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Développement de protocoles pour les essais cliniques décentralisés : les considérations nécessaires pour atteindre des résultats cliniquement et scientifiquement significatifs en s'appuyant sur la variabilité, l'intégrité et la traçabilité du data généré.

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Summary:

I. Abbreviations:

- DCT: Decentralized Clinical Trials
- CT: Clinical Trials
- SDTM: Study Data Tabulation Model
- eCOA: Electronic Clinical Outcome Assessment
- CRO: Contract Research Organization
- CRA: Clinical Research Associate
- IMP: Investigational Medicinal Product
- AE: Adverse Event
- ClinRO: Clinician-reported outcomes
- PA: Physical activity
- PRO: Patient-reported outcomes
- ObsRO: Observer-reported outcomes
- CF: Cystic Fibrosis
- ICC : intraclass correlation coefficient
- FEV1: Forced Expiratory Volume in 1 second
- SDV: Source Data Verification
- SDR: Source Data Review
- SDV: Source Data Verification
- SDR: Source Data Review
- Dtp IMP: direct-to-pation IMP
- GDRP: General Data Protection Regulation*
- HCP: Healthcare professionals
- ICH-GCP: International committee for harmonization- Good clinical practice

II. Introduction:

The decentralized clinical trial (DCT) approach is increasingly recognized for its potential to accelerate the development of therapeutic interventions. Central to DCTs is patient centricity, which involves designing and conducting trials that prioritize participants' needs, preferences, and experiences. These trials leverage technologies such as electronic clinical outcome assessments (eCOAs), eConsent, and telemedicine to capture data in real time. The extensive data generated by these technologies must be analyzed ethically and translated into clinically meaningful results. This necessitates a well-designed adaptive protocol with detailed procedures, appropriate endpoints, and biomarkers.

In this master's thesis, we address the lack of standard terminology in decentralized clinical trials and provide insights into the key considerations for designing and implementing DCTs. Our research involved conducting interviews with experts and professionals experienced in DCT implementation, alongside a thorough literature review.

III. Methods:

To develop the research and writing plan, an initial general literature search was conducted using Google Scholar with the following keywords: "main considerations for DCTs," "main considerations for decentralized clinical trials," "decentralized clinical trials design," "clinically significant data," and "decentralized clinical trials." While the results from this initial search were somewhat vague and required further investigation, they helped us outline the main topics for the plan, especially when combined with a literature review on the primary considerations of traditional clinical trials (CTs). This approach also allowed us to build a robust vocabulary for CT design in general, which could then be integrated with specific DCT terminology.

The literature review was organized into two main sections: Part I focused on the design of the DCT protocol, and Part II on the implementation of DCT. The writing plan was subsequently divided into eight parts. The following table details the number of articles

selected for each part, the articles deemed relevant, and the keywords used in search engines to locate them.

part	Number of articles preselected	Number of eligible articles	Key words used
Definition of DCTs	N=4	N=2	"Decentralized clinical trials "definition" "defining"
Endpoints	N=25	N=12	"DCT endpoints", "digital endpoints" and "clinical trials", "remote endpoints'' and "clinical trials", ''considerations'' and ''biomarkers"
Flexible design	N=10	N=6	"Main consideration" and "flexible clinical trial design", "adaptive clinical trials"
Dtp dispensing	N= 5	N=3	"IMP dispensing" and "DCTs" and "IMP direct to patient dispensing" and "clinical trials and "Europe"
Centralized monitoring	N= 10	N=3	"monitoring" and "DCT" or "centralized monitoring" and "risk-based monitoring" and "remote data monitoring"
Remote patient data monitoring	N= 13	N=11	"Data collection technologies", "eCOA" and "DCT",

			"eConsent", "informed consent" and "DCT"
Telemedicine	N=6	N=5	"considerations" and "telemedicine" and "in Europe"
Safety monitoring	N=4	N=3	"monitoring" and "DCT", "remote safety monitoring", "AE reporting" and "DCT"

Table 1 Distribution of Selected Articles and Keywords Used for Literature Review on Decentralized Clinical Trials (DCTs)

Between March and May 2024, semi-structured individual interviews were conducted with representatives from Contract Research Organizations (CROs), study coordinators, Clinical Research Associates (CRAs), and project managers. With the consent of the participants, some interviews were recorded, transcribed, and subsequently analyzed.

Potential participants were contacted through various methods: LinkedIn (n=15), email (n=3), and face-to-face interactions (n=2). Additionally, a recruitment post was uploaded on LinkedIn, with a screenshot of the post included in the annex section.

In total, six interviews were successfully conducted: two with study coordinators, one with an eCOA library director, two with senior CRAs, and one with a project manager. We were hoping to conduct interviews to capture the insight of data managers also but it was a very hard task due to their busy schedule and the thigh deadline.

The interview guide focused on three main questions:

1. What do we know?
2. What do we not know?
3. What needs to be developed?

The questionnaires are found in the annex section (annex 2)

We generally observed a lack of standardized terminology when referring to decentralized clinical trials, particularly among study coordinators. This issue is addressed in the following section. A summary of participants' responses is presented in the table below.

	What do we know?	What do we not know?	What needs to be developed?
Library director	- patient reported outcomes have become a new benchmark for regulators and payers to measure the quality of a drug or therapy -some CROs offer a standardized library of pre-built assessments is available for use in various trials to achieve patient-reported outcome objectives. Sponsors can quickly integrate these eCOA tools into their trial process.	-The impact of varying levels of patient access to technology and internet connectivity on trial outcomes needs further exploration. -the use of AI to further optimize (eCOA) libraries	-More (eCOA) should be added to the library and licensed -the sensibilization of sponsors on the impact of the use of licensed (eCOA) on the regulatory process and study initiation time frame
CRAs and project manager	DCTs are designed to be more flexible and patient-centric, often incorporating real-time or quasi-	-There is limited data on the long-term patient compliance and	-improved vendors engagement and proper training to the ICH-GCP requirements.

	real-time monitoring through wearable technology. -Sponsors need to engage early in the regulatory process because it might be more delicate to obtain CT authorization. - Centralized and risk-based monitoring (RBM) are critical for ensuring data quality and patient safety in DCTs.	retention in fully virtual trials. -How different regulatory environments will adapt to and standardize the rules for DCTs is still uncertain. -The long-term efficacy and safety outcomes of DCTs compared to traditional clinical trials are not fully known.	-Enhanced analytical tools for real-time data monitoring and interpretation. -improved engagement of investigator sites in the set-up of DCTs and communication on patient's retention and potential barriers.
Study coordinator	-DCTs are designed to reduce patient's burden to travel to study center and can potentially enhance patient's recruitment. - The high cost of the design and implementation of DCTs	-More information about the legal reliability of informed consent collection electronically. - How to deal with patients' technical issues in a timely manner. -Study coordinators might not be aware of the positive impact of capturing data in real-time.	-need for proper training to increase patient's retention and sensibilization of the patient centricity of DCTs and hence their crucial role in the conduct of these trials. -need for the engagement of centers early in the design process

			-Comprehensive training programs for investigative staff and patients on the use of digital tools. -Establishment of robust support systems to address technical issues and ensure smooth trial conduct.

Table 2

IV. Defining Decentralized Clinical Trials: Addressing Ambiguity in Terminology and Methodology

Decentralized clinical trials (DCTs) have emerged as an innovative approach to conducting clinical research. However, from my literature review and experience in the field I have noticed that its definition is ambiguous amongst stakeholders so precise quantification is not easy, given the extremely varied breakdown in terms of procedures used (from more or less hybrid to fully decentralized). In addition, the lack of uniform terminology in relation to DCTs makes it difficult to identify sensitive, specific search keys for exploration of the available databases. [2]

Moreover, the lack of standardized terminology for describing this operational model impedes discussions between stakeholders, because identical terms can be used to describe different operational clinical trial models or even different methodological aims, hampering discussions of the scope, suitability, and acceptability of trial models and specific trial activities [1]

As such, It is crucial to give a proper definition of decentralized clinical trial.

This lack of precision is due to many factors related to the dynamic nature of clinical trials with new methodologies and best practices continually emerging, the evolving landscape

of digital health technologies enabling the implementation of new methodologies as well as the diverse implementation of DCTs as they encompass a wide range of strategies, including virtual visits, remote monitoring, mobile health applications, wearables and the interdisciplinary nature of these trials and clinical trials in general that requires a collaboration between different teams and stakeholders including researchers, healthcare provides, technology developers, regulatory agencies and patients. Each of the stakeholders may have a different perspective on what constitutes a decentralized trial.

In addition to the lack of standardized regulations across different regions, All this factors make it challenging to establish a one-size-fits-all definition.

In order to tackle this problem and provide an overview of the terminology homogeneously, a thorough literature review was made in order to map the terminology.

As a result, we can define Decentralized clinical trials as a type of clinical research that utilizes telemedicine, mobile/local healthcare providers, and/or mobile technologies to manage participants within their usual environment. DCTs are characterized by less dependence on traditional research facilities or specialist intermediaries for data collection. They leverage tools, such as telemedicine, sensory-based technologies, wearable medical devices, home visits, participant-driven virtual healthcare interfaces, and direct delivery of study drugs and materials to participants' homes [1] in contrast of some commonly used like:

- remote clinical trial: where the term "remote" primarily emphasizes the distance between participants and trial sites, highlighting the ability for participants to participate without being physically present.
- virtual clinical trial: where the term "virtual" emphasizes the virtualization of trial activities, minimizing or eliminating the need for physical interactions between participants and researchers.

In summary, while there is some overlap between the terms, decentralized clinical trial encompasses a broader concept involving the distribution of trial activities across multiple locations and the involvement of local resources. As referring to a trial as a remote one can cause confusion because the activities are not done remotely in the perspective of the patient. Rather, the opposite is typically envisioned, because trial activities are centered around, or moved close(r) to, the participants' surroundings. [1]

V. The Importance of Endpoint Selection in Clinical Trials: Balancing Traditional and Digital Measures for Improved Decision-Making

It is a responsibility of those who design and conduct trials to choose endpoints which will influence decision-making by clinicians and policymakers. Endpoint selection is a complex process. End-users bring differing needs and perspectives. Poor selection of endpoints makes interpretation and implementation of findings difficult or impossible, limits evidence synthesis, and thereby diminishes the value of the research, resulting in wasted use of resources [3]

Selecting appropriate endpoints is critical in designing DCTs to ensure that the study adequately evaluates the safety and efficacy of the investigational product or intervention while considering the practicalities of the procedures.

These endpoints must be clinically significant and effectively enable the translation of promising results into proofs to support the approval of new medical products.

Conceptually, an ideal endpoint should be a valid and applicable measure of how a patient feels, functions or survives. [4]

However, it is important to note that remote endpoints require further validation before they are ready to be used as primary clinical trial endpoints, including (depending on the endpoint) evaluation of feasibility, accuracy relative to in-person collection and association with other clinical outcomes.

