CLINICAL TRIALS TRANSFORMATION INITIATIVE

Optimizing Data Quality and Flexibility in Clinical Trials

CTTI Expert Meeting

February 26, 2025

Welcome to CTTI's Optimizing Data Quality and Flexibility in Clinical Trials Expert Meeting

- This meeting is being recorded for note taking purposes only.
- Open discussion is encouraged and fostered by respect and collaboration.
- Virtual participants- please enter questions into the chat. Kindly no AI recording notetakers.

Here's to a great day of discussion and learning from one another!

Agenda

Time (EDT)	Content
08:30 a.m.	Welcome and Opening Remarks
09:00 a.m.	Project and Quality by Design Overview
09:20 a.m.	Session 1: State of Flexible Trial Approaches and Case Examples
10:30 a.m.	Break
10:45 a.m.	Session 2: Offering Flexible Approaches (Roundtable Discussions Part 1)
12:15 p.m.	Lunch
1:15 p.m.	Opening Remarks: Data Quality
1:40 p.m.	Session 3: Assessing Data Quality (Roundtable Discussions Part 2)
3:10 p.m.	Recap Discussion and Concluding Remarks
4:00 p.m.	Adjourn

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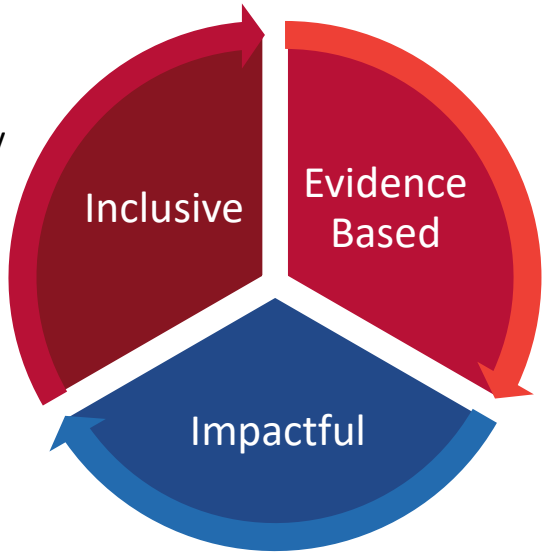
The Clinical Trials Transformation Initiative (CTTI)

MISSION

To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials.

VISION

A high-quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based therapeutic prevention and treatment options.



PUBLIC-PRIVATE PARTNERSHIP

- Co-founded in 2007 by FDA and Duke University
- Active collaboration with +500 individuals and groups
- All materials are freely available

SCOPE

Focus on clinical trials of FDA-regulated medical products, recognizing that clinical trials are international and acting as a collaborative global citizen.

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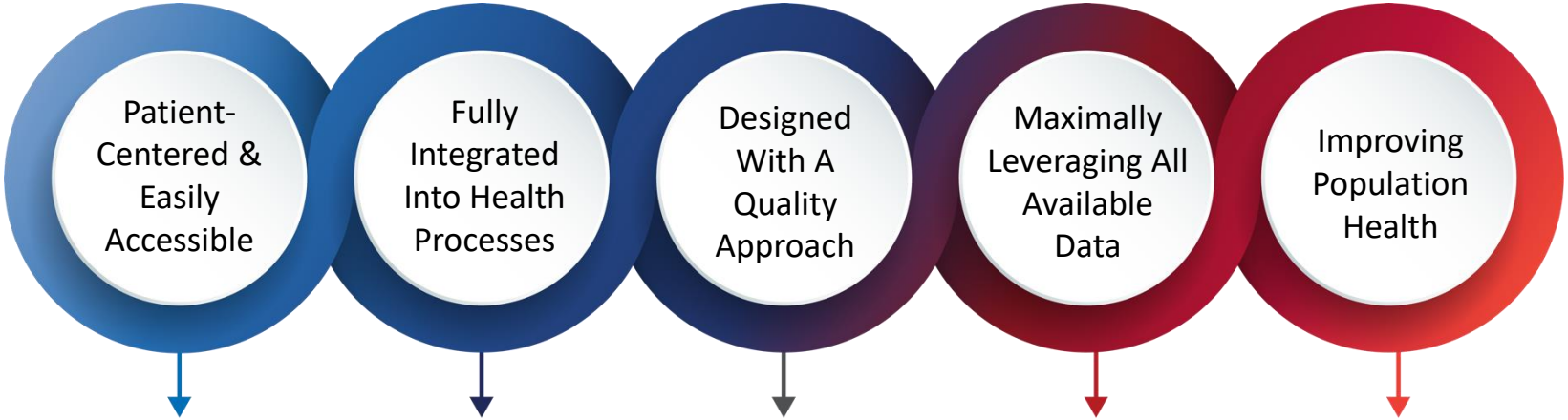
Transforming Trials 2030

By 2030, clinical trials need to be:



A critical part of the Evidence Generating System

https://ctti-clinicaltrials.org/who_we_are/strategic-vision/

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CTTI Membership

Version: February 4, 2025

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Social Media Sharing

- Social media is a great tool for sharing your CTTI involvement – and we'd love for you to share!
- We ask that you refrain from sharing sensitive information (i.e., photos of slides, information from private meetings, etc.)
- Please DO share:
  - Photos of yourself at meetings
  - Photos with others who have given you permission to share on social media
  - About your involvement/participation with CTTI meetings and projects
- When you share on social media, please tag us so we can re-share!
  - X/Twitter: @CTTI_Trials
  - LinkedIn: Clinical Trials Transformation Initiative

Example of a great social media post

Ricki Fairley

Chief Executive Officer

Touch, The Black Breast Cancer Alliance

touch
THE BLACK BREAST CANCER ALLIANCE

GET IN TOUCH!

MY STORY...


Kaiser Permanente
Certificate of Completion


WALKING IN BLESSINGS!


THRIVER


MAGIC TOUCH
MAGIC TOUCH
MAGIC TOUCH

The State of Black Breast Cancer

Breast cancer is the most fatal health issue for Black women. Our disease is different, unique and warrants special and focused attention. Black women diagnosed with breast cancer face:

41% **Higher mortality rate compared to white women.**

39% **Higher risk of breast cancer recurrence.**

71% **Higher relative risk of death compared to white women.**

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THE STATE

Black women under 35

Black women under 50

Black women are nearly twice

Black women are 3 times

The State of Black Breast Cancer

Black women with private insurance are 60% more likely to die of breast cancer than White women with private insurance

Black women residing in high socioeconomic neighborhoods are 126% more likely to die than white counterparts residing in similar neighborhoods

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Black women are more likely than White women to die of breast cancer at any age across any sub-type

Black women have the lowest 5-year relative breast cancer survival rate compared to all other racial/ethnic groups for every stage of diagnosis and every breast cancer subtype

The State of Black Breast Cancer

The physiology of Black women has not been a consideration in clinical trial research.

- The clinical trials for the current standard of care drugs have had little to no inclusion of Black women.
- The average Black women participation rate for current breast cancer clinical trials is less than 3%.

Clinical trial education, recruiting, and participation are not commensurate with the state of disease.

Dr. Sheeba Irshad, PhD, MRCP, MBBS, BSc

Breast Cancer Medical Oncologist

Cancer Research UK Clinician Scientist

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Clinical Trial Participation Needs to be Commensurate with the Burden of Disease!

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Why Don’t **BLACK WOMEN** Participate in Clinical Trials?

Doctors don’t invite Black women to clinical trials.

When the patient brings up the conversation, they still walk away not sufficiently informed.

Since we have negative history, and minimal awareness/understanding of clinical trials and research, Black women fear the unknown.

“Don’t do a clinical trial! You will get the sugar pill and die.”

Metastatic Patient

SOCIAL MEDIA, WEBSITE, AND ADS METRICS: CUMULATIVE & COMPREHENSIVE

01.26.22 - 12.31.24

WHEN WE TRI(AL) CAMPAIGN

WEBSITE VISITS
178,912

UNIQUE WEBSITE VISITS
54,095

WEBSITE SIGN-UPS
1,852

CLINICAL TRIALS SEARCH
22,642

SOCIAL IMPRESSIONS
1,228,623

SOCIAL INTERACTIONS
456,786

SOCIAL CONVERSIONS
126,392

SOCIAL CONVERSION RATE
43%

TOUCH Care

To facilitate the clinical trial process for Black women, TOUCH is providing a Nurse Navigator Service to assist patients with securing trials, the application process, managing the informed consent process and providing coaching and counseling throughout the trial.

PATIENT NAVIGATION

A navigation program that addressed insurance, food, housing, transportation, language, health literacy, social and clinical needs **increased participation in clinical research**:

	Before Navigation*	After Navigation*
Rural	19%	40%
Black	13%	41%
Hispanic	5%	33%

* Participation (% of patients)

AACR Cancer Disparities Progress Report 2024

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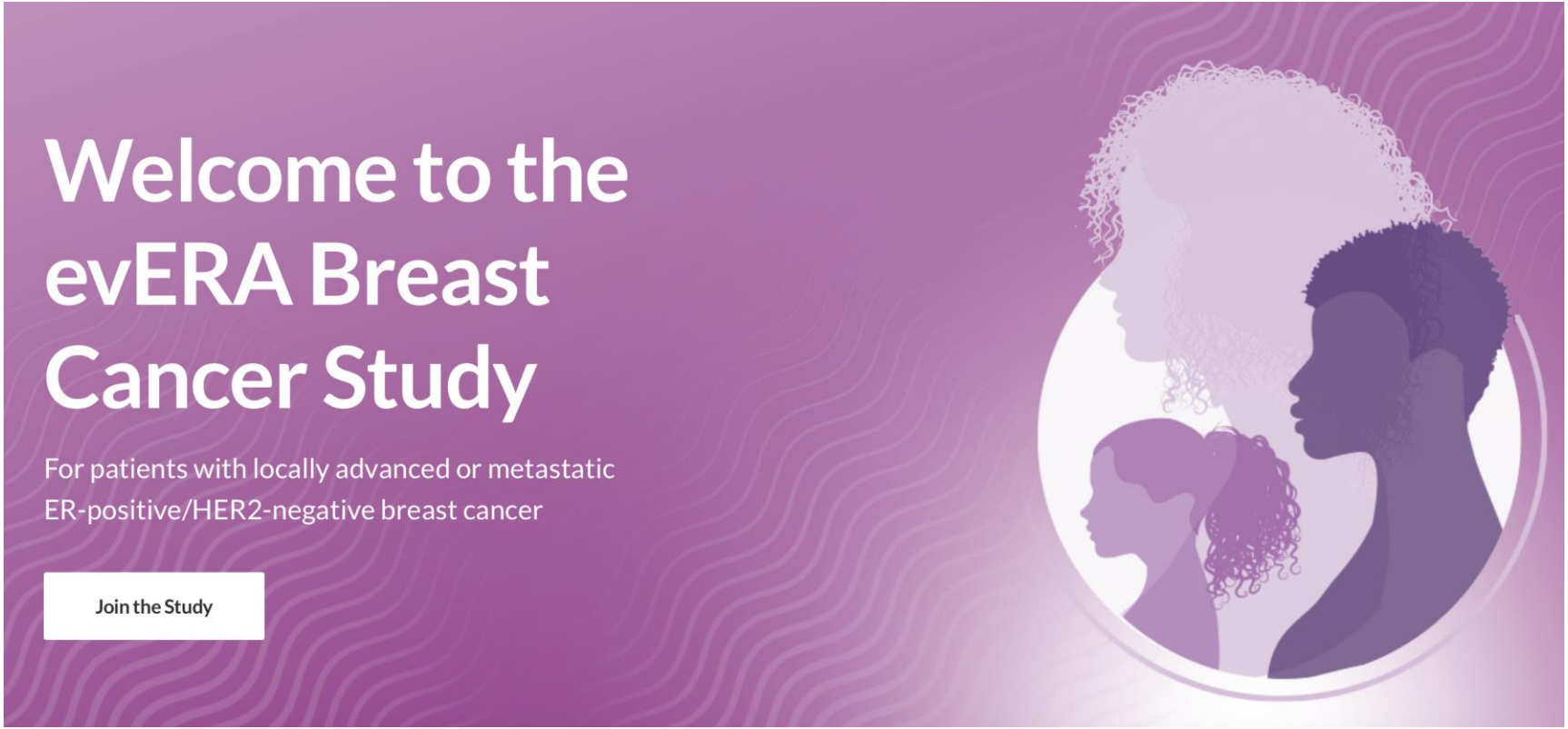

EveraBreastCancerStudy.com

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2% to 12%
Black Women in the Trial

"Participating in a clinical trial is like building a medical trust fund for my three babies."
Latoya Bolds-Johnson

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THE WHITE HOUSE

SEPTEMBER 13, 2023

FACT SHEET: As Part of President Biden's Unity Agenda, White House Cancer Moonshot Announces New Actions and Commitments to End Cancer as We Know It

- **TOUCH, the Black Breast Cancer Alliance, will bolster Black women's breast cancer clinical trial participation by 2025 committing to reaching 350,000 Black women and motivating 25,000 into trial portals.** Additionally, TOUCH Care, the first program to provide a nurse navigator service to assist Black breast cancer patients in clinical trials by developing culturally-agile recruiting materials, training trial staff, and coaching patients, is being piloted with Genentech, a member of the Roche Group, and will add five trials annually. Less than three percent of breast cancer clinical trial participants are Black.

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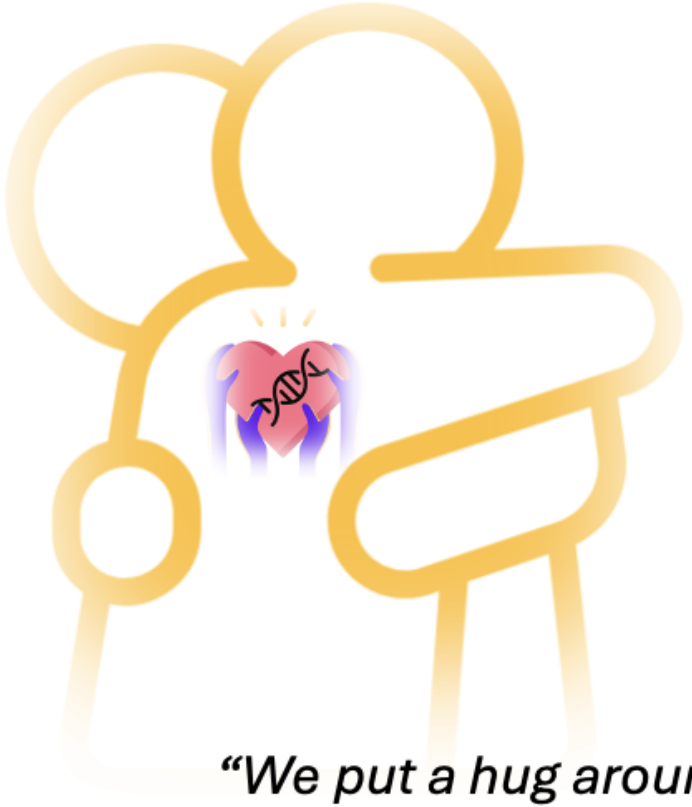
Ricki’s Ideal Clinical Research Scenario

The Golden Rule

Treat others the way YOU want to be treated.



“We put a hug around the science.”

THANK YOU!

Optimizing Data Quality and Flexibility in Clinical Trials

Project and Quality by Design Overview

Ann Meeker-O'Connell
Food and Drug Administration

Lindsay Kehoe
Clinical Trials Transformation Initiative

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Definitions

For the purpose of this project, CTTI defines:

- **Flexibility** as operational approaches that include:
  - (1) *integrating trials* into clinical practice (e.g., extracting data from EHR for trial purposes)
  - (2) incorporating *decentralized* elements (e.g., remote data collection, use of local health care providers, use of tele-visits and home study visits); and
  - (3) individualizing the setting for which data is collected during trial conduct, providing participants with *options* based on their individual needs and preferences (i.e. choice).
- **Data quality** as fit for purpose, credible and reliable*
  - Fit for purpose means the data are of sufficient quality to support good decision making and do not contain errors which may have a meaningful impact on the safety of trial participants or credibility of the results.

*reliability includes accuracy, completeness and traceability

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Bringing Quality Trials to Patients

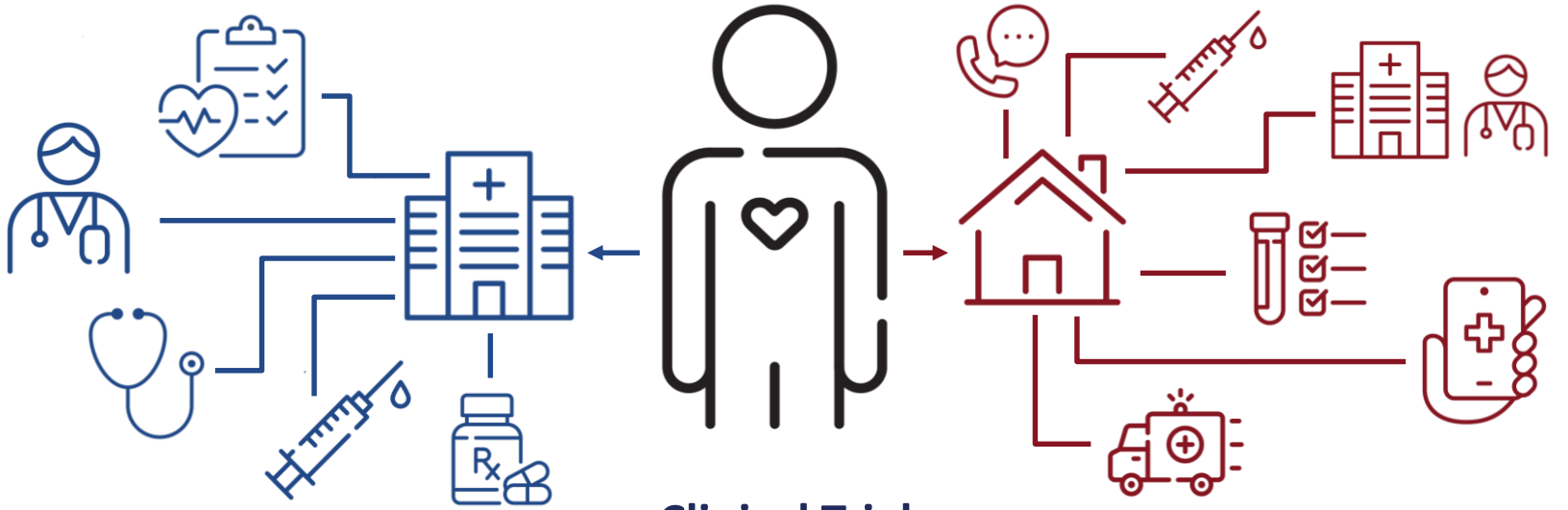
QbD Principles are Key: Address Important Risks to Study Quality

Meet with Regulators

Plan Ahead & Test New Approaches

Trials in Clinical Practice

Decentralized Approaches



Clinical Trials

Engage Relevant Parties Early and Often: Esp. Patient & Site Needs, Expectations

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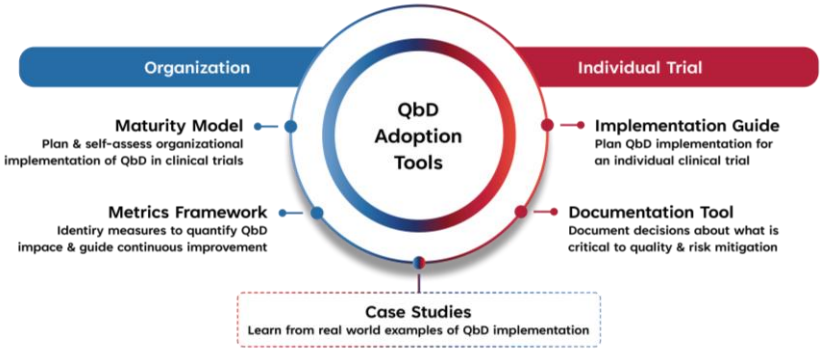
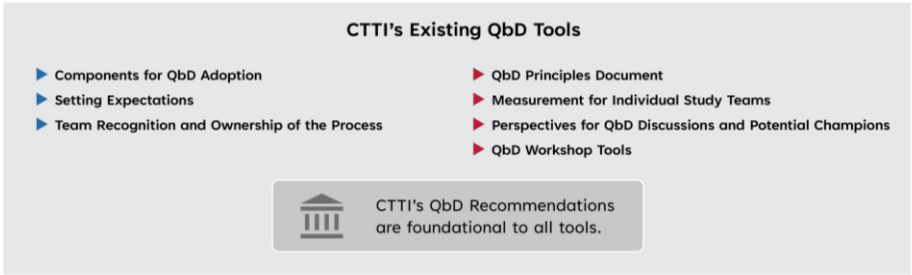
Foundational CTTI Work – Quality by Design (QbD)

- Incorporating quality into the scientific and operational design and conduct of clinical trials
  - identify critical-to-quality factors (i.e., those that are likely to have a meaningful impact on participant's rights, safety and well-being and the reliability of the results)
  - eliminate non-essential procedures and processes
- An element of CTTI's TT2030 Vision – Designing with a quality approach





https://ctti-clinicaltrials.org/our-work/quality/quality-by-design/

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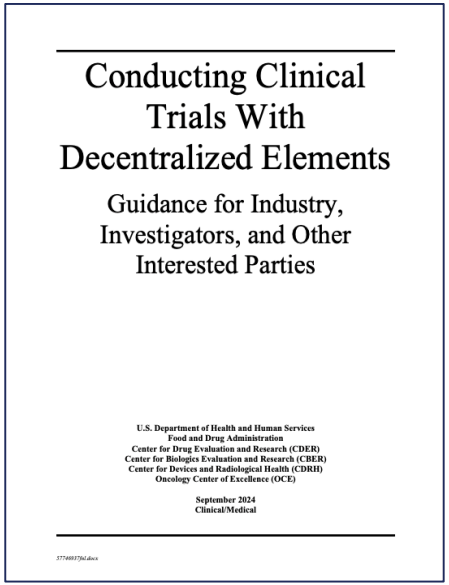
Newly Released Guidance Supporting Flexible Approaches and QbD



