A Pilot Study Involving Two Insulin Programs in Cystic Fibrosis-Related Diabetes

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ABSTRACT

Cystic fibrosis (CF) is the most common genetic disorder in Caucasians. Nearly half of all adults with CF will develop a comorbidity known as cystic fibrosis-related diabetes (CFRD). CFRD that is uncontrolled in this population can lead to weight loss and increased morbidity. Currently the only recommended treatment for CFRD is insulin therapy. Most individuals with CFRD will begin treatment using multiple daily injections of insulin (MDIs) to manage their blood glucose levels. However, the continuous subcutaneous insulin infusion (CSII) is another form of insulin administration that is not widely used in this population. Pilot trials can be used to assess feasibility of a larger-scale trial. A pilot trial involving a two-month period using MDIs and a two-month period using CSII will be described. Individuals newly diagnosed with CFRD will be recruited to join the trial, with the ultimate goal of the study to determine if the protocol is sound and effective for a larger-scale trial. Participants will also be asked to complete food records and food recalls with the registered dietitian throughout the study. Because insulin is currently the only recommended treatment for CFRD, it is expected that the study will be able to recruit and retain 10-15 participants to begin and complete the trial. Completion of various study steps by the participant will also be used to determine feasibility. A final discussion will identify strengths and limitations of the study design, a comparison to other studies, and ideas for future clinical trials in the area of CFRD.

Keywords: cystic fibrosis, cystic fibrosis-related diabetes, insulin, multiple daily injections of insulin, continuous subcutaneous insulin infusion, insulin pump

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Introduction

According to the Cystic Fibrosis Foundation (n.d.-a), cystic fibrosis (CF) is a progressive disease and the most common genetic disorder in Caucasians. An individual requires two copies of a defective cystic fibrosis transmembrane conductance regulator (CFTR) gene to have the disease. There are over 1,700 known mutations of the CFTR gene. The United States has more than 30,000 individuals with CF (Cystic Fibrosis Foundation, n.d.-a).

CF primarily affects the lungs and creates issues with breathing, although the disease can also affect the pancreas, intestines, and sex organs. According to Sabharwal (2016), individuals with CF can have a large range of gastrointestinal complications. Patients with CF can experience constipation, diarrhea, and abdominal pain. Additionally, individuals with CF can be pancreatic insufficient (Sabharwal, 2016) and require pancreatic enzymes to replace the enzymes not being secreted by their pancreas, an accessory organ in the gastrointestinal system. Due to the disease's impact on the pancreas, another common complication in this population is cystic fibrosis-related diabetes (CFRD) (Yen & Leonard, 2015). According to Moran et al. (2009), about 40-50% of those with CF will have CFRD. As life expectancy in the CF population increases, the number of individuals diagnosed with CFRD is similarly growing.

Background

The Cystic Fibrosis Foundation (n.d.-b) notes that individuals with CFRD share some characteristics to those with type 1 and type 2 diabetes. According to the Cystic Fibrosis Foundation, in individuals with CFRD, scarring of the pancreas prevents the organ from producing normal amounts of insulin, similar to those with type 1 diabetes.

Additionally, those with CFRD may not respond to insulin appropriately, similar to those with type 2 diabetes. Because the features of CFRD resemble those of both type 1 and type 2 diabetes, CFRD is a unique form of the disease.

Individuals with CF are screened and diagnosed using the oral glucose tolerance test (OGTT). The Cystic Fibrosis Foundation (n.d.-b) recommends all CF patients over the age of ten years old complete an annual OGTT. Unlike in type 1 and type 2 diabetes, hemoglobin A1c (HbA1c) is not recommended as a screening tool as it is often falsely low in this population (Cystic Fibrosis Foundation, n.d.-b).

