TITLE: CYSTIC FIBROSIS AND URINARY INCONTINENCE
NCT04922255
DOCUMENT DATE: 8/5/2020

RESEARCH PLAN

A. HYPOTHESIS AND SPECIFIC AIMS

With advancing treatments and management, the median life expectancy of people with cystic fibrosis (CF) has increased into the fifth decade of life.[1] As women with CF age, focus has shifted to previously overlooked aspects of care including sexual and reproductive health.[2] Urinary incontinence (UI), defined as the complaint of involuntary loss of urine,[3] is an understudied component of the lives of many women with CF. Previous work investigating incontinence in adult women with CF has reported a prevalence of 30-76% with associated impaired quality of life.[4–6] In general, UI is categorized as 1) stress urinary incontinence (SUI), related to effort or physical exertion including coughing, 2) urgency urinary incontinence (UUI), related to loss of urine associated with urgency, or 3) a combination of both, deemed mixed incontinence (MUI). Although it is reported that the majority of women with CF and UI experience stress leakage secondary to chronic cough and use of chest physiotherapy,[7,8], there has never been an objective investigation categorizing the type of UI experienced by this population. Ultimately, not enough is known about the characteristics of UI in women with CF, and this lack of data limits the ability of providers to make recommendations regarding treatment options. Furthermore, the impact of highly effective modulator therapy (HEMT) on coughing and resultant UI is unknown. Accepted nonsurgical therapies for UI include behavioral therapies such as bladder training and pelvic floor muscle training (PFMT)[9] or intravaginal mechanical devices.[10,11] There are also newer absorbent products for UI that may be preferred over disposable pads.[12] Surgical alternatives for UI do exist, but these are considered second or third line and are preferred only in women who have completed childbearing.[11,13] Very small studies have begun to investigate the improvement of symptoms in women with CF after PFMT,[14] but additional research surrounding treatment modalities and larger studies are imperative.
The overall aim of this project is to investigate symptoms and quality of life of women with CF and UI, to document objective exam findings, and to perform a feasibility and tolerability study of common non-surgical management options for UI.[15] We hypothesize that treatment adherence and tolerability of PFMT may be less than with reusable absorbent underwear or disposable intravaginal devise and that the majority of women with CF and UI will have objective SUI on exam. Through the application of well-established clinical and qualitative research methodologies, we will provide a rigorous investigation of UI in women with CF. We will take important steps towards improving the treatment of women with CF and UI, and inform the design of a larger, multi-center, randomized trial of treatment modalities.

Specific Aim 1 – **Explore the experiences, attitudes, and knowledge of women with CF related to UI and potential treatment modalities.** We will conduct individual, semi-structured interviews with women with CF with UI (n~20-30) to assess how UI impacts symptoms and quality of life, evaluate barriers they experience regarding access to care/treatment, assess knowledge of available treatment for UI, and determine factors that influence decision-making surrounding treatment options. Subjects will be recruited primarily through the Cystic Fibrosis Foundation's Community Voice registry.
Hypothesis: Women with CF will report UI symptoms, decreased quality of life, limited knowledge about potential treatments and preference towards treatment with low time commitments.
Specific Aim 2 – **Evaluate the feasibility of a randomized controlled trial of non-surgical UI management options for women with CF.** We will complete a pilot, feasibility study (n=30) to compare tolerability and symptom relief in women with CF and UI. Subjects will be recruited from both study sites after demonstrating bother from UI on standard questionnaires. They will undergo UI questionnaires and undergo a pelvic examination, non-invasive bladder scan ultrasound and a provocative stress test and then be randomized to either a disposable urethral support device (Impressa®), an absorbent product (Speax Reusable Underwear), or PFMT. Our primary outcome will be to determine the feasibility and tolerability of these options.
Hypothesis: All three non-surgical UI management options for women are feasible (as measured by 80% adherence to treatment assignment over 7 days) and tolerable (as measured by patient report via questionnaire).

The results from our proposed aims will provide important information about the experiences and symptom burden of women with CF and UI. Importantly, we will also be able to answer the important questions of "Can it work?" and "Does it work?"[15] as we seek to construct the definitive, adequately powered trial of these therapies in women with CF and UI.

B. INNOVATION STATEMENT:

This proposal is the first formative research exploring the mechanism of UI in women with CF and patient experiences and perceptions regarding UI and their treatment options. It will also be the first to assess feasibility and symptom improvement of nonsurgical treatment modalities for this population. As such, these are all important steps to 1) learn where to focus patient and provider education efforts and changes to the CF care model, 2) begin to understand what treatment may be preferred by and feasible for women with CF, and 3) clarify the underlying cause of UI. Results will inform the content and design of a future multi-center, randomized trial aimed at determining the best option for nonsurgical treatment of UI (PFMT with bladder training, urethral support devices, or reusable absorbent products) in women with CF. Importantly, subjective and objective data will provide key data points to allow for power calculations of this trial and multiple patient feedback assessments will be utilized to determine feasibility of future trial. Utilization of patient consultants will provide additional input to ensure successful completion of aims and design of future trial. Given that a robust feasibility trial ensures a realistic assessment and capability to conduct the clinical trial[16], we feel this proposal has the chance to innovate care of women with CF and UI.