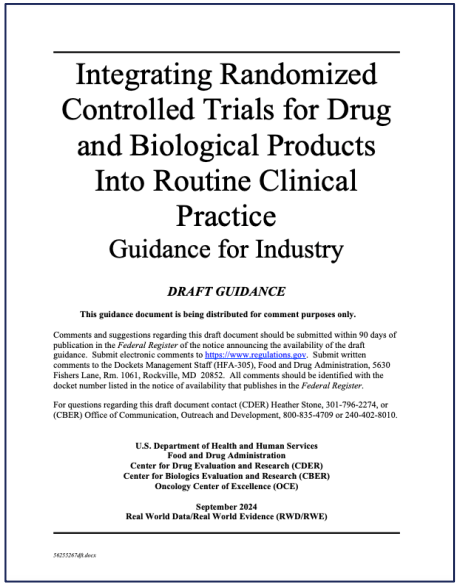
Conducting Clinical Trials With Decentralized Elements

Guidance for Industry, Investigators, and Other Interested Parties

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

September 2024
Clinical/Medical

https://www.fda.gov/media/181871/download



Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Heather Stone, 301-796-2274, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2024
Real World Data/Real World Evidence (RWD/RWE)

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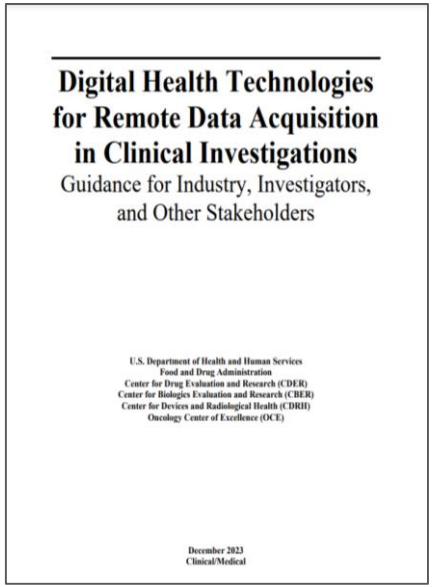


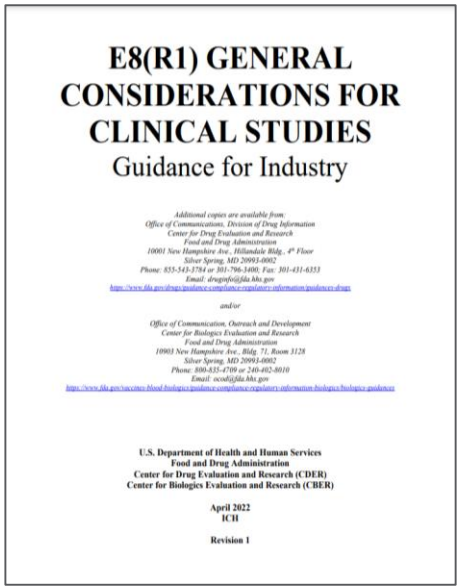
Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

December 2023
Clinical/Medical

https://www.fda.gov/media/155022/download



E8(R1) GENERAL CONSIDERATIONS FOR CLINICAL STUDIES

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2022
ICH

Revision 1

https://www.fda.gov/media/157560/download

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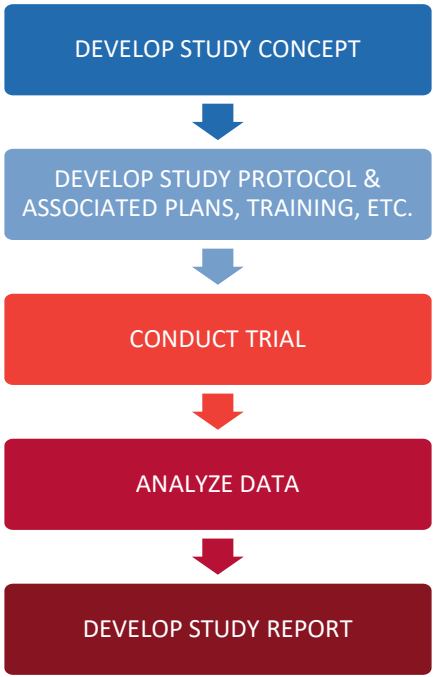
QbD Approach to **Study Design**



Engage all stakeholders to…

- **Identify critical to quality aspects** of trial design and potential challenges
- **Tailor design** to avoid errors that could undermine evaluability or safety
- **Streamline** trial where feasible
- **Verify** proposed design is consistent with scientific question
- **Highlight and evaluate** residual risks

- Operationally feasible trial designs
- Efficient, focused trial oversight plans (e.g., monitoring, data management)

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CTTI Project Objectives

Optimizing Data Quality and Flexibility in Clinical Trials

- Identify the range of flexible operational approaches and how the approaches might affect data quality
- Seek consensus around critical concerns for data quality
- Describe considerations for maintaining data quality when using flexible operational approaches in interventional clinical trials

Scope: Flexibility is scoped to operational approaches, not in terms of utilizing results accumulated in the trial to modify the trial's course (i.e. adaptive trials).

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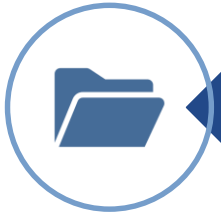
Potential Project Outputs



Case examples of Flexible Trials

Multi-partner Responses to Case Examples

Framework and/or Resource Library

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Project Team

Team Leaders

- **Cheryl Grandinetti** (FDA/OSI)
- **Pamela Tenaerts** (Medable)
- **Jimmy Bechtel** (SCRS)
- **Dema Hakim** (MJ Fox Foundation)

EC Champion

- **Ed Ramos** (CareEvolution)

Social Science Team

- **Amy Corneli** (Duke)
- **Blythe Fortino** (Duke)

Team Members

- **Elena Boley** (FDA/OSI)
- **Wes Burian** (Patient)
- **Jose Galvez** (FDA/OSP)
- **Catherine Gregor** (Florence Healthcare)
- **Raffaella Hart** (BRANY)
- **Sara Hassani** (NIH)
- **Patricia Hurley** (HRC Research Services)
- **Greg Licholai** (Yale)
- **Patrick Nadolny** (Sanofi)
- **Emma Ogburn** (Lindus Health)
- **Thomas Rauch** (BI)
- **Amy Rogers** (University of Dundee)
- **Michelle Rowe** (HCA Healthcare)
- **Jessica Shore** (Pulmonary Fibrosis Foundation)
- **Shari Targum** (FDA/CDER)
- **Michael Torok** (Roche)
- **Anne Trontell** (PCORI)
- **Salina Waddy** (NIH)
- **Marion Wolfs** (BMS)
- **Ken Wiley** (NIH)

CTTI STAFF

- **Lindsay Kehoe** (Project Manager)
- **Hannah Faulkner** (Communications Lead)

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Joan Chambers

Senior Consultant

Tufts Center for the Study of Drug Development

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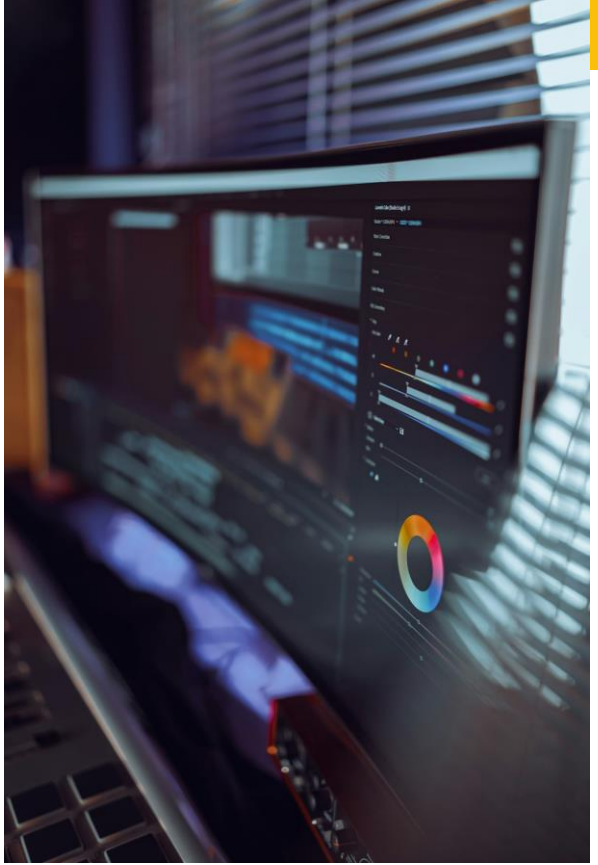
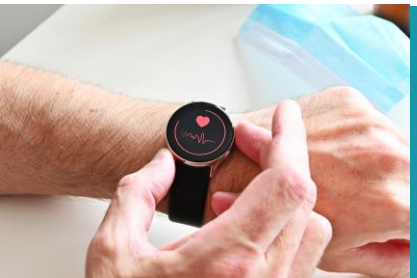
PACT
Partnership for Advancing Clinical Trials

February 26, 2025

CTTI's Optimizing Data Quality and Flexibility in Trials





Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

PACT
Partnership for Advancing Clinical Trials

Agenda

- Industry Insights
- PACT Consortium Overview
- Early 'Evidence' Characterizing DCT Usage and Experience
- Evolving Evidence Needs and Gaps
- Closing Comments

Industry Insights

- Patient recruitment is the leading reason most clinical trials fall behind schedule
- Only **2%-5% of U.S. patients** participate in clinical trials, prompting sponsors to enhance their recruitment support
- Just **27% of screened participants** meet the eligibility criteria, increasing screening costs due to high attrition
- Patients are central to clinical trials, driving progress in therapy development and care innovation
- Clinical trial sponsors prioritize patient participation and trial completion
- Research highlights key participation barriers, including access challenges and indirect expenses
- Studies also reveal that lack of support for baseline medications hinders participation and increases drop-out rates, particularly among socio-economically vulnerable populations
- An integrated, ecosystem-wide approach is essential for raising awareness and ensuring efficient, representative trials

Source: L.E.K. Consulting Executive Insights, Feb 2024

Study Volunteer Participation Burden

Pre-Study Experience

After Reviewing the Informed Consent From, what led you to decide NOT to participate	Percent of Total
Expected burden of participation	54%
Scientific/study risks	25%
Lack of sufficient information	14%
Concerns about privacy and confidentiality	7%

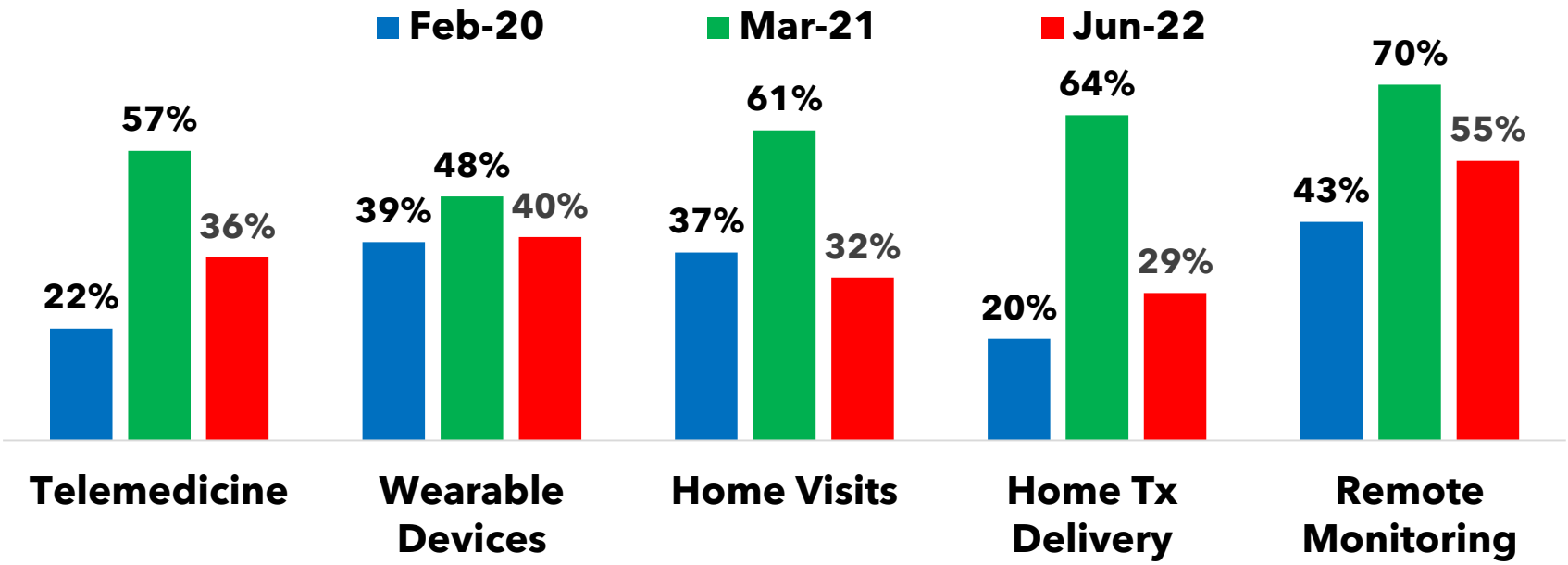
Post-Study Feedback

What did you least like about your participation experience? *(Top 5 mentions)*	Percent of Total
Not knowing whether I was getting the investigational treatment	30%
Location of the research center	22%
Study visits were too time consuming	19%
Compensation was not enough given the demands of the study	16%
Study procedures were too cumbersome	15%

Source: Tufts CSDD Analysis

Remote and Virtual Solutions Adoption

Percent of Companies Report Deploying

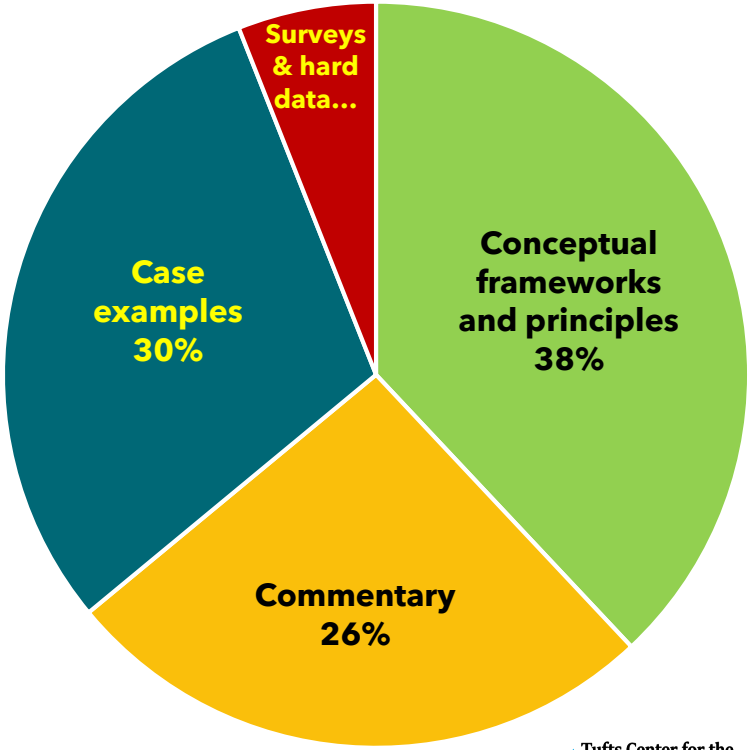


Source: Tufts CSDD; N=54 individual companies

MACRO Scan of DCT in the Literature

- **>16,500 total scholarly articles since 2022**
- **Very few with empirical evidence**

- **Root Causes:**
  - **Retrenchment, lower levels of adoption**
  - **Lack of consensus definitions and measurement**
  - **Highly customized deployments**
  - **Poor data collection practices**



CONSORTIUM 2024 – Methods

- **Sampling frame, variables of interest, and definitions via consortium consensus:**
  - **Sampling Characteristics:**
    - **Ongoing and recently completed clinical trials (database lock or primary completion data January 2018 or later)**
    - **All phases**
    - **All disease areas**
    - **All age groups**
    - **All countries**
    - **Traditional and adaptive designs**
    - **CROs only provide data on clinical trials from companies not participating in the consortium**
- **34 Member Companies (Sponsors & CROs)**
- **Baseline Assessment conducted in late 2023**
- **Data collection workbook, developed through consortium collaboration**
- **Data collection conducted between January 2024 and late spring 2024**
- **N = 69 total trials for which data was collected from 14 companies**

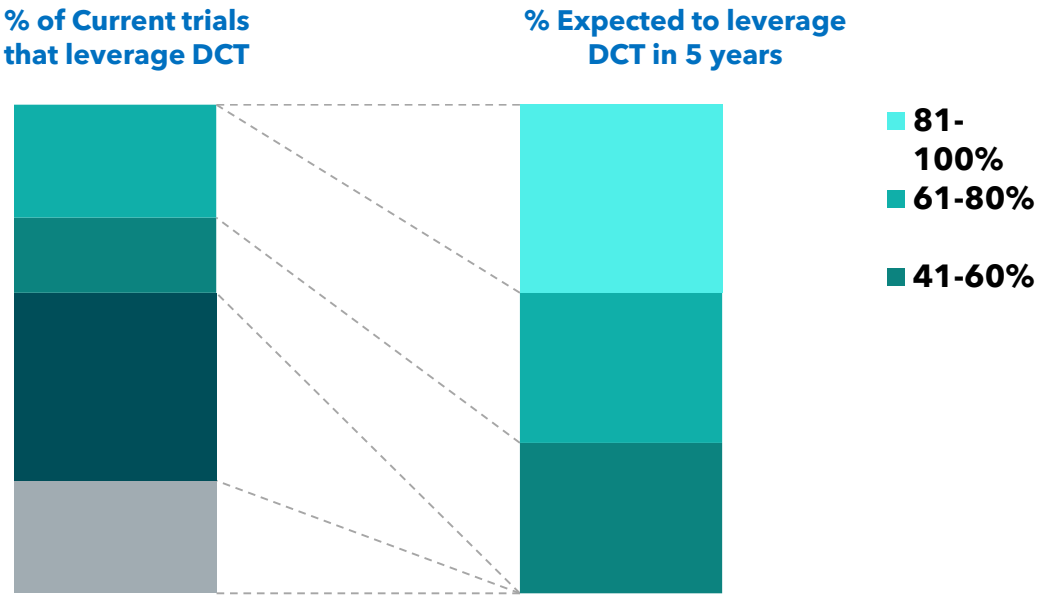
BASELINE Assessment

(n= 15 PACT Member Companies; end of 2023)

A Major Strategic Priority with Anticipated Growth	• **Over 75% consider hybrid DCT use a strategic objective** • **All members anticipate using DCT elements in >45% of trials in 5 years**
Expected Patient Benefit, Practical Challenges	• **Over 90% see benefits to patient participation, satisfaction, diversity, access** • **Main challenges (1) inability to monitor ROI; (2) costs and (3) technology**
Underutilization of Key DCT Elements	• **Over 65% do not deploy online recruitment, patient portals and remote consent** • **Most report infrequent use of telemedicine, mobile visits and wearable devices**
Actual Experience Has Been Sub-Optimal	• **69% report DCT experiences as Fair or Poor; 31% Good** • **No company reported experiences were Very Good or Excellent** • **Half rate their company as having only rudimentary DCT management skills**

Major Growth in Adoption Anticipated Over a 5-Year Period

~62% report using DCT components in less than 40% of their studies
100% anticipate using DCT components on more than 40% of their trials in 5 years



Source: Tufts CSDD | PACT Consortium 2024; n = 15 companies

2024 Dataset Overview (n=69 Protocols)

STATUS	Proportion of Total
Trial Completed	17.4%
Participant Visits Completed	15.9%
Participant Recruitment Completed	47.8%
Site Activation Completed	59.4%

Activity	Percent Using one or more DCT Solutions	Mean Number of DCT Solutions
Recruitment	20.3%	1.4
Screening	11.6%	1.8
Consent	20.3%	1.6
Training	4.4%	2.0
Study Visits	88.4%	2.8

Source: Tufts CSDD | PACT Consortium 2024; n = 69 Clinical Trials

Dataset Overview *(continued)*

Phase	n	Percent
Phase I	3	4.4%
Phase II	15	21.7%
Phase III	46	66.7%
Phase IV	5	7.3%

Therapeutic Area	n	Percent
Anti-Infective	8	11.6%
Cardiovascular	2	2.9%
Central Nervous System	14	20.3%
Endocrine	4	5.8%
Gastrointestinal	4	5.8%
Immunologic	13	18.8%
Oncology	8	11.6%
Respiratory	2	2.9%
Other	14	20.3%

