Title: Assessment of Contraceptive Safety and Effectiveness in Cystic Fibrosis: A Retrospective Analysis

Short title: CASE.4.CF Study (Contraceptive Assessment of Safety and Efficacy)
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Abbreviations:

ARF=Acute renal failure

DEXA/DXA=dual-energy x-ray absorptiometry (bone densitometry)

BMD=bone mineral density

BMI=Body Mass Index

CDC-Centers for Disease Control and Prevention

CFFPR=Cystic Fibrosis Foundation Patient Registry

CFQ-R=CF questionnaire-revised

DMPA=depo-medroxyprogesterone acetate

FDA=Food and Drug Administration

FEV1= Forced Expiratory Volume in the first second

ppFEV1=percentage of predicted FEV1

eGFR=estimated glomerular filtration rate

OCP=oral contraceptive pills

OTC=over-the-counter

IUD=intrauterine device

LEEP=Loop electrosurgical excision procedure (to treat abnormal cell growth on the surface tissue of the cervix)

MDR=multi-drug resistant

MSSA=methicillin-sensitive Staph aureus

MRSA=methicillin-resistant Staph aureus

NTM=nontuberculous mycobacteria

USMEC=United States Medical Eligibility Criteria for Contraceptive Use

WHO=World Health Organization

1.0. Summary

This proposal, originally submitted to the Cystic Fibrosis Foundation (CFF) Spring 2019, has been changed at the recommendation of the CFF to reflect a retrospective approach to determine safety and efficacy of contraception among up to 625 women of reproductive age with cystic fibrosis (CF). In planning for this retrospective approach, the University of Washington (UW) study team determined that the optimal way to collect contraceptive use data would be through patient self-respondent approach, since the Cystic Fibrosis Foundation Patient Registry (CFFPR) does not collect information on contraception, and electronic medical records (EMR) often have inaccurate information about contraceptive use and do not include over-the-counter (OTC) methods. Given the critical nature of collecting exposure (contraceptive) data for this retrospective approach, the UW study proposed using the first year to pre-test self-respondent questions with up to 50 women with CF. **The purpose of this pilot survey is to determine the best approach to collect reproductive health information due to the sensitive nature of questions on the topics of contraceptive use, pregnancy, and menstruation**. We will determine if responses about past contraceptive use are more complete when the survey is administered or when respondents answer questions on their own at home using an online survey.

Once the pilot phase is complete, we propose to conduct a retrospective observational cohort study of up to 625 women with cystic fibrosis aged 18-45 years at time of enrollment. Participants will be recruited from 10 separate CF centers. Participants will be recruited for the study from their CF center through email, postal service, or in-person contact. CF center research staff will inform interested patients about the study, check that the patient has a CFFPR ID number, and pass along the patient names, email addresses, and CFFPR number to the UW study team who will determine eligibility. If the potential participants meet enrollment criteria, they will be consented on-line, and continue to the online survey that they can complete at home. The self-reported data will be linked with CFFPR objective pulmonary data to examine the association of hormonal contraceptive use on pulmonary health, outcomes related to CF-liver dysfunction (CFLD), nutritional status, and venous/arterial thromboembolism. The UW study team will work with each of the 10 separate CF centers to provide a select number of dual energy X-ray absorptiometry (DXA) scan bone mineral density test scores from their center's EMR, which will be used to validate bone health information in the CFFPR.

2.0. Background/Rationale

Family planning decisions are increasingly important for women with CF as most reach reproductive age in reasonable health. As CF care management and directed therapies advance, the number of women with CF in the US over age 18 has nearly doubled over the last 15 years: from 4,000 to 7,200. The CFF has an existing comprehensive patient registry, the CFFPR, which captures annual data on over 90% of all persons with CF in the US (1). While it is comprehensive regarding most aspects of CF patients' health, the CFFPR currently only asks one question that addresses reproductive health for women over 18 living with CF: "Was the patient pregnant during the reporting year?".

Reliable information is urgently needed to enable healthcare providers to help CF women understand the effectiveness and safety of current contraceptive methods for them. While infertility usually affects men with CF, at least 50% of women with CF are estimated to be physiologically capable of becoming pregnant without fertility treatment (2); however, that percentage is expected to rise with the use of new life sustaining medications, such as the CFTR modulators and especially the newly Food and Drug Administration (FDA)-approved triple-combination modulator, TRIKAFTA® (3).

Our recently completed survey study among 150 women at three CF centers, suggests that only about 60% of reproductive–aged women with CF are using contraception (4). Among those who are, oral contraceptive pills (OCPs) and condoms are the most commonly reported methods. Gaps in quality contraceptive care for women with CF exist, in part because, surprisingly, women with CF prefer to receive their sexual health care within the CF clinics, but many CF providers do not feel prepared to deliver safe and detailed contraception care (5). This information gap is exacerbated by the limited data which exist to inform contraceptive care provision for women with CF. In fact, most studies evaluating contraceptive safety are limited to oral contraceptive pills, even though the number of choices of FDA-

approved contraceptives has increased significantly since 2001, especially with the FDA-approval of hormonal long-acting reversible contraceptive methods. In today's U.S. market, two types of hormonal contraceptives exist: estrogen-and-progestin-containing methods (a.k.a. combined hormonal methods) and progestin-only methods. Within the estrogen-containing methods, contraceptive choices include oral pills and non-oral methods, such as the transdermal patch and vaginal ring. Within the progestin-only methods, contraceptive choices include four different hormonal intrauterine devices (IUD), a subdermal implant, a 3-month injectable depo-medroxyprogesterone acetate (DMPA), and progestin-only oral pills

The most recent edition of the national contraceptive guidance for women with medical conditions called the United States Medical Eligibility Criteria for Contraceptive Use (USMEC), was released in 2016 by the Centers for Disease Control and Prevention (CDC), which lists CF as a chronic health condition (6). The USMEC lists all hormonal methods safe to prescribe without restrictions (USMEC = 1), except the 3-month injectable, depot-medroxyprogesterone acetate (DMPA). DMPA is listed as USMEC = 2, in which the advantages of using the method in a woman with CF generally outweighs the theoretical or proven risks because of concerns about DMPA on bone health. Despite these national recommendations, the data for women with CF and hormonal contraception are limited. Potential complications for CF patients include decreased pulmonary function, CF-related diabetes (CFRD), CFLD, increased gallbladder disease, decreased nutritional status, increased venous thromboembolism and poor bone health. There are theoretical concerns that hormonal contraception may adversely impact these complications. Another concern is the reduced efficacy of hormonal contraception, specifically oral contraceptive pills with concomitant use of CFTR modulators.