This interdisciplinary approach combines the expertise of the PI as a urogynecologist regarding evaluation and management of UI in women and the co-PI as a pulmonologist with an extensive expertise in women's health and qualitative research in the CF population. The proposal also leverages the existing collaborative relationships between both the CF centers and the Urogynecology departments at the University of Pittsburgh and Johns Hopkins University. We seek to extend the expertise of healthcare providers caring for women with CF beyond their pulmonologist. By learning about treatment seeking preferences, goals of care, delineation of underlying UI physiology and treatment tolerability, we will be able to grant women's health providers with the tools to care for women with CF and UI. Importantly, this is the beginning of a significant collaboration between providers with unique, relevant expertise that has the possibility of advancing the care and lives of women with CF.

C. BACKGROUND AND SIGNIFICANCE

Urinary Incontinence in Women - In women, UI is present in up to 37% of women age 20-39 years and "daily UI" is reported by up to 40% of women over age 60 years.[17] In younger, nulligravid women without CF, the presence of UI is associated with lower psychological well-being.[18] In general, UI is categorized as 1) stress urinary incontinence (SUI), related to effort or physical exertion including coughing, 2) urgency urinary incontinence (UUI), related to loss of urine associated with urgency, or 3) a combination of both, deemed mixed incontinence (MUI).

Urinary Incontinence in Women with CF - With advancing treatments and management, the life expectancy of people with cystic fibrosis (CF) has increased to a median of 44.4 years according to the CF Foundation 2018 Registry Report.[1] As women with CF age, focus has shifted to previously overlooked aspects of care including sexual and reproductive health.[2] UI, defined above as the complaint of involuntary loss of urine,[3] is an understudied component of the lives of many women with CF. Previous work investigating incontinence in adult women with CF has reported a prevalence of 30-76% with associated impaired quality of life.[4–6] Recent unpublished data from a large, multi-center survey of over 400 women with CF age 25 years and older has found that 49.8% of women have UI, with >13% experiencing daily symptoms. Activities such as coughing and airway clearance therapy (ACT) are reported as primary triggers, and, importantly, almost 40% of women report some degree of impact on their ability to effectively complete their chest physiotherapy.[19] Importantly, the impact of highly effective modulator therapy (HEMT) on coughing and resultant UI is unknown.

In the general population of women with UI, there has been extensive literature surrounding objective measurements for UI, ranging from complex, multi-channel urodynamics, which is an invasive procedure to measure a variety of values to describe UI parameters, to a non-instrumented cough stress test (CST), which is a non-invasive measure of objective SUI. Importantly, a positive CST has been shown to strongly correlate with subjective severity measures in the general population.[20] Currently, there *is no data* on the correlation between subjective measures and objective, physical exam findings in women with CF and UI. Although it is

reported that the majority of women with CF and UI experience stress leakage secondary to chronic cough and ACT,[7,8] there has never been an objective investigation categorizing the type of UI experienced by women with CF. Subjective and objective measures seem to be correlated in other populations,[21] as we seek to streamline care for women with CF, additional investigation is necessary. Importantly, a better understanding of the prevalence of SUI in women with CF and subjective UI will aide in the trial design and power calculations for future investigations.

Treatment modalities for UI - Accepted non-surgical therapies for UI are behavioral therapies such as bladder training and PFMT[9] or intravaginal mechanical devices for women with SUI.[10] Although surgical options such as midurethal slings for SUI[22] and intradetrusor onabotulinum toxinA (Botox) for UUI exist, guidelines recommend initial trials of conservative therapies.[13] There are also newer absorbent products for UI that may be preferred over disposable pads.[12] In the limited literature regarding treatment preference in women with UI, the individual experience of the population can significantly effect preferences for treatment. Some women may prioritize a risk-benefit balance while others may prioritize time commitment. Some women prefer utilization of web-based information and application based services while others prefer in-person contact with physicians.[23–25] Most qualitative studies focus on the experience of either women in the postpartum period[26]Very small studies have begun to investigate the improvement of symptoms in women with chronic lung conditions (including CF) after PFMT,[14] but additional research surrounding other treatment modalities and larger studies are lacking. Currently, not enough is known about the characteristics of UI in women with CF, and this lack of data limits the ability of providers to make recommendations regarding treatment options.

Feasibility studies can help determine whether an intervention should be recommended for efficacy testing.[15] Given that we currently do not have enough understanding of treatment preferences, prevalence of objective stress urinary incontinence, tolerability of interventions or effect size of improvement after these modalities, a feasibility study is imperative to inform a future, definitive and adequately powered randomized controlled trial.

