Session III: Sponsor Perspectives – What’s Working Now?

Facilitated by Megan Doyle, Amgen
10:40 a.m. – 12:15 p.m. EDT
Overview

Panelists

- Robert “Joe” Mather, Pfizer
- Alma Chavez, Duke Clinical Research Institute
- Scott Askin, Novartis
- Adam Hartman, NINDS
- Isaac Rodriguez-Chavez, ICON

Session Objectives

- Understand from sponsor perspective what works and what doesn’t for specific DCT solutions
- Discuss how to ensure DCT solutions are considered during study design, including as opportunities to streamline trials and reduce participant burden
- Identify considerations for effective and efficient safety monitoring in DCTs

Please share questions, comments, and ideas in the chat throughout the session
CTTI Case Study #1

Implementing a Decentralized Clinical Trial at Scale for COVID-19 Symptom Monitoring

Joe Mather
Executive Director
Head of Advanced Science Group

Early Clinical Development
August 26, 2021
Disclaimer

• This presentation is intended for non-promotional scientific purposes only and may contain information on products or indications currently under investigation and/or that have not been approved by the regulatory authorities

• This presentation is accurate at the time of presentation

• Any data about non-Pfizer products are based on publicly available information at the time of presentation

• Copyright vests with the respective author or owner of the title
1. Introduction
2. Case Study
3. Key Learnings
4. Summary
Decentralized or Flexible Clinical Trials

The FDA recently defined DCTs as the **decentralization of clinical trial operations** where technology is used to communicate with study participants and collect data.

Key elements of a decentralized or flexible trial design include:

- eConsent (electronic informed consent)
- Remote eConsent
- ePRO (patient reported outcomes or diaries)
- Home Health or Telehealth
- Direct to participant drug or investigational medical product delivery
- Participant self-collected samples
- Sensors/wearables
- Remote monitoring
- Remote source document review and source data verification
- Direct data capture (quality & reliability)

- **May provide patients more flexibility to participate in studies or recruit broader patient populations**
- **Heavy reliance on participant or caregivers to complete study activity**
- **Higher burden on vendors, technologies and site to ensure GCP guidelines are followed, that data quality and integrity as well as privacy and security are maintained and to ensure audit readiness throughout the study**
- **Critical need for study and site management & support systems**
Study Objectives
A Decentralized Clinical Trial at Scale for COVID-19 Symptom Monitoring

Primary objective build a voice and symptom algorithm(s) for detection and monitoring of SARS-CoV-2 illness and characterize the link between symptoms and voice features of SARS-CoV-2 positive participants.

Secondary objectives will assess app compliance; quality of voice recordings; infection rates for SARS-CoV-2/Influenza/RSV & feasibility of self-swabbing.

Impact:

- Characterizing self-reported voice and symptom profiles for acute respiratory illnesses and enabling their early detection benefits vaccine development.
- This study models concepts of efficient and flexible clinical trials: web-based participant recruitment, enhanced participant engagement and remote sample collection.
- This observational study will assess technology and its performance to enable deployment in future interventional studies.

BOYD App enabling remote ID verification, screening, consenting, symptom and voice recordings, and recording of self-swabbing.
Study Concept

Recruitment Screening & Testing
- Social media campaign advertising study website
- Study website with study requirements
- Links to download app.
- App download
- EULA/Privacy Terms
- In app pre-screening questions

Investigator & study team
- Confirm participant identity
- I/E questions
- Study Video
- ICD review
- eConsent signature

Study Participation
- Investigator & study & site support team
- Symptoms/Voice Daily Recording and Participant Initiated Swab/Testing
- Final Testing

Daily Tasks (Voice Collection & Symptom Reporting)
- Study data repository
- Study activity tracking
- PI review and eCosignature of ICD
- Dashboards for site & support staff & vendors
- Integrated test result review & return (participants & LHA)
- Payment tracking
- Email, phone & notifications
- Audit trail

Roles
- Participant
- App
- Recruitment
- Labs
- Investigator
- EDC
Remote eConsent
Remote eConsent

- eConsent on mobile app; fully remote and decentralized process
- Remote and automated identity verification in app - based on public data in of individuals
- Study video in app to inform participant
- Confirmation of individual’s understanding of the protocol elements and risks of the study
- Opportunity to ask questions and contact the investigator
- Relatively simple inclusion and exclusion requirements for study participation

