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Review Article

Decentralized Clinical Trials in Early Drug Development—A Framework Proposal

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ABSTRACT

The COVID-19 pandemic has led to a rethinking of clinical trial design to maintain clinical research activity, with regulatory changes allowing for the wider implementation and development of decentralized design models. Evidence of the feasibility and benefits associated with a remote design comes mainly from observational studies or phase 2 and 3 clinical trials, in which implementation is easier with a better-established safety profile. Early drug development is a slow and expensive process in which accrual and safety are key aspects of success. Applying a decentralized model to phase 1 clinical trials could improve patient accrual by removing geographic barriers, improving patient population diversity, strengthening evidence for rare tumors, and reducing patients' financial and logistical burdens. However, safety monitoring, data quality, shipment, and administration of the investigational product are challenges to its implementation. Based on published data for decentralized clinical trials, we propose an exploratory framework of solutions to enable the conceptualization of a decentralized model for phase 1 clinical trials.

Keywords: decentralized clinical trials, phase 1, drug development

CONCEPTUAL APPROACH TO DECENTRALIZED CLINICAL TRIALS

The COVID-19 Pandemic: Prime Time for Decentralized Clinical Trials (DCTs)

Decentralized clinical trials (DCT) comprise a modality of trials in which part or all trial-related activities are conducted outside the primary clinical trial site.

The COVID-19 pandemic has affected the organization of healthcare worldwide, forcing governments and healthcare providers to implement strategies to limit transmission, prioritize care, and protect the capacity of healthcare systems. Stay-at-home restrictions, social distancing, and the reallocation of medical and research staff lead to the deferred delivery of health services and disruptions in the conduct of clinical trials. The most affected parts of the trials were patient screening, enrollment, administration of investigational drugs, and safety monitoring. All these restraints fostered innovation in clinical trial design by implementing innovative solutions for telehealth, drug distribution platforms, technological solutions for safety monitoring, and regulatory disposals.

DCTs: A New Paradigm

Randomized clinical trials (RCT) are the gold standard for clinical research and remain the most robust method for assessing the efficacy and safety of new therapeutic interventions. However, the standard RCT model relies on an investigator-centered approach, in which all trial activities are conducted at the primary site. Patients travel to academic centers, where investigators, diagnostic tools, and experimental therapeutics merge in a highly regulated environment to produce unbiased, randomized evidence. However, inclusion in a clinical trial comes with a series of barriers (structural, clinical, demographic) [1] that contribute to low accrual and inclusion rates, with an estimated 10% inclusion rate in the US.[2]

Patient-centered clinical trials offer a design model capable of overcoming some of the constraints associated with traditional trial design and have emerged as a result of the technological evolution of remote healthcare.[3] From hybrid to fully remote, this model offers patients the flexibility of remote data, sampling, and drug supply, reducing the burden of participating in a clinical trial.[4]

This innovative design concept comprises a spectrum of organizational modalities, ranging from a fully decentralized model to a hybrid concept. A fully virtual trial has the most

complete articulation, with enrollment, assessments, and treatment taking place at the patient's home, enabled by end-to-end digital solutions. A hybrid clinical trial design merges the traditional concept of on-site interactions with the procedures performed outside the main location of the clinical trial. Pending on procedural complexity, a hybrid design with mobile units or alternative local sites close to the patient's home is a solution that allows decentralization of RCT with complex or lengthy treatment procedures. Network clinical trials are models of DCTs that rely on a network of cancer centers closer to patients' homes and can provide access to clinical trials. [5] These network trials provide community-based cancer care, allowing access to innovative treatment solutions while maintaining the support of family and friends.[6,7]

Current Landscape of DCT in Oncology

Since the pandemic, different fields, such as dermatology, psychiatry, and cardiology, have shown that conducting decentralized clinical trials is feasible. These trials combine local existing healthcare facilities (laboratories, imaging, and acute care centers) with decentralized supply chains and remote enrollment, capitalizing on the fast-growing home health platforms and remote operating capabilities.[8] Despite the feasibility demonstrated in other medical fields, implementation of DCT in oncology remains rare (Table 1). Examples such as Alpha-T and TELEPIK clinical trials demonstrate that designing and running a DCT is possible in the field of oncology. Alpha-T (ClinicalTrials.gov Identifier: NCT04644315) initiated recruitment in 2020 and aimed to identify patients other than those with lung cancer harboring an anaplastic lymphoma kinase alteration using next-generation sequencing and providing treatment with alectinib. Patient identification and enrollment were performed by a remote research team, and patient care was provided by a home nursing system with local facilities used for imaging and other in-person procedures. TELEPIK (ClinicalTrials.gov Identifier: NCT04862143) is a pilot trial evaluating the safety and utility of a hybrid decentralized clinical trial approach in patients with hormone receptor-positive and HER-2 negative advanced breast cancer with *PIK3CA* mutations under treatment with alpelisib plus fulvestrant. Twenty clinical trials with a partially or fully decentralized design are listed on the ClinicalTrials.gov webpage (Table 1), with the majority being observational and all interventional trials designed as phase 2 trials. Therefore, no current expertise exists on whether a decentralized clinical trial in a phase 1 setting would be possible, or which are the main barriers to its implementation.

