Decentralized studies - organization and challenges in project management

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***Abstract*—Clinical trials (CTs) are essential for advancing medical development and are subject to strict regulations to ensure participant safety. Therefore, frequent visits to the study site (hospital or doctor's office) are often required, which can be burdensome and involve high organizational efforts, especially for individuals who are already ill. A decentralized clinical trial (DCT) is a research study that alters the traditional structure. In this type of trial, study-specific assessments are conducted through digital technologies such as tablet-based questionnaires, meetings via video conferences, or data collection using motion sensors at participants' homes. This allows for a greater diversity of participants and improves access to the study. Decentralized clinical trials have the potential to increase research efficiency, speed, and reach, accelerating the development of new drugs/medical devices and therapies.**

This thesis aims to formulate a customized DCT framework specific to VASCage Company, concurrently assessing the practicality and attractiveness of shifting from conventional CTs to DCTs in project management. Its objectives include creating a viable DCT framework for the company and providing a comprehensive assessment of the potential benefits and considerations involved in adopting DCTs. The thesis explored the role of digital health technologies in DCTs and gathered insights from global companies and universities. Expert interviews provided firsthand perspectives on DCTs while understanding patients' needs was crucial. This analysis led to recommended solutions for addressing project management challenges in DCTs, including study design, participant recruitment, data management, technology, and ethical compliance.

Embracing decentralization can enhance efficiency and adaptability but requires robust communication and coordination. Technology plays a crucial role in facilitating decentralized project management by bridging geographical and organizational gaps. Customized strategies are essential for each project management, considering its scope, team, and industry. Quality control must be maintained. This exploration underscores the transformative potential of decentralization and provides guidance for VASCage to succeed in a decentralized collaborative world.

I. Introduction

CLINICAL trials are vital tools in evidence-based medicine, providing systematic evaluations of interventions to determine their safety, effectiveness, and efficacy. The history of clinical research has ancient origins, evolving from dietary treatments to drug development. Over time, clinical trial methodologies have improved, along with changes in regulations and ethics.[1]. Clinical trials are prospective studies that assess interventions in humans versus a control group. These interventions can be diagnostic, preventive, or therapeutic, following a standardized protocol to achieve a specific goal. Early phase pharmaceutical studies, often labeled as phase I and phase II trials, can be controlled or uncontrolled. However, a lack of control can make them less structured. Clinical trials are vital for advancing medicine by evaluating new methods to prevent, detect, or treat diseases through drugs, surgery, or devices, with the aim of improving the quality of life for those with chronic conditions. Participation in clinical trials can provide individuals with the opportunity to contribute to science, access cutting-edge treatments, and receive specialized care, offering hope for better future treatments [2]. Clinical studies come in various forms and are used depending on the circumstances. In some cases, researchers may employ different types of studies and target different groups of individuals to examine the same research question, depending on the available information [3]. CTs encompass various design types, including observational studies, interventional studies, and other approaches. As the 21st century commenced, the life sciences sector envisioned a new approach to conducting clinical trials, with the appearance of technology like Electronic Data Capture (EDC) serving as a catalyst for the first electronic CT systems. Subsequently, the industry introduced the launch of eCOA and eConsent [4]. Decentralized Clinical Trials (DCTs) have been a familiar concept in the industry for several years, dating back to Pfizer's pioneering "virtual" trial in June 2011. However, DCTs have recently gained more traction as a mainstream consideration, following years of testing and the COVID-19 pandemic's impact [5]. The COVID-19 pandemic has sped up the adoption of DCTs, emphasizing their benefits for virtual trials and improving the experiences of patients and physicians [6]. This trend was already gaining momentum before the pandemic, with the number of trials incorporating DCT elements increasing from 376 in 2016 to 526 in 2021. The COVID-19 pandemic disrupted traditional clinical trials, leading to the adoption of decentralized methods for participant safety and study continuity. This shift, while causing delays in bringing new treatments to market, also accelerated the use of virtual interactions between physicians and patients. This shift allowed for the continuation of care while adhering to social distancing measures and mitigating the spread of the virus [7]. The rapid growth of digital technologies has enabled decentralized studies by facilitating real-time data collection, remote/centralized monitoring, and virtual consultations. Remote data collection tools, like ePRO platforms, wearable devices, and health apps, have made it possible to capture data without physical site visits. This has increased the interest in DCTs, aligning with the acceptance of virtual medicine and encouraging changes in trial design [7]. Furthermore, there is regulatory support that facilitates the

