



Operational challenges and mitigation measures during the COVID-19 pandemic—Lessons from DELIVER

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Background Catastrophic disruptions in care delivery threaten the operational efficiency and potentially the validity of clinical research efforts, in particular randomized clinical trials. Most recently, the COVID-19 pandemic affected essentially all aspects of care delivery and clinical research conduct. While consensus statements and clinical guidance documents have detailed potential mitigation measures, few real-world experiences detailing clinical trial adaptations to the COVID-19 pandemic exist, particularly among, large, global registrational cardiovascular trials.

Methods We outline the operational impact of COVID-19 and resultant mitigation measures in the Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial, one of the largest and most globally diverse experiences with COVID-19 of any cardiovascular clinical trial to date. Specifically, we address the needed coordination between academic investigators, trial leadership, clinical sites, and the supporting sponsor to ensure the safety of participants and trial staff, to maintain the fidelity of trial operations, and to prospectively adapt statistical analyses plans to evaluate the impact of COVID-19 and the pandemic at large on trial participants. These discussions included key operational issues such as ensuring delivery of study medications, adaptations to study visits, enhanced COVID-19 related endpoint adjudication, and protocol and analytical plan revisions.

Conclusion Our findings may have important implications for establishing consensus on prospective contingency planning in future clinical trials. Clinicaltrial.gov: NCT03619213.

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Abbreviations: COVID-19, coronavirus disease-2019; ePRO, Electronic Patient Reported Outcome; KCCQ, Kansas City Cardiomyopathy Questionnaire.

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Key points

- The COVID-19 pandemic levied significant challenges in virtually every aspect of clinical trial conduct and affected trial participants who did and did not contract the virus during their participation in DELIVER.
- Flexible and lean study protocols, the ability to rapidly make necessary amendments to statistical analyses plans, and electronic case report forms may have also helped ensure rapid responses to the pandemic.
- Core learnings from this experience may have direct implications for study

sponsors and academic investigators facing future disruptions in clinical trial operations, including but not limited to infectious disease outbreaks, local or international conflict, political turmoil, and economic hardship, among others.

Background

Unexpected disruptions in health care systems may threaten operational efficiency and potentially even the validity of clinical research efforts, particularly randomized clinical trials.¹⁻⁴ Most recently, the coronavirus disease-2019 (COVID-19) pandemic presented significant challenges for the conduct of many cardiovascular clinical trials. Guidance documents have detailed potential mitigation strategies,⁵⁻¹⁰ however, real-world experiences of cardiovascular clinical trial adaptations have generally been limited to smaller trials enrolling in particular regions.^{11,12} Global, registration trials have important attendant regulatory implications; therefore, ensuring the fidelity of trial operations and data collection is exceedingly important. Mitigation measures in such trials may help inform the larger clinical research community. We outline the operational impact of COVID-19 and resultant mitigation measures in the Dapagliflozin Evaluation to Improve the LIVES of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial.

DELIVER and COVID-19

DELIVER was an international, multicenter, double-blind, event-driven clinical trial assessing the safety and efficacy of dapagliflozin 10 mg once daily vs. placebo in 6,263 patients with heart failure and mildly reduced (HFmrEF) or preserved (HFpEF) ejection fraction.^{13,14} Patients with symptomatic heart failure (HF), elevated natriuretic peptides, left ventricular EF > 40%, structural heart disease, and at least intermittent diuretic use were randomized. The primary endpoint was a composite of cardiovascular (CV) death or worsening HF event. The first patient was enrolled on August 27, 2018 and the last patient completed the last visit on March 27, 2022. DELIVER was conducted across 353 centers in 20 countries in North America, Latin America, Europe, and Asia.

