Welcome to CTTI's Trials in Health Care Settings Expert Meeting

- This meeting is being recorded.
- All participants are muted upon entry.
- Kindly unmute for speaking purposes only (i.e. during Open Discussion)
- Questions will be taken throughout the meeting via the chat box.
- Videos can remain off until the Breakout Group Sessions.
- Please contribute and make this Working Group Meeting a productive one!

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Agenda

Time (EST)	Content	Presenter
10:30 AM	Welcome Remarks and Introduction to CTTI	Sally Okun (CTTI)
10:35 AM	Trials in Health Care Settings Project Overview	Lindsay Kehoe (CTTI)
10:40 AM	Review of Project's In-depth Interview Results (Q&A to follow)	Amy Corneli (CTTI)
11:15 AM	Review of Project's Draft Recommendations (Open discussion to follow)	Mark Stewart (Friends of Cancer Research)
12:00 PM	Case Examples	Martin Landray (University of Oxford) Laura Esserman (University of California San Francisco) Ryan Ferguson (Department of Veteran's Affairs)
12:30 PM	Breakout Groups	All Attendees
2:00 PM	Implementation Opportunities (Open discussion to follow)	Kraig Kinchen (Eli Lilly and Company)
2:30 PM	Closing Comments and Adjourn	Lindsay Kehoe (CTTI)

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CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

May 11, 2022

Introduction to CTTI

Sally Okun, CTTI Executive Director

Clinical Trials Transformation Initiative

- ***Multi-stakeholder*** public-private partnership co-founded in 2007 by FDA and Duke University
  - Active collaboration with ±500 individuals and groups
  - Steering Committee with ±80 member organizations
  - All stakeholders have an equal voice

- ***Evidence-based*** research methods
  - Multi-method research
  - Systematic literature reviews
  - Expert meetings
- ***Impactful*** products and resources
  - Case Study Exchange
  - Policy adoption
  - Enterprise-wide engagement

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.

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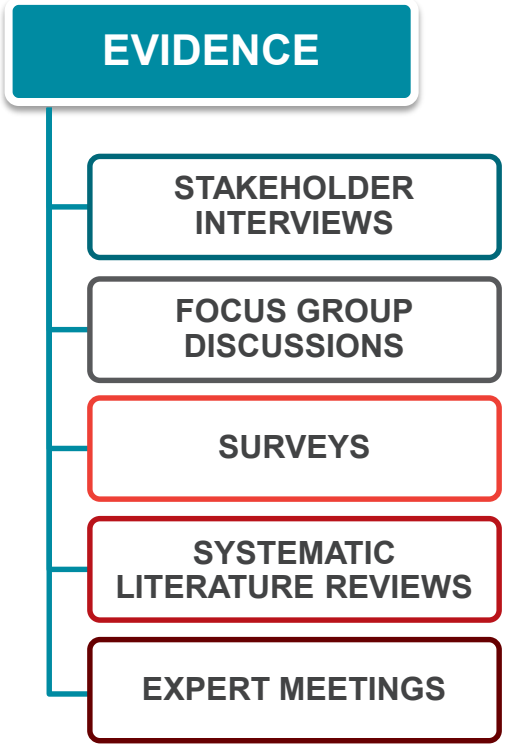
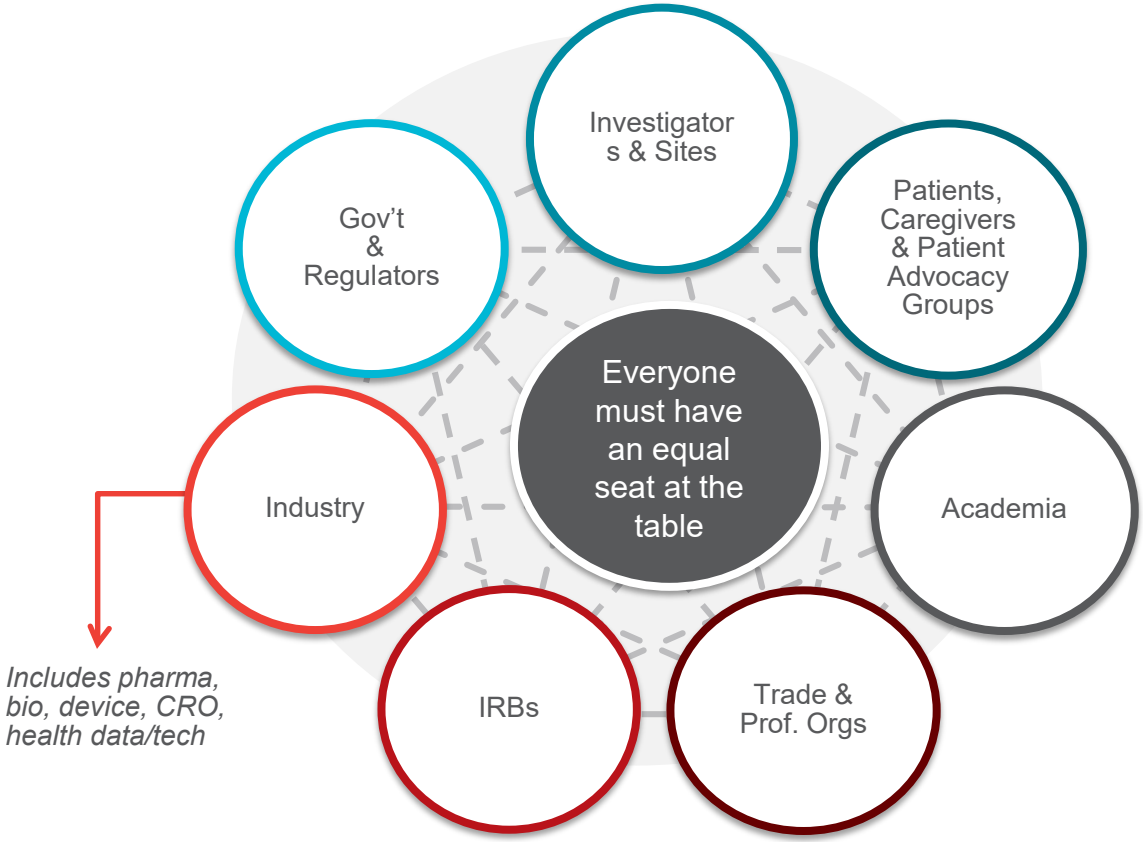
Evidence guides the journey to solutions

- We use quantitative & qualitative research methods, selecting those best aligned with each project's objectives, to:
  - Identify/describe "what is going on" to gain a better understanding of a particular phenomenon
  - Move beyond individual views to a more complete and objective understanding of the disincentives and motivators for change
- Equipped with data, we then challenge assumptions, identify roadblocks, build tools and develop recommendations to change the way people think about and conduct clinical trials.

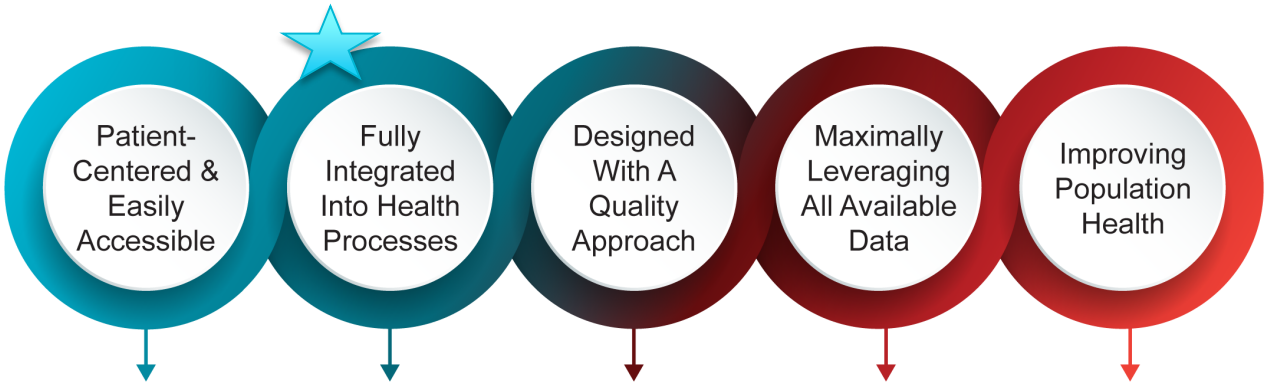


All stakeholders have an equal voice



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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CLINICAL TRIALS TRANSFORMATION INITIATIVE

May 11, 2022

Embedding Trials into Health Care Settings

Project Overview

Lindsay Kehoe, CTTI Project Manager

The Issue

- Traditional randomized control trials (RCTs):
  - Typically don't collect data through integration w/ clinical care
  - May have strict eligibility that limits the generalizability of trial results
  - May be inefficient, and expensive when they duplicate activities that already occur in clinical care
- Embedding trial components into clinical care can overcome these limitations
- Clarity around how to operationalize this integration is needed.

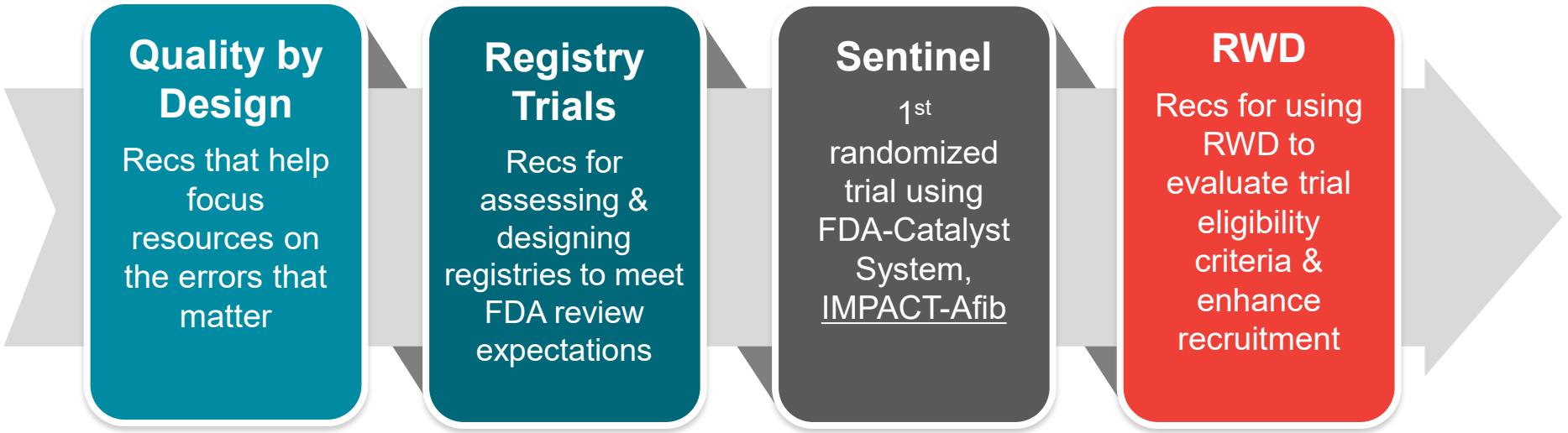
Embedded clinical trials have:

- Elements integrated into health care delivery
- Accessibility to patients at the point of routine care
- Close alignment with clinical workflows
- Elements built into existing infrastructure to use clinical care data, such as electronic health record (EHR), for research purposes

Ultimately, what is the trial purpose? What is the question to be answered?

