831458 – Trials@Home

Center of Excellence – Remote Decentralised Clinical Trials

WP4 – EAGLE

D4.5 EAGLE final report

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1- Introduction

In a traditional clinical trial (CT), participants are required to make regular visits to the trial site to monitor their overall condition and perform study-related activities. With the advent and use of several technologies, including wearable devices, it is now possible to organise trial activities around the participant's home, which reduces their time spent traveling to visit the clinic (Izmailova ES *et al*., 2018). Participants' time investment is essential because their recruitment and retention rely upon their compliance with travelling to the clinic in a traditional trial approach. Travel times and logistical barriers to the trial site can discourage overall participation and waiting times at clinics can affect participants' retention (Unger JM *et al*., 2019; Fogel DB, 2018). In the last two decades, technological improvements have been pushing the current site-based traditional trial approach towards one that incorporates features of remote and decentralised design. In 2017, a survey conducted with pharmaceutical companies and Contract Research Organisations (CROs) showed that 37% were using mobile technologies in CTs, and 68% of these were using mobile applications. The principal advantages that companies reported were real-time data acquisition (36%), improved data quality (25%) and higher participant compliance (30%) (MHealth in Clinical Trials Report; von Niederhäusern B *et al*., 2017). More recently, the COVID-19 pandemic forced many on-going CTs to switch to remote visits midstream, despite it being unchartered territory for many. The information on how stakeholders across the CT ecosystem have been adapting, overcoming challenges and discovering new best practices for conducting clinical research via remote visits, will be useful for the performance of CTs in the future.

Well-structured decentralised clinical trials (DCTs), whether fully decentralised or partly decentralised (hybrid), are expected by trialists to use fewer resources (hospital, health care providers (HCP), pharmacist, etc.) in the long run and to optimise participants' involvement. If successful, DCTs could make it easier to recruit and retain participants, including those living distant from traditional investigational sites and people from groups that are often under-represented in CTs, including the paediatric and elderly populations (Trials@Home – Centre of Excellence Remote and Decentralised Clinical Trials). Moreover, as data collection may be continuous over a period, in the participants' natural setting, the data collected could be richer and more reliable, thus providing a better representation of the real world.

In 2019, the Innovative Medicines Initiative (IMI) Trials@Home consortium was initiated with the aim to explore the concept of DCTs. The main objective of this multinational private-public partnership is "to reshape CT design, conduct, and operations, by developing and piloting standards, recommendations and tools for the definition and operationalisation of DCTs in Europe". Within the Trials@Home consortium, Work Package 4 (WP4, EAGLE - **E**thic**a**l regulatory, **G**CP, and **Le**gal aspects) was tasked with the following deliverables:

1. Map of the European Union (EU) legislation on DCTs including legal, regulatory, ethical and stakeholder recommendations for conduct of RADIAL the pan-EU pilot study.
2. SWOT analysis of ethical, legal and operational barriers and enablers for DCTs in the EU
3. Overview of technical and regulatory implications of DCTs for efficient regulatory decision-making
4. Overview of innovative scenarios for a responsible and sustainable DCT ecosystem

In this final WP4 report, the different deliverables are summarised in individual sections below and an overall discussion/ conclusion is provided.

2- Sections

2.1. Map of the EU legislation on DCTs including legal, regulatory, ethical, and stakeholder recommendations for the conduct of the pan-EU pilot

2.1.1. Introduction

In the EU, CTs are regulated by two forms of legislation: directives (requiring national implementation and interpretation) and regulations (EU-wide implementation). At the onset of the Trials@Home consortium in 2019, EU CTs were authorised and supervised at the national level. As a result, conduct of CTs could differ throughout Europe due to the impact of the relevant national legislation and guidance for CTs. The aim of this deliverable was to map and analyse the pre-COVID-19 legal and ethical framework at the EU and member state (MS) levels to identify opportunities and challenges and provide recommendations on how to perform DCTs. Eleven EU MS were included in the mapping conducted in 2020-2021. These countries were selected based on the number of registered CTs and geographical location to ensure suitable representation across Europe: Belgium, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Poland, Romania, Spain and Sweden. The mapping is summarised below, together with a brief discussion on the changing legislation in the EU since then.