Early responses to rising COVID-19 cases

The timeline of events and mitigation measures are outlined in the [Figure 1](#). On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic. At this time, DELIVER was still actively recruiting; the first reported COVID-19 infection in DELIVER was on March 16, 2020, at which time 5,153 (82.3%) of the total trial population had been randomized. Of

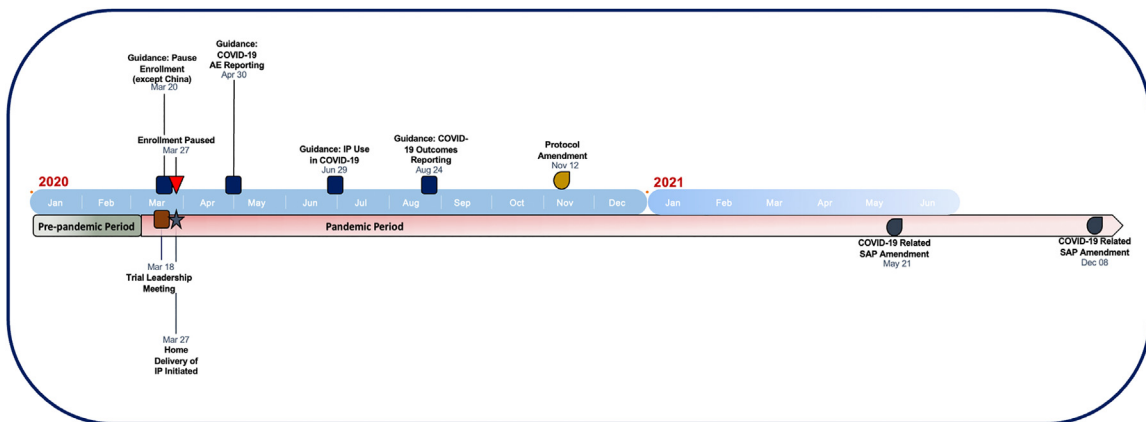
a planned target of 1,117 primary endpoint events 363 (32%) had already occurred, and 168 (3%) patients had died. While much of the trial population had been randomized prior to pandemic onset, most (76%) of total follow-up time (by participant years) occurred during the pandemic period ([Figure 2](#)).

On March 18, 2020, the clinical operations team and the academic executive committee met to discuss efforts to minimize risks to participants, investigators, and clinical trial site staff. On March 20, 2020, trial leadership issued communications to national trial leaders and local study staff indicating sites should pause enrollment; all sites, except those in China (where enrollment was just about to begin and COVID-19 cases were already declining), were instructed to pause enrollment. Enrollment was stopped in all non-Chinese sites on March 27, 2020; randomization continued for patients who had been previously enrolled but not yet randomized in sites which confirmed ability to continue monitoring/follow-up activities. Recruitment restart dates by country are listed in [Table 1](#); screening, recruitment, and screen failures over time is shown in [Figure 3](#).

Delivery and receipt of investigational products (IP)