Paving the Way for Embedded Trials

- National Academy of Medicine, FDA RWE Framework, NIH Collaboratory, PCORI, Veteran's Affairs, AHRQ…
- Existing CTTI work

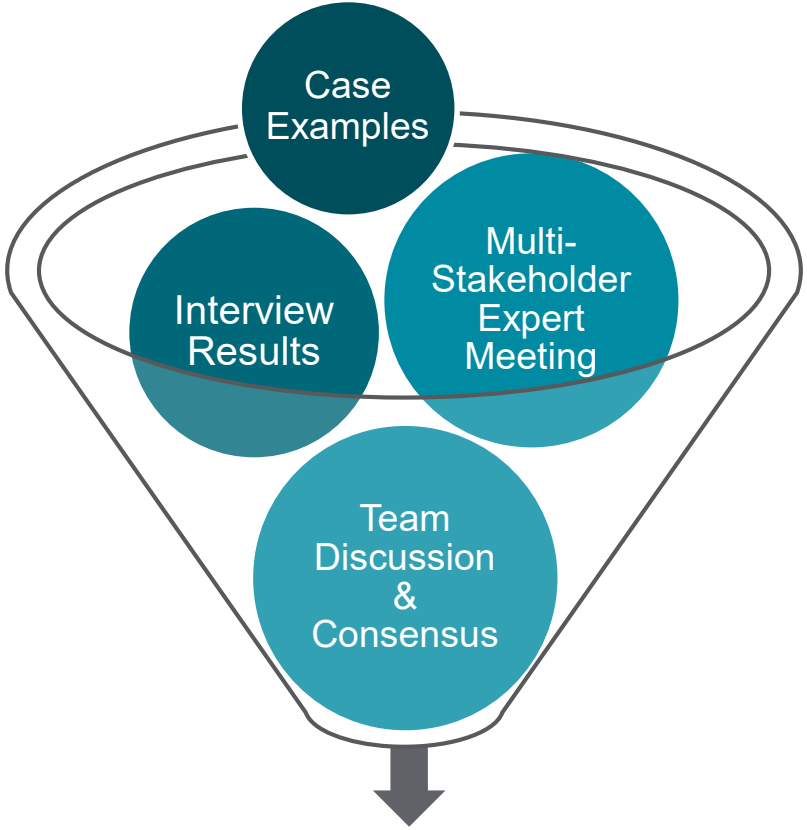


Embedding Trials into Health Care Settings

Project Overview

- **Purpose:** Facilitate the fit-for-purpose integration of clinical trials intended for, but not limited to, medical product review into clinical care
- **Objectives:**
  - Identify the barriers and potential solutions to incorporating interventional trials into clinical care settings
  - Identify when elements of interventional clinical trial integration into clinical settings would be feasible and the associated benefits and risks
  - Describe the operational approaches to incorporating interventional trials into clinical care settings

Project Deliverables



Today's Meeting Objectives

Present project findings: in-depth interviews with study designers and implementers

Refine draft operational recommendations

Begin to strategize implementation of recommendations

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

May 11, 2022

Summary of interview findings

Amy Corneli, PhD, MPH

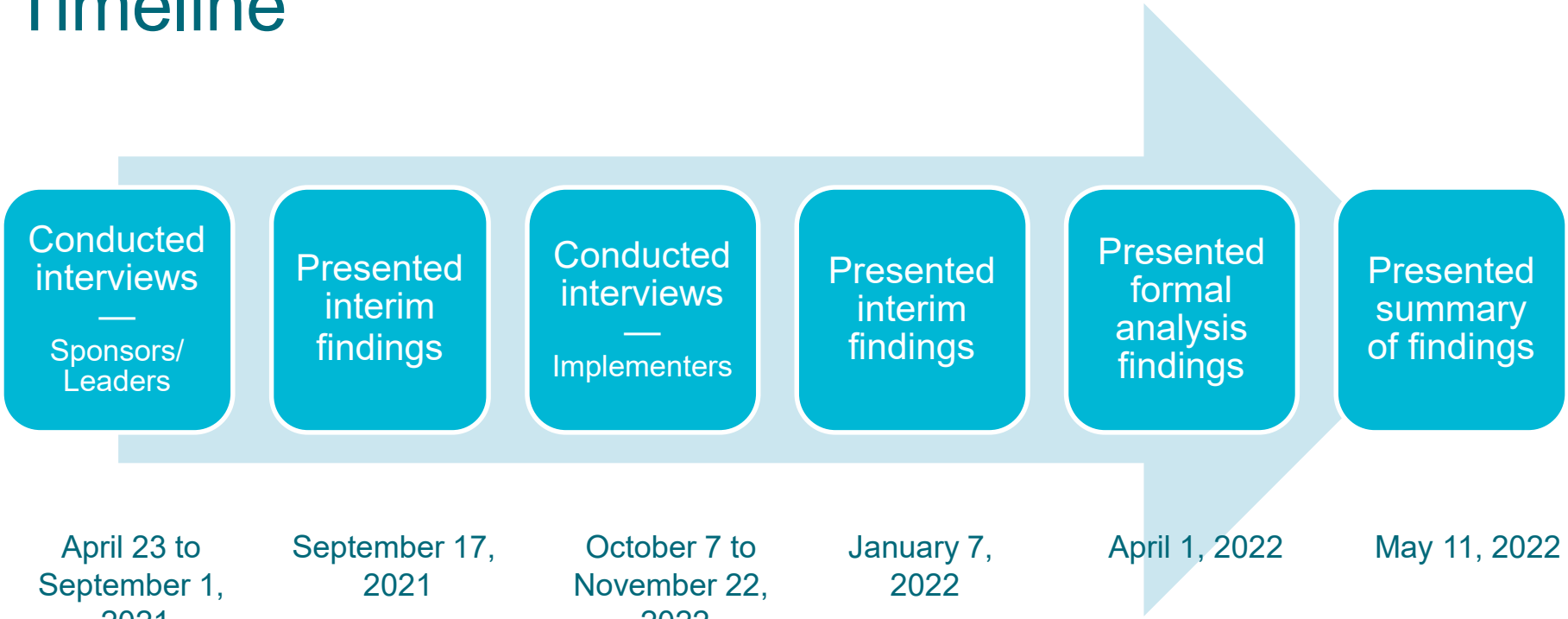
Lead Social Scientist, CTTI

Associate Professor, Duke University

Overview

- **Study design and method:** Qualitative descriptive study with in-depth interviews; iterative process
- **Participants:**
  - **9 sponsors/leaders**: Registrational trials (n=4) and non-registrational trials (n=5)
  - **7 implementers**: Registrational trials (n=3) and non-registrational trials (n-4)
- **Analysis:**
  - Rapid analysis reports and team presentations (n=2)
  - Formal thematic analysis report and team presentation

Timeline


Conducted interviews — Sponsors/ Leaders
Presented interim findings
Conducted interviews — Implementers
Presented interim findings
Presented formal analysis findings
Presented summary of findings
April 23 to September 1, 2021
September 17, 2021
October 7 to November 22, 2022
January 7, 2022
April 1, 2022
May 11, 2022

Today's focus

Motivations for conducting embedded interventional trials

Barriers to conducting embedded trials

Overcoming barriers to conducting embedded trials

Motivations for conducting embedded interventional trials

Motivations for conducting embedded trials

- Reasons for embedding trials
- Persuasive arguments toward health care settings to join embedded trials
- Perceived benefits of embedding trials

Motivations—Reasons for embedding

- Sponsors described **three** primary reasons for using an embedded approach

Reason #1

Want to use a learning health systems approach

- Narrows the gap between clinical research and care
- Improves knowledge generation and its translation to clinical care

We want to become the IOM's version of a learning health care system – where we're leveraging the informatics infrastructure, as well as the clinical experience and the research expertise, to really learn how to care for our patients.

– Sponsor, non-registrational trial

Reason #2

Enables the conduct of pragmatic or naturalistic studies

- Allows for the rigorous evaluation of treatment approaches in real-world clinical practice settings

And the idea is that it's a naturalistic study in the sense that what we're observing is not only the treatment philosophy but also how the treatment philosophy is used in clinical practice. So, we didn't want to constrain that by anything artificial… we really wanted to evaluate a treatment approach as used in clinical practice, but with the rigor of a randomized clinical trial.

– Sponsor, non-registrational trial

Reason #3

Cost-effective

- High costs of conducting conventional clinical trials deterrent to research
- Perceived cost savings from utilizing existing health networks, informatics infrastructure, and EHR data

… the main consideration was costs here…was that, if we were able to do this, integrate with healthcare systems, then we can take advantage of already curated data for any of these hundreds of thousands of patients.

– Sponsor, non-registrational trial

Motivations—Persuasive arguments

- Arguments focused on the prospective benefits of embedding trials

1. Benefits to patients
2. Benefits to health care settings

Persuasive argument: Benefits to patients

Results from embedded trials identify the best treatments and lead to better health outcomes for patients

Patients' own clinicians are engaged in evidence-based practice

Results are more generalizable to everyday clinical practice

Trials are sufficiently powered to detect small differences that matter to patients

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I think the biggest benefit is that you study the actual type of patients who are going to be receiving the intervention in the future, so that the results should be very generalizable to clinical practice. You use the measures of success that are used to measure success in everyday clinical practice, and so you're not extrapolating …[and saying] "Well, gee, 30% of patients met the trial endpoint, but that's not really an endpoint that we use every day, and so maybe it will be 40% of patients who would benefit using a different measure that fits with the clinical measure." So, I think that's a major benefit.
– Sponsor, non-registrational trial

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Persuasive argument: Benefits to health care settings

Increase visibility

Increases efficiency across clinical care and research; cost savings

Become known as a health care system where cutting edge clinical research is conducted

- May increase patients seeking care at setting
- May increase retention in care at setting because of access to latest medical knowledge

I think there's a belief, in some places, that clinical trials are optional, and I think that we need a different perspective… access to clinical trials is providing the best clinical care. As opposed to just being optional. …I think people are recognizing that they get to choose where they get their care, and if you're at a place where you can get access to newer therapies beyond top clinical care based on existing data, that's a positive thing. And so, I think that health care systems will increasingly recognize that's a real value to their membership if they can offer them – effectively offer them, of course.
– Implementer, registrational trial

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Motivations—Benefits of embedding

- Two main categories:

Operational benefits

Benefits to patients

Operational benefits

- Enabled larger trials
- More efficient trial conduct

I think being able to hopefully enroll larger numbers of participants because maybe the cost per participant is a little bit lower or the efficiency of recruitment is a little bit greater.

–Sponsor, non-registrational trial

Benefits to patients

- Have access to evidence-based care
- Have access to clinical trial participation
  - Can reach populations who are historically not included in research

Barriers to conducting embedded trials

Barriers

- Three groups of barriers
- 1—Site staff time and availability
  - Clinicians have limited time, limited incentives to participate
  - Challenging to familiarize clinicians with study protocol due to limited time
  - Training and start-up particularly time consuming for sites new to research
  - Screening and recruitment activities are new for for site staff

…identification and screening of patients is very difficult for them; getting them through the first stage because it's not part of their routine day-to-day efforts. And I think that's really been the biggest barrier is getting them to identify and start a screen on a subject.

The other big thing is we've had to work with them on kind of what's their elevator pitch for the study; so that when the patient comes in and they might be a participant, be excited to study, excited to participate, you can give them a two-minute elevator speech and get them excited enough to take the screen. And that is not part of what they do. They don't really understand that. We've had to work really hard to get them to get to that point.
– Sponsor, non-registrational trial

Barriers

- 2—Lack of leadership buy-in
  - Difficult to implement without support and engaged site personnel
  - Cannot do without top-level leadership, particularly IT
- 3—Data systems
  - Obtaining approval to export and use EHR outside of the health care system
  - Interoperability of systems

Most IT leaders in hospitals are "pull up the moat, throw the crocodiles in, fill it with boiling water, and never come near IT" people. But in order for data to be transferred, you have to be able to bridge that gap. And that's not how hospital IT people work. They work by thinking if there's a data breach, it's the end of the world. So, the way they achieve that is just by putting up the most colossal barriers to collaboration of anything I've ever seen in medicine…And so, we have to partner with the medical leadership to open the eyes and minds of the IT individuals. And once they see it, they're like "Oh, there's a huge improvement, we should definitely do this sometime." But they had to hear it first before you knew the chance was for the better, and not just super scary and a risk, something bad.

–Sponsor, registrational trial

Overcoming barriers to conducting embedded trials

Overcoming barriers

- Five suggestions
- **1—Culture change/paradigm shift**
  - Change perspectives—view research as part of regular clinical care, with clinicians serving as researchers
  - FDA being more open to embedded trials
  - NIH, FDA, others to learn from adjustments due to COVID-19

It really takes culture change. Embedding these trials, even though it's not a lot, takes a little bit of extra effort from everyone who's in that process of delivering care, without any recognition, without any reward. And, until the culture is changed so that it's expected that research is embedded in clinical care and good clinical care is defined by learning from every patient in a learning health system fashion, it's going to be really hard to do these as a one-off.
– Sponsor, non-registrational trial

Overcoming barriers

- **2—Healthcare buy-in and engagement**
  - Because participation often involves changing health care staff's usual procedures
    - e.g., Screen participants, describe randomization
  - Need both provider and patient engagement
    - Interested providers more likely to participate, encourage others
    - Patients more likely to enroll, stay in trial, contribute to study design

There's so much education required…
educating people to get the buy-in that you need.
Buy-in is so important. Buy-in of the patients,
buy-in of the providers, buy-in of leadership, buy-in of the pharmacy.
Everybody's got to be on board in order for this to run seamlessly
because they're all part of the usual care process.
If they don't understand, or they don't agree,
then it's going to break.

–Implementer, non-registrational trial

Overcoming barriers

- **3—Reduce burden and minimize negative impact**
  - Health care settings more likely to participate when burden is minimal
    - Regulatory reforms could reduce administrative burden on settings
    - Demonstrate that trial does not impede clinical work flow/ requires minimal effort
    - Provide research support to reduce extra workload/tasks
    - Reduce redundant data entry

Overcoming barriers

- **4—Invest in research infrastructure**
  - Research staff manage regulatory issues
  - Rely on research coordinators to play significant roles, e.g.:
    - Enroll and consent patients
    - Track and schedule data collection
    - Assist with data extraction and enter data
  - Include research clinicians, e.g.:
    - Oversee study personnel
    - Ensure proper study conduct
    - Conduct assessments outside of regular care

What we were asking the clinical people to do is do what you normally do. And so, we purposefully tried to change their flow and how they take care of patients as little as possible. And, what we tried to do is ask them to document things the way they normally would. And then, it would be our job to have a research person that would extract the data in a way that made it comparable and made its fidelity high…I think we've got something like 10 coordinators or something. So, we pulled our most senior coordinator at the time to be the one who ran the study…

– Sponsor, non-registrational trial

Overcoming barriers

- **5—Manage interoperability of EHR systems**
  - Most created templates to extract data from EHRs—or extracted data manually
  - Partnered with PCORNet, use common data model
  - Changes are necessary to EHR systems to facilitate interoperability

I think that this is an area that, whether it's clinical research or quality improvement or federal oversight of outcomes across health systems, there's definitely a recognition of the need to be able to leverage EHR data in a more consistent way; make these types of approaches more widespread.
– Sponsor, registrational trial

Questions & Comments?