2.1.2. Discussion

Methodology was based on Trials@Home building block classification scheme developed by Work Package 2, TECH (Technologies – barriers, enablers and data management). The building blocks aimed to divide the design, conduct, data collection and closing of a CT into different study phases (see Figure 2 in *Trials@Home building blocks classification scheme* IMI2_Deliverable-4.1_WP4_Final_updated-Mar2022.pdf). Sub-teams gathered information from EMA and national authorities' websites, as well as from international and national industry organizations where guidance and regulations are (publicly) available. In some cases, searches were also conducted in the local language and results were translated to English where necessary. These were then corroborated with in-country regulatory affairs personnel of the Trials@Home consortium who were fluent in the local language.

Results per building blocks and MS were collected where available for:

1. **Recruitment enrolment – Patient engagement:** including remote recruitment, remote consenting/eICF, remote screening, remote participant education, participant outreach.
2. **Operations:** including telemedicine, including direct to patient drug supply, remote study assessments e.g., home health visits, laboratories, imaging, patient reported outcome, wearables, omics.
3. **Data collection and quality:** including remote monitoring and oversight, electronic case report form, query management and audit.
4. **Data processing**: including electronic health records, data protection, database access and integration, analysis, data re-use.

The final output of the mapping from 2022 is provided in deliverable 4.1 (IMI2_Deliverable-4.1_WP4_Final_updated-Mar2022.pdf).

2. 1. 3. Conclusion

In 2021, throughout most of the countries investigated, there were no guidance, legislation or regulations for many of the DCT elements mentioned in Figure 2. Where national regulations on DCT elements existed, they were limited in number and only available in a few countries.

Notable findings at the time included that remote monitoring and oversight were not permitted in Belgium and Denmark; and direct-to-patient drug supplies and management were not permitted in France and Belgium.
The COVID-19 pandemic forced the clinical research community to re-evaluate how to conduct trials in a more participant-centric way, often away from the traditional trial site (de Jong AJ *et al*., 2022). Today, DCT elements are becoming increasingly used in studies with technology advancements at the heart of this trend. Using DCT elements in trials should continue to ensure trial participant's safety, protection of their rights/dignity, as well as data reliability/quality for publication and submission for regulatory decision-making, as per traditional site-based trials.
In December 2022, the Heads of medicines Agencies (HMA) Clinical Trial Coordination Group (CTCG) released a recommendation paper (RP) on DCT elements in CTs in the EU (Recommendation paper on decentralised elements in clinical trials - European Commission (europa.eu). 2ccc46bf-2739-4b9a-ab6b-6f425db78c61_en). In the appendix of this paper, there is a "National Provisions Overview" with individual MS' recommendations including the following DCT elements: delivery of investigational medicinal products (IMPs) from sponsor/site, shipment of IMPs from sponsor/site across borders within the EU; shipment and hand -out of IMPs from pharmacies; eConsent process, trial participant oversight and home visits, and Trial Monitoring using remote access to source data.

Various DCT elements are likely to evolve through updates in national guidance/ legislation/ standard operation procedures (SOPs) to be in line with current CT trends and evolving technology which will hopefully lead to more alignment across different MS compared to the situation presented in the HMA 2022 recommendation paper and the mapping presented in the Trials@Home analysis.
It is at the discretion of the MS involved in the assessment of a CT whether the use of certain decentralised elements is acceptable in a specific CT. Sponsors are therefore encouraged to seek advice with local health authorities (HAs) regarding the use of decentralised elements, especially on decentralised elements where experience and the evidence of their impact may be limited. The EU clinical trial regulation (CTR), implemented from 31 January 2022, will further support the smooth harmonisation of approval of clinical studies in the EU. The ICH E6(R3) Annex 2 including DCT elements implementation is currently undergoing revision, which will improve clarity on some DCT aspects. Therefore, even though some DCT activities have now been commonly conducted in many MS, national implementation of the CTR requires that the continuous evolution of relevant national regulations/legislation/guidance should converge so that eventually the same protocol containing various DCT elements can be smoothly implemented in any EU MS going forward. This will then help position the EU as an attractive region for participant-centric clinical development.

