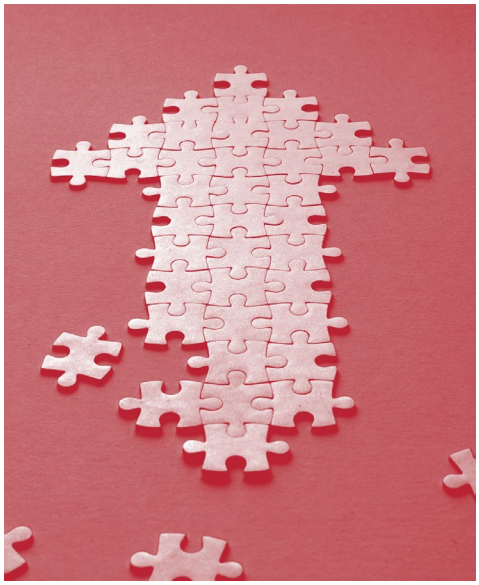
SCTO PLATFORMS

ISSUE 9, DECEMBER 2024

Innovation in clinical research: Decentralised and complex trials

REGULATORY AFFAIRS WATCH

EDITORIAL



DECENTRALISED AND COMPLEX CLINICAL TRIALS: SHAPING THE FUTURE OF CLINICAL RESEARCH

We are pleased to present the ninth issue of *Regulatory Affairs Watch* on innovative developments in clinical research, namely decentralised trial approaches and complex clinical trial designs.

Technological advances over the last few decades have opened up new possibilities for using innovative elements and designs in clinical trials. But it was the COVID-19 pandemic that really pushed their use in clinical research forward. When the pandemic imposed restrictions on travel and in-person interactions, decentralised solutions made it possible to conduct certain aspects of clinical trials remotely with the help of telemedicine, digital data collection, remote monitoring, and many other technologies. At the same time, complex trials with adaptive designs and master protocols accelerated the testing of COVID-19 treatments and vaccines, allowing researchers to modify ongoing trials based on real-time data.

Decentralised clinical trials (**DCTs**) and complex trials are now being adopted across many therapeutic areas due to their patient-centric focus and research efficiency, and they will certainly play an increasingly important role in clinical research in the future. Challenges, however, remain. DCTs face issues related to data security, the validation of digital tools (e.g. wearables), the digital divide, and the need for consistent regulatory standards across regions. And complex trials, while efficient, require advanced statistical expertise and careful coordination, making them resource intensive.

This issue of *RA Watch* includes a range of articles and viewpoints on these promising – and challenging – developments in clinical trial approaches and designs.

- **DEEP DIVE:** In our Deep Dive article, our new *RA Watch* project lead and editor Güliz Vanli Jaccard looks into how design innovation has transformed clinical research by providing new operational approaches, such as those applied in decentralised clinical trials, and new methodologies, such as those used in complex trials. She considers the advantages and disadvantages of using decentralised procedures in clinical trials and outlines key global regulatory advances. In addition, she delves into complex clinical trials, such as adaptive and platform trials, and explains how they are transforming the clinical trial landscape by offering more efficient and responsive methods for testing new treatments.

- **FEEDBACK FROM:** The current regulatory framework already regulates many aspects of DCTs with medicinal products in Switzerland. However, since these types of trials are relatively new, they pose challenges to various stakeholders. In our Feedback From section, Swissmedic looks at some of the challenges – and opportunities – DCTs bring with them. In addition, Swissmedic invites

stakeholders to liaise closely with regulatory authorities and to engage in the current dialogue. Having a variety of perspectives can better equip stakeholders to find solutions to DCT challenges and take advantage of their opportunities.

- **VIEWS AND OPINIONS:** For our Views and Opinions section, the *RA Watch*'s editorial team gathered multiple perspectives on decentralised and complex trials.

  Ethics perspective: What are the ethical considerations of remote informed consent in DCTs? In our first Views and Opinions article, ethicist Brenda Bogaert explores both the challenges and opportunities of remote informed consent for research participants. She also provides some approaches for mitigating related ethical problems.

  Industry perspective: Study sponsors must weigh many factors when considering using decentralised elements in their clinical studies. In our second Views and Opinions article, industry representatives from Roche and Takeda discuss different sponsor considerations for incorporating decentralised elements in trials. They also tackle the question of why decentralised elements are not yet routinely included in clinical trials despite their many promising benefits.

  Legal perspective: Digital health technologies (**DHTs**) have tremendous potential to bring innovation to clinical research processes and research participants. Yet a lack of harmonisation in privacy laws and guidance as well as the extra level of complexity DHTs add to trials can hinder research. In our third Views and Opinions article, legal expert Gabriel Avigdor looks at some of the legal, ethical, and practical challenges of using DHTs in clinical research.

  Patient advocacy perspective: A major benefit of decentralised clinical trials is their potential to make trials more flexible, personalised, and convenient for participants. In our fourth Views and Opinions article, Nicole Gusset, who advocates for people with spinal muscular atrophy (**SMA**) at the patient organisations SMA Schweiz and SMA Europe, discusses how innovative trial designs can directly benefit patients. She also highlights their enormous potential to further advance medicines for the good of patient communities, especially in the area of rare diseases.

- **CASE STUDY:** Although randomised clinical trials are considered the gold standard in clinical research, they often face challenges such as high cost, slow recruitment, and a limited generalisability of results. The authors of our Case Study are using the novel TwiCs (trials within cohorts) design in the Swiss HIV Cohort Study to overcome some of these challenges. In their article, they discuss why and how the TwiCs approach is implemented while also considering some of the design's limitations and several mitigation strategies.

This latest issue of *RA Watch* also gives us the opportunity to introduce Güliz Vanli Jaccard, our new SCTO Regulatory Affairs Platform coordinator and *RA Watch* project lead and editor, who joined the team at the Clinical Research Centre (**CRC**) Lausanne almost a year ago. With an academic background in molecular biology and experience in research and regulatory science, Güliz has acquired expertise in multiple aspects of clinical trials and regulatory processes. We greatly appreciate her leadership on this issue of *RA Watch* and look forward to future *RA Watch* issues with her at the helm! We must admit that after more than two years of searching for a permanent RA Platform coordinator and *RA Watch* project lead, we are especially grateful to have found this rare pearl. We warmly welcome Güliz to the *RA Watch*'s editorial team, to the RA Platform, and to the CRC Lausanne!

Aurélie Fayet: Head of Operations and Team Management of the Clinical Trial Unit at the Clinical Research Centre (**CTU-CRC**) Lausanne; Lausanne University Hospital (**CHUV**); Faculty of Biology of Medicine at the University of Lausanne (**FBM UNIL**)

Grégoire Wuerzner: Head of Medical and Scientific Affairs of the Clinical Trial Unit at the Clinical Research Centre (**CTU-CRC**) Lausanne; Lausanne University Hospital (**CHUV**); Faculty of Biology of Medicine at the University of Lausanne (**FBM UNIL**)

DEEP DIVE

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INNOVATIVE CLINICAL TRIALS: ADDRESSING THE EVOLVING NEEDS OF CLINICAL RESEARCH AND PARTICIPANTS WITH DECENTRALISED AND COMPLEX TRIALS

Author: **Güliz Vanli Jaccard**

Affiliations: Lausanne University Hospital (CHUV), Clinical Trial Unit at the Clinical Trial Centre Lausanne (CTU-CRC); University of Lausanne (UNIL), Faculty of Biology and Medicine (FBM); and Swiss Clinical Trial Organisation (SCTO), National Regulatory Affairs Platform Coordinator

doi: 10.54920/SCTO.2024.RAWATCH.9.4

In general, innovation in clinical research often stems not only from aspiration – for example to increase accuracy and efficiency or to optimise costs – but also from shifts in social paradigms or from changes in circumstances that lead to changes in practices, as experienced during the COVID-19 pandemic. Indeed, the challenges clinical research faced during the pandemic led to changes in how clinical trials are conducted. Healthcare personnel had to come up with nontraditional ways to connect with their patients and patients' families. Researchers had to develop new approaches since it was no longer possible to follow many everyday practices and because they had to answer even more complex questions – often with fewer resources. These challenges accelerated innovation in clinical research, particularly in the area of trial design. This article takes a deep dive into how design innovation has transformed clinical research by providing new operational approaches, such as those applied in decentralised clinical trials (**PART 1**), and new methodologies, such as those used in complex trials (**PART 2**).

PART 1: DECENTRALISED CLINICAL TRIALS

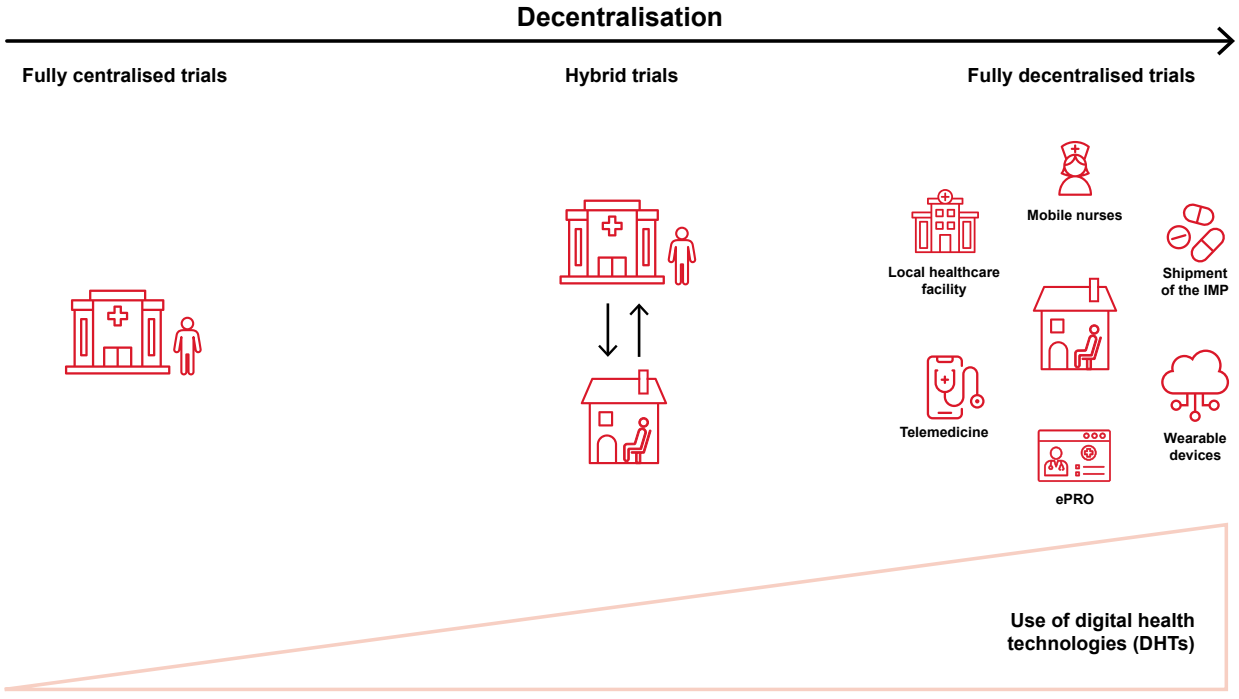
Features of decentralised clinical trials

Decentralised clinical trials (**DCTs**) are trials in which some – or all – trial-related procedures take place outside of the traditional clinical trial site. These alternative locations may include local healthcare facilities and participants' homes, and they tend to be more convenient for participants.[1] Although DCTs slowly started appearing on the clinical trial landscape a decade before the COVID-19 crisis, the circumstances surrounding the pandemic jump-started their adoption. Since the pandemic, DCTs have continued to gain ground as an alternative operational approach because they can circumvent some of the limitations of traditional randomised controlled trials (**RCTs**). DCTs promise not only to enhance patient inclusivity and centricity by increasing access to hard-to-reach populations with social or geographical constraints but also to reduce participant burden by making it possible to acquire data for clinical measurement from the comfort of participants' homes.

RCTs are considered the gold standard in clinical research for evaluating the safety and efficacy of interventions due their robust design, which includes randomisation, control groups, and blinding. However, the way RCTs are traditionally conducted has notable limitations that are largely due to their narrow eligibility criteria and strict protocol-based procedures.[2,3] These limitations often result in findings that are difficult to validate externally, which reduces their generalisability and creates challenges when applied to routine care in a real-world setting.[4,5] In contrast, a DCT model provides researchers with access to electronic, health-related data from a real-world setting that is similar to data from routine practice, where patients and clinicians commonly deviate from the optimal treatment protocol.[6]

Depending on their degree of decentralisation, DCTs fall at different places along the decentralisation continuum, with fully centralised (traditional) trials on the one end, and decentralised trials on the other (see **Figure 1**). It is important to recognise that decentralisation (using decentralised elements such as performing some trial-related activities remotely) and digitisation (using technology – such as digital health technologies (**DHTs**) like wearables, mobile applications, and monitors – to capture and transmit trial-related data) are not the same, although they often correlate.[7]

Figure 1: Decentralisation continuum for clinical trials



Trials can be placed on a continuum according to their degree of decentralisation. In fully centralised trials, all trial-related activities take place at the primary clinical trial site, and participants must travel to the site. In hybrid trials, some decentralised, trial-related activities take place off-site while other activities (e.g. screening visits and the administration of the investigational medicinal product (**IMP**)) take place at the clinical trial site. In fully decentralised trials, participants do not have to go to the clinical trial site; all trial-related activities are carried out remotely, predominantly with the use of digital health technologies (e.g. electronic patient-reported outcome (**ePRO**) tools and wearable devices).

