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Clinical trials tranformation intiative-decentralized clinical trials: a review article

Shirisha Jakkula[1*], Pravalika Pasupuleti[1], C.S. Mujeebuddin[2], Ravindra Pratap Gaur[3], Sujay S Patil[4]

[1]Intern at Clinosol Research Pvt. Limited, Ameerpet, Hyderabad, Telangana, India

[2]Founder and CEO of Clinosol Research Pvt. Limited, Ameerpet, Hyderabad, Telangana, India

[3]Associate Manager, Clinical Operations-Covance, Bengaluru, Karnataka, India

[4]Assistant Manager, Clinical Research & PV- Bharat Serums and Vaccines, Mumbai Suburban, district, Maharashtra, India

Abstract

In clinical research, Decentralized clinical trials (DCTs) can provide chances to maximize productivity. Unlike traditional clinical trial model, Decentralized Clinical Trials (DCTs) promote telemedicine, mobile/local healthcare providers (HCPs), mobile/web-based technology, and direct distribution of Investigational Medicinal Product (IMP) to patients, among other things. Hence, DCTs are in spotlight as a technology, infrastructure and knowledge providing a backbone in clinical research.

Background: Advances in electronic communication, data storage, emerging technologies and biosensor development provides new opportunities to exchange information, such as patient is tested from their home locations and are with locations distant from the investigator. Trials that take place at locations distant from the investigator (i.e., spectrum: CCTs → Hybrid Models → DCTs) in any or all study-related procedures and data is collected electronically fall in category of decentralized clinical trial. Trials should be designed to integrate the current healthcare system of the study subject, optimise convenience for study subjects and take advantage of existing programs and data sources including: The study subjects themselves through the utilization of telecommunication, videoconferences, mobile or internet-based tools for patient reporting, mobile technology tools and biosensors. Local healthcare providers, home based healthcare services, pharmacies, clinics, regional hospitals, their perceived obstacles have impeded the widespread clinical studies using portable devices. To encourage solutions to these challenges, The Clinical Trial Transformation Initiative (CTTI) has released best practices and practical methods to advance solutions to these issues that clinical trial sponsors can now use.

Conclusion: Decentralized clinical trials are not only possible from an operational standpoint, but they also have higher recruitment rates, better compliance, lower dropout rates, and can be completed faster. DCT satisfies the industry's goal of low-risk, high-return trials and can provide a dependable, time-based, and cost-effective solution.

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*Corresponding Author
Name: Shirisha Jakkula
Email: jakkulashirisha.53@gmail.com

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Introduction

In clinical research, Decentralized clinical trials (DCTs) can provide opportunities to maximize efficiencies. Unlike traditional clinical trial model, Decentralized Clinical Trials (DCTs) encourage the use of telemedicine, mobile/local healthcare providers (HCPs), mobile/web based- technologies and the direct shipment of Investigational Medicinal Product (IMP) to patient etc. Hence, DCTs are in spotlight as a technology, infrastructure and knowledge providing a backbone in clinical research. By removing the geographical obstacles that plague traditional trials, DCTs help the clinical research industry do a better job of reaching out to a wider range of people. This would ultimately boost enrollment and better generalizable results. Decentralized strategy also aids in trial participant retention and allows trials to be imported into local areas where trial participants live, thus expediting trial conduct activities, reducing clinical trial costs, participants burden, saving time for recruitment, travel, site staff. Besides the potential benefit of DCT, adoption of the same acceptance is low. In a risk averse, highly regulated environment which is generally difficult to change, but the evidence is clear, regulators do support decentralized or virtual trials [1]. Inadequate digital infrastructure, insufficient expertise with this method, and regulatory bodies perceptions of data acceptance might all be possible hurdles to the adoption of decentralized designs. Virtually all states now has telemedicine legislation that allow sponsors, Clinical Research Organizations, and other stakeholders to use it to conduct DCTs [2,3]. But, work is necessary to push DCT acceptability and deployment.