2.2. SWOT analysis of ethical, legal and operational barriers and enablers for DCT in the EU

2.2.1. Introduction

This document presents the results of a SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis of decentralised clinical trials (DCTs) in the EU, focusing on ethical, legal, and operational aspects. The analysis was conducted to identify the main challenges and propose potential solutions for implementing DCTs. The study employed a methodology that included a SWOT analysis, an evaluation by an expert panel comprising members of the

External Stakeholder Platform (ESP) and the Patient Expert Panel (PEP), and a Delphi study with an external panel of experts representing various stakeholders to generate and assess solution proposals.

2.2.2. Discussion

The SWOT analysis revealed 11 strengths, 14 weaknesses, 2 opportunities, and 4 threats for DCTs. The primary strengths identified include potential benefits of using electronic consent (eConsent), advantages of using digital technologies for other study procedures, remote access, facilitating participation of more diverse and geographically dispersed populations, freer decision-making by participants, and reduced burden for participants.
The most significant weaknesses include barriers due to the use of digital technologies; lack of face-to-face contact; difficulties in verifying participants' identities; privacy issues; and increased burden and responsibility for participants and healthcare providers.
The identified opportunities focus on harmonisation of regulation and legislation, and collaboration with local resources.
The main threats include lack of harmonisation in legislation and lack of specific knowledge for ethical, legal, and regulatory assessment of DCTs.
An expert panel evaluated the importance of each SWOT element, which led to the identification of six main challenges (Ch):

1. Increased burden or risk for healthcare providers (Ch 1)
2. Difficulties in logistics and management of investigational products and biosamples (Ch 2)
3. Ensuring effective collaboration with local resources (Ch 3)
4. Lack of harmonisation in regulation and legislation (Ch 4)
5. Improving the lack of specific knowledge and experience for ethical, legal, and regulatory assessment of DCTs (Ch 5)
6. Overcoming barriers due to the use of digital technologies (Ch 6)

A Delphi study was conducted with external experts to generate and evaluate the best proposals to address these challenges. The main proposed solutions are included in the conclusion section.

2.2.3. Conclusion

DCTs offer significant opportunities to improve clinical evidence collection, but they also present challenges. The main recommendations include:

Socioecological Model level	Recommendations to overcome the challenges (D4.2)
Individual level: Interventions directed at individuals, such as training, knowledge, and skills	• Developing and improving training and support (Ch 1 & 6) • Knowledge sharing and education on DCTs (Ch 5) • Simplifying and adapting technology for participants (Ch 6)
Interpersonal level: Interactions between people, such as mutual support or teamwork	• Maintaining communication between researchers and participants (Ch 6) • Raising awareness among HCPs and patients about the importance of clinical research (Ch 3) • Mutual support through learning networks (Ch 4&5)

Institutional level: Changes in systems, institutions, or work environments	• Validating products and services for logistics (Ch 2) • Promoting the gradual implementation of DCT elements adapted to local or national specificities (Ch 4) • Providing adequate financial and technological resources (Ch 6)
Community level: Actions with an impact on the community, such as local resources or community networks	• Raising awareness of the value of clinical research within the community (Ch 3) • Encouraging the use of local resources in collaboration with local stakeholders (Ch 3) • Sharing knowledge at the community level (Ch 5)
Policy level: Interventions related to policies, legislation, or regulation	• Promoting the harmonisation of guidelines at a European level (Ch 4&5) • Encouraging international regulatory learning (Ch 4) • Developing specific guidelines for DCTs (Ch 4)

The implementation of these solutions is expected to enhance the execution of DCTs, promoting effective, ethical, and high-quality research outcomes, whilst leveraging the advantages of decentralisation and mitigating its potential risks.