1. Comparison between Traditional and Novel Endpoints

Digital endpoints and traditional endpoints serve the same purpose in clinical trials, but they differ in their measurement methods, data sources, and sometimes in their ability to capture real-time, objective data. We propose the following table to synthesize our findings in the comparison of the main attributes of these two types of trials.

traditional endpoints	Digital endpoints
accepted status as the gold standard in clinical trial design	may require a more focused and pragmatic approach
may lead to inter-rater variability among clinicians, affecting the reliability and consistency of data.	often capture objective, quantitative data, reducing the influence of subjective biases and improving the accuracy and reliability of measurements.
measured during scheduled clinic visits, limiting the frequency and granularity of data collection compared to real-time monitoring.	facilitate continuous monitoring of participants' health parameters and behaviors over extended periods, capturing fluctuations and trends not observable with traditional endpoints.
Standardized scales and assessments used for traditional endpoints enable comparability across different studies and populations.	may lack established validation and standardization procedures, requiring rigorous validation studies to ensure accuracy, reliability, and comparability across different populations and settings.
often have a strong clinical basis and are well-established in medical practice, providing robust measures of efficacy and safety but analysis of datasets may be difficult because of their size and complexity.	can leverage advanced analytics, machine learning algorithms, and artificial intelligence techniques to analyze complex datasets and derive meaningful insights from large volumes of data.

Table 3 : Summary of main points of comparison between traditional endpoints and digital endpoints.

2. *Biomarkers vs clinical endpoints :*

Clinically meaningful endpoints relate to outcomes which capture how a person feels, functions or survives. These endpoints may be measured objectively or subjectively, and are either (i) reported by clinicians (ClinRO), which involves judgement or interpretation of clinical signs or events (such as stroke, myocardial infarct or cancer remission), (ii) assessed by standardized performance measures (6-min walk test), (iii) patient-reported (PRO), which are directly reported by patients (such as self-reported symptoms or function, or a measure of perceived quality of life) or (iv) observer-reported (ObsRO), such as a parent log of seizure activity in a child.

Non-clinical endpoints, including biomarkers, do not relate directly to how a person feels, functions or survives, but are instead objectively measured indicators of a biological or pathogenic process, for example a pharmacological response to a treatment intervention. Biomarkers may include blood tests (for example laboratory measures such as troponin and hemoglobin concentration or serological assays), tissue/fluid analyses (for example histopathological results), imaging results, or physiological measures (for example blood pressure) which are used for diagnostic, prognostic, monitoring (including safety) or predictive purposes [5]

3. *Main considerations for Digital endpoints:*

In order to use them as clinical trials endpoints, novel measurements should be demonstrated that they are fit-for-purpose. In other words, if they prove to be of near-identical or even superior value, they may eventually lead to reduced visits to the clinic and improved efficiency.

the main characteristics to consider when evaluating the validity of these endpoints can be summarized as follow:

- A good candidate endpoint must be accurate, reliable, and value-based and therefore directly measure meaningful outcomes for the individual subject (e.g., sleep, activity, pain, ability to move, gait) or be associated with important clinical outcomes (e.g., occurrence of mortality, morbidity, complications).
- the assessment or device must be usable, tolerable, and suitable for the intended users.

- It should have a plausible relationship with the studied disease or general quality of life.
- The technology used for the assessment must be easily usable, reliable, and reproducible.
- Data flow should be tested and validated.
- Intra-device and extra-device consistency.
- Compliance with regulations regarding audit trails and the storage and processing of source data.
- Amount of training and instruction necessary to ensure measurements are conducted correctly by patient must be well assessed.
- Must obtain a meaningful difference between patient group and control group results.
- The assessment should be Tolerable meaning minimally invasive and with minimal manual input in order to optimize retention and adherence to trial.
- It must be responsive to change in disease state.

4. *Validation Process:*

In order to make sure that all these criteria are met, a rigorous stepwise assessment framework was proposed by some researchers and tested on some digital endpoints.

The following diagram sums up the main stages of the validation approach, the main factors to consider during this assessment and the main questions to ask in order to do that.

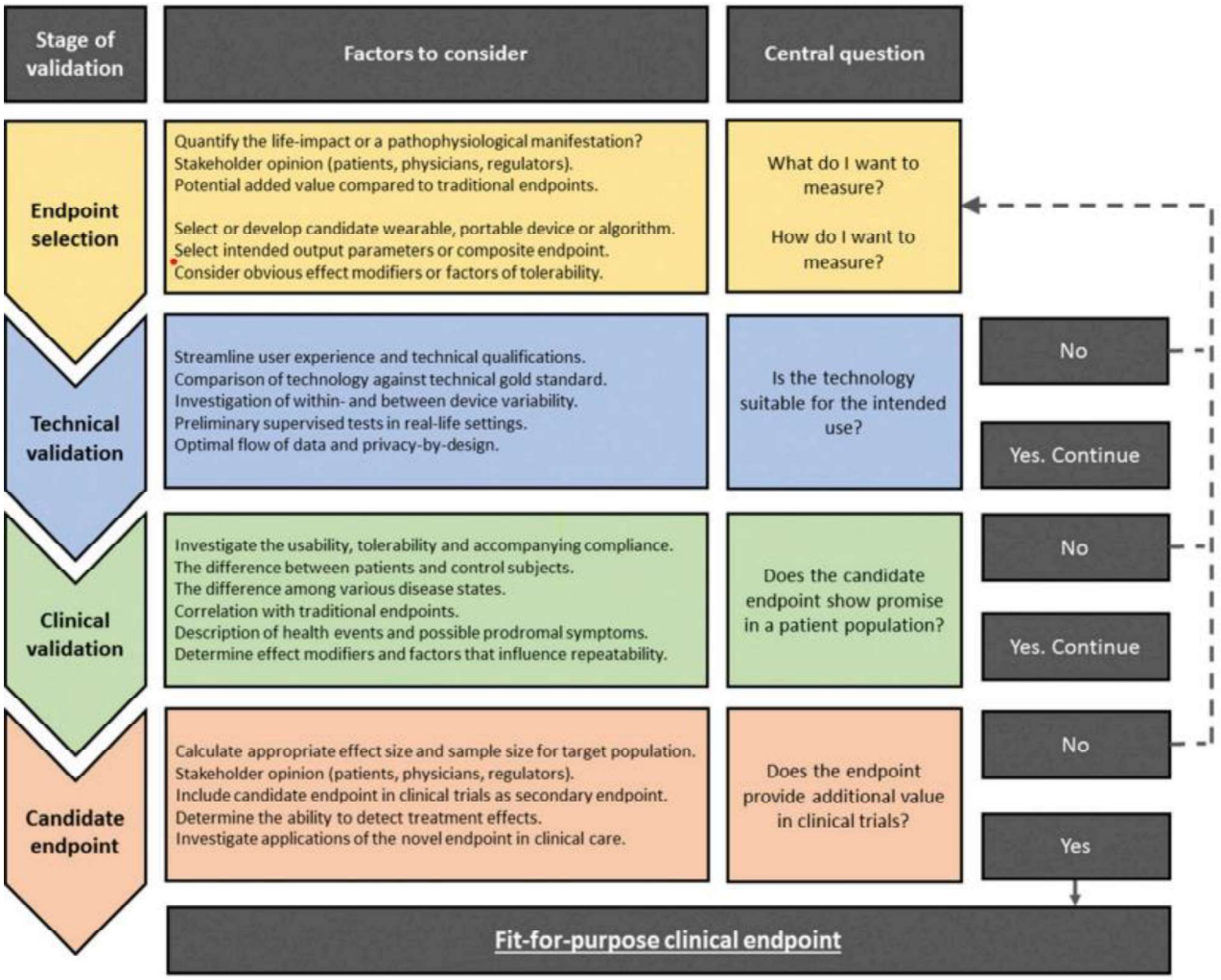


Fig. 1. Structured approach to developing a fit-for-purpose digital endpoint. Factors to consider during development and validation of novel digital endpoints. Source [8]

4.1. *Example: Validation of digital biomarkers for pediatric patients with asthma and cystic fibrosis:*

As an example of the application of the previously presented approach, a prospective cohort study including 60 children with asthma and 30 children with CF (aged 6–16 years) was carried out in order to clinically validate physical activity, heart rate, sleep and forced expiratory volume in 1 s (FEV1) as digital biomarkers measured by a smartwatch and portable spirometer in children with asthma and cystic fibrosis (CF). [6]

4.1.1. Endpoint selection:

The goal at this point is to obtain regulatory endorsement of the novel digital endpoint. Regulators advise early engagement to identify and define the "Concept of Interest" that underpins the digital endpoint from a regulatory point of view. This engagement also serves to identify appropriate regulatory interaction channels going forward and to discuss how a clinically meaningful change can be defined and investigated [7]

In the case of (M.D. KRUIZINGA ET AL. 200) study the endorsement was justified by the fact that relying on the self-parents reporting of symptoms of pulmonary diseases like asthma and cystic fibrosis may be biased and is considered subjective.

Additionally, new treatments have led to a slower decline of pulmonary function in CF patients and increasing numbers of patients have pulmonary function in the normal range while still perceiving a significant symptom load. [6] Similarly, pediatric clinical trials, which are difficult to conduct due to ethical and logistical barriers and low inclusion rates either rely on subjective endpoints or rare "hard" endpoints, such as hospital admission. Rare endpoints lead to unrealistically large sample sizes and long and costly studies, and although subjective symptom reports can be valuable from an investigational point of view, ideally, they should be collected with additional biomarkers that give a more objective indication of disease control. [9]

4.1.2. Technical validation:

The technical analysis sought to explore the technical validity of the Steel HR watch in free-living conditions included the averaging of Measured heart per hour, the calculation of average measurement error using the methods of Bland and Altman as well as Pearson correlations between Steel HR and ECG measurements and measurement error when wearing the watch on either hand were compared. It was concluded that average heart per hour is captured by the Steel HR watch with an acceptable measurement error.