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transition from conventional CTs to DCTs. Regulatory agencies, including the Food and Drug Administration (FDA), have issued guidelines that offer flexibility for virtual trials while ensuring data integrity and participant safety. These guidelines encourage the adoption of decentralized elements, like using local facilities for lab tests or conducting telemedicine follow-up visits in participants' homes, to advance medical product development and research [8]. It is widely recognized that DCTs are gaining popularity and many companies are integrating this trend into their workflow. The purpose of this paper is to provide essential information to comprehend the domain of traditional CTs and DCTs and subsequently create a project management concept on DCTs that will be further developed for VASCage GmbH.

II. Decentralized clinical trials

Research involving human subjects is necessary to advance medical development. Clinical studies are subject to strict legal regulations to ensure the safety and wellbeing of participants. Therefore, frequent visits to the study site (hospital or doctor's office) are often required, which can be burdensome and involve high organizational efforts, especially for individuals who are already ill. A decentralized clinical trial is a research study that alters the traditional structure. In this type of trial, study-specific assessments are conducted through digital technologies such as tablet-based questionnaires, meetings via video conferences, or data collection using motion sensors at participants' homes. This allows for a greater diversity of participants and improves access to the study. Decentralized clinical trials have the potential to increase research efficiency, speed, and reach, accelerating the development of new drugs/devices and therapies.

A. Advantages and challenges of decentralized clinical trials

The advantages include first, increased participant diversity and recruitment. It is imperative to not only increase the number of participants but also enhance their diversity. Achieving representative clinical research participant populations is essential, considering the impact of geographic, social, cultural, genetic, and racial factors on health outcomes [9]. However, with the advent of decentralized trial models that leverage technology and digital platforms, new opportunities have emerged to address these disparities. Digital and social media platforms offer multiple avenues to enhance patient recruitment while simultaneously reducing costs. Patients can actively participate in the recruitment process, thereby increasing their sense of ownership and involvement in the trial [10]. Second, increased convenience for participants. The study "Perceptions and Insights" [11] conducted in 2021 by CISCRP showed that there is considerable interest in DCT approaches, as long as they do not compromise the quality of the personal relationship between patients and study staff. Third, Reduced costs and time. Implementing decentralized clinical trials offers several advantages in terms of reduced costs and time compared to traditional clinical trial models. One example is reduced site-related costs. DCTs eliminate the need for physical site visits, reducing expenses associated with site infrastructure, maintenance, and staffing. This can lead to significant cost savings for sponsors and investigators [12]. Fourth, improved data quality. DCTs use digital technologies to remotely collect data, leading to improved data quality. Real-time and continuous data collection is made possible through wearables, sensors, and mobile apps, eliminating the need for patients to visit clinics/study sites for data entry. This enhances data accuracy and reliability by reducing errors and missing data points associated with manual entry and paper-based processes [13].