2.3. Overview of technical and regulatory implications of DCTs for efficient regulatory decision-making

2.3.1. Introduction

An analysis of the interaction between different stakeholders as well as the opportunities and challenges of DCTs from the perspective of EU regulators, HTA bodies, sponsors, study site staffs and EFPIA partners was conducted. This was done by selected semi structured interviews, surveys, and publications analysis.

2.3.2. Discussion

The terminology surrounding Decentralized Clinical Trials (DCTs) is diverse, and there was a consensus to use the term DCT to ensure clear and effective communication (Santa-Ana-Tellez Y *et al.*, 2023a).

Regulatory support on the Trials@Home consortium RADIAL study was positive, with consultations on the RADIAL study design with the EMA's Innovation Task Force (ITF) and through a scientific advice from a National Competent Authority (BfArM) in 2021. EMA and BfArM provided comments and recommendations addressing regulatory compliance of devices used, ethical implications and potential legal concerns with the investigators' roles and responsibilities in DCT, data handling, safety oversight and participant recruitment biases (Santa-Ana-Tellez Y*et al.*, 2023b).

The regulatory landscape for DCTs is complex, highlighting the importance of collaboration between regulatory agencies, clinical investigators, and sponsors to ensure participant safety and uphold data quality (de Jong AJ *et al.*, 2022). Through semi-structured interviews, EU regulators (n=20) emphasised the need for justification of DCT elements, clear delineation of sponsor and investigator responsibilities and interests, and maintaining high data quality. They also focused on risk mitigations, the appropriateness of DCTs for specific trial phases or disease types, and the generalizability of results. Additionally, they stressed the

importance of participant preference, big data management, data completeness, variability, validation of digital technologies, and adequate training. Challenges around the participant's burdens and delegation/training of third parties involved in some tasks was highlighted. Key opportunities such as reduced participation burden which could facilitate the participation of underserved populations, and collection of data more representative of the real world were also highlighted.

From **an HTA perspective**, based on the interviews of 25 representatives of European HTA bodies, challenges such as missing data and variability were viewed as significant (de Jong AJ *et al*., 2024). DCTs were deemed more suitable for simple measures requiring frequent monitoring, while they are less appropriate for complex physical examinations. From an economic perspective, DCTs could offer informative quality of life (QoL) data, by reducing recall bias and administration in a real-life setting and include a more diverse population though potentially creating a recruitment bias at the same time.

EFPIA representatives through a survey conducted in Q2 2023 identified challenges such as data quality, security, remote monitoring, data integration, and regulatory compliance (Santa-Ana-Tellez Y *et al*., 2023b). They proposed solutions including staff training, standardization of monitoring procedures, robust data management, enhanced security protocols, and acceptance of digital endpoints. They also highlighted the need for clear guidelines, harmonized regulations, and guidance on the use of technology for remote assessment of adverse events.

Recent **studies reflect on the privacy as well as the ethical aspects associated with DCTs**, such as, safety, accessibility, and informed consent (van Rijssel TI *et al.*, 2022; van Rijssel TI *et al.*, 2024). There is a lack of specific standards for the ethics review of DCTs, and it is recommended that sponsors and researchers reflect on existing evidence of both the risks and benefits of DCTs within research protocols to promote an evidence-based review practice. The impact of these changing practices should be carefully observed and reflected upon, allowing DCTs and hybrid trials to proceed while feeding learnings back into conduct and guidance for ethics review.

The informed consent process in DCTs is affected by several elements, including informing participants and testing their understanding, balancing freedoms with responsibilities and burdens, building trust in participant-researcher relations, and ensuring privacy and data protection. Evidence suggests that altering informed consent processes with new technologies may provide opportunities for improvement, such as using videos, interactive features, or gamification. However, the lack of visual body language cues requires better communication skills from researchers. The DCT approach offers more flexibility and freedom to participants but also places extra responsibility on them. Building trust is more challenging due to the lack of in-person contact, but frequent communications and multiple interaction methods can help. Privacy concerns are primarily related to data protection and control over personal information, with the use of apps and devices increasing the risk of passive data collection and sharing with commercial parties.