On the operational level, any trial-related procedure can be decentralised – for example using online platforms and social media to recruit and enrol participants, delivering an investigational medicinal product (IMP) to a participant's home or a nearby pharmacy, arranging home visits via mobile healthcare professionals or telemedicine, performing medical examinations or imaging at a suitably equipped local healthcare facility, collecting data remotely, or conducting centralised monitoring. However, these activities should always be aligned with regulatory and legal requirements to ensure compliance.

Each decentralised procedure comes with both opportunities and challenges. Most of these opportunities and challenges are well-documented in the literature, and a selection are listed in **Table 1**.[8]

Table 1: Opportunities and challenges of decentralised procedures in clinical trials

Trial-related procedure	Opportunities	Challenges
Web-based recruitment	Increased access to hard-to-reach and underrepresented populations	Risk of creating a digital divide (i.e. underrepresenting people with low digital literacy or socioeconomic status and/or elderly people), which can lead to a difference between study and target populations[I,II,III]
Remote informed consent	Greater flexibility and freedom to exercise autonomy	A shift in the responsibility of being informed from the investigator to the participant[IV]
Home delivery of investigational medicinal product (IMP)	Increased access to new and diverse populations beyond geographic or logistical barriers	Safety risks associated with the storage, administration, and disposal of the IMP
Patient-reported outcomes and safety reporting	Possibility to receive medical advice in real time and thus avoid retrospective recall inaccuracies that can occur with patient reporting	Self-reporting bias that may intervene with scientific validity Increased time and reporting burden for participants[II,V]
Involvement of alternative healthcare facilities	Greater convenience for participants in terms of access	Increased disparity in testing and imaging results

[I] Benedict C et al. (2019) Recruitment via social media: Advantages and potential biases. Digital Health. doi: 10.1177/2055207619867223
[II] Sehrawat O et al. (2023) Data-driven and technology-enabled trial innovations toward decentralization of clinical trials: Opportunities and considerations. Mayo Clinic Proceedings 98(9):1404–1421. doi: 10.1016/j.mayocp.2023.02.003
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Global regulatory advances

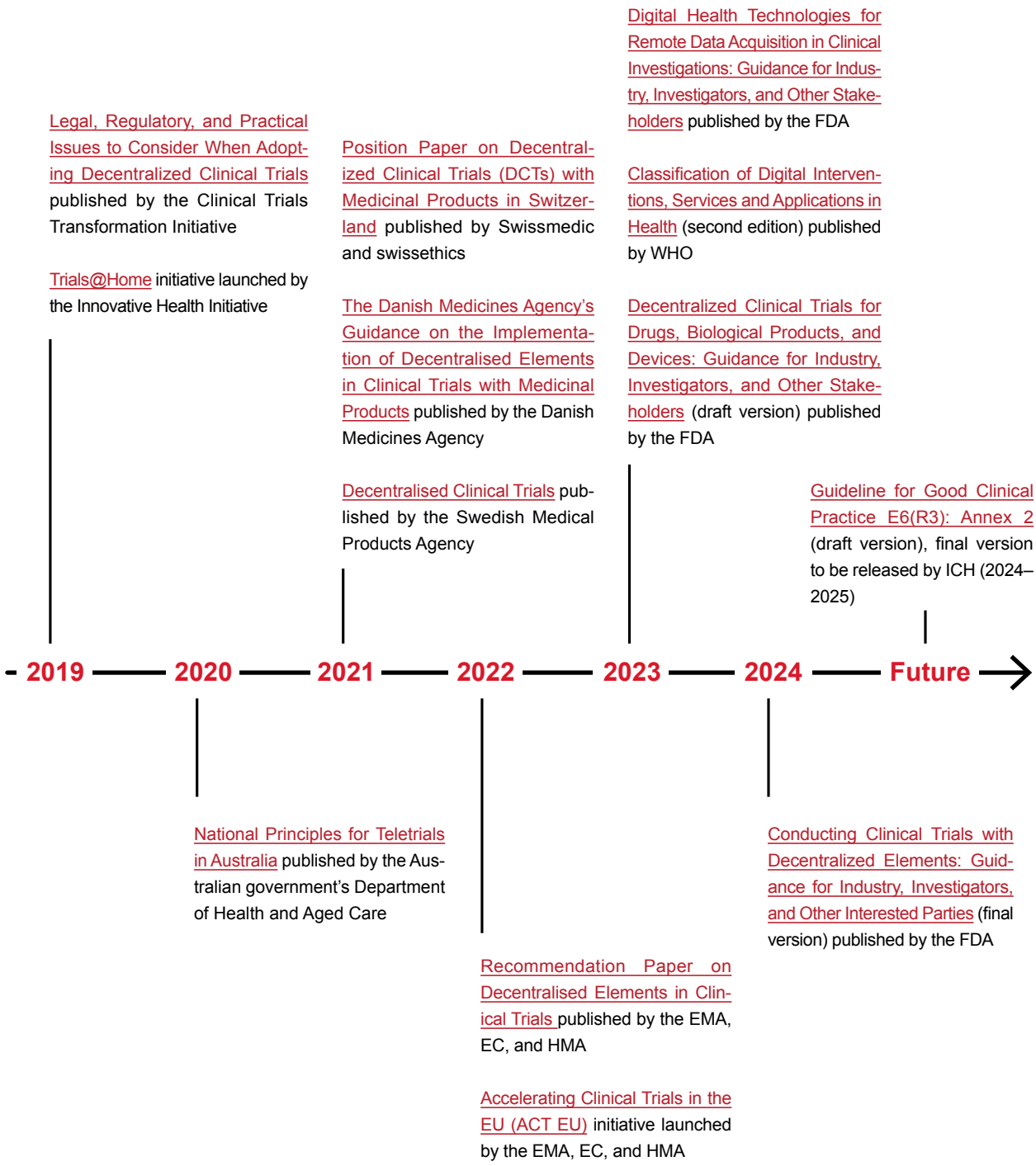
Regardless of whether they have a decentralised approach or not, all trials must abide by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (**ICH GCP**) and be conducted in accordance with the laws and regulations of the jurisdiction where they take place. However, these more general guidelines and regulations were written with traditional, site-based trials in mind and are not sufficient; the challenges posed by DCTs require the issuance of specific guidelines to address their unique aspects and particularities. This need for specific DCT guidance became very apparent during the COVID-19 pandemic. Thanks to prior discussions on patient centricity and inclusivity as well as initial frameworks for the use of DHTs and real-world data in clinical development that were created before the pandemic, regulators had a foundation that enabled them to rapidly develop formalised guidelines when the pandemic hit. Since then, many more DCT guidelines and initiatives have been developed (see **Figure 2**). In Switzerland, for example, Swissmedic and swissethics published a joint position paper on DCTs with medicinal products in 2021 and an updated second version in December 2022. Their paper discusses several key elements of DCTs, including ethical and legal frameworks and practical considerations for implementing decentralised elements in Switzerland.[9]

As can be seen in **Figure 2**, the landscape of DCT guidance is diverse and the task of harmonising this heterogeneity is both long and challenging. It is therefore a welcome opportunity that the upcoming ICH GCP E6(R3) Annex 2 will focus on the considerations for non-traditional interventional clinical trials, including decentralised trials. Despite this diversity in guidance, there are prevailing concepts that emerge from the majority of the guidance and recommendation papers. A detailed comparison of European and US regulators' approaches to DCTs shows that both assess the appropriateness of decentralised elements on the grounds of patient safety and data integrity.[10] Therefore, sponsors should plan which processes to decentralise and which digital tools to employ by carefully evaluating the risk-benefit ratio. Below are some factors sponsors need to consider during the design phase of a DCT (see also **VIEWS AND OPINIONS** article on p. 20):

- Shipment of the IMP to participants
  - » Safety profile, stability, storage, and administration route of the IMP
  - » Trial population
  - » Suitability of participants' homes for handling IMP
  - » National legal provisions
- Remote informed consent
  - » Trial population
  - » Complexity of the trial
  - » If consent is digitalised: confidentiality aspects and validity of e-signatures[11]
  - » National legal provisions
- Data protection and transfer
  - » Information and consent of participants regarding their data flow
  - » Mitigation strategies for cybersecurity risks
  - » Application of privacy by design and privacy by default approaches
  - » National legal provisions[12]

Another aspect emphasised by regulators, including Swissmedic (see **FEEDBACK FROM** article on p. 14), is the importance of early discussions between sponsors and regulators concerning the feasibility and implementation of DCTs.[13] The Clinical Trials Transformation Initiative (**CTTI**) recommends that sponsors seek input from all stakeholders – including ethics committees, clinical investigators, other site staff, and patient advocacy groups – at the earliest possible phases of study design in order to identify challenges and mitigate risks.[14]

Figure 2: Key regulatory publications and initiatives related to decentralised clinical trials and digital health technologies



Key collaborative initiatives related to decentralised clinical trials and digital health technologies and a selection of guidelines and position statements issued by national and international regulatory authorities.

EC: European Commission
EMA: European Medicines Agency
FDA: US Food and Drug Administration
HMA: Heads of Medicines Agency
ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
WHO: World Health Organization

Emerging regulatory themes: Using digital health technologies beyond decentralised clinical trials

Digitising activities in the medical and research fields is an ongoing trend, and the resulting growth in the use of DHTs has fuelled the discussion around the acquisition of health-related data from a real-world setting. This trend can enable researchers to expand data collection beyond episodic data input during clinical visits at a trial site; participants can feed data flows actively, passively, or even continuously from their DHTs at their chosen locations. This real-world data (**RWD**) provides better insights into the natural history of the disease being studied and holds the potential to not only define novel digital endpoints that complement standard endpoints but also generate real-world evidence (**RWE**).[5,15]

The use of RWE, namely clinical evidence that is put forward by the analysis of RWD, is not a new concept per se and is accepted by the regulatory authorities for post-approval safety monitoring. Until recently, however, RWE was mainly derived from retrospective RWD acquired from several sources, including electronic healthcare records, patient registries, observational studies, and medical claims. Now, regulators around the globe are discussing RWE's potential for regulatory decision-making, including its role in supporting product approval processes.[16–19]

Unlocking the full potential of decentralised clinical trials through collaboration

DCTs have ushered in advancements in clinical research; however, their implementation has encountered significant challenges. Key issues include regulatory uncertainty, concerns about ensuring data integrity, and maintaining participants' safety in diverse and non-traditional settings. Additionally, the integration of DHTs has raised issues surrounding data privacy and the standardisation of data collection practices. Despite these challenges, industry sponsors appear to be cautiously optimistic about the potential of DCTs, and they are actively exploring the use of hybrid models as a more practical and feasible approach.[20,21]

Moving forward, the key to overcoming these challenges and advancing the development of clear regulatory frameworks and best practices is collaboration. Multi-stakeholder initiatives such as Trials@Home, supported by the European Innovative Medicines Initiative, contribute to this effort by bringing together academia, industry, regulators, patient organisations, and technology providers in order to foster dialogue and address ethical, quality, regulatory, and legal gaps. These collaborative efforts highlight the path ahead on the journey to unlocking the full potential of decentralised trials.

PART 2: COMPLEX CLINICAL TRIALS

Methodological innovation is another transforming force in clinical research, driven by new and flexible trial designs that enhance efficiency, flexibility, and patient-centricity. Unlike traditional RCT designs that focus on a single intervention for a specific disease, complex trial designs – such as master protocol studies – make it possible to evaluate multiple interventions across diverse patient populations and/or disease types[22,23] Innovative designs such as trials within cohorts (**TwiCs**) also offer alternative approaches to addressing the evolving needs of research and health care when conventional approaches are not feasible or optimal. These evolving needs can be met mainly by accelerating or optimising product development. This makes it possible to obtain the maximum amount of information from research efforts as well as reduce the number of participants needed for a trial, which is particularly beneficial in settings where the population size is small (e.g. rare diseases and specific cancer subtypes).[24]

Regulatory perspectives on complex trials

From a regulatory perspective, the definition of complex trials is still evolving and not yet fully standardised.[25,26] The Clinical Trials Facilitation and Coordination Group (**CTFG**) defines complex trials as those containing multiple components that could constitute individual clinical trials and/or involve extensive prospective adaptations. Such adaptations include planned additions of IMPs or new target populations and the closure of subpopulations based on futility or safety analysis.[27] Similarly, the US Food and Drug Administration (**FDA**) describes complex innovative trial designs (**CIDs**) as trials that incorporate complex adaptive, Bayesian, or other novel clinical trial designs in order to improve clinical trial efficiency. According to the FDA, complex trials may utilise master protocols to study multiple therapies, diseases, or patient populations within a single framework, which allows greater adaptability and continuous enrolment.[28,29]

In Switzerland, Swissmedic aligns its approach to complex trials with the CTFG's Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials, which provides guidance on complex trials and offers a preliminary evaluation for complex trial designs.[27] Sponsors of trials in Switzerland can submit a protocol overview and study flow diagram for assessment, which Swissmedic then evaluates on a case-by-case basis. If any questions arise, sponsors may contact Swissmedic directly (ct.medicinalproducts@swissmedic.ch).[30]

Types of complex trial designs

Several complex designs have emerged over the past few decades. Within the context of master protocols, the complex designs most addressed by regulatory authorities are basket, umbrella, and platform trials.

- **Basket trials** consist of parallel substudies, each investigating a specific molecular compound across multiple diseases (e.g. multiple tumour types that share a common molecular alteration).
- **Umbrella trials** are designed to investigate different molecular targets within a single disease using parallel substudies and stratifying patients based on specific biomarkers.
- **Platform trials** are based on the umbrella trial model, allowing the ongoing addition of new study arms or substudies while discontinuing treatment arms that are considered unpromising based on interim analysis. This creates a nearly continuous evaluation process.[31]

These novel designs provide significant advantages in terms of efficiency, precision medicine, and lower costs by allowing for the targeted identification of effective treatments.[32] They also help to develop personalised medicine since they enable researchers to match the most efficient therapies for specific biomarkers.