The disadvantages include first, technical and logistical challenges. Selecting the appropriate technology is a crucial initial step that requires careful consideration. Additionally, the clinical study staff and the participants may have to learn how to deal with this new technology. Conducting DCTs requires enhanced training and support for participants, healthcare providers, and study staff. Ensuring that all stakeholders are comfortable with the technology, understand their roles and responsibilities, and can troubleshoot technical issues is crucial for the success of decentralized trials [14]. Additionally, if multiple technology vendors and platforms are involved a lack of standardization and interoperability can occur. Second, regulatory and ethical considerations. DCTs must comply with regulatory requirements set by agencies such as the FDA, the European Medicines Agency (EMA), and other regulatory bodies. These regulations govern aspects such as informed consent, data privacy, safety reporting, and protocol adherence. Ensuring that DCTs meet these regulatory standards can be complex, as the remote nature of the trials may require adaptations to existing guidelines and frameworks. Third, data privacy and security concerns. Data security must be prioritized at every stage of data collection, cleaning, and analysis to avoid penalties, data loss, and compromised integrity. Unlike traditional on-site visits, where data security measures could be implemented, DCTs face challenges in ensuring data protection, especially when participants are at home. Integration points in the data journey, including unsecured Wi-Fi, unprotected devices, and external vendors hosting data, pose risks beyond sponsors' control. Establishing standards for data collection in decentralized environments will require collaboration among regulators, industry experts, and academia [15].

B. Decentralized study design considerations

Decentralized study design considerations refer to the specific factors that investigators and sponsors must consider when planning and conducting clinical trials or research studies that utilize decentralized remote methods. Key considerations can be seen in figure 1. Sponsors need a proactive strategy that reduces site start-up and increases trial efficiency through various networks. Another crucial aspect to consider when implementing a DCT is agile design, which necessitates customizing trial designs to incorporate both remote and site-based components. This customization is essential because not all studies can transition entirely to a decentralized format. Regulatory agencies support DCTs, thanks to their flexibility during the pandemic. This makes early and regular engagement with regulators essential for compliance. Prioritizing

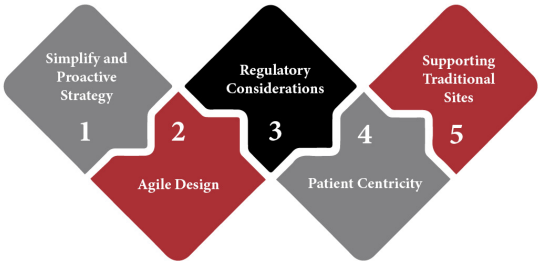


Fig. 1. Key considerations for implementing a decentralized study design.

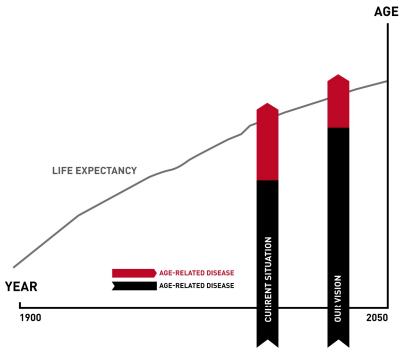
patient-centered approaches through ongoing dialogue with patients and their support networks is key in order to enhance the patient's experience. Additionally, sponsors must support traditional sites transitioning to virtual study sites by providing adequate training, communication, and ongoing support to ensure a smooth adaptation to DCT practices [16], [17], [18].

