

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

Embedding trials into health care delivery is possible. CTTI spoke with individuals from five different trials in which elements of the trial have been embedded into clinical practice. We provide an example of one trial, the [RECOVERY](#) Trial, below.

TRIAL OVERVIEW

- ▶ Adaptive, randomized, open-label trial
- ▶ Number of sites (as of April 2022): ~200 (hospitals primarily across UK but also in Nepal, Indonesia, Vietnam, South Africa, and Ghana)
- ▶ Number of patients enrolled (as of April 2022): ~47,500
- ▶ Ages eligible for study: Child, Adult, Older Adult (<6 weeks to >100 years; includes pregnant women unless drug-specific contraindication)
- ▶ Interventions: Repurposed drugs (11), investigational biologic (monoclonal neutralizing antibodies) (2), novel oral anti-virals (2), convalescent plasma (1)
 - 10 results in 2 years – 4 beneficial, 6 not effective
- ▶ Key outcomes/endpoints (initially at 28 days, with 6 month analyses pre-specified and ability to track for up to 10 years):
 - Primary: All-cause mortality
 - Secondary: Duration of hospital stay; progression to invasive mechanical ventilation (IMV) or death among those not on IMV at randomization

EMBEDDED TRIAL ELEMENTS

- ▶ *Patient Identification & Eligibility*: Identifies patients as part of acute hospital care for COVID-19
- ▶ *Randomization*: Randomizes allocation to interventions + usual care vs. usual care alone (via web-based randomization and adaptive trial design)
- ▶ *Data Acquisition*: Focuses on objective clinical endpoints (such as mortality) and captures data by single electronic case report form (eCRF) plus linkage to national healthcare datasets (e.g. mortality, hospital admission/discharge, SARS-CoV-2 testing, use of mechanical ventilator)

- ▶ *Evidence Integration*: Results of a diverse (representative) population are made available promptly and rapidly translated into clinical practice (within hours to weeks) nationally and globally

WORDS OF WISDOM

- ▶ Consolidate around a question that is big enough and important enough (public health mindset – change the course of the pandemic)
- ▶ Work out what matters, focus on what matters, do what matters (and don't get distracted or allow others to distract you)
- ▶ Focus on what matters to patients and to the reliability of the results (which influence the treatment of future patients)
- ▶ Randomize, have adequately large numbers, and see trial through to completion
- ▶ 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 – anybody can design a trial that nobody can do, the trick is to design a trial that will answer its question and that everyone can do (patients, clinicians, healthcare systems alike)
- ▶ Taking longer (e.g. contract approvals, IRB review) doesn't necessarily mean doing a better job ("can you just" is the enemy of progress)
- ▶ Communicate and be transparent (have protocols, recruitment progress, results all open access in real-time)
- ▶ Create a culture where we are all in this together

CHALLENGES

SOLUTIONS

Technology Infrastructure	Time and effort is required to embed randomization into the hospital electronic health record system, thus it was not done	Integrates randomization into care pathway via simple means e.g. by using a one-page web-based CRF (separate from the EHR) Leverages standalone system because it's flexible and easier to control and not under individual hospital IT department control
Data	Most data sets are shallow in that they don't capture every nuance and detail but they are	Pulls from multiple national data sources for a holistic picture of the outcomes that matter (provides almost complete follow-up for many years,

comprehensive in that they cover everyone, regardless of location

even if patients move hospitals or healthcare provider)

Utilizes a data monitoring committee (DMC) and algorithm for data discrepancies

Culture

There is a general lack of understanding that it takes large numbers to get clear answers and clear answers are important whether they're positive or negative.

Trials are often perceived as 'risky' but clinical care based on no evidence is risky. Many trials pose little or no additional risk to participants beyond that involved with routine clinical care.

False certainty and conflicting public information prior to trial completion

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

Process

Trial oversight and administration can too often be slow and overly emphasize what is easy to check rather than on what matters

Utilizes a central IRB (standard for the UK for >20 years) to help with speed and the quality of approvals

All hospitals sign one template contract (non-negotiable)

Engages with Chief Medical Officers (CMOs) and gets NHS leadership buy-in to promote the concept that "the randomized trial is part of clinical care, not an optional extra"

Suggests basing oversight on key principles of randomized controlled trials (trial team suggests referring to www.goodtrials.org) and focus on issues that have material influence on the trial participants and the reliability of the results (which impact future patients)