accelerated the process	• Sometimes insisted on administrative details • Initially slow, first joint guideline was published a bit late • Communication was slow for ongoing non-COVID-19 studies, (repeated questioning was necessary to receive answers)	• Keep email/electronic submission possible or even switch to an online submission portal • Develop guidance for future crises

Table 2: Experiences and recommendations from the CTUs/SAKK centres interacting with ECs, swissethics, and Swissmedic on COVID-19 projects during the first wave of the pandemic

Fast research project authorisations

The main positive aspect was the rapid approval of COVID-19 projects, both by ECs and Swissmedic. The teams from the authorities were available for exchanges, responsive, and often pragmatic when evaluating projects. It was sometimes felt that some ECs insisted on unimportant aspects, and some ECs did not always review the projects enough. The pandemic situation exacerbated some pre-existing differences in practices, and harmonisation among ECs should be improved. The advance electronic submission to Swissmedic permitted an acceleration of the process. It would be appreciated if such a facilitative procedure could continue or even be transformed into an online submission portal. ECs should also consider fast-track authorisation processes.

Guidance

The initial situation was difficult for investigational teams who had questions regarding how to manage

ongoing trials. swissethics published an initial version of a guidance document, which was a bit delayed due to circumstances surrounding the pandemic and was thus less applicable at the beginning of pandemic's first wave. In conjunction with what was already available at the EU level, the subsequent revised versions, which were aligned with Swissmedic, were much more useful.

Published list

The initiative from swissethics to publish lists of projects that have been approved and projects that have been submitted but not yet approved provided useful information about ongoing research projects. This information should be used to set up collaborations on common objectives instead of launching projects in parallel or – even worse – in competition with each other.

Funding

The network also discussed recommendations for funders. They appreciated that the SNSF was very quick to fund some research projects. In the future, SNSF could more quickly communicate postponed deadlines for project submissions. In order to minimise overlapping and small projects, the SNSF could also add more conditions for funding eligibility and promote national multicentre studies on key priorities by proposing more top-down calls.

Conclusions and future perspectives

All the collective efforts to launch COVID-19 studies during the first wave of the pandemic are paying off now. Studies are recruiting patients from the second wave, which is unfortunately still ongoing in March 2021. These studies help to better understand COVID-19 and will hopefully contribute to slowing down the pandemic. The CTU/SAKK network has gained much experience on how to manage such a high demand for support during a pandemic situation and was a key partner for some ambitious projects. In general, there is a call for a better coordination from the beginning of a crisis in order to reduce the redundancy of sometimes small projects in the event of another extraordinary situation. The CTU/SAKK network acknowledges all the decisive efforts made by the authorities to adapt their resources, provide services, and modify their procedures. The pandemic has shown that Switzerland can be considered a competitive place to launch studies in an emergency situation. There is also an opportunity for some effective, innovative practices to be applied to regular research activities and thus help to decrease the commonly perceived regulatory burdens associated with human research.