C. Digital health technologies in decentralized clinical trials

Digital health empowers individuals and communities to manage their health effectively through convenient and cost-effective means. The healthcare industry is rapidly adopting remote solutions and interconnected devices to triage and treat patients. These digital capabilities are integrated into various healthcare devices, generating continuous health data. This data is used to support patients, predict and prevent adverse outcomes, and inform better therapies, leading to improved overall health [19]. Digital health technology in DCTs reduces participant burden and improves trial efficiency. It includes remote data collection through different technologies, electronic informed consent, and telemedicine for virtual visits with healthcare providers. Electronic platforms simplify patient-reported outcomes collection, while smart devices manage remote medication adherence. Real-time data monitoring allows early detection of safety issues and timely interventions. Technology-driven participant engagement strategies, like mobile apps and online communities, enhance the trial experience, fostering communication and community among participants. Overall, digital health technology streamlines DCTs, benefiting both participants and investigators. More and more, digital health technology is finding its way into application which enables and facilitates the implementation of decentralized clinical trials. A study conducted with more than 200 healthcare decision-makers from leading companies demonstrated the digital health technology trends since 2021 [20]. Healthcare wearables, like fitness trackers and heart monitors, are a highly promising and exciting field. These devices can continuously monitor and transmit biometric data to users or connected platforms. The data collected serves various purposes, including offering guidance, timely interventions, and conducting analysis for improved healthcare outcomes [19]. Healthcare wearables and other digital health technologies are contributing to more efficient decentralized clinical trials. Healthcare providers are focusing on patient monitoring, diagnostic equipment, and wearable devices, with pharmaceutical devices and patient tracking leading in testing and validation. However, in-body devices like pacemakers and infection detection devices face challenges in the certification process, causing potential delays in deployment due to regulatory approvals [19].

III. Elaboration of concept for decentralized studies for VASCage GmbH

A. VASCage GmbH



VASCage envisions a future where the ageing community enjoys an extended and healthy lifespan through the promotion of vascular health. Distinguished by its cutting-edge scientific research in stroke, the company pioneers the development of innovative products, therapies, technologies, services, and solutions. Its primary focus encompasses prevention, diagnosis, therapy, recovery, and rehabilitation for stroke.

The mission of VASCage is to conduct top quality clinical trials and life science research to translate scientific findings into new products, processes, and services. With regard to clinical trials, both in academia and industry, VASCage effectively manages and supports the implementation of national and international trials. Its diverse trial portfolio encompasses epidemiological research, pharmaceutical products, diet and nutrition, medical devices, and therapeutic interventions. Collaborating closely with multiple clinical centers and stroke units, VASCage facilitates access to relevant patient groups and population cohorts while leveraging the comprehensive expertise of its partners.

Furthermore, VASCage maintains a global network of interdisciplinary experts. Collaborating with esteemed partners across more than 15 countries and 3 continents, the company actively seeks new cooperative ventures. This network comprises over 20 associated partners, 15 scientific partners, and 35 company partners, collectively fostering an environment of cross-disciplinary collaboration and innovation [21].

Roughly speaking, there are three different types of clinical studies that VASCage is focusing on. These are shown in figure 2.

Fig. 2. VASCage's three distinct categories of clinical studies

Clinical Trial: Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous [22]. A clinical investigation is a systematic investigation of one or more human subjects, undertaken to assess the clinical performance, effectiveness, or safety of a medical device [23]. Biomedical Research: clinical studies that do not fall under the provision of CTR or MDR, e.g. non-interventional studies (NIS), biomedical research projects (BMRP), registries, biobank studies, etc.VASCage is actively pursuing the implementation of a decentralized clinical trials concept as one of its future projects. This thesis aims to lay a solid foundation for the project, contributing to its successful realization.

B. Stakeholder Impact: External Environment Insights and recommendations

1) Expertise interviews: The interview portion within this thesis is centered on a specific section where valuable data and insights concerning DCTs were obtained through engagements with experts in the field. These interviews served to gather firsthand information, perspectives, and experiences directly from these experts. To ensure a comprehensive exploration of the intricate aspects surrounding DCT implementation, a total of four experts representing various disciplines were selected to participate in the interviews. These experts encompassed diverse backgrounds such as medical professionals, clinical experts, financial analysts, and innovation and (clinical) project management professionals. This deliberate selection aimed to gather diverse perspectives on the topic and provide a multifaceted understanding of DCTs.It's important to note that the results of these interviews partially guided the selection of the specific issues to be addressed in the work.