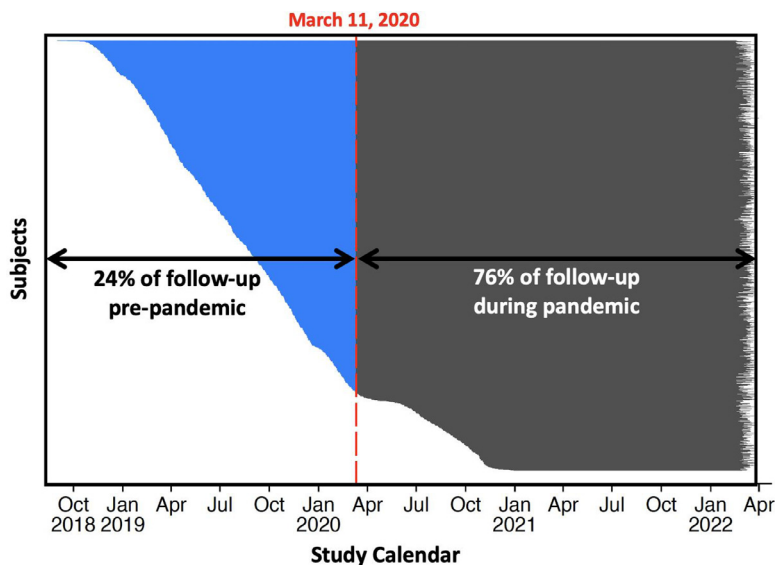
On March 27, 2020, protocols for home delivery of IP were initiated to minimize risk to participants and study staff. Home delivery was available to any clinical trial participant with concerns about coming into a study site to receive IP. A courier vendor was contracted by the sponsor to perform home IP delivery to ensure temperature control, product and data security. Once IP was delivered, a patient had to sign Proof of Delivery. Home deliveries of IP were documented and tracked in an electronic case report form (eCRF); delays in receipt of IP were recorded as nonimportant COVID-19-related protocol deviations. Standard IP returns and drug accountability processes were adapted to ensure assessment of compliance and adherence. For example, participants were initially asked to store used IP bottles at their homes, to be returned to study staff at the next in-person site visit. However, given persistent pandemic conditions and the conversion of study visits to virtual formats, pill count information was collected directly from participants during virtual visits and documented in a drug accountability section of the electronic data capture (EDC) platform. Couriers were dispatched to collect used IP bottles to confirm participant-reported drug accountability; discrepancies between participant-reported compliance and information from collected bottles were noted in the eCRF and patient record. With implementation of these strategies, there were no known cases of missed IP delivery during the pandemic; direct patient delivery was used in at least 16 participating countries. Overall treatment compliance was 79% (80% in those randomized to dapagliflozin and 78% in those randomized to placebo).

Figure 1



Timeline of mitigation activities in DELIVER during the COVID-19 pandemic

Figure 2



Study calendar in relation to the COVID-19 pandemic Legend: This figure shows enrollment through follow-up for each randomized participant in the DELIVER trial. March 11, 2020, corresponds to the date of the World Health Organization (WHO) declaration of COVID-19 as a pandemic.

Compliance rates of >80% were observed in 96% of trial participants.

Study visits and procedures

The original eCRF allowed for remote contacts to collect clinical outcomes and safety events. As the pandemic progressed, remote contact was increased for participants with concerns about on-site visits. Types of visits that were permitted included (1) telephone visits,

(2) home visits, and (3) collection from other contacts (eg, caregiver, physician, medical record review). Missed visits (defined as ± 14 days outside the visit window) rose from 3.9% prior to pandemic onset to 10.2% during the COVID-19 pandemic. Telephone visits increased from 1.8% prior to pandemic onset to 17.6% during the pandemic (Table II). Other visit modalities, including home visits and review of records with a family member/caregiver or a primary/treating physician were used

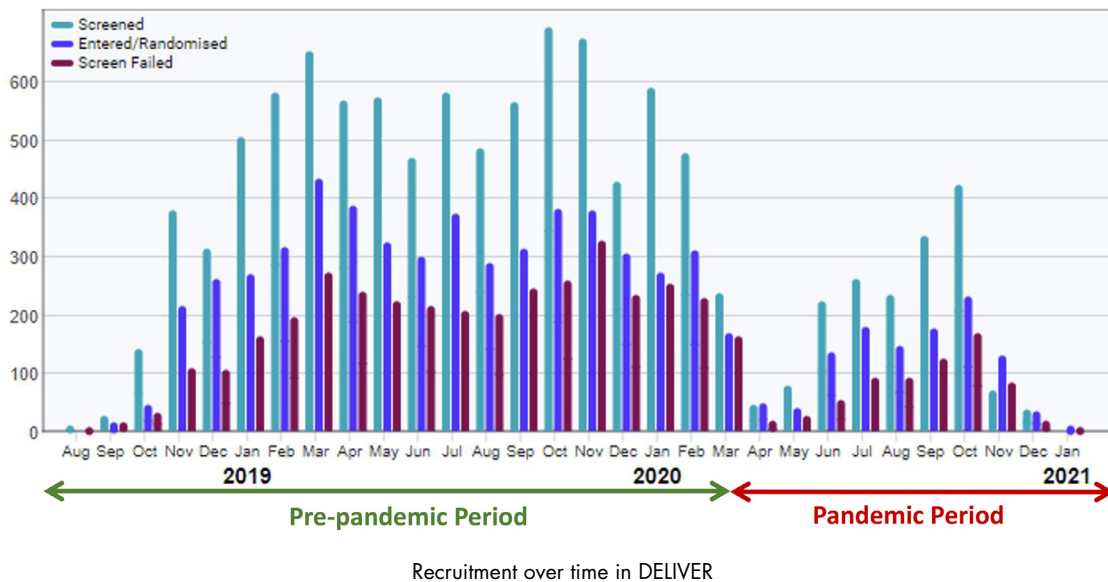
Table I. Recruitment by country in DELIVER during the COVID-19 pandemic