Direct-to-patient (DtP) solutions for investigational medical product (IMP) supply in Europe is hindered by the lack of harmonised regulatory guidance and the varying perspectives of national competent authorities (de Jong AJ *et al*., 2023). Various supply models for DtP include site-to-participant, local and central pharmacy-to-participant, and sponsor-to-participant, which need to be adapted based on the stability, safety profile, complexity of preparation and administration route of the IMP. Barriers to these models include regulatory inconsistencies, logistical burdens, and the need for appropriate infrastructure and technology.

The future implementation of innovative CT approaches such as DCTs can be facilitated by a European regulatory framework ready to implement and assess these approaches, using case studies (de Jong AJ *et al*., 2024). Ideas for regulatory readiness include timely guidance, identification of trends, explorative research on the effectiveness of innovative approaches, use of regulatory sandboxes, operational research questions within trials, and sharing learnings across the CT ecosystem. Regulators should aim for harmonization and avoid overregulation when establishing requirements for DCT oversight.

2.3.3. Conclusion

The research highlights the collaborative support from regulatory authorities such as EMA ITF and BfArM for DCTs, suggesting a promising future for decentralized elements in clinical research. However, challenges such as data management, third-party engagement, and the need for harmonized regulations must be addressed. Strategic planning, better guidelines, and collaboration among stakeholders are essential for successful DCT implementation. The research emphasises the importance of creating an inclusive and forward-thinking culture to overcome these challenges and revolutionize clinical research.

2.4. Overview of innovative scenarios for a responsible and sustainable DCT ecosystem

2.4.1. Introduction

The development of the practice of DCTs takes place in a regulatory system designed for traditional (site-based) trials. To realise the promises of decentralising elements of CTs, the regulatory context needs to be aligned with both the practice of DCTs as well as the ethical principles of responsible conduct on which the system is based.

Trials@Home encompassed a continuous process of identification, analysis and assessment of ethical and regulatory aspects of DCTs. We identified ethical and regulatory opportunities and challenges through stakeholder interviews and a ‘mock ethics review’ in which members of European ethics committees (ECs) and national competent authorities (NCAs) discussed and reviewed a DCT protocol. Based on the exploratory work, we prioritised topics for further analysis. Moreover, we broadened our perspective beyond the issues which have dominated the ethical debate on digitalisation, such as risks relating to e.g., data protection, safety, and data quality. We also focused on impacts of digitalisation such as shaping behaviours, experiences, social relations, and values. Ultimately, we integrated our work in four innovative scenarios for a responsible and sustainable DCT ecosystem.

2.4.2. Discussion

We synthesised our ethical analyses and empirical studies around several key issues, which can further the responsible and sustainable practice of DCTs. We address regulatory issues as well as topic relevant to the design and methodology of DCTs. Ultimately, we outline four scenarios picturing an ethical and regulatory ecosystem for DCTs.

Scenario 1*: Enhancing Participant-Centricity*

DCTs aim to reduce the burden on participants by allowing trial activities to occur in their own environment, improving flexibility and integration into daily life.

Scenario 2*: Real-World Data Generation*

DCTs collect data in participants’ natural settings rather than controlled clinical environments. This makes the data more reflective of real-life conditions, allow for more relevant measurements, improving data accuracy, protocol compliance, and participant retention.

Scenario 3: *Improving Efficiency*

DCTs can streamline trial processes by reducing in-person visits, enabling remote delivery of medications, and using digital monitoring for safety oversight.
***Scenario 4**: Increasing Population Diversity*
DCTs may improve the inclusivity of clinical trials by removing geographic and logistical barriers. This can make participation easier for underrepresented groups such as the elderly, people with comorbidities, those in rural areas, and minority populations.

Taking technologies' soft impacts into account
Aside from hard impacts such as breaches of rights, emerging technologies also have so-called "soft impacts". Examples are effects on social relations, values, and behaviours. These soft impacts are influenced by user interaction and are often difficult to predict. The philosophy of technological mediation emphasises that technologies actively shape human perceptions and behaviours rather than simply functioning as neutral tools (van Rijssel TI *et al.*, 2024a) This perspective suggests that instead of seeing new technologies as threats, ethical considerations should focus on how they can be responsibly implemented by anticipating their potential impacts. Applying this approach, we analysed the soft impacts of DCTs on informed consent procedures in clinical research. Taking these impacts into account in the design and conduct of DCTs can help ensure that digitalisation aligns with ethical and practical needs.