The spirometer was already technically validated as it figures in the list of potential devices for candidate endpoint. (table 4)

Device/Sensor	Candidate Endpoint	Patient Domain
Accelerometer	Physical activity Steps Gait patterns Tremor analysis	Mobility Symptom severity Symptom severity Symptom severity
Blood-pressure meter	Blood pressure	Cardiovascular health
Camera	Dermatological assessments Treatment adherence	Dermatological health Compliance
Dynamometer	Muscle strength	Musculoskeletal health
ECG	Event detection	Cardiovascular health
Glucose monitor	Glucose	Diabetic control
Oximeter	Oxygen saturation	Pulmonary healthy
GPS	GPS mobility Location type	Mobility Social behavior
Light sensor	Light intensity	Environment
Microphone	Event detection Voice analysis	Clinical events Mood
PPG	Heart rate	Cardiovascular health
Smartphone	App use Phone use (calls, sms) Patient reported outcomes	Social behavior Symptom severity Symptom severity
Spirometer	Pulmonary function	Pulmonary health
Thermometer	Temperature	Infection control Thermoregulation
Touch screen	Response time Speed of typing Custom tests	Dexterity Coordination Various

Table 4 Potential devices and candidate digital endpoints for use in clinical trials outside of clinical units. Source [8]

4.1.3. Clinical validation:

A rigorous clinical evaluation of the candidate endpoints was performed to determine the potential clinical value. Five criteria were performed in this matter:

4.1.3.1. **Tolerability** was assessed by calculating the compliance during the study and the end-of-study questionnaire outcomes. The median (interquartile range (IQR)) of the proportion of expected measurements that were performed was calculated for each individual endpoint, as well as for endpoints aggregated together. For physical activity and heart rate, a watch wear time ⩾50% was required for that day to be included in statistical analyses [12, 27, 28]. Prior to study initiation, a subject with an overall compliance across all measurements. [6] the results are shown in the following table:

Assessment	Compliance (%)
Step count	100 (100–100)
Heart rate	100 (96–100)
Sleep	85 (74–89)
Pulmonary function test	79 (46–93)
Questionnaire	78 (68–96)
All assessments	88 (76–95)

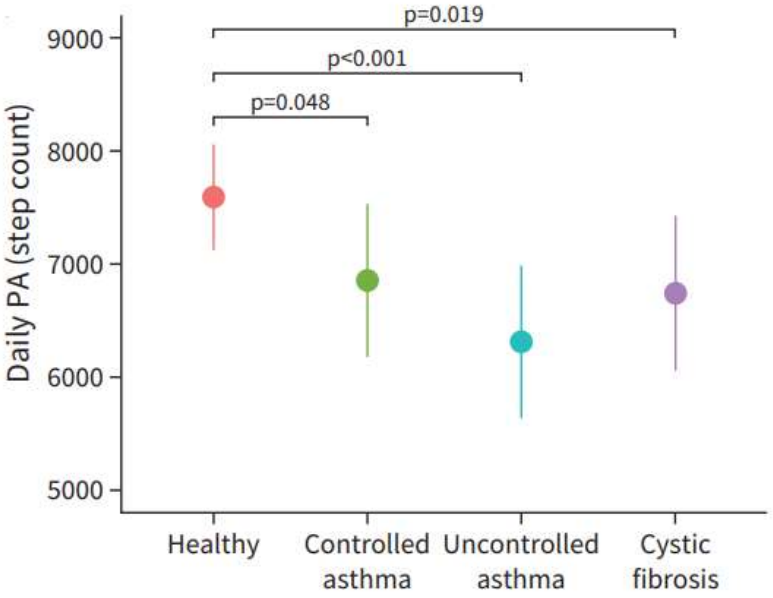
Data are presented as median (interquartile range).

Table 5 Compliance during all study period for all participants (n=90) [8]

4.1.3.2. **Intra-subject variability** was estimated for each condition and candidate biomarker via mixed effects models. For each condition (asthma, CF and healthy) and candidate biomarker, a separate model was fitted with subject as random intercept. The intraclass correlation coefficient (ICC) was calculated by dividing the random intercept variance by the total variance [6]. Which showed very good correlation between the different subject classes.

4.1.3.3. **The difference between patient groups and healthy subjects** was calculated with a mixed effects model with condition (healthy, controlled asthma, uncontrolled asthma or CF) as fixed effect and subject as random effect. [6] As an example, the following graphs display the difference between healthy participants and the ones with asthma and cystic fibrosis in : a) daily step count b) Heart rate in bpm.

a)



b)

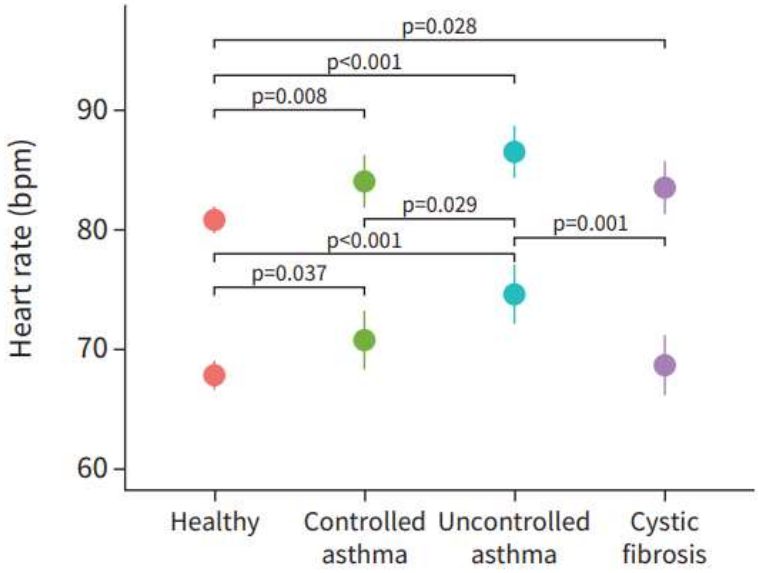


Figure 2: Difference between patients and control group a) Estimated marginal mean physical activity per day (daily PA) for the four study groups. b) Estimated marginal mean daytime and nocturnal heart rate per day. [6]

4.1.3.4. **Correlation with Existing Disease Metrics** To evaluate whether a change in a traditional endpoint, in this case symptom questionnaire scores, corresponds with a change in novel biomarker outcomes, the relationship between candidate endpoints and a symptom questionnaire was analyzed via mixed effects models. [6]

4.1.3.5. **Responsive to Change in Disease State** The final step before declaring a candidate endpoint fit-for-purpose is to investigate whether the endpoint will respond to changes in burden of disease. In this study, describing the change in disease was related to asthma and CF exacerbations which are defined as, respectively, the worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome [10] and as the need for additional antibiotic treatment as indicated by a recent change in symptoms or decrease in pulmonary function. [11]

VI. Flexibility and Adaptability in Decentralized Clinical Trial Designs

1. Definition:

In the decentralized clinical trials literature, the term « flexible » and « adaptive » were frequently used to describe the protocol design. That highlights the need for a flexible design as it accommodates the adoption of patient centric approaches, helps incorporating virtual Services and Technologies: DCTs often involve the use of digital technology, including real-time or quasi-real-time monitoring with wearable technology [14]. A flexible design allows for the integration of these technologies at appropriate points in the trial timeline [15], allows easy data reconciliation and vendor management throughout the study. Additionally, DCTs can range from completely virtual to partially decentralized with hybrid approaches. A flexible design allows for adaptability depending on the specific needs of the trial. Furthermore, DCTs often leverage real-world data sources, such as electronic health records and patient-generated data. Flexible designs facilitate the integration of these diverse data streams, providing a more comprehensive view of participants' health status and treatment outcomes.

Flexible clinical trials are designed to be adaptable, allowing for changes to the trial's course based on accumulating results. Adaptive designs allow for modifications to key

components. Unlike conventional designs, where the learning typically occurs after the trial is completed, adaptive designs intend for continual learning as the data accumulate.[12] It is said that trials with an adaptive design are often more efficient, informative and ethical than trials with a traditional fixed design since they often make better use of resources such as time and money, and might require fewer participants [13]

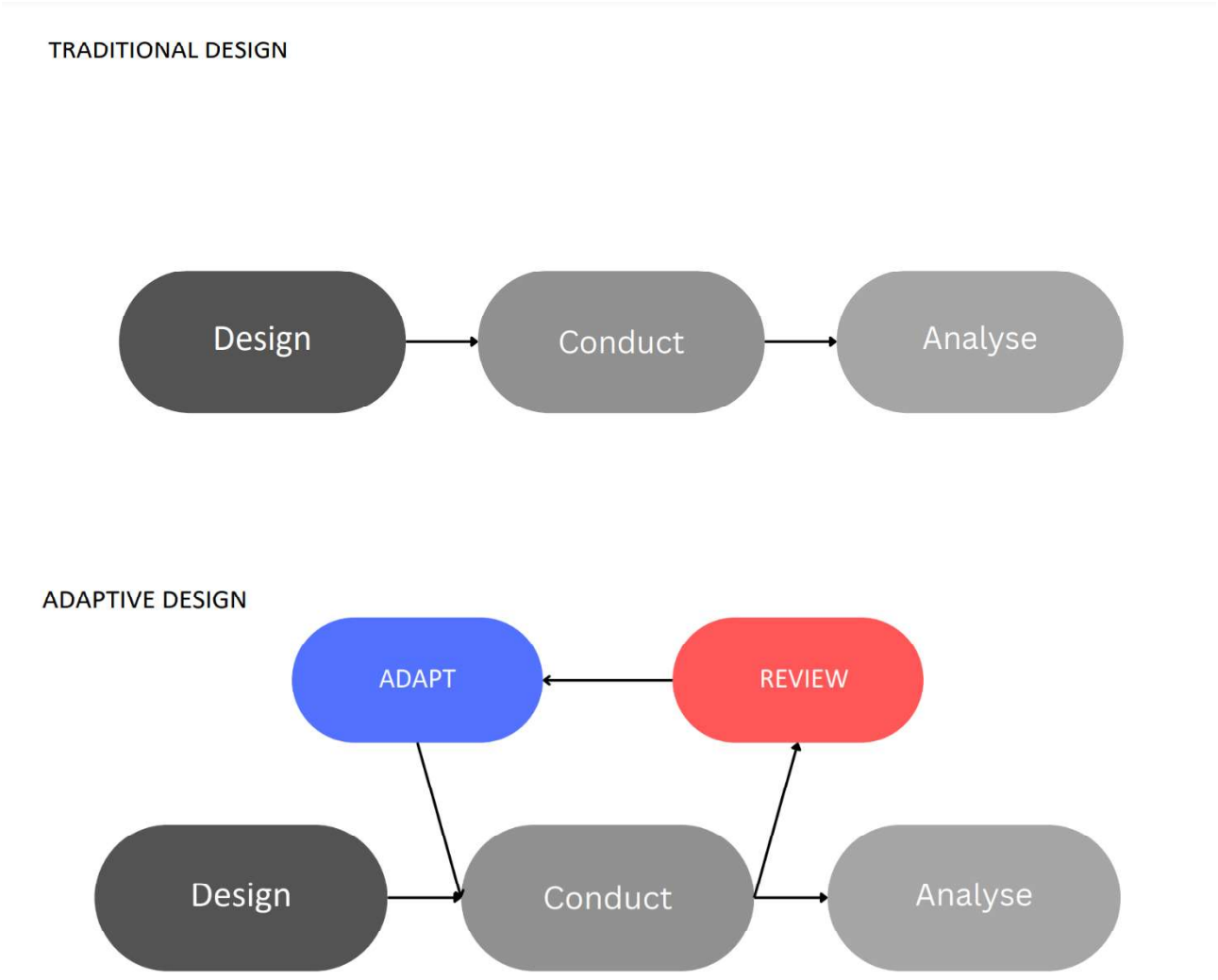


Figure 3 Schematic of a traditional clinical trial design with fixed sample size and an adaptive design with pre-specified review(s) and adaptation(s)

2. Main considerations for the adoption of adaptive clinical trials:

First of all, it is crucial to pre-specify decision rules before starting the trial and preset quantitative criteria0s for these decisions. The outcome for the decision rule should be clinically important and sufficiently correlated with at least one of the trial's primary outcomes. If the outcome fails to meet these criteria, the clinical merit and statistical robustness of any trial adaptation is likely to be inadequate. [16]

Additionally, Statistical planning is critical for any clinical trial design. For adaptive designs, the statistical analysis plan comprises the simulation, the interim analysis to inform potential adaptations, and the final analysis of the completed trial. Similarly to conventional trial designs, a number of factors such as observed and expected effects, trial budget, and total maximum sample size need to be considered. [16]

VII. Direct to patient Investigational Medical Product dispensing:

1. *Different models:*

For DCTs involving IMP delivery directly to trial participants, additional challenges regarding IMP accountability may need to be addressed. [17] the considerations differ according to the nature of the IMP, stability, storage and route of administration.