2) Patients survey: The survey component of this thesis was focused on a specific section where patients were engaged to collect valuable data and insights regarding DCTs. The survey served to gather firsthand information, perspectives, and experiences directly from the patients themselves. To ensure a comprehensive exploration of the intricate aspects surrounding the implementation of DCTs, a diverse group of 21 patients was carefully selected to participate in the survey. This group encompassed individuals with varying medical conditions, age ranges, and geographical locations. By deliberately selecting this diverse group, the aim was to gather a wide range of perspectives and provide a comprehensive understanding of the implications and advantages of DCTs from the patient's standpoint. While it is acknowledged that a sample size of 21 patients may not be considered statistically significant for drawing definitive conclusions, these findings provide a valuable glimpse into the opinions of the patients and offer a holistic assessment of their perspectives. It is important to note that these results serve as an initial overview, offering a preliminary understanding of patient viewpoints. A larger and more diverse population sample would certainly enhance the robustness of the conclusions drawn.

C. Recommended solutions for VASCage's clinical project management

To ensure a well-designed study, it is crucial to address several key factors related to decentralized research. These factors encompass the project designs' nature, the target population, available technology, regulatory and ethical guidelines, and data security. This section is dedicated to addressing the unique deviations and variations that arise in clinical project management when VASCage is implementing a DCT concept. It explores the anticipated modifications and discrepancies at each stage when compared to managing a traditional CT project.

1) Deviations of study design and protocol development: One of the initial stages in project management involves identifying the appropriate study design that is suitable for the clinical project. A wide range of decentralized and hybrid CT designs are available, providing diverse options. Depending on the purpose of the trial, different design types can be used. Figure 3 demonstrates a visualization of the board spectrum existing between the three main designs.

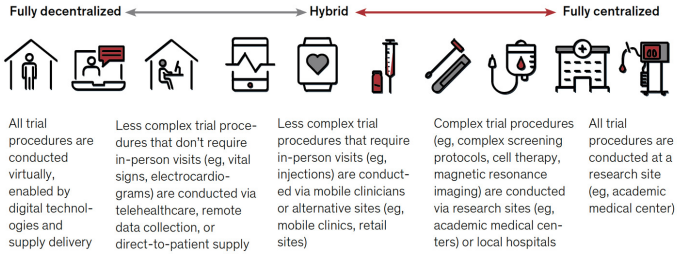


Fig. 3. Clinical trials designs [6].

VASCage must select a design based on the trial's objectives, purpose, complexity, size, endpoints, and available options. Trials can be fully virtual but are mainly limited to specific scenarios with well-characterized drugs/devices. Most trials will incorporate decentralization elements as needed for assessing endpoints, patient populations, and treatment facilitation [6]. A well-designed study protocol defines the study's objectives, methods, and procedures. In the context of decentralized studies, it is essential to consider aspects such as remote data collection, participant engagement, and the challenges of technology. Collaboration among stakeholders

is vital. Once the project's position is clear, further decisions can be made in the following sections.

2) Deviations of participant recruitment and engagement: For participant recruitment in decentralized studies, VASCage may consider involving leveraging digital channels such as online advertisements, social media platforms, and electronic health records. Engaging participants in decentralized studies requires clear communication, timely feedback, and incentives to promote active involvement. Strategies for participant engagement may include virtual support groups, educational webinars, and remote check-ins to enhance participant experience and retention. Concerning the informed consent process, VASCage may obtain the informed consent electronically through e-consent platforms or secure online portals. Investigators must provide comprehensive study information, clearly explain the study purpose and procedures, and provide avenues for participants to ask questions and withdraw consent anytime if needed [24]. Also, VASCage may establish channels for participants to seek assistance, address concerns, and provide ongoing support throughout the study. The company may provide adequate support to trial participants and/or investigators to facilitate the appropriate conduct of their tasks [24]. A viable approach to addressing this issue involves implementing a robust communication platform. Numerous HIPAA-compliant options are available, such as Rocket.Chat [25], RXNT [26], SolutionReach [27], Jotform [28], RevenueWell [29] and Weave [30], etc. Alternatively, VASCage could potentially develop a sustainable, long-term solution, which is developing its own communication platform.

