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One-year follow up of vascular intervention trials disrupted by the COVID-19 pandemic: A use-case landscape

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ABSTRACT

Introduction: The COVID-19 pandemic had an unprecedented impact on cardiovascular clinical research. The decision-making and state of study operations in cardiovascular trials 1-year after interruption has not been previously described.

Methods: In the spring of 2020, we created a pandemic impact task force to develop a landscape of use case scenarios from 17 device trials of peripheral artery disease (PAD) and coronary artery disease (CAD) interventions. In conjunction with publicly available (clinicaltrials.gov) study inclusion criteria, primary endpoints and study design, information was shared for this use-case landscape by trial leadership and data owners.

Results: A total of 17 actively enrolling trials (9 CAD and 8 PAD) volunteered to populate the use case landscape. All 17 were multicenter studies (12 in North America and 5 international). Fifteen studies were industry-sponsored, of which 13 were FDA approved IDEs, one was PCORI-sponsored and two were sponsored by the NIH. Enrollment targets ranged from 150 to 9000 pts. At the time of interruption, 5 trials were <20 % enrolled, 9 trials were 50–80 % enrolled and 3 trials were >80 % enrolled. At 1 year, the majority of studies were continuing to enroll in the context of more sporadic but ongoing pandemic activity.

Conclusions: At 1 year from the first surge interruptions, most trials had resumed enrollment. Trials most heavily interrupted were trials early in enrollment and those trials not able to pivot to virtual patient and site visits. Further work is needed to determine the overall impact on vascular intervention trials disrupted during the COVID-19 pandemic.

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1. Introduction

In January 2020, COVID-19 began to emerge across the world with dramatic impacts on healthcare infrastructure and on patient care. The COVID-19 pandemic also had a powerful impact on the state of clinical trials around the world. It has been estimated that there was an 80 %

reduction in patients entering clinical trials in April 2020 compared with April 2019 [1]. At the peak of trial disruption in February–March 2020, there were over 1200 clinical trials that had been interrupted at various points of trial activity. During this time and with emergency Guidance from Federal agencies such as the U.S. FDA and the NIH [2], many sponsors, investigators, and trial sites suspended enrollment in clinical trials and pivoted to remote site activation and/or remote patient monitoring/follow-up. A recent survey across human-subjects research efforts by Xue and colleagues demonstrated that 57 % of patient-site interactions and 79 % of sponsor-site interactions occurred remotely during the first six months of the pandemic [1]. Other strategies to mitigate disruption were adopted, including electronic and remote consent processes, online patient recruitment, and direct sponsor-to-patient medication/clinical supply.

Abbreviations: CEC, clinical endpoints committee; DSMB, data safety monitoring board; FDA, Food and Drug Administration; PAIINTERS, PAndemic Impact on INTErventional device ReSearch; PASSION CV, Predictable and SuStainable Implementation of National Cardiovascular Registries; PI, principal investigator; NESTcc, National Evaluation System for Health Technology Coordinating Center.

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There are many important factors to consider when examining the impact of the COVID-19 pandemic in the vascular and cardiovascular research space. The evolution of cardiovascular medicine relies on the evidence base that comes primarily from clinical trials, including both interventional and pharmacologic trials. The disruption of these trials may ultimately result in the delay in availability of new medications and devices/interventions for patients with cardiovascular disease. Additionally, trials in cardiovascular medicine typically include both hard clinical endpoints, including major adverse limb events, major adverse cardiovascular events, mortality, and hospitalization, as well as surrogate endpoints (i.e., patient-reported outcomes measures, imaging, and biomarkers) [3–5]. Some of these endpoints may be able to be obtained remotely during a pandemic, but others may require in-person follow-up [6]. As current confirmed cases in the U.S. top 81.3 million with 992,000 deaths with many of the patients previously infected with COVID-19 able to be re-infected or to experience “long-COVID”, there is likely to be significant overlap between COVID-related outcomes and clinical trial outcomes. While randomization would be expected to help mitigate some of the high prevalence of concomitant disease, many of the device trials in the vascular/cardiovascular space are single arm and may be vulnerable to the impact of this overlap. There is increasing evidence that hard clinical endpoints may be particularly vulnerable to COVID-related outcome overlap [7]. Additionally, patients with cardiovascular disease and concomitant COVID-19 infections have been shown to have significantly poorer clinical outcomes [8–10], which may further muddy distinguishing and adjudicating clinical events related to a trial intervention vs. COVID-19. Furthermore, as many vascular trials collect surrogate endpoints relying on physical activity, the reduction in physical activity due to quarantine and/or lockdown could significantly impact these outcomes [11].

