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Decentralised clinical trials (DCTs) with medicinal products in Switzerland

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1. Introduction

1.1. Content and objectives of DCTs

When conventional clinical trials are performed with medicinal products, trial subjects are sometimes required to commit a great deal of time and are also often expected to have a high degree of mobility since they have to travel to a trial site for trial-related visits. One objective of “decentralised clinical trials” (DCTs) is to partly transfer the trial-related visits or assessments from the trial site to the subject’s home in order to reduce the practical obstacles to trial participation and to integrate the visits more smoothly into the subject’s daily routine.

DCTs are research projects in which the digital recording and/or transmission of data in the context of trial-related interventions play a significant role. They may involve, for example, digital recruitment of trial participants, trial visits performed using telemedicine in the patient’s home or digital recording and transmission of data using wearables (computer technology worn on the body) or smart devices such as tablets or smartphones. Other aspects such as informed consent of subjects, monitoring and the associated verification of the source data are also affected by digital technologies.

A further characteristic element of DCTs is the direct delivery of the investigational medicinal product (IMP) to the trial subject at home, where it is stored and in some cases administered by qualified trial nurses. Wherever possible, trial-related interventions are performed and documented in the patient's home by trained trial nurses.

In "hybrid DCTs" some of the interventions are performed in the conventional setting at a trial site, and others are performed in a decentralised setting in the trial subject's home. Whether or not parts of a clinical trial can be performed in a decentralised way depends on many components – including the type of disease, the phase of the trial and the type of IMP, and on the prevailing legal framework.

There is great interest, both internationally and in Switzerland, in performing clinical trials in a decentralised way. The ICH (International Council for Harmonization) is planning to develop an Annex 2 on the topic of "Additional considerations for non-traditional interventional clinical trials" as part of the modernisation of the global GCP (Good Clinical Practice) Guideline ICH GCP E6 (R2). Work on drafting the Annex is already scheduled.[1] Additional considerations for DCTs will be one of the topics specified in detail in this document.[2] On 4 May 2021, the Danish Medicines Agency published guidance on the implementation of decentralised elements of clinical trials with medicinal products.[3] These guidelines explain the opportunities of the new trial setting and challenges while ensuring patient safety and data integrity during DCTs.

The stakeholders involved in clinical trials in Switzerland are convinced that DCTs are set to play an increasingly important role in the future. At the *Swissmedic Round Table Innovation* event held in October 2019 the stakeholders emphasised their wish to support innovation in Switzerland in this context. [4]

In an introductory summary they stated their intention of giving potential subjects in Switzerland the opportunity to take part in DCTs. The anticipated advantages are the following:

- rapid, digital recruitment through new channels;
- trial implementation that can be better integrated into trial subjects' day-to-day routine by reducing the time and mobility required;
- digital automation of data capture with a possible improvement in data quality;
- possibility of performing clinical trials for rare diseases.

1.2. Legal framework in Switzerland

In Switzerland, clinical trials with medicinal products are regulated in the Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA [SR 812.21]) and in the Federal Act on Research involving Human Beings (Human Research Act, HRA [SR 810.30]) and the associated ordinances[5]. The ICH GCP Guidelines E6 (R2) are also applicable in Switzerland (Art. 5 para. 1 ClinO). The requirements of the Federal Act on Data Protection (FADP [SR 235.1]) and the Ordinance to the Federal Act on Data Protection (OFADP [235.11]) must also be fulfilled.

[1] ICH E6 (R3) EWG Work Plan, 4 January 2021
[2] Final Business Plan ICH E6 (R3): Guideline for Good Clinical Practice dated 17 November 2019 endorsed by the Management Committee on 18 November 2019
[3] The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products (version 1.0; 4 May 2021)
[4] Proceedings of the 1st Round Table Innovation "Innovative Methods and Technologies in Clinical Trials" Monday, 7 October 2019 (Version 1.0 dated 05.12.2019)
[5] Ordinance on Clinical Trials with the exception of Clinical Trials with Medical Devices, Ordinance on Clinical Trials, ClinO [SR 810.305]; Organisation Ordinance to the Human Research Act, Organisation Ordinance HRA, OrgO-HRA [810.308]