COULD DECENTRALIZATION BE APPLIED TO CANCER PHASE I TRIALS?

Although some barriers to remotely running a Phase 1 clinical trial are the same as any other trial, early drug development poses unique safety and monitoring issues that can be difficult to overcome (Figure 1).

Recruitment and Enrollment

In the traditional model, patient recruitment for a clinical trial strongly depends on geographic proximity, with the main sites being in urban centers. A survey assessing patient engagement in clinical trials identified travel to and from sites as the major study burden, with 29% of the 12.000 participants classifying it as "somewhat or very burdensome."[9] A Dana-Farber retrospective study found significant racial and ethnic disparities in phase 1 versus phase 2 and 3 clinical trials, [10] reinforcing the need for a more inclusive design.

A decentralized approach removes most of the geographical constraints, allowing for a more diversified trial population by increasing the number of participants from social groups that traditionally face more barriers to enrollment (e.g., ethnic and other minorities, low socioeconomic groups, and rural areas).[11,12]

Remote Monitoring: Safety, Efficacy, and Trial Efficiency

Safety monitoring in traditional clinical research involves in-person visits with a review of adverse events, physical examination, biological sampling, and tests (safety and efficacy evaluation) performed at the center of the trial. The research team is responsible for ensuring that patients are eligible for the trial and that all procedures are properly executed to diagnose, manage, and report toxicities related to the investigational product (IP).

In a phase 1 setting, where the primary endpoint estimates the maximum tolerated dose based on protocol-specific defined dose-limiting toxicities (DLT), patients are treated at sequential dose levels. Trial progress depends on the accurate and timely identification and reporting of DLTs to allow progression to different dose levels. Running a phase 1 decentralized clinical trial challenges in ensuring adequate and detailed safety monitoring and reporting. Protocol design should ensure access to remote follow-up visits with trained health professionals able to accurately identify DLTs with timely access to safety tests and physical examinations and a data management team able to properly corroborate the findings of the investigator. Safety monitoring must balance the need to ensure individual patient safety and allow for efficient decision-making regarding dose escalation.

Patient-Centric Sampling: From Blood to Tissue

Early drug development clinical trials included frequent biospecimen (blood, tissue, and, occasionally, urine and stool) sampling and processing for assessing pharmacokinetics (PK), pharmacodynamics (PD), and biomarkers. In academic-centered trials, biospecimens are collected and processed by a protocol-trained research team, whereas sample analysis may be performed locally or in a central

Table 1. Trials with a decentralized design registered at clinicaltrials.gov (accessed December, 2023)