1.1. ***Investigative site-to-patient Model:*** in which the IMP is shipped from the investigative site or site's pharmacy to the participant's home or other address. [18]

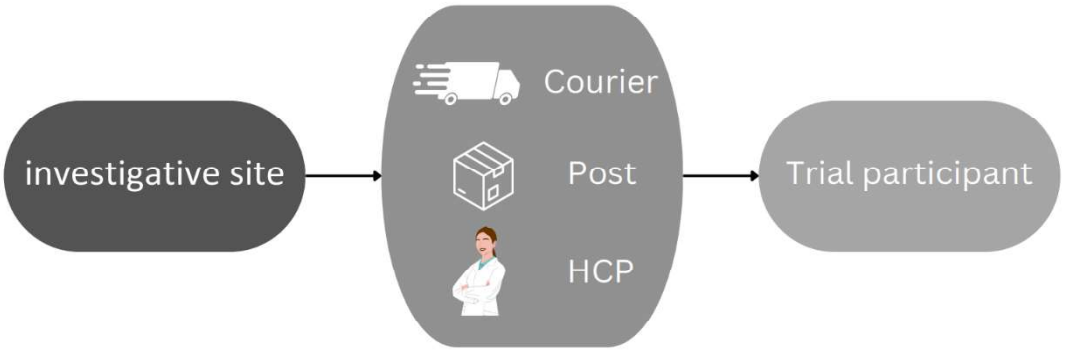


Figure 4: A schematic of the Investigative site-to-patient Model and means of IMP Delivery.

1.2. Central pharmacy/ pharmacy depot-to-participant Model: in which the IMP is shipped from a central (or remote) pharmacy depot with distribution facilities under the control of a pharmacist, and not the investigative site's pharmacy. In a multicenter clinical trial, one site's pharmacy could act as a central pharmacy, shipping the IMP to the trial participants. This can also include cross-border shipments. [18]

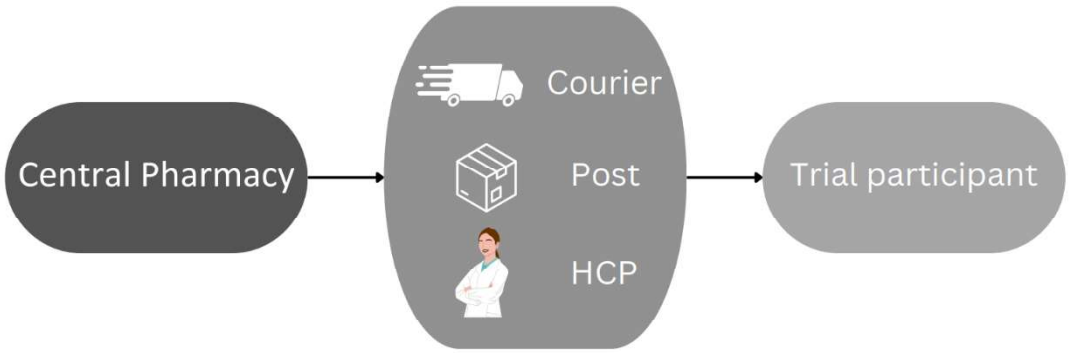


Figure 5: a schematic of central pharmacy/ pharmacy depot-to-participant Model and means of IMP Delivery.

1.3. Local pharmacy-to-participant Model in which the IMP is picked up by the participant or legal authorized representative at, or shipped from, a local pharmacy. A local pharmacy is a community or hospital pharmacy that is not the investigative site's pharmacy. [18]

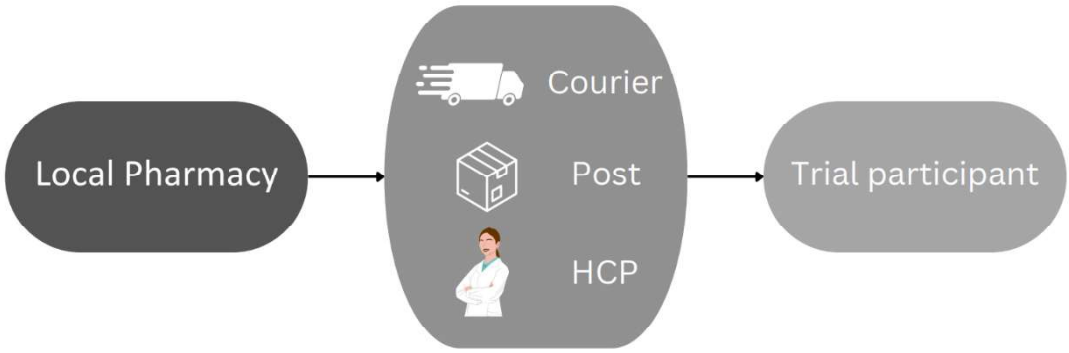


Figure 6: a schematic of Local pharmacy-to-participant Model and means of IMP Delivery.

1.4. Sponsor-to-participant Model in which the IMP is shipped from a private company sponsor depot, or a contracted manufacturing site, wholesaler depot or distributor location without the involvement of a pharmacist, to the participant [18]

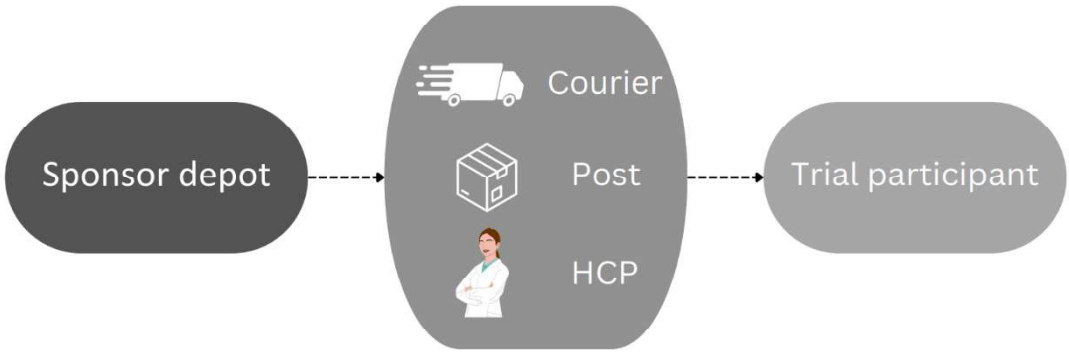


Figure 7: Schematic of Sponsor-to-participant Model and means of IMP Delivery

2. *Advantages and disadvantages of dtp IMP delivery model:*

MODEL	ADVANTAGES	DISADVANTAGES
Investigative site-to-patient	• Easier communication and tracking with patients. • Less on-site visits • Few regulatory barriers	• Increased burden for site staff • Increased cost because of the double shipping (shipping to the investigational center and then to the patient) • Hesitant Investigators about delegating, or unwillingness to delegate, tasks to third parties as he is

		the ultimate responsible.
Central pharmacy/ pharmacy depot-to-participant Model	• Reduced costs and IMP spillage • Enabling direct-to-participant delivery of IMP with stringent stability requirements	• Increased distance between site study staff/ pharmacist and the participant • Not accepted by regulators in all EU countries
Local pharmacy-to-participant Model	• Enabling low-intervention trials with authorized IMP • Less costly and safer because the patient's identity can be checked. • Suitable for IMP with previously obtained market authorization	• Increased burden for local pharmacists (eg, training) • Increased cost of training
Sponsor-to-participant Model	• Less training for third parties • Less costly for sponsor as the delivery is made directly	• Regulatory barriers • Patient identity privacy breach • Little to no experience of this model in Europe

Table 6 : summary of overall advantages and disadvantages of the four main direct-to-patient investigational medicinal products delivery models

3. *Main considerations for the implementation of these dtp IMP models:*

There are several considerations that needs to be carefully addressed in order to successfully implement DTP IMP delivery in decentralized clinical studies. Indeed, Pathway planning and documentation are critical. Procedures for direct-to-trial participant IMP shipment should be described in the protocol so that the process is clear to the investigator, IRB, and applicable regulatory agencies. Like traditional trials, formal standard operating procedures (SOPs) tied to the clinical trial protocol should also be utilized to outline accountable parties at each step of the supply chain, from the administration order through distribution to the participant and recovery of the IMP or container. [17] Additionally, the feasibility of the DTP model must be assessed. As not all models were considered suitable for all types of IMP, and the IMP characteristics, such as safety profile (and phase of development), stability, need for complex preparations and route of administration, should all be taken into account when considering DtP IMP supply solutions. [18] the Conduct of thorough risk assessments to identify potential risks associated with DTP IMP delivery, such as medication mishandling, theft, or loss during transit. Implement risk mitigation strategies, such as tamper-evident packaging, signature confirmation upon delivery, and insurance coverage for lost or damaged shipments is also necessary. Similarly, it is relevant consider patient's safety and education as the training of the participants should include how to handle the IMP once received (e.g., ensuring that the IMP is intact and stored appropriately), what participants should do with unused IMP, and who participants can contact if there are problems or questions with the IMP (e.g., the package is damaged in transit). [17] Hence, a patient centric communication between patients, study coordinators, and healthcare providers is mandatory to address any concerns or issues related to DTP IMP delivery promptly, there need because there needed to be measures in place to reassure all stakeholders that the IMPs would arrive in correctly controlled conditions and that the trial participants would be in a position to manage self-administration of the IMP. [19]

VIII. Centralized monitoring and Risk based monitoring.

1. *Definitions:*

Although it may seem contradictory to pair the concepts of trial decentralization and centralized monitoring, the relationship is synergistic. For a trial to be less location dependent and less reliant on on-site activities, there must be centralization of data collection and analysis. [20] Moreover, decentralized components cannot be successfully implemented without centralized monitoring due to the velocity and volume of data generated as well as the myriad of different data sources now in use. [20] it is relevant in this context to define centralized monitoring. It is an iterative process that involves periodic assessments. To account for the potential latency in identifying and addressing issues that emerge between these assessments, a parallel, daily process uses thresholds to generate triggered alerts and automated notifications and raises issues directly to site monitoring staff. [21] As source data verification is recently found be ineffective and costly because it only detects random errors and protocol deviations, Centralized monitoring enables the reduction of SDV/SDR by allowing organizations to focus on the datapoints that matters it also allows data visualization that provides insights beyond those that can be gained on-site from the perspective of the investigator or the clinical research associate (CRA) through SDR/SDV. The figure 5 from Transcelerate RBM solutions shows how centralized monitoring allows clearer identification of trends or aberrations in clinical trial data compared with monitoring by a CRA, who has a more siloed view of the data.