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May 11, 2022

Operational Approaches to Embed Trials

CTTI Project Draft Recommendations

Mark Stewart, Friends of Cancer Research

The Case for Embedding Clinical Trials in Health Care

Patients

Less burden to participate in research

Better, evidence-based care

Greater access to a variety of treatment options

Providers

Opportunity to engage in research with less burden than traditional RCTs

Addresses important questions to improve care in a broad population

Ability to offer variety of treatment options to patients

Sponsors & Investigators

Generalizable population

Insights into real-world implementation of health interventions

Potential for increased efficiency & cost savings by reducing duplication of trial & care activities

Regulators

Sufficiently sized trials with diverse populations

Leverages power of randomization & RWD in the context of regulatory decision-making

Generalizable evidence

Payers

More, diverse data for reimbursement decisions

A better understanding of the effectiveness and safety of health interventions

Health System Leaders

Opportunity to innovate and support quality care

Chance to engage new patients through additional research

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CTTI Draft Recommendations

For an Individual Trial

1. Recognize that embedding elements of a trial is not all or nothing
2. Assess whether clinical trial elements should be embedded based on the research question, target population, health care setting(s), and required data
3. Verify that available data sources used for embedded trials are fit for purpose –relevant, reliable, and of sufficient quality
4. Streamline trial design and conduct to minimize participation burden for patients, providers, and research staff
5. Ensure the appropriate level of resources are available for monitoring and safety reporting

For the Clinical Trial Enterprise

6. Recognize, reward, value and incentivize research activities
7. Promote the basis for and ways to embed trial elements into health care delivery

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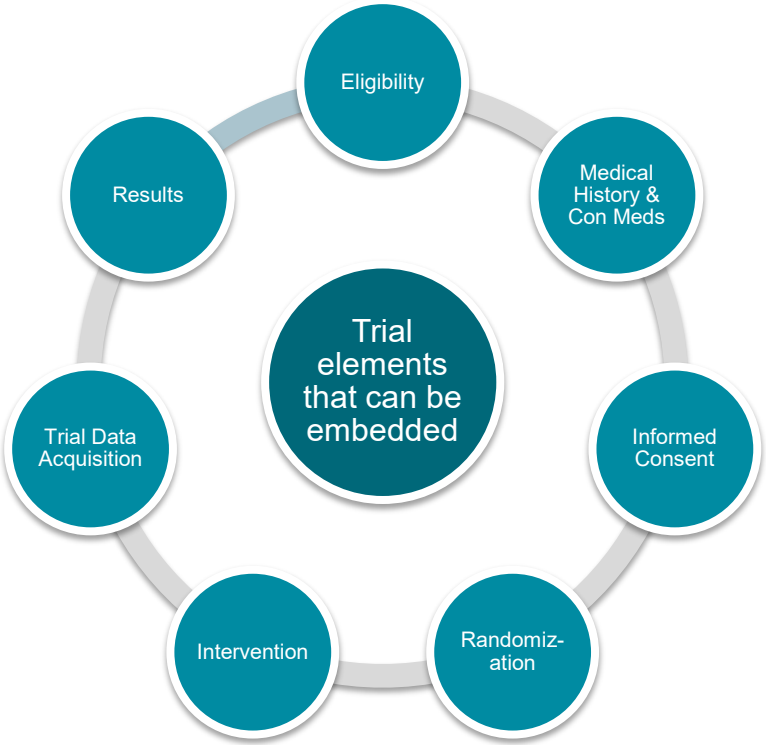
Recommendation #1

Recognize that embedding elements of a trial is not all or nothing



- Consider what aspects, if embedded, would improve the trial and answer the study question.
- Embedding trial elements into care is possible. CTTI has five Case Examples that reflect this at an individual study level.

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Recommendation #2

Assess whether embedded clinical trial elements should be considered based on the research question, target population, setting, & required data

Sponsor Considerations

- Do HCPs agree on the proposed, clinically relevant endpoints?
- Can logistics of implementation be integrated into clinical care workflow?
- Do regulatory bodies agree the study design can adequately address the research question?
- Can data be accessed, sorted, & extracted from EHR or other data systems?
- Is there site readiness to embed trial elements?

Health Care System Considerations

- Is the research question relevant to patients and HCPs in clinical settings?
- Can logistics of implementation be integrated into the clinical workflow with adequate reimbursement for clinician time?
- Are the processes used for embedding trial elements conducive for future trials (i.e. not continually redeveloped)?

Recommendation #3

Ensure available data sources used for embedded trials are fit-for-purpose – relevant, reliable, and of sufficient quality

Relevant

- Use data collected during routine care as the primary, foundational source data.
- Collect the least amount of data necessary to answer the research question.

Reliable

- Appreciate the intention and potential consequences of clinical care data collection and use.
- Validate the reliability of the clinical data through manual and automated data checks.

Sufficient Quality

- Perform a feasibility assessment for data missing-ness and to determine the need and availability of supplemental data.
- Ensure that clinical data incorporated into a trial database are complete, plausible, accurate, and traceable.
- Develop strong data privacy and security plans.

Consult early and often with regulatory authorities on data quality questions

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Recommendation #4

Streamline trial design and conduct to minimize participation burden for patients, providers, and research staff

- **Approach:** Determine which trial activities and data are essential and whether they align with clinical workflows (consider CTTI's Quality by Design recommendations)
- **Training:** Insert research education and training with minimal disruption to staff roles and responsibilities
- **Documentation:** Streamline documentation by using common documents (e.g., master service agreements, master protocols); Limit the amount of data queries
- **Compliance:** Use central IRBs or develop agreements with local reviewers to rapidly review new submissions
- **Data:** Work with IT leaders to automate trial prompts and flags into EHRs, and to develop strong data privacy and security plans; Minimize duplicate data entry and supplemental data collection

Recommendation #5

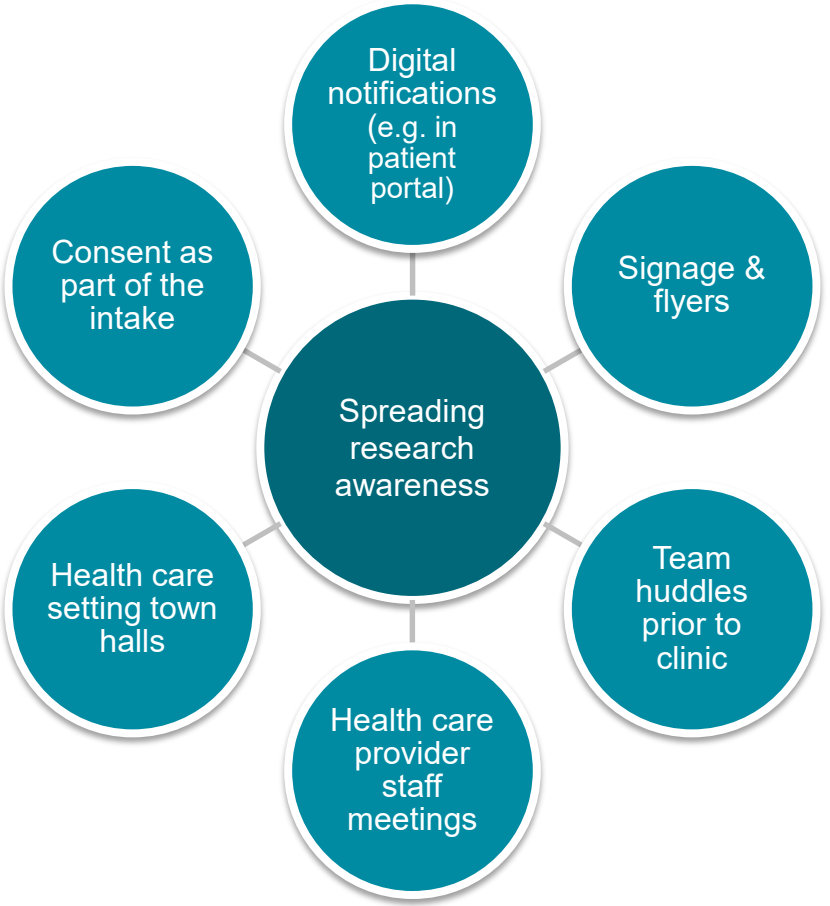
Ensure the appropriate level of resources for monitoring and safety reporting

- Align clinical trial oversight with the objectives and inherent risks of embedding trial elements
- Streamline trial processes into clinical care delivery and ensure GCP requirements for clinical staff and health care providers participating in embedded trials are not compromised
- Appreciate what role each clinical staff member can play in research activities and pro-actively train and support them
- Engage with regulatory authorities early with the goal to focus upon the most relevant and impactful potential safety hazards (risk-based monitoring approach)
- Leverage technology where appropriate

Recommendation #6

Recognize, reward, value and incentivize research activities

- Appreciate the patient and health care provider journey to introduce research at various touchpoints.
- Motivate, compensate, and support health care staff (including health IT) to prioritize research participation.



Recommendation #7

Promote the basis for & ways to embed trial elements into health care delivery

Health care system leadership can:

- Collaborate with operational tech providers to build a digital infrastructure.
- Work with trial sponsors to develop communication plans so results are fed back to leadership.
- Encourage standardization for how clinical care data are captured, documented, and validated by clinical care staff.

Government and policy led forums can:

- Promote the rationale for embedded trials as a means to improve evidence generation.
- Encourage regulatory and policy changes.
- Support sponsors, investigators, and operational technology providers to share learnings.

Leadership partnerships are needed across health care systems and the clinical trial enterprise (CTE) to embed trials.

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Open Group Discussion

Are these recommendations clear?

Where is there too much or not enough information?

Is there a place where a tool would provide needed detail?

BREAK

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

May 11, 2022

RECOVERY Trial: Using an Embedded Trial to Identify Treatments for COVID-19

Martin Landray, University of Oxford

Randomised controlled trials don't have to be complicated... they must be practical

- **Simple eligibility:** Hospitalised patients with SARs-CoV-2
- **Important outcome:** mortality (use of ventilation, duration of hospitalisation)
- **Randomization:** assigns patient between suitable and available treatments
- **Follow-up:** 1 page case report form + extensive linkage to routine NHS datasets

RECOVERY RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

Hospital: Patient Name:

1. Information about the study has been provided to me: I confirm that I have read and understood the Participant Information Leaflet (V1.0 13-Mar-2020) I have had the opportunity to consider the information and ask questions. These have been answered satisfactorily.

2. Voluntary participation: I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.

3. Access to study data about me: I give permission for relevant sections of my medical notes and information collected during the study to be looked at, in confidence, by authorised individuals from this hospital, the University of Oxford, and regulatory authorities to check that the study is being carried out correctly.

4. Access to my medical information: I agree that medical information collected by the doctors and hospitals which provide me with care and which may be located in local or national health and research organizations (including hospital admission, civil registration, audit and research data) may be provided to the study coordinating centre both during and for up to 10 years after the scheduled follow-up period. I understand that information that identifies me will be passed securely to such bodies to make this possible and that I can opt out of this at any time by writing to the coordinating centre team.

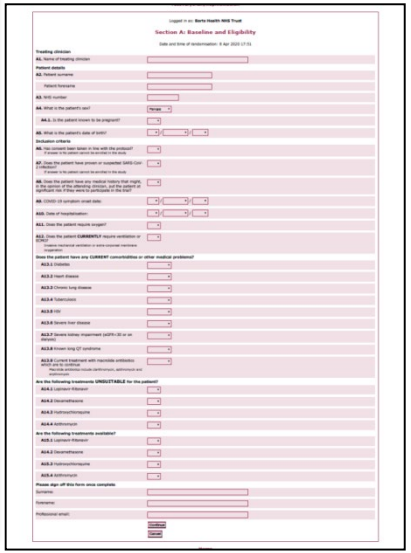
5. Data stored on computer: I understand that information about my progress in the study will be recorded on a computer database, and that this data will be stored on computers supervised by the University of Oxford. I understand that this information will be kept securely and confidentially.

6. Agreement to take part: I have read the information (or had it read to me), had an opportunity to ask questions and agree to take part in the above study.

