

## Transforming Clinical Research in the COVID-19 Era

Coronavirus disease 2019 (COVID-19) has had a profound effect on nearly every aspect of healthcare worldwide. While much has been written about the clinical aspects of SARS-CoV-2 infection, the current pandemic has created major setbacks for researchers engaged in clinical trials. From challenges to patient enrollment to regulatory constraints to concerns about interpretation of outcome data, there exists a growing need to provide guidance to the research community about the best means to overcome these problems.

To further address this, the American College of Cardiology (ACC) convened more than 40 experts on May 29, 2020, to partake in a virtual Heart House Roundtable on *Cardiovascular Clinical Research in the COVID-19 Era*. In addition to clinical trialists, leaders from academic medical centers, health systems, the FDA and industry were asked to participate. The meeting was divided into two parts, focused first on *what* can be done to address the many challenges faced by ongoing trials and then moving forward, *how* the ACC can support rapid knowledge generation through innovative research design.

Much of the work was carried out in small group sessions, where participants brainstormed about the best ways to overcome obstacles faced by researchers. Challenges and potential recommendations were catalogued, based on the key elements of a clinical trial.

### Patient recruitment and retention

Central to the success of any clinical trial is being able to recruit and retain patients for the entire trial duration. [Multiple barriers have been previously identified](#), including more restrictive enrollment criteria, longer treatment and follow up periods, the potential for negative side effects, as well as, uncertainty and distrust. Added to this now are additional pandemic-related issues of limited travel and the need to practice social distancing. Many of these issues existed previously, but were exacerbated during the pandemic.

- Challenges
  - Limited patient enrollment and engagement because of social distancing, quarantining and isolation
- Recommendations
  - Expanded use of direct to participant recruitment strategies
  - Design strategies in partnership with potential participants, understanding the participant perspective and optimizing the participant experience
  - Utilize the electronic health record (EHR) and other forms of technology to rapidly identify appropriate study participants (e.g. [computable phenotyping](#))
  - Leverage electronic consenting (e-consenting)
  - Tap into existing telehealth platforms for virtual engagement and follow up visits

### Study administration

Beyond design and onboarding of a clinical trial, much of its success hinges on how well it is conducted. COVID-19 has introduced extraordinary challenges in this regard, from limited ability of research subjects to come in for study visits, fewer on-site study personnel, and delays in study procedures, drug administration and/or follow-up monitoring.



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- Challenges
  - Diminished willingness by study participants to be seen for study evaluation and treatment
  - Limited availability of personal protective equipment (PPE)
- Recommendations
  - Mail order/delivery of drugs and devices
  - Utilization of home visits, virtual trials, or a hybrid approach
  - Collection of data using remote patient monitoring
  - Implementation of safe practices for clinical trial participants and research staff
  - Centralization of adverse event reporting

## **Data collection and analysis**

Rigorous data collection and analysis is the hallmark of well executed clinical research. If not challenging enough, the pandemic has introduced a number of additional [obstacles](#), including, among others, how best to accommodate protocol deviations, missing data, concomitant COVID-19 infection, as well as additional unrelated treatments.

- Challenges
  - Delayed and/or incomplete assessment of endpoints/outcomes
  - Sample size issues because of the noise introduced by COVID-19
- Recommendations
  - Utilization of real-world data sets, with use of digital platforms, artificial intelligence (AI) and/or natural language processing (NLP) to support data collection
  - Greater use of patient-reported outcomes
  - Adaptation of endpoint definitions to reflect current epidemiology
  - Consensus conferences and documents about appropriate ways to manage missing data and unanticipated competing risks and epidemiological patterns

## **Reporting**

Findings from clinical trials carry great impact for sponsors, investigators, and ultimately regulators. Many of the aforementioned obstacles are helping to shape contingency measures and recommendations for drugs and devices under investigation.

- Challenges
  - Lack of familiarity of new challenges to study designs imposed by COVID-19
  - Delays in non-COVID-19 publications because of a massive increase in publication submissions (>100% increase)
  - Lack of trust in the scientific process
- Recommendations
  - Need to extend study timelines

- Flexibility by sponsors, investigators and regulators to accommodate non-traditional study designs
- Reporting trial findings using comprehensive accounting of methods and results (CONSORT and STROBE frameworks)
- Protocol and data transparency, with public disclosure of datasets
- Use of preprint servers
- Establishment of best practices by stakeholders (trialists, editors and regulators)

With an uncertain timeline on the development of a vaccine, the future of clinical trials remains quite unclear. The pandemic has touched nearly every aspect of clinical research, inviting the need to make major changes in how studies are conducted. Future efforts should be focused on finding ways to increase trial access, create greater diversity among those that are enrolled, and encourage data transparency in service to improved patient outcomes.

For additional information, please read the recent [JACC Leadership Page](#), authored by the Roundtable Chairs, Dr. Harlan Krumholz and Dr. Jim Januzzi.