Figure 7 Monitoring of Siloed Data Versus Centralized Monitoring with Visualization of Aggregated Data. Source: [21]

Similarly, the definition of Risk-based monitoring is a systematic process put in place to identify, assess, control, communicate and review the risks associated with the clinical trial during its lifecycle.[22] One major advantage of RBM is its universal application to any phase trial and essentially any type of clinical study (including DCTs). [23]

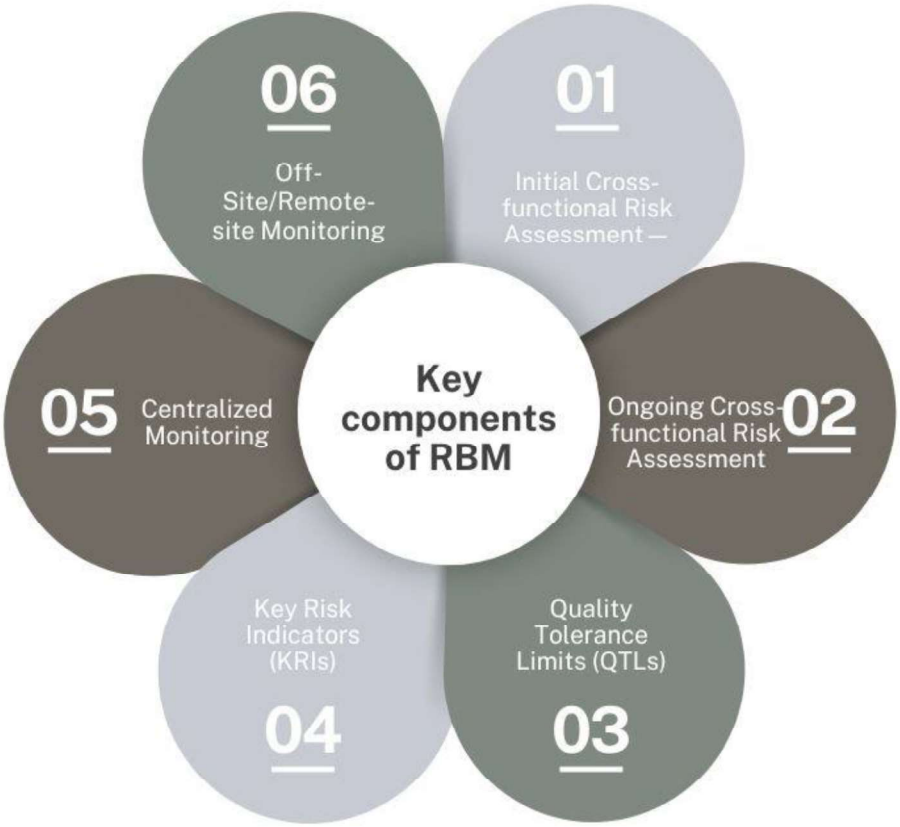


Figure 8 Diagram of key components of RBM

2. *Main considerations for monitoring in a Decentralized clinical trial design*

In order to ensure data quality, patient safety and regulatory compliance, there are many considerations to be addressed in the implementation of centralized and risk-based monitoring methods.

The main considerations are related to the key components of RBM that appear in Figure 6 and can be listed as following:

1. Initial Cross-functional Risk Assessment: many stakeholders must be Involved in this process during which critical-to-quality (critical data and critical process) risks across the entire trial lifecycle as well as mitigation strategies must be identified, which will inform project plans. [23]

2. Ongoing Cross-functional Risk Assessment: the implementation of a continuous process of revisiting and adjusting the initial risk assessment and planned mitigations as the trial proceeds based on incoming data and any new developments within or outside of the trial that could affect quality. [23]

3. Quality Tolerance Limits (QTLs): limits should be pre-determined for specific trial parameters that, when reached, signal that further evaluation is needed to determine if action is warranted. [23]

4. Key Risk Indicators (KRIs): Metrics used to assess site performance, either compared to other sites or to established values should be pre-defined and continuously monitored. [23]

5. Centralized Monitoring: continuous remote review of aggregated electronic data, including data analysis must be carried ou. [23]

6. Off-Site/Remote-site Monitoring—Replacement of some or all on-site monitoring visits with remote-site monitoring visits, where and when allowed by regulatory authorities. When monitoring remotely, a targeted and/or triggered review of documents and data is used. [23]

Furthermore, we should assess other aspects like the proactive outline of during protocol development how data will flow during the clinical trial [20]and the identification of potential critical-to-quality risks as well as the proper choice of fit-for-purpose technology. This concept was already brought up in the previous sections but it is relevant to bring it up again in this context.

Bias mitigation strategies can include hybrid (remote or on-site) consenting options to help ensure the trial population includes potential participants comfortable with digital mediums to receive information or with an in-person consultation. Access controls must also limit access to communications for only monitoring and auditing. [24]

According to the interviewed Clinical research associates and project managers, one of the most important factors to consider while designing a monitoring plan in DCT is patient convenience, engagement and minimization of the burden on participants. Additionally, the monitoring should be ethical and conducted in a manner that respects patient autonomy and confidentiality, adhering to ethical guidelines. Moreover, seamless communication and collaboration between the centralized monitoring team, site staff, and patients should be

facilitated and standardized processes for identifying, escalating, and resolving issues promptly are much needed.

IX. Remote Monitoring and Data Collection Technologies

1. *Remote patient monitoring vs source data monitoring*

We will start by emphasizing the importance to distinguish between the definition of remote monitoring in Source data monitoring/RBM and remote patient monitoring in DCTs as well as safety monitoring.

Based on the findings of the interviews with the CRAs, DCTs leverage technology to gather data directly from patients, wearable devices, electronic health records (EHRs), and other digital tools unlike traditional clinical trials that typically collect data at scheduled intervals during site visits.

Remote patient monitoring refers to the continuous and immediate collection, analysis, and review of clinical trial data from various sources using connected tools and devices to support monitoring of patient health and vitals remotely or outside of a traditional clinical trial site (eg, electrocardiography, pulse oximetry). [25]

There are many data collection technologies, during the interviews the participants identified three main technologies eClinical outcome assessment (eCOA), eConsent and telemedicine visits. In this section, we will define each one and discuss the main considerations for their implementation in Decentralized clinical trials.

2. *Data collection technologies:*

2.1. Electronic clinical outcome assessment (eCOA):

2.1.1. Definition of eCOA:

Today, the preferred mode for the collection of patient's reported outcome data in clinical research is electronic.[32] By definition, it is the electronic tools that allow the collection of data from patients, physicians, observers and caregivers using smartphones, tablets or the internet. [27] it includes [28]:

1. Patient-Reported outcomes (PRO)
2. Clinician-Reported Outcomes (ClinPRO)
3. Observer-Reported Outcomes (ObsRO)

2.1.2. Main consideration for eCOA

During our interview with a project manager of a DCT in pediatrics population, the respondent has stated that they had to switch from eObsPRO to the paper equivalent version of the assessment because of the lack of compliance with good clinical practices especially that they provided no audit trail.

In order to avoid such inconveniences, some recommendations need to be respected. Notably, the right choice of (eCOA) vendors as well as timely engagement in the decision process is recommended. It is also adequate to choose vendors with good experience in clinical trials and ideally pre-licensed library or an extensive licensing team to save time and ensure that remote endpoints are properly monitored. During my interview with a director of (eCOA) library he stated that the process of developing an electronic outcome assessment can be very time-consuming and burdensome for sponsors and their pre-licensed ecoa solution can help accelerate study startup by providing assessments that are preconfigured, author approved, system compatible and available in many languages.

It is also found that there is a need to better prepare sites to use (eCOA) pre-study and this starts by the proper assessment of the staff's experience which is key to providing adaptive training programs that is suitable. For this purpose, hands-on training at investigator meetings (IMs) is considered most effective. However, if logistical barriers are present, recorded training developed with the (eCOA) provider is recommended requiring completion and understanding before enrollment begins. [33]

(eCOA) site manuals are important for ensuring sites' success with (eCOA) especially for device preparation and management that provides adequate training and troubleshooting tips as well as quicker resolution that can be achieved by the implementation of a 24/7 live helpdesk chat. [33]

Additionally, it is recommended for sites to train participants on the importance of and the rationale for electronic patient reported outcome and their responsibility for record data per protocol in order to promote their engagement and compliance. For example,

one interviewed Study coordinator reported that they presented a new application to keep them informed of the latest news of the study and provides a gamified platform to keep them engaged in the process but only 2 out of 14 patients accepted to download and most of them also refused optional self-injection. This shows the need for a training material for patient that is not be very complicated to browse and as extensive as a quick reference guide and this could be achieved by taking sufficient time to train them to proficiency, the questionnaire schedule should be simplified, and it should capture only necessary data. [33]

It is also recommended to perform a rigorous user acceptance testing to confirm functionality and demonstrate usability of the (eCOA) [33]

Furthermore, issues with connectivity and technical problems like patients not charging or carrying the device issued by the sponsor may be tackled by a Bring your own device (BYOD) approach which could be a way to reduce logistics burden and increase convenience. [33] As well as the implementation of backup solutions for devices and data.

Further recommendations for the electronic patient reported outcome are important to define dataset structure because it is important to define data standards requirements early in the study setup process. Ideally, the standards applied to ePRO data should be applied at the origin of the data [34] Standard, clearly defined naming conventions for variables and domains should always be followed to reduce data errors, eliminate ambiguity, and enhance the transparency and traceability of ePRO data.