Title	NCT ID	Status	Intervention	Sponsor	Study Type	Phase
A home-based approach study to evaluate the efficacy and safety of alectinib in locally advanced or metastatic ALK-positive solid tumors (Alpha-T)	NCT04644315	Terminated	Drug: alectinib	Pharmaceutical	Interventional	2
Registry platform ovarian and endometrial cancer	NCT05129969	Recruiting	Decentralized biobank for advanced or metastatic OC or advanced or metastatic EC in Germany	Pharmaceutical	Observational	-
A noninterventional, nontreatment, nonrandomized, single coordinating center, decentralized biospecimen collection study in USA-based adult subjects with acquired resistance to KRAS inhibitors	NCT05272423	Recruiting	Diagnostic test: FoundationOne Liquid CDx	Academic	Observational	-
Pilot decentralized clinical trial in men and pre- and postmenopausal women with breast cancer and a specific mutation (*PIK3CA*) treated with alpelisib in combination with fulvestrant (TELEPIK)	NCT04862143	Terminated	Drug: alpelisib drug: fulvestrant	Pharmaceutical	Interventional	2
A retrospective analysis of magnetic resonance imaging data for breast cancer screening in the Open Consortium for Decentralized Medical Artificial Intelligence (ODELIA)	NCT05698056	Active, not recruiting	No intervention	Academic	Observational	-
A phase II study of subcutaneous atezolizumab in NSCLC patients using a decentralized clinical trial model	NCT05340309	Recruiting	Biological: atezolizumab and recombinant human hyaluronidase	Academic	Interventional	2
A study to examine the clinical value of comprehensive genomic profiling performed by Belgian NGS Laboratories: A Belgian precision study of the BSMO in collaboration with the cancer centre - Belgian Approach for Local Laboratory Extensive Tumor Testing (BALLETT)	NCT05058937	Recruiting	Diagnostic test: comprehensive genomic profiling	Academic	Interventional	-
Treatment and outcome of patients with breast cancer: clinical research platform for real-world data	NCT03417115	Recruiting	Registry	Academic	Observational	-
APOLLO 11, consortium of Italian centers involved in treatment of patients with lung cancer treated with innovative therapies: real-world data and translational research	NCT05550961	Not yet recruiting	Registry	Academic	Observational	-
A biomarker screening protocol to support preliminary eligibility for clinical trials evaluating safety and efficacy of adoptive T-cell therapies in participants with solid tumors (Lyell START)	NCT05891197	Recruiting	Biomarker	Academic	Observational	-
The effect of diet and exercise on immunotherapy and the microbiome (EDEN)	NCT04866810	Recruiting	Behavioral: intervention arm	Academic	Interventional	-
Liver Cancer Registry Platform (JADE)	NCT04510740	Recruiting	Decentralized biobank	Academic	Observational	-
Registry Platform Urologic Cancer (CARAT)	NCT03374267	Recruiting	Decentralized biobank	Academic	Observational	-
Shared care thyroid cancer follow-up utilizing thyroid cancer assessment reminder system (TCARS) study - a pilot study	NCT05510934	Not yet recruiting	Behavioral: shared-care model	Academic	Observational	-
Breast screening & patient navigation (BSPAN2): evaluating a de-centralized regional delivery system for rural underserved	NCT03052907	Completed	Behavioral: BSPAN	Academic	Observational	-

Table 1 continues on next page

Table 1. Continued

Title	NCT ID	Status	Intervention	Sponsor	Study Type	Phase
Myeloma Registry Platform (MYRIAM) (MYRIAM)	NCT03308474	Recruiting	Decentralized biobank	Academic	Observational	-
Clinical research platform into molecular testing, treatment and outcome of (non-)small cell lung carcinoma patients	NCT02622581	Recruiting	Decentralized biobank	Academic	Observational	-
Genome-based management of patients in precision medicine (Ge-Med) towards a genomic health program	NCT04760522	Recruiting	Genetic: WGS diagnostic: blood take for genetic diagnostic	Academic	Interventional	-
Zanubrutinib (Brukinsa®) in patients with Waldenström's macroglobulinemia (WM), chronic lymphocytic leukemia (CLL) and marginal zone lymphoma (MZL) - a prospective multicenter observational cohort study	NCT05326308	Recruiting	Drug: Zanubrutinib	Academic	Observational	-

Dash (-) indicates not applicable; NCT: national clinical trial; OC: ovarian cancer; EC: endometrial cancer; NSCLC: non–small-cell lung cancer; WGS: whole genome sequencing.

laboratory designed by the sponsor. Despite ensuring high-quality data, the traditional model relies exclusively on multiple visits to the site for PK and PD assessments.

Decentralized sampling collection or patient-centric sampling (PCS) relies on self-sampling or remote sampling performed by trained local health professionals or caregivers. This approach can be considered for less-invasive procedures with low complication rates, low-volume blood samples, and conventional sample processing requirements.[13] Despite reducing patient burden and increasing the efficiency and speed of clinical trials, the adoption of PCS in clinical trials has been slow. The main concerns in adopting a PCS model are sampling quality, stability, chain-of-custody, training, and comparability with standard sampling methods.[14] Evolving full PCS methods has been hindered by difficulties in outsourcing complex pharmacokinetic and biomarker analyses, inconvenient collection times, and lack of standardization of in-home sampling and processing.[15] During the COVID-19 pandemic, clinical trial procedures were adapted to social restrictions, with some trials designed using a PCS approach. Two clinical trials have demonstrated the feasibility of self-sampling systems, enrolling patients in self-blood sampling protocols to assess the prevalence of antibodies against SARS-CoV-2.[16,17] The evolution of sampling collection methods integrated with new technologies for home and remote data collection may help overcome the current challenges for the wider adoption of PCS.[18]

Tumor samples collected during treatment with experimental therapy are also key for developing targeted and immune therapies as cornerstones of cancer treatment. Biomarker development relies heavily on appropriate tissue sampling, high-quality processing, storage, and shipping.[19] Designing an adequate tissue-sampling protocol in a decentralized trial includes coordination with remote interventional radiologists for target selection, collection timing, sample processing and storage, and shipping to a central laboratory.

