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Approaches that use historical controls to meet modern needs in cystic fibrosis clinical trials

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Background: Cystic fibrosis (CF) transmembrane conductance regulator protein (CFTR) modulators are effective in reducing the disease burden of CF, and a little more than 90% of patients are eligible for CFTR modulators with the expansion of eligibility to those with a single copy of a F508del mutation. This broad success creates logistical challenges for clinical trials of new CF therapeutics for the small number of patients that remain ineligible for modulators. New logistically feasible trial designs must be developed to assess efficacy of CF therapeutics and CFTR restorative therapies. Novel study designs that use readily available external data sources, such as previous trial controls, must be rigorously developed and understood to meet these modern challenges.
Methods: In the context of a pulmonary exacerbation simulation study, we will examine an adaptive trial design and three analytic approaches that use historical data. The adaptive trial methodology contains a planned interim analysis at which congruency between the historical and active controls is assessed. If congruent, historical controls will be used in the analysis to reduce the need for active controls and reduce the active trial sample size. If incongruent, the historical controls will be discarded and more active controls recruited. The three analytic methods include inverse probability weighting, propensity score-based power priors, and commensurate priors. We will assess a simulated time-to-event outcome with Poisson regression and compare analytic approaches regarding their ability to estimate treatment effect accurately and reduce required active trial sample size.
Results: Early, limited simulation shows that the adaptive trial design and all three analytic approaches can be an improvement over naïve approaches under certain conditions. Inverse probability weighting can achieve unbiased results when most covariates measuring active trial and historical population differences were available. A hazard ratio of 0.63 (95% CI, 0.50–0.80 was obtained when historical participants were used exclusively as the control arm. The expected hazard ratio was 0.55 (95% CI, 0.34–0.86). Additionally, failure to adjust for differences between current and historical study populations results in biased estimates of efficacy and poor coverage. All methods will be compared in terms of coverage, power, and bias.
Conclusions: Evaluation of trial designs and analytic approaches that leverage historical data is critical because these tools will be necessary to meet the challenges of modern CF clinical trials. As traditional placebo-controlled trials become increasingly less feasible, it will be critical for researchers to make use of efficient and accurate alternative designs.

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Respiratory outcomes in the era of high-quality modulator therapies: Results from the Tennessee and Mississippi Cystic Fibrosis Consortium

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Background: Cystic fibrosis (CF) is an autosomal-recessive disease caused by mutations in the CF transmembrane conductance regulator *(CFTR)* gene that codes for the eponymous protein. Treatment modalities included therapies targeted at end organ damage until modulator therapy revolutionized CF care. Triple combination therapy with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) studied in people with CF (PwCF) with one or two copies of the Phe 508 del mutation [1,2] showed significantly better lung function and lower sweat chloride concentrations. On October 21, 2019, the Food and Drug Administration approved this medication for PwCF aged 12 and older with at least one Phe 508 del mutation [3]. After a phase 3 study in children ages 6 through 11 [4], the medication is now approved for ages 6 and older. After ELX/TEZ/IVA treatment, clinicians note fewer sick visits and better lung function. Patients report less cough and sputum production. To confirm these observations, we examined respiratory data at adult and pediatric centers in two states before and after ELX/TEZ/IVA therapy.
Methods: We analyzed Cystic Fibrosis Foundation Registry data on children and adults with CF at the five centers in Tennessee and Mississippi for the year preceding and year after initiation of ELX/TEZ/IVA. The best value for percentage predicted forced expiratory volume in 1 second (FEV_1 pp) for each study period was recorded. Respiratory culture results and sources (sputum versus oropharyngeal) were noted, as were the numbers of hospitalizations and exacerbations for both periods. Centers uploaded their results into a shared Excel file without patient identifiers. Statistical analysis was completed at the Pediatric Center at the University of Tennessee using SAS 9.4 software (SAS Institute, Cary, NC).
Results: Forty children and adults with CF were included from this analysis. For this small sample, FEV_1 pp improved significantly after starting ELX/TEZ/IVA therapy. More oropharyngeal than sputum samples were collected after ELX/TEZ/IVA therapy. Culture results for *Staphylococcus aureus* (methicillin sensitive and methicillin resistant) were similar for both periods, but fewer patients were culture positive for *Pseudomonas aeruginosa* after modulator therapy. Four patients grew *Burkholderia cepacia,* and 7 had *Stenotrophomonas* before therapy; all were culture negative after starting ELX/TEZ/IVA. Fewer hospitalizations and exacerbations were noted after therapy. Data are summarized in Table 1.
Conclusions: FEV_1 pp improved after ELX/TEZ/IVA therapy. Miller et al. [5] found fewer overall health care visits, inpatient stays, and sick visits in the year after starting high-quality modulator therapy. Our data support this observation and confirm that significantly fewer sputum samples were collected after ELX/TEZ/IVA therapy. Although the consortium has five CF

Table 1 (abstract 36):
Respiratory data before and after starting elexacaftor/tezacaftor/ivacaftor (ETI)

	FEV1 pp (mean ±SD)* $p < 0.0001$	Culture source# $p = 0.0007$	Pseudomonas aeruginosa	Hospitalizations	Exacerbations
Pre ETI	81.4 ± 22.70	Sputum : 31/40 OP: 9/40	17/40 (42%)	37	88
Post ETI	90.23±25.07	Sputum 16/40 OP: 24/40	5/40 (13%)	11	24

care centers, only a few patients from each center are included in this preliminary analysis. Future steps for the Tennessee and Mississippi consortium include analysis of the full patient population in the periods immediately before and after approval of ELX/TEZ/IVA to determine the effects of ELX/TEZ/IVA and the pandemic on observed CF outcomes. Culture positivity for acid-fast bacilli will be assessed. Data from children with CF will be compared with data from adults with CF.