The definitions for normal bone, osteopenia, and osteoporosis are based on bone mineral density (BMD) scores. BMD is measured by dual energy X-ray absorptiometry (DXA), which provides both T-scores and Z-scores. These scores are used to define whether a person is categorized as having osteoporosis, osteopenia, or normal bone. According to the World Health Organization (WHO), the T-score is the number of standard deviations (SD) above (+) or below (-) the mean BMD in a young, normal, sex-matched population and is preferred for postmenopausal women. The Z-score is the number of standard deviations (SD) above (+) or below (-) the mean bone density in a normal, sex- and age-matched population and is preferred in females prior to menopause (7). In contrast to WHO criteria, the CFF uses Z-scores for children less than 18 years, considers T- and Z-scores as nearly equivalent for persons between ages 18-30 years, and uses T-score findings for persons with CF ages 30 years and older (8).

Our project is specifically designed to collect more information on these critically important issues by expanding our pilot contraceptive CFFPR study and further assess the safety and efficacy of contraception among patients with CF. With pilot funding from the Society of Family Planning, Drs. Godfrey, Aitken, and Heltshe collaborated with two other CF centers to assess feasibility, data completeness, and data accuracy of a pilot contraceptive registry. Having successfully linked women with CF's self-reported information on current and prior contraceptive use with clinical data information obtained from the CFFPR, we are now ready to expand our work to include seven additional CF Centers for a total of ten centers (see Table 2).

The research questions we aim to answer for women with CF, aged 18-45 years in this retrospective study include:

(1) Are estrogen-containing or progestin-only hormonal contraceptives associated with improved objective pulmonary symptoms compared to women with CF who use non-hormonal methods (control)?

(2) Are estrogen-containing or progestin-only hormonal contraceptives associated with increased incidence of CF-related liver disease (as noted with increasing trend of liver enzyme tests), gallbladder disease or thromboembolism?

(3) Are estrogen-containing or progestin-only hormonal contraceptives associated with increased serum glucose trends (as measured by oral glucose tolerance testing) compared to women using non-hormonal methods?

(4) Does hormonal contraceptive use affect nutritional status for women with low body mass index?

(5) What is the percent agreement between CF Clinic DXA scan T-scores and CFFPR data about osteoporosis, osteopenia and bone fracture?

(6) Are women who use CFTR modulators and more likely to become pregnant unintentionally while taking hormonal contraception (compared to women on non-hormonal contraception)?

(7) Does use of hormonal contraception result in a higher proportion of patients with mucoid vs. non-mucoid *Pseudomonas aeruginosa* compared to non-hormonal contraceptive users?

3.0. Hypothesis

- Estrogen-containing methods, but not progestin-only methods, reduce the annual rate of pulmonary exacerbations, the microorganisms associated with a more rapid decline in lung function, and improve ppFEV1 (or absolute FEV1) of women with CF when compared to women with CF who use non-hormonal contraception (control group).
- Estrogen-containing oral methods of birth control are associated with higher incidence of gallbladder disease (defined as gallstones, requiring surgery), increased liver function enzyme values, and/or increased incidence of thromboembolism among women with CF.
- Both estrogen-containing and progestin-only hormonal methods improve BMI among women with CF, which is linked to nutritional status.
- The strength of agreement between DXA scan T-scores and CFFPR data about osteoporosis, osteopenia and bone fracture will be "substantial."
- The effectiveness of oral birth control is reduced compared to other methods of hormonal birth control in the presence of CFTR modulator use.
- Hormonal birth control use results in a greater proportion of patients with mucoid *Pseudomonas aeruginosa*, in patients who are *P. aeruginosa* positive, compared to non-hormonal contraceptive users.

4.0. Study Objectives

4.1. Primary Study Objective

- To assess the association of hormonal contraceptive use on frequency of pulmonary exacerbations, compared to non-hormonal contraceptive users (primary control) and non-contraceptive users (secondary control).

4.2. Secondary Study Objectives/Endpoints

- To assess the association of hormonal contraceptive use on trends in lung function (FEV1) over time, compared to non-hormonal contraceptive users (primary control) and non-contraceptive users (secondary control).
- To assess the association of hormonal contraceptive use on the incidence of venous or arterial thromboembolism.
- To assess the association of hormonal contraceptive use on prevalence of liver dysfunction, defined as gallstones (requiring surgery), hepatic steatosis, hepatic cirrhosis, and/or incidence of increased liver enzyme test values (ALT/GGT). Increased liver enzymes is defined as exceeding upper limit of normal on at least 3 occasions over 12-month period.
- To assess the association of hormonal contraceptive use on serum glucose trends, incidence of insulin resistance or time to CF-related diabetes (requiring insulin treatment).

- To assess association of hormonal contraceptive use on nutritional status through the evaluation of BMI trends.
- To validate bone health information in CFFPR with chart data obtained from one CF center (limited due to need for data use agreements between institutions for EMR data).
- To determine if those using hormonal contraception while using CFTR modulators report higher rates of unintended pregnancy compared to those taking non-hormonal contraception.
- To assess proportion of mucoid *P. aeruginosa*, in patients who are *P. aeruginosa* positive, among hormonal contraception users compared to non-hormonal contraceptive users.

5.0. Trial Design

This is a non-randomized, non-interventional, observational cohort design among reproductive-aged women (ages 18-45 years) with CF. **This protocol describes a pilot phase, as well as a larger retrospective approach**.