Source: Tufts CSDD | PACT Consortium 2024; n = 69 Clinical Trials

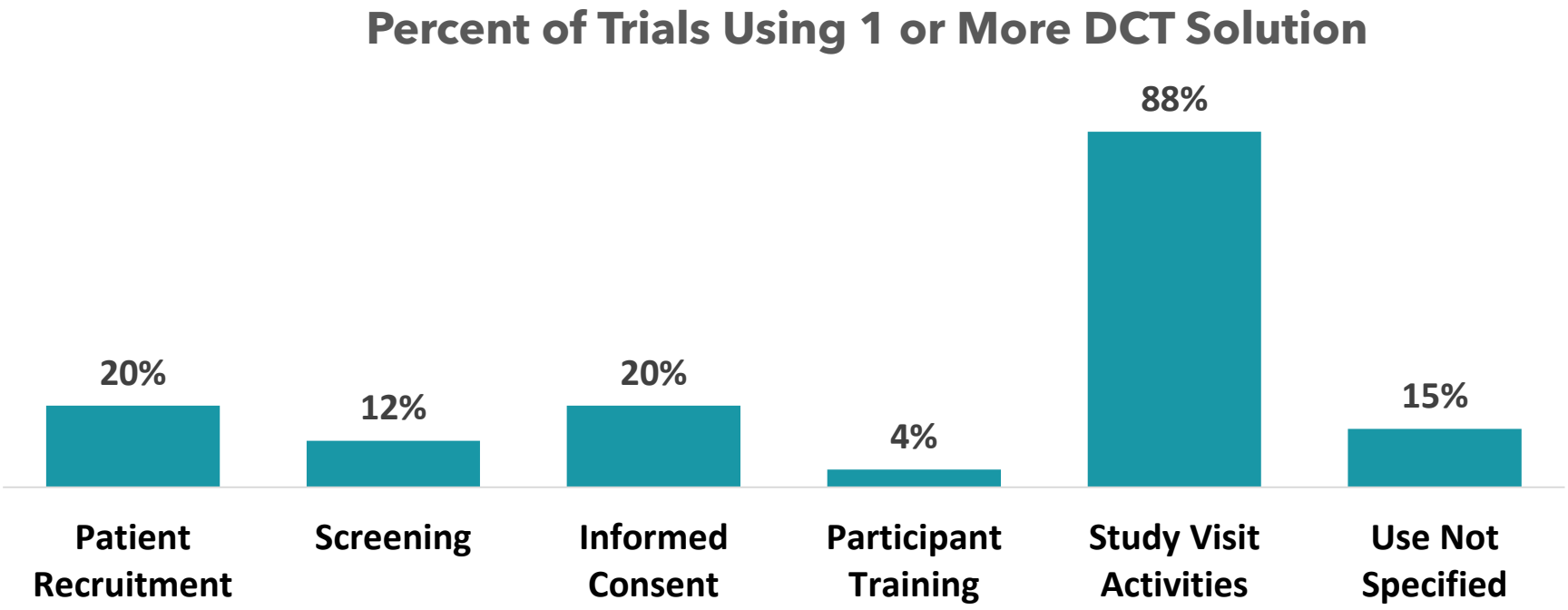
DCT Usage Expectations

	n	Mean (CoV)
Percent of Procedures that Could be Performed Remotely	39	35.6% (0.84)
Percent of Study Visits that Could be Conducted Remotely	47	41.0% (0.78)

EXPECTED/PLANNED Cycle Time Durations	Trials using DCTs		Benchmark (no DCTs used)	
(Days)	n	Mean (CoV)	n	Mean (CoV)
Protocol Approval to FPFV	57	250.3 (0.76)	66	182.2 (0.94)
FPFV to LPFV	56	759.6 (0.81)	67	464.7 (0.73)
LPFV to LPLV	54	613.8 (1.07)	69	378.7 (0.99)
LPLV to DBL	61	68.4 (2.23)	64	50.5 (4.06)
DBL to CSR	53	117.8 (0.57)	60	125.5 (0.83)
Protocol Approval to DBL	57	1,659.9 (0.62)	65	1,015.1 (0.51)

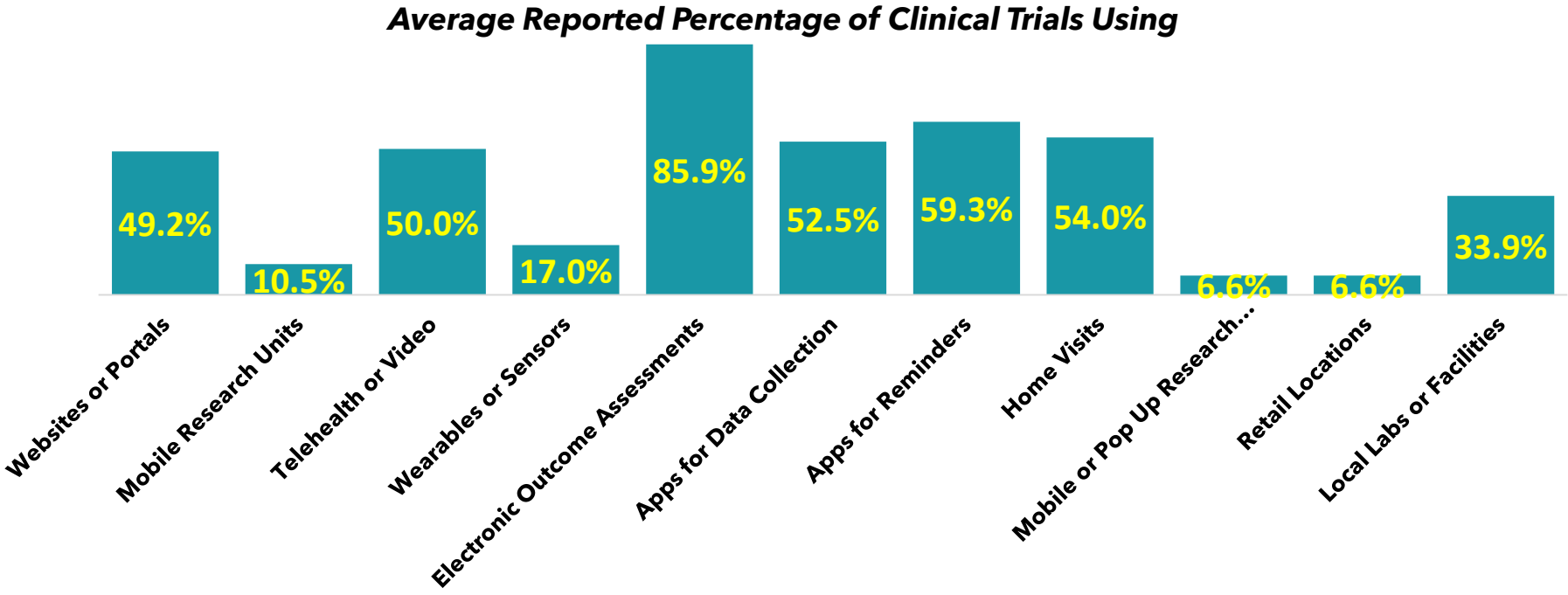
Source: Tufts CSDD | PACT Consortium 2024; n = 69 Clinical Trials

Incidence of Any DCT Component Use by Task



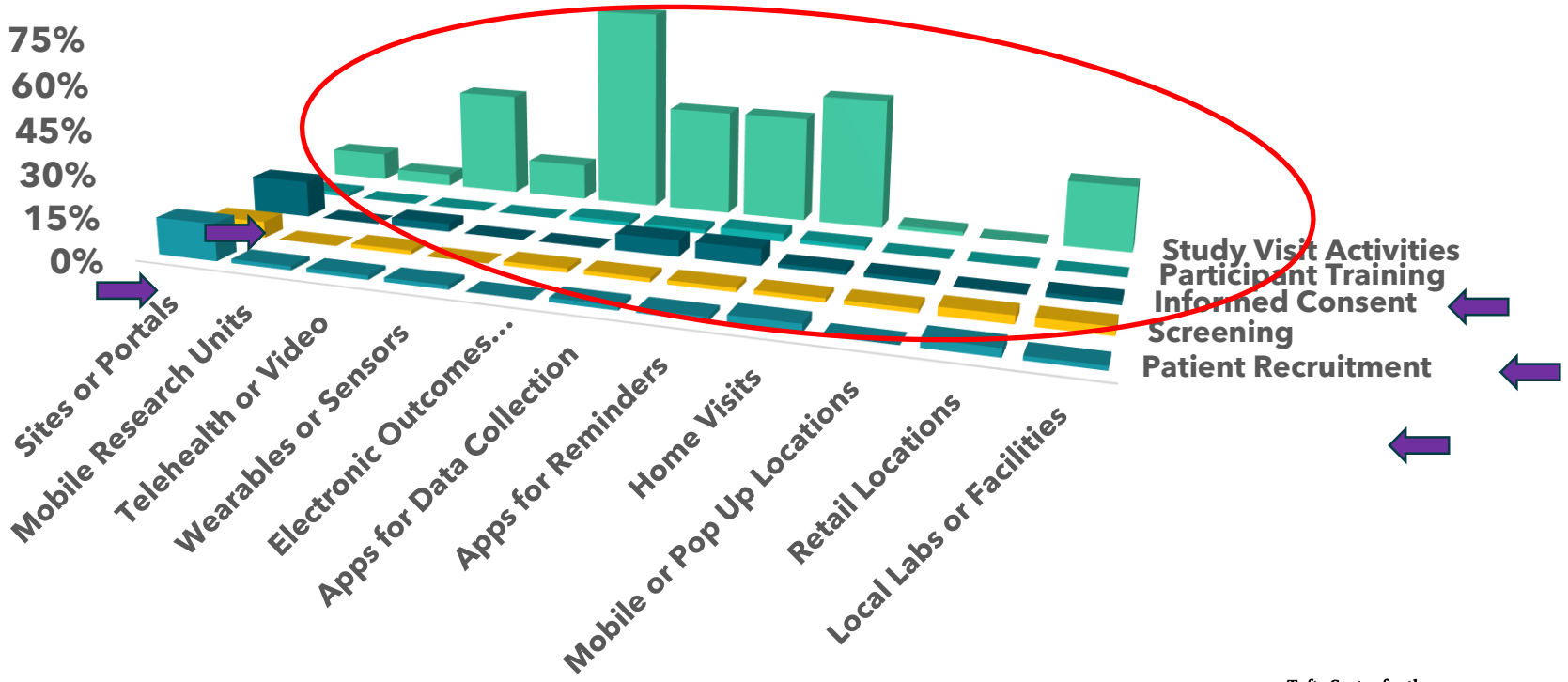
Source: Tufts CSDD | PACT Consortium 2024; n = 69 Clinical Trials

Incidence of Specific DCT Component Use for Study Visit Activities



Source: Tufts CSDD | PACT Consortium 2024; n = 69 Clinical Trials

How DCT Solutions Are Being Used



Source: Tufts CSDD | PACT Consortium 2024; n = 69

Study Budget Allocated for DCT Use

(based on planned budgets)	n	Mean
Total Budget	34	$48,627,341
Budget per Participant	33	$324,992
Budget for DCT Solutions	32	$4,274,370
DCT Budget per Participant	31	$34,947
Budget for IRB and Regulatory Body Work	7	$2,899,041
Number of Technology Vendors	41	2.8
Budget per Vendor	31	$1,723,973

Source: Tufts CSDD | PACT Consortium 2024; n = 69 Clinical Trials

Clinical Trial Performance with DCT

Actual Compared to Planned Timelines (n=69)	*Mean Days*	
First Site Activated to FPFV	2.3	Longer
Protocol Approval to FPFV	-11.4	Shorter
FPFV to LPFV	-22.3	Shorter
LPFV to LPLV	-171.1	Shorter
LPLV to DBL	4.7	Longer
Protocol Approval to DBL	-102.7	Shorter

- **Although site activation timelines are longer than planned and site activation rates are lower with DCT-supported studies, compared to Tufts CSDD benchmarks, each activated site in the PACT study enrolled twice the average number of patients (13.5 vs. 5.6).**

- **Faster enrollment times were significantly (p<.01) associated with a higher proportion of remotely performed procedures and approached significance (p<.07) with a higher proportion of remote visits performed**

Source: Tufts CSDD | PACT Consortium 2024; n = 69 Clinical Trials

DCT Use and Enrollment Diversity

Proportional Representation by Demographic Subgroup (mean percent)	DCTs Used (PACT Sample)	NO DCT SOLUTION USED (Benchmark*)
Gender		
Male	44.3%	51.0%
Female	55.7%	49.0%
Race		
American Indian or Alaska Native	1.9%	0.5%
Asian	20.9%	14.2%
Black or African Descent	7.3%	7.0%
White	72.6%	81.3%
Ethnicity		
Hispanic/Latino	14.9%	12.6%

**Benchmark drawn from 2023 Tufts CSDD Study, includes only trials that indicated no DCT use (n=756 protocols)*

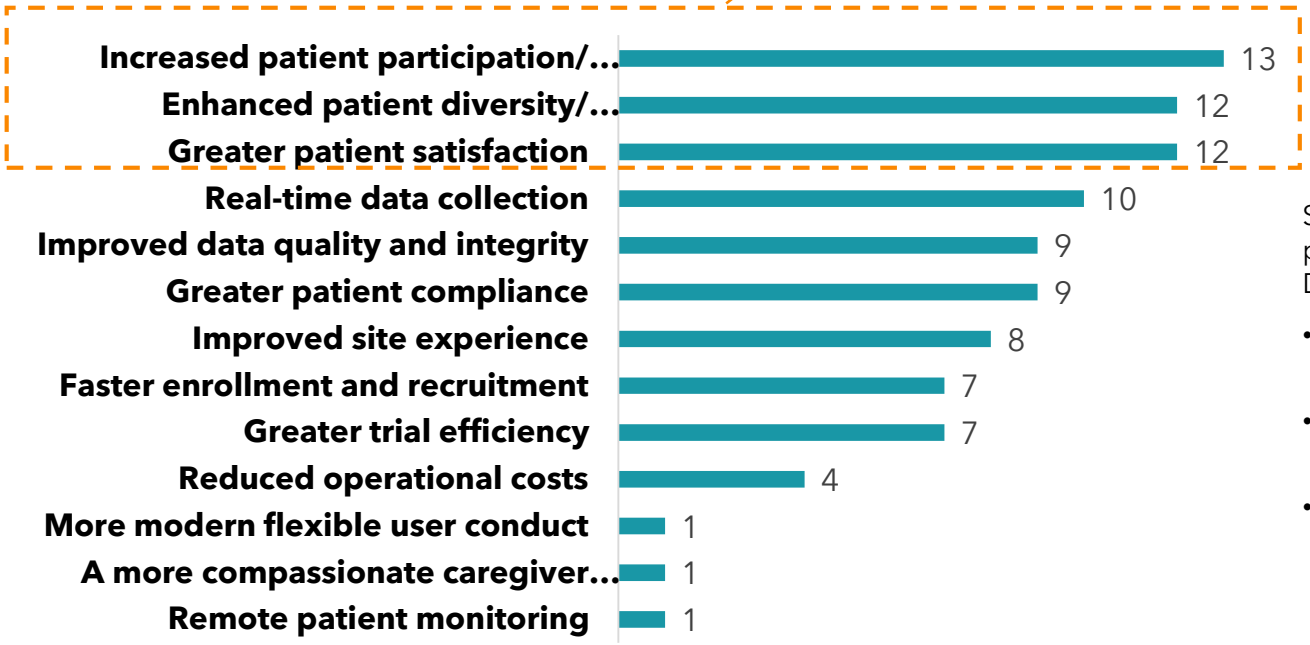
- **In a different 2024 study (n=194 phase II and III protocols), Tufts CSDD found that local locations were associated with significantly higher proportional representation, and virtual and home visits were associated with significantly lower proportional representation, of Black participants.**

Source: Tufts CSDD | PACT Consortium 2024; n = 69 Clinical Trials

A Range of Benefits Anticipated

Q: What are the benefits that you expect to achieve from DCTs? (select all that apply)

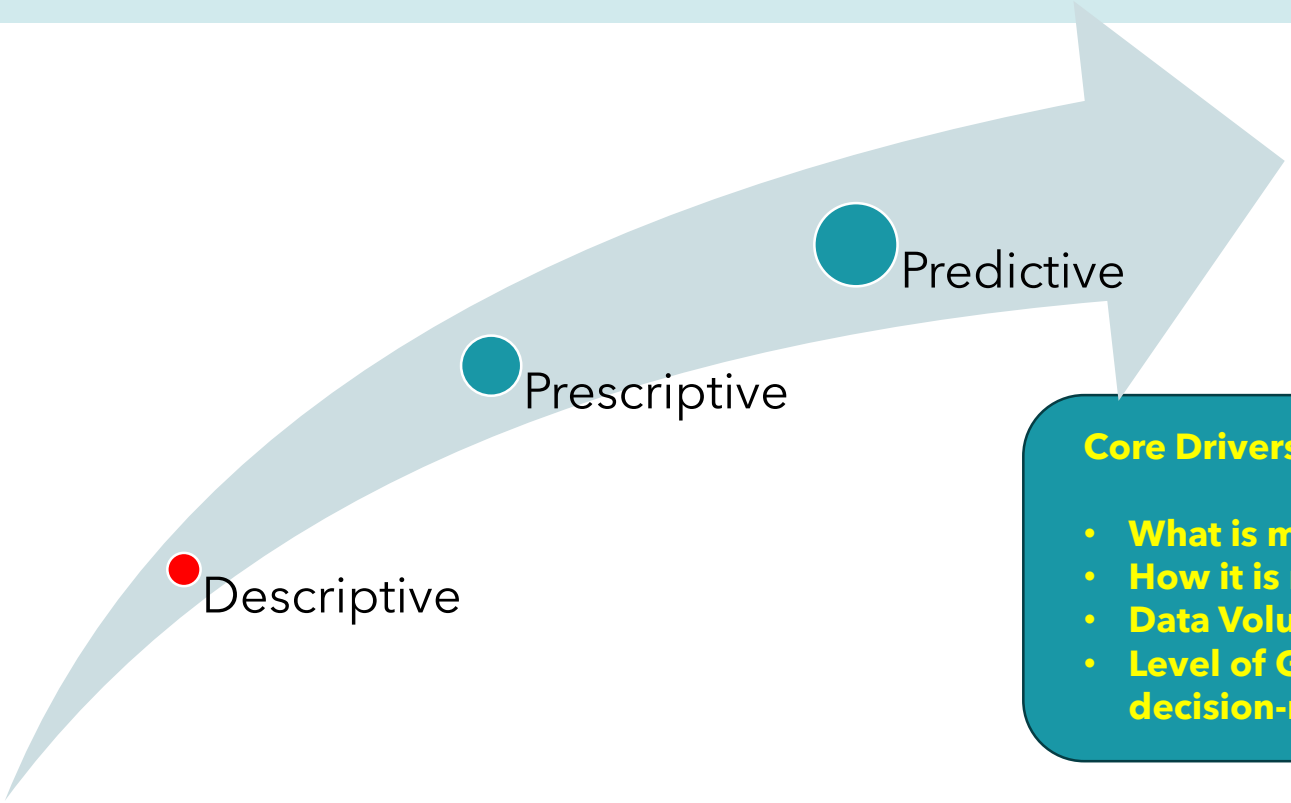
- Top-3 benefits cited point to patient-centric benefits
- All participants expect to recognize these benefits within 5 years, and ~54% within 2 years or less



Similarly, when asked to identify personal objectives when rolling out DCT, participants highlighted…

- Enhanced patient experience, optionality, and diversity.
- Enhanced understanding of best practices and technologies
- Optimization of internal practices were also highlighted.

Evolving Evidence Needs & Gaps



Core Drivers:

- **What is measured**
- **How it is measured**
- **Data Volume**
- **Level of Granularity to inform decision-making**

Evolving Evidence Needs & Gaps

How are data/evidence needs changing?