The existing legal framework already regulates many aspects of DCTs with medicinal products in Switzerland, although researchers are recommended to liaise closely with Swissmedic and the Ethics Committees beforehand in order to clarify specific questions relating to the conduct of DCTs. The aim of prior consultation/clarification is to identify ways in which DCTs can comply with the ethical and legal standards mandated by the existing regulatory environment and can therefore be carried out in Switzerland.
Swissmedic and swissethics are issuing the present publication with the aim of communicating the questions and considerations that have arisen so far. It is not possible to assess definitively on the basis of this document which provisions of national and international law are affected, and to what extent, and whether or how the required compliance of clinical trials with the legislation can be achieved by the modalities of different DCT settings. The document does not prejudice the necessary case-by-case examination of applications for approval of a clinical trial, nor does it set out the elements of a DCT which are permissible under current law. Furthermore, DCT elements must be examined on a case-by-case basis to establish whether they can be made compatible with the currently applicable legal provisions.

The question of whether DCTs are feasible within the current legislation requires a differentiated analysis and examination of the challenges and risks that arise. It has been shown on various occasions that Swiss law certainly contains possibilities for integrating new technologies without adaptation of the current law. It is therefore possible that solutions will be found in the course of the examination of the legal conformity of DCT elements. It is also possible, however, that areas of risk are likely to be identified which require modification of the law, perhaps even before a situation in which DCTs can be approved has been reached. Time and further experience will tell if and which new standards are needed to approve DCTs, and which practical requirements based on the application and development of the existing legislation are sufficient; these questions cannot be answered conclusively at the present time.

2. DCT aspects

In regulatory and ethical terms there are four main aspects related to DCTs, which are considered in detail below.

1. Optimal medical care, the rights and safety of subjects must be ensured at all times.
2. The IMP must be safely dispensed, ingested/administered and returned.
3. The data recorded during the clinical trial must be credible and reliable.
4. The data protection requirements must be met in full.

Re 1: Since the clinical trial is performed virtually, there is a risk that the personal relationship with the physician, which is the basis of mutual trust, cannot be established as personally and in the same way as in conventional clinical trials. The optimal care and treatment of subjects in the trial setting is a fundamental requirement for any form of research involving human beings and is therefore essential in the performance of DCTs, too. Optimal patient safety must also be ensured, even if subjects are not regularly physically present at the trial site.

Re 2: The IMP must be suitable for delivery to the subjects and for being ingested/administered at and returned from their homes. All the requirements regarding the quality of the IMP must be fulfilled during delivery and storage.

Re 3: Given the modalities of recruitment and selection, there is a risk that it will mainly be technically-versed individuals who decide to take part in the trials. A representative sample of trial participants must be ensured in order to avoid a selection bias. The data-recording tools (e.g. wearables) must generate correct and valid data.

Re 4: Data protection: Special attention must be paid to ensuring the highest security standards during data transfer, for example within a larger network and between all participants. This means that health-related data must be protected from unauthorised access at all time.

2.1. Recruitment through digital channels

In case potential trial subjects are informed about a trial through electronic media, swissethics draws attention to the guidance for producing and using electronic informed consent (eIC) in accordance with ClinO (link: guidance_e_consent_e.pdf (swissethics.ch)).

If the discussion about participation between the investigator, i.e. the trial physician, and the patient during the informed consent process is done via electronic platforms, several additional aspects have to be considered. Ethical principles like autonomy and ethical requirements like time to think about trial participation must be addressed. The requirements of the Swiss Data Protection Act, e.g. with respect to server location, must be fulfilled (Art. 7 FADP). The protection of personal data from unauthorised or accidental disclosure must be safeguarded, in particular by ensuring that during any data transmission these personal data are adequately protected from unauthorised or accidental disclosure to the sponsor or companies involved in this process (ICH GCP E6 (R2) 2.11; Art. 7 para. 1 FADP).