We intend to ask about 625 female participants to provide information about their types of past contraceptive use from 2008 through the most recent data available from CFFPR (2018 or 2019). Before initiating our trial among up to 625 respondents, we intend to pre-test the survey questions on our self-respondent questionnaire among as many as 50 women with and without CF through CFF Community Voice, the Cystic Fibrosis Research, Inc. (CFRI), and the Cystic Fibrosis Reproductive and Sexual Health Collaborative (CFReSHC). Pre-testing our survey questions will help ensure contraceptive, pregnancy, and other reproductive health data from respondents for the larger phase of this study are as complete and accurate as possible.

Once the survey has been piloted and revised accordingly, we will collect past contraceptive, pregnancy and other reproductive health data from up to 625 women at 10 different CF centers. We may over-sample by 25 participants because it is possible that some participants from UW, UTSW and National Jewish may have participated in our earlier published study related to contraceptive use and CFFPR (4). Recruiting through the CF centers will help ensure that women with a confirmed diagnosis of CF respond to the finalized survey. We will link respondent self-reported contraceptive and reproductive health data with CFFPR clinical data. We will ask for EMR data from the 10 different CF centers to validate DXA scan results with findings regarding osteoporosis, osteopenia, and bone fracture in the CFFPR. We plan to randomly select about 10 consented subjects from each of the centers for the EMR DXA scan chart review. Because of our need to link questionnaires and clinical case report forms correctly to the same women with CF in the CFFPR clinical data, we need to request identifiable information, including the CFFPR member ID number.

6.0. Pilot Survey Phase

Given the critical nature of collecting exposure (contraceptive) data for this retrospective approach, the UW study proposed using part of the first year of this grant to pre-test the self-respondent questions with up to 50 women with and without CF. **The purpose of this pilot survey is to determine the best approach to collection reproductive health information due to the sensitive nature of question on the topics of contraceptive use, pregnancy and menstruation**.

Because this phase may affect how we collect the data in the larger phase of this work, we will simultaneously be refining our analysis plan as we collect, summarize, and analyze our findings during this pre-test/pilot phase.

6.1. Pilot Recruitment

We intend to recruit up to 50 participants through the CFF Community Voice program, CFRI, and CFReSHC. We intend to enroll women between the ages 18-45 years with or without CF. We have chosen the CFF Community Voice program because participants have already agreed to participate in research and we believe they will be forthcoming about their thoughts about the understandability and format of our questions seeking to gather information about past contraceptive use. Inclusion/Exclusion criteria for the pilot phase are listed below:

Table 1: Pilot phase inclusion and exclusion criteria

Pilot inclusion criteria
Female
Aged between 18-45 years.
Functional email address
Has device capable of using Zoom
Pilot exclusion criteria
Receives CF care at one of the 10 collaborating CF centers

6.2. Pilot Process: Please see Pilot Pre-test Survey Protocol for Details

We will not be able to validate responses against the EMR because of research suggesting that EMR data are not accurate with regards to contraceptive information (9).

6.3. Pilot Duration

This phase is expected to take up to 5 months, depending on the number of interviewees needed for question pre-testing. During this phase, the research coordinator (RC) will schedule and enroll participants, pre-test the questions, and implement feedback. We will be working closely with the Washington State University (WSU) Social and Economic Sciences Research Center who will provide survey development guidance, as well as the UW Social Development Research Group (SDRG) who will provide expertise on cognitive interviewing.

7.0. Methods: Participants, Interventions, and Outcomes of Final Questionnaire Phase

Once the questionnaire is pretested (anticipated end date of pre-testing is July 2020), the final questionnaire will be revised accordingly prior to initiating the full, larger study.

7.1. Study Setting

We intend to enroll up to 625 women, aged 18-45 years, at 10 separate CF centers. We may over-enroll the sample by 25 women to account for women who may have participated in the prior contraceptive study in 2017. This will allow us to perform a sensitivity analysis excluding women who participated in the pre-study, while maintaining study power.

Table 2: Study sites and anticipated number of eligible participants

Name of Institution	**Institution PI(s)**	**Number of women with CF aged 18-45 years**
University of Washington	Emily Godfrey, MD, MPH Moira Aitken, MD	141
University of Texas Southwestern	Raksha Jain, MD, MS	140
National Jewish Hospital	Jennifer Taylor-Cousar, MD, MS	233
University of California San Diego	Douglas Conrad, MD Sheila Mody, MD, MPH	120
University of Pittsburgh	Traci Kazmerski, MD, MS	106
University of Pennsylvania	Denis Hadjiliadis, MD Andrea Roe, MD, MPH	128
John's Hopkins University	Natalie West, MD, MPH	159
University of Alabama	Marty Solomon, MD Sigrid Ladores, RN Leigh Ann Bray RN	135

Name of Institution	Institution PI(s)	Number of women with CF aged 18-45 years
Harvard U/Boston	Ahmet Uluer, MD	189
Mount Sinai	Patricia Walker, MD	51

We anticipate that each site will be able to enroll 50% of eligible women ages 18-45 years into the study. We have chosen the lower age range because of estimated age of sexual debut among young women with CF is between ages 16-17 years (5) and it is expected that some women aged 18 will have started using contraception. We have chosen the upper age range of 45 years because of the lower life expectancy of women with CF compared to the general population and inherent bias that adults with CF who live past the currently life expectancy are most likely healthier than younger adults with CF (10).

Table 3: Age distribution goals for study enrollment

Age Distribution of Women with CF	
Age Range (years)	*Approximate number of subjects planned*
18-35	383
36-45	192

7.1.1. Study Duration

Participant enrollment will take approximately 15 months for the finalized survey phase.

7.2. Eligibility Criteria

The study population will be women with CF who have used any form of contraception for protection against pregnancy or for treatment of dysmenorrhea, pelvic pain, abnormally heavy or prolonged menstrual bleeding, excessive uterine bleeding, endometriosis, acne, or amenorrhea.