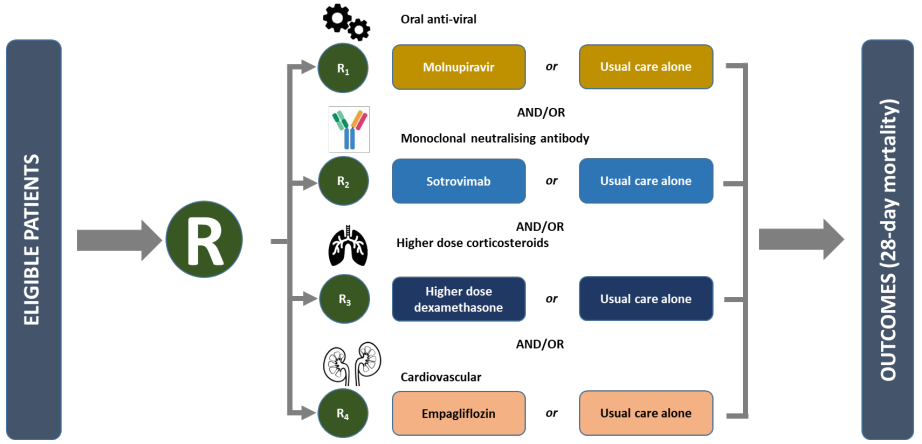
PRINTED name of participant ..... Signature ..... Today's date ...../...../.....

PRINTED name of person taking consent ..... Signature ..... Today's date ...../...../.....

*1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes



Section A: Baseline and Eligibility



EMBEDDED TRIAL ELEMENTS

- Patients recruited at point-of-care – admission to hospital for COVID-19
- Randomization to intervention + usual care vs. usual care alone
- Data collection
  - objective clinical endpoints
  - targeted adverse events of specific interest to intervention
- Data sources
  - electronic case report form (eCRF) at randomization and 28 days (or death)
  - linkage to 25 national routine healthcare datasets (including death registry, hospital ‘claims-like’ data, disease registries)
- All trial materials (protocol, recruitment numbers, training materials, results, etc) made publicly available in real-time www.recoverytrial.net

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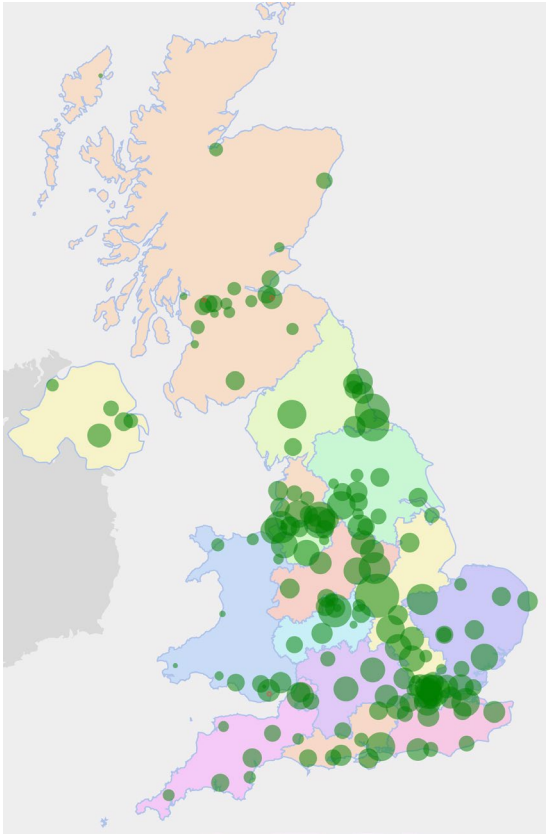
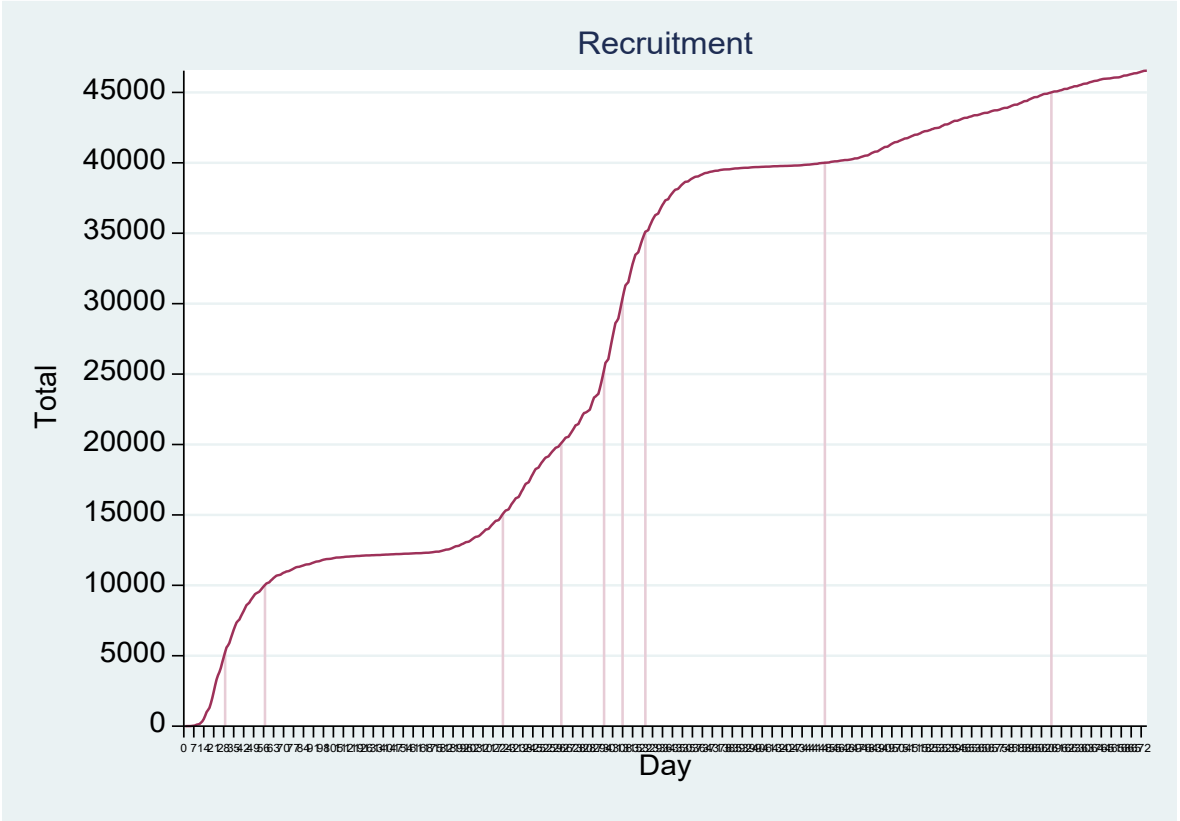
COVID can affect anyone... RECOVERY is open to everyone





Comprehensive follow-up through NHS data

Hospitalisation datasets

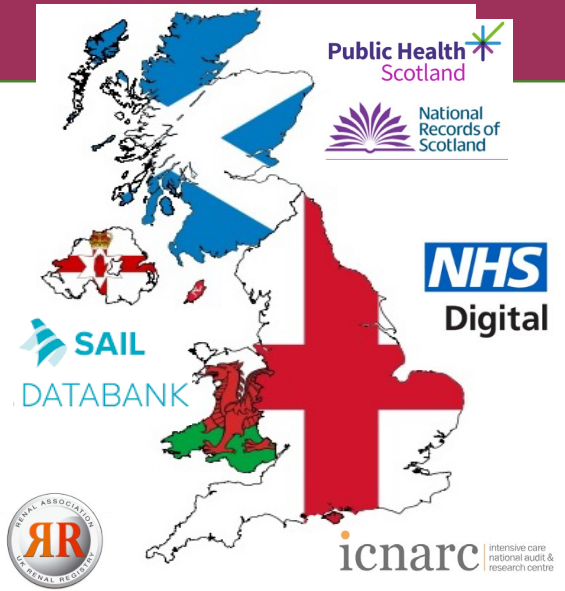
- ✓ Scottish Morbidity Records (SMR)
- ✓ Hospital Episode Statistics Admitted Patient Care (HESAPC)
- ✓ Secondary Uses Service Admitted Patient Care (SUSAPC)
- ✓ Patient Episode database for Wales (PEDW)

Mortality datasets

- ✓ Personal Demographics Service
- ✓ Civil Registrations
- ✓ NHS Scotland Central Register PDS
- ✓ Welsh Demographics Extract

Disease specific datasets

- ✓ UK Renal Registry
- ✓ Cancer Registry



Primary care datasets

- ✓ Business Services Authority (BSA) prescribing and dispensing data
- ✓ General Practice Extraction Service (GPES) Data for pandemic planning and research (GDPPR)

Critical care datasets

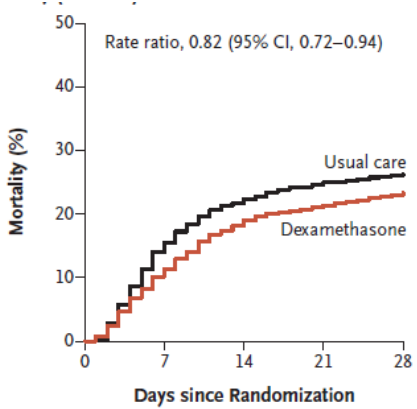
- ✓ Scottish Intensive Care Society Audit Group (SICSAG)
- ✓ Intensive Care National Audit and Research Centre (ICNARC)
- ✓ HES Critical Care Dataset (CCDS)
- ✓ PEDW Critical Care Dataset (CCDS)

COVID datasets

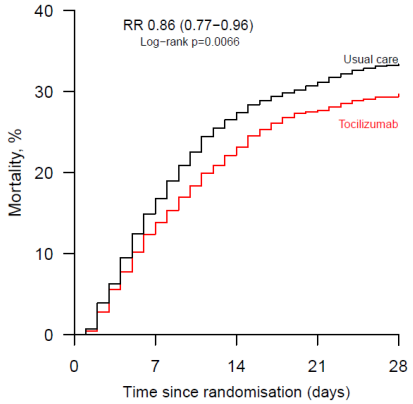
- ✓ COVID-19 Hospitalisation in. England Surveillance System
- ✓ Second Generation Surveillance System (SGSS)
- ✓ Electronic Communication of Surveillance in Scotland (ECOSS)
- ✓ Welsh Results Reporting Service (WRRS)

4 effective treatments for high-risk patients

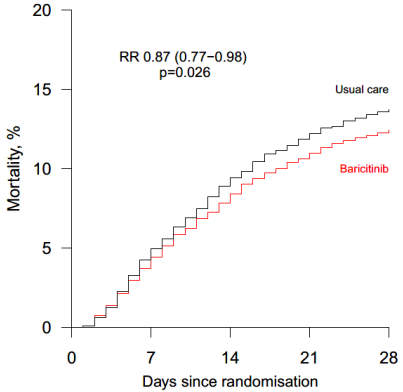
Dexamethasone



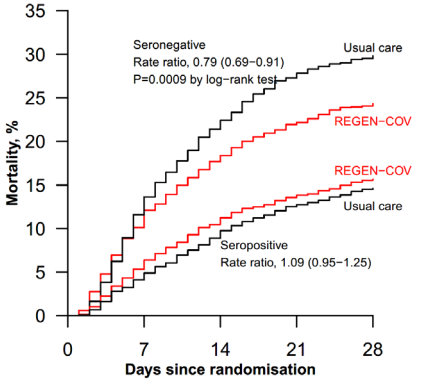
Tocilizumab



Baricitinib



Ronapreve
(casirivimab+
imdevimab)



RECOVERY
Randomised Evaluation of COVID-19 Therapy

Dexamethasone:
Adopted internationally within weeks

DOI: 10.1056/NEJMoa2021436

Department of Health & Social Care | Health, Social Services and Public Safety | The Scottish Government | Llywodraeth Cymru Welsh Government | NHS

From the UK CMOs and Medical Director of NHS England.
16 June 2020

CEM/CMO/2020/026

Dear colleagues,

Dexamethasone in COVID-19

The RECOVERY trial in COVID-19 has provided initial results of the dexamethasone arm https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_final.pdf

Dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days was compared with 4321 UK patients randomised to usual care alone. Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021).

There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14).

Normally we would advise waiting for the full paper before changing practice, to ensure final analysis and peer review do not lead to different conclusions. However, given this clear mortality advantage, with good significance, and with a well known medicine which is safe under these circumstances we consider it is reasonable for practice to change in advance of the final paper.

Please find more information below.

Best wishes,

Dr Frank Atherton
Chief Medical Officer for Wales

Dr Gregor Smith
Chief Medical Officer for Scotland

Dr Michael McBride
Chief Medical Officer for Northern Ireland

Professor Stephen Powis
National Medical Director
NHS England and NHS Improvement

Professor Chris Whitty
Chief Medical Officer for England

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

NATIONAL / SCIENCE & HEALTH

Japan approves dexamethasone as second drug for coronavirus treatment

the japan times

The health ministry has approved the use of the steroid drug dexamethasone for the treatment of novel coronavirus patients. | GETTY IMAGES / VIA KYODO

KYODO SHARE Jul 22, 2020

NIH | COVID-19 Treatment Guidelines

Home › Dexamethasone

- What's New
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- Introduction
- Overview +
- Critical Care +
- Antiviral Therapy +
- Immune-Based Therapy +
- Antithrombotic Therapy
- Concomitant Medications
- Panel Roster
- Panel Financial Disclosure

Guideline PDFs
Section Only (PDF | 147 KB)
Full Guideline (PDF | 1 MB)

Sign up for updates

The National Institutes of Health COVID-19 Treatment Guidelines Panel Provides Recommendations for Dexamethasone in Patients with COVID-19

Last Updated: June 25, 2020

Introduction

Patients with severe COVID-19 develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these harmful effects. Small, retrospective cohort studies and case series have yielded conflicting results; both beneficial[1-4] and harmful[5,6] effects have been reported in studies that have evaluated short courses of corticosteroids in patients with COVID-19.