Several working groups within the cardiovascular therapeutic area described the early effects of the COVID-19 pandemic on clinical trials within heart failure and structural cardiology. The Heart Failure Collaboratory developed a case report form for heart failure trials to adjudicate COVID-like illnesses [12,13]. The Structural Heart and Valve Working Group have also published guidance for resuming disrupted trials during the pandemic [14]. For cardiovascular intervention studies in coronary artery and peripheral artery disease (CAD and PAD), the impact of the pandemic included not only the ubiquitous risk for both patients and staff of contracting the highly contagious virus, but also the operational issues of substantial reduction in vascular presentations overall—even acute presentations such as acute MI and stroke—and the overlap between study endpoints such as vascular thrombosis and cardiorespiratory distress with the short and long term effects of COVID-19 infections in some patients. The PANDemic Impact on INTERventional device ReSearch (PAIINTERS) working group formed to: 1) identify trials in the coronary and peripheral vascular space that were interrupted because of the COVID-19 pandemic, 2) examine how trial progression and enrollment was impacted by the disruption; and 3) describe mitigation strategies and the status of these trials one year since the first surge of the pandemic.

2. Methods

The PAIINTERS working group convened in May 2020 to discuss how trials involving coronary and peripheral vascular devices had been disrupted during the COVID-19 pandemic, and what mitigation strategies had been used to foster patient and staff safety, as well as to preserve the integrity and interpretability of the evidence collected regarding device benefit/risk and safety. The group was configured across the PASSION CV community, a pre-competitive collaborative public private partnership [15], including academic clinicians and trialists, industry and Federal agency experts on cardiovascular devices. PASSION CV is actively conducting demonstration programs for the National Evaluation System for health Technologies (NEST) [16] leveraging complementary interoperable real work networks [17] in

cardiovascular devices including heart failure, heart valves, peripheral and coronary intervention. For this pandemic task force focused on vascular interventions, the RAPID and SAFE STEMI Demonstration Programs [18] were conjoined to provide an ecosystem perspective on the landscape of vascular device trials, their status and related issues of all kinds in the setting of COVID-19.

The working group created a comprehensive list of trials from the following treatment areas within cardiovascular medicine: acute coronary syndromes, interventional cardiology, peripheral vascular medicine, and device trials related to interventional and peripheral vascular medicine. Within each therapeutic area, we selected trials for use cases based on the point during the trial in which it was interrupted. We described trial use cases according to the following points of trial disruption: trial activation and start-up phase, early enrollment phase, late enrollment phase, and post-enrollment follow-up phase. We define the list of trial features examined in Table 1. Information about trial disruption was obtained from clinicaltrials.gov, as well as from individuals within the working group who are actively involved or engaged in trial activities. A comprehensive list of trials was then included in Table 2 to describe all trials recognized by the working group as having been interrupted during the COVID-19 pandemic. Fig. 1 illustrates a schema of major challenges in vascular intervention trials during the COVID-19 pandemic.

3. Results

3.1. SAFE STEMI for Seniors

A Study of Access Site for Enhancing PCI in STEMI for Seniors (SAFE STEMI for Seniors Trial) is a combined single-arm (single vessel STEMI) and randomized (STEMI with multi-vessel CAD) protocol within a senior population of patients presenting with STEMI treated with PCI in a “radial first” design. The protocol includes two investigational device exemption (IDE) components as labelling extensions for the Philips iFR diagnostic wire STEMI with MV CAD and for the Medtronic Onyx DES for STEMI [19]. The trial is planned to enroll 875 seniors at 70 sites. Enrollment was interrupted in April of 2020, at which time there were 137 patients enrolled. At the one-year mark after trial disruption, five sites had stopped performing clinical research and thus did not opt to restart enrollment, and three new sites had been activated. By April 2021, 201 patients had been enrolled. COVID-19 infection documentation was incorporated into the case report form, and adjudication rules now included evidence of a COVID-19 infection in conjunction with adjudicated endpoints. The 30-day clinic follow-up visit was changed to a remote visit. The 1-year pivotal endpoint visit was originally designed using centralized phone contact by the research organization, so no revisions of this critical follow up process were necessary. The twice-yearly investigator meetings (typically held at TCT or SCAI) were replaced by monthly zoom calls. Even though most sites are reporting more and earlier acute presentations than one year ago, numbers are still generally seen as lower than pre-pandemic. Despite this trend, during the first quarter of 2021, the trial has experienced brisk enrollment with an enrollment trajectory greater than the pre-pandemic enrollment. This has been attributed to the enthusiasm for “anything but COVID” attitude conveyed on the monthly Zoom meetings. To date, there are no AEs or SAEs related to COVID-19, and while a number of aspects of the study SAP are under discussion, no specific changes have yet been adopted.