Individuals with CF are at risk for malnutrition. The process of malnutrition development in CF is likely multifactorial, including increased calorie needs at baseline due to malabsorption of nutrients, heightened work of breathing leading to elevated calorie expenditure, and loss of appetite (Yen & Leonard, 2015). Malnutrition is exacerbated in those with CFRD, due to the process of glucosuria and protein loss. Glucosuria may put an individual into a net negative calorie balance, leading to weight loss (Pencharz & Durie, 2000). Yen and Leonard (2015) noted that insulin is an anabolic hormone; therefore, insulin deficiency can lead to loss of both fat and lean body mass, which can exacerbate malnutrition in individuals with CF. Since weight is closely linked to outcomes in the CF population, treating the nutritional side effects of CFRD appropriately and efficiently may help prevent further decline in these individuals.

Problem Statement

Ode et al. (2019) noted a lack of consensus regarding treatments for CFRD due to a scarcity of available research. No two CFRD treatments have been compared in a large

systematic trial. Specifically, no randomized control trials have compared insulin regimens and there remains little evidence surrounding the use of oral antihyperglycemics. Future research should aim to assess the best methods for controlling blood glucose in this population, as this subset of the CF population will continue to grow as life expectancy increases. There is a lack of available research to provide a consensus on the best method of treatment for CFRD to improve nutritional status.

Purpose of the Study

The purpose of the pilot study is to determine the feasibility of a trial which examines two different insulin regimens in the adult CFRD population and their effects on nutritional status. The two treatments chosen for this pilot study will be multiple daily injections (MDIs) of insulin versus a continuous subcutaneous insulin infusion (CSII) with an insulin pump. These methods were chosen because currently MDIs is the accepted method for treatment of CFRD in adults. It is unclear if CSII is also an appropriate method of insulin administration in this population. There is a limited amount of available research at the time of this proposal comparing the two treatments. This pilot study will assess whether a large-scale trial of similar design will be feasible. It will be advantageous for identifying aspects of the study which need to be altered before initiating a large trial.

Overall Pilot Trial Feasibility Research Question:

- In adults with a new diagnosis of CFRD, how feasible is a trial examining the effectiveness of multiple daily injections of insulin compared to the use of a continuous subcutaneous insulin infusion in improving nutritional status?

Feasibility Subquestions:

There are several questions that can be answered using a pilot trial. A list of feasibility subquestions for this pilot trial can be found in Table 1.1 using information from the National Center for Complementary and Integrative Health (NCCIH, 2017).

Table 1.1

Feasibility Subquestions

Feasibility Question	Measure of Success or Failure
Can the study design recruit enough participants for the trial?	- Ability to recruit the recommended sample size in a three-month period
Can the study design keep participants in the pilot study?	- Dropout rate (measured in percentage) will be used to assess retention.
Will participants do what they are asked to do?	- Attendance at clinic visits (measured in percentage) - Completion of two phone calls with the registered dietitian (RD), discussion of three-day food record and 24-hour diet recall. - Medication compliance assessed by the Certified Diabetes Educator (CDE) with used containers of insulin
Are the treatments safe and effective?	- Number of blood glucose readings outside of target range
Are the treatment protocols acceptable?	- Those who dropout will be asked to discuss their reason for leaving the study.

Nature of the Study

A detailed examination of the proposed pilot study can be found in Chapter 3. To summarize, each adult participant with a new diagnosis of CFRD will act as their own control. Participants will receive nutritional education which includes carbohydrate counting. Each participant will begin insulin therapy with MDIs and continue this treatment for two months. After two months, each individual will switch to using CSII.

They will again use this therapy for two months. Weight will be collected in kilograms at the beginning and end of each therapy, to determine change in weight after each period. The protocol listed in Chapter 3 will be used as a pilot study to determine feasibility of a larger-scale trial.

List of Definitions

Continuous glucose monitoring: A method of tracking blood glucose levels throughout the day and night at regular intervals using a small sensor under the skin. This type of tracking is useful for making decisions about increasing or decreasing an insulin dose (Dexcom, 2020).

Continuous subcutaneous insulin infusion: A method of insulin administration in which insulin is administered into the body using an insulin pump. There are no separate insulin injections.