Investigational Product: Shipping and Administration

Drug distribution, tracking, preparation, and administration are the main challenges to the design of remote clinical trials. Compared with centralized trials, where trial centers store and administer IP, DCT requires a well-established protocol to deliver the drug to remote sites or directly to patients' homes.

Regardless of the trial, drug formulation (e.g., oral, intravenous, or intratumoral), stability, and specific storage requirements define the process for proper drug administration. First-in-human drugs with limited safety profiles and pharmacological endpoints require a stricter chain of custody of the drug stock and drug delivery (while managing highly confidential material). For oral agents, when direct-to-patient (DTP) drug delivery is not possible, shipping to local pharmacies near the patient's home provides IP tracking and leverages staff knowledge on handling

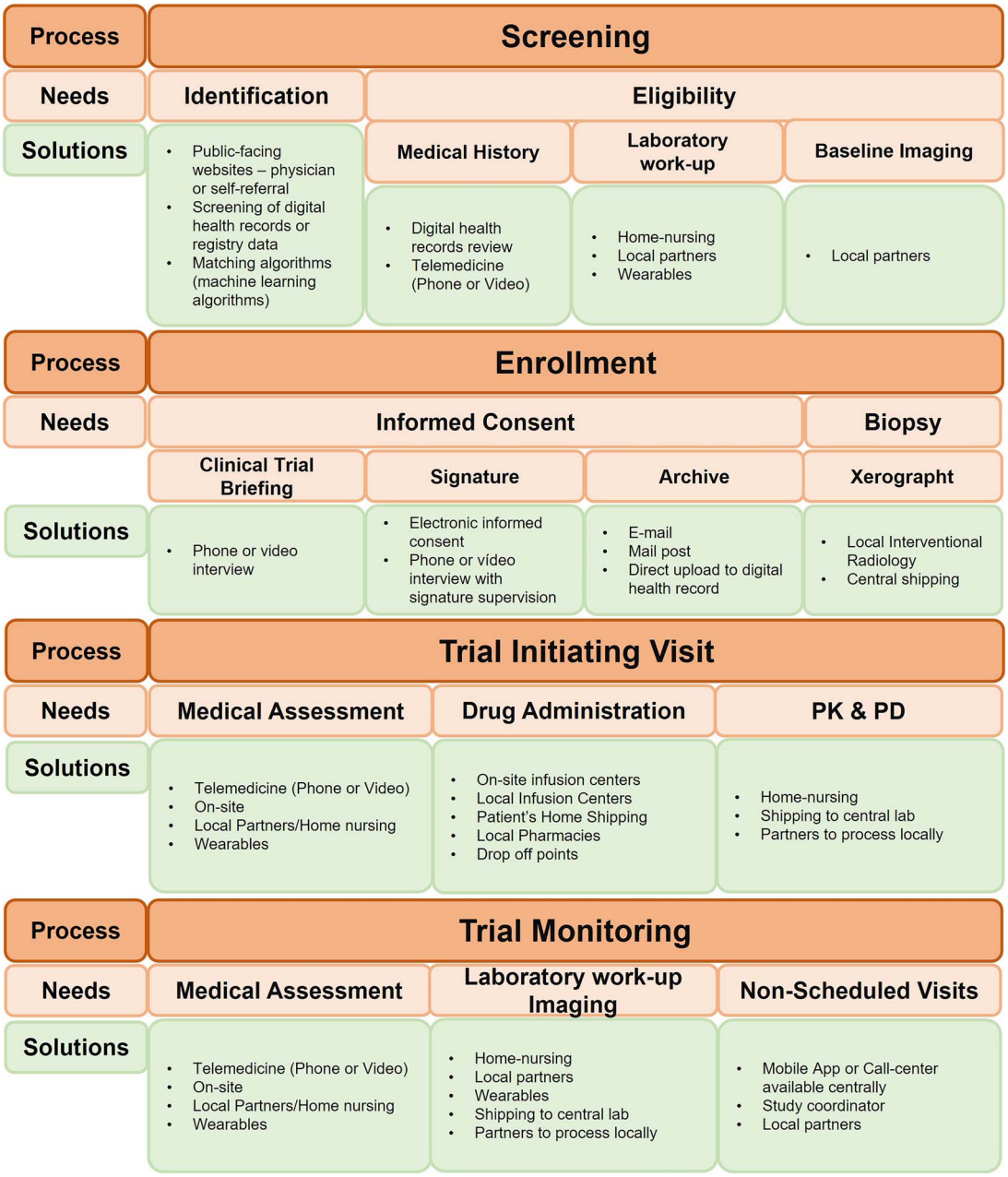

Figure 1. Needs and solutions for decentralized clinical trials in early drug development. PK: pharmacokinetics; PD: pharmacodynamics.

products with specific requirements (e.g., temperature control or light-exposure restrictions). If the IP is an intravenous formulation, partnering with local infusion centers and pharmacies provides the best option to ensure safe administration but requires local staff to be trained on the trial protocol.

Although different solutions are available, current methods for remote drug delivery (e.g., DTP, local pick-ups, and remote infusion centers) must account for the following three major aspects: patient privacy, IP tracking and confidentiality, and regulation. The research team must ensure that patients' personal data are kept private, the shipping process ensures drug stability, a chain of custody is in place from delivery to drop off, and timely refills are provided.

Regulation: Food and Drug Administration and European Medicines Agency

The increasing adoption of remote health solutions and decentralized trial designs in the United States and Europe has forced regulatory entities to develop a specific legal framework. The Food and Drug Administration (FDA) has developed guidelines on DCT for drugs, biological products, and devices that aim to provide a set of best practices for implementing and running DCTs. The FDA's guidance defines all aspects needed to properly run a DCT, from trial design to software specificities for telehealth. A relevant aspect addressed is the role of different elements that integrate the research team and delegate trial-related activities.[20] The FDA states that any personnel with a