3.2. Eclipse

The Evaluation of Treatment Strategies for Severe Calcific Coronary Arteries: Orbital Atherectomy vs. Conventional Angioplasty Technique Prior to Implantation of Drug-Eluting StEnts (ECLIPSE) trial is a 2000 patient multicenter randomized controlled trial with 2 year clinical follow-up comparing an orbital atherectomy-based strategy to

Table 1
Trial features examined for each CAD and PAD trial.

Trial recruitment	Trial management	Follow-up management	Statistical analysis
Planned enrollment	Management of study visits (remote study visits allowed for patient follow-up?)	Management of LTFU	Adjustment of SAP to allow for COVID-19 impact?
Trial Enrollment Disruption	Were remote visits allowed for interaction between trial leaderships and site leadership?	Management of missing data	Changes to enrollment targets made?
Pre- and post-enrollment	Impact on Budget?	Are there elements of follow-up that cannot be completed if follow-up visits remote?	
Enrollment Stage	For terminated trials, reasons for decision to terminate		

conventional balloon-based strategy to treat severely calcified coronary arteries [20]. The first patient was randomized on March 27th, 2017. In early 2020, with just over two thirds of the anticipated number of subjects enrolled, the COVID-19 pandemic struck. In order to preserve personal protective equipment and to limit hospital and research personnel and catheterization laboratory staff exposure, the trial steering committee and study sponsor recommended suspending enrollment in the ECLIPSE trial on March 20, 2020. All follow-up visits were transitioned to phone/telehealth, and a remote site monitoring program was initiated. Several additional fields were added to the trial case report forms in order to capture antecedent COVID-19 infections.

After several months of observation, the trial was cautiously re-initiated at selected sites in October 2020. Continued modifications have been made to study processes, and patients enrolled within the trial as well as study teams have no doubt been affected by the pandemic. Despite a randomized study design which could balance pandemic-related effects across trial arms, the impact of the pandemic upon enrollment, follow-up, and outcomes (for example, if a patient were to have severe COVID-19 related illness), is yet to be determined. Notably, while both study arms use approved devices, clinical field support is sometimes used for cases of atherectomy, and limitations to clinical support likely further restricted enrollment.

3.2.1. PIONEER III

PIONEER III is a prospective global randomized IDE clinical trial assessing the safety and efficacy of the BuMA Supreme Biodegradable Drug Coated Coronary Stent System for coronary revascularization in patients with stable coronary artery disease or non-ST-segment elevation ACS [21]. From October 2017 to July 2019, a total of 1629 patients were recruited from North America (50.1 %), Europe (39.9 %) and Japan (10 %), and randomly assigned to Supreme DES (1086 patients) or durable polymer everolimus-eluting stents (DP-DES, 543 patients). Enrollment was completed prior to the pandemic's start. Due to the timing of enrollment, the primary impact of the COVID-19 pandemic has been on subject follow-up. As of March 1, 2020, approximately 76 % of study subjects had passed the 12-month (± 30 days) follow-up window, with the remaining 24 % of subjects scheduled to complete this follow between March and July 2020. On March 26, 2019, the protocol was amended to permit telephone or virtual follow-up visits at 12 months, in addition to the previously mandated clinic visits. The study monitoring plan was also adjusted to a tiered approach based on site accessibility to in-person monitoring, incorporating both remote source data monitoring and remote data verification. One-year follow-up was completed on July 9, 2020 in 96.9 % (1036/1069) of Supreme DES and 98.3 % (521/530) of DP-DES groups. All subsequent follow-up from 2 to 5 years will be by phone contact, with the caveat the subjects who underwent phone follow-up at 1 year are asked to return to clinic if possible. Regarding data analysis, the Clinical Events Committee re-adjudicated all endpoint events based on relationship to COVID-19, and the electronic Case Report Form was modified to capture protocol deviations as related to COVID-19 to support separate reporting of these events. In addition, reporting of COVID-19 related study disruptions and sensitivity analyses to evaluate the effect of the COVID-19 pandemic on study results were agreed upon with the US FDA. Despite all these changes follow-up was completed in window without delay.