Cystic fibrosis-related diabetes: A form of diabetes that affects those with CF (Cystic Fibrosis Foundation, n.d.-b).

Multiple daily injections: A method of insulin administration in which insulin is injected into the skin at various times throughout the day. The injections in this study will be pre-meal and pre-snack for all participants, with an additional once daily, long-acting insulin injection in the morning for those diagnosed with CFRD with fasting hyperglycemia, as is the protocol described by Ode et al. (2019).

Nutritional status: Nutritional status will be assessed by average change in weight in kilograms and BMI during each of the two treatment periods.

Oral glucose tolerance test (OGTT): The screening tool for diagnosis of CFRD in this study will be conducted using the following method from Brunzell et al. (2015):

- The participant must have been fasting for minimally eight hours.
- A fasting blood glucose level will be taken to determine +/- fasting hyperglycemia. The cut-off for fasting hyperglycemia is a reading ≥ 126 mg/dL.
- A 75-gram glucose drink will be consumed by the patient
- Glucose levels will be tested after one and two hours
- The participant's diagnosis will be based off the categorizes of various glucose tolerance shown in Chapter 2, Table 1, "Various Diagnoses During the Oral Glucose Tolerance Test"

Self-monitoring of blood glucose (SMBG): Personal monitoring of blood glucose throughout the day by an individual with diabetes (Benjamin, 2002).

Assumptions:

- Insulin is a beneficial treatment for CFRD.
- Progression of disease is minimal during the course of the two treatment periods (4 months total).
- Participants will be proficient with carb counting at beginning of first treatment period.
- Participants will accurately follow study protocol.

Limitations:

Due to the nature of the pilot design, the study will not be able to test a research hypothesis. Because of this limitation, the trial will be unable to determine effectiveness

of the treatments. This trial will not allow generalization to the larger CFRD population as a whole. Additional limitations to the study include:

- Convenience sampling will be used to recruit participants.
- The study will be limited by participants' overall compliance with study protocol.
- The study will be limited by the drop-out rate of the participants.

Delimitations:

Certain delimitations will be outlined for this pilot study. Due to the pilot nature of the study, the delimitations are needed to provide boundaries before a larger-scale trial can be conducted. The inclusion criteria were delineated to restrict the scope of the study and to focus on only the adult population from a single-center CF clinic. A single clinic was chosen as it was deemed convenient for determining feasibility of a larger-scale trial. Exclusion criteria was limited for the pilot trial in order to recruit the maximum number of participants. Any instances of pulmonary exacerbations or new medications that affect blood glucose levels, such as steroids, will be noted by the researchers but will not be definite exclusion factors.

- Inclusion criteria: Adults (18+ years) with CF who come to their Cystic Fibrosis Clinic visit and have no previous diagnosis of CFRD and will complete their OGTT
- Exclusion criteria: Individuals with pancreatic sufficiency. Yen and Leonard (2015) note that at least 85% of those individuals with CF are pancreatic insufficient. Because CFRD development is an effect of the pancreas being affected, this study will focus only on those individuals with pancreatic insufficiency.

Significance:

The pilot study will inform clinical practice related to insulin administration for those with CFRD and serve as a stepping stone for further research studies examining MDIs and CSII. Due to the increase in life expectancy in the CF population within the last 20 years (Marshall et al., 2017), the number of CF patients with CFRD will also increase. Currently, there is no consensus on the best insulin therapy treatment for CFRD, and this study will determine the feasibility of conducting research trials in this area. Registered dietitians and other healthcare professionals who treat these patients will need to know the most effective treatments for CFRD, which are essential to ensure poor nutritional status is not a contributing factor to morbidity and mortality in these patients.

Summary:

Individuals with CF are at nutrition risk at baseline. CFRD is a common complication in this population that can contribute to malnutrition. There is currently no clear consensus on the best treatment for CFRD that will provide the most nutritional benefit through weight gain. CSII is a relatively new insulin administration option that is not used widely in the CF population.