Table 4: Full study inclusion and exclusion criteria

Inclusion Criteria
Females ages ≥ 18 and < 46 years at enrollment
Confirmed patients at one of the 10 participating CF centers (has been seen at least one time for a face-to-face office visit at the CF center in the last 2 years)
CFFPR participant (noted as having a CFFPR ID number)
Has internet access
Has a functioning email addresses or may create a functioning email address at enrollment
Willing to consent to obtain request of their identified data from CFFPR
Willing to consent to their CF center to provide data related to contraceptive medication and DXA scan test results as far back as 2013 in clinic EMR
Exclusion Criteria
Not in CFFPR
Non-functioning email address
History of organ transplant
Participant in pre-test phase of this study

7.2.1. Informed Consent

By obtaining informed consent from participants, the UW study team shall:

- Avoid any coercion of or undue influence to participate
- Sustain the candidate's legal rights
- Provide complete, detailed description of study, intent to link survey information with participant's clinical information in the CFFPR, follow up and costs/reimbursements using language that is non-technical and understandable to the participant
- Ensure the participant understands the risks and responsibilities
- Include contact information of the principal investigator and study site investigator
- Ensure protection of the participant's confidentiality

7.2.2. Enrollment

The participant is considered enrolled into the study after providing written consent and is found eligible based on history, eligibility screening questions, and confirmation as a participant in the CFFPR. Eligible consented participants who withdraw consent for any reason before completing the survey are considered screen failures. Eligible consented participants who cannot be verified as a participant in the CFFPR with a CFFPR ID number (confirmed by respective CF center) will be considered a screen failure.

7.3. Interventions

We will provide an online questionnaire to give to female participants in order to obtain exposure data (past contraceptive use). We will have participants complete the survey on their own, either in clinic or at home. The survey will include pictures, brand names, and descriptions to help respondents remember birth control method used retrospectively.

We will ask each CF center to provide DXA scan results for 10 participants (selected at random) from their respective EMRs in order to validate osteoporosis, osteopenia and bone fracture information in the CFFPR.

7.3.1. Treatment

N/A

7.4. Interventions: Modifications

N/A.

7.5. Outcomes (include DAG diagrams to show relationships between exposure and outcomes)

Table 5: Outcomes and associated confounders and covariates

Exposure of interest	**Outcome**	**Confounders/Covariates**	**Rationale**
Combined hormonal contraception (CHC) & Progestin-only contraception	**Pulmonary outcomes** • Annual pulmonary exacerbation rate (PEx) (defined as episodes requiring intravenous antibiotic use at home or in hospital) • Absolute change in FEV1 (in liters) **Prevalence of micro-organism** (defined as 1 or greater sputum culture within a 12-month period) • *P. aeruginosa*	Smoking	Affects lung function
		Insurance status (reflection of SES)	Will be used as socioeconomic indicator. Less access to meds may mean less compliance
		Age	Lung function worsens as one ages
		Education (reflection of SES)	Affects contraceptive knowledge decision making
		BMI	Associated with better or worse health status in general

Exposure of interest	Outcome	Confounders/Covariates	Rationale

	• MDR *P. aeruginosa*
	• Staph aureus
	  • MSSA
	  • MRSA
	Secondary infections:
	• *Burkholderia cepacia*
	• *Burkholderia cenocepacia*
	• *Mycobacterial species –includes M. tuberculosis and NTM species*
		Exercise	May reduce pulmonary exacerbation rates

		CF genotype class	Associated with severity of disease
		CFTR modulator treatment	Likely preserves pulmonary decline
		Comorbidity with CFRD (defined as requiring chronic insulin therapy) (11)	Associated with worse disease (reduced immunity)
		Length of hormonal contraceptive use (person-year of exposure)	
	Venous/arterial thromboembolism (VTE)	BMI ≥ 30	
	• Noted on self-respondent survey (defined as blood clot requiring anticoagulation treatment)	Age > 35 years	
		PMHx for thrombophilia	
		Arterial/venous lines or ports	
		Pmhx cancer	
		Smoking	
	Liver outcomes • Liver disease, non-cirrhosis • Gallstone, requiring surgery/procedure (defined as present or absent as recorded in CFFPR)	BMI	Obesity contributes to liver dysfunction
		Comorbidity with diabetes	Associated with worse disease (reduced immunity)
		Hepatitis	Risk factor for liver dysfunction
		CF genotype class	
		Length of hormonal contraceptive use (person-year of exposure)	
	• Serum ALT, GGT (meets criteria if hepatic transaminases and GGT levels exceed upper limit of normal on at least 3 consecutive occasions over 12-month period) (12)		Will track meeting criteria annually over time
	CF-related diabetes		
	• Serum ogtt trends		
	• New onset insulin resistance or diabetes (defined as		

Exposure of interest	Outcome	Confounders/Covariates	Rationale
	present or absent as recorded in CFFPR)		
	Nutritional status • Change in BMI	CF genotype class	
		CF-specific vitamins (Fat soluable A, D and E) (defined as present or absent as recorded in CFFPR)	
		Taking any pancreatic enzyme replacement therapy (noted under medications in CFFPR)	
		CFTR modulator use (will stratify by type of modulator)	
	Bone outcomes • Osteoporosis, fragile bone fracture	Length of oral steroid use (person-months of use)	Contributes to bone weakening
		Comorbidity with pancreatic insufficiency	Reduced Vit D/Calcium absorption
		Exercise	Help prevents osteoporosis
		Age	Known risk factor for osteoporosis
		BMI	Reduced BMI is a risk factor for osteoporosis
		CF genotype class	
		Length of hormonal contraceptive use (person-year of exposure)	
		Smoking	Known risk factor for osteoporosis

7.6. Participant Timeline – Full Study

7.6.1. Time 0: Invitation to inquire about enrolling in the study

Each CF center will contact eligible patients by whichever means approved by their IRB (email, phone), inviting all current female patients, ages 18-45 years who are participants in the CFFPR to participate in the study. Eligible patients will also be approached at their clinic visits. For CF centers who want the UW research team to contact eligible patients, they will send a list of eligible patients, email, and CFFPR member ID to the study team.

7.6.2. Time 1 (V0): Enrollment procedure

1. Each CF center will identify all female patients with CF, ages 18-45 years who have a CFFPR patient registry ID number.
2. Each CF center will send an email with information about the study to all female patients identified in step #1. If they prefer the UW research team to contact eligible patients, they will send a list of eligible patients, email, and

CFFPR member ID to the UW, and the UW research team will send an email with information about the study to eligible patients.