Considerations for Future Trials

- Dual approach with alternative for remote consent through secure video conference where participant can meet with site staff and show proof of identity
- Interventional drug trials will need to consider more strict identity verification field checks if using automated ID verification service
- Secure communications will allow participant questions in real time to reduce loss or screen failures
Information & Study Management
Study Management

**Study Implementation**
- Mobile App available on iOS and Android phones; dependent on OS requirements (acoustic quality)
- Participants enrolling with older models of Android phones; hardware on phones results in issues with voice recordings
- Operational team portals for site, vendors and study team to manage and monitor study
- Operational & study tracking reports
- Patient addresses and courier delivery services
- Virtual payment cards for participant payments
- Data triggered payments based on eDiary compliance
- Site support for compensation support to participants

**Considerations for Future Trials**
- Regulatory barriers (currently a COVID-19 guidance from FDA)
- Option to procure phones for participants to streamline type of device used and enhance participant study experience
- eConsent tools capable for capturing remote signatures, future studies
- Site capabilities and compliance of tools (e.g., DocuSign, etc.); secure messaging platforms to contact participants
- Not all participants may have bank accounts (requirement for virtual payment cards)
- Access to account registration emails and record of instructions available for both vendor and site to help resolve issues
Remote Sample Collection
At home biospecimen collection

Study Implementation

- Two at-home self swab kits were sent directly to participant’s home in single shipment to reduce costs and time
- Sample collection and shipping Instructions included in the box
- Return of results direct to the participant via HIPAA compliant mechanism and site reporting to required health authorities

Considerations for Future Trials

- Participant confusion on whether both swabs should be taken at once; consider shipping separately based on study design considerations
- Engagement of participants to complete both swabs at different time intervals is challenging - consider less samples or have additional site reminders; flexible collection options
- Some kits may get lost or stolen; no accurate way to tracking to understand confirmation of receipt

Shipping, shipping, shipping!
Summary

• The primary objective of the study is to obtain data to build a voice and symptom algorithm based on patient-reported symptoms, voice and PCR test results

• This study models the concepts of **efficient and flexible clinical trials**: web-based participant **recruitment**, enhanced **participant engagement**, and **remote sample collection**

• If successful, we hope that characterizing **self-reported voice and symptom** profiles for acute respiratory illnesses will **enable their early detection** and would benefit future vaccine development programs

• We have **demonstrated** some of the technical and operational hurdles we have overcome in implementing **a fully decentralized study at scale** under tight timelines

• Future clinical studies will benefit from technical and operational systems that enabled the study
Further Considerations

• Does your organization understand the risks associated with the study?
• Do you have the systems to collect, monitor and audit the quality of data collected?
• Do the patients understand what is being asked of them?
• Does the data collected meet the quality requirements for the study?
• Does the investigator and site have capacity to run the study?
• Do you have the vendor, site support and study monitoring systems in place?

Expect the unexpected!
Thank You
Acknowledgements

**ECD | DMTI**
- Paul Wacnik
- Mar Santamaria
- Pirinka Georgiev
- Charmaine Demanuele
- Yao Zhang
- Yiorgos Christakis
- Kara Chappie
- Tomasz Adamusiak
- Jessica Selig
- Stephanie-An Lyle
- Bhavna Adhin
- David Caouette
- Xuemei Cai

**GPD**
- Tim Joy
- Jennifer Wulff
- Penny Ross
- Brett Wilson
- Sarah Tweedy
- Pamela Lai
- Sherrie LaRue
- Patricia Phelps
- Charmagne Crescini
- Kimberly Ho
- Lily (Qiaoli) Chen
- Sara Pierson
- Susan Pagano
- Chris Dell
- Charmagne Crescini
- Jil Vosland
- Kris Kokomoor
- Meenal Gawas
- Sarah Jarvis
- Qing Zhou
- Helen Yang
- Lewis Watkins

**Diagnostics**
- Renee Yura
- Hakan Sakul
- Adriana Cahill
- David Cooper

**Digital**
- Sachin Karnik
- Robb Linde

**Legal**
- Christopher Eliopulos
- Parthena Psyllos

**Executive Sponsors**
- Kathrin Jansen
- Sandeep Menon
- Phil Dormitzer
- William Gruber
- Demetris Zambas
- Timothy McCarthy