3) Deviations of data collection and management: When collecting the data in decentralized studies VASCage can implement various methods such as electronic surveys, wearable devices, smartphone apps, and telehealth consultations. Data management requires secure storage, adherence to privacy regulations, and protocols for data transfer and integration. There is a rising model known as "direct-to-patient" or "remote" that focuses on collecting patient data within the comfort of their own homes or in their natural environment during a study. As a result, VASCage may adopt a hybrid approach by incorporating both traditional site-based visits and remote (from home or local doctor's office) [31]. The use and customization of electronic data capture (EDC) systems allows data collection forms to be tailored and specific validations to be implemented based on the nature of the study design. Additionally, remote and centralized monitoring employs technology to have an overview of study activities while ensuring data quality and verifying adherence to protocols from a distance.

4) Technological necessities: Selecting the right software for DCTs comes with challenges in ensuring data security and privacy. The priority is safeguarding patient health data by avoiding email and shared drives, choosing the right technology that takes into consideration privacy requirements, and demonstrating compliance with clinical research guidelines. Consequently, the new technology may require a large upfront investment increasing the costs for the implementation process. Moreover, VASCage should also consider the time and ease of implementation, emphasizing user-friendly software. Vendor-provided implementation and training programs are important, as well as post-implementation customer support, to ensure the team's comfort and proficiency with the chosen technology. During DCTs, both VASCage and participants may need to adapt to new technology, including wearable devices, smartphone apps, and computer software. This adds complexity, especially if participants are not familiar with the software. User-friendly software is crucial for both parties, and VASCage members should be trained to support participants in using the technology. By offering in-person orientation or appointments at the research site, VASCage staff can ensure that participants are using their devices or applications correctly and address any queries they may have. This hands-on approach promotes participant confidence and engagement in the decentralized trial process [14].

5) Ethical and regulatory considerations: VASCage should take into account essential ethical considerations when implementing DCTs. These considerations encompass the dynamics between patients and healthcare staff, the social dimension of patient care, data integrity and security, protection of personal data, potential risks to health and safety, inclusivity and representation, evaluation by ethics committees, and a dedicated focus on bioethics [32]. Overall, the ethical considerations revolve around maintaining patient well-being, ensuring data privacy and integrity, promoting inclusivity, and maintaining rigorous oversight and evaluation of DCTs to uphold ethical standards in clinical research. EMA has been actively involved in exploring and offering guidance on DCTs. While specific regulations solely dedicated to DCTs were absent for a considerable period, EMA took proactive steps to adapt its existing guidelines to suit decentralized approaches. Notably, in December 2022, EMA published a recommendation paper (RP) on decentralized elements in clinical trials, which included relevant guidelines pertaining to decentralized studies. The most important guidelines are the Guideline on Good Clinical Practice (GCP) [33], the Reflection Paper on Risk-Based Quality Management in Clinical Trials [34], the Guideline on Data Monitoring Committees [35], and the Guideline on Good Pharmacovigilance Practices (GVP) Module VI [36].

Taking into consideration the VASCage's location in Austria, the responses of Austria to the 15 questions outlined in the recommendation paper on decentralized elements in clinical trials [24] were analyzed. The specific focus is on the questions that received affirmative answers, which account for 5 out of the total 15. These responses indicate that:

- The delivery of Investigational Medicinal Products (IMPs) is feasible only if conducted directly to investigators from licensed distributors, manufacturers, or pharmacies situated in other European Union (EU) Member States, provided they are legally authorized to perform this function in their country of origin.
- The delivery or dispensing of authorized IMPs directly to trial participants from pharmacies not affiliated with the clinical trial sites is permissible. This includes the use of authorized investigational medicinal products in ways that deviate from their Summary of Product Characteristics (SmPC).
- Regarding the eConsent process related to the recommendation paper on decentralised elements in clinical trials

(RP) section 3, electronic signatures are accepted as valid alternatives to wet ink signatures.