3. Each CF center also approach female patient identified in Step #1 when they are seen in the clinic with written information about the study.
4. Interested potential participants will receive the link the online survey to complete the eligibility questions and consent form via email. This link will come from either the UW research team or CF center staff, depending on CF center preference.
5. The potential participant will answer screening questions via the online portal to ensure eligibility.
6. If the participant qualifies for the study, they will be consented to participate via the online portal.
7. Once consented, the participant will move forward to the online survey itself. To help reduce recall bias, pictures of most birth control pill packages as well as other birth control methods will be accessible as the participant completes the survey.
8. In order to maximize response rates, participants will be sent automatic reminders to complete their survey using REDCap reminder features.
9. Compensation to the participant will be provided by the UW research team once survey is complete and the UW research team has verified that they are in the CFFPR (about 2 weeks after completion of the survey).
10. The UW research team will receive CFFPR data, which includes whether patients have a diagnosis of osteopenia or osteoporosis. Among those with a positive diagnosis, the research team will randomly select 10 participants from each CF center, in order to compare CFFPR data to DXA scan results from CF centers.
11. Providing DXA scan results: Once the 100 participants have been confirmed as having completed the enrollment, consent form, and survey by the UW research team, and CFFPR data indicates a diagnosis of osteopenia or osteoporosis, the UW research team will provide the appropriate CF center with a case report form (CRF), labelled with the participant's survey study ID number only. The CF Center research staff will have access to a password protected database in REDCap that links the survey ID number with participant name and date of birth (for patients at their CF center only). The name and date of birth will be used for the CF Center to complete the case report form using the participant's electronic medical record (EMR) data.
12. The CF center research staff will complete the CRF that asks for DXA scan scores (from 2013 to 2018).
    a. CF research staff will report T-scores from 3 anatomical sites: femoral neck, lumbar spine and total hip.
    b. Verification with CFFPR: We will take the lowest BMD T-score reported for either the femoral neck, lumbar spine, or total hip when categorizing a participant as osteoporotic, osteopenia, or normal for a given DXA test within a given year and compare to the diagnosis of record in the CFFPR. Scores provided at other anatomical sites (forearm, heel, etc.) will not be considered.

Table 6: Outline of responsibilities of clinic

Clinic responsibilities			
	Pre-enroll	*Enrollment*	*Post-enroll*
Month	*0*	*1-12 months*	*13-15 months*
• Send invitations to participate in study, followed by phone call, and approach women in clinic to participate	X		
• CF center research staff to give patient's unique CFFPR ID number, name, DOB, and contact information to UW research team		X	
• CF clinic research staff to complete case report form:			X

○ DXA scan results: dates and results as far back as 2013. Results will include T-scores from 3 sites: femoral neck, lumbar spine and total hip and year that DXA scan was performed.			

Table 7: Outline of responsibilities of Study Participant (Patient)

Participant responsibilities		
	Pre-enroll	*Enrollment*
Month	*0*	*1-15 months*
• Enroll in study		X
• Be willing to be contacted by UW research team staff member		X
• Complete smoking and blood clot questions		X
• Complete CFTR modulator questions		X
• Complete surgical history questions		X
• Complete contraception questions		X
• Complete menstrual questions		X
• Complete pregnancy history questions		X

7.6.4. Interim or Off-cycle Visits

Because this is an online observational study, we do not anticipate any interim visits to occur that are related to participating in the study.

7.6.5. Early Discontinuation

Incomplete surveys will be excluded from the analysis. Persons who are not verified as participants in the CFFPR between 2010 and 2018 will be excluded.

7.7. Sample Size

During the pilot phase, the study team will further discuss the statistical plan to ensure adequate numbers of participants are enrolled in the study. Based on information from participating centers, we expect to enroll approximately 600 women and expect about half of them to be on hormonal contraceptives based on our pilot study. The following table shows the power for detecting different RRs of non-hormonal to hormonal contraceptives in women and baseline proportion of outcome in the non-hormonal contraceptives group.

Table 8: Sample size calculation

	Using Poisson Regression Power to detect a Rate Ratio (hormonal / non-hormonal)
Total Sample Size	**RR=0.70**
450	0.77
475	0.80
500	0.82
525	0.83
550	0.85
575	0.86

Recent data following the U.S. FDA approval of genetic modulators, show that in this population (mean age 25 years) there are approximately 0.8 PEx/year (13). Using Poisson regression, this study will have 80% power to detect a rate ratio of 0.70 between the progestin-only and combined hormonal groups with 575 enrolled women with CF (assuming alpha 0.05 and an estimated attrition rate of 15%). Although triple therapy has already been FDA approved, we do not anticipate this will affect our retrospective study design since we are evaluating years prior to FDA approval of triple modulator therapy.

7.8. Recruitment

We aim to recruit up to 625 female patients ages 18-45 years across 10 CF Centers. We may enroll an additional 25 participants to off-set participants who participated in a prior contraceptive study (4). The UW research team will ask each participating CF center research staff to invite all women ages 18-45 years who have been seen at their clinic within the last 2 years to participate in this retrospective contraceptive study. By inviting all potential qualified participants, we reduce selection bias of only those who physically come to the CF center on a regular basis. CF center research staff will send an email to all eligible women in their clinic and follow up with a phone call to recruit potential participants. In addition, women who come to the clinic for routine visits with their CF clinician during the first year of the study will be asked to enroll in the study by the CF center research staff member.

7.8.1. Participant Incentives

Participants will be paid for enrolling into the study and completing the questionnaire ($30). We have based this amount on the CFF hourly rate for research subjects of $30/hour.

8.0. Methods: Assignment of interventions

8.1. Allocation

Participants will belong to a group based on their choice of contraception. Women with CF will be allocated to hormonal group (intervention), non-hormonal groups (control), and never used contraception.

8.2. Blinding

This is a retrospective, observational study. This trial is not blinded.