Advantages of DCT

1. Continuous or more frequent collection of clinical data.
    - Potential data alignment with Standard of Care (SOC) guidelines.
2. Potential to reach a broader population–cohorts.
    - Access to subjects with limited mobility.
    - Broaden subject access and demographics: but need to be attentive to technology
    - Reduction of geographic barriers.
    - Rapid recruitment through increased access.
    - Improved retention rates
3. May align with clinical practice environment.
    - Use of Digital health technologies, telemedicine.
    - Usage of providers of local health care, laboratories, local imaging facilities.
4. Potential for long term follow-up if burden reduces.
5. Reduction of burden on study subjects, caregivers and clinical sites.
6. May lead to faster, less expensive trials.
7. Return on investment is better.
8. For patients-saves time, understands needs, cultural sensitivities and care is delivered at home.
9. Real time information.
10. Automated and objective data collection.
11. Access to Real World Evidence (RWD).
12. Contactless therapy.
13. Enhanced patient access[4].

Origin

The 21st Century Cures Act was signed into law on December 13, 2016, to aid in the development of innovative pharmaceutical solutions for people with unmet need. This provided the needy a quicker and more effective treatment regimen. The law builds on existing work of the FDA to integrate patient experiences into the production of medication, biological products, and devices in decision-making phase of the FDA. Cures boost the capacity of the FDA to modernize clinical test designs and reviews clinical outcomes, thereby speeding the occurrence and analysis of novel medical products, including medical counter measures [5].

Work Plan

The Cures Act authorized $500 million over 9 years to assist FDA cover the value of implementing the law. On June 9, 2017 the final work plan, which contains the FDA Science Board recommendations, was delivered to Congress.

Historical Perspective for DCTs: Guidance's

- Computerized Systems Used in Clinical Investigations (2007):
  Recommendations for the use of computerized systems in clinical investigations.
- E-Source Data in Clinical Investigations (2013):
  Data comes from multiple sources including patients, providers, devices, EHRs, etc.
- Use of Electronic Informed Consent (2016) :
  Informed consent can be obtained remotely via internet.
- Usage of E-records and E-signatures in clinical investigations under 21 CFR Part 11 (Draft, 2017):
  Defines the nature and implementation of the specifications of part 11 for clinical medical products investigations.
  Transmission of electronic data, audit trails from electronic devices.
- Digital Health Technologies Efforts:
  Use of mobile devices, biosensors, etc. in clinical investigations [4].

Clinical Trials Transformation Initiative (CTTI)

The Clinical Trials Transformation Initiative (CTTI) is a public–private collaboration co-founded by Duke University and thus the US Food and Drug Administration (FDA), whose goal was to establish and facilitate the implementation of practises enhanci ng the quality and efficacy of clinical trials followed by acknowledgement of promoting wider DCT use. CTTI established the Decentralized Clinical Trials initiative, which was led by the following goals:

(1) Distinguish apparent and genuine lawful, administrative, and useful boundaries for leading of DCTs (2) Recognise opportunities to clarify and advise arrangements impacting the execution of DCTs. This is one of several initiatives developed by CTTI to address difficulties associated with clinical trial design and execution utilizing mobile technology. [6].

The function of CTTI is based upon three strengths (Figure 1).

1. The CTTI is committed to ensure the fair participation of key stakeholders in the clinical trial enterprise, including clients, government, education, and industry.
2. CTTI develops substantial proof solutions to problems that obstruct high-quality, successful clinical trials using scientifically rigorous approaches.
3. This unique combination of stakeholder involvement and evidence-based methodologies aids in the production of CTTI recommendations and tools that have real-world impact.

The above three advantages serve as the foundation for the five interconnected metrics that form CTTI's approach. (Figure 2): (1) describe the problem and identify research hurdles(2) collect evidence to identify weaknesses and obstac les(3) assess findings by analyzing and interpreting data(4) clarify solutions by offering suggestions and methods (5) promote adoption by disseminating and applying guidelines and instruments [7].

Figure:1 CTTI's Three Strengths

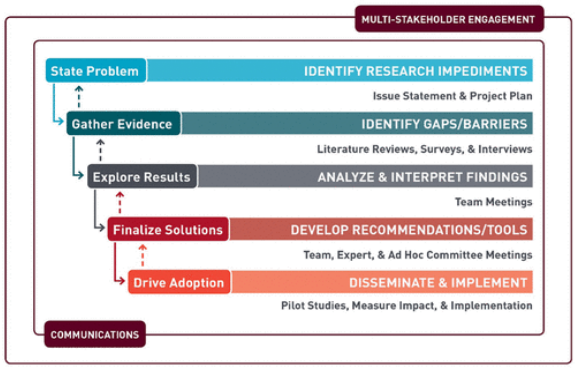

Figure:2 CTTI's Methodology

Overview

Extending the Scope of Conventional Clinical Trial locations

HCPs who practice telemedicine, on the go, or in their community (e.g., family doctors, general practitioners) need to be actively involved in the provision of healthcare, but have not yet been broadly integrated into the plan and execution of clinical preliminaries. This is owing in part to legal, legislative, and realistic concerns that might be viewed as possible obstacles. DCTs use telemedicine and other innovative and unique information technology (IT) capabilities to enable local HCPs to participate in clinical trials.In comparison to typical clinical studies conducted at more centralized clinical trial sites, DCT's can have some benefit, including the following:

- Faster recruitment of participants in the study, which can speed up access for trial participants to major medical interventions and minimize sponsor costs.
- Improved retention of participants in the experiment, reducing lost data, shorten timelines for clinical trials, lesser lost to follow up cases and increase data interpretability.
- For sponsor – enhances compliance and patient centricity
- For patient – provides comfort, convenience and care
- More prominent control, accommodation, and solace for participants in the investigation by conveying patient consideration at home or locally.
- Improved demographic diversity used in clinical trials.
- A motivator for home organization or home utilization of the IMP, which might be more intelligent of post-endorsement true organization/use [8].

Recommendations focused on key issues and topics resulting from descriptive conversations and multi-stakeholder professional meetings [9],On six DCT issues, the CTTI has developed general recommendations (Table 1) [10].

DCT Recommendations

1. DCT approaches and trial design
2. Telemedicine state licensing issues
3. Drug Inventory Management
4. Mobile HCPs
5. Investigator delegation and oversight
6. Safety monitoring

Table 1: CTTI Recommendations and Considerations for Decentralized Clinical Trials

CTTI Recommendations and Considerations for Decentralized Clinical Trials [11]	
Approaches and Protocol Design	• Designing and implementing DCTs does not have to be all or nothing. Use a semi-decentralized (hybrid) technique if possible. • Engage all stakeholders early and frequently. Use designs that are appropriate for their function. (see also Table 2). • Plan ahead of time for map data flow and communications. • Collaborate with others who have prior telemedicine expertise.
Telemedicine State Licensing	• Employ one investigator in every state where the DCT is carried out. • Make use of investigators who are licensed in various states. Hire competent mobile HCP research services. • Regarding telemedicine legislation, consult with competent specialists. • Obtain trusted legal counsel and/or partnerships.
Direct-to-Trial Participant IMP Accountability	• Consult with and verify compliance with applicable federal and state legislation and regulations. • In the protocol, clearly define IMP methods. • In the Investigational Plan, establish the responsible parties at each stage of the supply chain. • Involve suppliers who have direct-to-trial participant experience.
Mobile Healthcare Providers	• Consider it as an alternative for visiting research sites. • Delegate tasks exclusively to qualified staff in accordance with state laws and protocol. • Consider speaking with or collaborating with a mobile HCP provider.
Investigator Delegation and Oversight	• Maintain the same criteria as in traditional trials. • In the protocol, explicitly define "routine care"/"practice of medicine" as opposed to "clinical trial-related activities." • Examine the function of local and/or mobile HCPs in clinical trials and their link to FDA rules. • Allocate power and duties in the same manner as in traditional trials. • When deciding whether or not to list HCPs on Form FDA 1572, see FDA regulations and recommendations.

Safety Monitoring	• Maintain the same standard as in traditional trials. • Clarify remote safety monitoring methods and train investigative personnel. • To guarantee compliance, establish a record-keeping protocol. Create protocol-specific plans for safety monitoring and communication escalation.

Table:2 Considerations for Designing a Decentralized Clinical Trial

1. Determine which duties should be accomplished on-site, which tasks may be completed by a site or remote HCP, and which jobs are suited for mobile technological solutions.
2. Incorporate appropriate trial safeguards, protocols, training, and/or procedures to verify that the protocol is followed correctly.
3. At decentralized locations, assign responsibility for source document maintenance.
4. Specify where and how local source materials and electronic data will be maintained.
5. Plan for the necessary technological assistance, such as training and troubleshooting for all parties, as well as guaranteeing data integrity with device use and electronic system use.
6. Consider regional variations in telecommunications accessibility.

I.DCT Approaches and Protocol Design

The development and implementation of DCTs should never be an "all or none" approach. A fully decentralized strategy excludes the use of a central physical trial location in favor of telemedicine or mobile or local HCP trial visits as well as the use of mobile date recording technologies.