- Regarding trial participant oversight and home visits concerning RP sections 2 and 5, Principal Investigators (PIs) have the option to delegate specific tasks under their responsibility to qualified external healthcare providers for those delegated tasks. Given that some tasks or procedures conducted at home may require supervision by an investigator (e.g., a physician), remote supervision by the physician is permitted. Lastly, with regards to trial monitoring using remote access to source data, as outlined in RP section 7, monitors or auditors are allowed to remotely access medical records for monitoring purposes.

6) Summary of considerations for the clinical project management: The recommended solutions are visualized and categorized into short-term and long-term strategies, as illustrated in Figures 4 and 5.

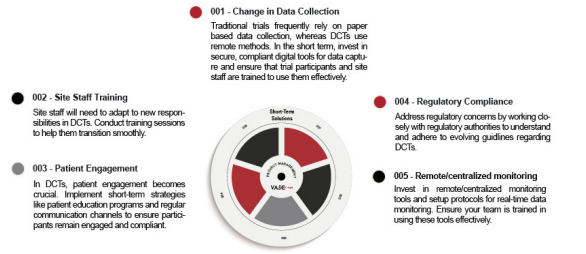


Fig. 4. Visualization of summary of considerations for the clinical project management: short-term solutions

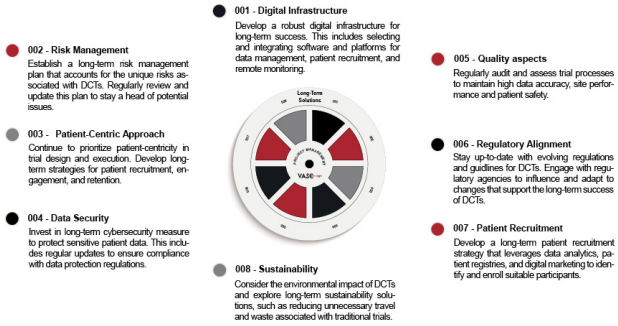


Fig. 5. Visualization of summary of considerations for the clinical project management: long-term solutions

IV. Conclusion

In summary, this paper presents a tailored framework designed specifically for the VASCage GmbH to facilitate a seamless transition from traditional clinical trial practices to decentralized clinical trial methodologies. The investigation of decentralized organization and its implications for clinical project management reveals a dynamic landscape that presents both opportunities and challenges. Embracing decentralization can lead to enhanced efficiency, faster advancement, and improved adaptability within project teams. However, it also brings about complexities related to coordination, data administration, and accountability. The challenges in project management within decentralized structures underscore the importance of robust communication channels, well-defined possibilities, and a shared understanding of objectives. It is clear that a delicate equilibrium must be struck between granting autonomy to teams and establishing mechanisms for cross-team coordination, regular updates, and shared goal attainment. This paper highlights the important role of technology in facilitating decentralized clinical project management. Tools that enable seamless communication, resource sharing, and progress tracking are essential for overcoming geographical and organizational barriers. Through the utilization of technology, organizations can bridge the gap between decentralization and effective collaboration. Consequently, the potential disparities and optimizing project workflows are reduced. While starting the transition from traditional CTs to DCTs, in clinical project management, organizations must acknowledge that a standardized approach does not apply. Each project, team, and context may require a customized strategy that embraces the principles of decentralization while considering the unique complexities of the industry, project scope, and team composition. To achieve this circumstance, the careful selection of design elements, participant recruitment strategies, and data collection and management methods must occur. Additionally, it is important to consider the deviations arising in the four main clinical project phases while ensuring ethical and regulatory standards. In essence, the exploration of decentralized studies in clinical project management highlights the transformative potential of reshaping organizational dynamics. It illuminates the journey toward finding a balance between decentralization and alignment, individual autonomy, and collective purpose.

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