Along with these advantages, however, complex designs also come with significant challenges for both sponsors and regulatory agencies. Subgroup stratification and frequent adjustments of the trial design increase the risk of statistical errors. Frequent protocol amendments add administrative complexity and entail close regulatory oversight, so they also require additional resources. Additionally, testing drugs across multiple conditions (as in basket trials) or multiple therapies within a single disease (as in umbrella trials) can complicate the establishment of a consistent safety profile since responses can vary.[26, 32–34] Platform, umbrella, and other types of adaptive trials also risk becoming "functionally immortal" if treatment arms are continually added without predefined stopping rules. Therefore, regulatory agencies, including the FDA, emphasise the importance of having clearly defined endpoints and structured reporting of interim results.[31,33] Ethical aspects, such as the potential need for re-consent, should also be considered since the evolving nature of adaptive designs may require re-consent if an investigation's risk-benefit ratio changes significantly throughout the trial.[31]

Trials within cohorts: An innovative design with complex features

Initially proposed by Relton et al. in 2010 under the concept of "cohort multiple randomised controlled trials", the trials within cohorts approach embeds RCTs into the infrastructure of existing observational cohorts.[35] Its ability to study multiple alternative treatments over time within a single cohort makes the TwiCs design stand out in the innovative trial landscape. This pragmatic trial approach can circumvent challenges that RCTs face, such as participant recruitment and retention.[36]

While trials with the TwiCs design share certain characteristics with platform trials, such as multiple interventions over time, the two designs are distinct in their structure and purpose. Platform trials use a master protocol to assess multiple treatments simultaneously within a unified and interconnected framework.[37] In contrast, TwiCs focus on taking advantage of a pre-existing patient population (i.e. a cohort) in order to test multiple treatments independently, with each intervention having its own protocol and specific research question. While there are examples of cohorts prospectively designed with TwiCs in mind, often TwiCs interventions are not defined in advance, which distinguishes them from platform trials. Additionally, TwiCs interventions do not necessarily relate to each other, which contrasts with the interconnected framework of platform trials.[37]

In the TwiCs design, the consent process is carefully structured to balance ethical considerations with research efficiency. Initially, participants consent to join a large observational cohort and agree to regular data collection and to the possibility of being invited to future RCTs embedded within the cohort. When a new intervention is introduced, eligible individuals within the cohort are identified and randomised into the intervention group or the control group. Participants who are randomised into the intervention group are informed about the investigational treatment and are asked to provide consent again, while those assigned to the control group receive care as usual and are not explicitly informed about serving as controls in a trial. This two-stage consent approach has sparked ethical debates, particularly concerning participant autonomy and transparency regarding the lack of explicit information to the control group. These issues have been discussed in forums such as the second international symposium on the ethics of trials within cohorts (TwiCs).[38] Despite these debates, the two-stage consent approach has been well received by participants: in a study published by Verweij et al. it was found that only 2% of participants in the usual care control group expressed dissatisfaction at having served as controls.[39]

Innovative trial designs that address the growing complexity of product development continue to shape the evolution of clinical research. Master protocols demonstrate the potential these designs have to streamline drug discovery and precision medicine by testing multiple hypotheses within adaptive frameworks. The TwiCs design provides a pragmatic approach that simplifies trial conduct through the use of pre-existing cohorts, which enhances recruitment and retention while also reducing logistical challenges.

CONCLUSION

Innovative trials: Similarities and differences

Innovative trials are at the forefront of clinical research, addressing challenges of clinical trials such as participant recruitment, data collection, and operational efficiency. DCTs, complex trials, and TwiCs are three types of innovative trial approaches that share similar goals but differ in their execution, design, and application.

One key feature of these three approaches is their flexibility. DCTs reduce geographical barriers by enabling remote engagement through telemedicine, wearable devices, and digital data platforms. This approach allows participants to take part in trials from home, thus improving trial accessibility and broadening recruitment. However, while DCTs are convenient for participants, they introduce operational complexity for sponsors, who must ensure data quality and security and coordinate across dispersed participants.

Complex trials also exhibit flexibility by allowing multiple interventions or patient populations to be studied within a single protocol. These trials often include adaptive elements that enable modifications, such as adding or removing treatment arms based on interim data. While this adaptive framework improves efficiency and optimises resource allocation, it requires careful planning and coordination and therefore makes execution challenging.

The TwiCs design offers a distinct form of flexibility by embedding trials within pre-existing cohorts. This eliminates the need to recruit entirely new participants for each trial and allows multiple interventions over time. This framework streamlines recruitment and operational efficiency, yet it may also introduce additional complexity in managing multiple interventions.

Despite these differences, all three of these innovative trial approaches share the goals of improving trial efficiency, enhancing participant engagement, and leveraging innovative methodologies in order to meet the evolving demands of clinical research. Each of them takes a unique approach to flexibility, offering distinct advantages while navigating its own set of challenges.

Paving the way for a dynamic future

From a regulatory perspective, there is a need for evolving frameworks to address the unique challenges posed by innovative trial approaches and designs. Collaboration among stakeholders – including regulatory agencies, sponsors, researchers, and patient representatives – plays a critical role in shaping an environment that balances flexibility with the rigor needed to ensure safety and effectiveness. And since innovative trials increasingly integrate advanced technologies, such as artificial intelligence and real-time analytics, their potential to enhance flexibility, efficiency, and inclusivity will continue to grow. Updating regulatory frameworks and harmonising global practices will help pave the way for a more dynamic and inclusive future in clinical research.

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FEEDBACK FROM

swissmedic

DECENTRALISED CLINICAL TRIALS: A NEW APPROACH WITH OPPORTUNITIES AND CHALLENGES

Authors: **Reto Iannaccone**[1] and **Simone Ferbitz-Scheurer**[2]
Affiliations: [1]Swissmedic, GCP/GVP Inspector and [2]Swissmedic, Head of Division Clinical Trials
doi: 10.54920/SCTO.2024.RAWATCH.9.14

Clinical trials are dependent upon the availability of participants who are willing and able to take part in them. At times, however, participating in a clinical trial requires a significant amount of time and travel. The aim of decentralised clinical trials (**DCTs**) is to move some of the trial-related visits and/or assessments from the trial site to a participant's home in order to reduce practical barriers to trial participation and to more smoothly integrate study visits into participants' daily routines. While DCTs open up new opportunities for trial participants and researchers, they also pose challenges in terms of ensuring both patient safety and adequate oversight as well as protecting participants' data privacy. Swissmedic recommends that researchers take an active approach by engaging in the current dialogue on DCTs and liaising closely with the authorities as they plan and conduct DCTs in order to ensure they fulfil applicable legal requirements.

Decentralised clinical trials (**DCTs**) are research projects in which the digital recording and/or transmission of data related to trial interventions plays an important role. This may involve digitally recruiting trial participants, conducting trial visits in a patient's home using telemedicine, or digitally recording and transmitting data using wearables (i.e. computer technology worn on the body) or smart devices such as tablets or smartphones. Digital technologies also affect other aspects of trials such as informed consent, monitoring, and the associated verification of source data. Another characteristic of DCTs is the delivery of the investigational medicinal product (**IMP**) directly to a trial participant's home, where it is stored and, in some cases, administered by qualified trial nurses. Wherever possible, trained trial nurses perform and document trial-related interventions that take place in a participant's home.

In hybrid DCTs, some procedures are performed in the conventional setting of a trial site, while others are performed in a decentralised setting at a participant's home by a general practitioner or in a laboratory near the participant's home. Whether parts of a clinical trial can be conducted in a decentralised setting depends on many factors, including the type of disease, the phase of the trial, and the type of investigational medicinal product as well as the applicable regulatory framework.

REGULATORY FRAMEWORK FOR DECENTRALISED CLINICAL TRIALS

In Switzerland, clinical trials with medicinal products are regulated in the Therapeutic Products Act (**TPA**), the Human Research Act (**HRA**), and their associated ordinances. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (**ICH GCP**) E6(R2) is also applicable in Switzerland (as set forth in Art. 5, para. 1 of Switzerland's Clinical Trials Ordinance (**ClinO**)). With the new ICH GCP E6(R3) (currently under revision), a whole new Annex 2 will be added specifically covering decentralised elements, among other topics.[1] Clinical trials must also fulfil the requirements of the Switzerland's Data Protection Act (**FADP**) and Data Protection Ordinance (**DPO**).

CHALLENGES FACING DECENTRALISED CLINICAL TRIALS

One of the key challenges for sponsors and investigators is to ensure the oversight of all involved parties. The delegation of tasks and functions to third-party service providers should be defined in written agreements. In addition, all individuals performing trial-related tasks must have the appropriate training.

As with traditional clinical trials, the investigator is responsible for ensuring adequate medical care in the event that adverse events occur outside the trial site as well as the standardised documentation and protocol-compliant reporting of those events (ClinO, Art. 39–41; ICH GCP E6(R2), Section 4.3.2). The procedure for reporting adverse events should be defined in the protocol, and patients should receive documented training on how to report them (e.g. via a telephone call or an application on a mobile device). Furthermore, it must be ensured that the investigator is informed of adverse events in a timely manner so that he or she can decide what action to take.

If trial monitors review uncoded personal data from trial participants (e.g. medical records) as part of source data verification and this review is not performed in person at the trial site but instead by employing electronic tools to access the information from outside (i.e. remote source data verification (**rSDV**)), appropriate technical and organisational measures must be taken to ensure compliance with the Swiss Data Protection Act. For example, the source data may be accessed by using two-factor authentication and a virtual private network (**VPN**). The trial monitor may be granted read-only rights, and access must be restricted to trial participants only.

AN ACTIVE APPROACH TO DCT CHALLENGES

There is great interest, both internationally and in Switzerland, in performing DCTs. Swissmedic and swissethics published a joint position paper on DCTs that aims to encourage and invite stakeholders to intensify the dialogue on this innovative way of conducting clinical trials.[2] The position paper considers the major challenges relating to DCTs. It is based on the current position of Swissmedic and swissethics and how they interpret their respective areas of responsibility (ClinO, Art. 25 and Art. 32). The existing legal framework already regulates many aspects of DCTs with medicinal products in Switzerland. However, researchers are recommended to liaise closely with Swissmedic and the ethics committees before setting up a DCT in order to clarify specific questions relating to the conduct of DCTs. Researchers should not hesitate to contact Swissmedic if they have any questions related to DCTs (ct.medicinalproducts@swissmedic.ch).

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VIEWS AND OPINIONS

ETHICS PERSPECTIVE

Institut des humanités en médecinee

INFORMED CONSENT IN DECENTRALISED CLINICAL TRIALS THROUGH AN ETHICAL LENS

Author: **Brenda Bogaert**

Affiliations: Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Institute of Humanities in Medicine

doi: 10.54920/SCTO.2024.RAWATCH.9.17

Decentralised clinical trials raise ethical questions regarding informed consent because the consent process often takes place remotely. This article explores the challenges (such as fewer in-person interactions) and opportunities (including new possibilities for exercising autonomy and engaging a more diverse research population) that a remote informed consent process raises for research participants. In addition, the article contains several approaches for mitigating the ethical problems that obtaining informed consent remotely raises in decentralised clinical trials, including moving toward a more dynamic informed consent process and using teleconference technologies to give regular feedback to participants, which may help increase transparency and foster trust between research participants and the research team.

The COVID-19 crisis led to a significant expansion of decentralised approaches to clinical trials, a tendency that is expected to increase even more in the coming years.[1,2] While these new decentralised models are considered a more cost-effective way to conduct trials, the ethical issues they raise have not yet been sufficiently explored. Because decentralised clinical trials (**DCTs**) involve the use of remote tools and methods to facilitate research without physical contact, they have had an important impact on participant recruitment, informed consent, and interactions between research participants and research teams. In order to understand the full implications of these new models, the participant's perspective is needed.[3]

INFORMED CONSENT IN DECENTRALISED CLINICAL TRIALS

This contribution looks at what DCTs change for participants, and in particular their capability for informed consent. In the context of this article, the term informed consent refers to the real opportunities and resources available to research participants that enable them to be adequately informed of their participation in a clinical trial and be empowered to act according to their desires. In medical ethics, informed consent is not just a tick-box exercise. Instead, it is considered necessary for guaranteeing that a research participant is able to act with intention, with comprehension, and without interference from others.[4] Ensuring informed consent is therefore quite demanding for participants and research teams, even in the usual consent process. It means giving participants the right to be informed and engaged in the research process and giving research teams the responsibility to produce an environment in which participants can be empowered.

In the new model of DCTs, the consent process may take place remotely. While methods vary, there is an increasing use of software that allows prospective trial participants to read and sign informed consent documents remotely. It is important to explore the potential harms and benefits of these models and, based on the challenges and opportunities identified, provide some ideas on how to move forward. Research on the patient's perspective is still needed, however, to fully grasp the ethical considerations of these new models.

REMOTE INFORMED CONSENT: CHALLENGES AND OPPORTUNITIES

To begin with, it is important to consider how a research participant's experience changes when consent is provided at home. Because decentralised trial models involve exchanging information at a distance, they offer fewer opportunities for a participant to interact and have discussions with the research team. While this may mean that participants have more time to read and understand information, fewer in-person interactions make it more difficult for them to ask questions and for the research team to understand their hesitations and concerns. Moreover – going back to the ethical framework – this long-distance interaction makes it challenging for the research team to ensure that a participant is acting with intention, with comprehension, and without interference by another person or group. While there is also no guarantee of this in more centralised trial models, decentralised models make this task harder due to the more limited opportunities for interaction.

On the other hand, from the perspective of participant autonomy, these models may give prospective research participants more time and space to read relevant documents, look for outside resources, and discuss the trial with their family members, friends, and other participants. They may also feel less pressured to give consent when the process is managed remotely compared to in person. All of these possibilities may help participants feel more in control and able to exercise their autonomy.