Key areas in discussion

- Deployment – offered vs. actually used by study participants (and by sites)
- DCT use by endpoint (e.g., supporting primary, secondary and exploratory endpoints)
- Participant motivation from DCT components
- Participant satisfaction with overall and specific DCT elements
- Impact of DCT components on retention rates – particularly early termination due to patient choice
- ICF considerations - Did the ICF include information about DCT and did it impact randomization
- Sponsor/CRO provided vs. Site provided DCT components
- Investigative Sites & 'other' stakeholder segments

PACT
Partnership for Advancing Clinical Trials

Participating Organizations

PACT
Partnership for Advancing Clinical Trials

Thank you

PACT Website:
https://sites.tufts.edu/pactconsortium

Joan A. Chambers
Senior Consultant
Joan.chambers@tufts.edu
Joan Chambers | LinkedIn

Christopher Horvat

Director, Health Informatics for Clinical Effectiveness,
UPMC Children's Hospital of Pittsburgh

REMAP CAP at UPMC:
an overview, lessons learned, and recommendations for the future

Chris Horvat, MD MHA

University of Pittsburgh

Assoc Prof Critical Care Medicine, Pediatrics, Biomedical Informatics, and Clinical & Translational Sciences

Sr Director of Clinical Informatics, UPMC and University of Pittsburgh

2024-09-05T18:00:00Z

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Outline

- An Overview of REMAP CAP at UPMC
- Lessons Learned
    1. Keep it simple
    2. Consider your data sources
    3. Align incentives
- Summary of Recommendations

The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study

Rationale and Design

Derek C. Angus[1], Scott Berry[2], Roger J. Lewis[2,3,4], Farah Al-Beidh[5], Yaseen Arabi[6], Wilma van Bentum-Puijk[7], Zahra Bhimani[8], Marc Bonten[7,9], Kristine Broglio[2], Frank Brunkhorst[10], Allen C. Cheng[11,12], Jean-Daniel Chiche[13], Menno De Jong[14], Michelle Detry[2], Herman Goossens[15], Anthony Gordon[5], Cameron Green[12], Alisa M. Higgins[12], Sebastiaan J. Hullegie[7], Peter Kruger[16], Francois Lamontagne[17], Edward Litton[18], John Marshall[8,19], Anna McGlothlin[2], Shay McGuinness[12,20,21], Paul Mouncey[22], Srinivas Murthy[23], Alistair Nichol[12,24,25], Genevieve K. O'Neill[12], Rachael Parke[20,21,26], Jane Parker[12], Gernot Rohde[27,28], Kathryn Rowan[22], Anne Turner[21], Paul Young[21,29], Lennie Derde[7,30], Colin McArthur[21,31], and Steven A. Webb[12,18,32]

Ann Am Thorac Soc Vol 17, No 7, pp 879–891, Jul 2020

Originally Published in Press as DOI: 10.1513/AnnalsATS.202003-192SD on April 8, 2020
Internet address: www.atsjournals.org

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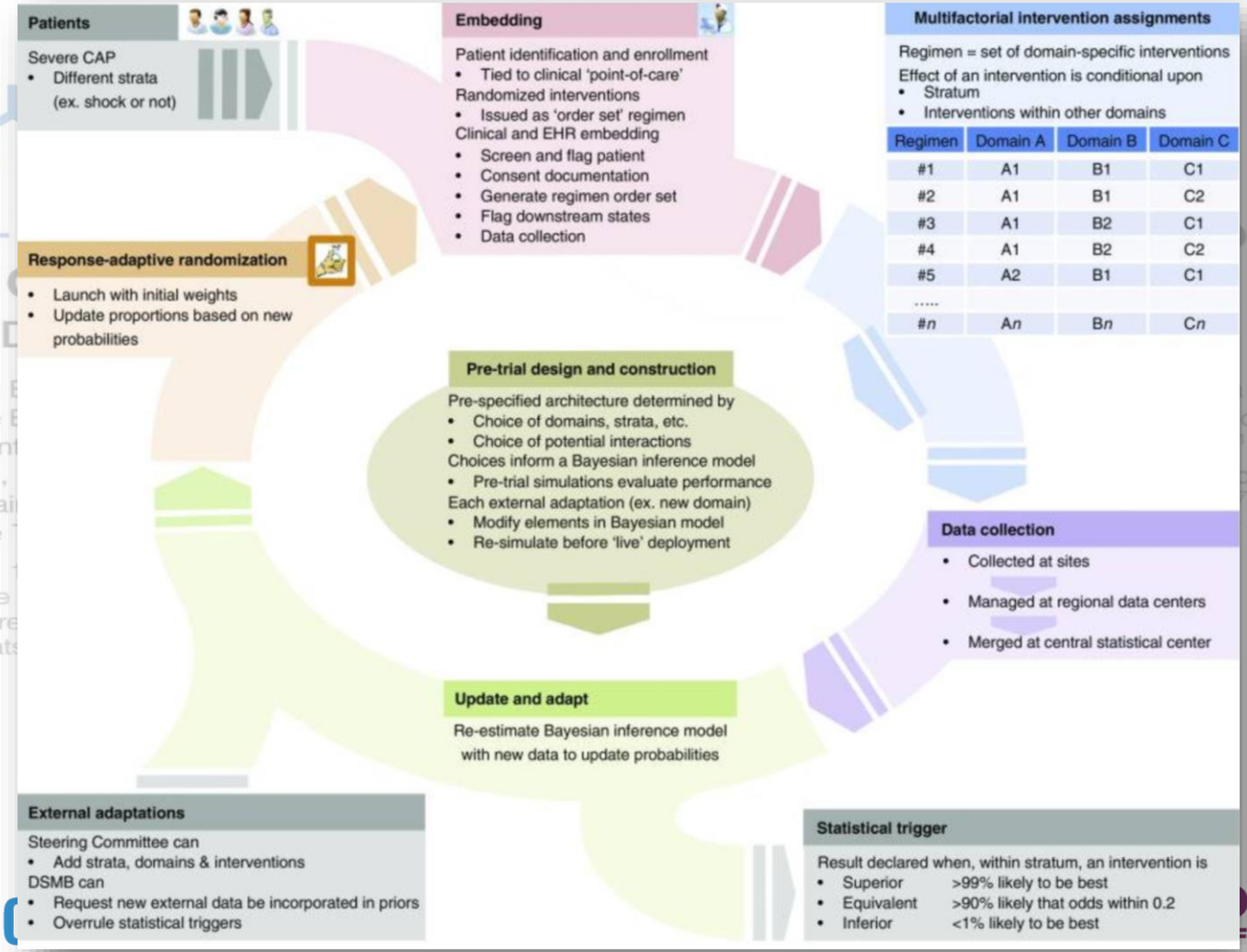
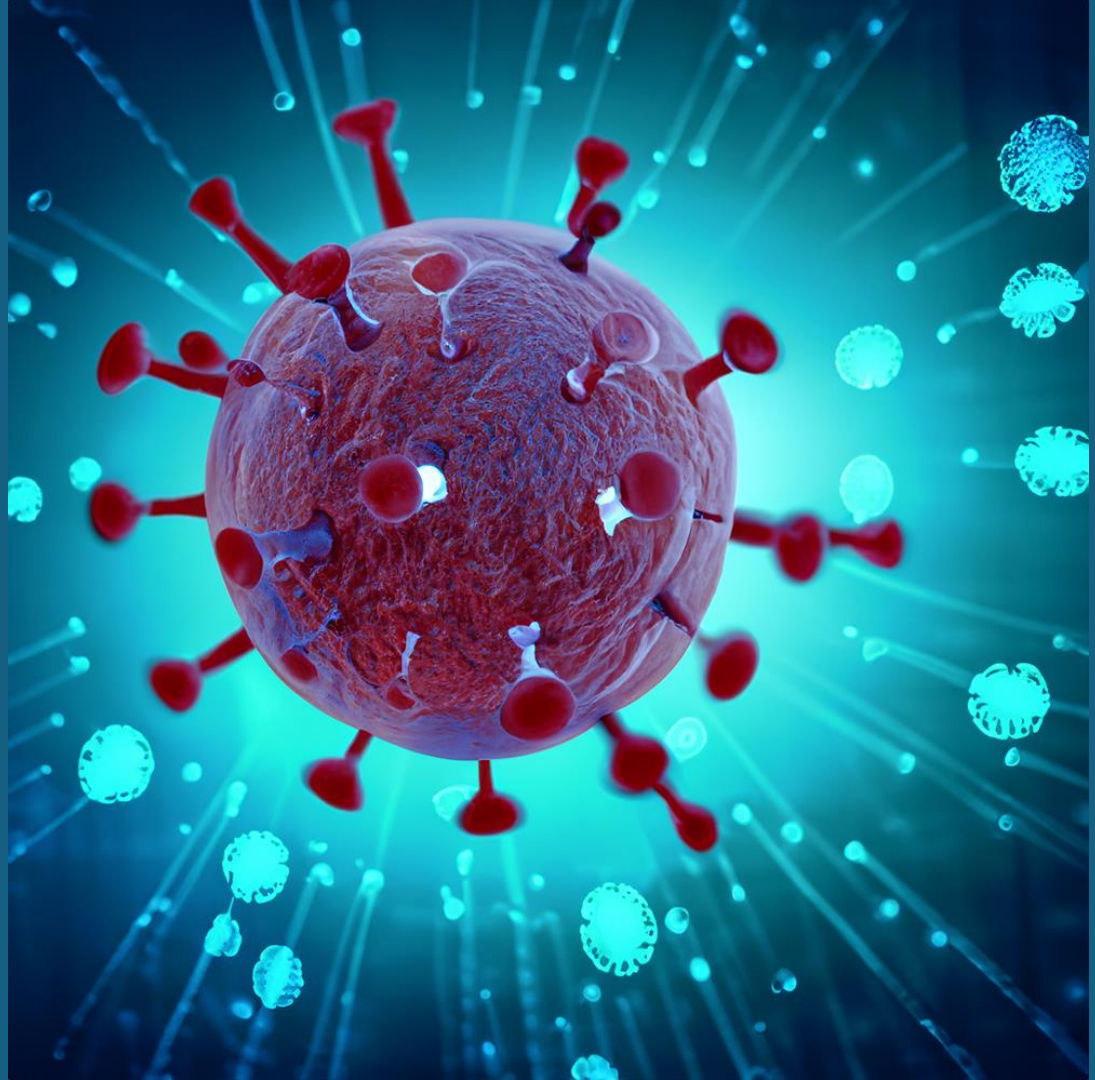
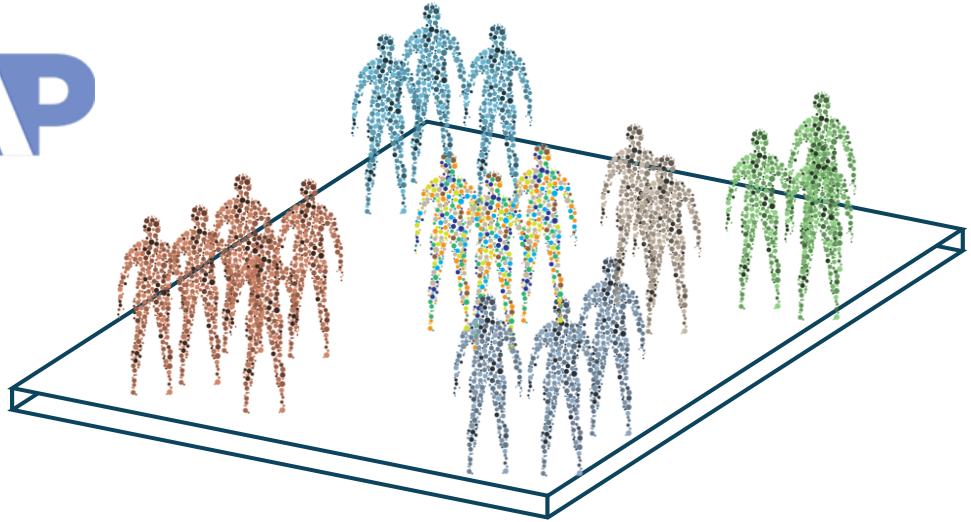




UPMC CLINICAL INNOVATION

REMAP



$$\log\left(\frac{\pi}{1-\pi}\right) = \sum_{R=1}^{R} \nu_R + \sum_{k=1}^{K}\sum_{s=1}^{S} \alpha_{s,g_k} + \sum_{age=1}^{AGE} \lambda_{age} + \sum_{T=1}^{T} \theta_T + \sum_{d=1}^{D}\sum_{j=1}^{Jd} \beta_{d_j}$$

$$+ \sum_{k=1}^{K}\sum_{d=1}^{D}\sum_{j=1}^{Jd} I(g_k = 2)\gamma_{kd_j} + \sum_{d=1}^{D}\sum_{j=1}^{Jd}\sum_{d'=d+1}^{D}\sum_{j'=1}^{J'_{d'}} \delta_{d_j d'_{j'}}$$

Unified Statistical Analysis Plan

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UPMC CLINICAL INNOVATION

REMAP

$$\log\left(\frac{\pi}{1-\pi}\right) = \sum_{R=1}^{R} \nu_R + \sum_{k=1}^{K}\sum_{s=1}^{S} \alpha_{s,g_k} + \sum_{age=1}^{AGE} \lambda_{age} + \sum_{T=1}^{T} \theta_T + \sum_{d=1}^{D}\sum_{j=1}^{Jd} \beta_{d_j}$$

$$+ \sum_{k=1}^{K}\sum_{d=1}^{D}\sum_{j=1}^{Jd} I(g_k = 2)\gamma_{kd_j} + \sum_{d=1}^{D}\sum_{j=1}^{Jd}\sum_{d'=d+1}^{D}\sum_{j'=1}^{J'_{d'}} \delta_{d_j d'_{j'}}$$

Unified Statistical Analysis Plan

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Streamline Trial Design to Fit with Workflows

The UPMC REMAP-COVID Group, on behalf of the REMAP-CAP Investigators *Trials* (2021) 22:100
https://doi.org/10.1186/s13063-020-04997-6

Trials

METHODOLOGY Open Access

Implementation of the Randomized Embedded Multifactorial Adaptive Platform for COVID-19 (REMAP-COVID) trial in a US health system—lessons learned and recommendations

The UPMC REMAP-COVID Group, on behalf of the REMAP-CAP Investigators[1]

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The UPMC REMAP-COVID Group, (2021) 22:100
https://doi.org/10.1186/s13063-02

METHODOLOGY

Implementa
Embedded
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recommend

The UPMC REMAP-COVID

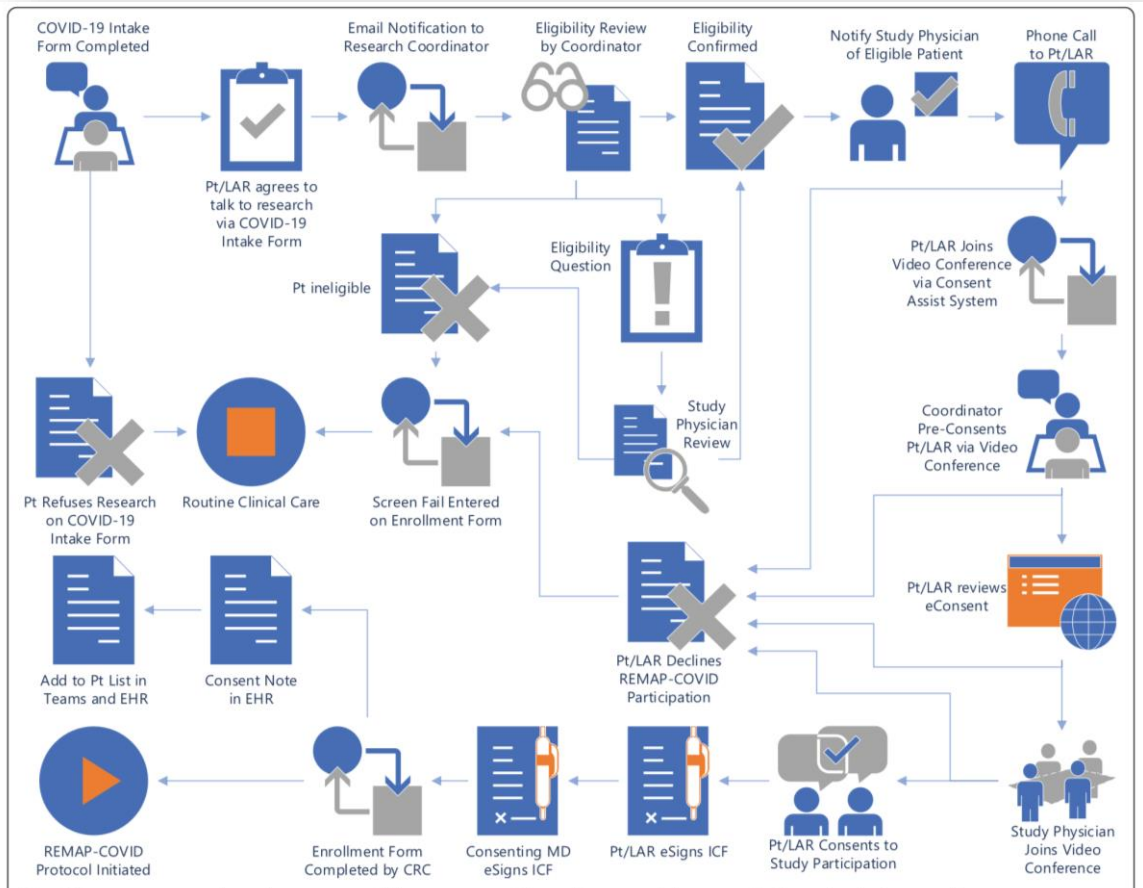

Fig. 3 Remote consent and enrollment process. This process uses videoconference and document signing technologies to enable remote consent and enrollment

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REMAP COVID Findings

REMAP COVID Findings

- **Corticosteroids associated with improved organ support-free days**

  JAMA. 2020 Oct 6;324(13):1317-1329.

- **Treatment with Interleukin 6 antagonists improve survival**

  N Engl J Med. 2021 Apr 22;384(16):1491-1502.

- **Lopinavir-ritonavir, hydroxychloroquine or both worsen outcomes including survival**

  Intensive Care Med. 2021 Aug;47(8):867-886.

- **Therapeutic anticoagulation improves survival in noncritically ill patients and does not improve survival in critically ill patients (MPRCT: REMAP, ATTACC & ACTIV-4a)**

  N Engl J Med. 2021 Aug 26;385(9):790-802.

  N Engl J Med. 2021 Aug 26;385(9):777-789.

- **Convalescent plasma has a low likelihood of improving outcomes**

  JAMA. 2021 Nov 2;326(17):1690-1702.

- **Aspirin and P2Y12 platelet inhibitors have a low likelihood of improving outcomes**

  JAMA. 2022 Apr 5;327(13):1247-1259.

180-day outcomes are consistent with shorter-term outcomes for most studied COVID-19 therapies

JAMA. 2023 Jan 3;329(1):39-51.

Treatment effects of therapeutic-dose heparin are heterogenous in patients hospitalized for COVID-19

JAMA. 2023 Apr 4;329(13):1066-1077.

ACE-Is and ARBs do not improve, and likely worsen, outcomes among critically ill adults with COVID-19

JAMA. 2024 Aug 20. doi: 10.1001/jama.2024.16951.

Intravenous vitamin C has a low probability of improving OSFDs and survival in hospitalized patients with COVID-19

JAMA. 2023 Nov 14;330(18):1745-1759.

Simvastatin may improve outcomes among critically ill patients with COVID-19

N Engl J Med. 2023 Dec 21;389(25):2341-2354.

Lesson #1: Keep it Simple

Setting Expectations Early

- Case Report Form – **53** pages
- Completion Guidelines – **253** pages

Reviewing Data Elements to Embed and Verification

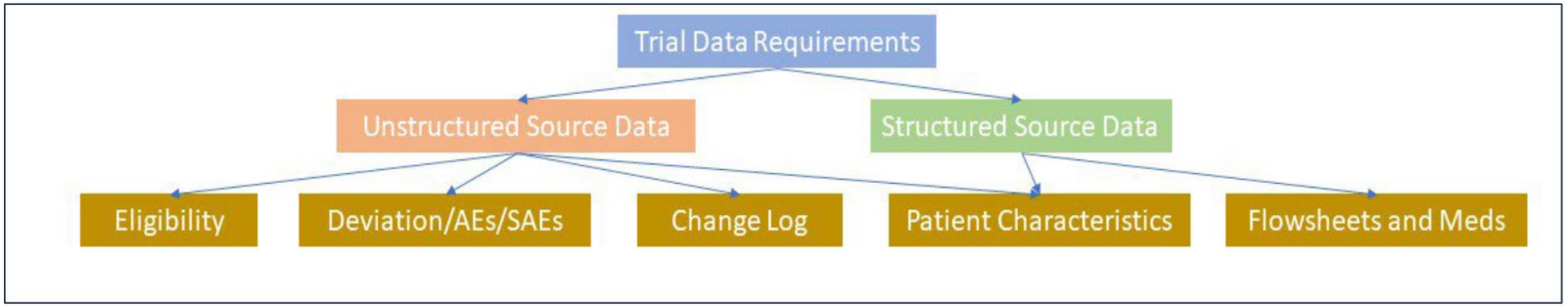
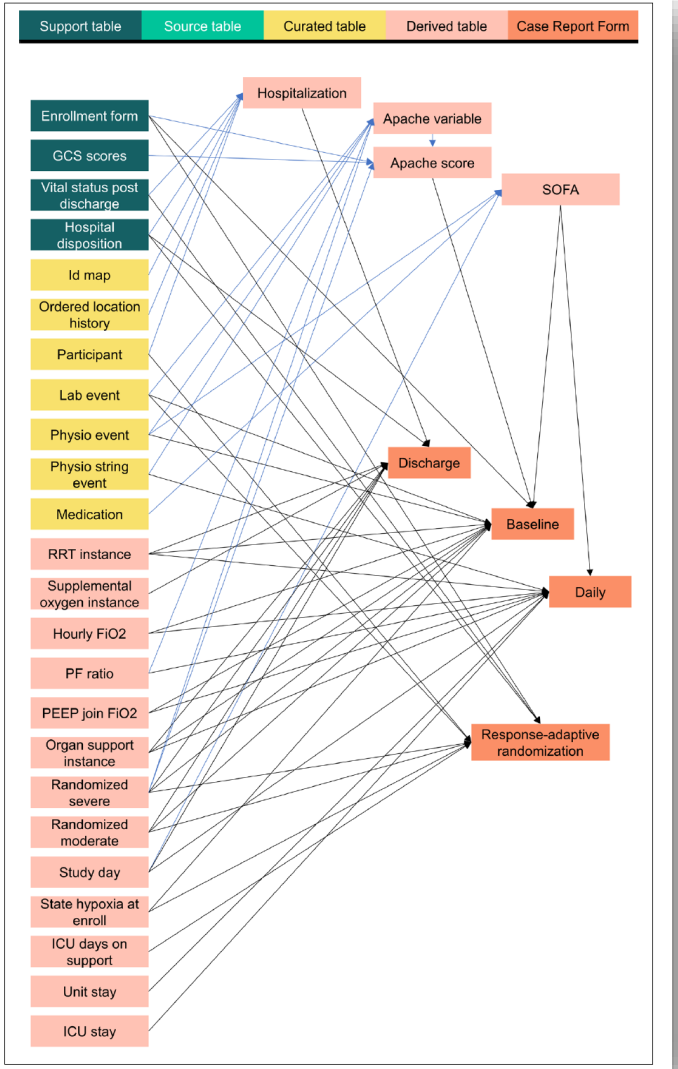
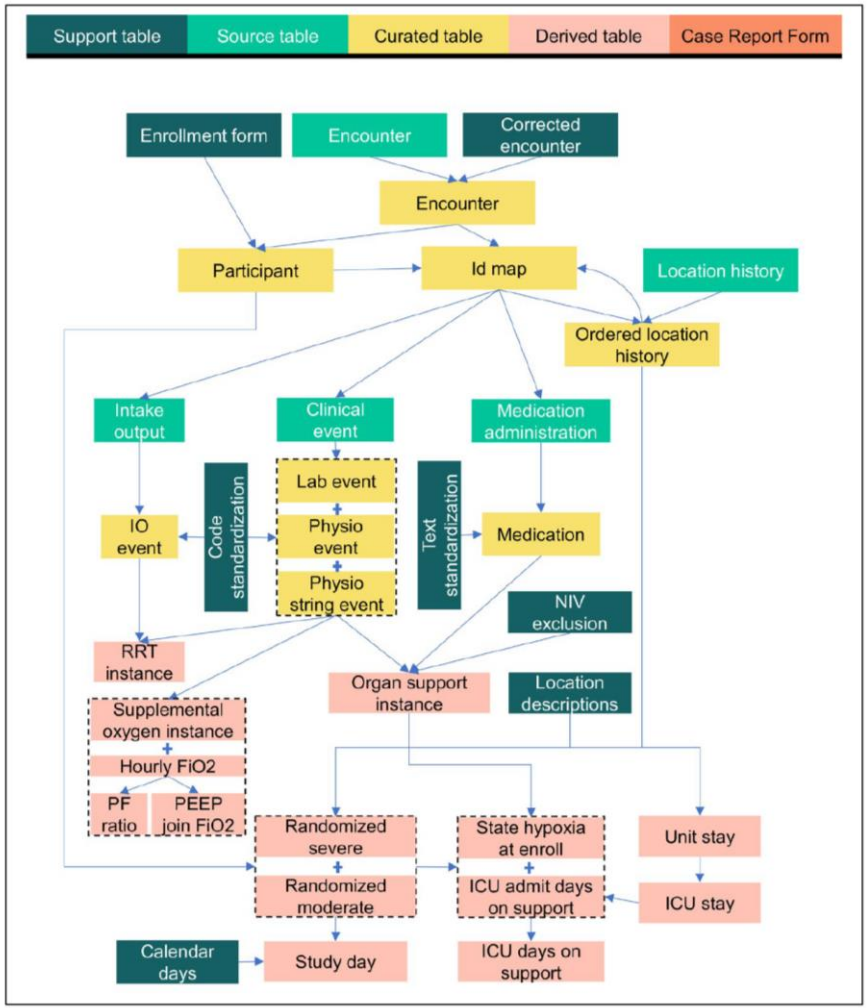


Figure 1. Trial data reporting requirements were categorized broadly as structured and unstructured data. Unstructured data elements were captured with electronic forms integrated into either research coordinator or clinician workflows. Structured data were collected from the EHRs relational databases. AE, adverse event; SAE, serious adverse event.