This research proposal outlines the designs for a pilot study to determine the feasibility of a trial examining two different insulin regimens in the CFRD population and their effects on nutritional status. Chapter 2 begins by exploring malnutrition and its relationship to CF. It examines CFRD as a complication of CF and why treatment of CFRD is a necessary component of CF therapy overall. Subsequently, multiple studies focusing on CFRD therapy options related to improvement in nutritional status are

reviewed and their conclusions compared. Chapter 3 provides a proposed pilot study design for comparing two of these treatments. This pilot study will be used to determine feasibility of a larger-scale trial. Chapter 4 outlines the expected outcomes of the proposed study, and Chapter 5 provides a discussion and concluding statements.

Review of the Literature

Introduction

According to the Cystic Fibrosis Foundation, cystic fibrosis (CF) is a genetic disorder that progressively affects the lungs, pancreas, intestines, and sex organs (n.d.-a). The disease manifests primarily as decreased breathing function and creates recurrent lung infections (Cystic Fibrosis Foundation, n.d.-a). At least 85% of those with CF are considered pancreatic insufficient, which involves the inability of the pancreas to produce or transport adequate amounts of pancreatic enzymes needed to break down nutrients (Yen & Leonard, 2015). Due to the impact of the disease on the pancreas, it can also affect nutritional status. CF is typically diagnosed two to three days after birth with an infant newborn screening test, a sweat test, and a clinical evaluation (Cystic Fibrosis Foundation, n.d.-a). The disease is life-long with no known cure, although many individuals hope to eventually obtain a lung transplant or a combination lung and pancreas transplant to alleviate their symptoms. Individuals afflicted with CF require close medical monitoring and a multi-disciplinary approach to treatment as many aspects of their lives are affected by the disease.

The United States is home to more than 30,000 individuals with CF, and greater than 1,000 people are diagnosed every year Cystic Fibrosis Foundation, n.d.-a). Due to advancements in treatment, more than half of the CF population is over the age of 18 (Cystic Fibrosis Foundation, n.d.-a). Individuals with CF are at higher risk of mortality at a younger age when compared to the average person. Marshall et al. (2017) reported only 40% of individuals with CF were over the age of 18 in the year 2002. The author also

reported in 2017 that the median survival age of a person with CF was 46.2 years. This is an increase from a median age of just over 28 years in the years 1986-1990.

Individuals with CF are at risk for nutritional deficiency. According to Yen and Leonard (2015), there are a variety of unique factors that have the potential to create nutritional deficits in this population, including increased energy expenditure, malabsorption, and decreased oral intake. The authors also mention that a chronic inflammatory state may also impact growth, although this mechanism is not well understood. Due to the compounding influence of these factors, individuals with CF have elevated calorie and protein needs, and thus are at risk for undernutrition.

The Cystic Fibrosis Foundation reports individuals with CF typically require 1.5 to 2 times the number of calories per day than a person without CF (n.d.-c). Individuals with CF are taught to follow an energy-dense, high-fat diet from a young age. They are instructed to snack in between at least 3 meals per day; however, this may be difficult to achieve due to other complications related to the disease, including shortness of breath, lack of appetite, and malabsorption. These factors can impact the ability to maintain the recommended BMI. The Cystic Fibrosis Foundation recommends that women over the age of 21 with CF maintain a BMI of ≥22 kg/m^2. Men over the age of 21 should maintain a BMI of ≥23 kg/m^2 (Cystic Fibrosis Foundation, n.d.-c).

Cystic fibrosis-related diabetes (CFRD) is another unique complication in this population that is related to scarring of the pancreas. Yen and Leonard (2015) report that CFRD occurs in 40-50% of adults with CF. Insulin is still made by the pancreas, but not at adequate levels to maintain blood glucose levels within a healthy range (Cystic

Fibrosis Foundation, n.d.-b). Left unchecked, chronically elevated blood glucose can lead to weight loss and a reduction in BMI (Cystic Fibrosis Foundation, n.d.-b). Diagnosis of CFRD is achieved with an oral-glucose tolerance test (OGTT) that measures blood glucose levels after an eight-hour fast (Yen & Leonard, 2015).