In terms of greater representation in clinical trials, using a remote consent process is promising. Given the need for a more diverse participant population, these new methods have been advocated as a way to increase access, in particular for those in rural areas who may not otherwise participate in trials due to transport and time costs or insufficient resources where they live. [5]

APPROACHES TO REMOTE INFORMED CONSENT

This brief discussion has demonstrated that obtaining consent remotely in DCTs offers several promising opportunities – but also entails risks. To prepare for its future implementation, several approaches may be pursued to identify these opportunities and address the challenges.

In the first place, under the DCT model, the relationship between a research participant and the research team needs to remain a priority. This is important not only to ensure that consent is obtained but also to develop the trusting relationship necessary to ensure study quality and mitigate potential harms for the participant. While some tools may be sent electronically, such as the informed consent form (e-consent), it is still necessary to plan in-person sessions to ensure that participants are fully informed and engaged.[6,A] Therefore, while it may be possible to perform some tasks remotely, the need for regular, in-person interactions still exists. Where this is not possible (e.g. when a participant lives in a rural area), regular communication opportunities (e.g. via teleconference technologies) still need to be provided.

Furthermore, in the overall discussion on informed consent, it is increasingly being recognised that consent does not happen in a vacuum, nor is it a one-off event. Indeed, there is increased advocacy for a more *dynamic* consent model.[7] In other words, consent is not "just" a document to be signed but a process that needs to continue throughout a trial to ensure that participants are adequately informed of each step of the process, that they are willing to continue, and that any harms or other unforeseen circumstances are addressed. In practice, this means the research team should regularly check in with participants to inform them of the study process, ensure participants understand the information being given to them, and make themselves available to answer participants' questions. This model also has the advantage of being compatible with both traditional and decentralised clinical trials since more regular communication is now possible with videoconference technologies.

THE NEED FOR A GREATER UNDERSTANDING OF THE PARTICIPANT'S PERSPECTIVE

This discussion underscores that, from an ethical standpoint, the fundamental principles of informed consent remain largely unchanged, even when consent is obtained remotely in decentralised trial models. Each participant continues to have rights related to informed consent, and the research team continues to have the responsibility to ensure consent is obtained. Furthermore, a relationship based on transparency and trust is the means to ensure research quality and avoid participant harm. In the end, decentralised clinical trials call for researchers to become more creative – but also critical – when deciding how to best use technology to better achieve these goals. Because this is an evolving subject, the participant's perspective (obtained, in particular, through qualitative research) is sorely needed in order to better understand and anticipate these and other emerging ethical challenges posed by these new models.

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[A] The use of e-consent is now permitted in Switzerland following the entry into force of the revised Human Research Act (**HRA**) ordinances on 1 November 2024. swissethics defines electronic informed consent as the "use of electronic systems and processes that may employ multiple electronic media […] to convey information related to the study and to obtain and document informed consent". For more details, see swissethics' guidance on electronic informed consent from 25 August 2024.

VIEWS AND OPINIONS

INDUSTRY PERSPECTIVE



WHY IS THE UPTAKE OF DECENTRALISED ELEMENTS IN CLINICAL TRIALS SLOWER THAN EXPECTED?

Authors: **Elizabeth Theogaraj**[1], **Lada Leyens**[2], and **Jamie Wingate**[3]

Affiliations: [1]Roche, Regulatory Program Management, Senior Group Director; [2]Takeda Pharmaceutical Company, EUCAN Regulatory Affairs Team, Senior Director; and [3]Roche, Clinical Study Management, Senior Clinical Operations Lead

doi: 10.54920/SCTO.2024.RAWATCH.9.20

In the swiftly changing realm of clinical research, incorporating decentralised elements into clinical trials is becoming a transformative approach to drug development. Driving this approach is the need to not only improve the desirability of participating in clinical trials by reducing participant burden but also increase the utility of the data/evidence collected. The philosophy guiding this approach is both participant- and site-centred, thus ensuring decentralised elements truly add value to the clinical trial experience while still meeting a trial's scientific objectives. As the potential benefits of these innovative trial methodologies have become more clear, regulatory agencies worldwide have released numerous guidelines for incorporating decentralised elements into clinical trials. Despite these promising benefits and regulatory guidance, the adoption of these elements has not progressed as rapidly as anticipated. This commentary delves into some of the factors sponsors consider with regard to integrating decentralised elements into clinical trials and discusses several challenges they face in practice.

THE NEED FOR DECENTRALISED ELEMENTS IN CLINICAL TRIALS

The conventional clinical trial model often faces significant challenges with participant recruitment, geographical constraints, and high dropout rates. Decentralised clinical trials (**DCTs**), which incorporate decentralised elements, can make it easier to recruit and retain participants, for example when the participant pool is small (e.g. with rare diseases) or when participants face unique challenges (e.g. with some neurodevelopmental disorders). By incorporating decentralised elements, sponsors can significantly reduce the number of on-site visits, which lowers the access hurdle for participants. This not only enhances the feasibility of trial participation but also underscores a participant-centred approach – and ultimately facilitates more inclusive and efficient clinical research processes.[1] In addition, incorporating decentralised elements can increase the catchment area for sites participating in trials, especially for geographically dispersed populations. Another benefit of using decentralised elements in clinical trials is the opportunity to enhance the scientific value of the trial design by utilising more meaningful endpoints that, in some cases, can only be measured remotely.[2]

SPONSOR CONSIDERATIONS FOR INCORPORATING DECENTRALISED ELEMENTS INTO CLINICAL TRIALS

When deciding whether and when to use decentralised elements in a trial (e.g. home health visits, telemedicine, community-based facilities, or shipping investigational medicinal products (**IMPs**) directly to participants), sponsors should consider a fit-for-purpose assessment that incorporates all factors for the different stakeholders (including sponsors, participants, investigators at sites, vendors, the regulatory landscape, and the local healthcare infrastructure). Sponsors also need to consider the safety profile of a drug as well as the trial phase, as decentralised elements are particularly feasible during the most established phases of a clinical trial. For example, in oncology trials decentralised elements might be most appropriate during the maintenance phase of the therapy, when participants have become used to the administered IMP and their disease is manageable with some level of stability.

Having options and flexibility are also key considerations. For example, home health visits can be alternated with on-site visits according to site and participant preferences, provided there is an adequate notice period to manage the logistics. The incorporation of decentralised elements should be evaluated on a case-by-case basis before they are offered, taking into account the assessment and safety considerations of the drug. These evaluations should be made before the protocol is finalised in order to ensure that data quality and integrity are not compromised. Furthermore, it is essential to ensure that optional decentralised elements do not introduce any bias in the analysis of critical data. This will help maintain the robustness and compatibility of data collected, for example through different visit types (home or local healthcare facility visits vs. on-site visits). This remains a crucial consideration for sponsors and requires careful implementation in a DCT.

WHY AREN'T DECENTRALISED ELEMENTS ROUTINELY INCLUDED IN CLINICAL TRIALS?

Additional oversight responsibilities

Regulatory guidelines such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (**ICH GCP**) clearly assign the responsibility for a trial's tasks, activities, and assessments – even those carried out by third-party vendors and local healthcare providers (**HCPs**) – to the principal investigator (**PI**). This can be problematic when these vendors and HCPs are not selected by the PI (e.g. selected by the sponsor). Understandably, PIs may be unwilling to accept oversight responsibility for organisations and individuals they may not have met or even spoken to, because they have not had the opportunity to develop the same level of trust and confidence as with their own staff or known vendors and HCPs (e.g. unknown mobile nurses compared to site nurses). This extra responsibility must be managed well in DCTs, for example by having a working agreement that clearly defines responsibilities and that can be created for new vendors and HCPs without significant administrative and legal efforts and by clearly assigning liability to third-party vendors when they do not follow the protocol and the PI's instructions. Additionally, PIs and their staff should be compensated for their additional oversight and responsibilities.

Impact on site revenues

When decentralised elements are used in a trial, it often means that tasks, procedures, and/or assessments traditionally performed at the trial site are instead performed by third-party vendors and local HCPs (e.g. local imaging facilities do computed tomography (**CT**) scans or home nurses perform physical exams). Along with this shift in tasks comes a shift in revenues, and sponsors need to make sure that the study site's revenue stream remains fair. Adequate compensation can be used to transform this potential risk of a decrease in revenue and an increase in responsibility into a potential opportunity to generate additional revenue. For example, having a site's own nurses perform tasks remotely and delegating tasks to local HCPs as an alternative to third-party vendor solutions has the potential to not only sustain revenue streams but also increase adoption at both the site level and the participant level (e.g. by reducing travel time and costs and by maintaining existing patient-physician relationships). In fact, the responsibilities and activities related to third-party vendors and local HCPs in DCTs have the potential to generate additional work, and thus additional revenue, for sub-investigators and PIs.

Numerous stakeholders

It is imperative to involve key stakeholders across the entire healthcare ecosystem – including investigators, hospital administrations, regulators, and participants – in order to develop feasible and effective trials with decentralised elements. Indeed, maintaining participant engagement and fostering the participant-investigator relationship can be challenging in a virtual environment. Only when key stakeholders are involved in planning a protocol for conducting a clinical experiment can the adoption of new and innovative elements be successful.[3]

Balance between customisation and feasibility

A successful DCT must tailor decentralised elements to the specific needs of both participants and study sites, which adds additional layers of complexity that need to be managed. Offering tailored options that accommodate participants' preferences and site capabilities can enhance both trial participation and retention. For example, allowing participants to choose between on-site visits and remote assessments can improve engagement. However, the decision to offer decentralised options needs to be determined prior to protocol finalisation and planned carefully in order to ensure that data quality and data integrity are not compromised.

Operational complexity

To minimise operational complexity and the resulting burden on sites, it is crucial to implement decentralised elements judiciously. For example, when sites are confronted with various technologies from different vendors requiring them to have multiple login credentials and interact with disparate systems, there is a risk of diminishing site engagement. This disengagement and frustration can affect recruitment rates. Mitigation strategies include utilising specialised DCT vendors that offer multiple decentralised elements under a single login, providing sites with robust help desk support, and ensuring thorough site training. Engaging with sites early on in the feasibility stage is essential for securing site acceptance of the proposed decentralised elements.

Regulatory and legal constraints

The extent of trial decentralisation varies across countries due to differing legal and healthcare frameworks. Globally, there is fundamental heterogeneity regarding the ability to implement decentralised elements, for example concerning who is authorised to perform specific assessments in a participant's home. These country-specific differences bring additional operational complexity when conducting global trials. Navigating these constraints requires not only engagement with local regulatory authorities and ethics committees early on but also a tailored approach for each country.

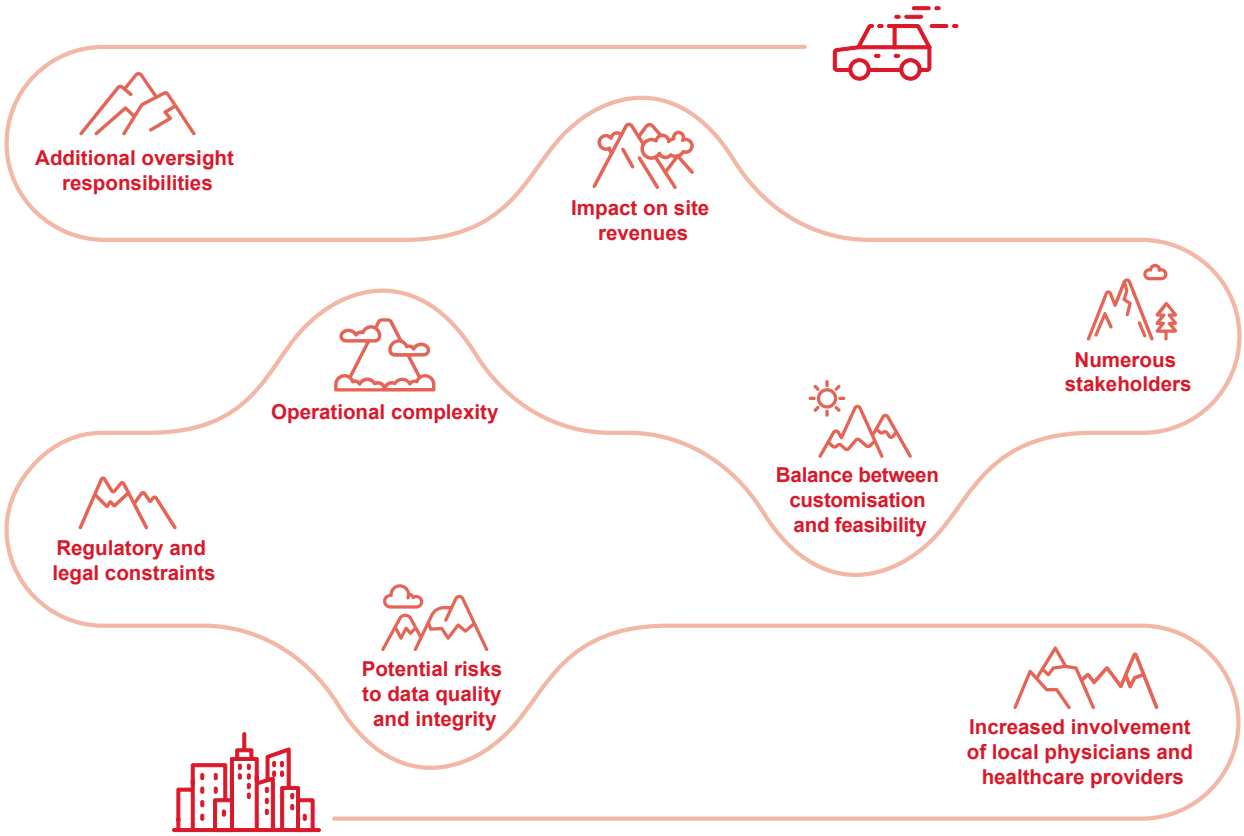
Potential risks to data quality and integrity

A trial's study design requires careful consideration when incorporating decentralised elements. Potential risks to a trial's integrity must be identified early on in the process so they can be mitigated. Key parameters for a specific strategy depend on the therapeutic area being studied and specific measures. Some assessments – for example lab parameters with well-established concordance between local and central labs – can be collected remotely without compromising data quality or otherwise impacting data integrity. For other data assessments, establishing data quality and equivalence with site-generated data can be more challenging; for example, many participant scale ratings and investigator-rated clinical measures are conventionally validated to be conducted in person. In these cases, it is necessary to plan carefully and potentially conduct feasibility or equivalence studies. Industry is addressing the multi-faceted challenges of decentralised data generation not only operationally (e.g. by establishing reliable frameworks that standardise DCT processes, training, and quality monitoring) but also scientifically (e.g. by developing data modelling approaches to account for biases and differences in data generation).[4]

Increased involvement of local physicians and healthcare providers

Delegating tasks to local physicians and healthcare providers in DCTs can reduce travel distances for participants, maintain existing patient-provider relationships, and sustain revenue streams. Yet facilitating local physician and HCP involvement beyond specialised research centres requires more administrative effort (e.g. making sure working agreements are in place and choosing suitable legal language related to responsibilities), involves transferring more data, and uses more personnel and financial resources (e.g. for reimbursement). Sponsors also need to address access barriers and simplify participation for local physicians and HCPs involved in trials with decentralised elements in order to increase their awareness and willingness to promote these options with their patients.