King AJ, Higgins L, Au C, Malakouti S, Music E, Kalchthaler K, Clermont G, Garrard W, Huang DT, McVerry BJ, Seymour CW, Linstrum K, McNamara A, Green C, Loar I, Roberts T, Marroquin O, Angus DC, Horvat CM. Automatic Population of the Case Report Forms for an International Multifactorial Adaptive Platform Trial Amid the COVID-19 Pandemic. AMIA Jt Summits Transl Sci Proc. 2024 May 31;2024:276-284. PMID: 38827056; PMCID: PMC11141839.


Support table
Source table
Curated table
Derived table
Case Report Form
Enrollment form
GCS scores
Vital status post discharge
Hospital disposition
Id map
Ordered location history
Participant
Lab event
Physio event
Physio string event
Medication
RRT instance
Supplemental oxygen instance
Hourly FiO2
PF ratio
PEEP join FiO2
Organ support instance
Randomized severe
Randomized moderate
Study day
State hypoxia at enroll
ICU days on support
Unit stay
ICU stay
Hospitalization
Apache variable
Apache score
SOFA
Discharge
Baseline
Daily
Response-adaptive randomization


Support table
Source table
Curated table
Derived table
Case Report Form
Enrollment form
Encounter
Corrected encounter
Encounter
Participant
Id map
Location history
Ordered location history
Intake output
Clinical event
Medication administration
IO event
Code standardization
Lab event
Physio event
Physio string event
Text standardization
Medication
NIV exclusion
RRT instance
Organ support instance
Location descriptions
Supplemental oxygen instance
Hourly FiO2
PF ratio
PEEP join FiO2
Randomized severe
Randomized moderate
State hypoxia at enroll
ICU admit days on support
Unit stay
ICU stay
Calendar days
Study day
ICU days on support


DO-OVER

Improving Efficiency

1. Whittle the CRF to the essentials
2. Define the schema in advance

Lesson #2: Consider your source(s)

The UPMC REMAP-COVID Group, on behalf of the REMAP-CAP Investigators *Trials* (2021) 22:100
https://doi.org/10.1186/s13063-020-04997-6

Trials

Patient Identification

Symptoms

What symptoms were present prior to or at the time of presentation? (Check all that apply)

- ☐ **Abdominal Pain**
- ☐ **Body Aches / Myalgias**
- ☐ **Chills**
- ☐ **Confusion**
- ☐ **Cough**
- ☐ **Diarrhea** (>/= 3 loose/looser than normal stools/24 hr period)
- ☐ **Fever** (Temperature >=38°C / 100°F) **or subjective fever**
- ☐ **Headache**
- ☐ **Malaise / Fatigue / Lethargy**
- ☐ **Nausea or Vomiting**
- ☐ **Shortness of Breath / Dyspne**
- ☐ **Sputum production greater th**
- ☐ **None**

How many days since the onset of symptoms? (The number of days since the first symptoms were recognized by the patient) ____

Anticipated Treatment

Please read the following to the patient or their representative and record their response:

"There are few known treatments for COVID-19. Would the patient like to hear about potential additional therapies and studies?" She or he will only be contacted if potentially eligible.

○ Yes ○ No ○ Unknown
(Please only click if the patient or representative is unable to respond. An unknown response will delay potential additional therapies and studies.)

Fig. 1 UPMC REMAP-COVID Intake Form. This form is embedded into a patient's electronic health record, solicits basic clinical information, and requests providers to ask the patient or legally authorized representative if s/he is interested in potential additional therapies for COVID-19. The intake form represents the singular route of entry into the REMAP-COVID trial at UPMC

Trial Data Collection

Deploy Interventions

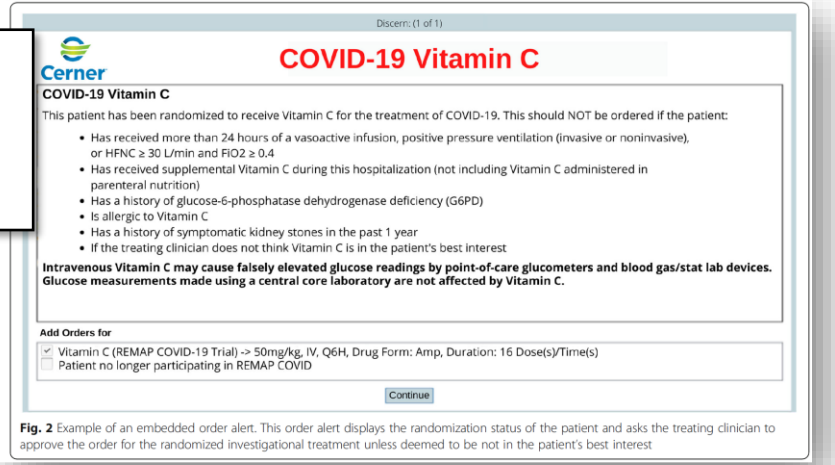


Fig. 2 Example of an embedded order alert. This order alert displays the randomization status of the patient and asks the treating clinician to approve the order for the randomized investigational treatment unless deemed to be not in the patient's best interest

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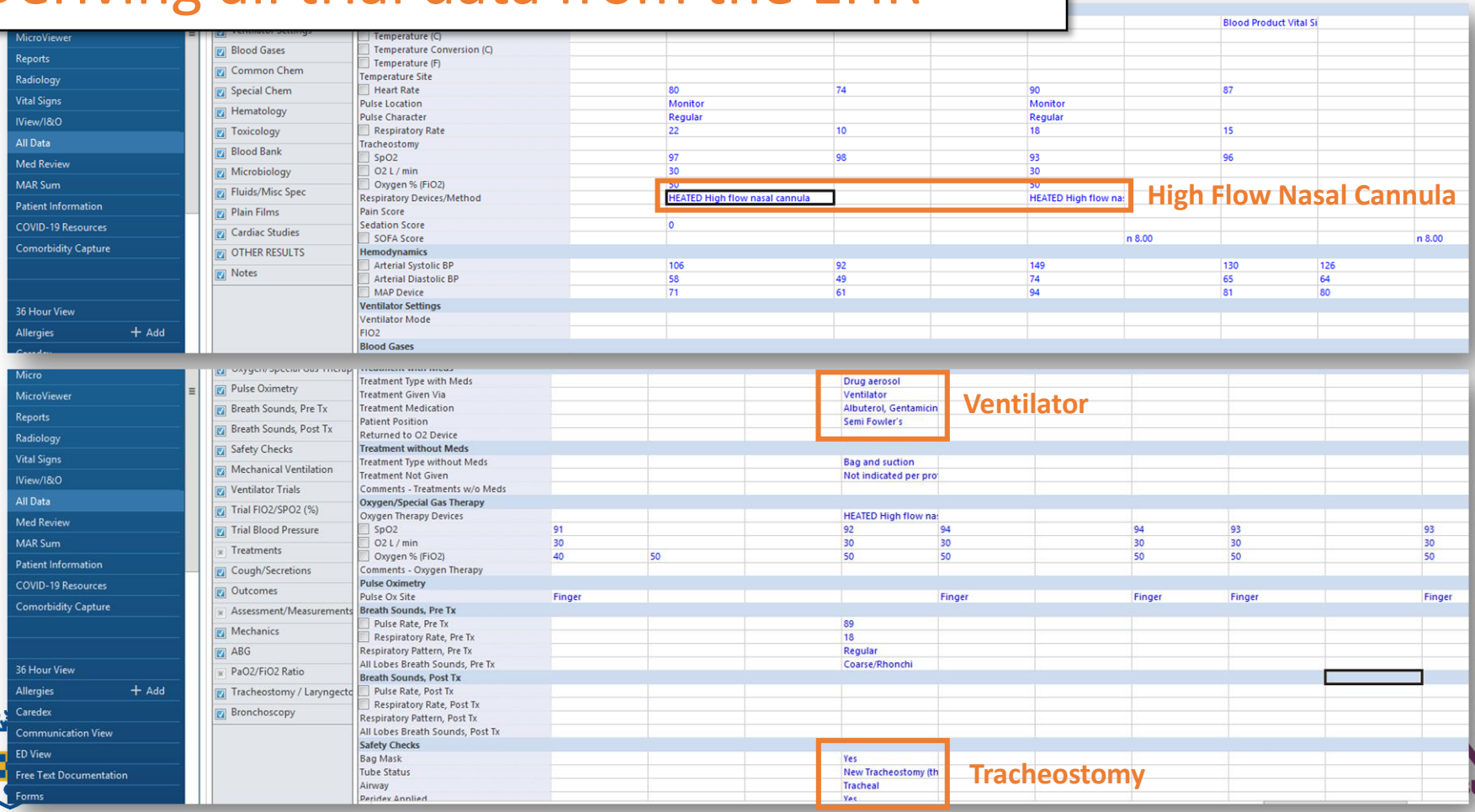
Primary Endpoint

- An organ support day defined as any of the following for more than one continuous hour:
  - Continuous vasopressor and/or inotrope infusion
  - High-flow O2 delivered via nasal prongs or cannula by a specialized device, with an FiO2 ≥ 0.4 and at a flow rate of at least 30 L/min
  - Non-invasive ventilation
  - Invasive mechanical ventilation

Deriving all trial data from the EHR



Qlik ··· Analyze Sheet | Narrate Storytelling | ICU

MeasureSelector Duration of Mech Vent (Days) | Bookmarks | Sheets

Measure Visuals

UPMC CLINICAL ANALYTICS

Next sheet: Patient Detail

Rolling 12 Months

Group

HOSPITAL

Location

ICU Admission Month Year

Jan-2025
Dec-2024
Nov-2024
Oct-2024
Sep-2024
Aug-2024

Measure Selector

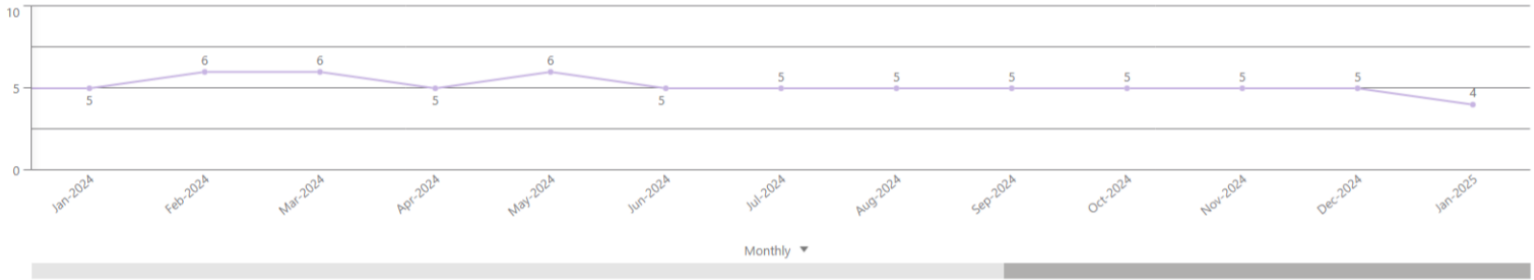
Compliance - Mouth Care
Compliance - Order To Accom Code Change
Compliance - SAT
Compliance - SBT
Delirium Evaluation
Delirium Present
Duration of Mech Vent (Days)
ICU Admissions
ICU LOS (Days)
ICU Mortality
ICU Returns
Mech Vent Pts

Measure Definition

Duration of Mech Vent (Days) #

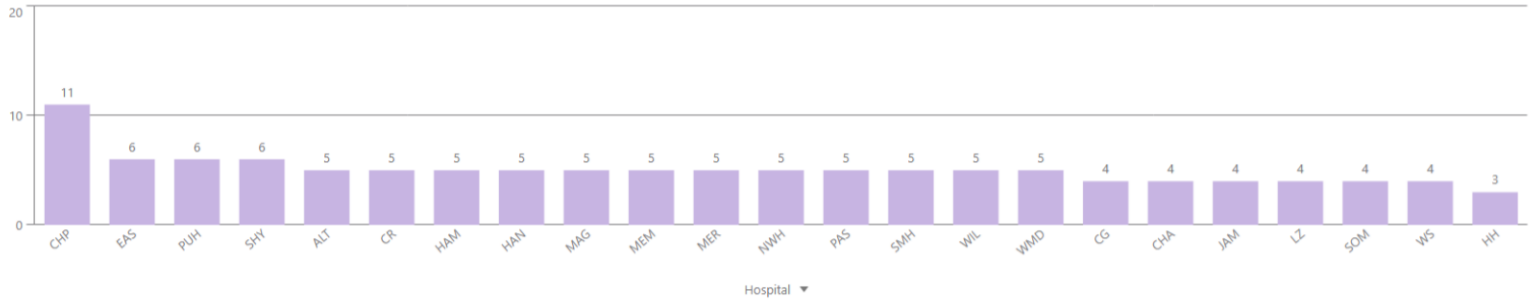
Average number of days per patient stay of mechanical ventilation.

Duration of Mech Vent (Days) #



Duration of Mech Vent (Days)

All ICU Admission Months



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Adding Flexibility for Efficiency

1. Structure definitions according to varied data sources
2. Consider whether a source is ‘good enough’ versus ‘perfect/ideal’

Lesson #3: Align Incentives

TRIB LIVE

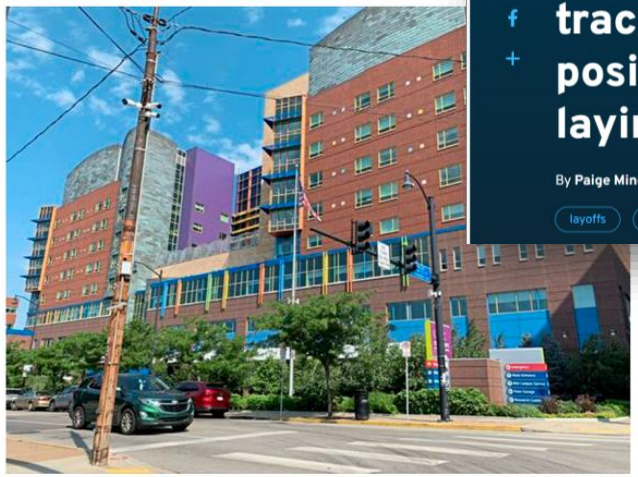
TUESDAY, SEPTEMBER 3, 2024

LOCAL SPORTS

PITTSBURGH

UPMC posts $
2024

JOE NAPSHA | Thursday, Aug. 29, 2024 7:55 p.m.



JUSTIN VELLUCCI | TRIBLIVE

UPMC Children's Hospital of Pittsburgh in the city's Lawrenceville neighborhood.

HOUSTON CHRONICLE

6 MONTHS FOR 99¢ Sign in

LIFESTYLE // HEALTH

Texas Children's H
recent job cuts, do

By Evan MacDonald, Staff writer
Aug 15, 2024

FIERCE Healthcare

Providers Health Tech Payers Regulatory Finance Special Reports Fierce 50

FINANCE

Fierce Healthcare layoff tracker—BCBSM eliminates 64 positions; Texa
laying off 5% o

By Paige Minemyer, Dave Muoio, Noah Tong

layoffs Healthcare Costs Highmark

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Patient Experience Pharmacy Care Coordination Legal & Regulatory Compensation Payer Rankings Workforce Specialties

Financial Management

47 hospitals, health systems cutting jobs

Kelly Gooch - Updated Friday, August 30th, 2024

BECKER'S HEALTHCARE

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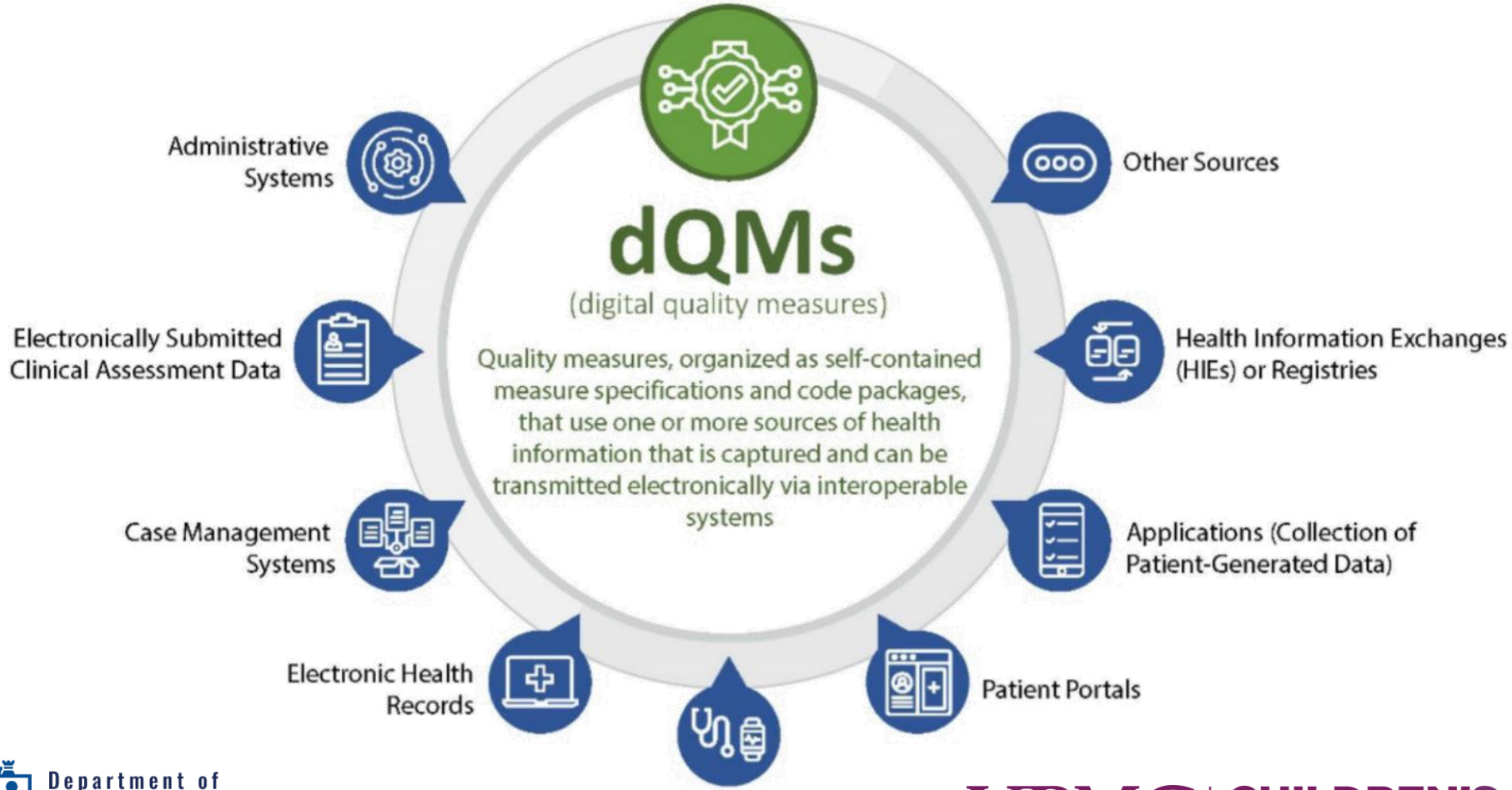
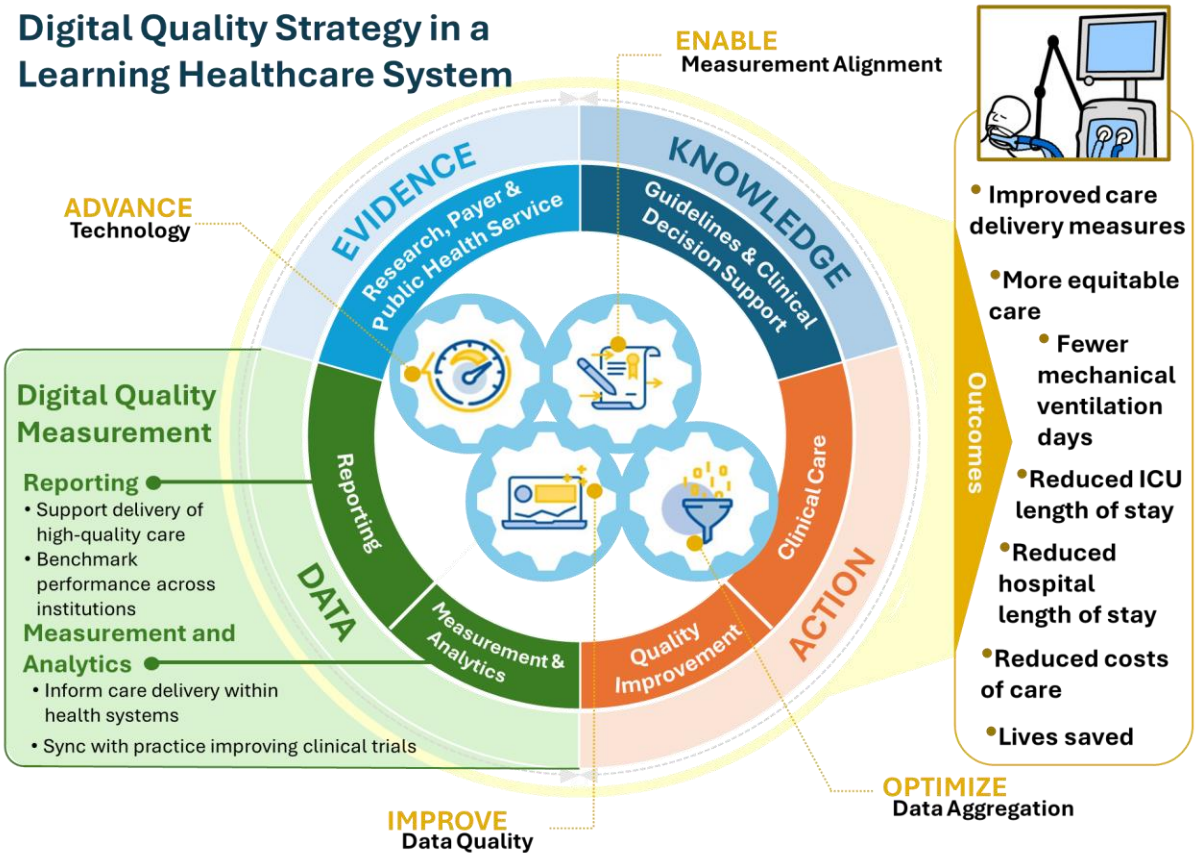
Courtesy of DALL-E

