Cardiovascular clinical trials in the era of a pandemic

Running title: *Siontis et al.; COVID-19 and cardiovascular research*

George CM Siontis, MD, PhD[1]; Romy Sweda, MD[1]; Stephan Windecker, MD[1]

[1]Department of Cardiology, Bern University Hospital, Bern, Switzerland

Correspondence:
George CM Siontis, MD, PhD
Department of Cardiology
Bern University Hospital, Inselspital
CH-3010 Bern, Switzerland
Email: georgios.siontis@insel.ch

Journal Subject Terms: Cardiovascular Disease; Epidemiology; Quality and Outcomes; Health Services; Mortality/Survival

Key words: cardiovascular disease; cardiovascular research; COVID-19; randomized controlled trial

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1161/jaha.120.018288

COVID-19 has reached pandemic levels in March 2020 and impacted public health with unpredictable consequences.[1, 2] The conduct of clinical research in areas unrelated to COVID-19 has been disrupted and will be further affected. Researchers, trial participants and study personnel have to overcome challenges to sustain proper and safe conduct of clinical trials (i.e. logistical challenges, lower enrollment than expected, difficulties in follow-up and outcome assessment/adjudication, incomplete data collection, research funding prolongation).[1] Of obvious concern are the risks of SARS-CoV-2 infection in study individuals as well as the corollary effects of broader health care consequences related to the global protective measures (i.e. health-care access for events unrelated to COVID-19, mental health conditions), which may act as competing risks and result in adverse clinical outcomes unrelated to trial's intervention(s) and conditions.

Accumulated evidence supports that SARS-CoV-2 is more frequently observed and associated with impaired prognosis in elderly, patients with cardiovascular disease (CVD) and related comorbidities.[3] Against this complex multidimensional crisis, we wonder in which extent contemporary randomized clinical trials (RCTs) in cardiovascular field can be potentially affected and are prepared to address such challenges; since trials' participants may be subject to events entirely different in nature (competing risks) owing to intrinsic vulnerability but also to corollary health effects of the global protective measures.

Methods

All data are available upon request.

We considered protocols of RCTs dealing with cardiovascular conditions in adults during the last 3 years (March 31, 2017 to March 31, 2020); a time-span that allowed us to capture contemporary ongoing trials. We focused only on peer-reviewed protocols published in PubMed in English to ensure clarity of required information. Protocols provided the recruitment and follow-up period were considered, if the cumulative time-period was overlapping and inclusive of the COVID-19 pandemic (later than January 01, 2020). The following search-terms were used: "random*", "study design", "protocol", "cardiac", "valvular", "heart", "coronar*", "arrhythm*". The periods of recruitment and follow-up were

extracted along with trials' characteristics. We also collected whether adaptive or analyses accounting for competing risks and methods to address incomplete data collection had been considered. Due to the nature of our study, no institutional review board approval was required.

Results

We identified 155 peer-reviewed protocols of unique RCTs in cardiovascular medicine fulfilling our inclusion criteria. The median (interquartile range) period of recruitment is 32 (23–46) months, ranging between the years 2014 and 2024. Follow-up duration among the trials has a median (interquartile range) of 12 (6–24) months (1 to 60 months) (**Figure 1**). The vast majority are multicenter studies (78%) recruited patients in Africa, Asia, Australia, Europe, and North America. Non-industry related funding sources are disclosed in 96 (62%) protocols. The median sample size reports 360 (144–1391) patients ranging from 24 to 32,000 individuals. RCTs with larger sample size report prespecified longer follow-up periods (p=0.002) (**Figure 1**). Strategies under investigation are drugs (58 (37%)), participative interventions (34 (22%)), surgical or minimal invasive interventions (31 (20%)), diagnostic tests (13 (8%)) and diverse (19 (12%)). The primary outcome is a composite endpoint in 60 trials (39%); all-cause mortality is component of it in 38 trials and infection in only 2 trials. All-cause mortality is the single primary outcome in 8 trials. An adaptive analysis plan is mentioned only in 2 trials, and survival analysis accounting for the competing risk of death is mentioned only in 7 trials. Methods to deal with missing data were reported only in 38 out of 155 (25%) of the trials' protocols.

Discussion

In a representative sample of contemporary ongoing RCTs in cardiovascular medicine, one third of the trials include all-cause mortality or infection-related events as part of the primary endpoint. An adaptive or competing risk analysis has been considered upfront by the investigators in less than 6% of the sample. Current projections of the future dynamics of SARS-CoV-2 infection suggest recurrent but less severe wintertime outbreaks,[4] which will further challenge the flow of clinical research; whereas accumulated evidence during the first wave of the COVID-19 pandemic suggest that the increased mortality may also be

attributed to causes other than the infection.[5] Above projections and observations suggest that researchers may face considerable challenges under the current circumstances in terms of continuation of clinical trials (i.e. nonadherence, lower recruitment rates, limited funding sources), achieving prespecified sample sizes during the recruitment period, appropriately follow-up trials' participants (alternative practices may be required i.e. visits through remote connections), and analyzing the acquired data (i.e. impact of competing events, inappropriate outcome adjudication). More specific, researchers may have to adopt the prespecified analysis plan of RCTs to address considerable imbalances between treatment arms, incomplete data collection, and to derive complementary information by applying competing risk models (joint hazard models for all of the different types of events) that properly account for competing risks for time-to-event primary outcomes analyses. Of note, such considerations are equally applicable to any research field dealing with extremely vulnerable patient-groups and high-risk features (i.e. patients with malignancies).