Some of the above characteristics are coupled with more traditional approaches by partly decentralized or hybrid approaches. The following may include these hybrid approaches:

• a specialized test location where specific trial-related activities (e.g., X-rays of the chest) take place while other procedures (e.g., sample collection, therapy administration) can take place elsewhere,

• collection of data both inside and outside of the clinical setting using mobile technologies, and/or Data collection through mobile technology both within and outside of the therapeutic context, and/or

• Such hybrid techniques will increase trial flexibility by allowing research participants and investigation site personnel to communicate both on-site and via video or teleconferencing.

A DCT will also necessitate certain fit-for-purpose protocol design and behavior concerns (Table 2). Consider incorporating DCT capabilities into a typical trial by modifying an existing protocol with remote methods where infrastructure is already in place and protection is fully described. By this investigators/sponsors develop experience in logistics, check user compliance, and compare data quality to data from conventional techniques. Sponsors and trial designers can examine use case examples [12–15] and best practices for selecting the proper technology16 for a trial. Patients and sites should be actively involved in the planning for the scientific and organizational design and execution of decentralized trials from the beginning stages of organizing a clinical trial utilizing mobile devices.

a. Data Reliability, Integrity, and Traceability:

In DCTs, data dependability and integrity may be a concern, which is why it's critical to correctly handle and map data flow, user access limits, data reconciliation, and storage [16].Managing data because data in DCT may be sent to and stored across multiple parties, locations, and systems, sponsors, CROs, and other stakeholders (e.g., IT suppliers) can monitor and maintain data flow (e.g., data use agreements, service level agreements). It can be best to start with the trial data source and then map data flow, validation, and storage depending on how data consistency and accuracy, as well as data control and protection, are ensured (see CTTI's Mobile Technologies standards [17]). This information is also of relevance to IRBs and should be disclosed in broad terms as part of the informed consent process, if feasible in accordance with data privacy and protection regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA]). DCT operators must also keep track of it. Because they are continuously evolving, individuals in charge of DCTs must guarantee that they have up-to-date information, particularly at the state level.

b. Engage and Partner

Meeting with regulatory bodies [18–23], recognising prospective participant perspectives, and engaging with experienced vendors are all important early in the protocol design process when considering the implementation of decentralised components to optimise clinical trial design. It can optimize implementation by working with investigative sites that are familiar with telemedicine. In Addition, because telemedicine is well used in many therapeutic areas (e.g., dermatology, psychiatry, stroke management) [24–33], it is possible to gain guidance from the principles and procedures developed in those fields. Engaging telemedicine providers in the creation of protocols can also be useful.

II. Telemedicine State Licensing

State Licensing for telemedicine in general, medical practitioners must meet the following requirements:

- Keep a license, including all medical practices conducted in clinical trials (e.g., ordering laboratory and imaging tests, conducting physical examinations). in the state in which they practice medicine
- Be licensed in the state in which the participant in the trial requires treatment (i.e., the practitioner is unable to administer medications or offer treatment to the participant in the trial in a state in which the medical practitioner is not licensed).

1. DCTs that operate across multiple states can manage state-by-state medical licensure concerns through the following methods:

- Maintain an investigator where services are expected in each state.
- Using investigators authorized in different states.
- Contract with companies in all US states (or at least in those states in which the trial will be conducted) offering approved mobile HCP testing services.

2. For sponsors planning to integrate telemedicine into clinical research, it is essential that they keep up to date with the complicated and varying legal landscape of relevant state laws. To become aware of the legal environment sponsors can adopt one or more of the following methods:

a) Use policy organization resource centers.

Online tools of policy groups specialized in telemedicine legislation should be considered by sponsors. There are many state and national resource centres for telemedicine [34] that publish online relevant state telemedicine laws.

b) Invest in appropriate legal resources.

To control state licensing laws, reliable legal expertise is recommended. Due to the many changes in the telemedicine laws of individual states that occur annually, constant monitoring of licensing laws is required. Alternative solutions, including such hiring outside legal counsel and/or forming agreements with or subscribing to firms that research and monitor state-by-state variations in laws and rules, may be required to relieve the sponsor's legal staffing burden.