Healthcare Data Life Cycle

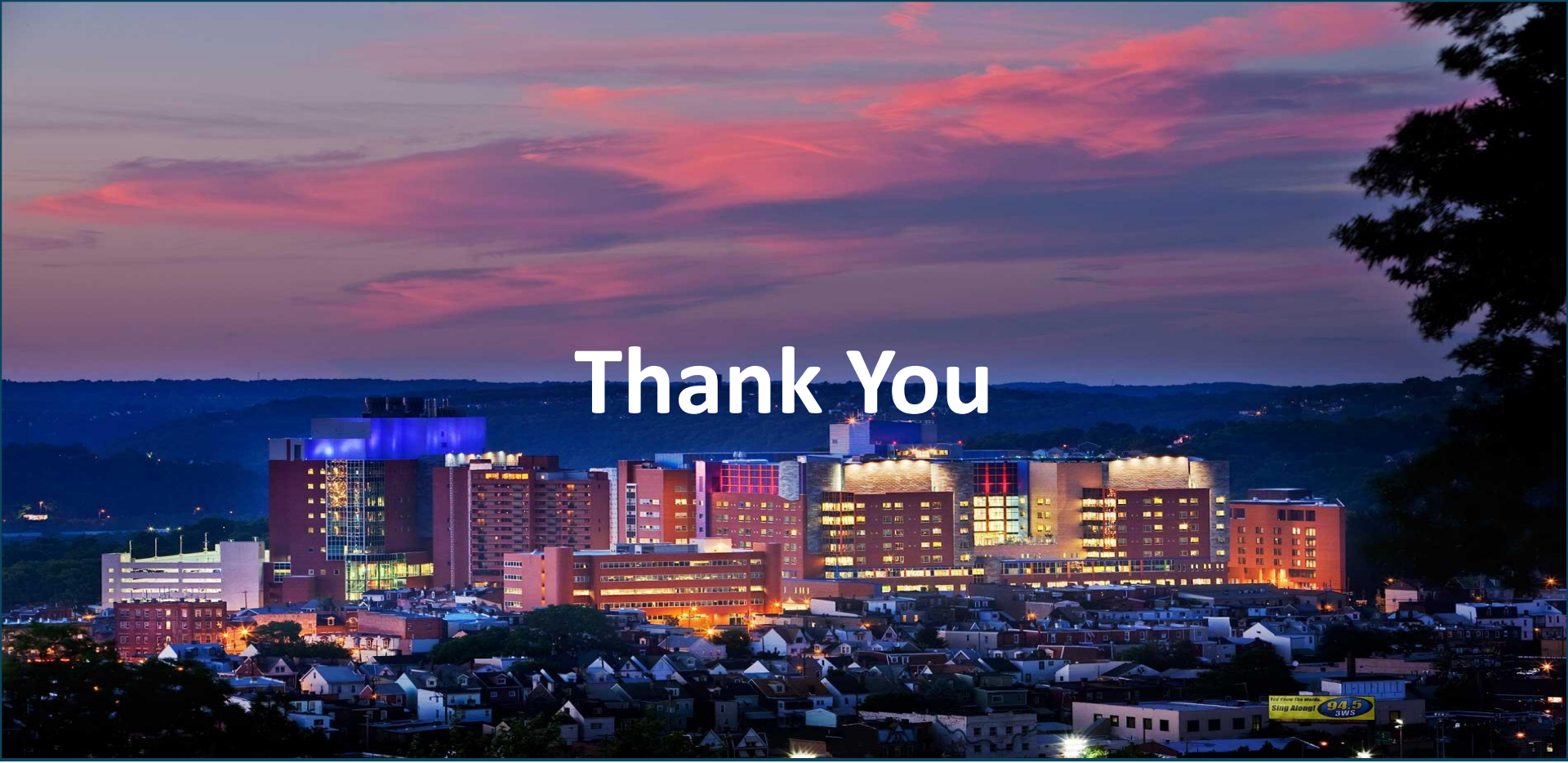
Adapted from CMS Digital Quality Strategic Roadmap (2022)


dQMs
(digital quality measures)
Quality measures, organized as self-contained measure specifications and code packages, that use one or more sources of health information that is captured and can be transmitted electronically via interoperable systems
Administrative Systems
Other Sources
Electronically Submitted Clinical Assessment Data
Health Information Exchanges (HIEs) or Registries
Case Management Systems
Applications (Collection of Patient-Generated Data)
Electronic Health Records
Patient Portals
Instruments (Medical Devices and Wearable Devices)


Digital Quality Strategy in a Learning Healthcare System
ENABLE
Measurement Alignment
ADVANCE
Technology
EVIDENCE
Research, Payer & Public Health Service
KNOWLEDGE
Guidelines & Clinical Decision Support
DATA
Reporting
Measurement & Analytics
ACTION
Clinical Care
Quality Improvement
Digital Quality Measurement
Reporting
• Support delivery of high-quality care
• Benchmark performance across institutions
Measurement and Analytics
• Inform care delivery within health systems
• Sync with practice improving clinical trials
Outcomes
• Improved care delivery measures
• More equitable care
• Fewer mechanical ventilation days
• Reduced ICU length of stay
• Reduced hospital length of stay
• Reduced costs of care
• Lives saved
OPTIMIZE
Data Aggregation
IMPROVE
Data Quality

Summary

- Keep it simple
- Consider your data sources
- Align incentives



Department of
CRITICAL CARE MEDICINE

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

Louise Bowman

Professor of Medicine and Clinical Trials
University of Oxford

Case examples of flexible trial approaches

Prof Louise Bowman

Professor of Medicine & Clinical Trials
University of Oxford, UK

louise.bowman@ndph.ox.ac.uk
26 February 2025

CTTI'S OPTIMIZING DATA QUALITY AND FLEXIBILITY IN TRIALS | EXPERT MEETING

What makes a GOOD clinical trial?

- Ask an IMPORTANT question
- Answer it RELIABLY
- Keep trial participants SAFE

Methodological streamlining

A relentless focus on **things that matter** and de-prioritising everything else

Things that matter

- Robust trial design
  - Statistical power
  - Large-enough population
- Efficient recruitment
  - Network of collaborators
  - Simple eligibility criteria
  - Use of electronic health records/registries
- Complete and high-quality follow up
  - Record only key study outcomes and related data
  - Record linkage during and beyond study
- Safety of participants

Making trials work

- Trials that are easy for participants
- Trials that are easy for site staff/local doctors & nurses
- Results that have impact

ASCEND: The Research Question

A Study of Cardiovascular Events iN Diabetes

- For people with diabetes who have not yet had a heart attack or stroke:
  - Is low-dose aspirin beneficial?
  - Are omega-3 fish oils beneficial?
  - Are these treatments safe?

The Problem

The Solution

- Streamlined
- Cost effective
- Simple eligibility criteria
- Mail-based trial design

- 15,480 UK participants

No study clinics required

Image courtesy of artur84/FreeDigitalPhotos.net

“Decentralised”

Image courtesy of artur84/FreeDigitalPhotos.net

Need help completing this form? Please call Freefone 0800 585323

Please read this **Agreement to Participate**, and if you are willing then please CROSS the boxes, SIGN and DATE the form using blue or black ink, and return it in the FREEPOST envelope provided.

7. Agreement to Participate

Please cross (☒) **EVERY box** to confirm that you have read and understood the following:

☐	I have read and understood the leaflet "**ASCEND: Invitation to join a large medical research project**" ASCEND Patient Information Leaflet Ver2 101109
☐	I have had an opportunity to telephone the Freefone number 0800 585323 and ask any relevant questions. All my questions have been answered to my satisfaction **OR** I decided that I did not need to ask any questions
☐	I understand that my participation in the ASCEND study is voluntary and that I am free to withdraw from the study at any time without my medical care or rights being affected
☐	I understand that information about my progress in the ASCEND study will be recorded on a computer database, and that those data will be stored securely and confidentially on a computer at Oxford University
☐	I agree that information about any serious illnesses (such as heart attacks, strokes or cancers) may be supplied in confidence to the study coordinators by my own doctors and by NHS and other central registries for use in the ASCEND study
☐	I agree that my hospital and other health records may be looked at in confidence by authorised individuals from the ASCEND study and by regulatory authorities to check the study is being carried out correctly
☐	I understand that my GP will be informed about this provisional agreement to participate in the ASCEND study, and that in about 2 months time I will have another opportunity to decide whether or not I want to join the long-term part of the study

I am happy to take part in ASCEND: ASCEND Screening Questionnaire (V1.4_220507)

Signature: _____ (Please use blue or black ink)

& PRINTED name: _____ Today's date: ☐☐ / ☐☐ / 2 0 ☐☐
(Day / Month / Year)

Please check that you have answered every question, and signed and dated the form. Return the completed form in the Freepost envelope provided (no stamps needed) to:-

Freepost RLUJ-TKES-SURR, ASCEND, Richard Doll Building, University of Oxford, Old Road Campus, Headington, Oxford, OX3 7LF

If you have any questions about the study, please contact the coordinating centre in Oxford on FREEFONE: 0800 585323 (preferably during office hours 9 am - 5 pm, Monday to Friday)

If this questionnaire indicates that you are suitable to enter the preliminary part of ASCEND, a box containing ASCEND tablets (aspirin or placebo) and capsules (one or other natural oil) will be mailed to you. A copy of this Agreement to Participate, for you to keep, will also be mailed.

If the questionnaire suggests that the study medications may not be suitable for you, then we shall write and tell you.

Thank you very much

The Pennine Acute Hospitals NHS
NHS Trust

Ref. A755-7320

ASCEND
Clinical Trial Service Unit (CTSU)
Richard Doll Building
University of Oxford
Old Road Campus
Headington, Oxford
OX3 7LF

Office Tel: 01865 743888
Office Fax: 01865 743981
Freefone: 0800 585323
E-mail: ascend@ctsu.ox.ac.uk
Website: www.ctsu.ox.ac.uk/ascend

Mr Thomas White
24 Raspberry Road
Gardentown
Gardenshire
GA3 6TR

Dear Mr White,

26 January 2010

ASCEND: A Study of Cardiovascular Events in Diabetes

We are writing to invite you to participate in the ASCEND research study of the prevention of heart attacks and strokes in people with diabetes. At **the Diabetes Centre at The Royal Oldham Hospital, we are working with Oxford University's Clinical Trial Service Unit to help identify suitable people for this nationwide study.** So, we are writing (having first informed your GP, Dr Rose Gardener) to all those people on our local diabetes register who are aged over 40 and may be suitable, in order to find out whether they might be interested in taking part. The purpose of the study is to assess whether aspirin and/or naturally-occurring oils are useful for preventing heart attacks and strokes in people with diabetes who have not had circulatory problems.

Please read the enclosed Information Leaflet entitled 'ASCEND: Invitation to join a large medical research project'. It is then up to you whether or not you would like to take part. If you would like to, then please complete the attached questionnaire. Based on your answers, the study coordinators will write and tell you whether or not you would be suitable.

If you have any questions regarding the study you may telephone the study co-ordinators (Professor Jane Armitage or Dr Louise Bowman) on Freefone 0800 585323. Alternatively, you may wish to discuss matters with your GP or diabetes nurse before deciding whether to join. If you do not want to take part this will have no effect on your usual medical care. If you want to join the study then please complete the questionnaire and sign the Agreement to Participate. We hope you will decide to take part in ASCEND. If you do not want to participate then please indicate this on the questionnaire on the back of this letter so that you do not get approached again. In either case, please return the questionnaire in the Freepost envelope provided.

Thank you for your help.

Yours sincerely,

Dr Deepak Bhatnagar
Consultant/Senior Lecturer in Diabetes & Metabolism
Royal Oldham Hospital

Dr Bleeka Mishra
Consultant Diabetologist and Endocrinologist
Royal Oldham Hospital

Enc: Information Leaflet
Freepost envelope

DRS [V1.13_061109] IN: D: A777-7777

ASCEND: Screening Questionnaire

INSTRUCTIONS FOR COMPLETION:

Please complete the questionnaire in BLOCK CAPITALS using blue or black ink.

Please place a cross in the appropriate box, e.g. Yes [X] No [ ]

(If you make a mistake, fill the entire box and mark the correct box, e.g. Yes [■] No [X])

OR write clearly in the appropriate boxes, e.g. 26 / 01 / 2007 (Day / Month / Year)

1. Contact Details

Please write your name and contact details clearly in the boxes provided.

Title: Mr [ ] Mrs [ ] Ms [ ] Miss [ ] Other

First name(s):

Surname:

Address:

Postcode:

Home telephone number (inc. code):

Daytime telephone number (inc. code):

2. Personal Details

Date of birth: ___ / ___ / 19__ (Day / Month / Year)

Sex: Male [ ] Female [ ]

3. Joining ASCEND

Please read the enclosed leaflet (**ASCEND: Invitation to join a large medical research project**), and indicate whether you are interested in taking part in ASCEND: Yes [ ] No [ ]

If you answered **YES**, then please complete **ALL** the remaining sections of this questionnaire, sign and date the form, and return it in the FREEPOST envelope provided.

If you answered **NO**, then return the questionnaire in the FREEPOST envelope provided (but do not complete the remaining sections).

4. GP Details

Please give your GP's surname and initials, as well as the address of the GP practice.

GP surname: GP initials:

Address:

Postcode:

Need help completing this form? Please call Freefone 0800 585323

5. Medical History

5.1 Has a doctor ever told you that you had any of the following?

Please cross ONE box only for each question

a)	Diabetes, Type 1 or Type 2 (i.e. "sugar" diabetes)	Yes [ ]	No [ ]
b)	Heart attack	Yes [ ]	No [ ]
c)	Angina (chest pain from the heart)	Yes [ ]	No [ ]
d)	Stroke or ministroke (sometimes called TIA)	Yes [ ]	No [ ]
e)	Coronary artery bypass operation (CABG or "cabbage")	Yes [ ]	No [ ]
f)	Coronary angioplasty ("balloon", "stent" insertion or PTCA)	Yes [ ]	No [ ]
g)	Other arterial surgery or angioplasty (e.g. leg bypass) (Do not include angiogram)	Yes [ ]	No [ ]
	If Yes, please specify:		
h)	Liver disease (active or chronic, or cirrhosis)	Yes [ ]	No [ ]
	If Yes, please specify:		
i)	Cancer **within the last 5 years** (e.g. skin, breast, lung, bowel etc)	Yes [ ]	No [ ]
	If Yes, please give the type of cancer:		
j)	Other serious illness	Yes [ ]	No [ ]
	If Yes, please specify:		

S-340007

5.2 In the last 6 months have you been in hospital with, or has a doctor said you have:

a)	Active peptic (stomach or duodenal) ulcer?	Yes [ ]	No [ ]
b)	Bleeding from the stomach or bowel?	Yes [ ]	No [ ]

6. Current Medication

As a participant in ASCEND, you would be asked not to use NON-STUDY aspirin, medications containing aspirin or blood thinning drugs on a regular basis (i.e. more than one day per week) unless this becomes necessary.

6.1 Do you currently take any of the following regularly?

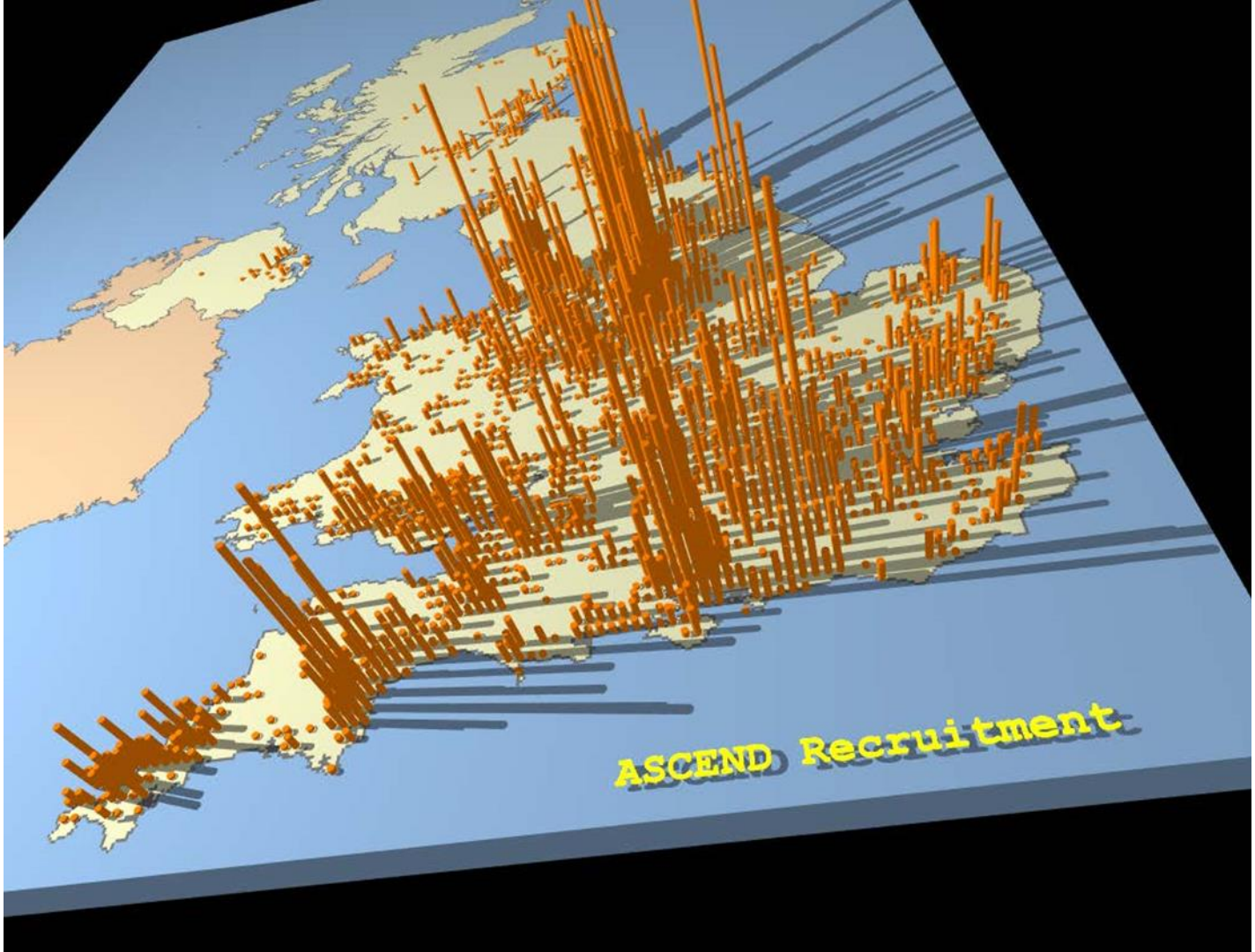
Please cross ONE box only for each question

a)	Aspirin (e.g. Anadin, Caprin, Disprin, Imazin, PostMI)	Yes [ ]	No [ ]
b)	Warfarin (Marevan), Acenocoumarol (Nicoumalone, Sinthrome) or Phenindione	Yes [ ]	No [ ]

6.2 Are you known to be allergic to aspirin or omega-3 fatty acid (fish oil) supplements? Yes [ ] No [ ]

6.3 Are you willing to avoid medications containing aspirin (apart from ASCEND study treatment) during the course of the study? (N.B. you could use paracetamol instead for pain relief) Yes [ ] No [ ]


ROYAL MAIL


ASCEND Recruitment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Group

ORIGINAL ARTICLE

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

ASCEND

A Study of Cardiovascular Events in Diabetes

NEJM animation illustrates ASCEND Aspirin trial results

22 October 2018

The New England Journal of Medicine has produced a short animation to illustrate the results of the ASCEND study Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

