Track 4: Decentralised Clinical Trials

Decentralised Trials In Cardiology – Challenges And Opportunities

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Outline

- Overview of decentralised clinical trials (DCTs).
- Patient engagement and data collection.
- Cardiology case studies of fully DCTs.
- Future Directions and Innovations

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Overview of DCTs

Definition of DCT **-** *a clinical trial where some (hybrid) or all (full) of the trial-related activities occur at locations other than traditional clinical trial sites (e.g., the participant's home or local health care facilities).*

Advances in digital health technologies and the COVID-19 pandemic (in-person visits limited/unavailable) have accelerated the development of DCTs.

Key advantages of DCTs:

- Convenience for trial participants
- Reduce the burden on caregivers
- Expand access to more diverse populations
- Improve trial efficiencies (e.g. engagement, recruitment, enrollment, and retention)

FDA recommendations for DCTs (May 2023)

Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Guidance for Industry, Investigators, and Other Stakeholders

Recommendations for sponsors, investigators, and other stakeholders for implementation of DCTs for drugs, biological products, and devices.

Informed Consent

Decentralised methods for obtaining ethics and remote informed consent.

- Via phone, video call, and signature via Docusign, email or Redcap.
- Synchronous or asynchronous and include interactive/multimedia components.

Potential limitations

- Technology issues e.g. poor internet connectivity, software glitches, hardware malfunction may disrupt the process and prevent effective communication.
- Consider privacy and security issues due to transmission of sensitive personal info over digital channels.
- Lack of face-to-face conversation may result in telehealth fatigue, limited non-verbal cues, and inadequate ability to ask questions of seek clarification which may compromise the participant's understanding and informed decision making.

Local challenges – obtaining remote e-consent for research currently not allowed in SG.

Participant-informed study design

Input on study design from participants can help investigators design studies that have increased impact and decrease participant burden

- Via teleconference session, remotely held community engagement sessions, and online surveys.

- No obvious drawbacks.

Screening

Determination of participant eligibility can be accomplished remotely via:

- Electronic health records
- Online surveys
- Leveraging technology advancements in algorithm development and machine learning to automate aspects of screening.

- These approaches can streamline the identification of potential study participants and facilitate clinical screening and consent more quickly.

Recruitment

Remote recruitment methods include

- EHR patient portals, social media, TV/radio announcements, and online ads.
- Recruitment strategies included brochures, flyers, postcards, self-mailers, social media, and teleconference meetings for interested participants.
- Informational videos provided on websites or via social media explain the study's conduct and requirements.

Potential limitations

- These approaches may unintentionally exclude individuals with limited access to technologies including Internet and EHR patient portals.
- Future considerations should include diverse recruitment methods that do not depend wholly on technology.

Confirmation of Eligibility

Confirmation of eligibility to participate in a research study can be via remote tools and methods, including:

- online survey responses
- phone interviews
- video calls
- electronic source (eSource) data entered directly into electronic case report forms (eCRFs)
- physiologic data (e.g., blood pressure, heart rate)
- EHR data, lab results, and
- digital biomarkers

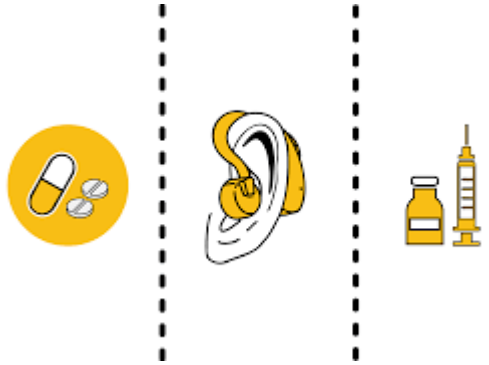
Potential limitations

- One concern in relying on remote evaluation would be the accuracy or even truthfulness of the data.

Intervention

DCTs may allow for the direct distribution of investigational products to trial participants at their locations.

- Maintain physical integrity and stability of the IP during shipment to trial participants, including appropriate packaging materials and methods (e.g., temperature control).
- Shipping containers should include clear instructions for handling and storing the IPs and instructions for returning unused IPs.
- The protocol should describe how investigators will track and document that trial participants receive IPs.



Data Collection

Participant outcome data can be collected remotely via different methods including:

- eSource data entered directly into eCRFs
- EHR data
- lab and scan results
- home sample collection
- smartphones with mobile apps
- ePROs (REDCap participant surveys, and NIH toolbox surveys)
- study visits over the phone
- sensors and wearable devices
- blood collection devices; and
- web-based patient portals.