significant contribution to the trial data should be included as sub-investigator, but local healthcare providers (HCP) that provide trial-related services as part of routine clinical practice not requiring familiarity with the protocol should not be listed as part of the research team. These recommendations are in line with the European recommendations provided by the Accelerate Clinical Trials in the European Union in 2022. Furthermore, both the FDA and European Medicines Agency state that the principal investigator (PI) is responsible for monitoring all trial aspects, including patient inclusion, safety, and data management.[20,21] Given the PI, the decision-making role allows for intra-trial consistency but raises questions regarding the trial's efficiency. With a local HCP requiring PI input to address any emerging question, the probability of delays on a trial's timeline increases substantially. Therefore, the protocol should consider a well-structured communication workflow and include a certain degree of supervised autonomy for local HCPs to maintain both safety and efficiency.

As both documents define broad recommendations for decentralized clinical trials in every medical field, some relevant questions regarding their application in early drug development remain unanswered.

NEW TOOLS AND FRAMEWORK THAT FACILITATE PROGRESSIVE DECENTRALIZATION

As stated before, decentralized clinical trials span from fully remote to hybrid trials, leveraging the facilities available at academic centers. A framework for early decentralized drug clinical trials should consider the following three major aspects: investigational product administration routes, safety monitoring, and drug logistics. Integrating these aspects allow us to define the best approach for designing the research protocol.

The framework offered here is preliminary. It leverages pilot trials already reported and translates existing technologies to early drug development. Table 2 summarizes the different steps and proposed solutions for running a decentralized phase 1 clinical trial.

Tools for Screening and Enrollment

Patient referral

Remote referral of patients to a phase 1 decentralized clinical trial requires mechanisms specifically designed to fit the inclusion/exclusion criteria and preselect the most biologically suitable diseases according to the IP mechanism of action.

Public-facing referral websites or social media platforms providing both a plain language and a scientific trial summary allow for patient self-referral or trial advertisements for local HCP referrals. These external referral solutions rely strongly on trial marketing strategies and do not provide a reliable estimate of the trial accrual rate. Despite all regulatory and logistic aspects associated with advertising clinical trials on social media, several clinical trials have demonstrated the feasibility of enrolling patients through social media platforms (e.g., Instagram, Facebook, Twitter).[22,23]

Other options include clinical staff or machine learning algorithms (based on natural language processing and artificial intelligence) that can identify eligible patients through digital health records and contact the attending physician or patient to promote the clinical trial.[24]