III. Drug Inventory Management

Drug inventory management, dispensing rules and policies changes depending upon federal and state laws and restrictions differ (investigative or authorized) based on the product's FDA registration status. Procedures for delivering IMP directly to trial participants, which are similarly dependent on the IMP's reliability and quality, as well as the protocol's design. The following was recommended by CTTI:

1. Examine the state law requirements for direct-to-trial participant shipments. Determine whether the states have rules or laws for direct-to-trial participant transportation of IMP for clinician, where the DCT is carried out. Sponsors/CROs should develop rules that ensure compliance regardless of whether specific laws or regulations exist. An investigatory site should have a point of contact for monitoring state-specific concerns. If an investigative site ships IMP over state borders, it should designate a point-of-contact who is knowledgeable with state pharmacy regulations and monitor changes to these requirements.

2. The processes for shipping IMP direct-to-trial individuals should be specified in the protocol so that the researcher, IRB, and relevant regulatory bodies are aware of the process. Listing these processes promotes transparency and aids in the development of SOPs.

3. Companies can also choose to collaborate with an IMP management company that has experience shipping direct to study subjects. This supplier must have pharmacy licences in all states where services will be supplied in the United States. Sponsors/CROs should employ a main pharmacy from which they can supply directly to trial participants. If working with this type of IMP administration provider is not possible,

SOPs for IMP monitoring chain should be formalized. Compare to conventional study, structured guidelines at each phase of the IMP supply chain should outline accountable parties, including the following:

- IMP order of administration
- Housing of IMPs as well as stock.
- IMP dispensing
- Delivery to a researcher, mobile HCP, drug store or study participant

Logistics and supply chain data (e.g., temperature-validated shipping containers), containing the following:

- Record of appropriate temperature monitoring and management within the boundaries of stability.
- Procedures for handling a temperature excursion or product damage while in the hands of the trial participant.
- Documentation of recognition of reception by the receiver.
- IMP or container recovery is required both after use (if the residual is to be collected and accounted for) and when a recall, such as expiration, is required.

Various SOPs may be required for various DCT scenarios, with the emphasis on maintaining compliance with relevant federal and state legislation.

IV. Mobile Healthcare Providers

Mobile HCPs, such as nurses, doctors, and phlebotomists, can be an effective alternative for some trips to investigation sites. Performing selected trial visits at the trial individual's residence, office, or other location can improve compliance and retention while also providing ease and safety. Only trial jobs should be assigned to employees who have been taught and practiced to do those activities, as well as those who have been approved by the protocol and applicable state legislation. Mobile HCPs may allow prospective trial participants to participate in studies depending on the length of the trial, number of visits, illness condition, distance from the trip location, school, job, or family responsibilities, or vacation/travel plans. To make the most of mobile HCPs, sponsors and trial managers should keep the following in mind: Consult or work with an experienced mobile HCP provider who is involved in clinical trial operations. When compared to traditional clinical research studies, doctors doing research require a distinct skill set than clinicians providing clinical care. Mobile HCPs should have degrees, skills and experience assigned under the relevant procedure and approved by state law to perform clinical trial operations including the following, as applicable:

- Excellent clinical practice training
- Trial-specific conditions education
- Human subjects' safeguards
- Data safety
- Billing for clinical trial

Under the protocol, mobile HCPs may be required to conduct th e following:

- Drawing of blood (e.g., safety lab testing, pharmacokinetics and genomics)
- Biological samples, such as pharyngeal and buccal mucosal swabs, urine, or feces
- Administration of the IMP
- Trial participant education and training, such as IMP self-administration [35-44]).

V. Investigator Delegation and Oversight

DCTs utilizing telemedicine or mobile HCPs should not be held to a different standard in terms of investigator delegation & monitoring than traditional trials. As with trials, conventional levels, prior to delegation determination, standard considerations exist, including the IMP development process, the clinical sensitivity and susceptibility of the study population, the IMP patient compliance, and the trial's

outcomes. Furthermore, the skills of individuals to whom authority and responsibility are delegated to implement DCT methods efficiently and effectively should be taken into account.

Initial idea may be required for DCTs to guarantee that appropriate resources are available for research locations that may register higher populations of individuals. To protect participants' rights, protection, and wellbeing, the IRB would be especially interested in determining whether the human and technical capability of the investigation sites is sufficient to carry out the trial as planned, correct any adverse events, and ensure that the action adequately minimizes risks to participants.