9.0. Methods: Data Collection, Management, and Analysis

9.1. Data Collection Methods

The women with CF who are enrolled at any of the 10 CF centers will complete the contraceptive and reproductive health questionnaire. We will ask for exposure data as far back as 2008. One way we will improve exposure data will be to reduce recall bias with pictures of most birth control pill packages and other birth control methods. Exposure questions will be piloted as described in 6.0 above. Survey responses will be entered directly into a REDCap database which will be developed at UW. REDCap is HIPAA compliant and securely accessible from anywhere with Internet access, and feasibly merges data from separate REDCap databases into a single database. Next, UW will send the CFFPR a list of patient names, their birthdates, and CFFPR ID. The CFF will provide UW with their CFFPR ID and requested registry data. UW will assign a central ID number for each participant, so that data from each of the databases can be connected for analysis. We will import data from CFFPR using Excel into a REDCap database housed at UW.

Data will be collated at the UW. When a computer is available, participants will answer directly into the database, which leaves less room for transposing errors. In case of technical difficulty with computer access to the REDCap website, the clinical site will receive paper source documents. Each survey (online and paper) will be identified by the participant's study number.

9.1.1. CFFPR Data Elements

A complete list of data points being requested from CFFPR are in the Appendix.

9.1.2. Clinic Case Report Forms (CRF)

We are requesting CRFs from each of the 10 CF centers in order to verify DXA scan findings with bone data reported in the CFFPR.

Table 9: Information sought on CRF

EMR Data Request
• DXA scan results: dates and results as far back as 2013. Results will include T-scores and Z-scores from 3 sites: femoral neck, lumbar spine, and total hip and date that DXA scan was performed.

9.1.3. Patient Surveys

Table 10: Information in online, self-respondent surveys

Survey Once Enrolled
• Demographics: marital status, race/ethnicity, and education
• Past medical history: ever smoked, ever had a blood clot requiring anticoagulation, # PICC lines placed, PORT in place (dates)
• Medication history: ever taken CFTR modulator (with start and stop dates)
• Surgical history: Tubal ligation, hysteroscopic sterilization, hysterectomy, bilateral oophorectomy, other operation that has made it impossible to get pregnant
• Menstrual history: menarche, regularity of menstruation, menopause
• Contraception questionnaire   ◦ Questions regarding types of contraception used since 2008, start and stop dates of each method or age at first/last use. Questions are based off of the National Survey of Family Growth (NSFG)

• Pregnancy history questionnaire
  ◦ Includes number of pregnancies in lifetime, year(s) pregnant, outcome of pregnancy, whether pregnancy was planned or not
  ◦ Additional questions to include for funded study (Taylor-Cousar and Jain): times visited CF center during pregnancy and type of provider who cared for participant during pregnancy, ART

9.2. Data Management

The University of Washington will have the overall responsibility of this project and will serve as the Data Coordinating Center. As the Data Coordinating Center, UW will create the source documents for the study and be responsible for creating and managing the web-based, password-protected database. Any paper copies of the survey responses will be maintained in locked files in a locked room.

Participants will enter responses to the questionnaires directly into a UW Web-based program (REDCap). In case of technical difficulty with computer access to the REDCap website, participants will complete paper source documents. In order to ensure that surveys are being completed only by eligible participants, patients will be sent unique survey links that are connected to their email address. Therefore, if patients share the survey link with others, they can be contacted if there are multiple survey responses connected to their email address.

Case Report Forms (CRFs) will be de-identified, with only the participant study ID number, and entered into REDCap, a web-based, password-protected database managed by UW. CF centers will have access to a separate password-

protected database that links the participant survey ID number with the name and birthdate of the participant, so that the selected CF center that is providing EMR data can complete the CRF with their institution's EMR.

The self-respondent contraception and reproductive history questionnaire will be entered into a separate REDCap database from the CRF information entered by the respective CF centers.

The UW will create a webpage for the study where CF centers can log in and view real-time, prepared reports that show response rates for patients at their CF center.

UW will send the CFFPR a list of participants and their birthdates, and CFFPR ID number. The CFF will provide UW with their CFFPR ID and requested registry data in Excel format. The UW will assign a central ID number for each participant, so that data from each of the databases can be connected for analysis.

9.3. Statistical Methods

Because this is a retrospective cohort study, we are most interested in determining whether this exposure (to hormonal contraception) is associated with our primary outcome (counting the number of pulmonary exacerbations requiring additional IV in a given year) and/or our secondary outcomes (new respiratory microbiology, liver disease/non-cirrhosis, gallstone, requiring surgery/procedure, improved BMI, incidence of VTE, osteoporosis and fragile bone fracture). Women on hormonal contraception will be compared to the primary control group of women on non-hormonal contraception. We will also compare to women on no contraception, as the secondary control group. We will exclude persons with these existing diagnosis at the start of the follow up period for outcome data (January 1, 2010). Within this objective we will be able to calculate incidence rates, relative risks and confidence intervals. We will use Poisson regression to calculate progestin-only and combined hormonal method to non-hormonal method pulmonary exacerbation rate ratios and 95% confidence intervals. This allows for adjustment of follow-up time of each individual.

(Objective 1a): We will evaluate lab values over time (ppFEV1%, serum AST, ALT, alkaline phosphatase) to determine if trends between hormonal contraceptive users and non-hormonal contraceptive users differ. See Table 5 for confounders and covariates that we will use to adjust for the primary and secondary outcomes.

We will model ppFEV1 via generalized estimating equations (GEE), allowing for correlation within a subject, and compare via a fixed effect for exposure. Among women who change or stop contraception, we will estimate and compare within-participant difference in outcomes via the model (if numbers allow). We will censor women who switch method types or become pregnant, and for 6 months post pregnancy, for the primary analysis and subsequently follow them to leverage within-patient data and analyze changes in pulmonary status and contraception. Presence of respiratory microbiology will be estimated longitudinally via GEE with a logit link function. Graphic displays and summary statistics will be used; all *p* values will be two-sided.

We will assess the strength of agreement between CFFPR reported data on osteoporosis, osteopenia and bone fracture compared to gold standard clinic DXA scan T-scores. We calculate the percent overall level of agreement between the CFFPR and clinical BMD scores using Cohen's kappa statistic calculation. Level of absolute agreement represents the proportion of participants for whom the CFFPR and clinic DXA scan T-score were correct. We will also report on proportion of scores entered within the year or year after DXA scan was completed, versus scores entered 3-5 years after DXA scan completed.