Country	First subject enrolled	Pause date	Restart date	Last subject enrolled	Number of patients randomized before and during the pause / total number of patients randomized (%)
Argentina	12/11/18	3/27/20	6/25/20	10/23/20	275/320 (86)
Belgium	1/22/19	3/27/20	6/8/20	10/14/20	58/64 (91)
Brazil	2/13/19	3/27/20	9/18/20	10/29/20	378/405 (93)
Bulgaria	10/23/18	3/27/20	5/18/20	10/23/20	437/493 (89)
Canada	8/27/18	3/27/20	6/10/20	10/30/20	236/299 (79)
China [^]	3/24/20	-	-	12/30/20	0/310 (0)
Czech Republic	11/6/18	-	-	2/10/20	274/274 (100)
Hungary*	11/27/18	3/27/20	5/18/20	9/29/20	462/466 (99)
Japan	10/15/18	3/27/20	6/1/20	9/14/20	380 /422 (90)
Mexico	7/9/19	3/27/20	5/26/20	10/27/20	137 /216 (63)
Netherlands	10/29/18	3/27/20	6/1/20	10/30/20	136/176 (77)
Peru	11/22/18	3/27/20	7/15/20	10/30/20	201/240 (84)
Poland*	10/15/18	-	-	2/7/20	572/572 (100)
Romania	1/23/20	3/27/20	6/9/20	10/30/20	13/61 (21)
Russia*	10/4/18	-	-	2/4/20	401/401 (100)
Saudi Arabia*	11/7/18	3/27/20	-	3/11/20	190/190 (100)
Spain	11/2/18	3/27/20	5/27/20	10/30/20	252/308 (82)
Taiwan	11/16/18	3/27/20	5/11/20	10/30/20	242/318 (76)
United States	8/29/18	3/27/20	6/5/20	11/6/20	433/552 (78)
Vietnam	1/7/19	3/27/20	5/11/20	10/30/20	158/176 (90)
Total	8/27/18	-	-	12/30/20	5235/6263 (84)

* Countries with completed recruitment before the pause date.

[^] Enrollment was not paused in China and commenced during the COVID-19 pandemic

Figure 3



in a minority of cases prior to and during the pandemic. Findings from monitoring visits and regional differences were not systematically reported or collated across trial sites in the context of this analysis. Missing data for

KCCQ-TSS were balanced between treatment groups, both in the pre-pandemic and in the pandemic periods.

For study visits conducted outside of in-person settings, vital signs and serum creatinine measurements

Table II. Study visits during the COVID 19 pandemic

	Dapagliflozin (N=3131)	Placebo (N=3132)	Total (N=6263)
Planned study visits			
Prepandemic period	6,304	6,328	12,632
Pandemic period	16,359	16,298	32,657
Performed visits, n (% of planned)			
Prepandemic period	6,057 (96.1)	6,057 (95.7)	12,114 (95.9)
Pandemic period	14,745 (90.1)	14,621 (89.7)	29,366 (89.9)
Missed visits, n (% of planned)			
Prepandemic period	233 (3.7)	255 (4.0)	488 (3.9)
Pandemic period	1,628 (10.0)	1,693 (10.4)	3,321 (10.2)
Visit modality, n (% of performed)			
Prepandemic period			
On-site visit	5,915 (97.7)	5,903 (97.5)	11,818 (97.6)
Telephone visit	113 (1.9)	109 (1.8)	222 (1.8)
Others*	29 (0.5)	45 (0.7)	74 (0.6)
Pandemic period			
On-site visit	11,616 (78.8)	11,632 (79.6)	23,248 (79.2)
Telephone visit	2,673 (18.1)	2,497 (17.1)	5,170 (17.6)
Others*	456 (3.1)	492 (3.4)	948 (3.2)