Figure 1: Challenges to navigate in decentralised clinical trials



CONCLUSION

The healthcare ecosystem is moving towards more flexible, decentralised care in general. Therefore, it is becoming increasingly important for clinical trials to provide at least the same level of flexibility in order to remain attractive and viable for all the stakeholders within this ecosystem. Incorporating decentralised elements into clinical trials represents a promising paradigm shift in clinical research, offering more flexibility and solutions to longstanding challenges in participant recruitment and engagement. Despite the many benefits of incorporating decentralised elements into clinical trials, many challenges exist for sponsors and PIs. These challenges can be overcome by planning carefully early on in the process, involving key stakeholders throughout the process, and promoting a mindset shift to embracing decentralised elements as an opportunity to increase site revenue streams and better accommodate patient preferences. Indeed, DCTs offer new opportunities for participants and sponsors alike and thus complement existing, more traditional trial work.

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VIEWS AND OPINIONS

LEGAL PERSPECTIVE

[datalex]

BALANCING THE LEGAL, ETHICAL, AND PRACTICAL ASPECTS OF USING DIGITAL HEALTH TECHNOLOGIES IN CLINICAL RESEARCH

Author: **Gabriel Avigdor**

Affiliations: Attorney-at-law; datalex LLC, founder; Certified Information Privacy Professional/Europe (CIPP/E); Bar Association of the Canton of Vaud (OAV), member; Swiss Bar Association (SAV), member; University of Geneva, Faculty of Medicine, MAS/DAS lecturer; and Haute Ecole Arc (HE-Arc), lecturer

doi: 10.54920/SCTO.2024.RAWATCH.9.25

Digital health technologies bring innovation to participants in clinical trials. They enable the collection, use, and sharing of large amounts of data for medical and scientific research purposes, which ultimately benefits patients. In the context of drug development, traditional clinical trials face significant privacy challenges due to a lack of harmonisation and diverging interpretations of privacy laws and authorities' guidance. Given the use of digital health technologies, decentralised trials in particular have to manage an additional level of complexity. Involving technology providers increases concerns around the access, storage, and security of study data. Authorities, ethics committees, and healthcare institutions often ask for various additional or bespoke requirements that may diverge from or even conflict with each other, which can lead to unintended consequences for research initiatives and for individuals who are willing to participate in innovative clinical trials. This article outlines some legal, ethical, and practical issues as well as their consequences when using digital health technologies in the research sector.

The COVID-19 pandemic motivated public and private stakeholders to make significant and fundamental changes to conservative practices in the healthcare sector, for example by allowing and adopting digital health technologies (**DHTs**). Within only a few months, authorities, academics, institutions, healthcare providers (**HCPs**), private actors, and people around the world had to start using technologies that, without the sense of urgency caused by the pandemic, would have taken decades to accept, adopt, and implement in the healthcare landscape.

In the context of clinical trials, health authorities granted approvals or concessions that were limited in time and allowed remote care, patient monitoring, and accelerated procedures in order to develop a COVID-19 vaccine. The adoption of such technologies set a standard and an expectation in the healthcare and clinical research sectors that remained after the pandemic, and it accelerated digital initiatives such as remote meetings, online medical screening tests, and decentralised clinical trials (**DCTs**). However, while the use of advanced technologies has increased since the pandemic and has led to significant progress in many sectors, the use of DHTs within clinical research activities has not kept pace with those developments.

FROM PRIVACY BENEFITS TO LEGAL ISSUES

DCTs aim for a decentralised study set-up, which means moving away from using only the infrastructure of the study site (centralised model) to having participants become the point of care, for example in their homes. Participants can take part in a study while interacting remotely with the study team, they can access additional medical materials through web applications, and it is possible to avoid travelling to or staying in the hospital. DCTs also have the potential to implement customised data privacy measures, a benefit that gives participants more control over their data and better security by using unique and controlled devices, applications, and processes specifically designed for and provided by the study.

Although not all participants may fully understand or appreciate how innovative web platforms and mobile application work in detail, the use of DHTs in clinical research still remains compatible with bioethical principles because they enable broader access (beneficence) for a more diverse part of the population (justice) to clinical trials and novel treatments.[1,2] As DHTs raise many other legal and ethical issues that cannot be covered in detail within this article, the focus will mainly be on the tensions between participants' fundamental rights to privacy and their access to innovative research initiatives.

Data privacy and data protection in the healthcare sector is a heavily debated topic, and the nuances and technical aspects are largely misunderstood by non-privacy professionals. Because DCTs combine technical, legal, and technology aspects in a heavily regulated environment that allows countries to provide their own legislation, national authorities have brought diverging interpretations and guidance on privacy and security requirements. Often, this forces sponsors to comply with practices that are not harmonised within the same study (e.g. multinational studies). The spirit of most emerging, comprehensive privacy laws focuses on clear goals: implementing privacy and security standards, increasing accountability and transparency, and enabling the enforcement of privacy rights while limiting the ability of big tech companies to conduct disproportionate data processing activities. Under the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (**ICH GCP**), there is no specific reference to data protection laws. Therefore, the relevant national or regional legislation applies. New privacy laws, such as the EU's General Data Protection Regulation (**GDPR**), have produced immediate and noticeably positive effects: a huge increase in the number of full-time privacy professionals, a higher level of knowledge and awareness among the general public, stricter obligations for organisations handling personal data for defined purposes (data controllers), robust privacy compliance programmes, and enforcement actions by authorities, especially in Europe.

Unfortunately, there are downsides to the increase in data protection, especially because everyone wants to have a say – including privacy experts and non-experts. As a result, fundamental privacy concepts and principles, which should remain the same everywhere, are not interpreted in the same way across regions, in different countries, and sometimes even within the same country. This creates legal uncertainty, a lack of harmonisation, delays in approving study protocols, and tough discussions in contract negotiations. Major differences exist in the following areas:

- **Roles of the parties:** Determining and allocating the roles of the parties as either data controller, data processor, or joint controller is still fundamentally different.
- **Choosing the appropriate legal basis:** Using consent or another legal basis for the use of personal data for primary research or further research differs drastically between countries, authorities, and research projects.
- **Informed consent forms:** The content and length of informed consent forms vary.

It is hard to justify to individuals willing to participate in the same trial how there can be many differences between one country and another, especially when such differences do not provide any additional privacy protections to their personal data. Instead, these differences create inconsistencies and make it more difficult to run multinational studies, in particular when new technologies are used. Privacy laws provide strict transparency requirements for participants and strong accountability obligations for data controllers handling participants' sensitive personal data. From an ethical point of view, all participants should be treated equally – even though this is not mentioned in privacy laws. Yet given these divergences, participants are not treated equally with regard to data protection.

Below are some more ethical, legal, and practical issues that are relevant when using DHTs in innovative trials but that can also become obstacles for research initiatives, thus hindering individuals' access to those trials.

DATA TRANSFERS

When conducting DCTs, sponsors need to work with specialised technology providers to facilitate the creation of a secure online infrastructure. Inevitably, data (including study participants' sensitive personal data) will have to flow between countries and will be accessible by multiple stakeholders who need to maintain the confidentiality, integrity, availability (**CIA**), and security of study data at all times. This originates not only from privacy laws but also from international standards such as the ICH GCP. The transfer of personal data to other countries has sparked animated discussions and debates. Indeed, after the uncovering of the Edward Snowden scandal on 5 June 2013[3] and the Schrems II decision from the Court of Justice of the European Union (**CJUE**) in July 2020 invalidating data transfers from Europe and Switzerland to the United States,[4] data transfer is still being hotly debated.

In reality, the risk that foreign authorities can request access to participants' personal data is extremely small. Moreover, they most likely have no interest in this data. Study participants' data is key-coded and thus particularly protected against re-identification, which is quite unique compared to other industries. Therefore, the debate around cross-border data transfers remains rather theoretical. Experience has shown that concerns about participants' information and sensitive data becoming accessible and thus being used by third parties outside of the research environment stems from fears of losing control, even though the use of a third-party secured solution is often inevitable and more secure when using new technologies and online platforms. Therefore, the focus on restricting cross-border data flow can be seen as pointless. In fact, companies and organisations conducting research globally already use IT systems running on secure, state-of-the-art, third-party infrastructures – even if they do not use DHTs.

DATA LOCALISATION

Using third-party IT systems usually involves cloud-based environments with foreign data centres belonging to big tech companies, such as Amazon Web Services or Microsoft Azure. These hosting providers have among the strongest and most reliable security infrastructures in the world, as opposed to local storage infrastructures at healthcare organisations. Even so, data localisation often creates emotional and animated discussions. Researchers are rightly concerned whenever participants' data leave their premises since they must preserve medical secrecy and prevent access to medical records by unauthorised individuals and organisations. Furthermore, authorities and ethics committees act as the ultimate guarantor of participants' interests.

Strict data localisation requirements, however, are often incompatible with cross-border data sharing and clinical research initiatives. In fact, most privacy laws around the world, including Switzerland's Data Protection Act (**FADP**), do not require any data localisation. A very limited number of countries close their digital borders in order to have political control over information in their territory, for example China,[5,A] France to a certain degree for the hosting of medical health data,[6,B] and Russia.[7,C] In general, privacy laws already strictly regulate the transfer of personal data to foreign countries that have no equivalent data protection legislation, and they require contractual, legal, and technical guarantees (i.e. appropriate safeguards and transfer impact assessments). As a result, data localisation requirements are not legally needed, and battling for data localisation or transfer restrictions does not add more protection for participants' personal data. Instead, it encourages country shopping (i.e. selecting countries that are more permissive) and decreases the chances of researchers sharing data across countries.

ELECTRONIC SIGNATURES AND CONSENT

Switzerland is one of the only countries to require a qualified signature (the digital equivalent of a handwritten or "wet" signature) to electronically sign documents.[D] However, using a qualified signature is a costly process in which the validation of a signature requires submitting a request and evidence to a trusted third party.[8–10, E] Requiring participants to use a qualified signature to sign their informed consent form electronically has proven unfeasible in practice. Instead, participants have been required to sign, scan, and send the document by email or post – or to travel to study site and deliver it personally. As a result, Switzerland has struggled to adapt to the digital age and favour innovation. The good news is that the since the revisions to the Clinical Trials Ordinance (**ClinO**) came into effect on 1 November 2024, the newly introduced Article 7c now permits using electronic means to obtain individuals' consent to participate in a clinical trial, provided that the authentication mechanism uses "a method which unequivocally identifies the person concerned". This marks a significant advancement, allowing the use of digital means of identification without requiring the strictest method of authentication.

TO IDENTIFY, OR NOT TO IDENTIFY, THAT IS THE QUESTION!

On the one hand, sponsors have to ensure they cannot access a participant's identifiers. And on the other hand, they must also be able to verify a participant's identity, for example when using an online platform, which is a challenging task. In addition, study participants' personal data must remain in a key-coded format (using a unique identifier or number for each participant),[F] and neither sponsors nor third-party providers should

[A] The Cyberspace Administration of China (**CAC**) reviews and approves transfers of personal data outside of mainland China. China had strict data localisation requirements, which have now been loosened. See Luo and Dan's 2024 blog post "China Eases Restrictions on Cross-Border Data Flows".
[B] The French data protection authority CNIL has introduced a unique privacy scheme requiring compliance with MR methodologies (*méthodologies de référence*), which require submission or prior authorisation for any major deviations. In addition, France has introduced data localisation requirements by updating its public health code under article L.1111-8 for hosting health data to cloud providers outside of clinical trials.
[C] In September 2015, Russia made it mandatory to localise databases containing the personal data of Russian citizens in the Russian territory. In addition, personal data transfers require prior notification to Russia's data protection authority (Roskomnadzor).
[D] See Articles 12–14 of Switzerland's Federal Code of Obligations, Article 2, letter e of the Federal Act on Electronic Signatures, and Article 16, paragraph 1 of the Human Research Act.
[E] In Europe, the Regulation on Electronic Identification and Trust Services for Electronic Transactions in the Internal Market (**eIDAS**) defines levels of signatures, including an advanced signature that provides less costly options. For more information, see the European Commission's "eSignature FAQ" web page.
[F] Pseudonymised data as defined by Article 4 of the General Data Protection Regulation (**GDPR**) is still considered personal data and is not considered anonymised.

be able to re-identify participants.[11,G] If a component used in a DCT involves a web portal, the simple fact that a participant logs into an online platform requires an authentication mechanism, which can include a full name, an email address, a password, and sometimes a phone number for two-factor authentication purposes. The collection of a participant's personal data is therefore inevitable at the login stage, unless a randomly generated code is sent to an email address that does not contain the participant's name, which is complicated. In all cases, participant identification is necessary yet restricted under the ICH GCP.