Studies are limited in the area of CFRD due to small sample sizes and shortened life expectancy in this population. This literature review will synthesize the current available information regarding nutritional and medical treatments of CFRD in the context of nutritional status maintenance. The purpose of the literature review is to critically analyze the evidence on the management of CFRD and its influence on weight status and body mass index (BMI) in the adult CF population.

Literature Research Strategy

Multiple strategies were used to identify appropriate articles for the following literature review. The background information summarized prior to the research articles was obtained from credible sources, such as the Cystic Fibrosis Foundation website and the National Institutes of Health website. Nutritional information related to CF and CFRD was also collected from the textbook *Nutrition in Cystic Fibrosis: A Guide for Clinicians* by Yen and Leonard (2015).

PubMed and EBSCO databases were used to search for primary sources. The term "cystic fibrosis-related diabetes" was initially used to determine the scope of available articles. Additional terms used to search along with "cystic fibrosis-related diabetes" were: "treatment," "therapy," "weight," "BMI," "adults," "insulin," "insulin pump," "continuous subcutaneous insulin infusion," "antihyperglycemic," "oral diabetes agent," and "glycemic index."

Background

Genetics and Physiology of Cystic Fibrosis

According to the National Institutes of Health: National Heart, Lung, and Blood Institute (NIH), CF is an inherited disease that is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (n.d.). The Cystic Fibrosis Foundation (n.d.-a) notes that there are over 1,700 known genetic mutations. Two mutated CFTR genes (one from each parent) must be inherited for an individual to have CF. When functioning normally, this gene codes for the chloride channel protein which can be found on all organs in the body that secrete mucus. A defect in the CFTR gene causes the protein to malfunction and produces thick, sticky mucus that subsequently creates blockages in those organs (National Institutes of Health: National Heart, Lung, and Blood Institute, n.d.).

The two most commonly affected organs are the lungs and the pancreas, which then produce the typical symptoms of the disease. Symptoms vary by mutation type and can range from mild to severe (Yen & Leonard, 2015). Individuals with CF will commonly demonstrate shortness of breath and a bloody or mucous-producing cough. A major focus for these individuals is maintaining a clear airway, which can be achieved through a combination of medications and breathing techniques (Cystic Fibrosis Foundation, n.d.-a).

Despite CF being considered primarily a pulmonary disease, Sabharwal (2016) reports individuals with the disease can demonstrate a myriad of gastrointestinal symptoms, including constipation, distal intestinal obstructive syndrome, pancreatitis, hepatobiliary disease, or chronic abdominal pain. Individuals can also be classified as

either pancreatic sufficient or pancreatic insufficient, with approximately 85% of CF patients considered pancreatic insufficient by the age of 1 or 2 years old. Those who are pancreatic insufficient are not able to secrete adequate amounts of enzymes to digest nutrients and fat-soluble vitamins (A, D, E, and K) thus limiting absorption. These individuals will experience maldigestion and malabsorption and employ pancreatic enzyme replacement therapy (PERT) in place of the enzymes which their body can no longer adequately secrete (Sabharwal, 2016).

Malnutrition Rates in the Cystic Fibrosis Population

Yen and Leonard (2015) note that an individual diagnosed with CF is at risk for a variety of nutritional issues, including malnutrition, which is common due to their extremely high calorie and protein needs, malabsorption, and decreased oral intake. It is widely accepted that those with CF who are undernourished tend to have worse outcomes related to morbidity and mortality (Yen & Leonard, 2015). A cross-sectional study by Barni et al. (2017) involving 73 CF patients 16 years and older found a 24.7% malnutrition rate when examining clinical assessments, nutritional assessments, pulmonary function tests, and pancreatic function. The researchers identified those with CF as either adequately nourished, at nutrition risk, or malnourished based on the participant's Shwachman-Kulczycki (S-K) score. The S-K score is used to determine severity of disease and is divided into four domains each worth 25 points - activity level, physical examination, nutrition, and radiology findings. A final score based on a scale of 0-100 determines the severity of disease: excellent, good, average, poor, or severe (Stollar et al., 2011). The Barni et al. (2017) study showed that the S-K score was significantly lower in the nutrition risk and malnutrition groups as compared to the

adequately nourished group. Both forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were significantly lower in the malnutrition group than in the adequately nourished and nutrition risk groups. The researchers determined there was an association between nutrition risk and lung function impairment in the CF population.