Data Collection

The remote acquisition of data requires an understanding of technical aspects related to how data are collected, stored, and transmitted.

- Methods include e-sourcing, direct entry, participant capture, and data augmentation (e.g., leveraging external data sources/linkages). decentralised tools can support participants to keep track of trial activities.
- Maintaining privacy during remote research processes can pose challenges for researchers.
- Systems need to be rendered secure, and participants need to feel reassured that their privacy and data are safeguarded in an online environment that might include recorded video calls or survey answers subject to unintended disclosure.
- Participants may also have trouble finding privacy within their homes; thus, the data gathered via video call or survey may be affected by this lack of privacy.

Monitoring

Participant adherence to study protocols can also be monitored remotely by a coordinating or data center.

- Hospital records and other source documents are uploaded to the HIPAA-secure system, or an approved electronic meeting platform is leveraged for screen sharing.
- This system, which replaces the traditional on-site monitoring visit, saves time, but can increase sites' document upload efforts.

Retention and reminders

Remote methods can be used to keep participants actively engaged in a trial, especially by providing automated reminders when study tasks are due.

- These can be delivered via phone calls or in-app notifications.

Potential limitations

- A drawback to these retention methods is the potential for participants to become frustrated by or immune to frequent task reminders (e.g., daily).
- Potential to customize frequencies for reminders.

Return of Results/Return of Value

Increased emphasis has been placed on returning value to research participants, which may include return of research results

- However, this needs a significant amount of community engagement and translation work to happen up-front to ensure planned content and delivery of results is meaningful to research participants and able to be interpreted by non-study team clinicians if needed.
- This is especially important for results transmitted remotely without a trained coordinator to help with explanations if there are questions.

Potential limitations

- Furthermore, participants are probably less likely to ask questions about results if the investigative team has not previously established a relationship with them.

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Patient Engagement and Experience

What strategies are most effective for recruiting and engaging patients in decentralised trials?

- Outreach through local health care institutions (e.g., pharmacies, clinics) may facilitate recruitment of diverse participants in areas where there are limited or no traditional clinical trial sites.
- Bringing trial-related activities to participants' homes, including through the use of digital health technologies, may reduce the need for travel and improve engagement, recruitment, and retention amongst potential participants with challenges accessing traditional clinical trial sites.
- The use of local HCIs close to potential participants' homes may improve engagement, recruitment, and retention of diverse participants (e.g., race, ethnicity, age, sex, and geographic location).
- Further, the use of local HCPIs may reduce cultural or linguistic barriers to participation in clinical trials.

Inclusive Recruitment and Participation of Marginalized Populations

Low levels of clinical trial participation among marginalized populations are a well-established challenge in clinical research.

- Generalizability of study results is impacted when trial participation is not inclusive.
- DCTs can reach a wide range of participants by removing geographic and time constraints associated with study participation, thereby reducing participation disparities.
- Rural populations can face substantial hurdles in traveling to clinical trial sites and thus are often underrepresented in clinical research - remote technologies.
- The multilingual needs of diverse trial participants need to be addressed.

Potential limitations

- Challenges for participants who are unaccustomed to using technology independently.
- PROs may require translation, cultural adaptation, and validation to be fully accessible in a multilingual context.
- The technology may be a barrier to culturally appropriate participation where survey-based outcomes reporting is required.

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Inclusive Recruitment and Participation of Marginalized Populations

Lack of trust has an impact on clinical trial participation, yet creating trust without in-person, face-to-face discussion can be challenging.

- Researchers may help overcome misgivings by meeting potential participants within a trusted environment such as their homes, community centres, local churches, and pharmacies.
- However, DCTs are new to these populations and a failure to establish a strong relationship with communities prior to engaging in research can jeopardize the participant-trial relationship.

Potential limitations

- Decentralization is not always an immediate solution to increased diversity in participation, particularly if trust with communities relevant to the study has not been established.

Data Collection, Quality and Integrity – challenges

How to ensure that the quality and reliability of data collected remotely in decentralised clinical trials?

- The variability and precision of the data obtained in a DCT may differ from the data in a traditional site-based clinical trial.
- Remote assessments may differ from on-site assessments, particularly when trial participants are responsible for performing their own physiological tests (e.g., measuring blood pressure).
- Assessments performed by local HCPs as part of routine clinical practice (e.g., evaluation of symptoms) may also be more variable and less precise than assessments conducted by dedicated trial personnel.
- Quality control measures should be in place to help reduce variability, including regular review by investigators of participant data entered by local HCPs, to assess consistency and completeness of the required procedures.

Software Used in Conducting DCTs

Software to support the conduct of DCTs can be run through a variety of platforms (e.g., tablets, cell phones, personal computers).