Patient enrollment

Patient enrollment is a multistep process to confirm full eligibility criteria and patients' understanding of the trial's endpoints, procedures, and safety aspects. Informed consent is known as one of the most challenging aspect of conducting a clinical trial and is a crucial step in trial enrollment. Electronic informed consent (eIC) is defined as the use of any electronic media (e.g., text, graphics, audio, video) to convey information related to the study and obtain informed consent via an electronic device (e.g., smartphone, tablet, computer).[25] This methodology for obtaining informed consent provides a platform that allows the enrollment of patients from diverse geographical areas, with evidence showing improvement in accrual rates, patient satisfaction, and trial knowledge.[25,26]

Informed consent is only valid when a patient can discuss and pose questions regarding the information provided. The protocol design must ensure that if prerecord elements are used to convey information, there are methods in place to ensure that the eIC process allows patients to ask questions about the study before consenting and at any time during the trial. Strategies that allow this interaction include telephone calls, video conferencing, chatrooms, and automatic chatbots.

Regarding regulation, European Union legislation sets a difference between eIC for clinical trial enrollment and eCI for processing participants' personal data, with different countries having different degrees of acceptance. In the US, eCI is legislated by the Code of Federal Regulations.[27]

Therefore, eCI is a valid and useful way to improve enrollment in a decentralized phase 1 clinical trial by overcoming geographic barriers with a wide range of technological solutions allowing its implementation.[28]

Tools for Treatment Initiation and Trial Monitoring

Safety and monitoring protocols in DCTs leverage technological solutions for telemedicine, providing virtual visits for both treatment initiation and safety monitoring. Even with all virtual solutions available, the remote patient assessment may fail to assess some aspects of clinical information (e.g., performance status or physical examination) to confirm the fitness for the trial. Home-based nursing solutions or local HCPs are valid solutions for filling the gap in in-person assessments. When in-person assessment is not necessary, virtual visits held through video or phone calls are a solution that is equivalent to in-person visits with high levels of patient satisfaction.[29]

Table 2. Framework proposal for decentralized phase 1 clinical trial

Clinical Trial Step	Procedures		Solutions for DCT
Screening	Referral and recruitment		Public-facing websites—physician or self-referral
			Screening of electronic health records or registry data
			Matching algorithms (machine learning algorithms)
	Eligibility	Comorbidities	Remote electronic health records review by trial staff
			Remote visit (Phone or Video)
		Comedications	Remote electronic health records review by Natural language processing and/or artificial intelligence software.
			Remote visit (phone or video)
		Laboratory work-up	Home nursing or local blood analysis facilities
			Shipping to central lab or local lab partnerships
		Baseline imaging	Local imaging centers
		EKG, echocardiogram and other safety tests (DEXA scans, ophthalmology exams)	Local specialty clinics
Enrollment	Informed consent	Clinical trial briefing	Remote visit (phone or video)
		Signature	Electronic informed consent
			Remote visit (phone or video) with signature supervision
	Tissue biopsy	Sampling and processing	Local interventional radiology or surgery partners
			Local laboratory for pathological analysis or for sample preparation for shipment to central laboratory
Treatment clearance visit (C1D1)	Initial visit	Medical history	Remote visit (phone or video)
	Review of eligibility	Performance Status	Remote visit (phone or video) or home nursing
		Physical exam with vital signs	Remote visit (phone or video) or home nursing
	IP	Oral drug	Direct-to-patient shipping (mail or courier)
			Local pharmacies partnership
		Intravenous drug	Home-infusions with trained health professionals
			Local infusion centers
		Other formulations	Consider a hybrid design with first administration at primary trial center
			Local infusion centers and/or home infusion
Treatment initiating visit (C1D1)	IP	Pharmacokinetics/pharmacodynamics	Sampling: home nursing or local blood analysis facilities
			Analysis: shipping to central laboratory
	Safety monitoring (after C1)	Patient general assessment (performance status and physical exam)	Remote visit (phone or video) or home nursing
		Adverse events/DLTs	Self-assessment scales and reporting
			Wearables
			Remote visit (phone or video) or home nursing
		Nonscheduled Visits	Acute care: local acute care/emergency room facilities
			Nonacute care: remote visit (phone or video) or messaging system
	Data management		Blockchain platforms
			Remote CRO
			Integrated web-based app
			Mailing system
	Drug logistics		Direct-to-patient shipping (e.g., mail, courier, pick-up locations or sponsor deliver)
			Community pharmacies
			Security protocol (identification, storage, and accountability) using a blockchain platform
			Drug drop-off (sponsor home pick-up, shipment to central storage or drop-off at community pharmacies)

DCT: decentralization clinical trials; EKG: electrocardiogram; DEXA: dual x-ray absorptiometry; IP: investigational product; CRO: contract research organization; DLT: dose-limiting toxicity.