Note: Prepandemic period refers to prior to the World Health Organization's declaration of COVID-19 as a pandemic on March 11, 2020. The pandemic period refers to March 11, 2020, and onward; A visit was included in the time period when it was performed and not when it was planned. Missed visits were defined as \pm 14 days outside the visit window.

* Other visits include home visits and review of records with a family member/caregiver or a primary/treating physician or medical records review and miscellaneous.

were not recorded; these were reported as nonimportant COVID-19-related protocol deviations. The central laboratory remained open and available during the pandemic. In November 2020, in response to delays in receipt of laboratory kits at specific trial sites, procedures were implemented, allowing (1) transfers of laboratory kits between sites and (2) the use of nonstudy-specific laboratory kits. Electronic Patient Reported Outcomes (ePRO) data were allowed to be collected outside of traditional in-person site visits via telephone visits, though ePRO data were not included in the prespecified secondary endpoint analysis of Kansas City Cardiomyopathy Questionnaire-total symptom score (KCCQ-TSS) assessment. Reasons for this included concerns that phone call related capture of KCCQ-TSS would differ from the more validated direct patient report. In addition, the collateral effects of the pandemic were expected to alter global health status among trial participants. Sites received dedicated training and a guide detailing optimal strategies for ePRO collection, which aligned with European Medicines Agencies (EMA) and US Food and Drug Administration (FDA) guidance.¹⁵ The contribution of individual institutional policies or guidelines on remote visit conversion was not systematically available across all trial sites.

Sites were encouraged to schedule on-site study closeout visits, but remote contacts were acceptable if local circumstances or participant preference precluded on-site visits. There were no missed study closeout visits, of which 86.5% were on-site, 10.2% were telephone visits, and the remainder used other platforms. Vital status was available at the end of the study for all but 4 patients, including 1 who withdrew consent.

Endpoint adjudication

Acknowledging the growing contribution of fatal COVID-19 infection to overall mortality in the early months of the pandemic, the steering committee asked the Clinical Endpoint Committee (CEC) in April 2020 to adapt the adjudication process was altered to capture the contribution of COVID-19 illness to deaths occurring during the trial. All deaths, regardless of adjudicated cause, were subsequently adjudicated with regards to their relationship with COVID-19. Deaths as a direct consequence of COVID-19 or those in which COVID-19 was a major contributor to death were classified as “definitely” COVID-19 related. “Definite” cases had symptoms, signs, and clinical trajectory typical of COVID-19 infection in association with confirmatory laboratory testing or diagnostic imaging. Cases in which there was high clinical suspicion for COVID-19 infection in the absence of confirmatory testing were classified as “possibly” COVID-19 related. To ensure consistency in assigning the contribution of COVID-19 to death, all deaths that were potentially related to COVID-19 were reviewed in committee meetings and adjudicated by consensus. As well, all deaths adjudicated prior to the update of the CEC charter were rereviewed by the CEC Chairs to retrospectively assign any possible contribution of COVID-19 to death. Relatedness to COVID-19 for HF hospitalizations was not formally adjudicated.