D. Preliminary Results

The co-investigator conducted an anonymous survey exploring self-reported general and CF-specific sexual and reproductive health concerns with adolescent and young adult women with CF ages 15-24 years from five U.S. CF centers.[2] Questions included UI prevalence, age of onset, severity, triggers, and patient burden. Among the 188 participants (mean age 19.7±2.7 years), one out of six adolescent and young adult women with CF reported ever having experienced UI with a mean age of onset of 15.7±4.5 years. Only 15% of all participants reported ever discussing UI with their CF team with a mean age of first discussion of 16.0±2.7 years. One-fifth of those reporting UI experienced symptoms more than once a day. Of those affected by UI, the top triggers reported were bad coughing fits (87%), laughing (40%), sneezing (27%), and any coughing (20%). One-third of those affected reported that UI sometimes prevented them from coughing effectively and performing full ACT sessions. UI was significantly associated with lower self-reported FEV_1 ($p<0.01$). No significant association between UI and self-reported CF severity, BMI, CF-related diabetes, CF-related liver disease, or presence of a gastrostomy tube was found.

In a similar ongoing survey of women with CF ages 25 years and older from 10 U.S. CF centers (currently, n=452, mean age 36.2 ±10.2 years),[19] 50% (n=224) have experienced UI with 83% reporting symptoms once a month or more. Of those affected by UI, the top triggers reported were bad coughing fits (87%), laughing (40%), sneezing (40%), physical activity (25%), any coughing (22%), and chest physiotherapy (17%). Nearly half of those affected (45%; 100/224) reported that UI sometimes or often prevented them from coughing effectively and performing full ACT. Twenty-seven percent never discussed UI with anyone and less than 30% of women with CF have spoken to their CF team about UI.[27] Analysis of UI with self-reported CF outcomes is in progress.

E. EXPERIMENTAL DESIGN AND METHODS

<u>Aim 1.</u> Explore the experiences, attitudes, and knowledge of women with CF related to urinary incontinence and potential treatment modalities.

<u>Overview:</u> Women with CF age 18 years and older who have experienced UI (n~30) will be recruited to participate in individual, semi-structured interviews. We have selected qualitative methodology to avoid

approaching the topic with preconceived theories or hypotheses.[28] This will be the first study to explore the patient experience surrounding their care for UI. Based on prior research by the coinvestigator, we believe that women with CF will have significant bother from their UI but that, given the burden of their other disease-related comorbidities, treatment preferences will be skewed towards options with low time commitment.

Description of Participants and Participating Study Sites: *Inclusion criteria:* 1) Female age 18 years or older 2) Diagnosis of CF 3) Reports UI 4) Fluent in spoken English
Recruitment sites: The Cystic Fibrosis Foundation's Community Voice registry which is composed of more than 1,100 members, including people with cystic fibrosis and their families.[29] We will send out a call for subjects through our partnership with Community Voice to include women who report urinary incontinence. A letter of support is attached.
Sample size: Determining sample size in qualitative research is a matter of judgment and experience in evaluating data collected guided by content saturation.[30] For this project, we estimate the need for approximately 30 participants based on previous qualitative work of a similar nature.[31] We will purposively sample a range of patient ages and previous pregnancy history (as pregnancy can influence incidence of UI) to gain a breadth of perspectives.

Study Procedures: Participants will be recruited to participate in individual telephone interviews with the PI or a RC to understand their experiences and knowledge surrounding management of UI. The interview guide will be developed from existing work in other disease populations about similar themes[18, 19, 26,27] and will explore participants': a) experience with UI in daily life (and impact of HEMT on symptoms if applicable); b) care-seeking decision making; c) knowledge of available treatment and management options; d) preferences for treatment including perspectives on acceptable clinical venue for screening and factors that may influence tolerability of treatment options; e) support needs and preferences (Table 1). Interviews will be audio-recorded and transcribed verbatim. All participants will receive compensation for their time.

Table 1: Interview constructs and key questions[18, 19, 26–31]

Constructs	*Key Interview Questions*
Urinary incontinence (UI) experiences	• Tell me about your UI. • Tell me about the amount of UI you experience? • What activities tend to cause your UI? • How does your UI affect your daily life? • How has UI affected your CF? • [If applicable] Did HEMT change your experience with UI? • Did you ever seek treatment for your UI? If so, tell me more about that. • What are ways that you alter your daily life due to your UI?
Care-seeking decision making related to UI	• Did you discuss your UI with anyone? • Did you ever discuss UI with your CF care team or another healthcare provider? If so, tell me more about that. • What led you or would lead you to seek care or treatment for your UI?
Knowledge of UI treatment modalities	• Tell me what you know about the options for treating UI. • What do you know about physical therapy or pelvic floor muscle training (PFMT) to treat UI? • What do you know about other nonsurgical options to treat UI? (disposable pads, urethral support devices, absorbent products) • What do you know about surgical options to treat UI? • Where would you go to learn more about treatment options for UI?
Preferences for UI treatment	• In your opinion, what is the best way to identify women with CF who are experiencing UI? • Would you want to discuss UI with your CF team? Would you want to discuss UI with a women's health provider? • What factors play into the choice of how to treat UI for women with CF? (time burden, effectiveness, invasiveness of therapy/procedure, comfort, ease, etc.) Which of these factors is most important to you? • Explain how need to go to weekly appointments for physical therapy would affect your life? What factors would play a role in decided to pursue this therapy? • What is your goal for treatment of your UI? • How much time would you want to commit to your treatment of UI?
Support needs and preferences	• What advice do you have for other women with CF who are experiencing UI? • What would you like to tell your CF team when telling them about supporting women with CF who are experiencing UI? • What do you expect from your CF team regarding discussions and support for you related to your UI?