Secondly, once a participant logs into a platform and is authenticated, the platform will have to track the participant's identity for security, traceability, and safety purposes, especially if the individual uses a web portal to sign an electronic informed consent form (**eICF**) agreeing to participate in a study, access specific medical information, plan online meetings, access study data, use an e-diary, or agree to have medical equipment shipped to his or her home. Managing and controlling how these platforms' technology providers and sponsors access participants' health data without having the right to identify them is a technical and legal catch-22 situation. Therefore, in order for it to be possible to conduct innovative trials such as DCTs more efficiently, authorities and ethics committees must admit and authorise the use of certain limited personal data for identification, authentication, and security purposes.

STUDY CONSENT AND PRIVACY CONSENT: A BIG MISUNDERSTANDING

Under most countries' data protection laws (including those in Switzerland, the UK, and the European Economic Area), the processing of sensitive health data does not always require obtaining consent. Data controllers often have a transparency obligation and can rely on a legal basis other than consent, such as using exemptions or derogations based on legitimate interest, private interest, vital interest, scientific research, fulfilment of a contract, or a legal obligation (e.g. to monitor patient safety and adverse events). An informed consent form (**ICF**) typically includes a detailed, bespoke, clear, concise, and unambiguous text in the form of a privacy notice or privacy statement section to explain what data will be collected, why it will be collected, and how and by whom it will be used for the purpose of the study.[H]

However, some authorities and national guidance still request two different types of consent: the first is consent to participate in a trial (i.e. allowing an individual to decide whether or not to participate), and the second is consent for the processing of personal data. Informed consent is the expression of a free choice and remains valid only if sufficient information is provided and consent is freely given. When an individual decides to participate in a clinical trial, obtaining consent to participate is mandatory. In clinical research, though, asking for the second type of consent for using sensitive personal data does not constitute a free choice. Since a participant's data are necessary for a study, an individual cannot freely decide to participate in a study while simultaneously refusing to share his or her personal data. This contradiction should be self-evident. In practice, though, requests for consent to process personal data are often treated independently of the choice to participate in a clinical trial. And yet if an individual does not consent to share their personal data for a study, they cannot participate in the study. This means that when an ICF contains a specific and separate consent for the use of personal data for the study, consent cannot be freely given because participation is contingent upon it. As a result, such consent becomes invalid, rendering the processing of personal data unlawful.

Well-drafted privacy notices should provide enough information and transparency to enable participants to make an informed decision while ensuring that competent bodies and institutions have the assurance that study data will remain secure, available, traceable, confidential, and of good quality for research purposes. When appropriate and relevant, an ICF should also outline in broad terms which technology is optional or mandatory for participants, who will access participants' personal data, and for what purposes their data will be accessed.

With all the debates around privacy, it is easy to forget that the main goal of a study is to improve participants' health through new treatments. Individuals will likely prioritise understanding the potential adverse effects of an investigational medicinal product when deciding whether or not to participate in a clinical trial. Therefore, while privacy remains an important fundamental human right that requires due care, it is essential not to lose sight of the fact that individuals with a serious illness or condition most likely focus more on improving their health and accessing new medicines or novel treatments than on concerns about documents and data they consent to share.

[G] See sections 1.58 (subject identification code) and 5.17.1 (adverse drug reaction reporting) of the European Medicines Agency's Guideline for Good Clinical Practice E6(R2).
[H] See, for example, Article 12 of the EU's GDPR and Article 19 of Switzerland's FADP.

CONCLUSION

The emergence of modern data protection legislation – such as the EU's GDPR and Switzerland's FADP – has led to positive outcomes that have improved the respect of privacy as a fundamental human right and the protection of trial participants' sensitive personal data. This is especially relevant as digital health technologies are increasingly being used in clinical trials. Position papers, recommendations, and guidance developed by authorities are legally non-binding. However, in practice they are closely monitored and analysed by clinical research sponsors and technology providers. Given their inconsistencies and sometimes excessive requirements, research initiators may choose to conduct their trials in more permissive countries with less burdensome administrative and legal conditions – potentially to the detriment of trial participants. Most privacy-related debates in clinical research do not focus on what can be considered important for the participant's ultimate benefit. The creation of detailed, specific, and local deviations or requirements in Europe and among authorities (including in Switzerland) has generated an ecosystem of divergences and restrictions and led to disharmonised practices that are extremely difficult to navigate when considering starting a multinational clinical trial.

Decentralised clinical trials offer many promising benefits. However, they are conducted within a political landscape where countries and authorities view strict consent requirements (as a wrong sense of choice), data localisation, and transfer restrictions as the solution to competitiveness. Unfortunately, the significant divergences in legislation and guidance, the lack of harmonisation in practices, and obstacles for initiating trials with decentralised components all affect innovation and hinder some participants from benefiting from scientific research globally. The result is a paradoxical situation in which placing too much emphasis on the protection of participants' data (resulting in excessive measures) can undermine research initiatives that predominantly aim to improve people's health and well-being. It also results in study participants in the same study being treating differently in different countries or regions, which can be considered unethical. Privacy protection and the security of participants' data is paramount. However, the importance of privacy and its weight in discussions and negotiations to initiate trials have direct consequences for individuals willing to participate in trials. Data protection remains a fascinating, crucial, and technical area that continues to evolve over time. Driving innovation by implementing new technologies in clinical trials initiatives presents legal, ethical, and practical challenges. In order to facilitate scientific research initiatives using new technologies and favour innovation for the ultimate benefit of participants, authorities and all stakeholders involved in clinical studies should strive to develop harmonised practices and common guidelines that promote and accelerate research instead of introducing overly strict regulations, requirements, and restrictions.

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VIEWS AND OPINIONS

PATIENT ADVOCACY PERSPECTIVE

EMBRACING INNOVATION: A PATIENT ADVOCACY PERSPECTIVE ON EVOLVING TRIAL DESIGNS

Author: **Nicole Gusset**
Affiliations: SMA Schweiz, President and SMA Europe, CEO
doi: 10.54920/SCTO.2024.RAWATCH.9.31

SMA Schweiz and SMA Europe, two patient advocacy organisations for the rare condition spinal muscular atrophy (SMA), work towards promoting the fastest possible access to safe and effective medicines for all individuals who can benefit from them. Their experience has shown that patient and public involvement at the design stage of clinical research directly impacts a product's pathway to patients and leads to a better understanding of a product's value later on. Furthermore, recent discussions about how complex clinical trial designs and decentralised clinical trials use innovative methods to conduct clinical research indicate their potential to make trials more flexible, personalised, and convenient for participants. In addition to helping shift current paradigms, innovative trial designs hold enormous potential to further advance medicines for the good of patient communities, especially in the area of rare diseases.

Science has evolved significantly in recent years, thanks to innovative approaches to biomedicine, engineering, and data science as well as the combination of different research fields. Advances in science and research, however, usually outpace changes to regulatory frameworks, leading to misalignments in innovation and regulation and ultimately delaying patients' access to new treatments. One of the current challenges in research is determining how to integrate innovative approaches into product development so that these advances can create value for society.

COMPLEX TRIAL DESIGNS: ACHIEVING GREATER EFFICIENCY THROUGH FLEXIBILITY

Although the randomised controlled trial (**RCT**) design is standard in clinical research, it may not always be the most appropriate approach to address complex research questions. Complex innovative trial designs integrate novel statistical and methodological techniques to address new, more complex biomedical research questions. These trials designs can be particularly promising when conventional approaches may not be feasible or optimal, such as for rare diseases where population sizes are small or for conditions that cover a wide spectrum of phenotypes, and when outcome measures are complex and not tailored to specific conditions. In these cases, the RCT design is often too rigid with narrow eligibility criteria for homogeneous study populations, results are limited in their capacity to be generalised and to reflect the real world, and the studies often take too long.

Patients need more flexible and efficient ways to assess the safety and efficacy of medical products. Adaptive designs allow changes to be made to the study protocol during the trial based on (preliminary) analyses of collected data. More efficiency can also be obtained by using computer simulations and natural history models, by recruiting more heterogeneous study populations, by using external or historical control data, and by incorporating prior knowledge into the design to supplement or replace placebo arms. These new methods have practical implications and can translate into a reduction in the number of participants needed, greater diversity in inclusion criteria, faster recruitment, accelerated and optimised product development, and more tailored treatment decisions. They may also increase feasibility, particularly for studies of rare and ultra rare conditions whose communities have unmet medical needs. Using a complex innovative trial design may be the only way to develop and deliver a product to these communities, which in turn increases knowledge about rare conditions.

DECENTRALISED CLINICAL TRIALS: INTEGRATING CLINICAL RESEARCH INTO PARTICIPANTS' DAILY LIVES

Traditional clinical trials require participants to invest a significant amount of time, cause inconvenience, and require a high degree of mobility since participants must travel to the trial site for study visits. This can place a burden on participants in terms of managing the logistics of their daily lives and organising travel when living with a disability or an illness. Trial participation also has an impact on participants' work, school, social environment, and family members (e.g. spouses, children, and siblings). The burden of participation and disruptions to participants' daily routines can be minimised in decentralised clinical trials (**DCTs**) because study visits are (partly) transferred from the trial site to participants' homes. DCTs also increase autonomy and convenience. In addition to benefiting participants with rare diseases such as spinal muscular atrophy, DCTs can positively impact participants recruited across borders. Traditionally, SMA Europe has supported cross-border recruitment because cross-border studies are often the only opportunity for individuals with a severe, progressive condition to gain access to a potentially life-saving product. Being selected to participate in such clinical trials is often the last ray of hope for patients with no other treatment options. Therefore, the opportunity to participate in a study outweighs the direct and indirect costs associated with travel. Any tool that can ease this enormous, but sometimes necessary, burden is welcome.

MOBILE TECHNOLOGIES: INCREASING THE RELEVANCE OF OUTCOME ASSESSMENT

Not only is trial design undergoing a transformation, but the way data is collected in clinical trials is becoming more patient-centric – a trend driven by the COVID-19 pandemic. Mobile technologies (e.g. wearables) offer potential value, especially when studying conditions for which outcome measures are complex. In many rare conditions, defining endpoints and measuring them with traditional methods does not adequately capture meaningful outcomes. Mobile technologies provide the opportunity to innovatively collect data during studies, including real-time data and more continuous data in people's living environment. Especially in rare disease communities, the opportunities to bring treatments to a specific community are limited. It is no longer acceptable to run the risk of a therapy being rejected that is effective in itself because researchers have not been able to measure potential, patient-relevant effects using traditional measurement approaches. Collecting data using mobile technologies can be a tool to address this issue. However, this should not be limited to capturing electronic patient-reported outcomes, collecting information on physical function, or gathering spatial information (e.g. movement) – the sky should be the limit.

PATIENT INVOLVEMENT: PURSUING A TRANSDISCIPLINARY APPROACH TO CLINICAL RESEARCH

As mentioned above, it is crucial to minimise the risk of hampering clinical development for rare diseases. This applies not only to systemic frameworks and investments but also to study participants. It is paramount to recruit informed participants who have the capacity to comply with study requirements (e.g. have the language, cognitive, and mental capacity as well as the technological savviness required), even more so in the light of the advances described above. In addition, study teams need to reassure participants about the data security and the safety of using continuous mobile monitoring tools in their private environment. Researchers must also work together with patient organisations – not only to educate and raise patient communities' awareness of these tools and opportunities but also to consider their lived experiences, understand their needs and preferences, and identify what endpoints are most relevant to patients in order to best capture them using all the technological advances available.

INNOVATIVE RESEARCH APPROACHES: MOVING CLINICAL RESEARCH FORWARD

More individualised and precise research approaches are important in clinical research, particularly for rare diseases. They can lead to protocols and data collection that are more convenient and relevant to patients and can promote the inclusion of a larger part of the population, which further improves study recruitment and retention rates and leads to earlier trial completion. Further, they have the potential to generate more data and knowledge on safety and efficacy across the spectrum of a condition and can have a direct, positive impact on the availability of products to patients. The broader application of innovative and adaptive research and the increased use of (mobile) technology-assisted methods can help to bridge today's gaps and move clinical research forward – while making sure no one is left behind.