Missing Data

We will plan to impute missing data as our primary analysis. Should we discover large amounts of missing data, we will perform a sensitivity analysis excluding women with missing data to explore how findings differ from those without missing data.

Computer Facilities

Appropriate computer facilities are readily available for data analysis. REDCap will be used for entry and preparation of data for statistical analysis. Statistical analysis will be performed using STATA 12.

10.0. Methods: Monitoring

10.1. Disposition

The study ends for the participants once participants complete the survey and the CF center research staff complete the case report forms.

10.2. Safety Assessment Methods

Because this is an observational study, we do not anticipate any adverse events on account of this study. Participants may feel uncomfortable answering questions about their medical history, birth control and pregnancy history. They may decline to answer any of the online survey questions at any time. Participants may feel uncomfortable with the research team accessing their data from CFFPR. The research team will do their best to protect your privacy during this process.

10.3. Adverse Event Management and Reporting

An adverse event for this study may include a breach of confidentiality. Should a confidentiality breach occur, it will be reported to the Institutional Review Board by the investigator (according to the local policies). No Data Safety Monitoring Board will be used for this study.

Participants will also be provided the site PI and study PIs contact information should a participant believe they have a medical problem or illness related to this research. The principal investigators at each site will be responsible for monitoring participant confidentiality.

10.4. Duration of Project (see Table 11)

- The duration of the project is expected to be about 36 months.
- Recruitment is expected to take 12 months.
- Merging of the data and cleaning the database is expected to take up to 4 months.
- Data analysis will take 3 months.
- Creation of the web-based REDCap database for data entry will occur before enrollment begins, and data entry will be ongoing throughout the study.

11.0. Ethics and Dissemination Plan

All of the information participants and clinics provide for this study will be kept confidential. When participants open the online survey, they will automatically be assigned a subject ID number. Based on the assigned ID number, centers will be able to identify which of their patients have already enrolled in the study. This number will be connected to the identifying information provided by participants to locate their records in the CFFPR. After participants complete their online survey, UW will send the identifying information (CFFPR ID or name, date of birth, and zip code) along with the subject ID number assigned by UW to the CFFPR team. They will use this information to pull participant data from 2010-year as recent as possible. They will provide us with this data attached to the subject ID number. The link between participant identifiers and the research data will be destroyed after the records retention period required by state and/or federal law.

Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, participant records may be examined. The reviewers will protect the subjects' privacy. The study records will not be used to put participants at legal risk of harm.

We plan to present our data at the North American CF Conference and the Society of Family Planning Conference. We will develop a summary paper from this feasibility study consistent with "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines for reporting observational studies for publication (14).

Table 11: Project Timeline

Activities & Timeline	Pre-Award Period	YEAR 1							YEAR 2					
		2019			2020						2021			
		Aug - Sep	Oct - Nov	Dec	Jan-Feb	Mar - Apr	May - Jun	Jul	Aug - Oct	Nov - Dec	Jan - Feb	Mar - Apr	May - Jun	Jul
IRB application submission and approval														
Institutional subcontract finalization														
Interdisciplinary Team meetings (Zoom for remote participants)														
Progress report due to CFF (due 90 days before start of next award period)							Due 5/1/20						Due 5/1/21	
Financial report due to CFF (due 90 days after completion of prior award period)										Due 11/1/20				
CFFPR Data Application submission and approval														
CFF Confidentiality Agreement and Information Use Agreement														
Create recruitment letters for clinical sites														
Pilot and finalize patient questionnaire														
Set up questionnaire in REDCap														
Recruit patients from CF Centers (on-going)														
Database design and setup														
Data control quality checks for patient questionnaire														
Self-respondent and CF Center CRF database cleaning														
Prepare and submit NACFC and NAPCRG abstracts														
Prepare manuscript on pilot study for publication														
Submit manuscript for publication (journal TBD)														

Activities & Timeline	YEAR 3							
	2021			2022				
	Aug - Sep	Oct - Nov	Dec	Jan - Feb	Mar - Apr	May - Jun	Jul	Post Award Period
Progress report due to CFF (due 90 days before start of next award period)						Due 5/1/22		
Financial report due to CFF (due 90 days after completion of prior award period)		Due 11/1/21						
Final project/scientific report and final report of expenditures due to CFF								Due no later than 11/1/22
Interdisciplinary Team meetings (Zoom for remote participants)								
Import and merge data from CFFPR								
Determine randomized group of women from each of the 10 CF centers whose EMR will be reviewed for DXA results								
CF centers do EMR data pull								
Additional database cleaning post merging of databases								
Conduct analysis								
Prepare manuscripts for publication and abstracts to NACFC								
Submit manuscript to CFF for review								
Submit revised manuscript to peer-reviewed journal (J of CF)								

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APPENDIX: List of CFFPR cariables that will be requested from the CFF once recruitment of up to 625 respondents is complete. Data will include years 2010-to most recent year available.

I. DEMOGRAPHICS

- *Birth characteristics*
  - Date of birth (mm/dd/yyyy) [PHI]
- *Race/Ethnicity*
  - Race includes 'White'
  - Race includes 'Black or African American'
  - Race includes 'American Indian or Alaska Native'
  - Race includes 'Asian'
  - Race includes 'Native Hawaiian or Other Pacific Islander'
  - Race includes 'Some other race'
  - Patient is Hispanic
- *Health insurance*
  - Health insurance policy (i.e. private insurance)
  - Medicare
  - Medicaid
  - State special needs program (BCMH, CCS, CRS, GHPP...)
  - TriCare or other military health plan
  - Indian Health Service
  - Other health insurance
  - Patient has no health insurance for the entire year
  - Patient covered on their parents' insurance plan
  - Receives free medicine/assistance from patient assistance program
- *Socioeconomic characteristics*
  - Patient's education
- *Smoking*
  - Patient smokes cigarettes during the reporting year
- *Research involvement*
  - Patient participated in interventional (drug) studies
- *Patient pregnancy*
  - Patient was pregnant during the reporting year
  - Outcome of patient's pregnancy

II. DIAGNOSIS

- *Diagnosis date*
  - First year in the CFF Patient Registry
  - Research involvement
  - Patient participated in interventional (drug) studies
- *Genotyping*
  - Has this patient been genotyped
  - Mutation classification
  - Name of the first mutation
  - Mutation 1 Class
  - Name of the second mutation
  - Mutation 2 Class
  - Delta F508