Special thanks to the investigators, site staff and vendors that made this possible!
Study Status

Milestones
- Study launched April 15th, 2021
- 1,241 of 6,250 participants enrolled in 28 days!
- 50% enrollment completed by June 30th, 2021

Enrollment
Total 3,514 enrolled including screen failures
- 404 have screen failed
- 105 participants are currently enrolled in the study now
- 2,737 have completed their eDiary activities/the study
- 268 have been discontinued
- Demographic, diversity recruitment objectives are on track with goals

BOYD App enabling remote ID verification, screening, consenting, symptom and voice recordings, and recording of self-swabbing
CTTI
Decentralized Clinical Trials Expert Meeting
August 26, 2021
Sponsor Perspectives – What’s Working Now?
PROACT Xa Trial Design

Patients with On-X aortic valve replacement >3 months prior (n=1000)

Randomize

Apixaban 5 mg BID
Apixaban 2.5 mg BID in selected patients

Open Label

Continued warfarin
INR goal 2.0 – 3.0

2 year follow-up (≥800 patient-years in each arm)

Primary endpoint: composite of valve thrombosis or valve-related thromboembolism
Secondary endpoints: components of primary composite endpoint, major bleeding

Co-Primary Analyses:
1) Apixaban non-inferior to warfarin with absolute NI margin of 1.7%/patient-year
2) Apixaban primary outcome 95% CI below objective performance criteria (OPC) of 3.4%/patient-year
Rationale and design of PROACT Xa: A randomized, multicenter, open-label, clinical trial to evaluate the efficacy and safety of apixaban versus warfarin in patients with a mechanical On-X Aortic Heart Valve ☆, ♦, ⋆, ✴

Objectives

- Understand from sponsor perspective what works and what doesn’t for specific DCT solutions
- Discuss how to ensure DCT solutions are considered during study design, including as opportunities to streamline trials and reduce participant burden
- Identify considerations for effective and efficient safety monitoring in DCTs

Landscape Scan for CTTI DCT Update Project
Completed 16 April 2021
I. High Level Findings

**Anticipated Benefits of DCT Solutions Adoption**
- Higher participant enrollment, compliance, satisfaction and retention
- Broader geographic reach (e.g. rare disease)
- Shorter drug development timelines
- Cost savings
- Data captured in real world settings, improving the validity and generalizability of results
- Decentralized elements can be used selectively on a fit for purpose basis for a given trial

**Barriers to Decentralized Clinical Trial (DCT) Solutions Adoption**
- Variations in global legal and regulatory requirements and uncertainty around future change
- Technology platform variations across sites
- Lack of data demonstrating cost vs benefit
- Lack of data demonstrating impact on and preferences/needs of sites and participants
- Need for practitioners to share methods and evidence for those methods
- Need for change management within sponsor organizations
- Need for new processes and procedures to optimize implementation of DCT elements
Sponsor Perspective: Overview of “Deliverables”

Significant timelines:

- 02/Sep/2019 - Study May Proceed
- 15/Jan/2020 - protocol finalized
- 23/Mar/2020 - Investigators Meeting

🌟 = Activated
🌟 = Enrolling
Stakeholders

- CryoLife
- Duke Clinical Research Institute (DCRI)
- ThermoFisher / Fisher BioServices
- WCG / local Institutional Review Boards
- Investigative Sites
- Patients / participants
- Anyone & Everyone
Significant timelines:
- 02/Sep/2019 - Study May Proceed
- 15/Jan/2020 - protocol finalized
- 23/Mar/2020 - Investigators Meeting
- 24/Apr/2020 - 1st site activated
- 04/May/2020 - 1st participant enrolled
- 26/Aug/2021 - 54 sites activated
  # participants enrolled

= Activated

= Enrolling
Objectives

- Understand from sponsor perspective what works and what doesn’t for specific DCT solutions

- Identify considerations for effective and efficient safety monitoring in DCTs

- Discuss how to ensure DCT solutions are considered during study design, including as opportunities to streamline trials and reduce participant burden
...And that is why we lift on three...
Decentralized Clinical Trials
Multi-Stakeholder Expert Meeting

Sponsor Perspectives – What’s Working Now?