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Trends in Canadian cystic fibrosis health care use amidst the COVID-19 pandemic

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Background: The COVID-19 pandemic has resulted in widespread changes in health care use for Canadians with cystic fibrosis (CF). The objective of this analysis is to describe the impact of the COVID-19 pandemic on the delivery of usual CF health care.

Methods: The Canadian Cystic Fibrosis Registry is a national repository of longitudinal data from 42 CF clinics across Canada. This study included data on clinic visits (including virtual and telemedicine), hospitalizations, home intravenous (IV) medicine courses, and microbiology cultures recorded in the registry from 2016 to 2020. Clinical measurements typically collected during clinic visits include height, weight, and lung function—measured as percentage predicted forced expiratory volume in 1 minute (FEV_1pp). Lung function is not typically measured in young children, so analyses of FEV_1pp are restricted to individuals aged 6 and older. Health care use is described as the proportion of individuals who had at least one recorded measurement or encounter in the reporting year.

Results: The number of clinic visits, hospitalizations, and home IV medicine courses recorded monthly in the registry remained relatively stable from 2016 to 2019, averaging 1,528 clinic visits, 130 hospitalizations, and 81 home IV medicine courses per month from 2016 to 2019. With the declaration of the COVID-19 pandemic in early March 2020, the overall number of CF health care encounters decreased substantially. There were 29.7% fewer clinic visits in April 2020 than in April 2019, 67.6% fewer pulmonary exacerbation (PEx) hospitalizations, and 39.6% fewer home IV courses. Looking at month-to-month changes in 2020, the trends in health care encounters appear to be inversely related to the number of COVID-19 cases recorded in Canada—although infection rates increased, CF health care use decreased. The proportion of individuals with at least one FEV_1pp measurement decreased from a mean of 97.0% during 2016 to 2019 to 89.0% in 2020, PEx hospitalizations decreased from a mean of 20.9% during 2016 to 2019 to 14.8% in 2020, and microbiology cultures (excluding COVID-19) decreased from a mean of 92.6% during 2016 to 2019 to 85.4% in 2020. It follows that the mean number of health care encounters (e.g., FEV_1pp and body mass index measurements, clinic visits, microbiology cultures) recorded per individual was also lower in 2020 than over the previous 4 years (Figure 1).

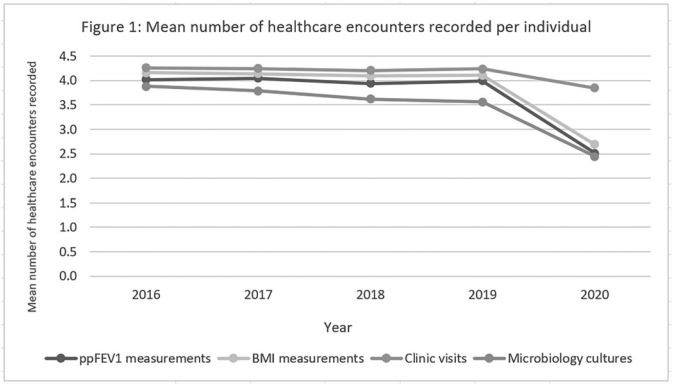

Figure 1. Mean number of health care encounters recorded per individual

Conclusions: The reduction in number of health care encounters for Canadians with CF provides insight into the impact of COVID-19 on delivery of CF care in 2020. The resulting lack of objective measurements typically assessed during clinic visits, such as lung function or new-onset infections, may not be appreciated or recognized until later than usual. Coinciding with the COVID-19 pandemic, some Canadians with CF also became eligible for the highly effective modulator therapy elexacaftor/tezacaftor/ivacaftor, which could be a confounding factor in the decrease in number of clinic visits or hospitalizations. Disentangling the combined effects of these events on the delivery of CF care will be an important subject for future analysis.

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Cutaneous rash with elexacaftor/tezacaftor/ivacaftor in children with cystic fibrosis

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Background: Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is a triple-therapy modulator used to treat patients with cystic fibrosis (CF) since late 2019. It was approved in June 2021 for clinical use in children aged 6 to 11. Clinical trials of ELX/TEZ/IVA have reported skin rash as a commonly observed side effect. The rash is reported to be mild to moderate in severity and self-resolving in most cases. Clinical trials have also reported that the rash is more commonly seen in younger children (24% in aged 6–11) and children and adults with a single delta F508 mutation [1–3].

Methods: A retrospective chart review was conducted in all pediatric patients aged 6 and older with CF prescribed ELX/TEZ/IVA between October 2019 and April 2022. Patients were excluded if they were started on this