Software can be used to perform multiple functions to manage DCT operations, including:

- Managing remote electronic informed consent (e.g., maintaining approved versions of informed consent, documenting IRB approval, archiving signed forms)
- Capturing and storing reports from remote trial personnel, local HCPs, and local clinical laboratory facilities
- Managing electronic case report forms (eCRFs)
- Scheduling trial visits and other DCT-related activities
- Tracking IPs that are shipped directly to trial participants
- Syncing information recorded by DHTs
- Serving as communication tools between DCT personnel and trial participants

*These programs must ensure data reliability, security, privacy, and confidentiality.

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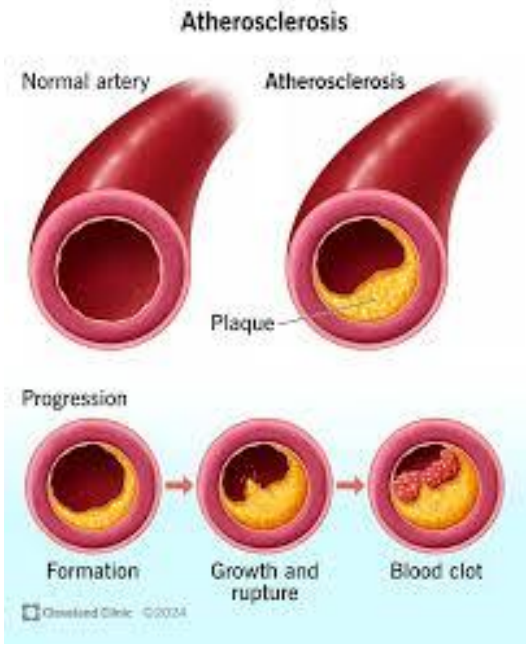
Case Study 1 of Fully DCT: ADAPTABLE

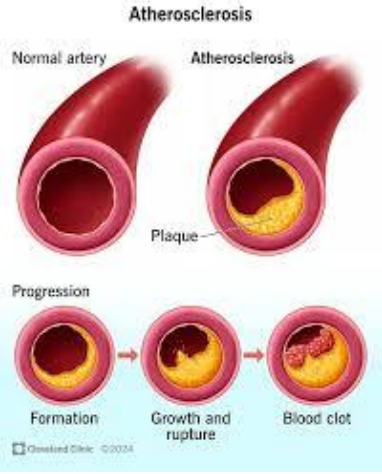
The Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness (ADAPTABLE) was designed to be a completely DCT.



- ***Aim*** *- Determine the appropriate dose of aspirin to lower the risk of death, myocardial infarction, and stroke and to minimize major bleeding in patients with established atherosclerotic cardiovascular disease.*
- ***Primary endpoints*** *- The primary effectiveness outcome was a composite of death from any cause, hospitalization for myocardial infarction or stroke. The primary safety outcome was hospitalization for major bleeding, also assessed in a time-to-event analysis.*
- ***Results*** *– 15,076 patients were followed for 26 months. No differences primary safety of efficacy endpoints (7.28% in the 81-mg group and 7.51% in the 325-mg group).*

Jones et al N Engl J Med. 2021 May 27; 384(21): 1981–1990

Case Study 1 of Fully DCT: ADAPTABLE



- **Screening/recruitment** - Leveraging new electronic methods to recruit 15,000 patients from only 40 centers in the USA with the use of multimodal, low-touch recruitment strategies, electronic informed consent, and a patient-specific access code that linked the patients to health-system data.
- **Patient Engagement -** The protocol and all patient-facing materials were designed with a group of nine patient-partners, The trial was created with a group of nine patient-partners who guided the trial from start to finish; reviewed the protocol, protocol amendments, and all patient-facing materials; and provided in-depth, patient-centered decision making on all important matters.
- **Intervention –** Patients were randomly assigned through the patient portal in a 1:1 ratio to take 81 mg or 325 mg of daily aspirin, and they purchased the assigned dose over the counter.
- **Follow-up** - There were no in-person visits during follow-up and follow-up was undertaken via patient portal.
- **Outcomes** - Multiple data sources, including patient report at scheduled trial encounters, queries of EHR data organized according to the PCORnet linkage with data sources from PCORnet private health plan partners, and linkage with Medicare and Medicaid Services claims data.