COVID-19 adverse event reporting

COVID-19 infections were requested to be reported as SAEs. Recording of COVID-19 testing results from Visit 2 onwards was added to safety assessments; the type and results of tests were added to the eCRE COVID-19 diag-

Table III. COVID-19-related protocol deviations

	Number of participants (%)		
	Dapagliflozin (N=3131)	Placebo (N=3132)	Total (N=6263)
COVID-19-related important protocol deviations			
≥ 1 important deviation	4 (0.1)	1 (0.0)	5 (0.1)
Failed inclusion criteria	1 (0.0)	–	1 (0.0)
Fulfilled exclusion criteria	–	1 (0.0)	1 (0.0)
Received IP not allocated by randomization	1 (0.0)	–	1 (0.0)
Other important deviations	2 (0.1)	–	2 (0.0)
COVID-19-related nonimportant protocol deviations			
≥ 1 nonimportant deviation	1,270 (40.6)	1,301 (41.5)	2,571 (41.1)
Study procedures and assessments	1,147 (36.6)	1,163 (37.1)	2,310 (36.9)
Visits performed outside ± 14-day window	384 (12.3)	424 (13.5)	808 (12.9)
SAE reported > 24 hours after awareness	42 (1.3)	45 (1.4)	87 (1.4)
Inappropriate ICF administration	41 (1.3)	28 (0.9)	69 (1.1)
Study sample management	6 (0.2)	10 (0.3)	16 (0.3)
Incomplete AE/SAE reporting	5 (0.2)	4 (0.1)	9 (0.1)
Nonimportant inclusion/exclusion criteria deviation	2 (0.1)	3 (0.1)	5 (0.1)
Inappropriate concomitant medication use	–	2 (0.1)	2 (0.0)

Relatedness to COVID-19 determined by investigators.

AE, Adverse events; COVID-19, Coronavirus disease 2019; ICF, Informed consent form; SAE, Serious adverse event

nosis was investigator reported and based on local regulations; central lab or protocol was not specified. Furthermore, adverse event reporting included data collection of the COVID-19 events resulting in or prolonging hospitalization and COVID-19 events with a fatal outcome. On June 29, 2020, the executive committee issued guidance to sites regarding using sodium-glucose cotransporter 2 inhibitors (including IP) in patients at risk for COVID-19 infections. Investigators were recommended to consider interruption of IP in patients at risk or with COVID-19 who had diabetes and known DKA risk factors or prior DKA. Sites were instructed to continue IP in patients with or at risk for COVID-19 who were nondiabetic patients and without risk factors for DKA. Diabetic ketoacidosis was collected as an adverse event throughout the study, including during or following COVID-19 event; an independent DKA adjudication committee reviewed all potential cases. There were no adjudicated cases of DKA among trial participants who developed COVID-19 during DELIVER in either study arm.

Adaptations to the statistical analysis plan (SAP)

There were 4 SAP amendments (November 6, 2020, December 9, 2020, May 21, 2021, and December 8, 2021) during the pandemic prior to unblinding; 2 SAP amendments were specifically COVID-19 related. On May 21, 2021, an SAP amendment redefined the population considered for prespecified analysis of the impact of therapy on Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS) as those participants with planned or completed 8-month assessment prior to March 11, 2020. The SAP amendment on December 8, 2021 (prior to unblinding), instituted a formal COVID-19 sensitivity analysis, evaluating the effect of therapy on

the clinical endpoints in the full study population with censoring at the time of the first recorded AE associated with COVID-19.

Protocol deviations related to COVID-19

Protocol deviations related to COVID-19 were defined and determined to be either important or nonimportant. Important COVID-19-related protocol deviations included randomization despite failing inclusion criteria and receipt of different IP than allocated by randomization, which each occurred in one trial participant. Important COVID-19-related protocol deviations occurred infrequently, affecting only 5 (0.1%) trial participants. Nonimportant COVID-19-related protocol deviations included visits outside the ± 14-day window and serious adverse event (SAE) reporting >24 hours of awareness, among others. Nonimportant COVID-19-related protocol deviations were common, affecting 2,571 (41.1%) trial participants; relatedness to COVID-19 was based on sponsor-led monitor reporting. The most common reason for a nonimportant COVID-19 protocol deviation was missed study procedures and assessments, occurring in 2,310 (36.9%) trial participant. Nonimportant COVID-19 related protocol deviations were balanced by treatment assignment (Table III).

