Swiss participation in the WHO’s Solidarity trial to test the efficacy of repurposed drugs for treating COVID-19: What the research community has learnt so far

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The World Health Organization’s Solidarity trial is one of the largest international randomised clinical trials for COVID-19 treatments in the world and provides an excellent example of a global effort to fight the pandemic. When Switzerland was invited to participate in the trial, the Swiss research community gave a resoundingly positive response.

Researchers, investigators, hospitals, ethics committees, and authorities all worked together and made extraordinary efforts – in the midst of the difficulties brought on by the pandemic – to get the trial up and running in Switzerland in a relatively short amount of time.

Lausanne University Hospital (CHUV) and the Clinical Trial Unit (CTU) Lausanne coordinate these remarkable efforts. In this article, two national coordinators for the Solidarity trial provide an overview of the trial, address some of the challenges encountered and solutions found when preparing for and conducting the trial in Switzerland, and discuss some of the lessons learnt so far that can be carried into the future.

Solidarity trial

Solidarity is an international clinical trial launched by the World Health Organization (WHO) to help find an effective treatment for COVID-19 using repurposed drugs for this new indication. This platform trial is one of the largest international randomised trials for COVID-19 treatments, with an enrolment of almost 12,000 patients in 500 hospital sites in over 30 countries (latest update on 15 October 2020). An interim analysis in October 2020 showed that all four treatments evaluated up to that time (remdesivir (RDV), hydroxychloroquine (HCQ), lopinavir/ritonavir (LPV/r), and interferon beta-1a (IFN B1a)) had little or no effect on overall mortality, the initiation of ventilation, and the duration of hospital stay in hospitalised patients compared to the standard of care (see related NEJM.org article from 2 December 2020). In July 2020, the WHO accepted the recommendation from Solidarity's International Steering Committee to discontinue the hydroxychloroquine and lopinavir/ritonavir trial arms (see the WHO's website). This decision was also supported by the results of the RECOVERY trial, which is another large trial on COVID-19 treatments based in the UK. The discontinuation of the interferon beta-1a arm in October 2020 meant that patients could only be included in the standard-of-care or remdesivir arms. Other treatments strategies are now being evaluated in order to continue the search for effective COVID-19 therapeutics. So far, only corticosteroids have been proven effective against severe and critical COVID-19 (see NEJM.org article from 17 July 2020).

Swiss participation in Solidarity

On 16 March 2020, a few days before the peak of the first COVID-19 wave in Switzerland, the WHO contacted the Swiss National Science Foundation (SNSF) and the Swiss Federal Office of Public Health (FOPH) in order to start a Solidarity feasibility study in Switzerland. Very rapidly, many Swiss investigators from university and non-university hospitals showed high interest in participating. This momentum resulted in the creation of a Swiss consortium of 17 clinical sites (represented in green in **Figure 1**) on 26 March 2020. The CTU Lausanne was approached by the national coordinating investigator Dr Oriol Manuel to collaborate and provide support on all aspects of coordination, including budget preparation, project management, monitoring, pharmacovigilance, and regulatory duties. One of the first tasks was to set up a study budget, which allowed the consortium to be rapidly granted funding from the SNSF. Another priority was to validate the distribution of study responsibilities among institutions (WHO, FOPH, SNSF, and CHUV) since the WHO was requesting governmental commitment into co-sponsorship of the trial. Lausanne University Hospital (CHUV) was to act as the sponsor's (WHO's) representative in Switzerland and the SNSF as the funding body. The trial's coordination was assumed by the CTU Lausanne, and close collaboration with the CTU Bern was set to ensure high-quality multilingual monitoring of German speaking sites. This collaboration between the two CTUs was established very rapidly since they experienced working together in the context of the Swiss Clinical Trial Organisation's (SCTO's) CTU network. The WHO independently mandated the CTU Bern to perform Central Data Monitoring, Data Management and Statistics. At the end of March, a race

against time started that resulted in successful ethical and regulatory authorisations four weeks later as well as the inclusion of the first Swiss patient in the trial on 21 April 2020. This remarkable feat was accomplished thanks to the extensive expertise, exceptional collaboration, and great dedication of all parties involved. **Table 1** summarises the main milestones in 2020 and at the beginning of 2021.