	• What resources would be helpful for you as a person with CF and UI?

Data Analysis: Transcripts will be analyzed through an iterative process of coding to identify themes. The principal investigator (PI) will develop an initial set of codes. Two coders will then independently review each transcript to apply the initial codebook and to identify additional codes using the NVivo qualitative analysis program. Using a consensus coding approach, after the first few transcripts are independently coded, the coders will meet to review their coding, discuss any discrepancies, and define any new codes; this will be repeated with subsequent transcripts using an iterative process until no new codes emerge. A senior co-investigator will be available to adjudicate any differences in interpretation and review the codebooks. The final coding scheme will be applied to all transcripts and the investigative team will identify central themes on the UI patient experience and treatment knowledge and preferences of women with CF. Representative quotations will be selected to illustrate themes identified.

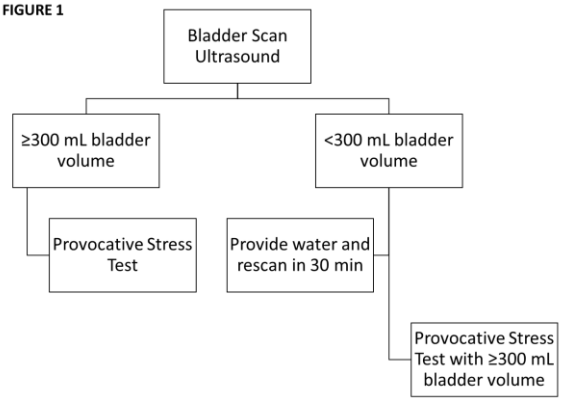
Aim 2. – **Evaluate the feasibility of a randomized controlled trial of non-surgical UI management options for women with CF.**

Overview: Nonsurgical therapies for UI include 1) behavioral training (e.g., bladder training, to teach one to gradually hold urine for longer periods), 2) PFMT to improve function of the pelvic musculature, and 3) urethral support devices.[38] Additionally, newer reusable absorbent underwear have been used to decrease common issues with disposable pads such as vulvar irritation.[12] To inform a larger trial, we propose a randomized, feasibility trial of a disposable urethral support device (Impressa®), Speax™ Reusable Underwear, or PFMT. As there *is no current data* on objective physical exam findings in women with CF and UI and, thus, limited evidence supporting the belief that this is SUI, all subjects will have a non-invasive pelvic exam to complete a non-instrumented cough stress test (CST) with a full bladder.[39] Together, data on objective findings, baseline subjective bother on validated questionnaires, and improvement of symptoms will aid in power calculations for future, multi-center trial for treatment options in women with CF and UI.

Description of Participants and Participating Study Sites: *Inclusion criteria*: 1) Female age 18 years or older 2) Diagnosis of CF 3) Self-reported UI (at least answer of "a little" on King's Health Questionnaire – Question #2) 4) Fluent in spoken English 5) Ability to present for in-office exam and study procedures

Recruitment sites: Cystic Fibrosis Center (CF Center) at the University of Pittsburgh and the Johns Hopkins Cystic Fibrosis Center. These two sites have a current working relationship and also the capabilities for study procedures as discussed in facilities section. Study Procedures: Participants will be recruited at routine CF clinic visits and via telephone screening. Informed consent will be obtained before any study procedures are initiated. **Baseline visit.** Initial demographic questions and the King's Health Questionnaire[40] will be completed at the baseline visit. Subjects will be given materials to complete a 2-day bladder diary.[41] Participants will then have a pelvic exam for a visual urethral mobility examination[42] and assessment of pelvic floor muscle strength.[43] This exam will be completed by the urogynecology faculty at either site. We will first perform a bladder scan ultrasound to assess current bladder volume and then a cough stress test (CST). (Figure 1) The exam will be performed in the supine/lithotomy position with ≥300 mL of fluid in the bladder. We will have the subject cough forcefully 1-4 times and the examiner will directly visualize the urethral meatus for the presence of leakage. Leakage of fluid from the urethral meatus coincident with/simultaneous to the cough(s) is considered a positive test consistent with SUI.