Sponsors should create comprehensive data models (like the one presented in Figure 5) that are applicable across all studies and share these models with eCOA providers. These data models should include standardized variable naming conventions that align data collection with the final SDTM variables and domains. Adhering to these naming conventions enables the development of uniform programming logic, facilitating traceability of data from entry through to transmission and analysis. This invokes the Findable, Accessible, Interoperable, Reusable principles to ePRO data (FAIR). [35]

In order to allow the reuse of existing data and avoid useless duplications, data should also be made Findable, Accessible, Interoperable and Reusable (FAIR) [38]

Data must be: Attributable, Legible, Contemporaneous (i.e., recorded at the time the activities are carried out), Original (or true to the original), Accurate (ALCOA) [37]

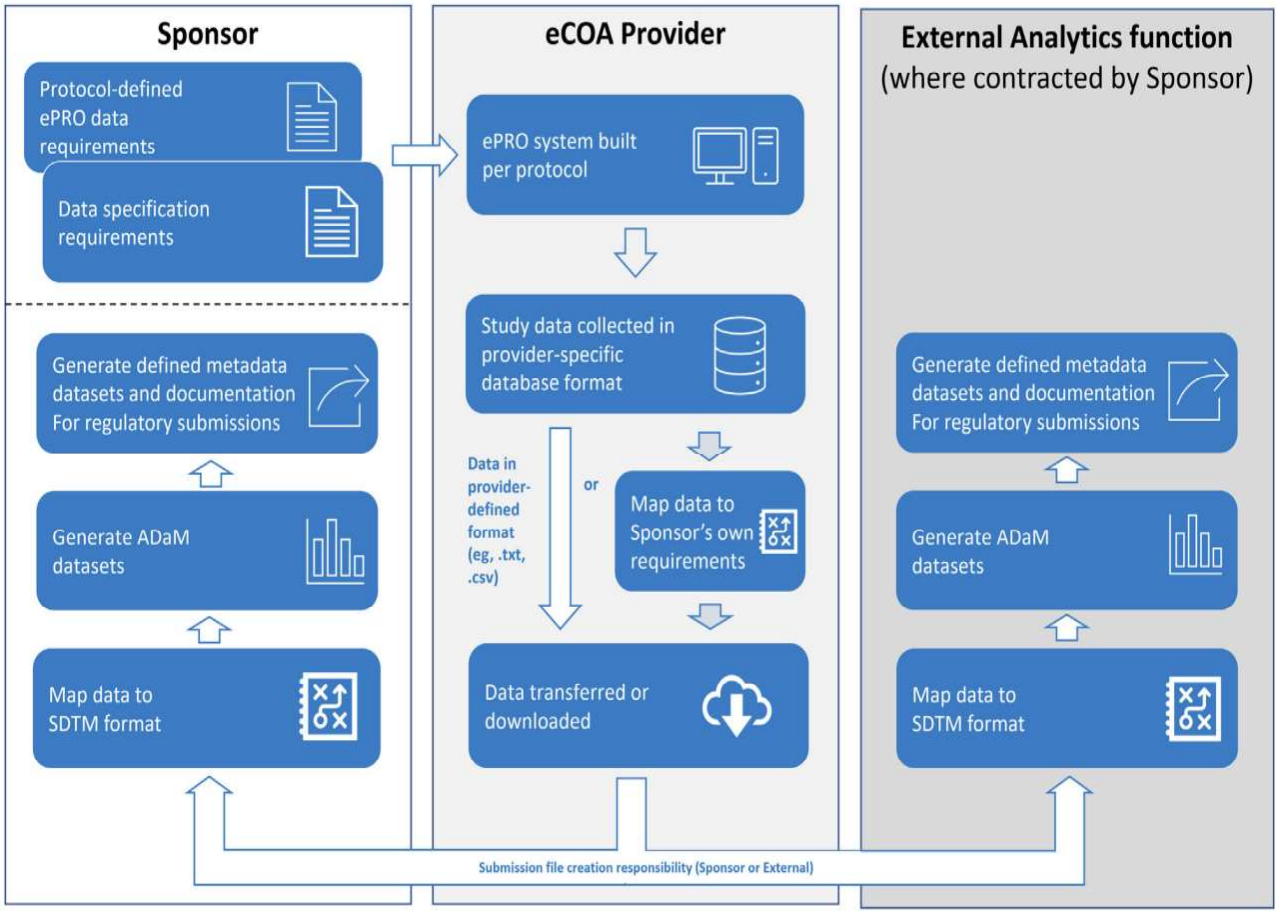


Figure 9: an example of data flow mapping where ADaM indicates Analysis Data Model; .csv, comma-separated values; ePRO, electronic patient-reported outcome; SDTM, study data tabulation model; .txt, text. SDTM provides a standard for organizing and formatting data to streamline processes in collection, management, analysis and reporting. Source: [34]

It is also important to form a strategy for the following components:

Missing data handling: considering item-level missing (ePRO) data is often overlooked. The systems configured to allow skipping items should include "ND" (not done) or ask participants to confirm their intent by responding to a programmed edit check.

(ePRO) controls: it can ensure optimal data quality. It can prevent multiple responses and the missing of entire assessments by providing timed, protocol aligned reminders

and the disabling of assessments outside prespecified time windows or flagging entries that violates a constraint.

Quality control and validation of datasets: Given that there is no hard copy source reference document for data entered electronically, a documented process for prospectively monitoring ePRO data held on the provider's server is needed.

Use of read-only-datasets: it is recommended to implement a read-only approach in the file transfer or the automated and automated downstream handling of files to ensure transparency and avoid corruption due vulnerability of the format of the files like (.txt) and (.csv).

Finally, it is essential to address the primary ethical considerations for data processing in clinical research within the European Union, as outlined by the General Data Protection Regulation (GDPR). Figure 6 provides a concise summary of these key requirements.

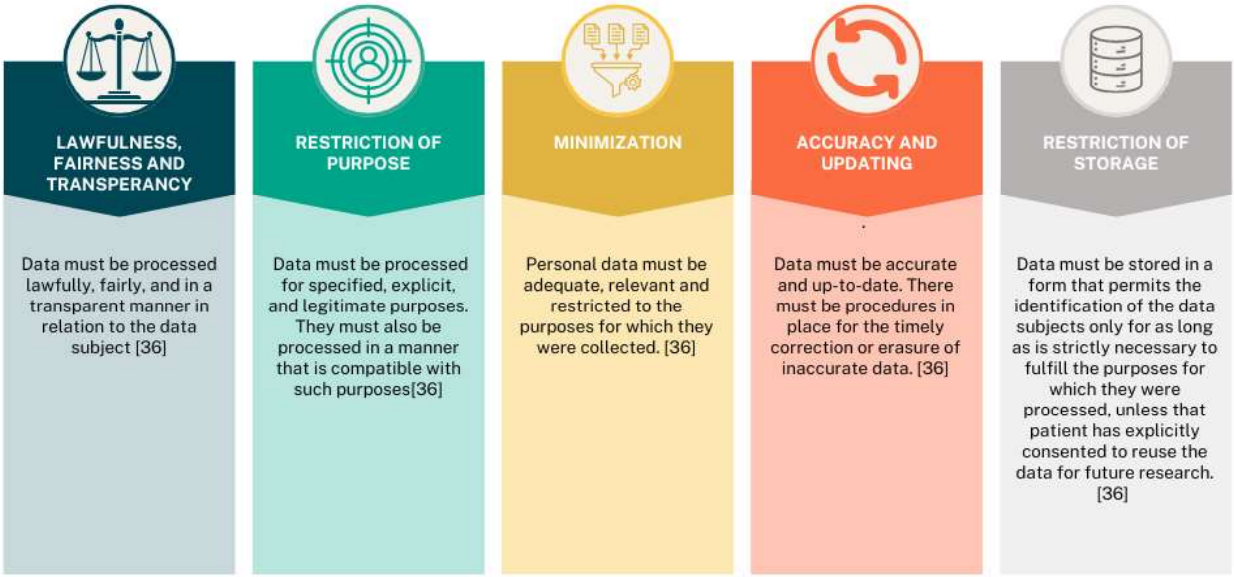


Figure 10: main ethical consideration pertaining to all data processing in the European union.

2.2. eConsent:

2.2.1. Definition of eConsent:

eConsent includes multimedia components which can be used to develop an interactive and engaging informed consent experience, offering flexibility for diverse learning styles (e.g., auditory, visual). eConsent is not simply a paper document transcribed onto a mobile device [29]

2.2.2. Main considerations for eConsent:

There are three main aspects to informed consent: firstly, to engage in a comprehensive discussion with the patient about the characteristics, goals, and procedures of the study with an emphasis on voluntary participation and option to withdraw from the study at any time; secondly, to allow the patient to use this information to make an informed decision; and finally, to ensure the patients' decision is accurately documented. [39]

In this perspective, it is important to ensure that the systems used for e-consent have proportionate security levels, and safeguards regarding confidentiality are in place. Special care must be dedicated to the clarity and completeness of the information provided to the patient. In the case of fully-digital consent, the validity of the signature must be guaranteed from a legal perspective as well. Since relationship between HCPs is important in the information and conventional consent as it is even more needed in DCTs eConsent procedures, face-to-face communication should take place between the investigator and the potential trial participant. If this discussion takes place in a digital / virtual mode, this should be generally performed in real time where the parties are able to see and communicate with each other via audio and video, and to ask questions. [36] Moreover, there is a need to create practical and pragmatic guidelines for the implementation of eConsent in clinical trials and here again, clear and transparent communication between stakeholders is required about the existing and

new drafted laws and regulations.

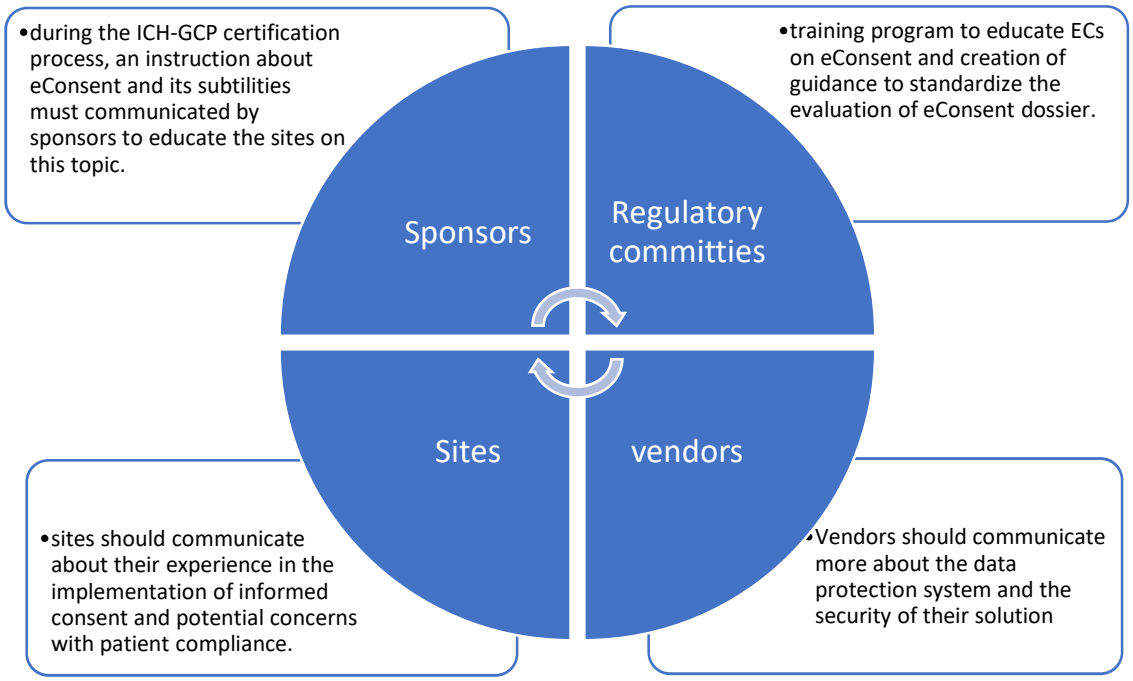


Figure 11: diagram of main responsibilities of stakeholders in the efficient communication in econsent implementation.