Site monitoring

Risk-based monitoring continued during the pandemic; on-site monitoring was frequently replaced by remote monitoring due to pandemic-related challenges to conducting on-site visits. In addition, centralized monitoring activities were increased to evaluate completeness of adverse event reporting and assessments of study drug compliance. There were instances where video confer-

encing capabilities were implemented in addition to accessing source documentation from electronic medical records. The trial sponsor ensured privacy remained in accordance with local regulations. Appropriate informed consent was obtained from trial participants to ensure privacy of participant data when sharing via electronic means instead of in-person study visits. As on-site monitoring resumed, priority items included ensuring appropriate documentation of informed consent and primary efficacy and safety endpoint documentation.

Conclusions

The COVID-19 pandemic levied significant challenges in virtually every aspect of clinical trial conduct and affected trial participants who did and did not contract the virus during their participation in DELIVER. Prior reports have indicated post hoc analyses or changes in statistical analysis plans describing the impact of the pandemic on clinical events and treatment effects^{11,16}; however, to our knowledge, this represents one of the first and largest descriptions of comprehensive responses to a global pandemic in the context of a large, multinational cardiovascular randomized clinical trial. Early mitigation strategies focused on the safety of trial participants and study staff, while maintaining the study integrity. Ensuring timely delivery of IP to participants, maintaining drug accountability, and ascertaining the effects of the pandemic on data collection and analyses minimized the impact of the pandemic on threatening the validity of clinical trial findings; vital status was known at the end of the trial in all but 2 patients in the dapagliflozin group and 2 patients in the placebo group. Furthermore, flexible and lean study protocols, the ability to rapidly make necessary amendments to statistical analyses plans, and electronic case report forms may have also helped ensure rapid responses to the pandemic. In addition, prospective attempts to improve flexibility in statistical analyses, including the use of adaptive clinical trial platform with prespecified action plans in response to changes in enrollment and event rates, may help make trials more resilient. The emerging use of technology and remote-based operational aspects may have important implications for the design and conduct of future clinical trials, particularly those operating under fully virtual protocols. Of note, many of mitigation efforts in DELIVER were reactive to the unique, unexpected demands of the pandemic. Moving forward, core learnings from this experience may have direct implications for study sponsors and academic investigators facing future disruptions in clinical trial operations, including but not limited to infectious disease outbreaks, local or international conflict, political turmoil, and economic hardship, among others. Codifying successful strategies and establishing consensus across study sponsors, academic investigators, and regulators on important mitigation features that can be

prespecified in clinical trial design may aid in prospective contingency planning for future clinical trials.

Conflict of Interest

ASB has no relevant disclosures to the content of this manuscript. **DL** was an AstraZeneca employee when the DELIVER trial was conducted, **AN**, **NZ**, **AML**, and **MP** are employees and shareholders of AstraZeneca. **BLC** has received consulting fees from Amgen, Cardurion, Corvia, and Novartis. **MV** has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, speaker engagements with AstraZeneca, Novartis, and Roche Diagnostics, and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. **MNK** has received research grant support from AstraZeneca, and Boehringer Ingelheim; has served as a consultant or on an advisory board for Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Sanofi, Pharmacosmos and Vifor Pharma; has received other research support from AstraZeneca; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. **CSPL** is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Actelion, Allevant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., EchoNous Inc, Eli Lilly, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd., Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder & non-executive director of Us2.ai. **AFH** has received research grants from American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Somologic and Verily; and has served as a consultant or on the Advisory Board for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Eidos, Intercept, Merck, and Novartis. **FAM** has received consultation fees and research grants from: AstraZeneca, Baliarda, Bayer, Boehringer Ingelheim, Bristol Meirs Squibb, Gador, Milestone, Novartis, Pfizer, and St Lukes University. **SEI** has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lexicon, Merck, Pfizer, vTv

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