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

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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

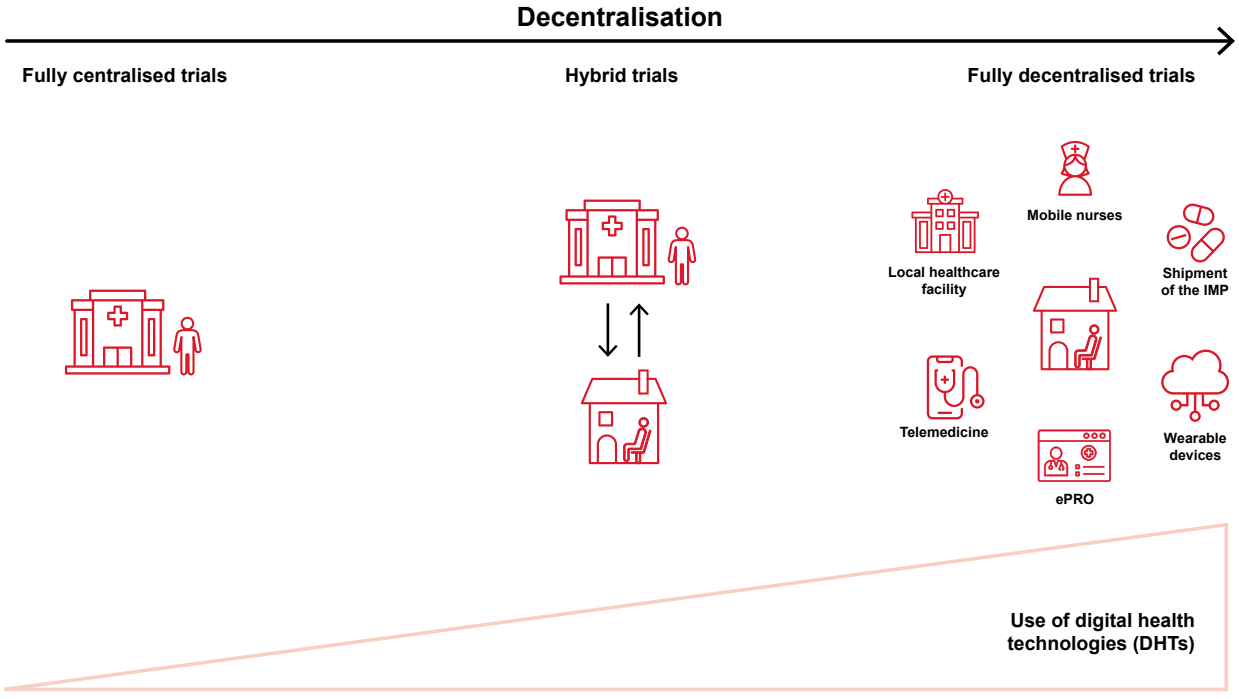
Features of decentralised clinical trials

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
[III] Adedinsewo D et al. (2023) Health disparities, clinical trials, and the digital divide. Mayo Clinic Proceedings 98(12):1875–1887. doi: 10.1016/j.mayocp.2023.05.003
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[V] Vayena E, Blasimme A, and Sugarman J (2023) Decentralised clinical trials: Ethical opportunities and challenges. The Lancet Digital Health 5(6):e390–e394. doi: 10.1016/S2589-7500(23)00052-3

Global regulatory advances

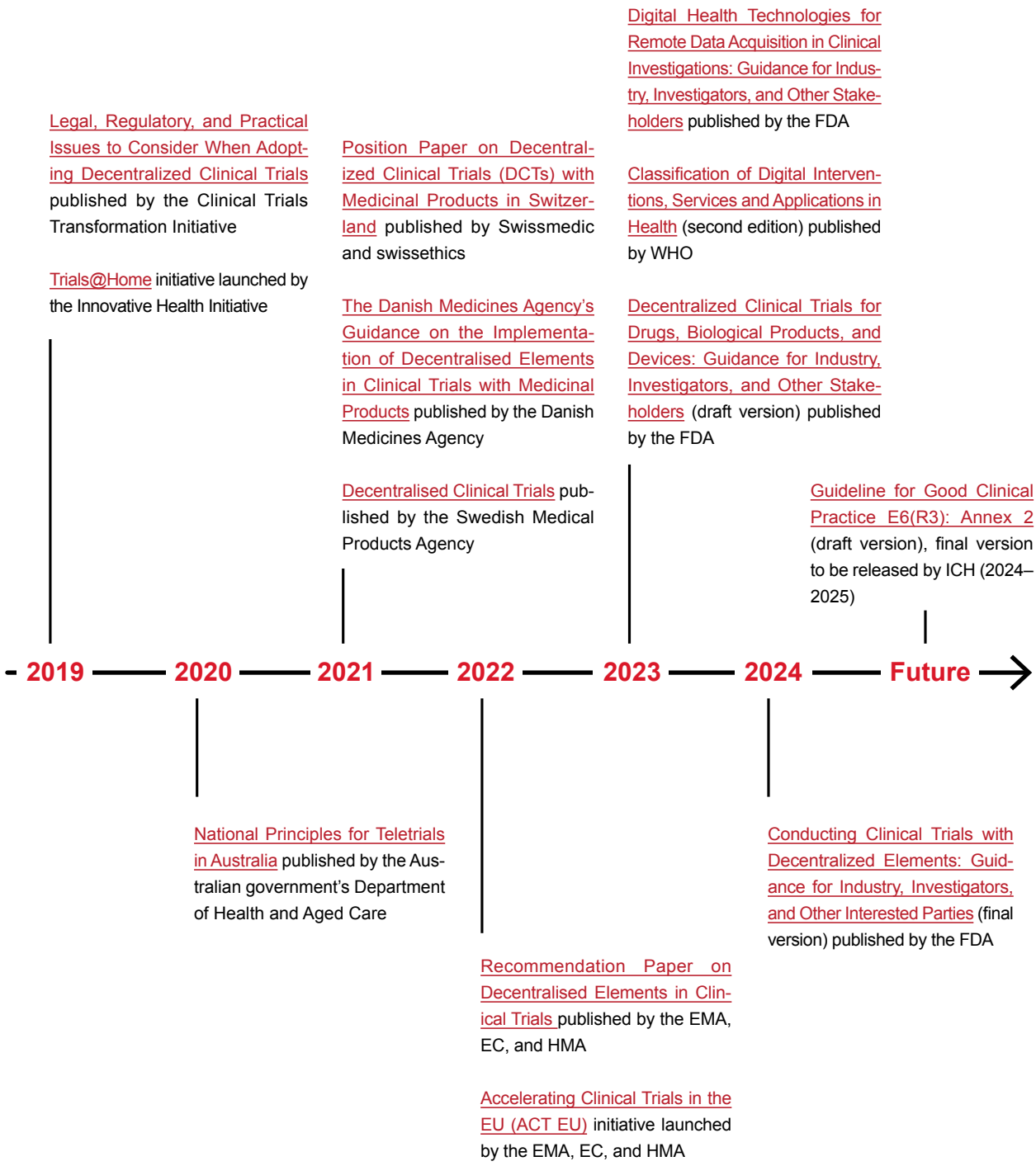
Regardless of whether they have a decentralised approach or not, all trials must abide by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (**ICH GCP**) and be conducted in accordance with the laws and regulations 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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