Similarly, a cross-sectional study of 68 patients (including children) with CF conducted by Panagopoulou et al. (2013) found a 22.1% malnutrition rate in their study sample. Participants were classified as either malnourished, having normal nutritional status, or as overweight/obese. These researchers also found an association between nutritional status and FEV_1. Those in the overweight/obese category had a significantly higher FEV_1 percentage as compared to the other two groups.

Although the previous two studies reported malnutrition rates in the range of 20-25%, malnutrition rates may be even higher. A third study examining malnutrition rates in the cystic fibrosis population was conducted by Dray et al. (2005). This cross-sectional study of 163 adults with CF in France demonstrated a malnutrition rate (determined based on BMI <18.5 kg/m^2) of 49.7%.

Nutritional Interventions in Cystic Fibrosis

Some nutritional interventions are implemented almost universally in this population. Yen and Leonard (2015) report that a high calorie, high fat diet is the classic approach for these individuals. Fat intake is emphasized due to its caloric density relative to carbohydrates and protein. Individuals are instructed on ways to increase calories at meals and snacks and may use oral nutrition supplements to meet these elevated needs (Cystic Fibrosis Foundation, n.d.-c). Yen and Leonard (2015) report those who are pancreatic insufficient use pancreatic enzyme replacement therapy (PERT) to mimic the

function of enzymes produced by a healthy pancreas. The enzymes assist with breaking down the fat in meals, thereby helping with both digestion of nutrients and increasing availability and absorption of fat-soluble vitamins. In addition, many individuals will require further supplementation of fat-soluble vitamins, and blood levels of these vitamins are checked yearly.

Cystic Fibrosis-Related Diabetes

Yen and Leonard (2015) report cystic fibrosis-related diabetes (CFRD) as another complication of CF. The complication is related to the dysfunctional pancreas not being able to secrete adequate amounts of insulin (Yen & Leonard, 2015). Insulin is still made by the pancreas, but not at adequate levels to maintain blood glucose within a healthy range. Diagnosis of CFRD is achieved with an oral-glucose tolerance test (OGTT) that measures blood glucose levels two hours after an eight hour fast. Left unchecked, chronically elevated blood glucose can lead to weight loss, fatigue, and reduction in lung function (Cystic Fibrosis Foundation, n.d.-b). Brunzell et al. (2015) categorizes various blood glucose levels during the OGTT and their subsequent diagnoses, which is shown in Table 2.1.

Table 2.1.

Various Diagnoses During the Oral Glucose Tolerance Test

Blood Glucose Value	Diagnosis
2-hour glucose > 200 mg/dL	CFRD
2-hour glucose 140-199 mg/dL	Impaired glucose tolerance (IGT)
Mid-OGTT glucose ≥ 200 mg/dL, with OGTT otherwise normal	Indeterminate glycemia (INDET)
2-hour glucose < 140 mg/dL	Normoglycemia

Malnutrition and Its Relationship to CFRD. According to Yen and Leonard (2015), insulin is an anabolic hormone. The pathophysiology of CFRD indicates that individuals with CF are at risk for both insulin resistance and insulin deficiency. Therefore, if left untreated, CFRD can lead to loss of fat and lean body mass. Ultimately, this increases the risk for malnutrition in a population that already requires elevated calorie and protein intake. Additionally, according to Pencharz and Durie (2000), CFRD increases caloric losses through glucosuria. If blood glucose is not controlled, these urine losses may create an overall net negative caloric balance, and thus lead to weight loss and malnutrition. Timely identification and treatment of CFRD is a necessary portion of overall CF therapy.

