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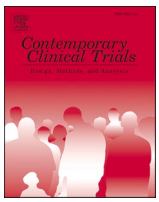

The impact of COVID-19 on a large pragmatic clinical trial embedded in primary care

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ABSTRACT

Introduction: The COVID-19 pandemic had significant impact on clinical care and clinical trial operations, but the impact on decentralized pragmatic trials is unclear. The Diuretic Comparison Project (DCP) is a Point-of Care (POC) pragmatic trial testing whether chlorthalidone is superior to hydrochlorothiazide in preventing major cardiovascular (CV) events and non-cancer death. DCP utilized telephone consent, data collection from the electronic health record and Medicare, forwent study visits, and limited provider commitment beyond usual care. We assessed the impact of COVID-19 on recruitment, follow-up, data collection, and outcome ascertainment in DCP.

Methods: We compared data from two 8-month periods: Pre-Pandemic (July 2019–February 2020) and Mid-Pandemic (July 2020–February 2021). Consent and randomization rates, diuretic adherence, blood pressure (BP) and electrolyte follow-up rates, records of CV events, hospitalization, and death rates were compared.

Results: Providers participated at a lower rate mid-pandemic (65%) than pre-pandemic (71%), but more patients were contacted (7622 vs. 5363) and consented (3718 vs. 3048) mid-pandemic than pre-pandemic. Patients refilled medications and remained on their randomized diuretic equally (90%) in both periods. Overall, rates of BP, electrolyte measurements, and hospitalizations decreased mid-pandemic while deaths increased.

Conclusions: While recruitment, enrollment, and adherence did not suffer during the pandemic, documented blood pressure checks and laboratory evaluations decreased, likely due to fewer in-person visits. VA hospitalizations decreased, despite a considerable number of COVID-related hospitalizations. This suggests changes in clinical care during the pandemic, but the limited impact on DCP's operations during a global pandemic is an important strength of POC trials.

Clinical Trial Registration: NCT02185417

Abbreviations: DCP, Diuretic Comparison Project; POC, Point of Care; VA, Veterans Affairs; SBP, Systolic blood pressure; EHR, Electronic health record; CMS, Centers for Medicare & Medicaid Services; ORD, VA Office of Research and Development; CDC, Centers for Disease Control and Prevention; IRB, Institutional Review Board.

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1. Introduction

In March 2020 the World Health Organization declared the COVID-19 outbreak a global pandemic. The global pandemic has had significant impact on clinical trials. Novel obstacles such as quarantine, travel restrictions, reduced in-patient visits, and unknown medication availabilities have proved difficult for study teams to carry out their protocols [1]. Sponsors and regulatory bodies have scrambled to adapt protocols and change review processes to continue ongoing trials and to initiate others. Many trials were left to delay, terminate or start over to adapt to a new healthcare environment [2]. As a result, the FDA estimates that the pandemic threatened to set non-COVID-19 clinical trial research back by several years [1]. While most traditional trials were left scrambling to adjust protocols and worrying about statistical integrity, the impact on pragmatic embedded Point of Care trials, such as the Diuretic Comparison Project (DCP), is less clear. We aimed to assess the impact of the pandemic on the operations of a pragmatic embedded Point of Care trial.

1.1. Study design

DCP was a pragmatic embedded open-label randomized clinical trial designed to assess the comparative effectiveness of hydrochlorothiazide and chlorthalidone for treatment of hypertension in the prevention of major cardiovascular events. Details of the study design are presented elsewhere [3,4]. In brief, the trial was centrally run and substituted centralized study processes for site-level activities. All engaged research staff were centrally located either at the Boston or Minneapolis VA Healthcare Systems. Specifically, these teams were responsible for: 1) identification of eligible patients using the VA electronic health record system (EHR), 2) centralized recruitment and enrollment, involving permission from the patient's primary care provider, a patient recruitment letter, and informed consent obtained by telephone, 3) centralized randomization, ordering of study intervention and notes using the VA EHR, 4) notifying care teams about how enrolled patients should continue to have usual care, including management of the study drug, and 5) centralized extraction of relevant outcomes and process variables using administrative data sources.