A preliminary, unpublished analysis from a large, multicenter, randomized, open-label trial for hospitalized patients in the United Kingdom showed that patients who were randomized to receive dexamethasone had a reduced rate of mortality compared to those who received standard of care.[7] This benefit was observed in patients with severe COVID-19 (defined as those who required supplemental oxygen) and was greatest in those who required mechanical ventilation at enrollment. No benefit of dexamethasone was observed in patients who did not require supplemental oxygen at enrollment.

Based on these preliminary results:

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**.

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EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation

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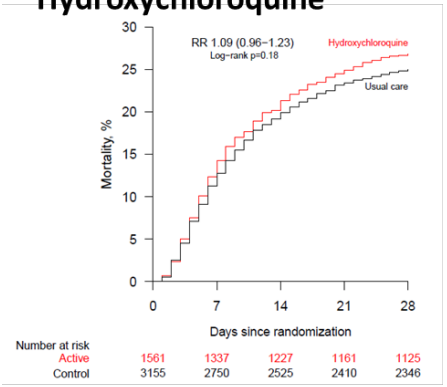
News 18/09/2020

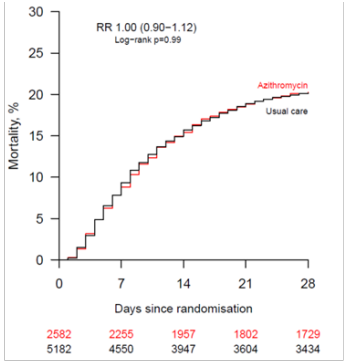
Widely recommended, loudly promoted, extensively used...

Hydroxychloroquine, lopinavir, azithromycin, convalescent plasma, aspirin, colchicine...

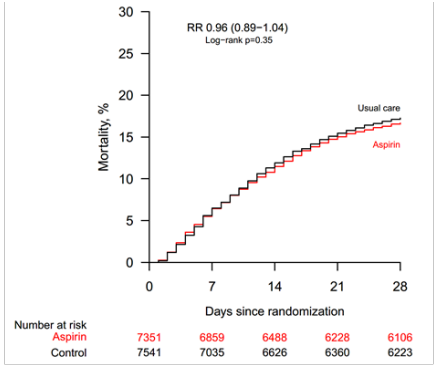
Hydroxychloroquine



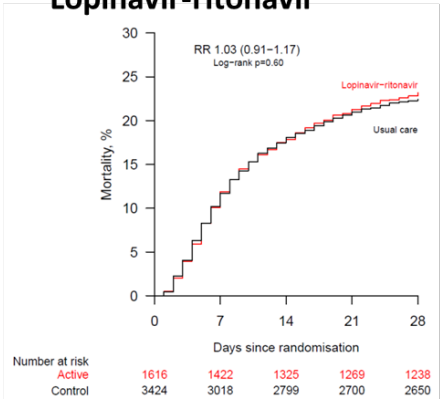
Azithromycin



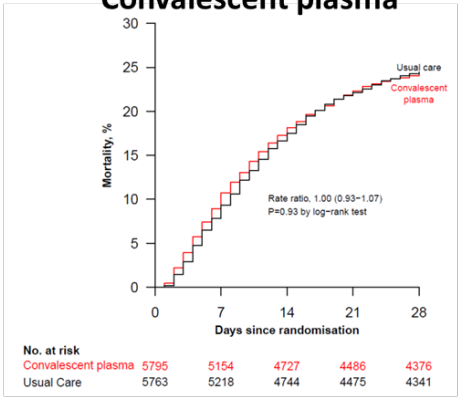
Aspirin



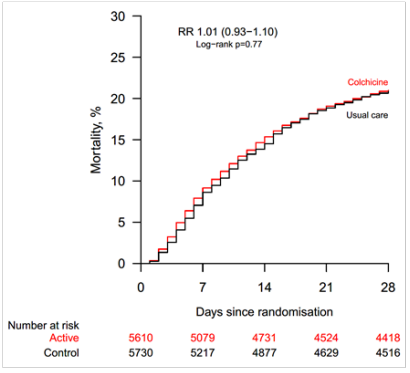
Lopinavir-ritonavir



Convalescent plasma



Colchicine



CHALLENGES	SOLUTIONS
Technology Infrastructure: • Time and effort is required to embed randomization into multiple hospital EHR systems	**Technology Infrastructure**: • Integrates randomization into care pathway via simple means • Leverages standalone system because it's flexible and easier to control
Data: • Most data sets are shallow (but they are comprehensive in that they cover everyone, regardless of location)	**Data:** • Pulls from multiple national data sources for holistic picture of outcomes that matter (provides almost complete follow-up for many years, even if patients move) • Algorithmic approach to aggregate and interpret information from multiple data sources
Culture: • False certainty/conflicting public information prior to trial completion • General lack of understanding that it takes large numbers to get clear answers (whether they're positive or negative) • Trials often perceived as 'risky' (but clinical care based on no evidence is risky)	**Culture**: • Ensures clinicians feel that both the research question is important and participation in the trial would not unduly complicate patient care • Restricts data collection to essential items only and supplements if needed • Transparency of design, processes, progress, and results from the outset
Process: • Lengthy approval and site initiation processes delay discovery of true effects of treatments, harming patients and public health	**Process**: • Utilizes central IRB • All hospitals sign one template contract (non-negotiable) • NHS leadership promote the concept that "randomized trial is part of clinical care, not an optional extra" • Base approaches on key principles of RCTs (e.g. www.goodtrials.org) and focus on issues that have a material influence on the trial participants and the reliability of the results

Comments from NHS doctors

"Coming in to work each day, people would say to me 'they've chosen the wrong drugs'. I'd say 'let's see'.

I didn't know this [dexamethasone] would work. No one knew which drugs would work. But I thought we should help find out.

Three months on from the start of the trial, we have a therapy which is cheap & readily available. Millions could benefit.

I'm glad we helped contribute 1% of the data. Thank you to the patients who when offered to participate, agreed."

"[The RECOVERY trial] has inspired many of the more junior Doctors in our trust to look again at a career in research and we feel has given an opportunity / access to treatment to our patients that they otherwise would not have"

"We have been very pleased to have been able to help contribute to this effort that has helped to provide some clear answers."

Patients are the why and the how

“When he left in the ambulance I really didn't think I would ever see him again.”

https://www.recoverytrial.net/case_studies/a-brush-with-death-2013-a-recovery-trial-participant2019s-story

Feedback from RECOVERY participants

"Being given the opportunity to participate in the RECOVERY trial was very humbling, knowing that the information they were collecting had a direct impact on the treatment of patients, and signing on was something I did gladly."

Kimberley

"I was already so ill that I was willing to give anything a go if it might help me to recover more quickly. But I also knew that it would help the researchers studying the coronavirus to work out which treatments actually help people… I'm really glad that NHS patients can take part in the RECOVERY trial because otherwise no one would know what treatments work for the people actually suffering from COVID-19.."

Claire

"It is a miracle how things have progressed in such a short time. A year before I caught COVID-19, we had only just heard about this disease but now we have these treatments that can be offered to people like me. If nobody took part in clinical trials such as these, we would still be looking for something that worked against this illness."

Dennis

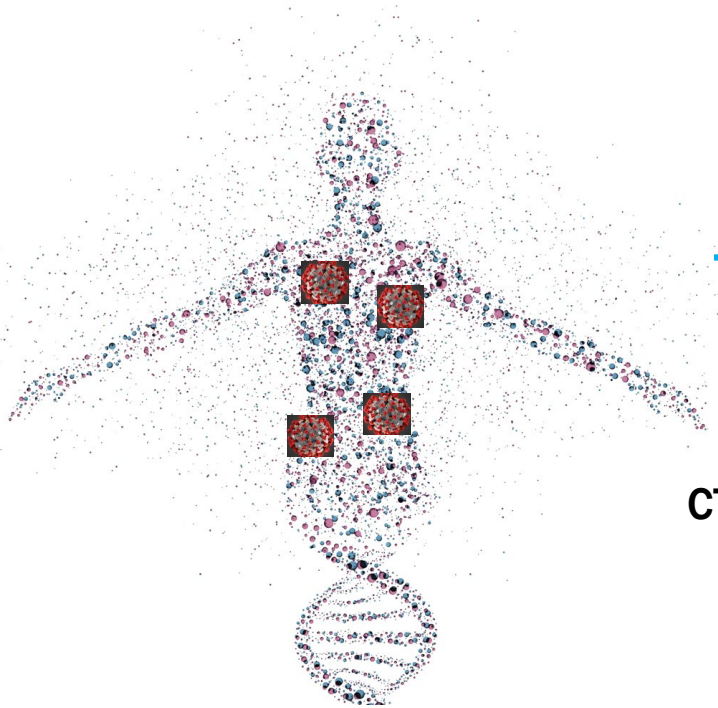
"COVID-19 was such a big unknown and I knew that clinical trials were the only way we would find out what treatments actually work or not…I really do think the treatment (tocilizumab) made a big difference. Up until then, it was quite scary as I didn't know if I was going to make it or not."

Wendy

WORDS OF WISDOM: Compelling results save lives

- **Science**
  - Consolidate around a question that is big enough and important enough
  - Work out what matters, focus on what matters, do what matters (don’t get distracted or allow others to distract you)
  - Randomize, have adequately large numbers, and see trial through to completion
- **Approach**
  - Learn from successful trials but don't copy and paste
  - Use what you've got from existing data sources, even if it’s not perfect
  - If a trial is not practical, it won’t get done
- **Timeliness**
  - Taking longer (e.g. contract approvals, IRB review) doesn’t necessarily mean doing a better job – but it certainly means it takes longer (delaying evidence-based care)
- **Environment**
  - Communicate and be transparent (protocol, progress, results all open access in real-time)
  - Create a culture where we are all in this together

CTTI



I-SPY COVID TRIAL

Investigation of Serial studies to Predict Your Therapeutic Response with biomarker Integration and Adaptive Learning

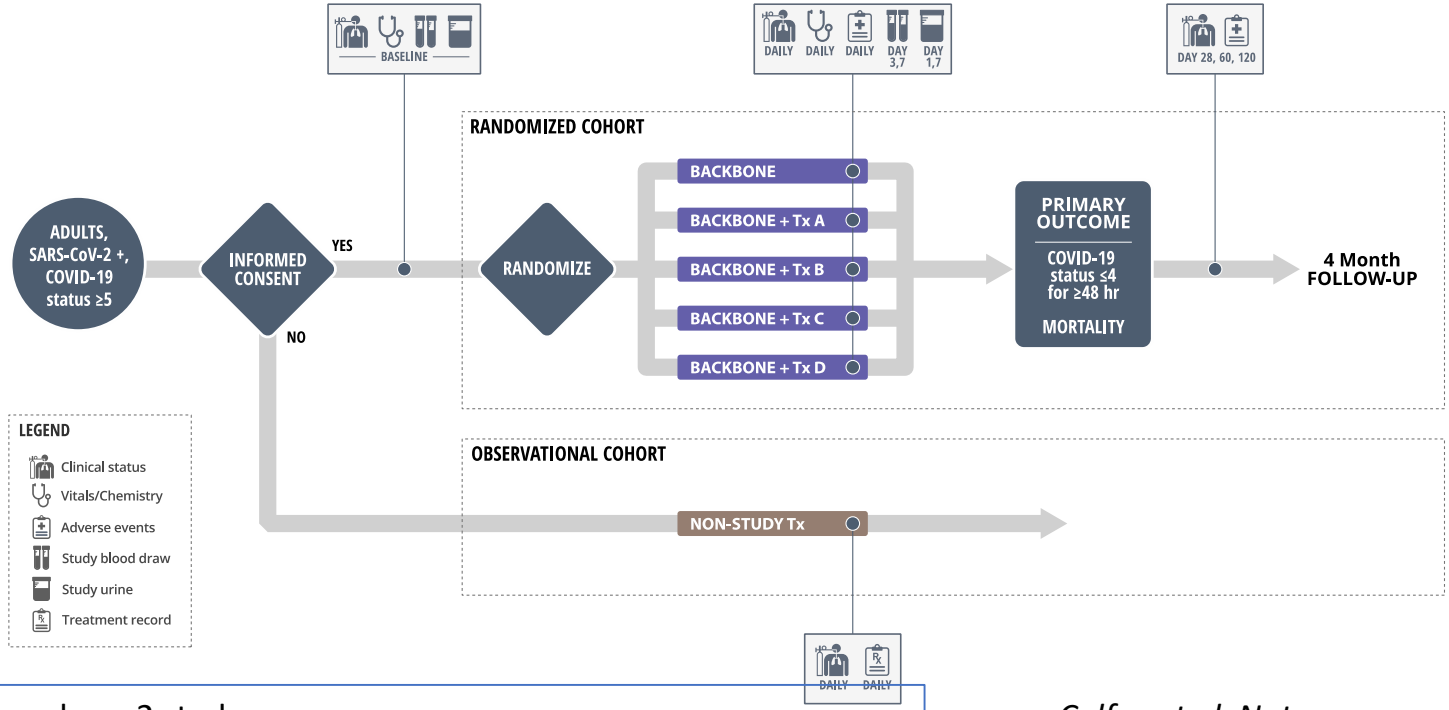
CTTI Embedding Clinical Trials in HealthCare Settings