III. CLINIC VISITS

- *Visit details*

  - Date of Encounter [PHI]
  - Encounter age [PHI]
- *Pulmonary exacerbation - encounter level*
  - Assessment of potential pulmonary exacerbation
- *Pulmonary exacerbation - summarized by calendar year*
  - Any pulmonary exacerbation assessment in the year
  - Any pulmonary exacerbation assessment positive in the year
  - # encounters with pulmonary exacerbation assessments: absent
  - # encounters with pulmonary exacerbation assessments: mild exacerbations
  - # encounters with pulmonary exacerbation assessments: moderate exacerbations
  - # encounters with pulmonary exacerbation assessments: severe exacerbations
  - Encounter exacerbation treatment: Incr. airway clearance
  - Encounter exacerbation treatment: Oral NON-quinolone antibiotic
  - Encounter exacerbation treatment: Oral quinolone antibiotic
  - Encounter exacerbation treatment: Inhaled Antibiotic
  - Encounter exacerbation treatment: Inhaled + Oral NON-quinolone antibiotic
  - Encounter exacerbation treatment: Inhaled + oral quinolone antibiotic
  - Encounter exacerbation treatment: None of the above

IV. CLINICAL MEASUREMENTS

- *Anthropometric measures - encounter level*
  - Patient's height
  - BMI Value
  - BMI Percentile
  - Weight of Patient
- *Pulmonary function tests - encounter level*
  - Measure of FVC
  - Percent predicted relative to predicted FVC
  - Predicted Value for FVC using GLI reference equations
  - Measure of FEV1
  - Percent predicted relative to predicted FEV1
  - Predicted Value for FEV1 using GLI reference equations
- *Lab values - encounter level*
  - Alanine Aminotransferase (ALT or SGPT), IU/L
  - Fecal elastase value (microg/g of stool)
  - Alkaline phosphatase 2 hour blood glucose (mg/dL)
  - Total bilirubin, mg/dL
  - Hgb A1C value, %
  - Liver enzymes drawn (pre-2010) Aspartate aminotransferase
  - GGTP (gamma glutamyl transpeptidase), IU/L
  - Fasting glucose level (mg/dL)
  - OGTT Fasting glucose level (mg/dL)
- *Lab values - summarized by calendar year*
  - Fasting glucose level (mg/dL)
  - OGTT fasting glucose level (mg/dL)
  - 2-hour blood glucose (mg/dL)
- *Screening tests*
  - Liver function tests performed
  - DEXA scan for bone density performed in the reporting year
  - DEXA scan result is normal

- DEXA scan result is osteopenia
- DEXA scan result is osteoporosis
- DEXA scan result is other
- DEXA scan result is unknown

V. MICROBIOLOGY

- *Bacteria - encounter level*
  - Was bacterial culture done?
  - Date of bacterial culture [PHI]
  - Culture results
  - Staphylococcus aureus
  - MRSA
  - Any Burkholderia Complex species
  - Multidrug-Resistant P. aeruginosa (MDR-PA) Infection
  - Stenotrophomonas
  - MSSA
  - Pseudomonas aeruginosa found in the culture
  - Mucoid Pseudomonas aeruginosa
  - Non-mucoid Pseudomonas aeruginosa
  - Mucoid Pseudomonas aeruginosa status unknown
- *Mycobacteria - encounter level*
  - Was mycobacterial culture done?
  - Date of myco culture [PHI]
  - Myco culture results
  - Mycobacterial tuberculosis
  - Mycobacterium terrae
  - Mycobacterium other
  - Mycobacterium abscessus/chelonae
  - Mycobacterium avium complex
  - Mycobacterium fortuitum group
  - Mycobacterium gordonae
  - Mycobacterium kansasii

VI. TREATMENTS

- *Antibiotics - encounter level*
  - Chronic oral macrolide antibiotic
  - Azithromycin
  - Clarithromycin
  - Sulfa
  - Amoxicillin
  - Tetracycline
  - Other oral antibiotic
  - Other chronic oral antibiotic
  - Quinolone
  - Cephalosporin
- *CFTR modulators - encounter level*
  - On Ivacaftor medication (VX-770)
  - VX770 (Ivacaftor) dosage
  - Ivacaftor/Lumacaftor (i.e., Orkambi)
  - Ivacaftor/Lumacaftor (i.e., Orkambi) dosage
- *Other treatments - encounter level*

  - Patient is taking enzymes
  - CF-specific vitamins (i.e. vitamins A, D, E and K)
  - Exercise
- *Other treatments - annual*
  - Was the patient started on treatment for NTM

VII. COMPLICATIONS

- *CF related diabetes - encounter level*
  - CFRD Status
  - Chronic renal insufficiency
  - Chronic renal failure requiring dialysis
- *Liver disease - encounter level*
  - Gall stones
  - Gall stones, requiring surgery/procedure
  - Liver disease, cirrhosis
  - Acute hepatitis
  - Acute hepatitis - infectious
  - Acute hepatitis - non-infectious
  - Acute hepatitis - unknown
  - Liver disease, non-cirrhosis
  - Hepatic Steatosis
  - Liver disease, other Acute liver failure
- *Other complications - encounter level*
  - Bone fracture
  - Osteopenia
  - Osteoporosis
  - Cancer confirmed by histology

VIII. CARE EPISODES (HOSPITALIZATIONS/HOME IV)

- *Care episodes*
  - Start date for care episode [PHI]
  - End date for care episode [PHI]
  - # home IV nights with reason pulmonary exacerbation
  - # hospitalization nights with reason pulmonary exacerbation
- *Care episodes - summarized by calendar year*
  - Total # pulmonary exacerbations treated by IV antibiotics
  - # nights in hospital for pulmonary exacerbations
  - # nights on home IV for pulmonary exacerbations
  - Total # pulmonary exacerbation treated by IV antibiotics (incl unknown)
  - # nights hospital for pulmonary exacerbation (incl unknown)
  - # nights home IV for pulmonary exacerbation (incl unknown)