1.2. VA Response to COVID-19

In March 2020, the VA Office of Research and Development (ORD) required all active clinical research studies to limit face-to-face contact for patients, providers, and study staff to decrease risk and hospital burden since COVID-19 care took priority for hospital resources. In July 2020, ORD issued guidance for reactivating research studies, including a list of requirements that a study and its corresponding sites must meet in order to resume study activities. Requirements included a patient COVID-19 screening plan for face-to-face research visits, a plan to continue study protocols remotely (including sending study medications directly to participants and conducting study-specific procedures remotely), plans to decrease face-to-face contact, and local Research and Development Committee approval.

1.3. DCP Response to COVID-19

By design, DCP did not require face-to-face contact, hospital visits, or local staff/provider time. However, on 3/17/2020 the study placed a voluntary administrative hold on participant recruitment in accordance with ORD's cessation of research activities. New recruitment activities were paused until the voluntary hold could be lifted and limit perceived burden on primary care providers during the early months of the pandemic. Routine care of patients (in a reduced capacity in accordance with local medical center policy), and thereby data collection, continued during this time. For Veterans that were consented but not yet randomized on 3/17/2020 an IRB-approved letter was sent explaining that the study would be on hold until the circumstances surrounding the pandemic changed. Additionally, there was a disruption in the availability of certain team members as they were assigned to pandemic efforts elsewhere within their local medical center.

DCP did not resume recruitment until both of its engaged sites were released from ORD's research hold. The study adopted a soft restart on 7/1/2020, re-opening in monitored stages, allowing for site feedback and easy re-initiation of the study hold, if needed. The study began with randomizing patients consented prior to the voluntary hold. Additional study activities were then slowly added including, sending out provider participation requests for all 62 participating sites and sending recruitment materials to new patients. Two weeks later the call center resumed consent calls to eligible Veterans.

The study team actively monitored COVID-19 admissions at recruiting sites using a database jointly managed by the CDC and VA [5]. This dynamic database summarizes active positive cases treated at a VA facility and known COVID-19 deaths by VA medical center. Medical sites in high transmission regions were temporarily held until COVID-19 cases decreased. Recruitment efforts were adjusted in an ongoing way in regions experiencing a surge in COVID-19 cases.

2. Methods

To assess the impacts of the COVID-19 pandemic and associated changes to study activities, we compared data from two time periods: 1) July 2019 – February 2020 (Pre-Pandemic) and 2) July 2020 – February 2021 (Mid-Pandemic). All provider, patient and follow-up metrics were calculated and compared for these two periods.

Consent and randomization rates were calculated as the number of patients or providers that consented or randomized in a given period divided by the number that provided a decision about participation (i.e., consented or declined). If no response was given or a potential participant could not be reached, they were not included in the denominator for these rates. Provider time to consent is calculated as the number of days from receiving a request to participate in DCP through an EHR order to signature of that order.

All follow-up data were extracted from the VA electronic health record. Adherence to study medication was calculated as the proportion of randomized subjects with a refill of study medication, a switch in diuretic, or no diuretic refills in each time period. Rate of blood pressure, serum potassium, and serum sodium follow-up was calculated as the proportion of randomized subjects with a non-baseline measurement during each time period. Outcome and hospitalization rates were calculated in each time period as the proportion of randomized subjects with at least one event.

3. Results

From July 2019–February 2020, seventeen new sites initiated recruitment and from July 2020–February 2021, seven new sites initiated recruitment.

Providers agreed to participate at a lower rate mid-pandemic (65%) than before (71%) but agreed to randomize their patients at the roughly the same rate in the two time periods (Table 1). Providers responded to consent requests in the same amount of time in both periods. One PCP withdrew participation citing COVID-19 as the reason for withdrawal.

Patient availability increased during COVID. The consent callers reached 42% more patients mid-pandemic (n = 7622) than pre-pandemic (n = 5363). The rate of patient consent was lower mid-pandemic (44%) than pre-pandemic (55%), but 670 more patients were consented in the mid-pandemic period. There was an increase during the pandemic in patients citing a desire to continue with hydrochlorothiazide as their reason for declining participation. The patient randomization rate was slightly higher mid-pandemic (79%) than pre-pandemic (73%).