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CASE STUDY

TRIALS WITHIN COHORTS (TWICS)



TRIALS WITHIN COHORTS (TWICS): A NOVEL DESIGN TO EFFICIENTLY EMBED PRAGMATIC RANDOMISED TRIALS INTO COHORT STUDIES

Authors: **Christof M. Schönenberger**[1],**Felix Gerber**[1], and **Alain Amstutz**[1,2,3]

Affiliations: [1]University of Basel, University Hospital Basel, Department of Clinical Research, Division of Clinical Epidemiology; [2]University of Oslo, Oslo University Hospital, Oslo Centre for Biostatistics and Epidemiology; and [3]University of Bristol, Bristol Medical School, Population Health Sciences

doi: 10.54920/SCTO.2024.RAWATCH.9.34

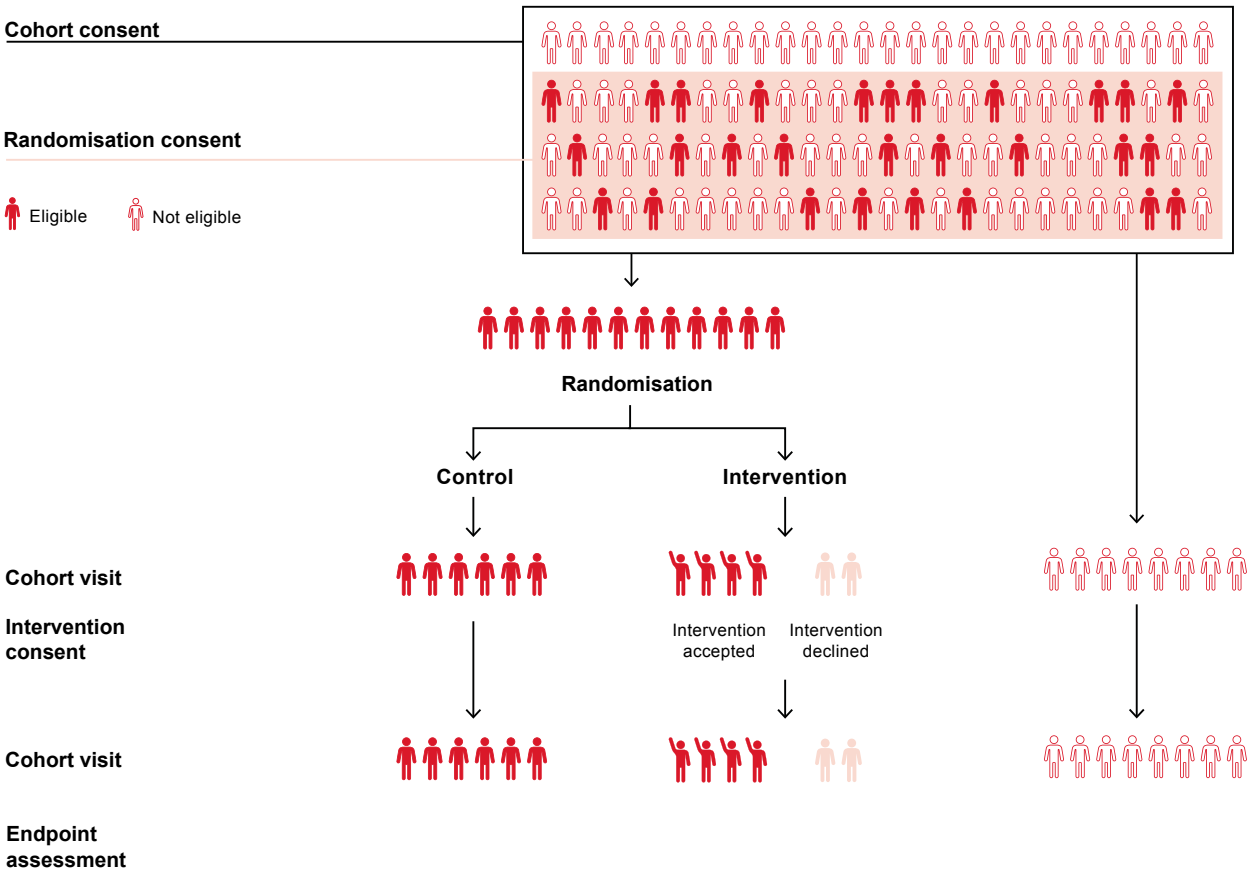
Trials within cohorts (**TwiCs**) is a novel trial design that promises to overcome frequent challenges of traditional randomised clinical trials, such as high cost, slow recruitment, and a limited generalisability of results. In studies with a TwiCs approach, a randomised comparison is nested into an observational cohort by design in order to use synergies in infrastructure for recruitment and data collection. The TwiCs design has been applied to the assessment of interventions in different medical fields in several countries using three different consent patterns. In Switzerland, the Swiss HIV Cohort Study is taking a pioneering role as the first cohort in the country to implement the TwiCs design.

TWICS: WHY AND HOW?

Randomised clinical trials are the gold standard for causal inference in medical research. However, randomised clinical trials often face various challenges, including high costs, slow participant recruitment, limited generalisability, burdensome consent procedures, and a disappointment bias that may occur in open-label trials if participants and providers change their behaviour when participants are not allocated to their preferred group.[1-3]

In recent years, trials within cohorts (**TwiCs**) has emerged as a pragmatic trial design with the potential to overcome these challenges.[4-9] Studies with the TwiCs design involve recruiting participants with a condition of interest into a prospective cohort. At enrolment, not only is consent obtained for regular prospective data collection, but participants are also informed about randomisation into future trials nested within the cohort. In a future trial using the TwiCs design, participants are approached only if they are randomised to the intervention group and are then given the option to accept or decline the proposed intervention. The participants randomised to the control group are not informed about the intervention being offered to other cohort participants but continue usual care and regular data collection as part of the cohort (see **Figure 1**). This consent procedure mimics usual care in that individuals are informed about new treatment options but not about treatments they may not receive. Additionally, the TwiCs design offers a comparison to a real-life control group, allows researchers to recruit efficiently from a well-described cohort, and embeds outcome collection efficiently within the cohort's follow-up structure.

Figure 1: Trials within cohorts (TwiCs) design according to the *Dutch* consent pattern



Cohort participants can agree to be randomised in future TwiCs (randomisation consent) for which they might be eligible. Participants who are then randomised to receive an intervention are asked to accept or decline the intervention (intervention consent). Participants randomised to the control group are not informed about the intervention and receive usual care according to the cohort's procedure. Participants who decline the intervention remain in the intervention group for analysis according to the intention-to-treat principle.

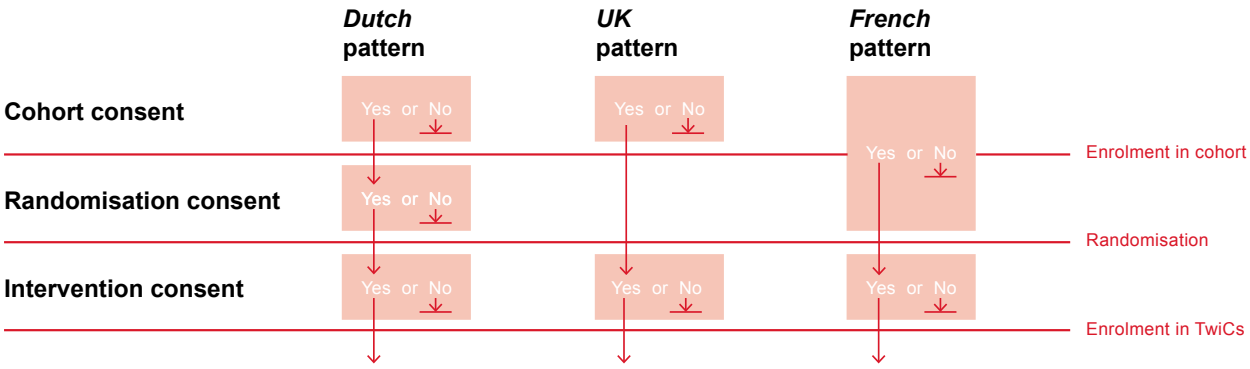
Source: Adapted from figure provided by the Division of Clinical Epidemiology at the University of Basel

TWICS: WHAT DO WE KNOW?

In a recent scoping review, Amstutz, Schönenberger, Gerber, et al. identified 46 trials in 14 different countries that were conducted with a TwiCs design up to December 2022.[10] The most common medical fields in which the design was applied were oncology (24%), infectious diseases (17%), and mental health (15%). A typical trial with a TwiCs design was investigator-initiated, was publicly funded, and recruited outpatients. The TwiCs in the review evaluated various types of interventions – mostly behavioural, psychological, or complementary interventions (42%) – as well as drugs (13%) and radiotherapy (9%).

Based on how ethics committees in three different countries guided trialists who implemented the TwiCs design, three major consent patterns have emerged (see **Figure 2**). In the *Dutch* pattern, there are three separate consent steps for cohort participation, randomisation, and intervention; in the *French* pattern, there is combined consent for cohort participation and randomisation and separate intervention consent; and in the *UK* pattern, there is consent only for cohort participation and intervention (randomisation consent is not mentioned). Among the 46 trials with the TwiCs design, the *UK* pattern was the most common (41%), followed by the *Dutch* pattern (37%) and the *French* pattern (22%).

Figure 2: Consent patterns in trials with a TwiCs design



The vertical axis shows three different stages of consent (cohort consent, randomisation consent, and intervention consent). In the *Dutch* pattern, there are three separate consent steps. In the *UK* pattern, there is no explicit consent for randomisation. In the *French* pattern, consent for being part of the cohort and for randomisation are combined.

Source: Adapted from Amstutz, Schönenberger, Gerber, et al. (2024), Figure 2[10]

TWICS: WHAT ARE THE DESIGN'S LIMITATIONS AND MITIGATION STRATEGIES?

The TwiCs design presents several challenges and limitations. First, the consent procedure involves multiple stages with tailored information provided at each stage, which requires training the participating sites and carefully communicating consent information when initially implementing the TwiCs design. Nevertheless, once cohort consent and randomisation consent are part of routine cohort enrolment procedures, participants will only be asked for intervention consent in all future TwiCs. Because intervention consent is closer to routine clinical decision-making, the consent process in these trials promises to be less burdensome, less complex, and less distressful than the consent process in traditional trials.[11–13]

Second, the control group in a TwiCs study is, by design, always receiving usual cohort care. Consequently, a placebo-controlled comparison is not possible, and participants and providers are aware of the intervention received/provided. In most pragmatic trials, however, a usual care comparator is the option of choice. Therefore, the TwiCs design may even offer a comparison group that is closer to reality since the randomised groups do not know there are other groups (masked allocation). To mitigate undesired open-label effects, researchers may choose clinical endpoints that are hard to modify (e.g. survival) or blinded outcome assessors.

Third, trials with a TwiCs design are embedded in a cohort, and data collection is strictly dictated by the type and frequency of the routine follow-up visits in the overarching cohort. Since the control group remains unaware of the trial, additional assessments and visits are generally not possible. However, if the cohort is built up with the first TwiCs study in mind, as was the case for more than 50% of the trials with a TwiCs design reviewed by Amstutz, Schönenberger, Gerber, et al., the follow-up can be tailored to meet the necessary data collection frequency and endpoints. This was demonstrated in some radiotherapy TwiCs conducted in Utrecht and some COVID-19 drug TwiCs conducted in Paris.[14–19]

Fourth, while in the control group all eligible participants are included by design, some eligible participants will decline the proposed intervention (non-uptake), resulting in an imbalance of uptake across the groups. Across all the trials with a TwiCs design that were reviewed, non-uptake was highly variable, ranging from 0% to 75%. If non-uptake is high, the intention-to-treat estimand will not reflect a direct *intervention* effect but merely an *offer-of-intervention* effect. Moreover, non-uptake should be accounted for in the sample size calculation, which only 37% of TwiCs in the review did.[10] While an intention-to-treat estimand is of interest to policymakers, it may have limited value for participants and treating physicians.[20] Instrumental variable and inverse probability weighting can be applied to estimate per protocol estimands accounting for non-uptake, but they depend on the data available and the type of non-uptake (time-varying versus one-time) and require careful consideration of the underlying assumptions of such observational causal inference approaches.[21-27]

TWICS: HAS THE DESIGN BEEN USED IN SWITZERLAND?

The Swiss HIV Cohort Study (**SHCS**) is the first Swiss cohort – and, notably, the first HIV cohort worldwide – to implement the TwiCs design. Over a ten-month period with various stakeholder meetings, the SHCS worked closely with patient representatives to adapt the cohort protocol to reflect the *Dutch* consent pattern. The SHCS obtained ethics approval for the amended protocol, and in August 2024 it started rolling out randomisation consent across its sites in order to prepare for the implementation of future trials using the TwiCs design. The first such trial is to be started by the end of 2024 and will test the effect of a preference-based choice of different nicotine replacement products on smoking cessation in people living with HIV in Switzerland. The TwiCs design may enable researchers to efficiently generate high-quality, randomised evidence using existing cohort infrastructure in Switzerland and elsewhere. Early insights from the pioneering roll-out of the design and the first TwiCs study in the SHCS will determine if the anticipated benefits of the TwiCs design – such as a more realistic comparator, less burdensome consent procedures, and improved recruitment efficiency – outweigh its limitations.

To follow developments related to the TwiCs design or receive information about and support with the approach, researchers may visit the TwiCs network's website (www.twics.global).

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REGULATORY NEWS, EVENTS, AND PUBLICATIONS

SWITZERLAND

Coordination Office for Human Research (Kofam)

PUBLICATION

● **SEPTEMBER 2024**

Report on ethics committees' activities in 2023

Kofam has published its summary report Activities of the Research Ethics Committees 2023. This annual publication informs the public about operations and developments within Switzerland's ethics committees, thus fulfilling the Human Research Act's (**HRA's**) requirement for transparency in human research practices.

Source: FOPH website (Tasks of the FOPH: information and coordination)

Federal Council

NEWS

● **JULY 2024**

Amendments to HRA ordinances

The Federal Council approved modifications to HRA ordinances on 7 June 2024. The modifications aim to strengthen the protection of research participants and improve the regulatory framework for researchers. The amended ordinances entered into force on 1 November 2024, except for the provisions relating to transparency, which will enter into force on 1 March 2025.

Source: Federal Council website (Press releases), available in DE, FR, and IT

NEWS

● **MAY 2024**

Gender disparities in health care and research

The Federal Council adopted a report emphasising the need to address gender disparities in health care and medical research. Swissmedic has been mandated to evaluate and integrate sex and gender factors into clinical research guidelines and communities. Additionally, the Federal Office of Public Health (**FOPH**) and the State Secretariat for Education, Research and Innovation (**SERI**) will review and propose measures to ensure gender considerations are part of healthcare professionals' training. The responsible federal offices are expected to implement research-related actions and report back to the Federal Council by the end of 2029.