FIGURE 1



Randomized feasibility trial (Table 2). At the baseline visit, women will be randomized to either a disposable urethral support device (Impressa®), Speax™ Reusable Underwear, or PFMT. Randomization will be in a 1:1:1 allocation stratified by site. The disposable Impressa® urethral support is a tampon-like device that is available over the counter to help women with UI. Speax Reusable Underwear are similarly available for purchase online and are absorbent underwear for bladder leak protection. Urethral support device cohort - A week supply of the Impressa device will be provided and participants will be asked to complete a daily bladder

diary for a total of 7 days. Reusable absorbent pad cohort – Two pairs of Speax underwear will be provided and subjects will complete a similar daily UI diary for 7 days. PFMT cohort - Experienced pelvic health physical therapists (at both University of Pittsburgh and at Johns Hopkins University) will complete two visits one week apart. We will develop a standardized pelvic floor exercise intervention based on previous RCT for PFMT in women with MUI.[44] The intervention will comprise: 1) Bladder training and delayed voiding techniques 2) Urgency suppression 3) SUI strategies (e.g., 'knack') and 4) PFM training for those agreeable to internal exams.[45] We were aware of the potential challenges for standardization of this type of intervention and ensuring consistency across multiple sites. We will limit the involvement to one experienced PT at each site and create a standardized protocol guided by both patient consultants, previous evidence, and expertise of Karen Von Berg, RT. Subjects will not be blinded to their group assignment given the nature of the differences in management options. At the end of the treatment assignment all subjects will repeat the KHQ and a patient global impression of improvement (PGI-I). The PGI-I is a validated one question measure rating their urinary tract condition now, as compared with how it was prior to before beginning treatment on a scale from 1 (Very much better) to 7 (Very much worse).[46]

Given the opportunity to gather acceptability on these options for a sensitive issue, subjects will be offered an option to further participate in one alternate therapy of their choosing. If they select this option we will organize an additional week of therapy and have them complete another PGI-I at the end of therapy. *Acceptability and Feasibility assessment:* Urethral support device cohort and Reusable absorbent pad cohort: Feasibility will be evaluated through assessment of use and product performance. Logs regarding utilization of assigned product will be completed daily. Patient treatment preference will be assessed after completion of both therapies utilizing the product performance questionnaire (PPQ).[47] The PPQ is a 17-item product questionnaire that consists of product questions that are specific to incontinence products and includes questions about overall impression of product, ability to hold urine, ability to prevent odor, fit, discreteness, comfort when wet and dry, and ability to keep skin dry.[47] PFMT cohort: Feasibility will be evaluated through assessment of adherence and self-reported success with ability to perform exercises. Adherence to intervention sessions will be documented by physical therapist using attendance logs. Adherence to home practice will be documented by participants in home logs that included the dates and times of practice. At the end of each physical therapy visit, participants will be asked to rate their confidence in performing the PFMT exercises featured in their program (extremely, very, moderately, somewhat, and not at all confident).

At the end of the cohort, all participants will be asked to indicate how easy it would be to continue practicing their assignment intervention (extremely, very, moderately, somewhat, and not at all easy).[48] All subjects will complete a Benefit, Satisfaction, and Willingness to Continue (BSW) questionnaire.[49] We will consider therapy feasible (as measured by 80% adherence to treatment assignment over 7 days) and tolerable (as measured by patient report via questionnaire). By allowing subjects to choose another one of the arms after their randomization this will give us further, important information about feasibility and patient preference for a larger trial.

Table 2: Study Flow

	Pre-baseline visit	Baseline Visit (in-person)	Randomized Trial Period							One week Cross-Over Period (optional)	End of Study
			D1	D2	D3	D4	D5	D6	D7		
Informed Consent	x	x									
KHQ		x									
Bladder diary		x	x	x	x	x	x	x	x		
Cough Stress test		x									
Randomization		x									
PGI-I									x		x
BSW									x		x
Cohort Specific Measures											
Urethral support device Cohort										x	
Reusable Underwear Cohort										x	
Utilization log			x	x	x	x	x	x	x		
PPQ			x	x	x	x	x	x	x		
Physical Therapy Cohort										x	
Physical Therapy Visit			x						x		

Attendance Log			x					x		
Confidence scale			x					x		

KHQ, King's Health Questionnaire; PGI-I, Patient Global Impression Improvement – Incontinence; PFMT, pelvic floor muscle therapy; PPQ, product performance questionnaire; BSW, Benefit, Satisfaction, and Willingness to Continue questionnaire

Data analysis: Descriptive statistics will summarize feasibility survey measures and use log data with sample means and standard deviations calculated for continuous variables and sample proportions for categorical variables with 95% confidence intervals. Due to the pilot nature of this trial, our analytic strategy centers on calculation of point estimates and 95% confidence intervals of our feasibility measures as primary outcomes, rather than hypothesis testing. We will compare initial subjective scores of UI to objective measures utilizing correlation coefficients. To explore preliminary efficacy, PGI-I score will be compared between groups utilizing ANOVA and post-hoc testing. Paired t-test will be used to examine if there is statistically significant difference in the average KHQ scores between arms. The mean PPQ scores will be compared between the Impressa® urethral support and Speax™ underwear and mean BSW score will be compared between all groups. For our randomized trial, we will recruit a total of 30 patients in order to have 80% power to detect at least a 10 point difference in total KHQ score with a significance level of 0.05 and assuming upwards of a 20% attrition rate for the study. Again, the feasibility trial is primarily designed to provide data to utilize for power calculations in future study designs.