Blood sampling

Two approaches can be considered for pharmacokinetic, pharmacodynamic, and biomarker collection, depending on the complexity. The first is a fully decentralized approach relying on home nursing or clinical staff trained to perform phlebotomies or participant self-collection using blood sampling kits.[30] A trial comparing a blood self-collection system with routine phlebotomy enrolling 100 patients showed a 90% acceptance rate, with 70% of patients being able to adequately collect blood sample.[31] The other option consisted of a hybrid design with patients traveling to the trial's primary site during the first cycle to collect pharmacodynamic or pharmacokinetic samples with subsequent assessments performed remotely. Opting for the first requires a well-structured processing and/or shipping pathway to a central lab or partnering with local facilities that can perform sample analysis. Mounting evidence shows that capillary blood sampling is as accurate as venous puncture for drug concentration [32–34] and organ dysfunction assessment.[35]

Safety monitoring

Safety monitoring is a fundamental aspect of early drug development, as the identification of drug-limiting toxicities is the primary endpoint for most trials. Although decentralized clinical trials are designed to reduce the number of interactions between the research team and participants, robust safety monitoring is possible with interventions such as real-time patient consultations by video or phone, electronic patient records, and specialty services.[36] The ASCO Telehealth Standards Expert Panel provided a set of recommendations and best practices for telehealth in oncology, stating that telehealth via telephone or videoconferencing is a reasonable option for general cancer care with no formal certification needed.[37]

A prospective exploratory survey matching patients' and clinicians' perceptions of telehealth in oncology care found high acceptability rates among both groups.[38]

With telemedicine solutions as the core elements for protocol safety design, other technological solutions enable more detailed monitoring during treatment. Electronic patient-reported outcomes (ePRO) obtained through electronic surveys using validated scales enable continuous monitoring of treatment-related adverse effects, disease complications, and functional status. ePRO provides better information on subjective symptoms than physicians' reports on medical records.[39] Liu JF et al[40] developed a pilot trial to assess the feasibility of a mobile medical application to monitor adverse events of special interest during a clinical trial assessing the combination of olaparib with ceritinib. The authors demonstrated that a targeted symptom app can provide adequate support to rapidly assist in managing acute treatment-related side effects and positively impact the overall patient experience.[40]

If ePROs provide a reliable subjective assessment of the trial's impact on participants' quality of life, Internet of Things sensors applied to patient monitoring increase the quantity and maybe the quality of the collected data. Wearable devices (e.g., smartwatches and wristbands) enable real-time data monitoring (e.g., blood pressure, blood sugar, heart rate, and oxygen levels) that can be used to monitor treatment toxicity and with adequate algorithms to report or predict DLTs. Evidence of the benefit of monitoring wearables in cancer care has focused on monitoring physical activity. A clinical trial from the Alliance of Clinical Trials in Oncology demonstrated that sensor-derived daily activity, median heart rate, and patient-reported symptom burden were strong performance status predictors and, consequently, predictors of patient fitness in a clinical trial.[41] Even under intensive treatment protocols, continuous monitoring using a wearable device is feasible with high adherence and relevant usage time.[42] Recent evidence also shows that wearable monitoring is a valid solution for identifying life-threatening situations and activating an emergency team response or referral to a nearby acute care center.[43]

Providing safety monitoring through the Internet of Things also allows the use of machine learning algorithms to predict the safety of dose escalation cohorts based on the first cohort dataset.[44] By being able to detect complex patterns from big data sets, these artificial intelligence solutions may help to better and more efficiently decide when to escalate the dose and predict both the maximum tolerated dose and recommended phase 2 dose.

Investigational product administration and accountability

Protocol design must ensure that shipping and administration of the IP are in accordance with Good Clinical Practice regulations, minimizing any impact on the quality and integrity of the drug. Some mandatory aspects that should be considered are security (e.g., avoiding tampering, adulteration, and theft) and shipping/transportation accountability (e.g., identification, packing, transport conditions, route, and handling supply chain documentation) at the outsourced resources needed for administration.[45] The supply chain definition relies on IP formulation, storage conditions, and route of administration. For framework purposes, we explored the requirements of the two most frequent routes of oral and intravenous drug administration.