Art. 14 para. 1 of the Code of Obligations (CO, SR 220) requires the signature to be *handwritten* and Art. 14 para. 2bis defines a qualified electronic signature as equivalent to a *handwritten* signature[6]. However, the use of a qualified electronic signature does not yet appear as a practicable solution, because of the effort every single trial participant would have to undertake to be able to deliver such a qualified electronic signature. At least as long as an e-ID is not established in Switzerland. Conventional, handwritten ("wet-ink") signature will thus be regularly required in Switzerland, unless the trial participant can provide a qualified electronic signature that meets the legal requirements of the Federal law on electronic signatures (ZertES, SR 943.03). The original "wet-ink" signed informed consent form or the certified proof of the e-signature signed by the trial participant must be archived in the "investigator site file" (ICH-GCP E6 (R2) 8.3.12).

If new information important for the participating trial subjects emerges while a clinical trial is in progress, it is necessary to ensure – also when electronic media are used – that the subjects are informed in a timely manner and, where applicable, receive an updated consent form and sign it by hand ("wet-ink"). Such changes include, for example, the occurrence of new side effects that are relevant for safety and may alter the subject's willingness to take part in the trial. swissethics draws attention to the guidance and the template for supplementary concise information on consent in clinical trials available at swissethics.ch.

It is also necessary that, even when using electronic media, the information and consent process as well as the respective versions of the patient information and declaration of consent used are documented in a GCP-compliant manner and are available for monitoring, audits and inspections. The statutory archiving obligation for these source data must be observed (Art. 45 para. 2 ClinO).

[6] The electronic signature is a technological means of verifying the authenticity of a document. It is based on a certification infrastructure managed by reliable certification service providers. Only qualified electronic signatures with a qualified time stamp are recognised in Switzerland as being equivalent to a handwritten signature. The Swiss Electronic Signature Act (ZertES; SR 943.03) defines a qualified electronic signature.

2.2. Performance of trial-related interventions outside the trial site

If trial-related interventions are performed outside the trial site with the trial subjects' consent, e.g. in their homes, these tasks may be performed by commissioned service providers who supply the corresponding trial nurses, known as "mobile nurses". It is necessary for each person who performs these interventions – at the responsibility of the investigator as part of the study team – to have appropriate training and have proven knowledge and experience with regard to the relevant specialist field and the performance of a clinical trial (Art. 6 para. 4 ClinO, ICH GCP E6 (R2) 4.2.4).

In this situation it is the responsibility of the investigator in Switzerland to monitor that the trial nurses carry out and document the study-specific interventions on the patients at home in accordance with the protocol. Some medical examinations cannot be performed by the trial nurses or at home (e.g. specific neurological examinations, computed tomography). These must be performed at the trial site or at a suitably equipped facility by qualified personnel or in the course of a personal visit to the patient's home by the investigator or a delegated physician.

The sponsor must ensure that the trial subjects' needs are taken into account in respect of doctors' visits carried out using telemedicine. The trial subjects should be given the opportunity to see the doctor in person if needed. The investigator in turn must also be able to pay a personal visit if they consider it to be necessary for the optimal medical care of trial subjects.

The investigator must ensure adequate medical care if adverse events occur outside the trial site and the standardised documentation and protocol-compliant reporting of adverse events (Art. 39 – 41 ClinO, ICH GCP E6 (R2) 4.3.2).

If the investigator in Switzerland instructs or performs the trial-related interventions in patients' homes using digital platforms, e.g. video calls (telemedicine), compliance with the Swiss Data Protection Act must be guaranteed by end-to-end encrypted communication. If cloud systems are used, these must comply with the requirements of this Act. The server supporting the systems used should be located in Switzerland or a country according to the list of countries whose legislation ensures an appropriate level of data protection (Art. 6 para. 1 FADP). The trial subjects must be informed comprehensively about processing of their data and explicitly consent to this processing (Art. 4 para. 5 FADP).

The trial nurses who perform the trial-related interventions outside the trial site have access to uncoded personal data by virtue of their activities in the trial subjects' homes. Suitable technical and organisational measures must therefore be taken to ensure that these personal data are protected from unauthorised or accidental disclosure to the sponsor or, when data are transmitted to involved companies (Art. 18 para. 1 ClinO; Art. 3 let. c no. 2, Art. 7 para. 1 FADP).

Source data recorded in the context of trial-related interventions outside the trial site must be documented in compliance with GCP and available for monitoring, audit and inspection purposes (ICH GCP E6 (R2) 4.1.4). The statutory archiving obligation for these source data must be observed. Source data recorded directly in the CRF must be identified as such in the protocol (ICH GCP E6 (R2) 6.4.9).