Furthermore, the trial participants may be geographically separated from the investigator and/or the rest of the study team. Any trial techniques may be carried out remotely or by study subjects, individual HCPs, local clinical personnel, a sub investigator, distant research workers, or a mobile HCP. Because of potential ambiguities in terminology between "basic care" and "practice of medicine" as opposed to clinical trial related activities, the division of "routine care" or "practice of medicine" and clinical study actions must be well established in the protocol to clarify the duties and responsibilities of the trial team, and should be in compliance with relevant FDA regulations (i.e., 21 CFR 11, 50, 50, 50) and guidance.

When evaluating the amount of participation of local providers, a critical choice for clinical trials would be whether to classify HCPs on form 1572. If HCPs help the investigator by providing a direct and significant contribution to the data. Form FDA 1572 (investigators statement [33]) contains specific factors for deciding who and which facilities should be included, and the delegation log contains the purpose of the investigators to track the conduct of the trial, the credentials and licenses of the local HCP/subinvestigators/other trial staffs, and the terminology of the protocol on trial specific procedures that can be conducted by a local HCP [45-47].

VI. Safety Monitoring

Following the previous section, safety monitoring measures for DCTs should not be held to a different standard than those for regular trials unless justified by unique circumstances. In comparison to traditional investigative settings, DCT trial planners and operators must exhibit a functional understanding of similarities and variations in safety monitoring activities.

- To assist with reporting, properly explain remote safety management standards and educate investigator employees on DCT-specific methods.

Factors would include, but are not limited to, the following:

- Ascertain that the study participant knows the protocols and ways to access information in a remote area to resolve potential adverse effects (e.g.a list of authorized local medical facilities and/or physicians).
- Pre-coordination of approved care, input methods, and reporting criteria among investigators and authorized centres near the study participant's location.
- Establishing a record-keeping protocol will help ensure that training standards and safety monitoring protocols are up to date for investigators.
- Develop safety management and contact escalation pl ans specific to the procedure for trial participants, trial employees, third party suppliers, an d clinical investigators:
- Depending on the IMP's safety profile, a greater standard of patient safety monitoring may be required. i.e., more frequent disease management and plan modification, might be considered than those utilized in studies at traditional trial sites [34].

Table:3 Differences between traditional clinical trials and virtual clinical trials [48].

	Conventional clinical trials	Virtual clinical trials
Recruitment method	Hospital, medical clinics, newspaper	Web based, e.g., social media
Available patient population	Local (near the study site)	No limits (worldwide)
Pre-screening	Telephone calls	Electronic questionnaire
Study sites	Many	Few (site-less)
Patient visits	Many (in person)	Less frequent (home-based patient)
Informed consent	In person	Electronic consent
Trial activities, e.g., education, in-formation	In person at study site	Videoconference, telehealth
Physical examination	At study site	By photos, remote visits, in-home nurse visits
Laboratory testing	At study site	Microsampling, home-kit, mobile phlebotomist, clinic local to patient
Medical imaging	Study site	Clinic local to patient
Data collection	Collected by study team	Mobile device, e.g., phone, apps, watch, electronic patient-reported outcomes, e-diaries, interactive response technol-ogy
Dispensing of medications	At study site	Shipping drugs to home
Outcomes	Collected via study team	Electronic clinical outcome assessment, consumer-generated physiological and behavioral measures collected through connected digital tools, e.g., digital biomarkers
Study setup	Many study sites and study teams	Single virtual coordinating center with a virtual principal investigator
Duration	Time-consuming	Timesaving
Cost	Costly	Cost-effective
Patient retention	High drop-out rate	High retention rate
Enrollment	Restricted by access to study site	Maximizes enrolment

Conclusion

Decentralized clinical trials are not only possible from an operational standpoint, but they also have higher participation rates, better compliance, lower dropout rates, and can be completed faster. DCT satisfies the industry's goal of low-risk, high-return trials. Patient-centric approaches are becoming more desirable, which provides the convenience of participation in the comfort of his/her own home. In comparison to traditional clinical trials, DCT will run at anytime, self-manageable, real-time snapshot, it has two-way communication and employee-centric. DCTs can offer a reliable, time based and cost-effective approach. The effect of site less trials on clinical development lies in the richness and

completeness of data sets that can be captured with this model. Not only will we be able to enroll trials faster, we would be able to improve the ethnic diversity of patients in the study to represent the population properly possibly see safety issues and efficacy signals sooner.

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