3.2.1.1. Peripheral artery disease trials

3.2.1.1.1. SAVAL (mid phase enrollment trial). The SAVAL Trial (The Drug Eluting Stent Below the Knee Vascular Stent System vs. PTA in Subjects with Critical Limb Ischemia) began enrolling patients in August 2018 with an anticipated completion date of July 2021 [22]. The targeted enrollment was 301 patients with 201 randomized in a 2:1 fashion in the first phase (SAVAL: PTA). In a second non-randomized phase, an additional 100 patients will be enrolled to receive the SAVAL device BTK. Enrollment was never officially paused during the study, but recruitment was delayed by several months when compared to the targeted schedule. Patient visits, for the most part, continued in person, and when not possible, have occurred virtually. This transition resulted in missing datapoints in some cases. As of one year from March 2020–March 2021 there had been a 30 % reduction in the trial enrollment rate. There had also been an increase in the overall trial budget because of extended timelines and fees to assist research centers in establishing remote source review capabilities. Trial leadership noted that it was critical to have SAPs that addressed how to handle missing data and to closely monitor primary endpoint data that requires imaging to ensure that missing data will not impact primary statistical analyses.

3.2.1.1.2. BEST-CLI (post-enrollment trial). The Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI), funded by the NHLBI, examined an open surgical vs. endovascular management for the treatment of patients with CLI [23]. The trial started in August 2014 with a targeted enrollment of 2100 patients with expected follow-up of 24 months. The trial completed enrollment prior to the onset of the pandemic, but there were some notable fluctuations in patient follow-up during the pandemic. In March 2020, the trial was in its sixth month of a planned 24-month follow-up period. At peak enrollment there were 135 active sites. As sites completed follow up for last patient(s) enrolled, by April 2020 there were 107 active sites, and by mid-April 2021, 105 active sites. However, at the end of 2020, trial leadership determined that the lost-to-follow-up rate (LTFU) was unacceptably elevated. After extensive efforts during the first five months of 2021, over 20 % of the previously consider LTFU patients were identified through vital status and events data. Additionally, during the pandemic, the trial pivoted to site visits with PIs occurring completely via Zoom or by telephone. While some aspects of the patient's follow-up were difficult to obtain virtually, vital status and amputation status were easy to record through virtual platforms. Patient visits and follow-up occur either virtually or in-person based on clinical need or patient preference.

3.2.1.1.3. Torus 2. Torus 2 Study is an IDE examining the safety and effectiveness of the Torus Stent Graft System for the treatment of obstructive lesions of the superficial femoral or proximal popliteal arteries. Enrollment began in November of 2019 and was anticipated to be completed in March 2021 [24,25]. The total sample size is 188 subjects. Enrollment was not interrupted by trial leadership, but it slowed as elective cases were canceled or placed on hold, particularly as patients coming in for revascularization of intermittent claudication were deemed non-urgent. Once elective cases resumed in May and June 2020, enrollment started to improve. Unfortunately, with the second wave in the fall, cases for claudicans were again put on hold, resulting in a recurrence of slow enrollment. As of March 2020, seven patients had been enrolled. Between March 2020–April 2021, the trial enrolled

Table 2
Trials in the coronary or peripheral vascular therapeutic areas that were interrupted during the COVID-19 pandemic.