Sources of Funding: None.

Disclosures: Dr. Siontis reports honoraria from Abbott outside the submitted work. Dr. Sweda has nothing to declare. Prof. Windecker reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, Sinomed. Prof. Windecker serves as unpaid member of the steering/excecutive group of trials funded by Abbott, Abiomed, Amgen, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Polares, Sinomed, V-Wave and Xeltis, but has not received personal payments by any pharmaceutical company or device manufacturer. Prof. Windecker is also member of the steering/excecutive committee group of several investigated-initiated trials that receive funding by industry without impact on his personal remuneration.

References:

1. Bagiella E, Bhatt DL, Gaudino M. The consequences of the COVID-19 pandemic on non-COVID-19 clinical trials. *J Am Coll Cardiol*. 2020:76:342-345.

2. Khullar D, Bond AM, Schpero WL. COVID-19 and the Financial Health of US Hospitals. *JAMA.* 2020 May 4 [epub ahead of print].

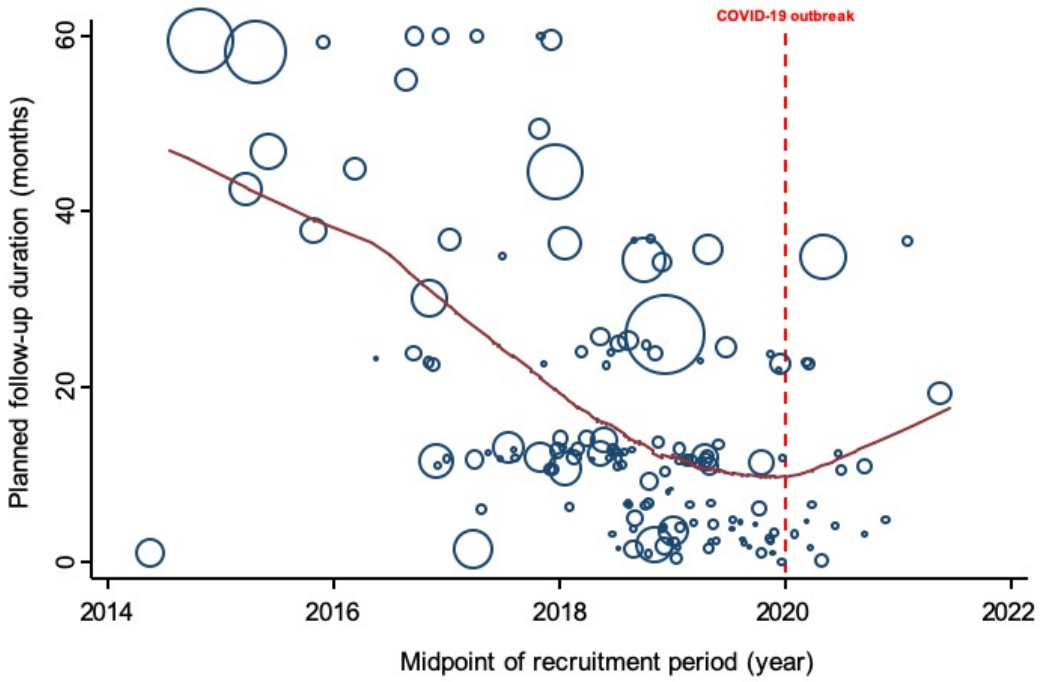
3. Gupta AK, Jneid H, Addison D, Ardehali H, Boehme AK, Borgaonkar S, Boulestreau R, Clerkin K, Delarche N, DeVon HA, et al. Current Perspectives on Coronavirus Disease 2019 and Cardiovascular Disease: A White Paper by the JAHA Editors. *J Am Heart Assoc*. 2020;9. doi: 10.1161/JAHA.120.017013.

4. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science.* 2020;368:860-868.

5. De Filippo O, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, Secco GG, Campo G, Gallone G, Verardi R, et al. Reduced Rate of Hospital Admissions for ACS during Covid-19 Outbreak in Northern Italy. *N Engl J Med.* 2020;383:88-89.

Figure Legend:

Figure 1. Distribution of 155 ongoing contemporary clinical trials over time in cardiovascular medicine overlapping with the COVID-19 pandemic. Each circle represents a clinical trial and it is weighted according to the respective sample size of the trial. Trials shown overlap with the COVID-19 pandemic either with respect to recruitment periods and/or follow-up duration. X-axis corresponds to the midpoint of the recruitment period of each trial. Y-axis corresponds to the planned follow-up duration (months). The dark red continuous line represents a smooth line (non-parametric) through the scatter plot (locally weighted scatterplot smoothing) to illustrate the relationship between the two variables and foresee any potential trends over time.



jah3_5570_f1.jpg