5.11.22

Laura Esserman, UCSF

I SPY COVID Design: Enrollment Jul 30, 2020→; >3000 pts to date

Modelled after I SPY 2 Breast Cancer Platform



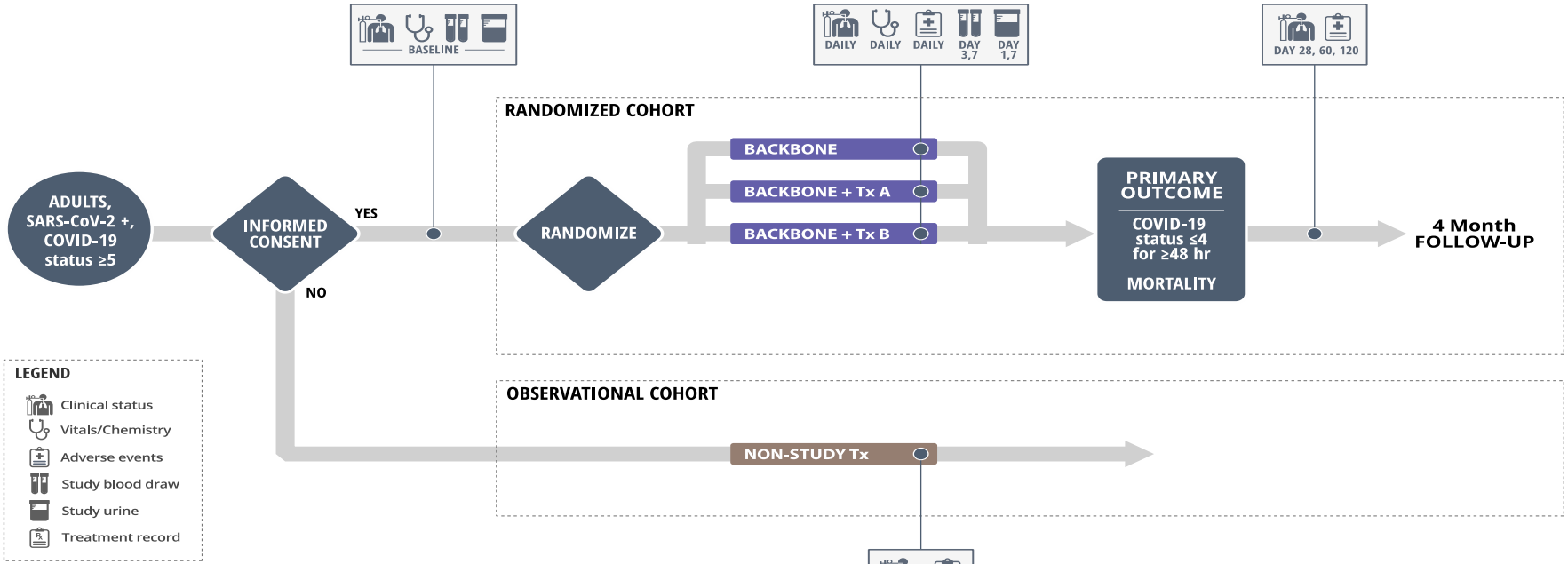
Screening phase 2 study

Look for agents with big effects (30% ⬇ time to recovery, mortality)

Biomarker rich trial with goal of integrating into std in the future

Calfee et al. Nature communications 2021

I-SPY COVID TRIAL: Design adjustment over time



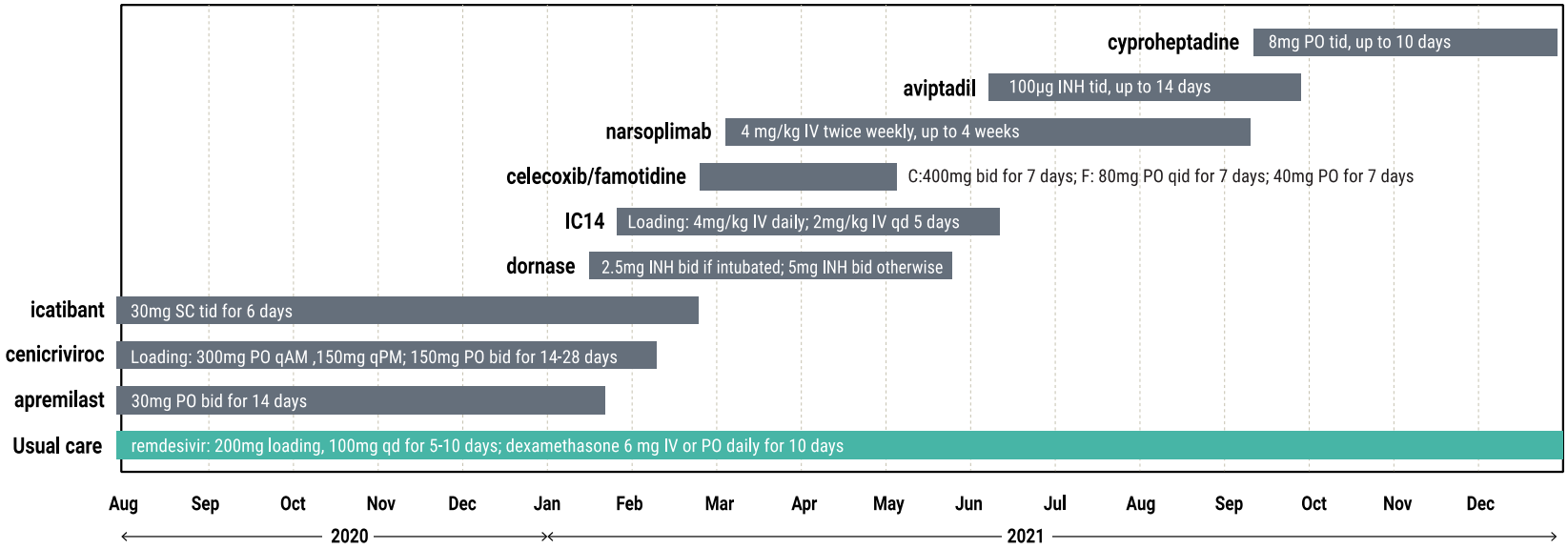
BACKBONE : All patients will get **best standard of care** (optimal ve management) + Remdesivir + steroids
every patient gets some treatment with proven efficacy. Backbone updated as

GOAL: Rapidly screen agents for a BIG IMPACT

There is a 120 hour (+/- 6 hours) window to enroll patients from the first day they require high flow O2 (6L+) or intubation

Agent Timeline

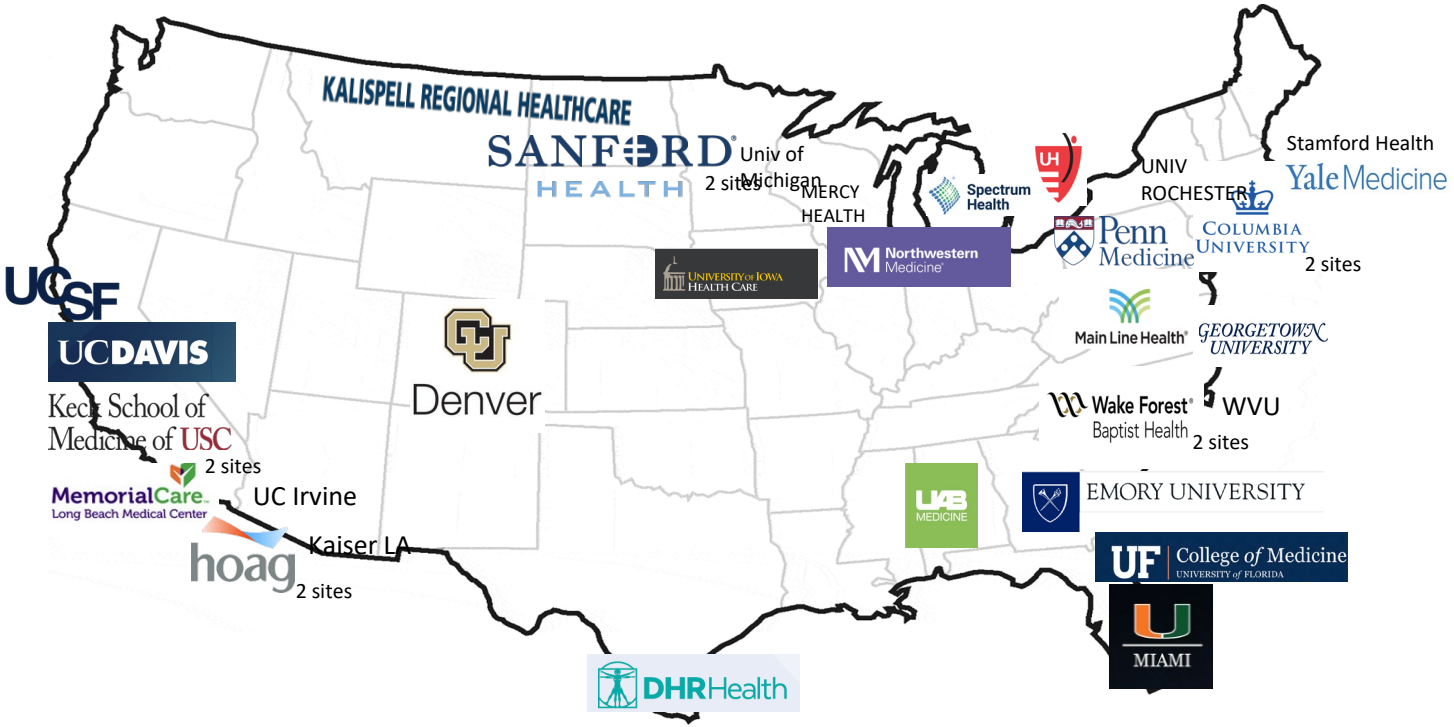
Bayesian platform design, DMC monitors data every 2 weeks