F. Limitations and Potential Pitfalls:

Strengths of our study include the ability to quickly complete Aim 1 to allow for adequate time to complete Aim 2. The main limitation of our study is the small sample size in Aim 2, but given the primary goal of assessing feasibility, these aims primarily serve to inform our larger trial design. Additionally, in view of the lack of available data, these will be important stepping stones to adequately power future studies. Although the lack of a control group could be seen as a limitation, there is such a vast body of literature surrounding prevalence and quality of life in pre-menopausal women with UI.[50] Recruitment and retention of subjects can always pose a challenge. We will leverage the strong background of recruitment at our sites and the experience of our research coordinators to ensure adequate completion of aims. For Aim 1, we have a plan to recruit from Community Voice for aim 1 but can also recruit directly from participating centers. We have already communicated with Community Voice and have a letter of support included in our application. For Aim 2, we will start our feasibility trial by the end of year one of the grant period, so we are confident in our ability to complete our proposed aims in the study period. Additionally, the co-investigators Drs. Kazmerski and West are well-connected in the CF community and members of the CFF Women's Health Research Working Group. Thus, we foresee minimal issues forming additional partnerships with another CF center (such as University of Texas-Southwestern, University of Washington, or National Jewish), if necessary.

G. Consultant Arrangements: Ms. Lori Ferro and Ms. Joanna Conroy, both women with CF who have sought care for their experience with UI, will serve as a consultants on this grant. They will assist in study design, interview guide development, data analysis, and the writing and preparation of all manuscripts resulting from this research. In particular, they will provide a patient perspective, which is vital to this project. A Letter of Support is attached.

H. TIMELINE

	Year 1					Year 2			
	Pre-award	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
IRB application and approval aim 1									
Protocol final aim 1									
Aim 1 "Qualitative Interviews"		Recruit Participants			Transcription and Data Analysis				
		Complete Interviews							
Aim 2 "Randomized Feasibility Trial"			Finalize protocol using data from Aim 1						
					Recruit Participants				
					Begin and Execute Trial			Complete Trial	
								Data analysis	

Manuscript 1: Qualitative Interviews					Writing and submission			
Manuscript 2: Objective Exams and Questionnaires (from baseline visits)					Writing and submission			
Manuscript 3: Randomized Feasibility Trial								Writing and submission

I. Literature Cited

1. Fibrosis Foundation C. *2018 PATIENT REGISTRY ANNUAL DATA REPORT*.

2. Kazmerski TM, Prushinskaya O V., Hill K, et al. Sexual and Reproductive Health of Young Women With Cystic Fibrosis: A Concept Mapping Study. *Academic Pediatrics*. 2019;19(3):307-314. doi:10.1016/j.acap.2018.08.011

3. D'Ancona C, Haylen B, Oelke M, et al. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. *Neurourology and Urodynamics*. 2019;38(2):433-477. doi:10.1002/nau.23897

4. Frayman KB, Kazmerski TM, Sawyer SM. A systematic review of the prevalence and impact of urinary incontinence in cystic fibrosis. *Respirology*. 2018;23(1):46-54. doi:10.1111/resp.13125

5. Vella M, Cartwright R, Cardozo L, Parsons M, Madge S, Burns Y. Prevalence of incontinence and incontinence-specific quality of life impairment in women with cystic fibrosis. *Neurourology and urodynamics*. 2009;28(8):986-989. doi:10.1002/nau.20732

6. Reichman G, De Boe V, Braeckman J, Michielsen D. Urinary incontinence in patients with cystic fibrosis. *Scandinavian Journal of Urology*. 2016;50(2):128-131. doi:10.3109/21681805.2015.1096826

7. Nixon GM, Glazner JA, Martin JM, Sawyer SM. Urinary incontinence in female adolescents with cystic fibrosis. *Pediatrics*. 2002;110(2 Pt 1). doi:10.1542/peds.110.2.e22

8. Cornacchia M, Zenorini A, Perobelli S, Zanolla L, Mastella G, Braggion C. Prevalence of urinary incontinence in women with cystic fibrosis. *BJU international*. 2001;88(1):44-48. doi:10.1046/j.1464-410x.2001.02242.x

9. Gormley EA, Lightner DJ, Faraday M, Vasavada SP, American Urological Association, Society of Urodynamics, Female Pelvic Medicine. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment. *Journal of Urology*. 2015;193(5):1572-1580. doi:10.1016/j.juro.2015.01.087

10. Lipp A, Shaw C, Glavind K. Mechanical devices for urinary incontinence in women. *Cochrane Database of Systematic Reviews*. 2014;2014(12). doi:10.1002/14651858.CD001756.pub6

11. Conservative management - Urinary Incontinence in Women - NCBI Bookshelf. Accessed July 24, 2020. https://www.ncbi.nlm.nih.gov/books/NBK328050/

12. Alam PA, Burkett LS, Clark BA, White NC, Tefera EA, Richter LA. Randomized Cross-over Comparison of Icon^{TM} Reusable Underwear to Disposable Pads for the Management of Mild to Moderate Urinary Incontinence. In: *Female Pelvic Medicine and Reconstructive Surgery*. Vol 24. Lippincott Williams and Wilkins; 2018:161-165. doi:10.1097/SPV.0000000000000519

13. Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. *Journal of Urology*. 2019;202(3):558-563. doi:10.1097/JU.0000000000000309

14. Button BM, Holland AE, Sherburn MS, Chase J, Wilson JW, Burge AT. Prevalence, impact and specialised treatment of urinary incontinence in women with chronic lung disease. *Physiotherapy*. 2019;105(1):114-119. doi:10.1016/j.physio.2018.07.006

15. Bowen DJ, Kreuter M, Spring B, et al. How We Design Feasibility Studies. *American Journal of Preventive Medicine*. 2009;36(5):452-457. doi:10.1016/j.amepre.2009.02.002

16. Rajadhyaksha V. Conducting feasibilities in clinical trials: an investment to ensure a good study. *Perspectives in clinical research*. 2010;1(3):106-109.

17. Buckley BS, Lapitan MCM. Prevalence of urinary incontinence in men, women, and children-current evidence: Findings of the fourth international consultation on incontinence. *Urology*. 2010;76(2):265-270. doi:10.1016/j.urology.2009.11.078

18. O'Halloran T, Bell RJ, Robinson PJ, Davis SR. Urinary incontinence in young nulligravid women: A cross-sectional analysis. *Annals of Internal Medicine*. 2012;157(2):87-93. doi:10.7326/0003-4819-157-2-201207170-00005

19. Kazmerski, T.M., Stransky, O.M., Taylor-Cousar, J.L., Sawicki, G.S., Ladores, S.L., Godfrey, E.M., Aitken, M.L., Sufian, S., Jain, M., Barto, T.L., Billings, J., Hadjiliadis, D. and RJ. *Sexual and Reproductive Health Behaviors and Experiences of Adult Women with Cystic Fibrosis*.; 2020.

20. Nager CW, Kraus SR, Kenton K, et al. Urodynamics, the supine empty bladder stress test, and incontinence severity. *Neurourology and Urodynamics*. 2010;29(7):1306-1311. doi:10.1002/nau.20836

21. Elser DM, Fantl JA. Comparison of "subjective" and "objective" measures of severity of urinary incontinence in women. *Neurourology and Urodynamics*. 1995;14(4):311-316. doi:10.1002/nau.1930140403

22. Ford AA, Rogerson L, Cody JD, Aluko P, Ogah JA. Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database of Systematic Reviews*. 2017;2017(7). doi:10.1002/14651858.CD006375.pub4

23. Basu M, Wise B, Duckett J. A qualitative study of women's preferences for treatment of pelvic floor disorders. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2011;118(3):338-344. doi:10.1111/j.1471-0528.2010.02786.x

24. Pfisterer MHD, Johnson TM, Jenetzky E, Hauer K, Oster P. Geriatric Patients' Preferences for Treatment of Urinary Incontinence: A Study of Hospitalized, Cognitively Competent Adults Aged 80 and Older. *Journal of the American Geriatrics Society*. 2007;55(12):2016-2022. doi:10.1111/j.1532-5415.2007.01457.x

25. Wessels NJ, Hulshof L, Loohuis AMM, et al. User Experiences and Preferences Regarding an App for the Treatment of Urinary Incontinence in Adult Women: Qualitative Study. *JMIR mHealth and uHealth*. 2020;8(6):e17114. doi:10.2196/17114

26. Best Practices in Diagnosis and Treatment of Asymptomatic Bacteriuria and Urinary Tract Infections | Agency for Health Research and Quality. Accessed February 6, 2020. https://www.ahrq.gov/antibiotic-use/acute-care/diagnosis/uti.html

27. Kazmerski TM, Sawicki GS, Miller E, et al. Sexual and reproductive health care utilization and preferences reported by young women with cystic fibrosis. *Journal of Cystic Fibrosis*. 2018;17(1):64-70. doi:10.1016/j.jcf.2017.08.009

28. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care A. Are the results of the study valid? *Journal of the American Medical Association*. 2000;284(3):357-362. doi:10.1001/jama.284.3.357

29. Community Voice | CF Foundation. Accessed March 21, 2020. https://www.cff.org/Get-Involved/Connect/Community-Voice/

30. Ando H, Cousins R, Young C. Achieving Saturation in Thematic Analysis: Development and Refinement of a Codebook. *Comprehensive Psychology*. 2014;3:03.CP.3.4. doi:10.2466/03.cp.3.4

31. Kazmerski TM, Gmelin T, Slocum B, Borrero S, Miller E. Attitudes and Decision Making Related to Pregnancy Among Young Women with Cystic Fibrosis. *Maternal and child health journal*. 2017;21(4):818-824. doi:10.1007/s10995-016-2181-z

32. Mendes A, Hoga L, Gonçalves B, Silva P, Pereira P. Adult women's experiences of urinary incontinence: a systematic review of qualitative evidence protocol. *JBI database of systematic reviews and implementation reports*. 2015;13(3):103-110. doi:10.11124/jbisrir-2015-1789