Source: Federal Council website (Press releases), available in DE, FR, and IT

Federal Office of Public Health (FOPH)

EVENT

● **NOVEMBER 2024**

Symposium: Ten Years of the Human Research Act – past, present and future

2024 marks the 10th anniversary of the Human Research Act. Together with its four implementing ordinances, the HRA established a uniform framework and has greatly improved transparency and safety standards in human research. To commemorate this milestone, the FOPH hosted a symposium on 22 November 2024, during which experts discussed the HRA's past achievements, current impact, and future direction.

Source: Kofam website (Research on humans, Symposium)

Swiss Clinical Trial Organisation (SCTO)

EVENT

● **JANUARY 2025**

SCTO Forum 2025

The SCTO Forum 2025 will take place on 29 January in Bern and will focus on the latest revisions to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH GCP E6(R3)). The forum will discuss how these updates modernise and improve global clinical practices, emphasising flexibility, efficiency, and data integrity. More information will be available soon on the SCTO's website.

Source: SCTO website (Forum 2025)

EVENT

● **SEPTEMBER 2024**

D|A|CH Symposium für klinische Prüfungen

A delegation from the SCTO Executive Office participated in the 2024 D|A|CH Symposium für klinische Prüfungen in Berlin. The event featured engaging and insightful presentations and provided a valuable opportunity for clinical research communities across Switzerland, Austria, and Germany to connect.

Source: D|A|CH website, available in DE

EVENT

● **JUNE 2024**

SCTO Symposium: Working towards efficient clinical data-driven research in Switzerland

The SCTO Symposium 2024 was held on June 11 in Lausanne. The event addressed the growing volume and complexity of data in clinical research, emphasising the need for efficient data management and sharing. Discussions included challenges faced by clinical researchers, such as regulatory requirements, IT infrastructure needs, and data governance.

Source: SCTO website (Symposium 2024)

swissethics

PUBLICATION

● **SEPTEMBER 2024**

Report on human research in Switzerland in 2023

swissethics has released its statistical report Human Research in Switzerland 2023. The report provides descriptive data on research projects submitted to and approved by the ethics committees under the HRA. The report supports transparency in research and informs stakeholders on trends and activities in ethical review.

Source: swissethics website (Publications)

NEWS

● **SEPTEMBER 2024**

Updated templates

swissethics updated its templates to ensure compliance with the revised HRA ordinances. The updated templates are available on swissethics' website.

Source: swissethics website (Templates / Checklists)

PUBLICATION

● **JANUARY 2024**

swissethics' 2023 annual report

In its 2023 annual report, swissethics highlights a year of significant initiatives, including expanded training initiatives for members of ethics committees, strengthened partnerships with federal authorities, and its progress in harmonising ethical standards across cantons.

Source: swissethics website (Publications), report available in DE and FR

Swissmedic

NEWS

● **NOVEMBER 2024**

Implementation of revised HRA ordinances

As of 1 November 2024, the revised HRA ordinances have officially come into effect. The provisions on transparency will enter into force on 1 March 2025. Information on submission procedures, updated guidelines, and specific requirements can be found on Swissmedic's website.

Source: Swissmedic (Implementation of new ordinances)

NEWS

● **SEPTEMBER 2024**

New forms and information sheet for combined studies

New forms and an updated information sheet were introduced on 1 September to facilitate submissions to Swissmedic for combined studies. Additional details and access to the forms can be found on Swissmedic's website under the "Clinical Trials, Combined studies" section.

Source: Swissmedic website (Announcements, Combined studies)

NEWS

● **JULY 2024**

Fee reduction for non-commercially funded clinical trials

On 1 July, Swissmedic introduced an 80% fee reduction for processing applications for non-commercially funded clinical trials. This initiative aims to reinforce Switzerland's position as a research hub while maintaining the quality and assessment standards for submission. More information on how to apply for a fee reduction for a clinical investigation or a performance study can be found on Swissmedic's website.

Source: Swissmedic website (Announcements, Academic trials)

NEWS

● **JUNE 2024**

Changes to declaration of goods for the export of medicinal products

On 17 June, Swissmedic announced updates to the declaration process for exporting medicinal products, including those for clinical trials and narcotics. These changes, effective on 4 November 2024, require exporters to provide additional information (e.g. establishment licence number and licence holder details) in the Federal Office for Customs and Border Security's (**FOCBS's**) Passar system. The transition to the Passar system, which began on 17 March 2024, will be completed on 1 January 2026.

Source: Swissmedic website (General communications, Changes to declaration of goods)

PUBLICATION

● **JUNE 2024**

Swissmedic's 2023 annual report

On 7 June, the Federal Council approved the Swissmedic Annual Report 2023, which covers Swissmedic's performance, its finances, and its strategic initiatives for 2023–2026. The report also highlights the agency's achievements; for example, the World Health Organization (**WHO**) has designated Swissmedic as a WHO Listed Authority (**WLA**), an accomplishment that solidifies Swissmedic's role as a key player in global health regulation.

Source: Swissmedic website (Annual Report 2023)

EUROPE

European Medicines Agency (EMA)

NEWS

- **JANUARY 2025**

End of the CTR transition period

The transition period for the EU's Clinical Trials Regulation (**CTR**) is reaching to end. All EU clinical trials are required to be moved to the Clinical Trials Information System (**CTIS**) by 30 January 2025. This shift aims to streamline clinical trial processes across Europe, thus enhancing the region's appeal for clinical research.

Source: EMA website (Clinical Trials Regulation)

PUBLICATION

- **SEPTEMBER 2025**

Guidance on the use of large language models

EMA and the Heads of Medicines Agency (**HMA**) have published Guiding Principles on the Use of Large Language Models in Regulatory Science and for Medicines Regulatory Activities. Aimed at enhancing tasks such as documentation and administrative support, these guidelines emphasise safe and responsible use and cover data input, critical thinking, and staff training.

Source: EMA website (News, Harnessing AI in medicines regulation)

NEWS

- **JUNE 2025**

Revised CTIS transparency rules

New CTIS transparency rules aimed at balancing public health protection and sponsor interests in EU medical research took effect on 18 June. The revised rules clarify confidentiality protections, thus ensuring that key clinical trial information relevant to patients is published promptly while keeping CTIS user-friendly.

Source: EMA website (News, Revised transparency rules for the EU CTIS)

NEWS

- **MARCH 2024**

DARWIN EU updates

On 6 March, the EMA announced an expansion of the Data Analysis and Real World Interrogation Network's (**DARWIN EU's**) capacity to conduct real-world data (**RWD**) studies across Europe. DARWIN EU now has access to data from approximately 130 million patients.

Source: EMA website (News, DARWIN EU)

INTERNATIONAL

Council for International Organizations of Medical Sciences (CIOMS)

PUBLICATION

- **MAY 2024**

Real-World Data and Real-World Evidence in Regulatory Decision-Making

CIOMS has released a report exploring the role of real-world data (**RWD**) and real-world evidence (**RWE**) in regulatory and healthcare decision making.

Source: CIOMS website (Publications) (report doi: 10.56759/kfxh6213)

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

PUBLICATION

- **AUGUST 2024**

ICH adopts E11A guideline for paediatric drug development

Initially released for consultation in April 2022, the ICH has finalised its Pediatric Extrapolation E11A guideline. The guideline creates a standardised framework for using adult drug trial data to support paediatric drug approvals.

Source: ICH website (Efficacy Guidelines)

US Food and Drug Administration (FDA)

PUBLICATION

- **SEPTEMBER 2024**

Guidance on decentralised clinical trials

The FDA has released its final guidance document Conducting Clinical Trials with Decentralized Elements, which was initially released as a draft in May 2023. This guidance offers recommendations for sponsors and investigators on implementing decentralised approaches that allow trial-related activities to occur remotely.

Source: FDA website (Conducting Clinical Trials With Decentralized Elements)

World Health Organization (WHO)

PUBLICATION

- **SEPTEMBER 2024**

Best practices for clinical trials

The WHO's Guidance for Best Practices for Clinical Trials aims to enhance the quality, efficiency, and ethical standards of clinical trials globally. It offers recommendations to strengthen clinical research ecosystems, focusing on patient safety, scientific rigor, and community engagement. In addition, it emphasises the importance of conducting sustainable, high-quality clinical trials in order to ensure equitable access to health innovations worldwide.

Source: WHO website (Publications, Guidance for best practices for clinical trials)

World Medical Association (WMA)

PUBLICATION

- **OCTOBER 2024**

Revision of the Declaration of Helsinki

The WMA has adopted the 2024 revision of the Declaration of Helsinki, which reinforces ethical standards in human clinical research. The new version emphasises greater safeguards for vulnerable populations, improves transparency in clinical trials, and promotes fairness in research practices.

Source: WMA website (WMA Declaration of Helsinki)

PUBLICATIONS

- **Ohmann C et al. (2024) Survey by ECRIN about National Registries for Observational Studies and Sharing of Individual Participant Data** (version v1 dated 25 March 2024).
doi: 10.5281/zenodo.10868392

  This collaborative survey by the European Clinical Research Infrastructure Network (**ECRIN**), featuring contributions from the SCTO, explores national registries for observational studies and the sharing of individual participant data. The report aims to highlight current practices and address challenges in data sharing and to advance transparency and accessibility in clinical research.

- **Ormond KE et al. (2024) What are the bottlenecks to health data sharing in Switzerland? An interview study.** Swiss Medical Weekly (154):3538.
doi: 10.57187/s.3538

  This interview study, co-authored by members of the SCTO's Regulatory Affairs Platform, explores obstacles to health data sharing in Switzerland. The study was conducted in collaboration with several organisations, including the Health and Policy Lab at ETH Zurich, the Swiss Personalized Health Network (**SPHN**), the Swiss Biobanking Platform (**SBP**), and the Bern Center for Precision Medicine (**BCPM**), and delves into key challenges and possible improvements related to sharing health data.

ABBREVIATIONS

BCPM	Bern Center for Precision Medicine
CHUV	Lausanne University Hospital
CIA	confidentiality, integrity, and availability
CID	complex innovative trial design
CIOMS	Council for International Organizations of Medical Sciences
CJEU	Court of Justice of the European Union
ClinO	Ordinance on Clinical Trials in Human Research; Clinical Trials Ordinance
COVID-19	Coronavirus disease 2019
CRC	Clinical Research Centre (CTU in Lausanne)
CT	computed tomography
CTFG	Clinical Trials Facilitation and Coordination Group
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation (EU)
CTTI	Clinical Trials Transformation Initiative
DARWIN EU	Data Analysis and Real World Interrogation Network
DCT	decentralised clinical trial
DHT	digital health technology
DPO	Data Protection Ordinance
EC	European Commission
ECRIN	European Clinical Research Infrastructure Network
eICF	electronic informed consent form
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
EU	European Union
FADP	Federal Act on Data Protection
FDA	US Food and Drug Administration
FOCBS	Federal Office for Customs and Border Security
FOPH	Federal Office of Public Health
GDPR	General Data Protection Regulation (EU)
HCP	healthcare provider
HMA	Heads of Medicines Agencies
HRA	Human Research Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH GCP	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice
IMP	investigational medicinal product
Kofam	Coordination Office for Human Research
PI	principal investigator
RA Platform	Regulatory Affairs Platform (SCTO)
RCT	randomised controlled trial
rSDV	remote source data verification
RWD	real-world data
RWE	real-world evidence
SBP	Swiss Biobanking Platform
SCTO	Swiss Clinical Trial Organisation
SERI	State Secretariat for Education, Research and Innovation
SHCS	Swiss HIV Cohort Study
SMA	spinal muscular atrophy
SPHN	Swiss Personalized Health Network
swissethics	Swiss Association of Research Ethics Committees
Swissmedic	Swiss Agency for Therapeutic Products
TPA	Therapeutic Products Act
TwiCs	trials within cohorts
UNIL	University of Lausanne
VPN	virtual private network
WHO	World Health Organization
WLA	WHO Listed Authority
WMA	World Medical Association

REGULATORY AFFAIRS WATCH

***RA Watch* project lead and editor, RA Platform coordinator**
Güliz Vanli Jaccard

Publication coordinator and copy editor
Meg Züblin

Graphic designer
Aliénor Held

We gratefully acknowledge contributions to this issue from:

Alain Amstutz
Gabriel Avigdor
Brenda Bogaert
Aurélie Fayet
Simone Ferbitz-Scheurer
Felix Gerber
Regina Grossman
Nicole Gusset
Reto Iannaccone
Lada Leyens
Fanny Muet
Sabine Rütti Roch
Christof M. Schönenberger
Fabienne Suero
Elizabeth Theogaraj
Jamie Wingate
Grégoire Wuerzner

Sources of information

- We gather news on regulatory topics related to human research.
- We regularly read newsletters and visit the websites of relevant sources, including regulatory authorities in Switzerland, Europe, and the United States; ICH and WHO; at Swiss academic organisations and health associations; and professional associations.
- Additionally, we review major clinical research journals.

Regulatory Affairs Platform

The Regulatory Affairs Platform is one of the Swiss Clinical Trial Organisation's (**SCTO's**) eight topic-based platforms that promote excellence in clinical research in Switzerland. Find out more about the Regulatory Affairs Platform and read past issues of *Regulatory Affairs Watch* on the SCTO Platforms' Tools & Resources website.

Contact information

For feedback or questions regarding *Regulatory Affairs Watch*, please contact the Regulatory Affairs Platform Coordinator at regulatoryaffairs@scto.ch.

ISSN 2813-2548 (print)
ISSN 2813-2556 (online)
DOI (Issue 9): 10.54920/SCTO.2024.RAWatch.9