Patients filled medications and remained on their randomized

Table 1
Participation metrics pre- and mid-COVID-19.

	Pre-Pandemic (July 2019–February 2020)	Mid-Pandemic (July 2020–February 2021)
Providers		
Approached for study consent, N	1150	1158
Consented, N(%)	817 (71.0%)	747 (64.5%)
Provider permission requested to randomize consented patients, N	2651	3283
Permission received, N(%)	2469 (93.1%)	2997 (91.3%)
Patients		
Reached by telephone, N	5363	7622
Declined participation, N (%)	1837 (34.3%)	3059 (40.1%)
Wish to continue with HCTZ	1024 (55.7%)	2081 (68.0%)
Not interested in research study	219 (11.9%)	420 (13.7%)
Refused to answer or other	594 (32.3%)	558 (18.2%)
Consented, N(%)	3048 (54.9%)	3718 (43.7%)
Randomized, N(%)	2231 (73.2%)	2933 (78.9%)

Table 2
Study follow-up metrics pre- and mid-COVID-19.

	Pre-Pandemic (July 2019–February 2020)	Mid-Pandemic (July 2020–February 2021)
Patients randomized, N	7685	10,915
Medications		
Study treatment refills, N (%)		
On randomized therapy	6905 (89.9%)	9758 (89.6%)
Switched diuretic	417 (5.4%)	564 (5.2%)
Lapse in diuretic	363 (4.7%)	593 (5.4%)
Other antihypertensive drug fills, N(%)	7589 (98.8%)	10,669 (96.0%)
Drug classes prescribed in addition to study diuretic, N(%)		
0	2 (0.03%)	2 (0.03%)
1	110 (1.4%)	275 (2.5%)
2	1021 (13.3%)	1449 (13.3%)
3	2494 (32.5%)	3539 (32.4%)
4	2365 (30.8%)	3318 (30.4%)
5+	1693 (22.0%)	2332 (21.4%)
Clinical Measurements		
Systolic blood pressure (all clinical settings), N(%)	7011 (91.2%)	8439 (77.3%)
Systolic blood pressure (primary care settings), N (%)	6367 (82.8%)	7426 (68.1%)
Serum potassium level, N (%)	6219 (80.9%)	8111 (74.3%)
Serum sodium level, N(%)	6210 (80.8%)	8099 (74.2%)
Hospital Utilization		
VA Outpatient visits	97.8%	97.7%
Telephone, home or virtual visit	63.6%	87.0%
Emergency or urgent care visit	31.3%	32.3%
Other outpatient clinic visits	97.2%	91.9%
Clinical Outcomes		
Major cardiovascular event, N(%)[1]	160 (2.1%)	240 (2.2%)
All-cause hospitalization, N (%)[1]	781 (10.2%)	1097 (10.1%)
COVID-related hospitalization, N(%)	–	138 (12.6%)
All-cause death, N(%)	74 (1.0%)	197 (1.8%)
COVID-related death, N (%)[2]	–	28 (14.2%)

[1] Identified through VA EHR and Medicare.
[2] As could be verified by chart review of VA records.

diuretic at the same frequency in both periods (Table 2). Blood pressure evaluations in all clinical settings decreased during the mid-pandemic period, and frequency of serum potassium and sodium evaluations was only slightly lower (6–7%) mid-pandemic. Outpatient clinic utilization remained roughly unchanged during the mid-pandemic period, though the frequency of telehealth visits increased by 23%. The rate of major cardiovascular events and all-cause hospitalizations was roughly the same in both periods, but the rate of death was roughly double mid-pandemic. Only 14% of the deaths in the mid-pandemic period were attributed to COVID-19.

4. Discussion

Very few study operations were impacted by COVID-19, with the exception of temporary, voluntary changes made to study procedures early in the pandemic. Other pragmatic clinical trials with decentralized and embedded features have reported similarly limited impact as a result of the COVID-19 pandemic [6]. While the entire clinical trial community was impacted by changes in care and the research ecosystem during this time [7], the DCP required no changes to study design or procedures to continue operations after the initial VA-wide pause on research.

