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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