Challenges, solutions, and successes

One major challenge was obviously time pressure. Reorganisation within the CTU Lausanne was essential since the staff had to be rapidly reallocated to new tasks. The strategy was to create a pool of persons fully dedicated to the trial (at least in April 2020) to handle the high workload that Solidarity generated, while other CTU staff continued with some routine activities (e.g. those trials not suspended during the pandemic) and at the same time remained involved in an institutional task force coordinating more than 75 COVID-19 research initiatives. Another high priority for CHUV was the initiation of other key research on COVID-19, which required the CTU to allocate significant resources, including study nurses, coordinators, data managers, and regulatory support. Finally, how staff worked had to be reorganised since almost all the staff who were normally in the office worked remotely during the first COVID-19 wave. During the first lockdown, the uncertainties on the incidence of COVID-19 infections pushed the team to move forward with preparations as quickly as possible. Preparing study documents for 17 sites in three different languages required the coordinating team to be well organised. In terms of the regulatory aspects of the trial, the team chose to concentrate first on the approval of the documentation for the national coordinating site in Lausanne (the country-specific addendum to the master protocol, informed consent documents, site agreements, etc.) and then adapt the documentation for the other 16 sites. Preparing and signing off agreements was especially challenging due to work-from-home requirements in most hospitals' administrative departments.

On the whole, the coordinating team's successful strategy ensured a very quick and easy review and approval process with the lead and local ethics committees (ECs) and a rapid initiation of the trial at all Swiss sites. As shown in **Table 1**, both Swissmedic and the Swiss ECs usually reacted to the submitted dossier within 24 to 48 hours, even though the standard timelines (as per law) are 30 days (or 45 days for multicentre trials). Close phone contact with the authorities and the possibility of electronic submissions – both exceptionally authorised by Swissmedic during the COVID-19 pandemic – greatly simplified exchanges. Grouped and remote site initiation visits, a novel approach for monitors, allowed the very rapid activation of all 17 sites. Even though these efforts to initiate the trial at all sites as quickly as possible were successful, the incidence of COVID-19 rapidly decreased in Switzerland, which resulted in the inclusion of fewer than 10 patients at the end of the first wave (**Figure 2**). However, all these efforts were not vain since sites were ready to enrol patients when the second wave arrived in autumn. As a result, in mid-December more than 200 patients were included in the trial. Unfortunately, the discontinuation of most of the trial arms and a shortage of the remdesivir drug provided by the WHO resulted in a temporary suspension in the inclusion of patients in the trial in Switzerland until new drugs to be tested in Solidarity are selected by the trial's International Steering Committee.

Lessons learnt and future perspectives

Because the COVID-19 pandemic is unfortunately not yet under control and the Solidarity trial is still running worldwide, it is not yet time to discuss the final lessons learnt. However, an interim picture can be formed. Looking back at 2020, we can proudly state that Swiss participation in Solidarity has been a success, and it definitely demonstrates that Switzerland is an attractive country for running clinical trials in emergency situations. Investigators, CTUs, ethics committees, and regulatory authorities are all able to rapidly adapt together to reach the same objective without sacrificing quality. As representatives of investigators from all parts of Switzerland and the Swiss CTUs, the authors would like to thank the authorities in particular and encourage them to keep their much-appreciated collaborative attitude, which contributes to reducing the gap

usually felt between researchers and ethics bodies/the authorities. Requesting feedback within a few days is clearly unrealistic in the long term after this pandemic is over since all stakeholders have accumulated massive amounts of overtime. However, the scientific community would definitely appreciate the possibility to continue to make electronic submissions to Swissmedic. Finally, the CTU Lausanne and the CTU Bern also demonstrated their synergetic collaboration, which was undoubtedly built on previous exchanges within the SCTO network and will pave the way for future collaboration on clinical trials within the CTU network.