33. Whale K, Cramer H, Wright A, Sanders C, Joinson C. "What does that mean?": A qualitative exploration of the primary and secondary clinical care experiences of young people with continence problems in the UK. *BMJ Open*. 2017;7(10). doi:10.1136/bmjopen-2016-015544

34. Griffith JW, Messersmith EE, Gillespie BW, et al. Reasons for Seeking Clinical Care for Lower Urinary Tract Symptoms: A Mixed Methods Study. *Journal of Urology*. 2018;199(2):528-535. doi:10.1016/j.juro.2017.07.067

35. Pintos-Díaz MZ, Alonso-Blanco C, Parás-Bravo P, et al. Living with urinary incontinence: potential risks of women's health? A qualitative study on the perspectives of female patients seeking care for the first time in a specialized center. *International Journal of Environmental Research and Public Health*. 2019;16(19). doi:10.3390/ijerph16193781

36. Williams BR, Nodora J, Newman DK, et al. I never knew anyone who peed on themselves on purpose: Exploring adolescent and adult women's lay language and discourse about bladder health and function. *Neurourology and Urodynamics*. 2020;39(1):225-236. doi:10.1002/nau.24174

37. Brucker BM, Nitti VW, Kalra S, et al. Barriers experienced by patients with multiple sclerosis in seeking care for lower urinary tract symptoms. *Neurourology and Urodynamics*. 2017;36(4):1208-1213. doi:10.1002/nau.23101

38. Balk E, Adam GP, Kimmel H, et al. *Nonsurgical Treatments for Urinary Incontinence in Women: A Systematic Review Update*.; 2018. doi:10.23970/AHRQEPCCER212

39. Guralnick ML, Fritel X, Tarcan T, Espuna-Pons M, Rosier PFWM. ICS Educational Module: Cough stress test in the evaluation of female urinary incontinence: Introducing the ICS-Uniform Cough Stress Test. *Neurourology and Urodynamics*. 2018;37(5):1849-1855. doi:10.1002/nau.23519

40. Rajkumar GN, Small DR, Mustafa AW, Conn G. A prospective study to evaluate the safety, tolerability, efficacy and durability of response of intravesical injection of botulinum toxin type A into detrusor muscle in patients with refractory idiopathic detrusor overactivity. *BJU International*. 2005;96(6):848-852. doi:10.1111/j.1464-410X.2005.05725.x

41. Cameron AP, Wiseman JB, Smith AR, et al. Are three-day voiding diaries feasible and reliable? Results from the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) cohort. *Neurourology and Urodynamics*. 2019;38(8):2185-2193. doi:10.1002/nau.24113

42. Robinson BL, Geller EJ, Parnell BA, et al. Diagnostic accuracy of visual urethral mobility exam versus Q-Tip test: a randomized crossover trial. *American journal of obstetrics and gynecology*. 2012;206(6):528.e1-6. doi:10.1016/j.ajog.2012.02.015

43. Amaro JL, Moreira EC, De Oliveira MG, Padovani CR. Pelvic floor muscle evaluation in incontinent patients. *International Urogynecology Journal*. 2005;16(5):352-354. doi:10.1007/s00192-004-1256-3

44. Sung VW, Borello-France D, Dunivan G, et al. Methods for a multicenter randomized trial for mixed urinary incontinence: rationale and patient-centeredness of the ESTEEM trial. *International Urogynecology Journal*. 2016;27(10):1479-1490. doi:10.1007/s00192-016-3031-7

45. Burgio KL. Update on behavioral and physical therapies for incontinence and overactive bladder: The role of pelvic floor muscle training. *Current Urology Reports*. 2013;14(5):457-464. doi:10.1007/s11934-013-0358-1

46. Yalcin I, Bump RC. Validation of two global impression questionnaires for incontinence. *American Journal of Obstetrics and Gynecology*. 2003;189(1):98-101. doi:10.1067/mob.2003.379

47. Clarke-O'Neill S, Pettersson L, Fader M, Cottenden A, Brooks R. A multicenter comparative evaluation: disposable pads for women with light incontinence. *Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society*. 2004;31(1):32-42. doi:10.1097/00152192-200401000-00006

48. Huang AJ, Chesney M, Lisha N, et al. A group-based yoga program for urinary incontinence in ambulatory women: feasibility, tolerability, and change in incontinence frequency over 3 months in a single-center randomized trial. *American Journal of Obstetrics and Gynecology*. 2019;220(1):87.e1-87.e13. doi:10.1016/j.ajog.2018.10.031

49. Pleil AM, Coyne KS, Reese PR, Jumadilova Z, Rovner ES, Kelleher CJ. The validation of patient-rated global assessments of treatment benefit, satisfaction, and willingness to continue - The BSW. *Value in Health*. 2005;8(SUPPL. 1):S25-S34. doi:10.1111/j.1524-4733.2005.00069.x

50. Robinson D, Cardozowan L. Urinary incontinence in the young woman: Treatment plans and options available. *Women's Health*. 2014;10(2):201-217. doi:10.2217/whe.14.1