Comparison to Type 1 and Type 2 Diabetes. Brunzell et al. (2015) compared CFRD to both type 1 and type 2 diabetes. CFRD is a unique category of diabetes that combines both insulin dependence, as in type 1, and insulin resistance, as in type 2, diabetes. Because CF affects the pancreas, the organ does not make enough insulin as in type 1. This occurs mainly through scarring, or fibrosis, of the pancreas. Those with CF also require more insulin than normal due to insulin resistance, similar to type 2 diabetes. Contributing factors to insulin resistance and to the development of CFRD include chronic inflammation and steroid use (Brunzell et al, 2015).

Insulin and Its Usage in CFRD. There are essentially 5 types of insulin used in the management of CFRD. Table 2.2 distinguishes the 5 types, using information from the American Diabetes Association (2020).

Table 2.2.

Action, Peak, and Duration of Various Insulin Types

Type of Insulin	Onset of Action	Peak	Duration of Action	Instructions for Eating
Rapid-acting	15 minutes	About 1 hour	2 to 4 hours	Eat a meal within 15 minutes
Short-acting	30 minutes	2 to 3 hours	3 to 6 hours	Eat a meal within 30 minutes
Intermediate-acting	2 to 4 hours	4 to 12 hours	12 to 18 hours	Eat 4 hours after taking AM insulin
Long-acting	Several hours after injection	Relatively flat	24 hours	Take insulin even if you do not eat
Pre-mixed	Based on each individual insulin mixture	Based on action of insulin mixture	Based on action of insulin mixture	Individualized based on insulin mixture

A review of medical management of CFRD was discussed by Ode et al. (2019). The most common type of insulin usage in CFRD is MDIs. This involves injections of rapid-acting, “bolus” insulin with meals. If an individual has fasting hyperglycemia, they also require long-acting, “basal” insulin once daily as background coverage in between meals. If they do not have fasting hyperglycemia, only bolus insulin is needed. This type of insulin regimen is administered via insulin syringes or pens. In CF, patients are instructed to snack frequently between meals due to elevated calorie and protein needs. Rapid-acting insulin must be given for each meal and snack in CFRD. A typical starting dose of rapid-acting insulin is 0.5 units per each carbohydrate exchange (15 grams carbohydrate). Based on an individual’s glycemic control, this 1:30 ratio may need to be adjusted up or down. Individuals with CFRD using MDIs should perform self-monitoring of blood glucose (SMBG) multiple times during the day, including before breakfast, two hours after breakfast, before lunch, two hours after lunch, before supper, and before bed (Ode et al. 2019).

A newer form of insulin administration also examined by Ode et al. (2019) is the use of CSII. This therapy involves an insulin pump device with tubing connected to an insulin reservoir. Insulin administration is controlled by electronics. There are two versions of an insulin pump. A “pump patch” includes a pump attached to the individual’s body and a small catheter inserted into subcutaneous fatty tissue. The pump can be controlled by the individual’s smartphone via Bluetooth. In contrast, another form of pump involves tubing that connects a device with an insulin reservoir (typically worn on a belt) to the skin and subcutaneous tissue. Both the pump patch and the infusion site for a pump with tubing must be changed every 48-72 hours (Ode et al., 2019).

Ode et al. (2019) note that insulin dosing for an insulin pump is similar to that of MDI dosing. The basal rate is calculated based on the appropriate amount of basal insulin required over 24 hours, and this is delivered continuously throughout the day and night. Similarly to MDIs, the insulin to carbohydrate ratio is determined based on glycemic control. This ratio can be pre-programmed into the pump. When an individual enters the amount of carbohydrate they will be consuming into the pump, it automatically calculates a suggested dose of insulin, which the individual can then accept or reject. If accepted, the insulin bolus is administered to the patient. SMBG should be completed at the same times as for MDIs. Brunzell et al. (2015) lists the following blood glucose goals for adults with CFRD:

- Fasting and pre-meal: 80-130 mg/dL (4.4-7.2 mmol/L)
- 2-3 hours after eating: <180 mg/dL (<10.0 mmol/L)
- Bedtime: 90-150 mg/dL (5.0-8.3 mmol/L)

Ode et al. (2019) acknowledges a gap in the literature regarding management of CFRD due to lack of conclusive systematic data. The authors state there are currently no large trials comparing any two treatments for CFRD. A lack of trials leads to conflicting data reports and conclusions, which will be evident in the following literature review.