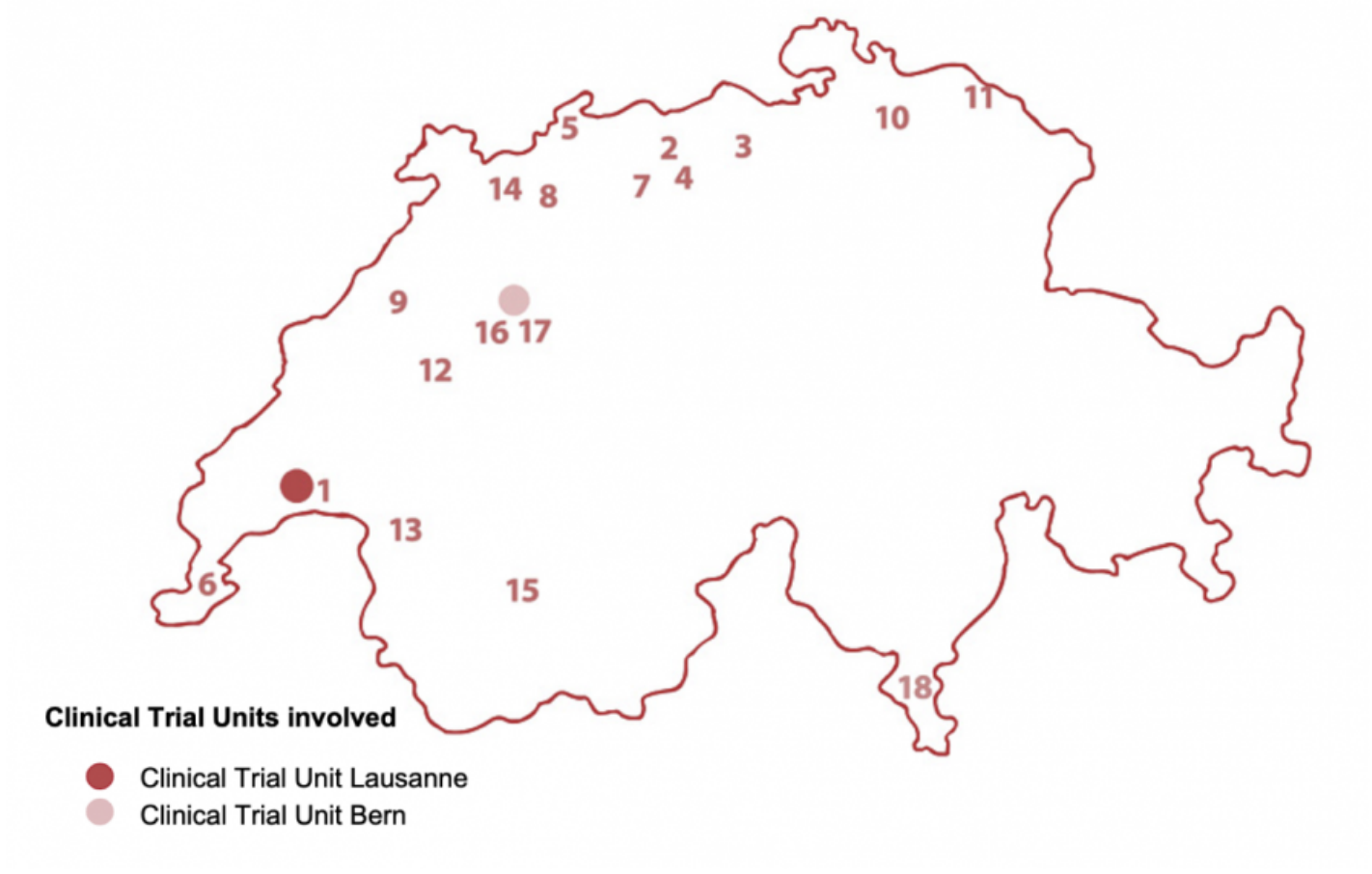

Figure 1

Approved and activated sites:

1. Lausanne University Hospital (CHUV) : **Sponsor's representative in Switzerland and the study's coordinating site**

2. Kantonsspital Aarau

3. Kantonsspital Baden

4. Hirslanden Klinik Aarau

5. University Hospital Basel

6. Geneva University Hospitals (HUG)

7. Solothurner Spitäler AG, Kantonsspital Olten

8. Solothurner Spitäler AG, Bürgerspital Solothurn

9. Réseau hospitalier neuchâtelois Neuchâtel

10. Spital Thurgau AG, Kantonsspital Frauenfeld

11. Spital Thurgau AG, Kantonsspital Münsterlingen

12. Hôpital fribourgeois Fribourg

13. Hôpital Riviera-Chablais Rennaz

14. Hôpital du Jura Delémont

15. Hôpital du Valais Sion

16. Insel Gruppe AG, Inselspital Bern

17. Campus SLB, Lindenhofgruppe Bern

Approved but not yet activated site:

18. Clinica Luganese Moncucco Lugano

Dates	Solidarity trial: Main milestones in Switzerland
16.03.2020	SNSF and FOPH contacted by WHO to initiate Solidarity feasibility study in Switzerland
25.03.2020	Teleconference organised by WHO to inform all interested Swiss investigators
26.03.2020	Dr Oriol Manuel (CHUV) chosen as national coordinating investigator; start of CTUs' involvement
02.04.2020	Study budget submission to SNSF
06.04.2020	Study budget pre-approval from SNSF
07.04.2020	Submission of Lausanne site to lead EC (EC Vaud)
08.04.2020	CHUV (Lausanne) designated as sponsor's representative in Switzerland according to FOPH–WHO agreement; initial submission to Swissmedic
09.04.2020	Official letter from SNSF granting budget for study conduct in Switzerland *(investigational medicinal products (**IMP**s) to be provided by WHO)*; research service agreement involving CTU Lausanne signed
10.04.2020	Initial submission to Swissmedic; approval with conditions
14.04.2020	Submission of Lausanne site to lead EC; official feedback with questions
15.04.2020	Submission of Lausanne site to lead EC; final approval
21.04.2020	Initial submission to Swissmedic; final approval
21.04.2020	First patient enrolled (in Lausanne)
21.04.2020 to 28.04.2020	Submission of 16 additional local sites to lead and local ECs
23.04.2020 to 29.04.2020	Submission of 16 additional local sites to lead and local ECs; approval (with charges for some sites)
05.05.2020	Submission of 16 additional local sites to lead and local ECs; final approval
24.05.2020	Decision of WHO to suspend HCQ arm; communication to lead EC and Swissmedic on 24.05 and 25.05 respectively
04.06.2020	Decision of WHO to restart HCQ arm; request to restart with HCQ sent to Swissmedic *(which was not restarted, see below)*
18.06.2020 and 03.07.2020	Decision of WHO to definitively stop the three following arms: HCQ and LPV/r +/- IFN B1a; communication to lead EC and Swissmedic on 22.06 and 09.07 respectively
11.09.2020	Official submission to lead EC of amendment including two new arms: acalabrutinib (**ACA**) and IFN B1a (Lausanne first)
02.10.2020	Official submission to Swissmedic of amendment including two new arms: ACA and IFN B1a
15.10.2020	Decision of WHO to definitively stop the IFN B1a arm; communication to lead EC and Swissmedic on 20.10 and 22.10 respectively
26.10.2020	Official submission to lead EC of amendment including two new arms: ACA and IFN B1a (Lausanne first); approval of ACA only (*IFN B1a alone was never approved*)
11.11.2020	Official submission to Swissmedic of amendment including two new arms: ACA and IFN B1a; approval of ACA only (*IFN B1a alone was never approved*)
13.11.2020	Official submission to lead and local EC of amendment including ACA for all local sites plus one new site
13.11.2020	Decision of WHO to definitively stop ACA arm (*ACA was never started nor shipped to Switzerland*); communication to lead EC and Swissmedic on 16.11 and 20.11 respectively
07.12.2020	Official submission to lead and local EC of one new site; approval with charges
18.12.2020	Patient recruitment put on hold due to RDV being sold out in Switzerland (208 enrolled patients); communication to lead EC and Swissmedic on 30.12.
07.01.2021	Official submission to lead and local EC of one new site; final approval
27.01.2021	Decision of WHO to definitively stop RDV arm

Table 1

**Solidarity trial's CTU Lausanne team: Yoanne Boulez, Monica von Brevern, Laurene Cagnon, Fady Fares, Aurélie Fayet-Mello, Marc Froissart, Isabelle Guilleret, Sara Mantero, Séverine Méance, Christiane Pellet, Laura Pezzi, Loredana Sene, Vassili Soumas, Laure Vallotton, Andreja Vujicic-Zagar, and Loane Warpelin-Decrausaz*