Trial	Sponsor	Study population	Study design	Planned enrollment	Enrollment stage	Number of sites	Duration of follow-up	COVID interruption date	Enrollment resumption date
Coronary and ACS trials									
COBRA REDUCE	CeloNova Biosciences	Patient on oral anticoagulant undergoing PCI due to stable/unstable angina or NSTEMI	RCT	996	Late-phase enrollment	60	6 months primary, 12 months overall	March 2020 (enrollment never stopped)	May 2020
HARMONEE	OrbusNeich Medical	Ischemic heart disease	RCT	572 subjects		50	12 months	Enrollment was not interrupted	N/A
AEgis-II	CSL Behring	Post-ACS patients	RCT	17,400 subjects			4 years	Paused enrollment in March 2020	Summer-Fall 2020
SAFE-STEMI	Medtronic, Philips, Terumo	STEMI patients	RCT	875 subjects	Mid-phase enrollment		1 year	Paused enrollment in March–April 2020	Summer-Fall 2020
ReVEAL iFR	Philips	Patients undergoing coronary angiography	Observational, prospective	450 subjects		35		March 2020	May 2020
iMODERN	Philips	STEMI patients	RCT	1146 subjects		40	1 year	March 2020 (enrollment was not interrupted)	May 2020
ECLIPSE	CSI	Calcified coronary lesions	RCT	2000 subjects	Mid-phase enrollment		2 years	March 2020	October 2020
XIENCE 90/28	Abbott	Patients with high bleeding risk	Non-randomized, single group assignment			100	12 months	March 2020 (enrollment was not interrupted)	N/A
Ilumien IV	Abbott	High-risk patients or patients with complex lesions	RCT	3656 subjects		125	2 years	March 2020 (enrollment was not interrupted)	N/A
Peripheral vascular trials									
SAVAL	Boston Scientific	Critical limb ischemia- Rutherford 4–5	Phase III RCT	Phase A- 201 subjects, Phase B- 100 subjects		44	6 months	Enrollment slowed but never stopped	Enrollment continued throughout but was slowed
EMINENT	Boston Scientific	Claudication	RCT	750 subjects		60	12 months	Enrollment slowed but never stopped	Enrollment. Continued (though slowed) until 775 patients enrolled June 2020
ILLUMENATE-BTK	Philips	Occlusive BTK PAD	RCT	354 subjects		31	6 months	March 2020 (enrollment never stopped)	March 2020
TANGO	Mercator MedSystems	Rutherford 3–5 BTK PAD	RCT	100 subjects	Terminated	7	6 months primary, 12 months overall	March 2020	Not resumed
TAP-DANCE	Mercator MedSystems	Rutherford 2–4 fem-pop PAD	Open label study without randomization; Serial cohorts, single arm	60 subjects	Terminated	10	12 months primary, 60 months overall	March 2020	Not resumed
BEST-CLI	NHLBI	Critical Limb Ischemia	Prospective, randomized, multidisciplinary, controlled, superiority trial	2100 subjects	Post-enrollment	174	24 months	Enrollment ended prior to COVID-19 pandemic	N/A
LIFE-BTK	Abbott	Critical Limb Ischemia	RCT	225 subjects	Early phase enrollment	45	6 months primary endpoint	Enrollment started in August 2020	Enrollment. Started in August 2020
PROMISE II	LimFlow	Critical Limb Ischemia (Rutherford 5/6)	Single group assignment, prospective multi-center pivotal study	120 subjects		20	6 months primary; 3 year follow-up	Enrollment slowed but never stopped	Enrollment continued throughout but was slowed

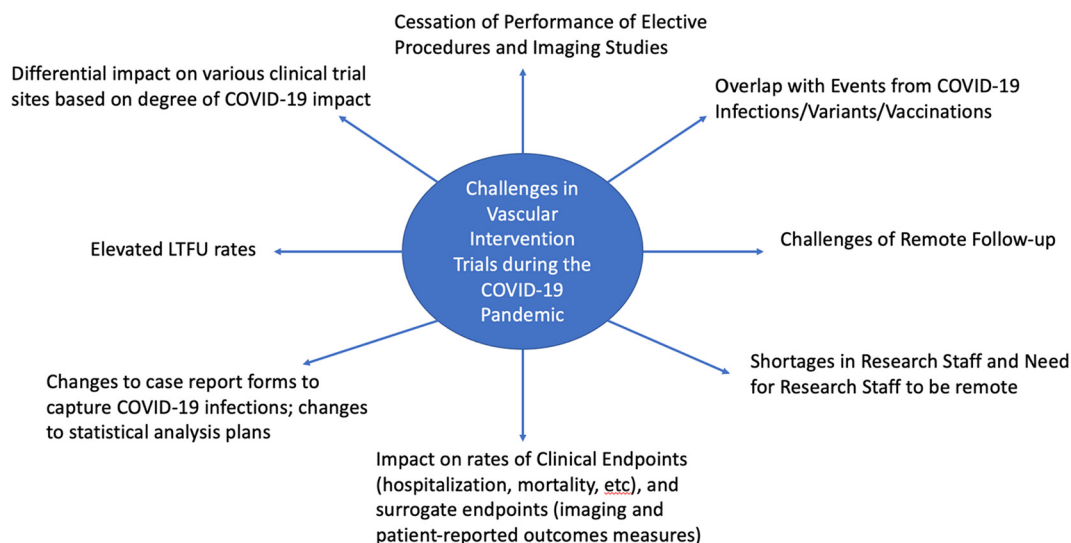


Fig. 1. Major challenges faced by vascular intervention trials during the COVID-19 pandemic.