2.3. Telemedicine:

2.3.1 definition of telemedicine:

Telemedicine denotes a health-related service based on telecommunication and electronic information technologies, including a broad range of uses, such as patient consultations, remote control, telehealth nursing, and remote physical and psychiatry rehabilitation [30] for instance, Telemedicine has found several applications in cardiology, including the early prehospital diagnosis of acute myocardial infarction based on transmitted EKG data, monitoring patients with chronic heart failure, monitoring arrhythmias, and transmitting echo images to a level III center for a second opinion [31] in the context of the implementation of DCTs, the trial visits could be conducted via telemedicine or via mobile healthcare providers (HCPs).

Another term commonly found in scientific articles in the field is mobile HCPs. In fact, visits from mobile HCPs may be an appropriate substitute for selected clinical trial visits to investigative sites and may promote participants' compliance and retention by providing convenience and comfort in the home, office, or in certain circumstances

while traveling out of town. Activities that mobile HCPs may be able to perform include clinical assessments, blood draws, IMP or treatment administration, participant education, and in-home compliance checks. [17]

2.3.2. Main considerations for Telemedicine:

Sponsors planning to incorporate telemedicine in clinical research should be informed of the landscape of applicable laws. [17] it is important to ensure that healthcare providers conducting telemedicine sessions are licensed to practice in the jurisdictions where participants are located as different regions may have varying telemedicine regulations. [40]

Regarding the patient- centricity of DCTs, it is required to provide adequate infrastructure to ensure sufficient broadband access. To optimize the likelihood of successful telemedicine encounters, it is important to ensure adequate videoconferencing capability, to test and document the system's minimum requirements for broadband speed and connectivity and rectify difficulties. More technical specifications include computer and other electronic devices configurations to meet technical and ergonomic specifications. For instance, minimal memory, clear video and audio transmission and a webcam easily manipulated by patients. [40]

A variety of different telemedicine platforms exist, but for optimal, safe, and compliant operability, the platform should be easy to install, deploy, and operate. We found that the preferred specifications included: cloud-based service, Health Insurance Portability and Accountability Act (HIPAA)-compliant, and independent of local network hardware systems that would need to be installed and maintained. [40]

Here, again, proper training is a very important component to consider. Support staff in the clinic are needed to educate patients about telemedicine and to facilitate the actual visit. In a two-way telemedicine interaction between a patient and an HCV provider, the clinic staff are responsible for the bulk of the physical portion of the visit. [40]

X. Safety monitoring

1. *Definition of Safety monitoring:*

Similarly, safety monitoring can be defined as provisions for monitoring of data collected for scientific validity and safety of research participants [26] and the reporting of AE and SAE by patients in DCTs.

2. *Main considerations for safety monitoring:*

it is recommended to hold this part to the same standards as traditional trials, clearly articulate remote safety monitoring procedures and train investigative staff and establish record-keeping protocol to ensure compliance. Additionally, protocol-specific safety monitoring should be developed, and communication escalation plans should be previously established. A potential safety issue's effect on the use of mobile/remote technologies by the participant to report an adverse event (e.g., blurred vision may make it difficult to use a tablet, phone app, or computer) may be an important consideration. Sites should be properly resourced to review data in a timely manner and have contacts/infrastructure in place to react over distance (with or without a local investigator) accordingly, as necessary.

Moreover, Designing and incorporating simple safety reporting mechanisms using mobile technologies should be considered and potentially require more active participant engagement and understanding of, as well as comfort with, these technologies. And most importantly, Explicit protocol inclusion/exclusion criteria may help to ensure participants have the requisite technological skill and means to be successful in these trials, while balancing justice and equity considerations for participant selection. [17]

XI. Conclusion

Bringing together the diverse facets of decentralized clinical trial (DCT) implementation, from digital endpoints to direct-to-patient investigational product delivery, telemedicine, and safety monitoring, reveals a transformative landscape in clinical research. The amalgamation of novel technologies, such as eConsent and remote patient monitoring, with traditional methodologies underscores a pivotal shift toward patient-centricity, efficiency, and adaptability.

In ensuring that the data collected at DCTs are clinically significant and the results are exploitable to demonstrate clinically relevant efficacy and an acceptable safety profile with sufficient evidence in the clinical context obtain the Marketing authorization hinges on several critical considerations. First and foremost is the assurance of regulatory compliance and patient safety across all aspects of trial conduct. From the selection and

validation of digital endpoints to the secure delivery of investigational products, adherence to regulatory standards must remain paramount. Moreover, the integration of telemedicine necessitates a comprehensive understanding of legal frameworks and technological infrastructure to ensure seamless and ethical patient care.

Equally crucial is the emphasis on patient engagement and convenience throughout the trial journey. Strategies such as user-friendly eConsent platforms and mobile healthcare visits not only enhance participant experience but also contribute to improved retention and adherence rates. However, these innovations must be accompanied by robust training and support mechanisms to empower both patients and healthcare providers in embracing digital technologies.

Furthermore, the evolution of safety monitoring in DCTs underscores the need for proactive risk mitigation strategies and clear communication channels. As adverse event reporting transitions to digital platforms, it becomes imperative to streamline processes while upholding data integrity and participant confidentiality.

In conclusion, the successful implementation of decentralized clinical trials requires a delicate balance between innovation, compliance, and patient-centricity. By harnessing the potential of digital solutions and embracing a collaborative approach among stakeholders, DCTs hold promise not only for accelerating the pace of clinical research but also for advancing healthcare outcomes in an increasingly interconnected world.

XII. Tables and figures:

1. ***Tables:***

2. ***Figures:***

XIII. Table of contents:

XIV. References:

[1] ***Decentralised, patient-centric, site-less, virtual, and digital clinical trials: From confusion to consensus*** Yared Santa-Ana-Tellez, Bart Lagerwaard, Amos J. de Jong, Helga Gardarsdottir, DiederickE. Grobbee, Kimberly Hawkins, Megan Heath, Mira G.P. Zuidgeest, Trials@Home Consortium

[2] Decentralized Clinical Trials: experience and examples Eugenio Santoro, Roberto Ascione, Mariacristina Fest, Ilaria Marut, Elisabetta Ravo

[3] ***Increasing value and reducing waste in biomedical research: who's listening?*** Dr David Moher PhD, Paul Glasziou FRACGP, Iain Chalmers DSc, Mona Nasser DDS, Pat rick M M Bossuyt PhD, Daniël A Korevaar MD, Prof Ian D Graham PhD, Prof Philippe Ravaud MD, Prof Isabelle Boutron MD

[4] ***https://www.ncbi.nlm.nih.gov/books/NBK326791/***

[5] Choosing primary endpoints for clinical trials of health care interventions Charlie McLeod, Richard Norman, Edward Litton, Benjamin R. Saville, Steve Webb and Thomas L. Snelling

[6] Clinical validation of digital biomarkers for pediatric patients with asthma and cystic fibrosis: potential for clinical trials and clinical care Matthijs D. Kruizinga, Esmée Essers, Frederik E. Stuurman, Yalçin Yavuz, Marieke L. de Kam, Ahnjili Zhuparris , Hettie M. Janssens, Iris Groothuis, Arwen J. Sprij , Marianne Nuijsink , Adam F. Cohen, and Gertjan J.A. Driessen

[7] Digital technologies for medicines: shaping a framework for success. Cerreta F, Ritzhaupt A, Metcalfe T, Askin S, Duarte J, Berntgen M, and Vamvakas S

[8] Development of Novel, Value-Based, Digital Endpoints for Clinical Trials: A Structured Approach Toward Fit-for-Purpose Validation M. D. Kruizinga, F. E. Stuurman, V. Exadaktylos, R. J. Doll, D. T. Stephenson, G. J. Groeneveld, G. J. A. Driessen, and A. F. Cohen

[9] Perceived barriers to pediatrician and family practitioner participation in pediatric clinical trials: findings from the Clinical Trials Transformation Initiative. Greenberg RG, Corneli A, Bradley J, et al.

[10] ***. Asthma outcomes: exacerbations. J Allergy Clin Immunol 2012; 129: 3 Suppl., S34–S48.*** Fuhlbrigge A, Peden D, Apter AJ, et al

[11] Treatment of pulmonary exacerbations in cystic fibrosis. Eur Respir Rev 2013; 22: 205–216 Bhatt JM.

[12] Key design considerations for adaptive clinical trials: a primer for clinicians Kristian Thorlund, professor, Jonas Haggstrom, team lead, data sciences, Jay JH Park, research scholar1, Edward J Mills, professor

[13] What Are Adaptive Clinical Trials? (and why use them) (statsols.com). (2020)

[14] Decentralized Clinical Trials: Scientific Considerations Through the Lens of the Estimand Framework Rima Izem PhD, Emmanuel Zuber PhD, Nadia Daizadeh PhD, Frank Bretz PhD, Oleksandr Sverdlov PhD, Pascal Edrich MSc, Janice Branson PhD, Evgeny Degtyarev MSc, Nikolaos Sfikas PhD & Robert Hemmings MSc

[15] The Benefits of Flexible, Decentralized Trial Designs — And How to Make Them Happen. By Jonathan Andrus.

[16] Key design considerations for adaptive clinical trials: a primer for clinicians Kristian Thorlund, professor, Jonas Haggstrom, team lead, data sciences, Jay JH Park, research scholar, Edward J Mills, professor

[17] Legal, Regulatory, and Practical Issues to Consider When Adopting Decentralized Clinical Trials: Recommendations From the Clinical Trials **Transformation Initiative.** Maria Apostolaros, David Babaian, Amy Corneli, Annemarie Forrest, Gerrit Hamre, Jan Hewett, Laura Podolsky, Vaishali Popat & Penny Randall.

[18] Direct-to-participant investigational medicinal product supply in clinical trials in Europe: Exploring the experiences of sponsors, site staff and couriers. Amos J. de Jong, Yared Santa-Ana-Tellez , Mira G. P. Zuidgeest, Renske J. Grupstra, Fatemeh Jami, Anthonius de Boer, Helga Gardarsdottir on behalf of the Trials@Home Consortium.

[19] The ASAP Framework: A New Tool for Regulatory Agencies to Facilitate Adoption of Pandemic Approaches. Brenda J. Huneycutt and Virginia Acha.

[20] Risk-Based Monitoring in Clinical Trials: Increased Adoption Throughout 2020 Nicole Stansbury, Brian Barnes, Amy Adams, Ruth Berlien, Danilo Branco, Debby Brown,

Paula Butler, Lauren Garson, Debra Jendrasek, Garrett Manasco, Nycole Ramirez, Nelly Sanjuan, Gillian Worman, Anina Adelfo.