During the hold on research activities enacted by VA, some of the DCP study staff were temporarily reassigned to other initiatives and projects, including deployment to the labor pool, medical center disaster operations, and execution of a COVID-19 clinical trial. Since DCP activities were also suspended during this time, the impact of staff reassignment on recruitment during this time was limited.

While approximately the same number of providers agreed to participate in the two periods, the rate of participation decreased marginally during the mid-pandemic period, likely due to increased demand on provider time or reluctance of the provider in making medication changes during the pandemic. Given the profound impact of COVID-19 on clinical operations, providers may have been reluctant to agree to additional optional work. And, without study staff at the sites, there was very little advocacy for the study and its limited impact on routine workloads. However, once consented, providers agreed to randomize their patients at the same rate in both time periods.

Similarly, substantially more patients were reached by phone mid-COVID, but the rate of consent decreased. The increase in patients reached is likely due to patients spending more time at home near their telephones during times of quarantine and reduced travel. Of patients consented, the rate of randomization was slightly higher mid-pandemic. The improvement in randomization rate is likely a product of the way eligibility criteria were reviewed, though the success of decentralized recruitment methods in DCP is consistent with the experience of other pragmatic clinical trials [8]. Patients could not have a SBP lower than 120 mmHg in the 90 days prior to randomization. Fewer visits during the pandemic resulted in fewer BP measurements on record, thus likely resulting in fewer patients with disqualifying BP measurements in the 90 days preceding their randomization.

Study medication adherence does not appear to have been impacted by the pandemic. Patients refilled and remained on their randomized diuretics at the same rate during both periods. Similarly, sodium and potassium levels were measured with roughly the same frequency during both periods, indicating continued proper clinical follow-up of patients switching diuretics. However, the rate of in-clinic systolic blood pressure measurements decreased drastically during the COVID period. This is expected because of the increase in telehealth appointments during the pandemic. While many patients measure their blood pressure at home and during telehealth appointments, these measurements may be recorded in clinical notes, but are not systematically captured in the patient's medical record in a structured way.

Despite the national impact on hospitals during the pandemic, the rate of all-cause hospitalizations remained fairly constant in the two periods, with only 13% of hospitalizations being attributed to COVID.

Hospitalization for major cardiovascular events (a component of DCP's primary outcome) also remained unchanged. However, the rate of death appears to have nearly doubled during the pandemic, but only 14% of the additional deaths were attributed to COVID-19. This increase may be due to reduced access to care, a general delay or avoidance to receiving medical care during the pandemic, or unrecognized COVID deaths [9,10].

It is possible that pandemic onset and the addition of sites are confounded. However, site initiation generally started 6–8 months prior to beginning recruitment, with some sites taking over a year to begin. Sites beginning recruitment during the pandemic had agreed to participate before the onset of COVID-19. Additionally, the majority of patient recruitment (~90%) and virtually all of provider recruitment occurred within 6 months of a site's initiation. Thus, a comparison of only sites that began recruitment before the pandemic in the two defined periods would provide inadequate recruitment data mid-pandemic. It should also be noted that the trial completed recruitment in November 2021 with continued high levels of recruitment until this time [11].

5. Conclusions

The Diuretic Comparison Project was able to recruit and maintain critical data collection at pre-pandemic levels without need for changes to study design or procedures. Though changes in clinical care impacted the rate at which some clinical measurements were collected, overall data collection persisted through the pandemic. DCP has demonstrated that the Point-of-Care pragmatic embedded clinical trial design is a low-risk, successful methodology for conducting clinical trials in the midst of a global pandemic.

Ethics approval and consent to participate

The Diuretic Comparison Project was reviewed and approved by the VA Central Institutional Review Board January 4, 2016.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available but are available on request with an IRB-approved protocol and upon completion of a VA-approved data use agreement.

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Authors' contributions

The authors confirm contribution to the paper as follows:

- Study conception and design: SML, AK, CH, PAG, WCC, AI
- Data collection and analysis: CH
- Interpretation of results: SML, CH, PAG, REF, WCC, AI
- Draft manuscript preparation: SML, CH, AK, PAG, AAT, REF, WCC, AI

All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

Data will be made available on request.

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