CTSU

MRC Medical Research Council

haiku

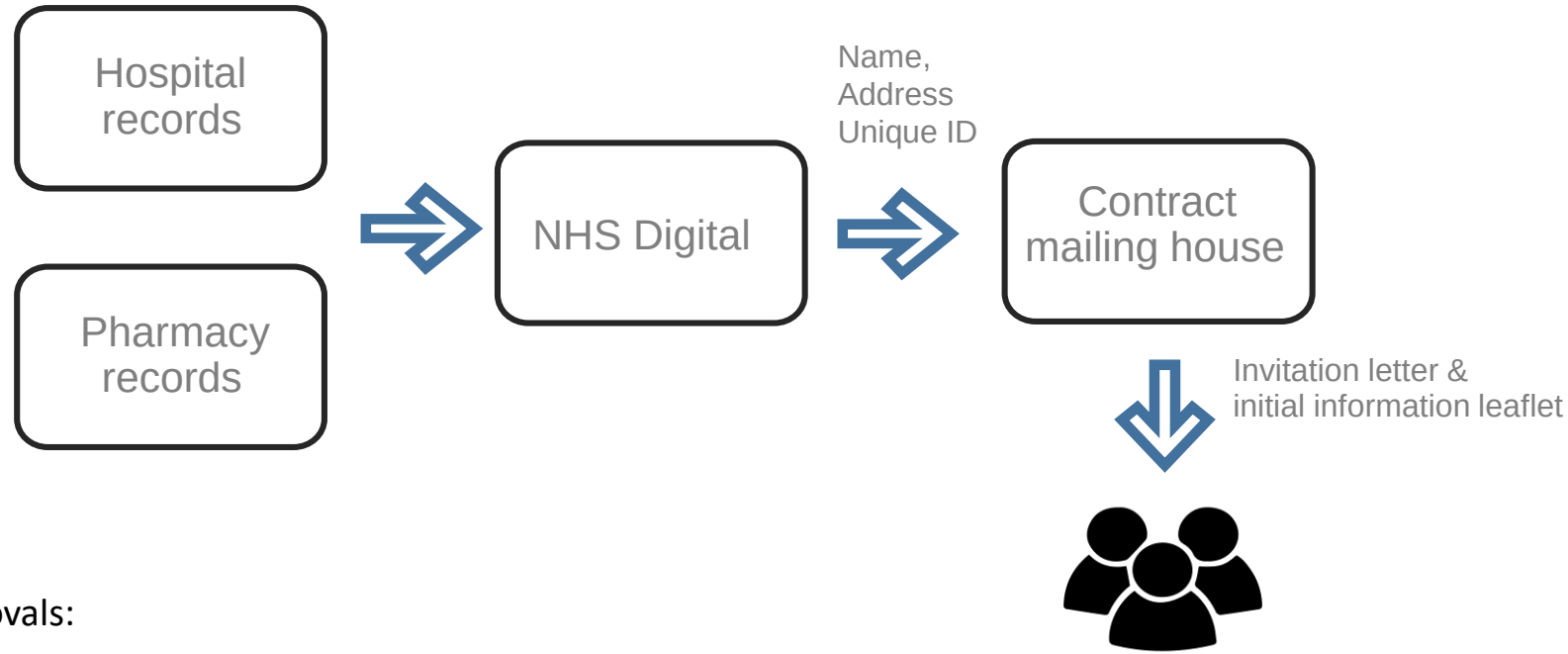
800 million

ASCENDPLUS
A STUDY OF CARDIOVASCULAR EVENTS IN DIABETES

- UK trial
- 20,000 participants
- Type 2 diabetes
- No previous CVD
- Oral semaglutide vs placebo
- ~5 years follow-up
- Primary endpoint: MACE+

- No physical trial sites
- Extensive use of electronic health data/digital technologies

Identification & invitation in ASCEND PLUS



Approvals:

- Research Ethics Committee (REC)
- Confidentiality Advisory Group (CAG)
- IGARD

Participant Ref: 999-999-999
Mailing Ref: 117999999

ASCEND PLUS
A STUDY OF CARDIOVASCULAR EVENTS IN DIABETES

Mr Peter Patient
Flat 4
Honeysuckle House
85 Sunflower Street
West Roosebeck
Beckshire
PT1 8BC

ASCEND PLUS Coordinating Centre
Clinical Trial Service Unit (CTSU)
Richard Doll Building
Old Road Campus
Roosevelt Drive
Oxford, OX3 7LF

Freephone: 0808 164 5090
Email: ascend-plus@ndph.ox.ac.uk
Website: www.ascend-plus-trial

Dear Mr Patient,

ASCEND PLUS: a national clinical trial in diabetes

If you would like this information in a non-English language or other format, such as large print, please contact us

You are invited to take part in a major national clinical trial to help us find out if a new treatment for type 2 diabetes can prevent heart attacks and strokes. If you choose to take part, your help could benefit people for years to come, not just in the UK but around the world. Please read the enclosed information leaflet that explains more about the study.

What should I do next?

If you would like to know more to help you decide if you want to take part, please detach and complete the reply form, and return it to the Coordinating Centre in the FREEPOST envelope.

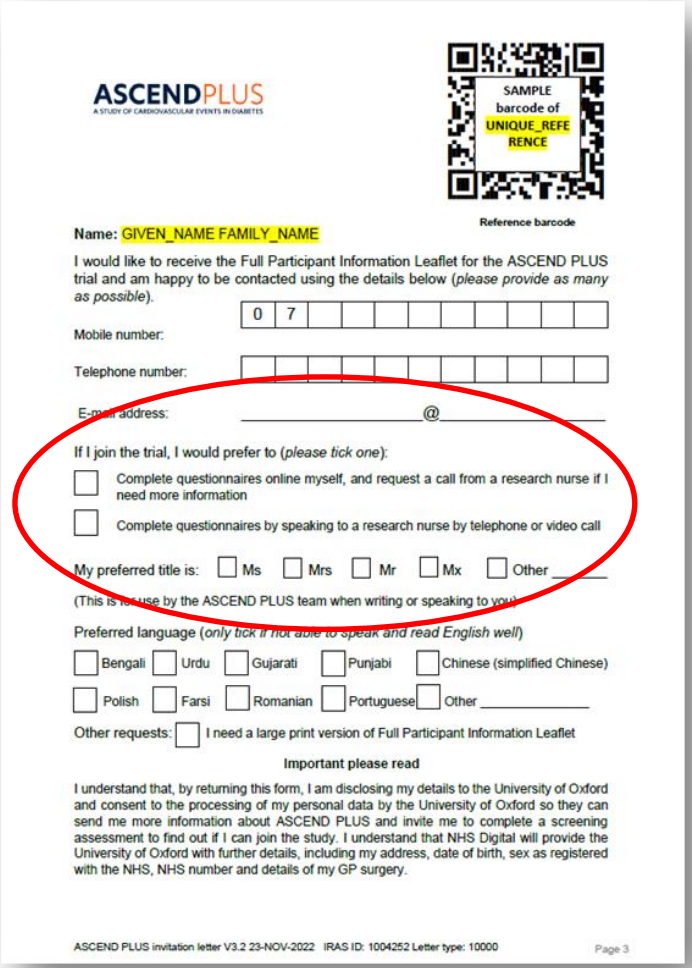
Thank you for taking the time to read this letter. We hope you will be able to join us in this important study.

Yours sincerely,

Dr David Preiss

Dr Marion Mafham

The ASCEND PLUS Lead Investigators, University of Oxford



ASCENDPLUS
A STUDY OF CARDIOVASCULAR EVENTS IN DIABETES

SAMPLE barcode of UNIQUE_REFERENCE

Reference barcode

Name: GIVEN_NAME FAMILY_NAME

I would like to receive the Full Participant Information Leaflet for the ASCEND PLUS trial and am happy to be contacted using the details below (*please provide as many as possible*).

Mobile number: 0 7

Telephone number:

E-mail address: _____@_____

If I join the trial, I would prefer to (*please tick one*):

☐ Complete questionnaires online myself, and request a call from a research nurse if I need more information

☐ Complete questionnaires by speaking to a research nurse by telephone or video call

My preferred title is: ☐ Ms ☐ Mrs ☐ Mr ☐ Mx ☐ Other _____

(This is for use by the ASCEND PLUS team when writing or speaking to you)

Preferred language (*only tick if not able to speak and read English well*)

☐ Bengali ☐ Urdu ☐ Gujarati ☐ Punjabi ☐ Chinese (simplified Chinese)

☐ Polish ☐ Farsi ☐ Romanian ☐ Portuguese ☐ Other _____

Other requests: ☐ I need a large print version of Full Participant Information Leaflet

Important please read

I understand that, by returning this form, I am disclosing my details to the University of Oxford and consent to the processing of my personal data by the University of Oxford so they can send me more information about ASCEND PLUS and invite me to complete a screening assessment to find out if I can join the study. I understand that NHS Digital will provide the University of Oxford with further details, including my address, date of birth, sex as registered with the NHS, NHS number and details of my GP surgery.

ASCEND PLUS invitation letter V3.2 23-NOV-2022 IRAS ID: 1004252 Letter type: 10000 Page 3

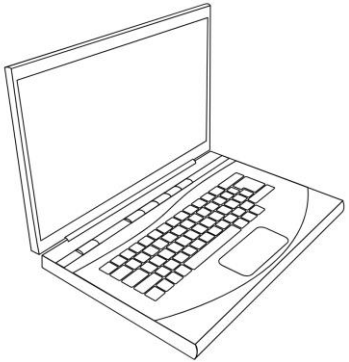
If I join the trial, I would prefer to:

Complete questionnaires online myself, and request a call from a research nurse if I need more information

Or

Complete questionnaires by speaking to a research nurse by telephone or video call

Participants take part from home

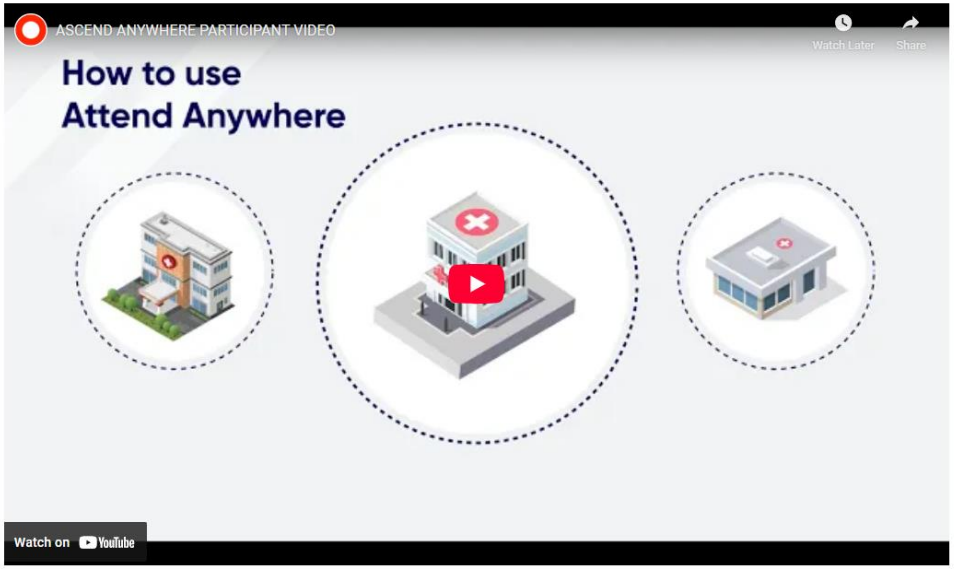


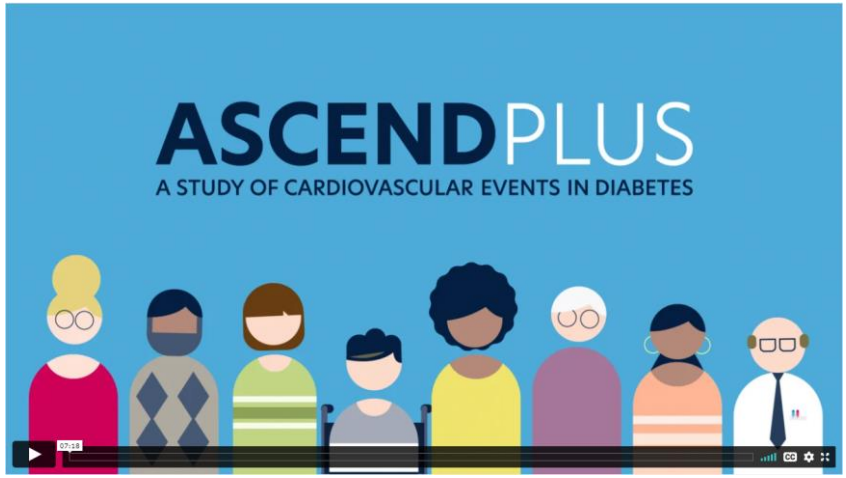
PARTICIPANT CHOICE

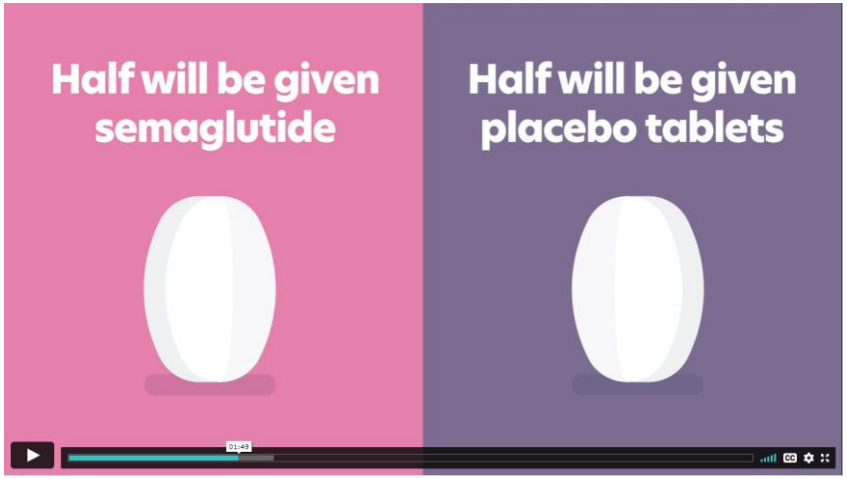
Video appointments

The ASCEND PLUS team is pleased to be partnering with Attend Anywhere during the trial. Attend Anywhere already provides software for NHS hospitals across the UK, allowing nurses and doctors to speak to people in their own homes.

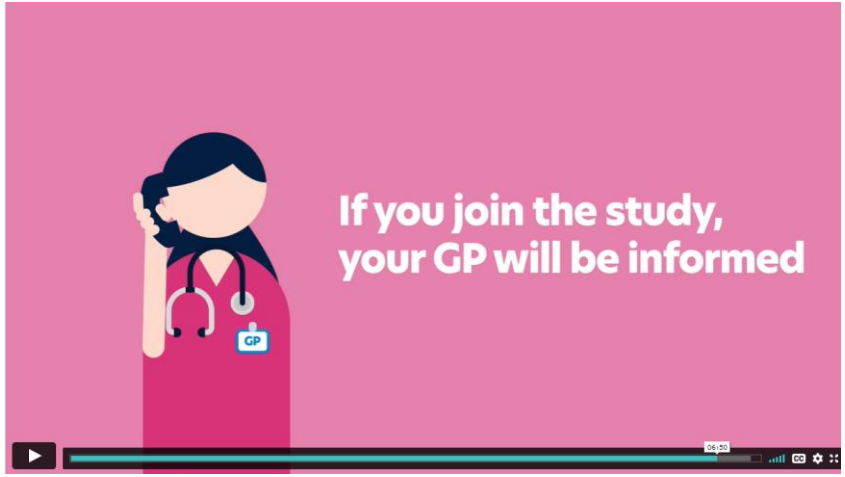
We are using Attend Anywhere software to conduct video calls during the ASCEND PLUS trial. If you have chosen to speak to the ASCEND PLUS research nurse by video call for your next appointment, find out how to join the call in this video.



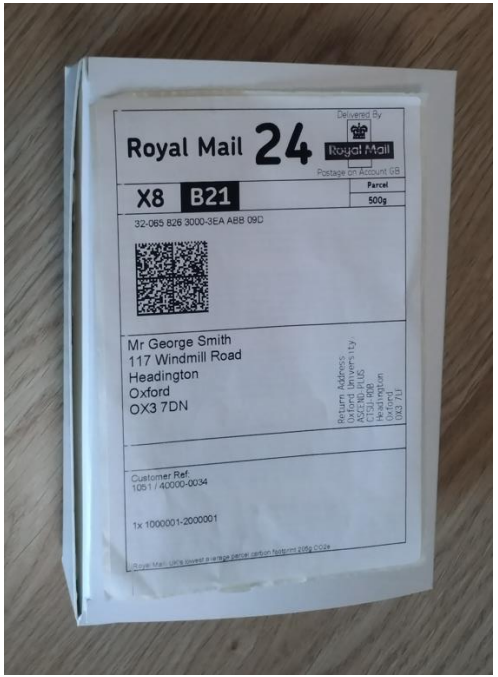

ASCENDPLUS
A STUDY OF CARDIOVASCULAR EVENTS IN DIABETES


Half will be given semaglutide
Half will be given placebo tablets


Start
5 years
20 years


If you join the study, your GP will be informed

Study treatment mailed to participants' homes

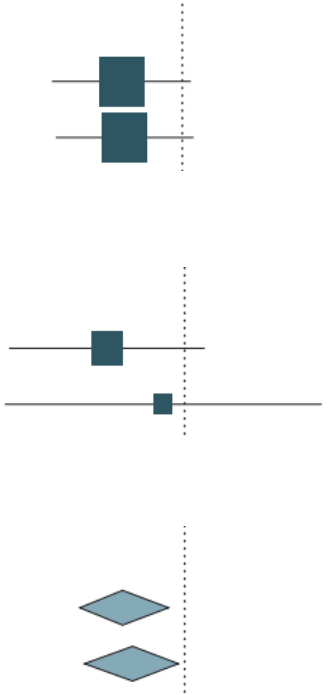


Extensive data linkage for outcomes

- Hospitalisations
- Cause of death
- Medicines dispensed in the community
- National Diabetes Audit (NDA)
- Other national registries

ASCEND – adjudicated outcomes vs. NHS data linkage

Any arterial revascularization			
Adjudicated direct follow-up	340 (4.4)	384 (5.0)	0.88 (0.76-1.02)
Routine data follow-up	347 (4.5)	389 (5.0)	0.89 (0.77-1.02)
Transient ischemic attack			
Adjudicated direct follow-up	168 (2.2)	197 (2.5)	0.85 (0.69-1.04)
Routine data follow-up	68 (0.9)	71 (0.9)	0.96 (0.69-1.33)
Any serious vascular event or revascularization			
Adjudicated direct follow-up	833 (10.8)	936 (12.1)	0.88 (0.80-0.97)
Routine data follow-up	726 (9.4)	805 (10.4)	0.90 (0.81-0.99)



Harper et al. JAMA Netw Open. 2021;4(12):e2139748.

ASCENDPLUS
A STUDY OF CARDIOVASCULAR EVENTS IN DIABETES

Site Map Accessibility Cookies Log in

OXFORD POPULATION HEALTH

HOME OUR TEAM PARTICIPANTS JOINING THE STUDY HEALTH PROFESSIONALS CONTACT US DATA PROTECTION
PUBLIC INVOLVEMENT

Public involvement

Public involvement

The ASCEND PLUS trial was developed in partnership with patients and members of the public, to help ensure that:

- the participant experience is relevant and beneficial to them
- the safety and wellbeing of the participants is protected
- recruitment to the trial is successful
- participants remain engaged throughout the trial.

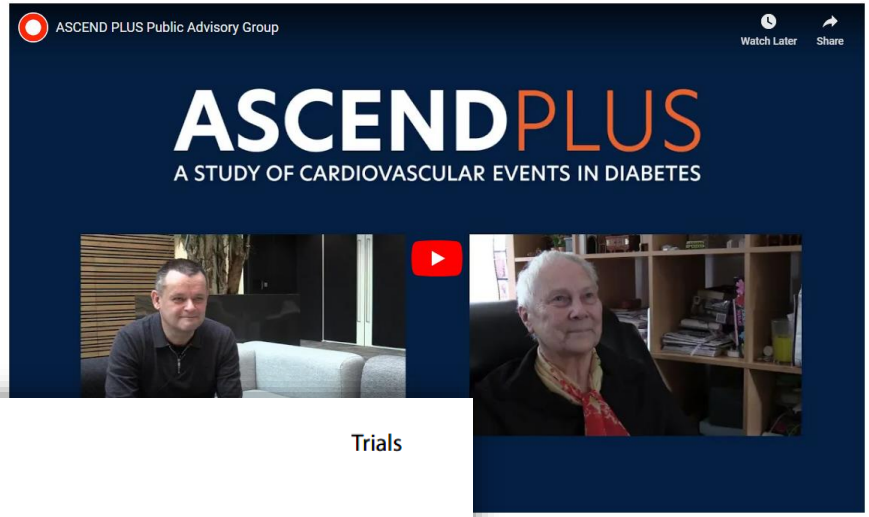
The patient and public involvement activities focused on three aspects:

1. Six patient and public focus groups addressed specific issues before the trial started. These focus groups largely involved people with type 2 diabetes and includ
   diverse backgrounds across the UK.
2. An ASCEND PLUS Public Advisory Group (PAG) was e
   advice, and opinions on many different aspects of ASC
3. Two members of the PAG have joined the Trial Steering

The PAG was crucial in helping to design the trial, including de
will continue to contribute throughout the whole trial, for examp
interpretation and presentation of the ASCEND PLUS results a

Listen to our public contributors, Andrew Toal and Dianna

Listen to our public contributors, Andrew Toal and Dianna Moylan, sharing their experience of patient and public involvement in ASCEND PLUS.