[21] Risk-based Monitoring of Clinical Trials: An Integrative Approach Dimitris. K. Agrafiotis, PhD; Victor S. Lobanov, PhD; Michael A. Farnum, PhD; Eric Yang, PhD; Joseph Ciervo, MS; Michael Walega, MS; Adam Baumgart, BS; and Aaron J. Mackey, PhD.

[22] ACRO. Establishing Risk-Based Monitoring within a Quality-Based System as "Best Practice" for Clinical Studies – ACRO [Internet]. 2019.
https://www.acrohealth.org/rbqm-report/. Accessed 8 October 2020

[23] Risk-Based Monitoring in Clinical Trials: Past, Present, and Future
Brian Barnes. Nicole Stansbury, Debby Brown, Lauren Garson, Geof Gerard, Nickolas Piccoli, Debra Jendrasek, Nick May, Vanesa Castillo, Anina Adelfo, Nycole Ramirez, Andrea McSweeney, Ruth Berlien, Paula Jo Butle.

[24] DMA the Danish Medicines Agency's guidance on the implementation of decentralized elements in clinical trials with medicinal products. Dan. Med. Agency. 17 (2021).

[25] Remote Monitoring and Data Collection for Decentralized Clinical Trials Bobby Daly, MD, MBA; Otis W. Brawley, MD; Mary K. Gospodarowicz, MD; Olufunmilayo I. Olopade, MD; Lola Fashoyin-Aje, MD, MPH; Victoria Wolodzko Smart, BA; I-Fen Chang, PharmD; Craig L. Tendler, MD; Geoffrey Kim, MD; Charles S. Fuchs, MD, MPH; Muhammad Shaalan Beg, MD, MBA; Lianshan Zhang, PhD; Jeffrey J. Legos, MD, MBA; Cristina Ortega Duran, CIMA; Chitkala Kalidas, PhD; Jing Qian, LLM; Justin Finnegan, MBA; Piotr Pilarski, MD; Harriet Keane, PhD; Johanna Shen, MS; Amy Silverstein, PhD; Yi-Long Wu, MD; Richard Pazdur, MD; Bob T. Li, MD, PhD, MPH

[26] Safety Monitoring https://www.umc.edu/Research/Research-Offices/Clinical-Trials/Researchers/Road-Map/Study-Conduct/Participant-Management/Safety-Monitoring.html

[27] Patient noncompliance with paper diaries. BMJ 2002; 324: 119 one AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR.

[28] How Getting the Right Data in the Right Way Supports the Risk-Benefit Equation across the Product Lifecycle. Personal communication (2013) Halling K.

[29] ***(eCOA) vs (COA) pros and cons kayentis whitepaper*** by Olivier Chassany, Patient-Reported Outcomes & Clinical Endpoints Methodology Research, at University Paris-Diderot (2017)

[30] Telemedicine for healthcare: Capabilities, features, barriers, and applications. Sens. Int. 2021, 2, 100117.Haleem, A.; Javaid, M.; Singh, R.P.; Suman, R.

[31] A Review of Digital Health and Biotelemetry: Modern Approaches towards Personalized Medicine and Remote Health Assessment by Ștefan Sebastian Busnatu, Adelina-Gabriela, Alexandra Bolocan, Octavian Andronic, Anca Mihaela Pantea Stoian,Alexandru, Scafa-Udriște, Ana Maria Alexandra Stănescu, Dan Nicolae Păduraru, Mihnea Ioan Nicolescu ,Alexandru Mihai Grumezescu and Viorel Jinga.

[32] Equivalence of electronic and paper-based patient-reported outcome measures. Qual Life Res. 2015;24(8):1949–1961Campbell N, Ali F, Finlay AY, Salek SS.

[33] Flexible approaches to eCOA administration in clinical trials: The site perspective: Estelle Haenel a,* , Celeste A. Elash b , Katie Garner c , Megan Turner d , Scottie Kern e , on behalf of the Electronic Clinical Outcome Assessment (eCOA) Consortium and the Patient-Reported Outcome (PRO) Consortium

[34] Best Practice Recommendations for Electronic Patient-Reported Outcome Dataset Structure and Standardization to Support Drug Development. Stacie Hudgens, MSc, Scottie Kern, BSc (Hons), Alexandra I. Barsdorf, PhD, Sally Cassells, BS, Alison Rowe, PhD, Bellinda L. King-Kallimanis, PhD, Cheryl Coon, PhD, Geoff Low, PhD, Sonya Eremenco, MA

[35] Wilkinson M, Dumontier M, Aalbersberg I, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data. 2016;3:160018 [published correction appears in Sci Data. 2019;6(1):6]

[36] Decentralized clinical trials (DCTs): A few ethical considerations Carlo Petrini, Chiara Mannelli, Luciana Riva, Sabina Gainotti and Gualberto Gussoni.

[37] US Department of Health and Human Services. Data Integrity and Compliance with Drug CGMP. Questions and Answers. Guidance for Industry. Washington DC: Food and Drug Administration (2018). Available online at: https://www.fda.gov/media/119267/download

[38] The fair guiding principles for scientific data management and stewardship. Sci Data. (2016) 3:160018. doi: 10.1038/sdata.2 016.18 Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al.

[39] Informed consent. N Engl J Med. 2017;376(9):856–67. Grady C, Cummings SR, Rowbotham MC, Mcconnell MV, Ashley EA, Kang G.

[40] A framework for patient-centered telemedicine: Application and lessons learned from vulnerable populations Andrew H. Talal a, Elisavet M. Sofikitou b, Urmo Jaanimägi a, Marija Zeremski c, Jonathan N. Tobin c d, Marianthi Markato

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développement de protocoles pour les essais cliniques décentralisés : les considérations nécessaires pour atteindre des résultats cliniquement et scientifiquement significatifs en s'appuyant sur la variabilité, l'intégrité et la traçabilité du data généré.

Nous explorons ici le développement de **protocoles** pour les **essais cliniques décentralisés** (DCTs), en nous concentrant sur les considérations essentielles nécessaires pour obtenir des résultats **cliniquement** et scientifiquement **significatifs**. Le passage des essais cliniques traditionnels aux modèles décentralisés présente des défis et des opportunités uniques, en particulier dans l'utilisation des **digital endpoints** pour la collecte, la gestion et l'analyse des données, **la livraison de médicaments** d'essai clinique directement aux patients, et la surveillance de la sécurité à distance. À travers une revue exhaustive des méthodologies et technologies actuelles, ainsi que des entretiens avec des experts dans le domaine, cette recherche fournit des lignes directrices pour concevoir des protocoles DCT efficaces qui maintiennent des normes élevées de rigueur scientifique et de pertinence clinique, tout en garantissant la **sécurité** des **patients**.

Mots-clés : Protocoles, essais cliniques décentralisés, cliniquement significatifs, digital endpoints, livraison des médicaments, sécurité des patients.

___ Designing Protocols for Decentralized Clinical Trials: Essential Considerations for Ensuring Clinically and Scientifically Valid Outcomes through Data Variability, Integrity, and Traceability

Here, we explore the development of **protocols** for **decentralized clinical trials (DCTs**), focusing on the critical considerations necessary to achieve **clinically** and scientifically **significant** outcomes. The shift from traditional clinical trials to decentralized models presents unique challenges and opportunities, particularly in the use of **digital endpoints** for **data collection**, management, and analysis, **DTP IMP delivery, remote safety monitoring**…. Through a comprehensive review of current methodologies and technologies, alongside with interviews with experts in the field, this research provides guidelines for designing effective DCT protocols that maintain high standards of scientific rigor and clinical relevance as well as **patient safety**.

Key-words: **protocols, decentralized clinical trials (DCTs), clinically significant, digital endpoints, data collection, DTP IMP delivery, patient safety.**

XV. Annexes:

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Study coordinator/Healthcare business and clinical research Masters
1 mois •

🔍 📝 Seeking Interviews for master's thesis 📚 (French version bellow)

Hello everyone!

I'm currently working on my thesis focusing on the development of protocols for decentralized clinical trials. I'm particularly interested in the necessary considerations to achieve clinically and scientifically significant results, emphasizing variability, integrity, and traceability of generated data.

N.B: The degree of decentralization doesn't really matter
If you work in this exciting field or have relevant expertise to share, I would love to interview you to enrich my research. Your insights and perspectives are invaluable for advancing our understanding and practice in this crucial area of clinical research.

Please feel free to contact me via direct message if you're interested in participating or if you know someone who might be. Thank you very much for your support and contribution to my research!

Annex 1: Linkedin post seeking interviews

Econsent Questionnaire english version

Interview script: eConsent

Introduction:

Hello, thank you so much for accepting the invitation to the interview on a short notice. By this initiative, you are going to contribute to my master's thesis about the design of decentralized clinical trials.

- I structured my thesis as following:

I. main considerations for protocol design and implementation
II. main considerations for eCOA
III. main considerations for eConsent
IV. main considerations for data management
V. main regulatory and approval considerations

- As a *ROLE OF THE PERSON INTERVIEWED*, I thought it most adequate to ask you questions about the II and III parts. About what do we know? what we don't know? And what we need to develop?
    1) General question
    2) Do you think all studies are eligible for eConsent implementation? If not, What kind of studies are eligible for this kind of consent procedure? even legally?
    3) Apart from trial management staff , can you think of any other actors involved in the design and implementation of econsent?
    4) What are the main guidelines surrounding the implementation of econsent?
    5) What are the next steps???

Econsent Questionnaire english version

Interview script: Protocol design implementation

Introduction:

1) Comment évaluez-vous la faisabilité d'un essai décentralisé dans un site ?
2) Quels types d'études sont éligibles au consentement électronique ? même légalement ?
3) Quelles sont les principales lignes directrices autour de la mise en œuvre des DCTs ?
4) Quel est le processus réglementaire pour transformer une étude clinique en
5) Comment vous vous assurez durant l'étude que les données recueillies sont précises

Interview script: eCOA library

Introduction:

Hello, thank you so much for accepting the invitation to the interview on such a short notice. By this initiative, you are going to contribute to my master's thesis about the design of decentralized clinical trials.

- I structured my thesis as following:

I. main considerations for protocol design and implementation
II. main considerations for eCOA
III. main considerations for eConsent
IV. main considerations for data management
V. main regulatory and approval considerations

- I came across your profile while exploring the IQVIA eCOA solutions.
- As an eCOA associate director, I thought it is most adequate to ask you questions about the eCOA part. About what do we know? what we don't know? And what we need to develop?

1- I have seen on you linkedin page that you Manage the eCOA Library Team, what kind of profiles and backgrounds is this team composed of?
2- In which fields do you reckon you have the most extensive library?
3- How does eCOA Library tools to reduce rater's drift and improve data quality?
4- How do you ensure in-study data quality?
5- How do you ensure that the parameters used in the eCOA are fit for purpose and are accurate and precise?
6- What are the risks and potential delays in the deployment of eCOA studies?
7- What are the main regulatory considerations for eCOA licensing in Europe? Is it a burden?

Thank you so much for sharing your valuable perspective.

Annex 2: initial interview scripts with questions.