Jones et al N Engl J Med. 2021 May 27; 384(21): 1981–1990
**PCORnet- National Patient-Centered Clinical Research Network to conduct comparative-effectiveness research, with a focus on pragmatic clinical trials*

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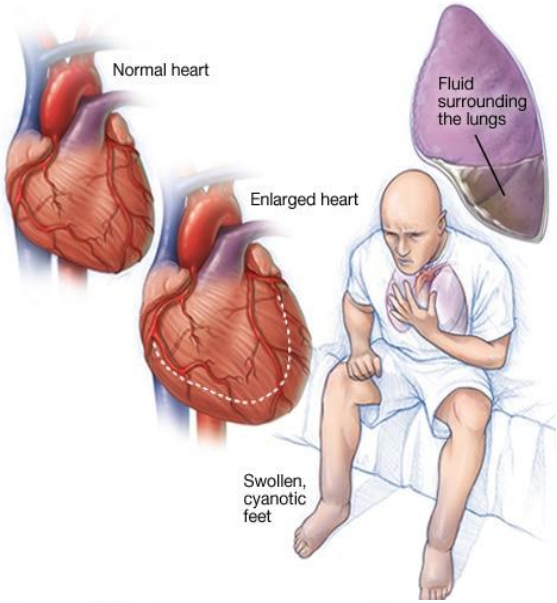
Case Study 2 of DCT: CHIEF-HF

The Canagliflozin: Impact on Health Status, Quality of Life and Functional Status in Heart Failure (CHIEF-HF) was designed to be a completely DCT without any in-person interaction with participants

HEART FAILURE

Undertaken at the start of the COVID pandemic, addressed the call for more efficient and cost-effective clinical trials.



- ***Aim*** *- Determine whether SGLT2i therapy can improve the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) at 12 weeks in patients with HF, when compared to placebo.*

- ***KCCQ*** *- 23-item self-administered questionnaire to measure patient's perception of their health status (HF symptoms, HF impact on physical/social/QOL).*

- ***Results*** *– 476 HF patients recruited from 18 sites in the USA, canagliflozin treatment resulted in a higher 12-week change in KCCQ TSS of 4.3 points (P=0.016) when compared to placebo in all types of HF.*

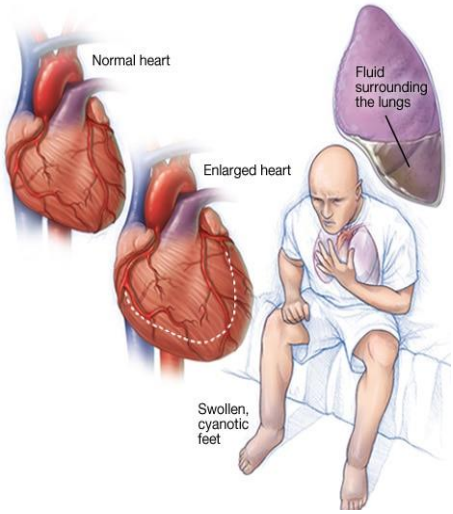
Spertus et al Nature Medicine | VOL 28 | April 2022 | 809–813

Case Study 2 of DCT: CHIEF-HF

HEART FAILURE

Patient recruitment and randomisation

- Patients were identified from 18 large health networks and large physician practices via EHRs.
- Patients were initially engaged via email and a study website.
- Underwent remote electronic informed consent (eConsent)
- Received study medication through home delivery.
- Computerized randomization.
- SAEs were collected from self-reporting and medical claims data



Primary and secondary endpoints

- Patient completion of the primary endpoint (KCCQ TSS) by a mobile application
- Study app asked patients, each week, to report the number of days they took the study dru
- Fitbit to monitor physical activity (change in total daily step count) other outcomes via EHR.

Personal data protection

- Protection of participants' personal health information (PHI), the mobile application was compliant with 21 CFR part 11 with access only by study participants; all potential sources of PHI collection were disclosed during e-consent; PHI was firewalled from the sponsor and contract research organization; and insurance claim information was presented in de-identified formats.

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Case Study of Fully decentralised Clinical Trial: CHIEF-HF

Outcomes

- The diagnosis of HF was confirmed by claims data in all participants.
- The compliance with completing an eDiary of medication use was 95%, and 91% reported taking more than 80% of their study medications.
- Participants' Fitbit data transmissions indicated that 94% wore their Fitbit 70% or more of the time.
- The KCCQ data >97% completed.
- The enrollment of women and minorities is higher than in most previous SGLT2i trials, including 50% women and 15% African American participants.