114. More recently, there has been an increase in screen failures due to more severe disease.

Follow-up visits were not significantly impacted. Overall, subjects returned to the office for their follow-up visits; however if a subject was not comfortable returning for their follow-up visit, telehealth or phone visits were allowed. Many sites did not allow for onsite monitoring visits, resulting in remote monitoring visits. There has been an impact on budget due to the delay in enrollment and due to the costs of remote monitoring visits. There is an ongoing review of data to assess any impact to primary safety and effectiveness endpoints. Language was added to the SAP regarding potential missing data points as a result of the COVID-19 pandemic.

3.3. TAP-DANCE

The Temeirolimus Alone or Paired with Dexamethasone Delivered to the Adventitia to Enhance Clinical Efficacy after Femoropopliteal Revascularization (TAP-DANCE) is an open-label study examining the adventitial deposition of temeirolimus with vs. without dexamethasone in maintaining luminal patency in patients with moderate or severe claudication or critical limb ischemia [26]. Drug is delivered via the FDA cleared Bullfrog® Micro-Infusion Device, a system designed to inject therapeutic agents directly, and safely through blood vessel walls into adventitial tissues. The study start date was October 1, 2019 with a targeted primary completion date of December 31, 2020. At the time of disruption in March 2020, the trial had only enrolled 11 subjects. It was ultimately decided by the sponsor not to reactivate the trial.

4. Discussion

In this analysis of vascular intervention trial disruption due to the COVID-19 pandemic from March 2020 through April 2021, the PAIINTERS working group examined 17 multicenter trials in various phases of trial enrollment. Trials that were least impacted (in terms of impact on enrollment, completion of the trial, and/or follow-up) included those that were nearing the close of enrollment or were in follow-up, such as the BEST-CLI trial. Trials that were not able to pivot to virtual site and patient follow-up visits were more heavily impacted as many hospitals and health systems heavily restricted in-person research practices, particularly during the first six months of the pandemic. Additionally, trials that enrolled patients for procedures deemed elective (i.e., patients with intermittent claudication undergoing revascularization – Torus trial) were impacted by the pandemic, as most health systems limited elective cases during the peak waves of the

pandemic. The factors associated with successful completion and/or progression of trials despite the pandemic, included an advanced phase of enrollment, a seamless change to virtual site and patient visits or to flexible site-specific or “patient preference” strategies, and lack of reliance on performance of mostly elective procedures as a part of trial practices.

From this use-case overview, we demonstrated that a primary factor across these vascular intervention trials that determined the likelihood of resumption was not only whether enrollment was formally interrupted, but the phase of enrollment during which they were disrupted by the pandemic surge. While not included in our use case overview, there is evidence that trials in the process of start-up in early 2020 were disproportionately subject to substantial delay or termination as the pandemic surged [27,28]. Some trials that were in the early-mid phase of enrollment continued to enroll while others decided to interrupt completely, but in both cases slowed enrollment later in the year was widely experienced. With revenue losses at many sites from restricted urgent-only services, staffing shortages as research staff were detailed to front-line clinical settings, and other budgetary constraints, several trials that resumed enrollment lost previously activated sites that were focused on projects/studies that had the highest margins or required less of their research staff (SAFE STEMI). There has been increasing guidance on how these issues have been managed during pandemic surges [29].