Scott Askin, Global Program Regulatory Director, RA Innovation
Presented at CTTI Workshop 26th August 2021
Disclaimer

- This presentation is intended for non-promotional scientific purposes only and may contain information on products or indications currently under investigation and/or that have not been approved by the regulatory authorities.
- This presentation is accurate at the time of presentation.
- Any data about non-Novartis products are based on publicly available information at the time of presentation.
- Copyright vests with the respective author or owner of the title.
Agenda

▪ Identifying DCT Opportunities
  – A Systematic Evaluation of the Portfolio

▪ Case Study
  – Lesson’s Learned from the Trial

▪ Why is Moving to Scale Challenging
  – Complexity & Risk

▪ Lesson’s Learned - A European Perspective
  – Areas still to be Addressed
Identifying DCT Opportunities
Systematic Evaluation of the Portfolio
Identifying near-term Trials that may benefit from DCT Implementation

- **Background:** Agreement with Development Units to systematically evaluate whether upcoming trials could benefit from DCT elements
- **Purpose:** Understand what trials are interested in DCT elements and reasons for low / lack of interest
- **Scope:** Interventional trials (Phase II-III) with planned FPFV within the next year
- **Format:** Qualitative self-assessment of interest in DCT elements

**What teams were asked;**
- How could your target patient population (& caregivers) benefit by incorporating remote trial options?
- Could the study treatment be administered at home, either self-administered or with support of a nurse?
- Could the objectives of the trial be reliably measured using DCT remote option(s)
Greatest interest was in Offsite Healthcare Professionals (i.e. Home Nursing)

Direct to Patient Drug Shipments also featured very heavily in interest & value to trials

Use of Telemedicine not featured as heavily as anticipated

Local Healthcare Providers (HCPs) also perceived as adding value to trials

Outcome of Systematic Evaluation

*Of the trials evaluated, 19 expressed an interest in implementing 1 or more DCT elements*

- IMP safety concern
- Patient safety concern
- Subjective endpoint requiring assessment by specialist
- Procedure not suited to home setting (e.g. MRI, invasive)
- Program timelines

Next Steps; Deeper dive into trials that expressed interest to support implementation, & further investigate those trials not expressing interest to determine rational (i.e. lack of awareness, disease related etc)
Case Study
Global Phase III, open label extension

Adolescent & Adult Sickle Cell Disease patients participate via Traditional on-Site model for first year after which, at selected sites & with PI's discretion, and based on defined criteria, patients offered a switch to a Hybrid approach.

- Monthly visits take place in between these, where patients may be offered remote visits supported by offsite Healthcare Professionals & a telemedicine platform, along with other services listed.

- Patients attend at least bi-annual visits (in-person) at their existing site, throughout the trial.

Traditional Onsite | “Hybrid Approach” (Onsite+Offsite)

Year 1 | Years 2 to 5
Key Learnings so Far?

Learnings primarily relate to trial initiation & set up activities as implementation of the remote DCT elements are in their relative infancy

- Tri-party agreement/contracts, which are recommended by EMA in the case of Home Nursing/Offsite Healthcare Professionals, take time to implement
- Privacy is often raised as a concern, but GDPR interpretation differs across EU National Competent Authorities, so tailored solutions may be required
- An “Operations Manual” has been required as part of the Clinical Trial Application in some countries, so early assessments of local requirements are encouraged
- Transportation of IMP to the patient’s home requires additional effort to demonstrate stability
- Go/No Go criteria required to support PI in decision making that enables patients to transition to home visits
Why is Moving to Scale Challenging?
Complexity & Risk Increase with Scale!

1 Country x 3 Technologies/Services = 9 Items to Evaluate

CTTI Decentralized Clinical Trials Multi-Stakeholder Expert Meeting – August 2021

*DCT Model = Fully Remote, Hybrid, Side-by-Side
Complexity & Risk Increase with Scale!

2 Countries x 3 Technologies/Services = 18 Items to Evaluate

- Procedures/Tests
- Patient Population
- DCT Model*
- Home Nursing
- Local HCPs
- Telemedicine

*DCT Model = Fully Remote, Hybrid, Side-by-Side
Complexity & Risk Increase with Scale!

4 Countries x 3 Technologies/Services = 36 Items to Evaluate

- Telemedicine
- Home Nursing
- DCT Model*
- Local HCPs
- Procedures/Tests
- Patient Population

*DCT Model = Fully Remote, Hybrid, Side-by-Side
Complexity & Risk Increase with Scale!