2.3. Dispensing and administration/ingestion of the IMP outside the trial site

IMP whose stability and safety profile has not yet been adequately characterized due to an early stage of development is unsuitable for dispensing and administration to the trial subjects at home. IMPs which require preparation, e.g. in a sterile environment, before administration or those that are associated with a high risk of possible adverse reactions (e.g. anaphylactic

shock) are not suitable as well. Precautions must be taken to ensure the medical care of trial subjects should adverse reactions occur during or after the administration/ingestion of the IMP by the trial subject at home (ICH GCP E6 (R2) 4.3.2).

If the IMP is dispensed outside the trial site, the requirements of Good Manufacturing Practice (GMP) must be fulfilled (Annex 1 of the Ordinance on Licensing in the Medicinal Products Sector, MPLO [812.212.1]; Art. 32 para. 1 let. d ClinO). Moreover, the requirements of the Good Distribution Practice (GDP) for the IMP and the applicable cantonal provisions in Switzerland must be fulfilled. It is furthermore recommended that the details of a planned implementation in Switzerland be discussed in advance with Swissmedic and the competent Ethics Committee and, if applicable, the competent cantonal authorities.

The following models are being discussed at the international level for the dispensing of IMP in DCTs:

- Direct delivery of the IMP to trial subjects by the trial site.
- Delivery of the IMP directly to trial subjects by a central pharmacy.
- Delivery of the IMP by a central pharmacy to a local pharmacy near the trial subject's home. The trial subjects or trial nurses pick up the IMP in person.
- Delivery of the IMP directly to the trial nurses by a central pharmacy.

If trial subjects are supplied directly, they must be given appropriate information and agree to the personal data necessary for this being passed on. Steps must be taken to ensure that personal data are protected from unauthorised or accidental disclosure (Article 18 para. 1 ClinO). If the trial subjects are supplied directly, they must be instructed in advance about the correct storage and use of the IMP.

Until it is administered/ingested, the IMP must demonstrably be stored in such a way that its quality (protocol-compliant storage, shelf-life) is not impaired (ICH GCP E6 (R2) 4.6.4). Care must also be taken to ensure that the IMP is used only in accordance with the approved protocol ("compliance", ICH GCP E6 (R2) 4.6.5).

The sponsor must provide suitable means (e.g. using electronic tools) for performing the regular review of quality and compliance. The investigator in Switzerland is responsible for this review and must therefore be able to access these data at all times (ICH GCP E6 (R2) 8.1). The investigator may delegate the review to the mobile trial nurses. Like the return of unused IMP to the sponsor and its disposal, the review of quality and therapy compliance must be documented in compliance with GCP and the documentation must be available for monitoring, audit and inspection purposes.

2.4. Data capture outside the trial site using mobile technologies

Where the intention is to use mobile technologies to record data outside the trial site, it must be ensured that the trial subjects have given their prior consent to data being recorded by the device (e.g. wearables) or entered by the trial subjects, e.g. electronic patient reported outcome (ePRO). The trial subjects must also be trained in the correct use of the mobile technologies. If source data are recorded directly in the CRF, this must be identified as such in the protocol. If data are recorded automatically, e.g. by wearables, it should be ensured that only trial-specific data are recorded by the mobile technology being used. The data which are considered to be source data must be stated in writing before the clinical trial begins, e.g. if data are only stored for a short time on the mobile technology.

The mobile technologies must be demonstrably validated and comply with the relevant standards for accuracy, precision, reproducibility, reliability and responsiveness (sensitivity to

technological changes over time, ICH GCP E6 (R2) 5.5.3). Furthermore, the equivalence of the mobile technology used across various data-collection platforms or methods must be ensured. It must be possible to trace data entry and data changes by means of an audit trail. If the data generated this way are source data, the sponsor must ensure that they are documented in compliance with the legislation and that the statutory archiving obligation is observed. Access to this documentation must be ensured.

The sponsor must define measures in order to ensure that the recorded data actually originate from the trial subjects or were generated by the trial subjects (and not, for example, by a third person). Here it must be ensured that the sponsor has no access to personal or identifiable information relating to the trial subjects.