Files et al BMJ in press, Med Archives

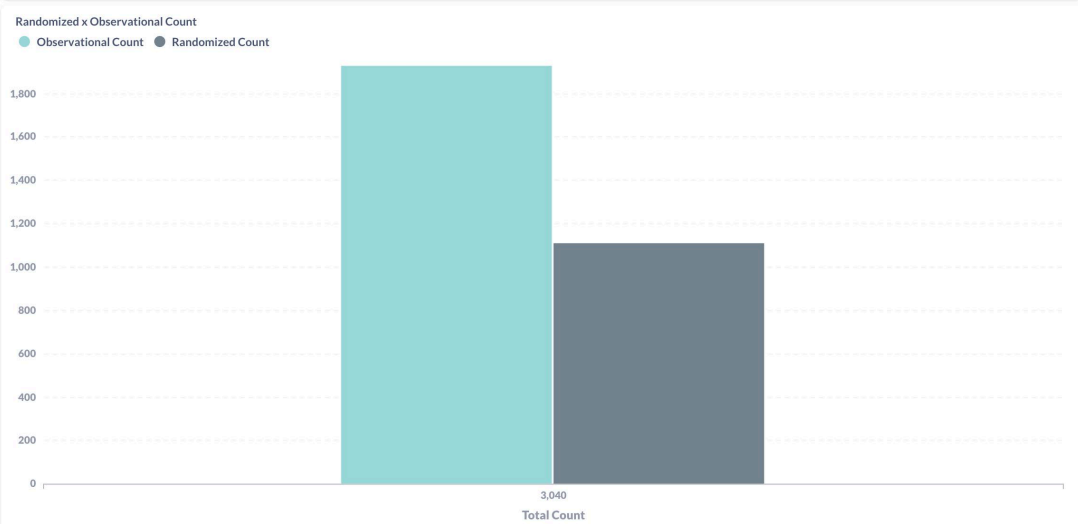
35 sites as of March 15, 2022

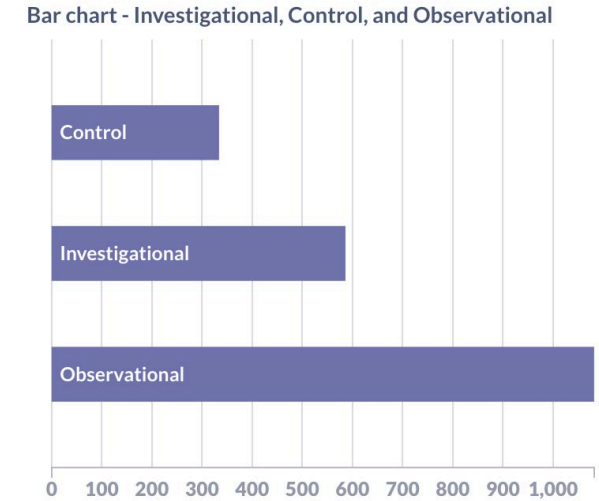
Mix of Academic and Community Centers



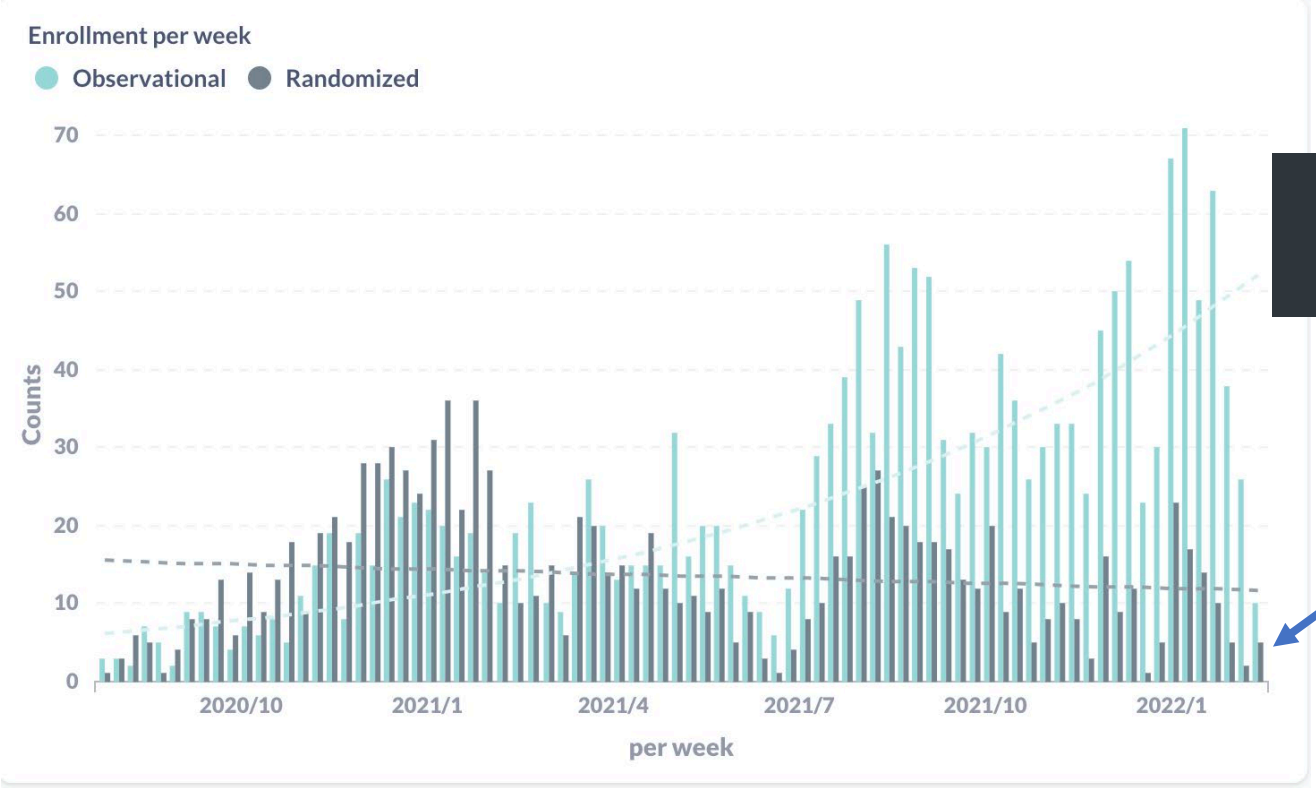
Enrollment as of 17-Feb-2022

Randomized Count:	1,112
Observational Count:	1,928
Total Count:	3,040





Enrollment Patterns Over Time: Willingness to Randomize Changed



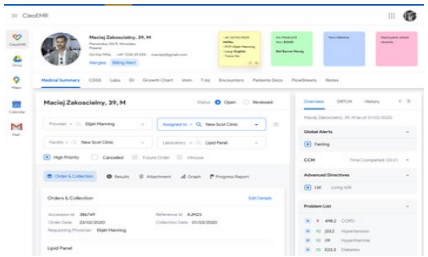
Study Event Start: February 13 – 19, 2022
Observational: 10
Randomized: 5

As of this am, 2 more days to go in the week

Transform Approach to Data Collection

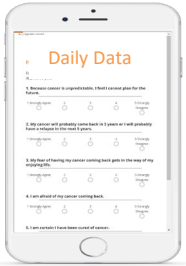
OneSource
Integrating Clinical Care and Research

INNOVATIVE PRACTICES AWARDS
WINNER
BioIT World 2022



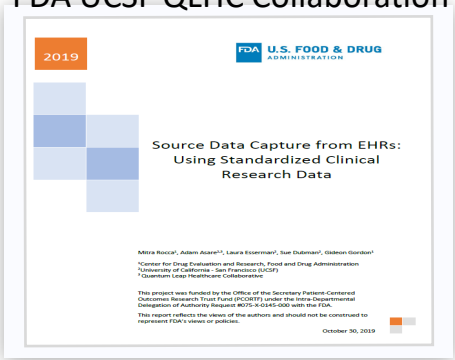
Pull discrete data from EHR

Study reports sent back



Receive alerts; monitor participants

FDA UCSF QLHC Collaboration



EHR Systems

I-SPY COVID Study System

- **EHR Integration for seamless data capture for care and trials**
  - Automates capture of demographics, medications, and labs
  - Supports decisions for both clinical care and research
  - Facilitates capture of ***initial screen*** and ***daily data check list***
    - summaries/trial reports can be back to EHR system (notes)
- **Generalizable approach across sites and EHR systems**
- **Implementation in 8 sites to date, 8 more by June**
  - Time savings dramatic

https://www.fda.gov/science-research/advancing-regulatory-science/source-data-capture-electronic-health-records-ehrs-using-standardized-clinical-research-data

https://aspe.hhs.gov/patient-centered-outcomes-research-trust-fund-reports

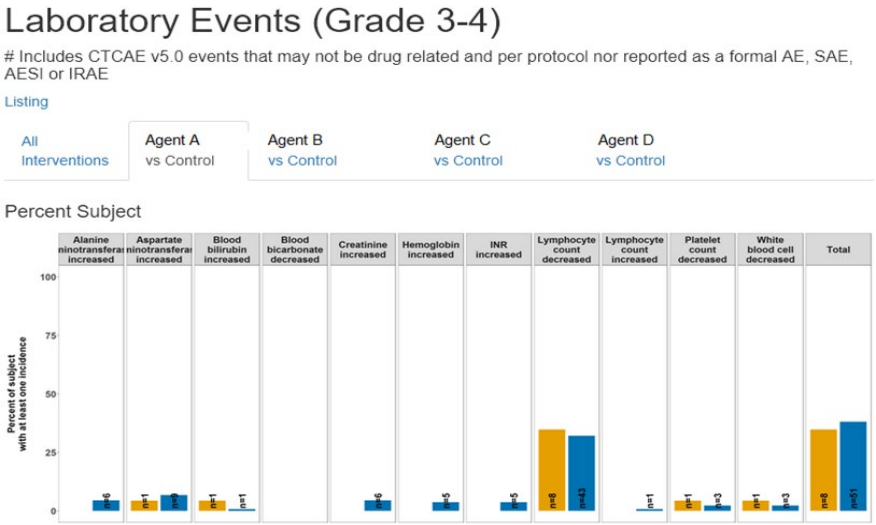
Support from BARDA made the system integrations and implementation possible

Centralized monitoring can help detect adverse events much sooner than on-site monitoring

On-site monitoring does not allow for detection of patterns across time & sites

Figure adapted from: Stansbury et al., Risk-Based Monitoring in Clinical Trials: Increased Adoption Throughout 2020, Therapeutic Innovation & Regulatory Science (2022)

Aggregate view of data in our trial platform allows for detection of concerning patterns



Labs, Clinically important events can be assessed in setting where disease has high rate of events

Risk-based monitoring can increase data quality, and enhance patient safety : But not well accepted across oversight agencies such as BARDA

More Efficient Monitoring
Centralized monitoring allows targeting of on-site activities, so trial staff to focus on what matters[1,2,6,7]

Cost Reduction
Risk-Based monitoring can reduce trial cost[6,7]

Improved Data Quality
Centralized Monitoring employs statistical techniques that can detect outliers and anomalies that could indicate fraud[1,3,4,5]

Earlier detection
Performance metrics can help detect and address compliance issues early[2]

Easier collaboration
Digital tools enable more frequent communication between monitors, data managers, and site staff[2,3]

Enhanced Patient Safety
Centralized monitoring allows early detection of adverse events [2,3,4]

There is a growing consensus that **risk-based approaches to monitoring,** focused on risks to the most critical data elements and processes necessary to achieve study objectives, **are more likely than routine visits** to all clinical sites and 100% data verification to **ensure subject protection and overall study quality** [1]

1 FDA 2 TransCelerate BioPharma,3 SOCRA, 4 Baigent (2008), 5 Venet (2012), 6 Yamada (2021), 7 Brosteanu (2017)

Observations

- Endpoints
  - Time to recovery was initial endpoint, but mortality added as co-primary within 4 months of opening the trial
  - Mortality is likely a better endpoint, but varies with time as well as by site (and patient mix)
    - Concurrent controls important, but smaller numbers of controls add some variability

- Efficiency in data collection can and should be improved
  - Normalizing lab values using Ref range upper limit of nl facilitates grading

- Timing of consent
  - Initially a 2 step consent (4 active agents): Are you willing to participate in study → Randomize → consent to assigned arm
  - Transition to 2 active agents: Consent→ randomization

- RWD very helpful and confirmed importance of randomization, concurrent controls
  - Observational patients have lower risk than randomized patients
  - Underlines importance of tracking outcomes for ALL patients as a standard of care-> transformative

Future

- Implement OneSource at all sites to decrease time required for high quality data, integrate care and research
- Integrate real time biomarker assessment, recognizing heterogeneity
- Integrate disease classification prospectively
  - Anticipate the future of care in the conduct of trials
- Build agent combinations into the study
  - Augment adaptive, virus-specific immunity
  - Ameliorate secondary inflammatory effects of tissue injury
  - Prevent later deterioration and accumulation of injuries from other sources. Reduce risk for secondary complications – organ failure, infections, reduce time on ventilator, RRT etc
    - Vascular-endothelial
    - Tissue injury, repair

OneSource Acknowledgements

UCSF / CERSI

Laura Esserman (Project PI)
Adam Asare (Co-Investigator)
Kathleen Liu (Co-PI
Carolyn Calfee (Co-PI)
Heidi Collins (Co-Investigator)
Anna Northrop (RA)
Anne Patterson (RA)
Alejandra Jauregu (RA)

I-SPY COVID TRIAL

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Paul Henderson
Karyn DiGiorgio
Ami Okada
Jasmine LaCoursiere
Michael Szymanski
Steven Cosari

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Derek Russell (Univ Alabama)

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Jacqueline Corrigan-Curay (SME)
Courtney McGuire (SME)
Laura Lee Johnson (SME)

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Frank Weichold (SME)

BARDA

Kimberly Armstrong (PO)
Peter Adams (PO)

Industry Partners

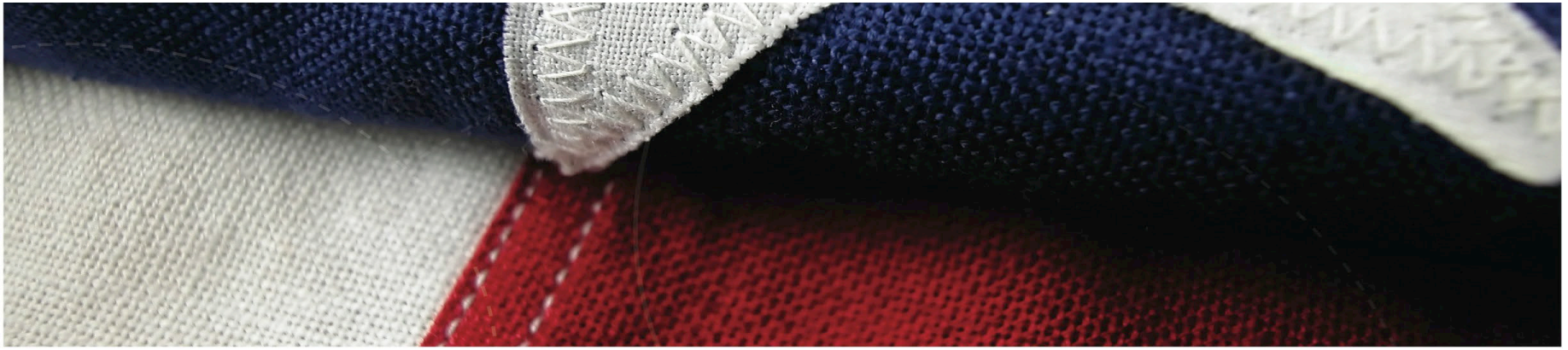
Cal Collins (OpenClinica)
Chris Weiss (OpenClinica)
Glenn Jacques (Slalom)
Mark Wheeldon (Formedix)

Abbreviation Key
PI - Principal Investigator
PM - Project Manager
PO - Program Official
SME - Subject Matter Expert
RA - Research Assistant

Acknowledgements

This work has been supported by the FDA through the PCOR Trust Fund and through the 21st Century Cures Act Funds through the Center of Excellence for Regulatory Science and Innovation (CERSI)

This work was supported, in part, by the Biomedical Advanced Research and Development Authority (BARDA), part of HHS within the office of the Assistant Secretary for Preparedness and Response, and Joint Program Executive Office, a part of the Department of Defense, under the Medical Chemical, Biological, Radiological, and Nuclear (CBRN) Defense Consortium (MCDC).



