

RESEARCH LETTER

The Landscape of Cardiovascular Clinical Trials in the United States Initiated Before and During COVID-19

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The coronavirus disease 2019 (COVID-19) pandemic has taken an unprecedented toll on the American healthcare system and economy. While numerous COVID-19 clinical trials have been initiated in hopes of curtailing its impact, most preexisting clinical trials have been forced to suspend or limit activity, which itself can have significant consequences. Missed or postponed trial-related assessments may hinder data quality, and heterogeneity in data collection both across the country and over time introduces bias.¹ In addition, COVID-19 may lower specific event rates due to patients avoiding the healthcare system that could result in underpowered outcome analyses, or conversely, some end points (mortality) may be inflated.² Nonetheless, while the pandemic has exerted a significant toll on preexisting clinical trials, the increasingly recognized interplay of COVID-19 with the cardiovascular system has prompted an urgent need for new studies.³ As such, clinical trials have rapidly commenced to study the impact of COVID-19 on cardiovascular populations and outcomes, as well as to test the effects of cardiovascular therapies on COVID-19 disease course (eg, inhibitors of the renin-angiotensin-aldosterone system).⁴ However, to date, the impact of COVID-19 on the landscape and scope of preexisting and newly initiated cardiovascular clinical trials has not been systematically studied.

We extracted data from clinicaltrials.gov to describe characteristics of (1) cardiovascular clinical trials before COVID-19 and (2) COVID-19 trials with a cardiovascular

focus in the United States as of May 13, 2020. All trials were required to be recruiting, enrolling by invitation, active but not recruiting, or suspended. Two reviewers classified all data not populated by the trials database. To define pre-COVID-19 cardiovascular clinical trials, we used the preferred search term “cardiac disease” (which simultaneously searches synonyms), initially identifying 905 trials. We then excluded trials with a start date after March 16, 2020, when national guidance for social distancing was issued (final $n=892$). COVID-19 trials were similarly identified by the preferred search term “COVID-19.” From these COVID-19 trials ($n=156$), we defined cardiovascular COVID-19 trials by any of the following: a specific cardiovascular patient population (ie, patients with heart failure), a cardiovascular intervention (ie, primary cardiac drug therapy), or cardiovascular outcome (ie, cardiac events or biomarkers) (final $n=25$). Corresponding coronavirus case load on May 13, 2020, per state was downloaded.⁵ Our investigation did not require institutional review board approval because all data were acquired from the public domain.

Among 892 pre-COVID-19 cardiovascular trials (Table), the most common trial topics are heart failure (29%), electrophysiology (25%), and interventional cardiology (18%). Approximately half (54%) receive industry or federal funding, and trial phases are roughly evenly distributed. Most pre-COVID-19 trials occur in states with a substantial COVID-19 case load (New York, California, and Pennsylvania). The median (25th–75th

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percentile) time until anticipated trial completion is 414 (171–932) days.

Among 25 cardiovascular COVID-19 trials (Table), 7 (28%) specifically enroll a cardiovascular population, and 13 (52%) employ a cardiovascular intervention (with renin-angiotensin-aldosterone system–based interventions occurring in 6 [24%]). Sixteen trials (64%) assess a cardiovascular outcome, and 8 (32%) specifically study a biomarker outcome (7 prespecified troponin and 5 prespecified natriuretic peptides). The most frequent trial sites are located in New York, California, and North Carolina. Fourteen studies are in phase II, and 4 receive industry or federal funding. The median (25th–75th percentile) time until anticipated trial completion is 232 (180–323) days.

Here, we describe the characteristics of active cardiovascular clinical trials initiated before COVID-19 as well as recently initiated COVID-19 trials with a cardiovascular focus. Of the 892 pre-COVID-19 clinical trials, many enroll in states with substantial COVID-19 burden that are likely suspended or limited in activity. Further, more than a quarter were anticipated to complete within 6 months. Heart failure, electrophysiology, and interventional cardiology trials are the most frequent ongoing trials. In the COVID-19 era, a modest number of studies (25) include a cardiovascular patient population, intervention, or outcome. These trials, mostly in phase II, reflect the substantial interest in renin-angiotensin-aldosterone system–based therapies, principally use biomarker

Table. Characteristics of Cardiovascular Clinical Trials Initiated Before and During COVID-19

Characteristic	Cardiovascular Trials Initiated Before COVID-19 (n=892)	COVID-19 Trials With a Cardiovascular Focus (n=25)	P Value*
Phase of trial, n (%)			0.005
I	51 (5.7)	2 (8.0)	
II	102 (11.4)	14 (56.0)	
III	103 (11.5)	4 (16.0)	
IV	85 (9.5)	1 (4.0)	
Not available	551 (61.8)	4 (16.0)	
Target enrollment (median, 25th–75th percentile)	100 (40–359)	200 (70–626)	0.15
Time from trial initiation (median, 25th–75th percentile)	846 (441–1563)	27 (18–34)	<0.001
Anticipated time until trial completion (median, 25th–75th percentile)	414 (171–932)	232 (180–323)	0.014
Source of funding, n (%)			0.002
Industry	330 (37.0)	2 (8.0)	
Federal	141 (15.8)	2 (8.0)	
Both	13 (1.5)	0 (0.0)	
Other [†]	408 (45.7)	21 (84.0)	
States with the highest number of trials (COVID-19 cases per state)			
State 1	California: 293 (73 218)	New York: 6 (345 828)	
State 2	New York: 263 (345 828)	California: 5 (73 218)	
State 3	Pennsylvania: 245 (62 194)	North Carolina: 3 (15 850)	
Cardiovascular trial field(s), n (%) [‡]			
Heart failure	260 (29.1%)	...	
Electrophysiology	223 (25.0%)	...	
Interventional	160 (17.9%)	...	
Pediatric or congenital	81 (9.1 %)	...	
General	67 (7.5 %)	...	
COVID-19 trial with cardiovascular patient population, n (%)	...	7 (28.0%)	
COVID-19 trial with any cardiovascular intervention, n (%)	...	13 (52.0%)	
COVID-19 trial with RAAS active agent, n (%)	...	6 (24.0%)	
COVID-19 trial with any cardiovascular outcome, n (%)	...	16 (64.0%)	
COVID-19 trial with biomarker outcome, n (%)	...	8 (32.0%)	

Data are in reference to May 13, 2020. COVID-19 indicates coronavirus disease 2019; RAAS, renin-angiotensin-aldosterone system.

*P values shown for chi-square and Wilcoxon rank-sum tests, as appropriate.

[†]Other funders include individuals, universities, and community-based organizations.

[‡]The 5 most frequent fields classified by investigators are listed (remaining categories include critical care, genetics, imaging, cardio-oncology, pulmonary hypertension, prevention, cardiac surgery, and other). Each clinical trial was categorized in up to 2 fields.

outcomes, and are largely anticipated to report in 2021.^{3,4}

While systematically searched, our data are limited to documented fields, and are thus predicated on accurately entered and updated information. In addition, these data will continue to evolve as further research is stimulated during the pandemic.

In conclusion, we present the landscape of ongoing cardiovascular clinical trials that were initiated before COVID-19, as well as the characteristics of recently initiated COVID-19 clinical trials with a cardiovascular focus. Such data underscore the magnitude of the toll COVID-19 has taken on the clinical trial community and provide insight into new directions of cardiac-focused COVID-19 research.

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