To ensure the protection of personal data from unauthorised or accidental disclosure, the sponsor must protect these data from any form of intervention from outside, whether accidental or intentional. This protection applies to all personal, identifiable information, to all personal health-related data and to devices and mobile technologies used to collect, store or transmit data. If sensitive personal data are stored on a central server, the server must be located in Switzerland or the EU or a country whose legislation guarantees adequate data protection according to the Art. 6 para. 1 FADP (see list of countries with legislation which ensures an appropriate level of data protection).

2.5. The question of CE certification of the technology employed

A distinction must be made for mobile technologies according to whether they are used solely for research purposes or whether they have an additional medical purpose. Mobile technologies with an additional medical purpose (i.e. medical devices) are regulated by the medical devices legislation. A medical purpose exists if the data generated by the medical device influence medical decisions. It is forbidden to dispense non-compliant devices for a medical purpose (Art. 1, Art. 6. para. 1, Art. 8 para. 2, Art. 14, Art. 21 para. 2, Art. 23 of the Medical Devices Ordinance (MedDO) [SR 812.213]).

If the medical devices employed, including apps and software, are marked with a CE label for medical devices and are employed according to the approved intended use (not off-label use), the trial is purely a trial of a medicinal product (IMP). If, on the other hand, the medical devices employed do not bear a CE label for medical devices, or if they are employed for an off-label use, the trial is a combined trial of a medicinal product and a medical device.

If the mobile technologies are not medical devices, the data are not considered to be trustworthy for individual medical purposes. The sponsor must ensure that such data does not erroneously influence medical decisions by mistake. In particular, these data must not be filed in patients' records, nor should they be communicated to trial subjects, treating doctors, therapists or trial nurses without a compelling reason.

2.6. Remote source data verification

If persons commissioned by the sponsor ("Monitors") review uncoded personal data from trial subjects (e.g. medical records) in the course of source data verification and this review is not performed in person at the trial site but by employing electronic tools outside the trial site (remotely), suitable technical and organisational measures must be taken to ensure compliance with the Swiss Data Protection Act.

If the trial site sets up separate electronic access for the Monitors to the trial patients' source data for the purpose of verifying the source data, measures must be taken to ensure that this

application is protected appropriately, e.g. with two-factor authentication and a VPN (virtual private network). The Monitor may only be granted read-only rights. Remote source data verification should be performed from Switzerland.

The Human Research Act regulates the export of health-related data to foreign countries and distinguishes between export of non-genetic data versus genetic data/biologic material. Swiss law allows the export of non-genetic data without a written informed consent when the requirements of Art. 6 FADP are met (Art. 42 HRA). In contrast, a written informed consent is obligatory for the export of genetic data/biological material. However, since most clinical trials process both non-genetic and genetic data, a clear-cut distinction between the two is not satisfying and therefore not really possible from a practical perspective. Moreover, there are ethical justifications to inform the persons in a transparent manner according to ethical standards that are higher than the legal minimum. Therefore, whenever uncoded personal data, regardless of whether non-genetic or genetic, are reviewed (monitored), the trial subjects must be informed comprehensively about this and must give their explicit consent to it. Similarly, if coded personal data, regardless of whether non-genetic or genetic, are accessed from outside Switzerland, the trial subjects must be informed comprehensively about this and must give their explicit consent to it.

If, in the course of verifying uncoded personal source data, data are stored in systems abroad, these must comply with the requirements of the Swiss Data Protection Act. If servers are used, the server should be located in Switzerland or a country on the list of countries whose legislation guarantees adequate data protection (Art. 6 para. 1 FADP).

3. Summary and outlook

There is great interest, both internationally and in Switzerland, in performing decentralised clinical trials. Both Swissmedic and swissethics are committed to support researchers and sponsors in this innovative step. The present document focuses on clinical trials with medicinal products and is intended for sponsors and researchers who are planning DCTs and want to perform them in Switzerland.

This document considers the major challenges relating to DCTs and is based on the current position of Swissmedic and swissethics interpreting their respective areas of responsibility (Art. 25 and Art. 32 of the Ordinance on Clinical Trials with the Exception of Clinical Trials with Medical Devices (ClinO) [SR 810.305]). The continuation of the present dialogue will identify areas in which further action or adaptation is required in the future.