Responsibility, attribution and implementation
Responsibilities in clinical research are primarily governed by laws, regulations, and guidelines, with sponsors holding overall responsibility for study management, compliance, and safety, even when tasks are delegated to third parties. In DCTs, the use of digital health technologies shifts research activities away from traditional sites, introducing new challenges in oversight and responsibility distribution. AI-driven systems further complicate accountability by raising questions about responsibility for algorithmic decisions. Existing guidelines primarily attribute responsibility to sponsors, but decentralised elements demand clearer communication and coordination mechanisms. To address these challenges, a new approach is needed, including a structured framework for ensuring responsibilities are effectively implemented in technology-driven research. This involves mapping responsibilities, identifying risks and challenges for fulfilling these responsibilities, and organising adequate communication channels.

Risk-benefit assessment of DCTs in ethics review
Hesitancy toward DCTs and focus on potential risks and burdens was common among members of ECs and NCAs when performing a mock ethics review of a DCT. Moreover, the literature is unclear on how some of the benefits of DCTs fit into the existing definitions of research benefits and the process of risk-benefit assessments by for example Medical Research Ethics Committees. For example, participants in DCTs may receive (medical) devices as a part of the study. This can be considered a *collateral* benefit (van Rijssel TI *et al., 2024b)*, but also as a form of non-monetary compensation, which may need to be assessed differently. To achieve more clarity and guidance on this issue, we reconsidered the various types of research benefits, and their position in risk-benefit assessments. Subsequently we analysed the position of these benefits in risk-benefit assessments, with a particular focus on collateral benefits. Based on this analysis, we advocate for the inclusion of collateral benefits in ethical assessments under certain conditions, providing these benefits can make research more participant-centred and fair.

Innovative scenarios for DCTs
The acceptance and regulation of DCTs are still evolving, as ethical and regulatory frameworks were primarily designed for site-based trials. In Trials@Home, we aimed to contribute to the development of standards, recommendations, and tools for responsible and sustainable DCT implementation. Focusing on ethical, regulatory, and Good Clinical Practice

(GCP) aspects we identified four key aims of DCTs and the challenges in achieving them: (i) To enhance *participant-centricity*, researchers should focus on participant involvement, empowerment, and reducing trial burdens through effective use of technology; (ii) *Real-world data collection* requires careful planning of digital endpoints to avoid unnecessary data collection without clear analytical strategies; (iii) For *efficient trial conduct*, maintaining adequate oversight is crucial, particularly for participant safety in the absence of in-person contact (iv) Lastly, achieving *diversity* in DCTs demands a clear understanding of what diversity means in each context and how to implement it effectively.

2.4.3. Conclusion

Our work amounts to four recommendations which can be used as guidance in achieving DCTs main goals.

1. Soft impacts of DCTs such as shifting responsibilities, changes in existing relationships within the healthcare and research context, new impacts on privacy, and trust are difficult to measure or predict and not immediately addressed by the existing regulatory frameworks. It is important to monitor and address these soft impacts for implementing DCTs successfully. The soft impacts of decentralised informed consent are further described in van Rijssel TI *et al., 2024a.*
2. Technologies used in DCTs may diffuse responsibilities among multiple actors and technologies. Diffusion diminishes the ability of actors to fulfil responsibilities. Responsibility, attribution, and implementation should receive more attention in the design of DCTs. The challenges of diffused responsibility are described and addressed in Muller SHA *et al., 2025*.
3. We propose that both the (collateral) benefits and risks of DCTs should be carefully monitored to advance the review and practice of this innovative approach to ethically optimise drug development. To understand more about the **collateral benefits** how these can be included in ethical risk-benefit assessments for DCTs, see van Rijssel TI *et al., 2024b.*
4. To examine what is needed from an ethical and regulatory perspective to further the practice of DCT in a responsible and sustainable manner, sponsors, regulators and researchers can use the four scenarios developed within Trials@Home, and the accompanying advice for researchers on ways of mitigating challenges and proposals for adjustments of the regulatory framework. Innovative scenarios for a responsible and sustainable DCT ecosystem are described in deliverable report D4.4 https://trialsathome.com/wp-content/uploads/2023/08/831458-Trials@Home-D4.4-Overview-of-innovative-scenarios.pdf