Even more than trials in other clinical cardiovascular spaces, trials in the device space or that focus on procedures were particularly disrupted during the pandemic [28]. More than 80 % of trials in the vascular clinical space were disrupted or not started due to mandated institutional shutdowns and patient concerns for direct interaction with the health system [28]. Many sites paused or completely stopped performing elective procedures for months beginning in March–April 2020 to limit patient exposure [30], as well as to open up bed capacity to ensure that hospitals had capacity to manage COVID-infected patients. Trials, such as ECLIPSE, found resumption at certain sites challenging due to limitations in scheduling elective, outpatient procedures. Device- or procedural-based trials needing imaging (i.e. follow-up echocardiograms or lower extremity doppler ultrasound or CT) or ABI performed on follow-up were more limited in the degree to which virtual follow-up could be utilized [31]. Patients with PAD, for instance, may be able to describe symptoms or fill out PROs on their disease state, but virtual visits limit performing an assessment of lower extremity pulses or ulcers. Additionally, many trials often require imaging or clinical evaluation above the standard of care as a part of the eligibility criteria. If these studies were limited due to staffing shortages or institutional

mandates, this would either limit patient enrollment or halt trial enrollment at the site.

The impact on follow-up for many of the trials in the vascular interventions space was also challenging. Many institutions developed restrictions on the performance of elective and non-urgent vascular and coronary procedures to protect both the workforce and vulnerable patient populations [32]. Many patients with vascular disease are at the highest risk for COVID-related complications, and many of these patients were hesitant to present for in-person follow-up for research purposes during the pandemic. Indeed, in a survey of over 5000 adults, over 40 % reported having delayed or avoided seeking medical care because of fear of exposure to COVID-19 [33]. There are several publications with recommendations on how to remotely adapt clinical trials during the pandemic [34,35]. For example, the BEST-CLI was disrupted during follow-up and experienced a higher-than-expected LTFU rate. Fortunately, this elevated LTFU rate was largely resolved with increased and continued searches of vital status and other event records.

Many of the vascular interventions trials had to quickly adjust policies around site monitoring, and pivot to avoid impact of COVID-19 on data collection and CEC adjudication [6,36,37]. PIONEER allowed for tiered site monitoring to allow for sites in various regions that may have been experiencing either an increase or decrease in COVID-19 positivity to flex to remote monitoring when needed. Trials also had to quickly build in data regarding COVID-19 infection into the case report form, particularly to document concomitant positivity with a vascular endpoint or event [6]. As there is an increased risk of thrombotic complications from COVID-19 infections [38,39], it is necessary to be able to discern events related to trial interventions from events related to a COVID-19 infection. Adding to the complexity of adjudicating clinical events during the pandemic was the additional uncertainties about how the vaccine, booster, and various variants might impact clinical event rates differentially [40,41]. It is clear, however, that for most device/vascular trials performed during the pandemic, and even now, that these trials were not just device trials, but device and COVID-19 trials.

While there have been discussions for most of the vascular trials around statistical analysis plans (SAPs), formal decisions have not been made for any yet. The FDA has published guidance for statistical considerations for trials disrupted during the pandemic [42]. For the PIONEER trial, there was a decision made, in conjunction with the FDA, to conduct sensitivity analyses to evaluate the effect of the COVID-19 pandemic on study results. Undoubtedly, all trials in this space conducted during the pandemic will require additional analyses to determine if event rate and outcomes significantly differed during the pandemic as compared with either before or after the pandemic.

4.1. Future uncertainties

While we have highlighted areas where many vascular interventions trials were able to pivot and adapt to the challenges created by the COVID-19 pandemic, there remains uncertainties around certain aspects of trial data quality, follow-up, and event adjudication. There is increasing evidence that COVID-19 may have long-term effects on the cardiovascular and pulmonary systems, making vascular event adjudication more difficult. Additionally, it is difficult to know what impact the COVID-19 vaccine and subsequent boosters could have on outcomes in vascular clinical trials. Additionally, with new variants of COVID-19, we may continue to see surges around the U.S. and the world that require continued trial flexibility. Many concerns remain regarding the impact of the pandemic and remote monitoring on actual data quality. Uncertainties also remain around final adjustments to SAPs and true impact of the pandemic on event rates, LTFU, and appropriate event adjudication.

4.2. Conclusions

In an overview of 17 interventional CAD and PAD trials profiled for 1 year from the March 2020 pandemic surge, we observed many areas

where trials were impacted and disrupted. Most commonly, trials that were just being initiated or were early in enrollment were most impacted in terms of trial continuation and completion. While many trials were able to quickly pivot to remote monitoring, remote monitoring limited some data collection and follow-up required for several of the interventional trials. While there is ongoing discussion about adjustments to SAPs as a result of the pandemic, what these adjustments will ultimately entail remains unknown at this time.

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