8 Countries x 3 Technologies/Services = 72 Items to Evaluate

- Telemedicine
- Local HCPs
- Home Nursing

Procedures/Tests
Patient Population
DCT Model*

US
Germany
Japan
China

*DCT Model = Fully Remote, Hybrid, Side-by-Side
Lesson’s Learned - A European Perspective
Consolidated Lesson’s Learned & Feedback

The benefits of DCTs with its enabling technologies are broadly endorsed and the need for global adoption is recognized, however....

• Health Authorities advise 1) “Baby Steps”, 2) Early advice meetings, 3) Describing DCT elements in CTA Cover Letters

• Compliance with ICH GCP guidelines for digital approaches is critical, but not well defined

• Demonstration of Investigator oversight of Patients, Local HCPs & offsite health care providers is required

• Data quality & Investigator Control of data must be ensured for all digital approaches

• Comparability between onsite and remotely assessed endpoints is critical

• Some HA’s require/prefer initial visits to be conducted on site

• Risk assessments requested for DCT elements being implemented

• Whilst COVID-19 has increased the awareness of DCT and demonstrated some feasibility, it hasn’t “flipped the switch” regarding Health Authority acceptance

• Not all countries are in the same place: understanding, experience and stage of guideline development

• Complexity is driven by many factors, in addition, not everything is under the responsibility of HAs
Back-Up
Spotlighting some Key European DCT Activities
DCT Projects in the Nordics

Initiatives in Sweden and Denmark

Denmark’s DKMA has initiated an industry forum to have open dialogue with the research community, including hospitals, patient associations, CROs and pharma, on the topic of decentralization.

Sweden’s MPA has developed a pilot program, where they plan to initiate up to 5 DCT trials in Sweden. Free trial application and Scientific Advice is also provided to successful applicant.
The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking (H2020-JTI-IMI2) Trials@Home grant n° 831458.

Innovative Medicines Initiative

Europe’s Partnership for Health

- IMI1 programme (2008-2013), the total budget was €2 billion
- IMI2 programme (2014-2020), the total budget was €3.276 billion
- Innovative Health Initiative (replacement for IMI), has a proposed budget of €2.4 billion

~50% comes from the European Commission
~50% comes from EFPIA (IMI 1 & 2) and COCIR, EFPIA, EuropaBio, MedTech Europe and Vaccines Europe (IHI)

Under IMI 1 & 2

<table>
<thead>
<tr>
<th>€5.3bn</th>
<th>168 PROJECTS</th>
<th>5,244 PARTICIPANTS</th>
<th>&gt;7,000 PROJECT OUTPUTS</th>
<th>&gt;3,800 PUBLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUDGET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

https://www.imi.europa.eu/
Centre of Excellence for Remote & Decentralized Clinical Trials

Trials@Home aims to reshape clinical trial design, conduct and operations, by developing and piloting standards, recommendations and tools for the definition and operationalization of remote decentralized clinical trials (RDCTs) in Europe.

Key objectives:

- Defining the best practices for the conduct of RDCTs.
- Identifying technologies and other operational innovative approaches for RDCTs and selecting the appropriate technology package to be used for the pan-EU pilot.
- Designing and running a pan-EU pilot, comparing the scientific and operational quality of the RDCT with traditional trial approaches and evaluating the feasibility of the RDCT.
- Identifying, mapping and analysing the relevant ethical, quality, regulatory, legal and organisational barriers and enablers of RDCTs.
- Consulting with stakeholders and promoting the outcomes from the Trials@Home consortium through targeted communication, dissemination and training activities.
- Providing recommendations with supporting tools for implementing RDCTs in Europe and contributing to the update of ICH guidelines on RDCTs.
The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking (H2020-JTI-IMI2) Trials@Home grant no. 831458.

Project Organization: Work packages
The six Work Packages (WPs) of Trials@Home and their interdependencies
The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative (H2020-JTI-IMI2) Trials@Home grant no. 831458.
Panel Discussion

- Megan Doyle, Amgen (Moderator)
- Scott Askin, Novartis
- Alma Chavez, Duke Clinical Research Institute
- Adam Hartman, NINDS
- Robert “Joe” Mather, Pfizer
- Isaac Rodriguez-Chavez, ICON