El-Nayir *et al. Trials* (2024) 25:554
https://doi.org/10.1186/s13063-024-08393-2

Trials

METHODOLOGY Open Access

Patient and public involvement and engagement in the ASCEND PLUS trial: reflections from the design of a streamlined and decentralised clinical trial

Muram El-Nayir[1†], Rohan Wijesurendra[1*†], David Preiss[1], Marion Mafham[1], Leandros Tsiotos[1], Sadman Islam[1], Anne Whitehouse[1], Sophia Wilkinson[1], Hannah Freeman[1], Ryonfa Lee[1], Wojciech Brudlo[1], Genna Bobby[1], Bryony Jenkins[1], Robert Humphrey[1], Amy Mallorie[1], Andrew Toal[2], Elnora C. Barker[2], Dianna Moylan[2], Graeme Thomson[2], Firoza Davies[2], Hameed Khan[2], Ian Allotey[2], Susan Dickie[2†] and John Roberts[2†]

“Streamlining and quality are not opposed”

Rob Califf,
outgoing Commissioner,
US FDA

Safety of future patients if the trial doesn’t get done

https://www.ndph.ox.ac.uk/study-with-us/msc-clinical-trials

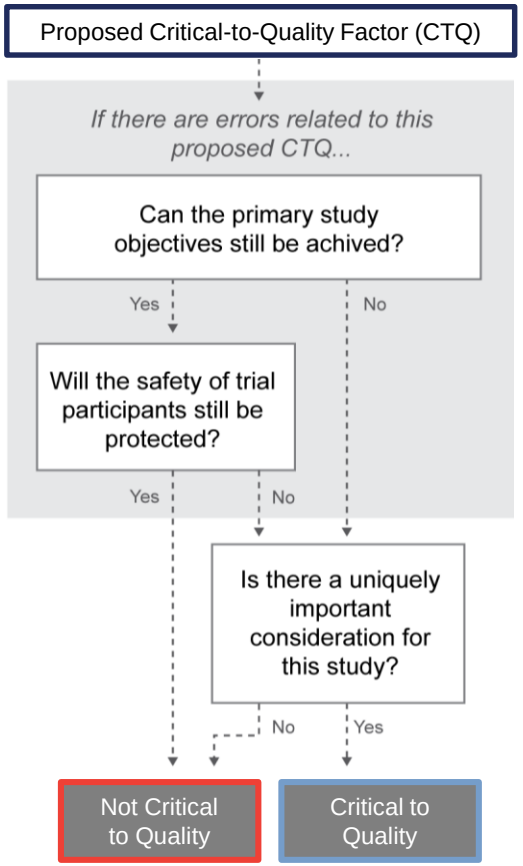
Thank you

Louise.bowman@ndph.ox.ac.uk

Q&A

Adopting a QbD mindset

- Evaluate for what's essential
- Eliminate nonessential activities
- Control for errors that matter to ensure the safety of trial participants and the credibility of key study results

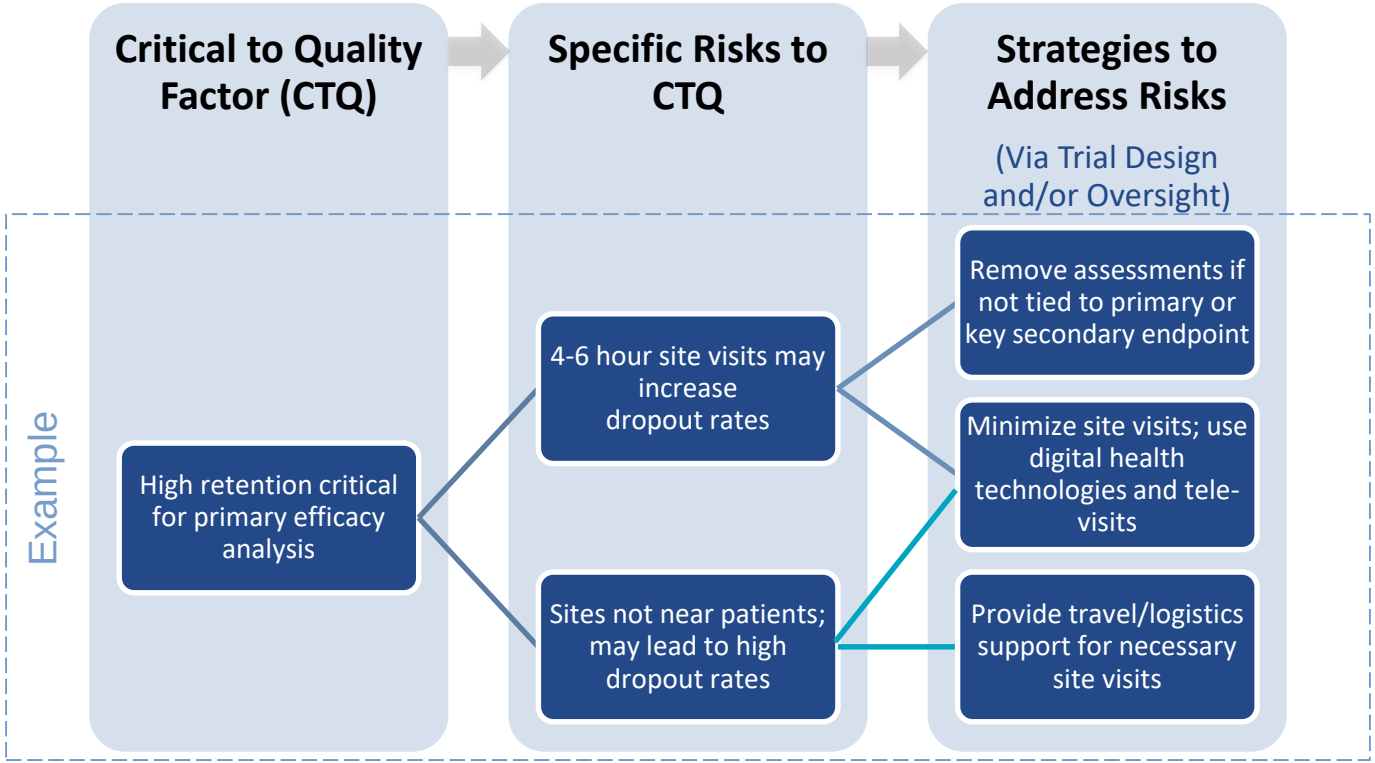


Any Element of the Study Can be “Critical to Quality”

Topic	Examples of Potential CTQ Factors
Protocol Design	Eligibility Criteria
	Randomization
	Masking
	Types of Controls
	Data Quantity
	Endpoints
	Procedures Supporting Study Endpoints and Data Integrity
	IP Handling and Administration
Feasibility	Study and Site Feasibility
	Accrual
Patient Safety	Informed Consent
	Withdrawal Criteria and Trial Participant Retention
	Signal Detection and Safety Reporting
	Data Monitoring Committee /Stopping Rules
Study Conduct	Training
	Data Recording and Reporting
	Data Monitoring and Management
	Statistical Analysis
Study Reporting	Dissemination of Study Results
Third-Party Engagement	Delegation of Sponsor Responsibilities
	Collaborations

CTTI

Critical to Quality Factor Example



CTTI

Roundtable Discussions

Part 1: Offering Flexible Approaches

Members of CTTI Social Science Team will moderate each roundtable discussion

Amy Corneli, PhD, MPH

Carrie Dombeck, MA

Kevin McKenna, MPH

Blythe Fortino, PhD

Jamilah Taylor, BS

Summer Starling, DrPH, MPH

Roundtables – Recording Disclaimer

- We will record audio to capture everything said and transcribe each group's discussion
- Any identifying details shared will be removed from the transcripts
- The audio recordings will be stored securely and later destroyed
- Please keep the information shared by others private
- Groups are pre-assigned to ensure diverse representation of stakeholders
- Each group will also include a notetaker

CTTI

Randomized Trial Case Scenarios: The Basics

	Scenario 1	Scenario 2	Scenario 3
Overview	Phase 3 international, cardiovascular study	Phase 2 study rare disease study	Phase 2 personalized medicine oncology study
Intervention	Oral anticoagulation new drug vs a known drug	An oral drug (NMDA receptor antagonist)	New drugs in sequence with standard chemotherapy vs standard therapy alone prior to surgical tumor removal
Population	Adult patients with atrial fibrillation at risk for stroke	Female pediatric patients with a rare neurodevelopmental syndrome	Male and female adults with locally advanced breast cancer
Purpose	Show non-inferiority and demonstrate superiority (compare efficacy and safety) to prevent stroke or systemic embolism	Assess the safety, tolerability, and efficacy of a repurposed drug	Identify improved treatment regimens for patient subsets on basis of molecular characteristics (biomarker signatures) of the disease
Flexible approach	Conventional model or a fully remote decentralized clinical trial (DCT) model	Hybrid decentralized trial with wearable for continuous monitoring	Trial integrated into routine care

CTTI

Please take 5 minutes to review your case study

You can ask brief, clarifying questions afterward

Break Out Group Overview

- **6 Break Out Groups** designated by colored dots on back of your name tag:
  - Group 1 = red  Kingsman Park with Blythe
  - Group 2 = orange  Burnham C with Carrie
  - Group 3 = yellow  Storey Park Room with Amy
  - Group 4 = green  Stanton Park Room with Kevin
  - Group 5 = blue  Lincoln Park with Jamilah
  - Group 6 = virtual Zoom/Virtual Room with Summer
- Duration = ~65 minutes (pre lunch) and ~75 minutes (post lunch)

CTTI

Regulatory Advances in Support of RWD & Data Quality

CDER establishes new Center for Real-World Evidence Innovation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 November 2024
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Committee for Medicinal Products for Human Use (CHMP)

Data Quality Framework for EU medicines regulation: application to Real-World Data
Draft

Medicines & Healthcare products Regulatory Agency

Corporate report
MHRA Data Strategy 2024 -2027
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Elements of Real World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle

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Peter Stein

Director of CDER's Office of New Drugs
Food and Drug Administration

Clinical Trial Quality – A (brief) Regulatory Perspective

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Peter Stein, MD
Director
Office of New Drugs / CDER / FDA

Approving a new drug: “two components”

- **Demonstrating effectiveness**: meeting the substantial evidence standard

  and

- **Concluding that the drug’s benefit outweighs its risk:** how FDA interprets “safe for use….”

Substantial evidence: the statutory standard for approval

- *As defined in Section 505(d), substantial evidence is*:
  - "evidence consisting of **adequate and well-controlled investigations**, including clinical investigations, by **experts qualified by scientific training and experience to evaluate the effectiveness** of the drug involved, on the basis of which it could **fairly and responsibly be concluded** by such experts that the drug will have the effect it purports or is represented to have **under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.**"

- The FDA *standard* requirement for *two* A&WC studies
- Replication is a scientific standard, reduces risk of false positive findings, bias or confounding in a single trial
- No mention of "p values" in statute

Effectiveness for what?…endpoints that can support approval

- Not defined in statute or regulation…FDA has long considered that drugs must provide a **meaningful clinical benefit to support approval**
  - Not just statistical significance

- Drugs must improve how a patient….
  - **Feels**: improvements in pain, dyspnea, depression, other relevant symptoms

    or
  - **Functions**: ability to care for themselves, ability to work, participate in social activities, ambulate

    or
  - **Survives**

Persuasive evidence that an effect *is* present
= statistical assessment

and

Evidence that the effect is clinically meaningful
= clinical assessment

For a trial to provide interpretable and reliable evidence, what are the scientific design/execution principles?

- **Pre-specify the study objectives** and the analysis: avoid post-hoc “cherry-picking”
- Have an appropriate comparative **control group** to separate the disease natural history or trial effects from the drug effect
- Be sure the patients in the trial have the **disease to be studied**
- Minimize bias **in assignment of patients** to treatment or control
- **Minimize bias** on the part of subjects, observers, and analysts of the data
- Make sure the **endpoint is well defined and reliable**—reflects a clinically meaningful aspect of the disease
- Assure that the **analysis is properly conducted** with reliable methods

Regulatory definition of an adequate and well-controlled investigation

*Selected Key Characteristics**
• There is a **clear statement of objectives** of the investigation and **methods of analysis**
• The study uses a **design** that permits **a valid comparison** with a **control to provide a quantitative assessment of drug effect**: *placebo-control, dose-comparison control, no treatment control, active-treatment control, historical control*
• The **method of selection** of subjects provides adequate assurance that they have the disease/condition being studied.
• The **method of assigning patients** to treatment and control groups **minimizes bias** and is intended to **assure comparability of the groups** with respect to pertinent variables. Ordinarily….assignment is by randomization…
• Adequate measures are taken to **minimize bias** on the part of the subjects, observers, and analysts of the data
• The **methods of assessment** of subjects' response are **well defined and reliable**.
• There is an **analysis of the results of the study adequate to assess the effects of the drug**

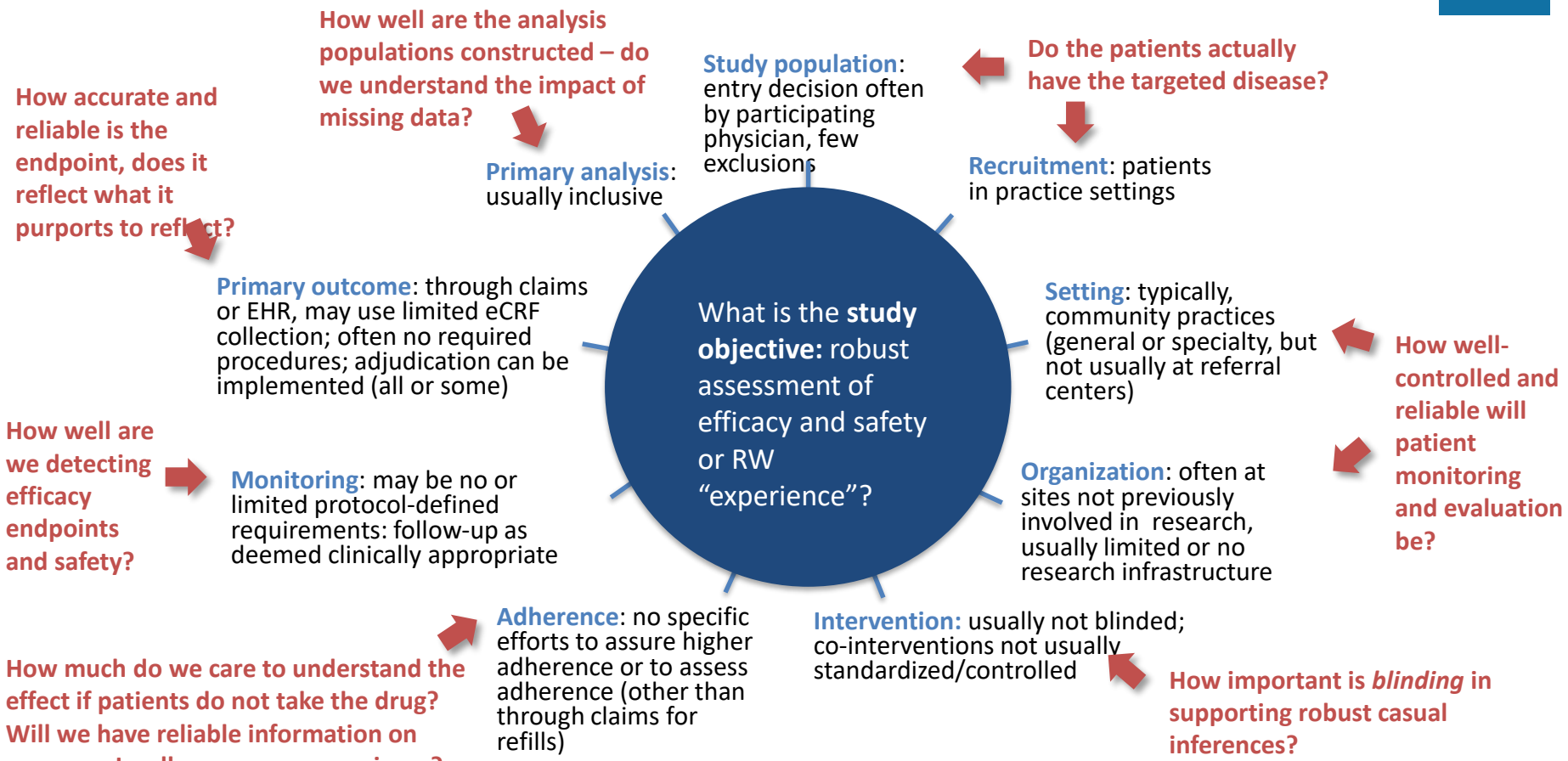
***From 21 CFR 314.126**

Some principles in getting to an AWC investigation

*Selected Key Characteristics**	
• There is a clear statement of objectives of the investigation and methods of analysis	**Assure that the study design features and study implementation focus on the key objectives: avoid unnecessary complexity**
• The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect: *placebo-control, dose-comparison control, no treatment control, active-treatment control, historical control*	**Select a study design that can properly address the study objectives – and accounts for other key criteria needed for study interpretability**
• The method of selection of subjects provides adequate assurance that they have the disease/condition being studied.	**Keep the enrollment criteria as broad and simple as possible—but assure that the population is consistent with the study objective**
• The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables.	**Assure the selected AWC study design is fit-for-purpose: can the comparison group assure an interpretable result?**
• Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data	**If blinding is not feasible, assure that the study design, conduct, and analysis can still provide interpretable results**
• The methods of assessment of subjects' response are well defined and reliable.	**Assure the endpoint is reliable and fit-for-purpose in addressing the study objective**
• There is an analysis of the results of the study adequate to assess the effects of the drug	**Prespecify the approach to avoid Type I error, and assure that the analytic method provides interpretable results**

***From 21 CFR 314.126**

"Traditional" vs "pragmatic" trials: an overview of components



Based on: The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel BMJ 2015

The changing "face" of clinical trials

What's changing in the clinical trial enterprise? → ***What's <u>not</u> changing…***

- Decentralized trials
- Digital health technology endpoints
- Adaptive designs; Bayesian approaches
- Pragmatic trial designs; point of care trials
- Use of RWE – observational analyses as AWC studies
- Master protocols

To approve a drug or a new indication, the data must provide **substantial evidence of effectiveness** from AWC investigations ("persuasive evidence") **and sufficient safety** to assess **benefit and risk**

Quality by design – regulatory considerations

- Consider the regulatory criteria for an adequate and well controlled investigation: the key “currency” to support regulatory decisions
- Avoid *unnecessary* study complexity – as it can undermine quality (too much noise, easy to miss critical study failures)
- Assure that *necessary* complexity (in patient selection, visit structure, endpoints, data collection, safety assessments) is identified and the protocol, study conduct, and study monitoring are designed around assuring quality
- Identify and focus on the study elements critical to interpretable and reliable results – and target trial design, conduct and monitoring towards these critical elements
- For studies to support regulatory decision-making, assure that trial data is verifiable—line of site from the point of collection to the data sets to the study results and reports

Resources to support incorporation of innovative approaches to trial design and conduct – with a focus on quality

- ICH E8(R1) General Considerations for Clinical Studies (2022)
- ICH E6(R3) Good Clinical Practice (2013)
- Applicable FDA guidances:
  - **Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (2013)**
  - **A Risk-Based Approach to Monitoring of Clinical Investigations: Q&A (2023)**
  - **Conducting Clinical Trials with Decentralized Elements (2024)**
  - **Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (2023)**
  - **Integrating Randomized Controlled Trials for Drugs and Biological Products into Routine Clinical Practice (2024)**
- C3TI (launched 2023): focused on clinical trial innovation

CDER Center for Clinical Trial Innovation

CDER launched C3TI in April 2024

to enable and amplify innovative approaches to clinical trials that are designed to improve the efficiency and effectiveness of drug development.

CDER Center for Clinical Trial Innovation (C3TI)

C3TI is an embedded, cross-disciplinary program

C3TI is governed and supported by a team of existing leaders and experts from across CDER

INITIAL PROJECT AREAS

Bayesian Supplemental Analysis – Increase CDER staff and drug developers' utilization of innovative statistical approaches.

Selective Safety Data Collection – Focus on streamlining data collection in clinical trials of drugs with well-known safety profiles to reduce the burden of collecting unnecessary data.

Streamlined Trials Embedded in clinical Practice – Incorporate features such as real-world data collection, decentralized procedures that can be performed in the clinical practice setting, and other innovations aimed to use resources effectively, conduct trials efficiently, and encourage trial recruitment and retention.

Roundtable Discussions

Part 2: Assessing Data Quality

Break Out Group Reminder

- **6 Break Out Groups** designated by colored dots on back of your name tag:
  - Group 1 = red  Kingsman Park with Blythe
  - Group 2 = orange  Burnham C with Carrie
  - Group 3 = yellow  Storey Park Room with Amy
  - Group 4 = green  Stanton Park Room with Kevin
  - Group 5 = blue  Lincoln Park with Jamilah
  - Group 6 = virtual Zoom/Virtual Room with Summer
- Duration = ~65 minutes (pre lunch) and ~75 minutes (post lunch)

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Scenario Recap

For your Group…..

Provide 1 or 2 reflections of where flexibility and data quality were well balanced or where things could have been done differently*

*E.g. flexible approach = mobile nurse collects necessary blood sample at home balanced by training to ensure data integrity

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Optimizing Data Quality and Trial Flexibility Project Next Steps

Project Objectives

- Identify the range of flexible operational approaches; their advantages, disadvantages, implementation practicality; and how the approaches might affect data quality
- **Seek consensus** around critical concerns for data quality, including the acceptable ranges for which errors in the data can be tolerated and best practices to ensure data meet their intended purpose
- Describe considerations for maintaining data quality when using flexible operational approaches in intervention clinical trials

Approach

- ✓ Expert Meeting
- ❑ Surveys?
- ❑ Develop library of resources?
- ❑ Interviews?
- ❑ If generalizable themes emerge, develop recommendations

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Expert Meeting Next Steps

Social Science Team – will analyze today's discussions for key themes

Project team – will assess key themes to inform next steps

CTTI– will summarize meeting and post on our project page in near future

Attendees - Kindly Complete the Evaluation survey!

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Evaluation Survey

https://duke.is/TrialFlexEval

Thank you!

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

@CTTI_Trials

Thank you Experts, CTTI Staff, and Social Science Team!

THANK YOU

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