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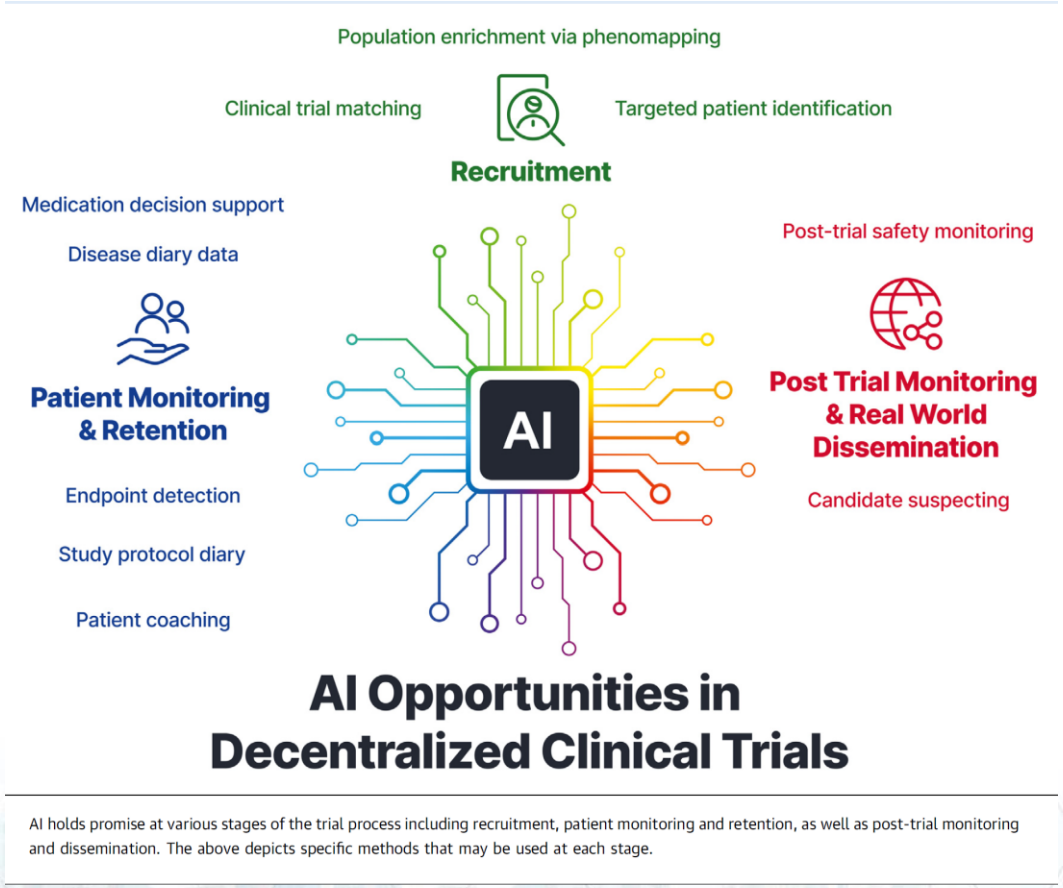
Future Directions and Innovations – AI in DCTs

- ***Artificial Intelligence*** *is a branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions/predictions.*

- ***Machine Learning*** *is a subset of AI that allows models to be developed through analysis of data, without models being specifically programmed.*

Utilization of AI-based algorithms to optimize patient selection and recruitment shows promise in improving trial efficiency.



Goldberg et al JACC Advances VOL. 3, NO. 8, 2024

Future Directions and Innovations – AI in DCTs

Population matching via Phenomapping

- Adaptive trial design using interim analysis can enrich a cohort with patients who are most likely to respond to treatment – reduce sample size by 18% in simulation of 2 large CV RCTs[1].

Natural language processing (NLP)

- NLP techniques may be applied to EMR to extract info for clinical trial endpoints and clinical eligibility databases for purposes of recruitment.
- A recent cardiology study multicenter INVESTED trial compared the effect of 2 influenza vaccines in reducing HF hospitalisation in 5260 participants with cardiovascular disease at 157 sites.
- They examined an Community Care Cohort Project (C3PO) NLP model (developed at one site) to adjudicate HF hospitalization when compared to the gold standard clinical events committee in the - excellent agreement of 93% with endpoints committee[2].

1. *Oikonomou et al npj Digital Medicine 2023 6:217.*
2. *Cunningham et al JAMA Cardiol. 2024 9(2):174–181.*

Summary and Conclusions

- Advances in digital health technologies and the COVID-19 pandemic have accelerated the development of DCTs.
- DCTs have the potential to reduce the burden on caregivers, expand access to more diverse populations, improve trial efficiencies (e.g. engagement, recruitment, enrollment, and retention).
- Mainly hybrid DCTs in cardiology, although there are examples of fully DCTs.
- Local challenges in implementing fully DCTs in SG (e.g. remote informed e-consent not allowed currently, data governance issues).