We address another important issue, the diversity of study populations in DCTs in van Rijssel TI *et al*., 2025. Finally, our other papers and a PhD thesis on DCTs: van Rijssel TI. *et al., 2022* and *PhD Thesis:* van Rijssel TI, *2024*. *Bringing clinical research to patients: Ethical aspects of decentralised clinical trials. Diss. Utrecht University.*

3- Overall discussion and conclusion

EAGLE played an important role both in supporting the design and approval of the RADIAL trial, as well as generating useful learnings from a regulatory, ethical and legal perspective role in the consortium. Through EAGLE's activities in Trials@Home and investigation related to the four deliverables summarised above, the following recommendations for improvement of DCT's implementation in EU can be drawn:

- **Harmonisation at the EU national level is required**
  DCT activities have now been commonly conducted in many MS, but the relevant national regulations/legislation/guidance should continue to evolve and converge to harmonisation, so that eventually the same protocol containing various DCT elements can be smoothly implemented and managed in any of the MS under the CTR. This will increase DCT valorisation and uptake, increase CT efficiency, and position the EU, as an attractive region for participant-centric clinical development.
- **Target interventions at different levels**
  - *Individual level intervention interventions*
    Developing and improving training and support aimed at individuals. Knowledge sharing and education on DCTs. Simplifying and adapting technology for participants.
  - *Interpersonal level intervention*
    Interactions between people, such as mutual support through learning networks or teamwork. Maintaining communication between researchers and participants. Raising awareness among HCPs and patients about the importance of clinical research.
  - *Institutional level intervention*
    Initiation of changes in systems, institutions, or work environments through gradual promotion of the implementation of DCT elements adapted to local or national specificities. Validation of products and services for logistics. Provision of adequate financial and technological resources.
  - *Community level intervention*
    Actions with an impact on the community, such as local resources or community networks. Raising awareness of the value of clinical research within the community. Encouraging the use of local resources in collaboration with local stakeholders and sharing knowledge at the community level.
- **The collaborative support from regulatory authorities**
  Positive experience through the interaction with EMA ITF and BfArM for DCTs, suggests a promising future for DCT elements in clinical research. However, challenges such as data management, third-party engagement, and the need for harmonised regulations must be addressed. Strategic planning, better guidelines, and collaboration among stakeholders are essential for successful DCT implementation. The research emphasises the importance of creating an inclusive and forward-thinking culture to overcome these challenges and revolutionize clinical research.
- **Soft impacts of DCTs**
  Such as shifting responsibilities, changes in existing relationships within the healthcare and research context, new impacts on privacy, and trust are difficult to measure or predict and not immediately addressed by the existing regulatory frameworks. It is important to monitor and address for implementing DCTs successfully.
- **Technologies used in DCTs**
  May diffuse responsibilities among multiple actors and technologies. Diffusion diminishes the ability of actors to fulfil responsibilities. Responsibility attribution and implementation should receive more attention in the design of DCTs.
- **Continuous monitoring of benefits and risks of DCTs**
  We propose that both the (collateral) benefits and risks of DCTs should be carefully monitored to advance the review and practice of this innovative approach to ethically optimise drug development.
- **Use the four scenarios developed within Trials@Home**
  To examine what is needed from an ethical and regulatory perspective to further the main aims of DCT in a responsible and sustainable manner, sponsors, regulators and researchers can use the four scenarios developed within Trials@Home, and the accompanying advice for researchers on ways of mitigating challenges and proposals for adjustments of the regulatory framework.

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