Oral route administration: Per os administration comprises any formulation deemed to be taken orally and usually comprises a set of stable formulations that can be shipped. The DTP supply of clinical trial medications allows the implementation of remote clinical trials by facilitating drug delivery to patients' homes or pick-up facilities (e.g., lockers, convenience stores, local pharmacies).[46] The DTP approach eliminates the need for study visits with operational benefits by reducing local storage requirements and staffing costs. The Febuxostat versus allopurinol trial proved the reliability of a DTP with a bespoke web-based software package designed to facilitate the direct supply of IP, delivering 65.467 packs of medication to 3978 patients.[47] The CHIEF-HF trial was designed as a fully remote trial with IP delivered to the patient's home by a trial sponsor team member.[48]

Partnering with community pharmacies to deliver cancer drugs is another option to allow patients access to clinical trial IP without traveling to the primary site. This model would require pharmaceutical staff to be trained on investigational protocols and be equipped with a direct line of contact with the research team.[49]

Parental administration - intravenous or subcutaneous drugs: The remote parental administration of anticancer drugs is a controversial issue regarding the safety of drug administration. Strategies to provide intravenous or subcutaneous cancer drugs remotely include partnering with local infusion sites or professional health teams that can deliver home infusions.

Published evidence from many oncology programs demonstrates the feasibility and safety of home-based administration of several chemotherapeutic regimens, ranging from oral (etoposide) to injectables (leuprolide) and chemotherapy infusions.[50–52] Supported by this evidence, Penn Medicine launched The Cancer Care at Home program in November 2019, demonstrating that many infused or injected cancer drugs can be delivered safely at home to a selected cancer patient population.[53]

The National Home Infusion Foundation performed a retrospective analysis of 328 patients who received home infusions of chemotherapy during the COVID-19 pandemic to assess the main reasons for treatment discontinuation and satisfaction. The majority (73.21%) of patients answered, "I was satisfied with the overall quality of the services provided," and the main reason for treatment discontinuation was treatment completion per physician orders (89.54%). None of the patients discontinued treatment because of adverse drug reactions.[54]

Several other studies have analyzed home infusions of approved conventional cytotoxic agents, but data regarding remote infusion of investigational drugs are scarce. Phases 1 and 2 and clinical trials of velaglucerase alfa replacement therapy for type 1 Gaucher disease allowed at-home infusion transition during the expansion phase, with seven patients receiving at least 10% of the treatment at home.[55] The infusion-related adverse events related to home infusions were mild to moderate and manageable at home, with all patients being confident about home infusion safety.[56]

Considering this, in addition to local infusion sites, home infusion of investigational drugs could be a safe option for certain drugs in development if performed by trained healthcare professionals.

BLOCKCHAIN TECHNOLOGY FOR DATA MANAGEMENT

Decentralized clinical trials rely on remote data management to integrate and analyze all health data produced. In the traditional design, local systems and firewall-protected systems are used to store patient data. In a remote trial design, different health data streams would feed information from electronic health records by different healthcare providers, safety monitoring systems (e.g., wearables), pharmacy tracking systems, imaging centers, and laboratory data.[8] A network that connects all trial facilities and staff must be in place to provide integration, guarantee data privacy, and manage cybersecurity issues.

Blockchain technology enables decentralized data management that has become known to the public with the advent of cryptocurrency, recording all transitions in a secure and verifiable manner without needing a third party.[57] In general, a blockchain is a public, secure, and decentralized data store of chronologically ordered records that is not managed by any central regulatory entity. Applying blockchain technology to DCT data management allows data integrity, traceability, and secure cloud data sharing. Wong et al[58] developed a proof-of-concept prototype phase II clinical trial using a private blockchain for all exchanges of information related to the trial and demonstrated that it could reliably safeguard data in an immutable and fully traceable storage system.

From a user perspective, Rebecca et al[59] demonstrated how blockchain technology could be applied to address the following three major aspects of clinical research: healthcare data exchange and interoperability, drug supply chain integrity, remote auditing, and data integrity.

CONCLUSION

Current technological developments in telehealth provide a wide range of solutions that enable the conceptualization of progressively more decentralized designs for early clinical drug research. Drug administration and safety profiles are cornerstone aspects to consider when defining the degree of decentralization—fully versus hybrid models—as they have direct implications for safety monitoring protocols and resources needed for trial implementation. Other important aspects to consider when conceptualizing a phase 1 decentralized clinical trial are drug administration, accountability, and data management.

Despite the current data on DCTs deriving from observational rather than interventional trials, a clinical research protocol based on virtual visits (video or phone) incorporating remote monitoring solutions (e.g., wearables) for safety and leveraging blockchain technology for data management (e.g., health records, drug logistics, and staff communication) appears to be a promising model for early drug development.

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