The Diuretic Comparison Project : Practical Issues with a Pragmatic Trial

Ryan E. Ferguson, ScD, MPH

Director, Boston CSP Coordinating Center

May 2022

Veterans Health Administration
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Annals of Internal Medicine

IDEAS AND OPINIONS

Chlorthalidone Versus Hydrochlorothiazide: A New Kind of Veterans Affairs Cooperative Study

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Ann Intern Med. 2016;165:663-664.

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Diuretic Comparison Project
Study Question

Does treatment with chlorthalidone (CTD) reduce major adverse cardiovascular events (MACE) compared with hydrochlorothiazide (HCTZ) in older veterans with hypertension?

DCP Study Design

- Prospective randomized open-label blinded-endpoint trial.
- Centralized informatics-based clinically integrated structure.
  - Embedded within EMR or backend database.
  - Clinical workflows used to facilitate training.
- N=13500 (target) 13,523 enrolled
- HCTZ users randomized to stay on current therapy or to initiate CTD

Inclusion/Exclusion Criteria

Inclusion:

1. Over age 65 years (half outcomes outside VA)
2. On HCTZ 25 or 50 mg/d from VA (not combo)
3. Most recent SBP (in CPRS) ≥ 120 mm Hg, & no SBP < 120 mm Hg w/in 90 days before randomization (minimize risk, maximize benefit)

Exclusion:

1. Considered incompetent to consent
2. Death expected within 6 months
3. Na < 130 meq/L or K< 3.1 meq/L in past 90 days (enroll them later)
4. Known to be in Medicare Part C

   (HMO pts, no outcome data)

Study Intervention

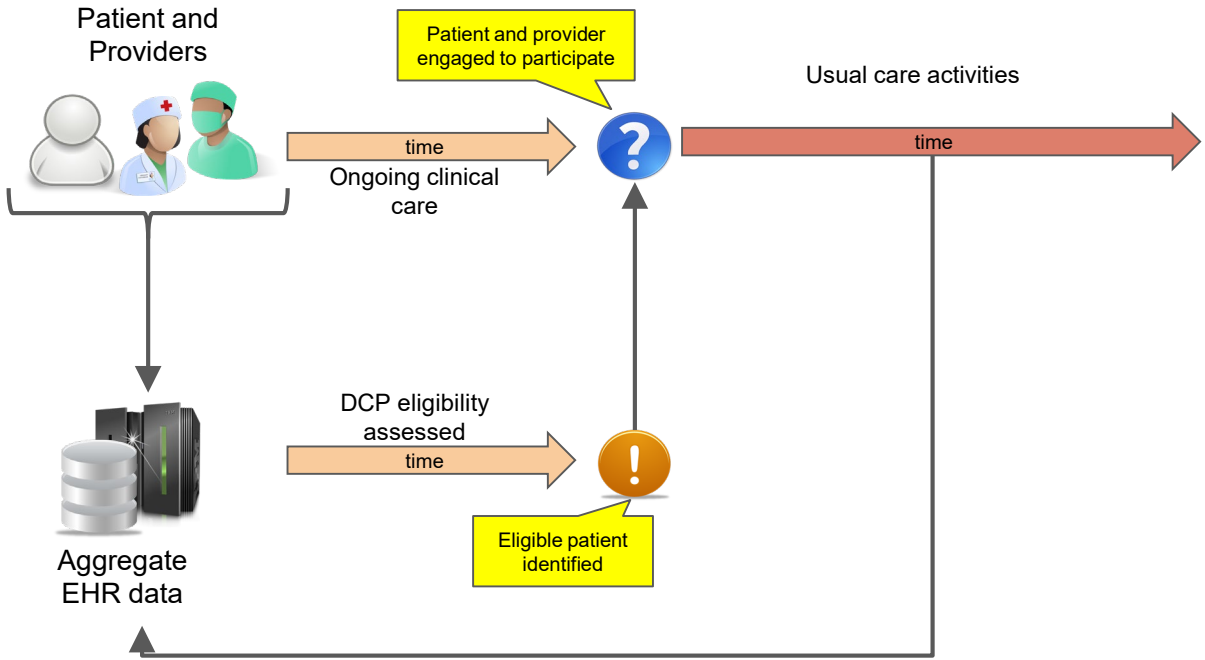
- Drug is open-label but allocation is concealed
- Randomize to current dose HCTZ (25 or 50 mg), or half that dose of CTD (12.5 or 25 mg)
- Change to CTD → order to PCP
  - For 12.5 mg, send tablet splitter with rx
  - Reimburse pt for co-pay of discarded HCTZ
- All management by PCP (lab, drug, dose)

The primary outcome - MACE

Time to first occurrence of any of the following:

1. Stroke
2. Myocardial infarction
3. Urgent coronary revasc 2° unstable angina
4. Hospitalization for acute decompensated HF
5. Non-cancer death

Simplified DCP Workflow



Pragmatic Features:

1) Design with technology as a force multiplier
2) Embedded within VA Information Systems & EMR
   - find eligible patients using VA EMR
   - centralized recruitment and enrollment
   - centralized placement of notes & orders
   - PCPs: permission & pt care (including study drug)
   - centralized collection of outcomes from EMR database

Pragmatic Features:

3) Clinical sites not "engaged in research" - no local personnel (10% cost)
4) Telephone based informed consent for participants with a clinical assent to maintain clinical autonomy
5) Minimal perturbation of the clinical workflow. Study designed to "fold into" PCP processes

Lessons Learned

- Adaptability of the EHR is the *sine quo non* for pragmatic embedded trials.
- Alignment of incentives is important.
- Focus groups for implementation:
  - Providers – clinical autonomy, consent, buy-in.
  - Patients – worry about a lot less than we worry about.

Lessons Learned

- Design of projects:
  - Limitations of real-world data need to be accounted for and mitigations/controls built into system
- Data Systems:
  - Robust algorithms for ascertainment planned and operationalized prior to launch
  - Accuracy and Cleanliness of Data are not perfect – secondary use of medical record reshapes convention

Closing

- Reduction in barriers to participation has a real-world impact.
  - Consent rates higher than traditional trials.
  - Assent rates and PCP participation higher than other CSP trials
- Use of real-world data from healthcare settings is challenging, but a reality for the clinical trials enterprise.

Breakout Groups

Breakout Group Overview

- **Objective:** Help to refine CTTI's draft recommendations
- **Logistics:**
  - 4 Groups: Operations, Data, Tech Implementation, Future Directions
  - Breakouts will be 60 mins long and recorded
  - Each participant will quickly introduce themselves (state name, role, and organization- <1 min each)
  - Facilitator will ask the discussion questions
  - After 60 mins follow the prompt to reconvene to the main session, then take a 10 min break.
  - Reconvene at 1:40 pm ET for a recap (provided by each facilitator)

Here's to a great discussion!.....Now get ready to transfer…..

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Elements of a trial that are possible to embed

- Eligibility criteria
- Medical History and Concomitant Meds
- Informed Consent
- Randomization
- Intervention
- Trial Data Acquisition
- Results

Operations Breakout Group

How do we encourage participation in embedded research at all levels?

- Health care leadership:
  - What health care setting changes are needed (administrative/personnel, equipment, etc.) to enable embedded research?
  - What commitment and resources are needed to facilitate patient engagement and increase awareness of research?
- Health care providers:
  - How can we address concerns about accountability and liability?
  - What types of financial recognition and incentives are needed?
- Patients:
  - What recruitment approaches as part of routine care will be successful and not disruptive?
- Study Designers:
  - What types of questions would you ask in a decision framework for whether to embed elements of a trial into care?
  - What type of study questions are appropriate for embedding trial elements?

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Data Breakout Group

Using data collected during routine care to embed trials…

1. What type of reusable data and technology infrastructure is needed?
2. How can we repurpose EHR data for research purposes (trial databases) in the most cost-effective and least disruptive manner?
3. How can an EDC platform (to collect supplemental trial-specific data not captured in the EHR) be integrated into the clinical workflow?
4. What is required to ensure data quality, traceability, and adequate regulatory oversight? (Sponsors and regulators may need access to data)
5. What would you add or change to CTTI's recommendation #3 to ensure that data collected for embedded trials are relevant, reliable, and of sufficient quality? (see next slide)

Recommendation #3

Ensure available data sources used for embedded trials are fit for purpose – relevant, reliable, and of sufficient quality

Relevant

- Use data collected during routine care as the primary, foundational source data.
- Collect the least amount of data necessary to answer the research question.

Reliable

- Appreciate the intention and potential consequences of clinical care data collection and use.
- Validate the reliability of the clinical data through manual and automated data checks.

Sufficient Quality

- Perform a feasibility assessment to assess data missing-ness and determine the availability of supplemental data to fill gaps.
- Ensure that clinical data incorporated into a trial database are complete, plausible, accurate, and traceable.
- Develop strong data privacy and security plans.

Consult early and often with regulatory authorities on data quality questions

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Tech Implementation Breakout Group

Reusable data and technology infrastructure for embedding elements of trials

1. How can technology facilitate the planning and operational execution of embedding trial elements?
2. What funding will be needed and from what funding sources?
   - Are there innovative funding models that should be explored?
3. How can EHR vendors be involved? Can we encourage certain trial elements to be routinely incorporated into their systems?
4. How can technology support patient engagement with embedded trials?
5. If time allows: What have been the most instructive experiences to date for incorporating innovative technology solutions into the planning, design, and execution of embedded trials?

Future Directions Breakout Group

Future Directions for Embedding Trial Elements Across Health Care Settings

1. What needs to happen in the U.S. to build sustainable research networks that can support and execute embedding trial elements?
2. What are the “asks” of key government agency leaders (e.g., FDA, NIH, CMS) to support, incentivize, and encourage funding organizations to embed more trials for regulated medical products?
3. How can sponsors be encouraged to conduct trials using embedded elements? What are the real or perceived barriers to implementing these trials for use in regulatory decision-making?
4. How can CTTI take a more pro-active stance to help drive the uptake and adoption of embedded trials?

Transfer back to main session

(then take a 10 min break)

Break

Return at 1:40

Breakout Debrief

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

May 11, 2022

Opportunities to Implement CTTI Recommendations

CTTI Project Draft Recommendations

Kraig Kinchen, Eli Lilly and Company

CTTI Strengths

- **Multi-stakeholder** public-private partnership co-founded by FDA and Duke University
  - Involvement of ±500 individuals and groups
  - Participation from ±80 member organizations
  - All stakeholders have an equal voice
- **Evidence-based** research methods
  - Stakeholder interviews, focus groups, surveys
  - Systematic literature reviews
  - Expert meetings
- **Impactful** products, tools and engagement
  - Case Study Exchange
  - Policy adoption
  - Organizational-level adoption

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“The best big idea is only going to be as good as it’s implementation”

- Jay Samit (author)

Purpose of Recommendations & Target Audience

- Purpose: Facilitate the fit-for-purpose integration of randomized, interventional trials into clinical care

Target Audience
Clinicians interested in conducting research
Research sponsors
Health care settings
Regulatory bodies
Operational technology providers
Clinical Research Organizations
Patient advocacy groups
Health system leaders
Funders
Payers

Road to Implementation: Open Discussion

- How do we best communicate the rationale for embedding trials?

- Are the key players ready to implement the recommendations?

Road to Implementation: Open Discussion

- What does success look like?

- How would implementation of the recommendations enable the achievement of a successful outcome?

Poll

1. Are there potential trials, in early planning phases, that might benefit from implementation of the CTTI recommendations?

2. Are you aware of organizations that are looking to make advances with embedding trials?

Next Steps

- This summer, CTTI Project team will:
  - Incorporate your input and refine the draft recommendations
  - Develop supporting tools (e.g. a Decision Tree for embedding trials)
- Expert Meeting #2: Wednesday, September 21st (in person in Washington D.C.)
  - Potential Meeting Objectives:
    - Develop an implementation strategy for how these recommendations could be applied to different scenarios
    - Develop metrics of recommendation implementation and potential impact

Be on the look out for the 2nd Expert meeting invitation. Let's implement what you've helped to create!

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"Without deviation from the norm, progress is not possible."

– Frank Zappa

THANK YOU

www.ctti-clinicaltrials.org