Current Research on CFRD Treatment and Its Effect on Weight and BMI

BMI is closely related to healthy outcomes in CF (Cystic Fibrosis Foundation, n.d.-c). The Cystic Fibrosis Foundation (n.d.-c) states that higher weight, and therefore a higher BMI, is associated with better lung function. Uncontrolled blood glucose levels can create issues with increased catabolism and difficulty with maintaining body weight, which may have negative impacts on morbidity and mortality. This literature review begins with a study investigating nutritional decline prior to diagnosis of CFRD and an additional study evaluating compliance with CFRD guidelines. Subsequently, multiple research studies examining treatments for the complication are analyzed.

Prevention of Nutritional Decline in CFRD

A case control study conducted by White et al. (2009) examined whether intensive nutritional interventions prevent pre-diagnosis nutritional decline in adults with CFRD. In total, 48 patients with CFRD from a CF clinic in Leeds, UK, were matched to a control patient with CF who did not have a CFRD diagnosis. Data were collected from six years before diagnosis of CFRD to two years after, and included weight, BMI, FEV_1, and FVC. Enteral feeding (EN) via enteral tube and oral nutritional supplementation (ONS) was also documented. There were no significant differences between participants and controls for any nutritional criterion in the six years before diagnosis.

White et al. (2009) found that as CFRD diagnosis approached, the number of patients receiving enteral nutrition increased with significant differences being seen at one year before diagnosis. At the time of diagnosis, CFRD was four times as prevalent in those with enteral nutrition. The average percent body weight loss in the one year prior to EN initiation was 8.5% for those with CFRD and 2.9% for those without CFRD. EN created a 9.9% weight gain at 2 years after initiation in those with CFRD versus a 7.2% gain in the controls.

White et al. (2009) also discovered a difference between those who had continued growth in the six years before diagnosis and those who were done growing in that time period. The younger patients had differences in nutritional status compared to their matched controls at two years before diagnosis and this continued until insulin therapy started. Once insulin therapy started, this group returned to the same BMI level as their controls. These individuals were also twice as likely to require ONS and four times as likely to need EN, although this was not significant. These differences were not seen in the older group where the growth stage was complete.

In the study by White et al. (2009), difficulties in maintaining weight in the pre-CFRD group resulted in a greater use of both ONS and EN. This demonstrated that a more intensive nutritional intervention is needed in this group as compared to their controls. Researchers also suggested that perhaps the intervention itself (EN or ONS) may be a factor that increases risk for CFRD, perhaps via an increase in insulin secretion. The authors reported an overall benefit with insulin therapy usage, which was most evident in younger patients who were still growing. The observed poorer weight gain and

lower BMI in the younger age group was attributed to pubertal growth spurts and additional stress on the body.

Future research needs that were identified in this study were the effects of ONS and EN on diabetes risk and combined interventions in the older adolescent population. A strength of the study was the separation between younger adults and older adults, which helped the researchers determine differences in nutritional needs and outcomes in these populations. A limitation of the study is the inability to infer incidence because of the retrospective, case-control design. Cause and effect cannot be determined based on the design used in this study. This study contributes to the current knowledge surrounding CFRD and BMI because it was able to demonstrate that even before diagnosis, those patients who would develop CFRD had a higher prevalence of EN use, indicating the need for additional calories.

Compliance to CFRD Guidelines

Scheuing et al. (2014) examined compliance with CFRD guidelines provided by the American Diabetes Association and the Cystic Fibrosis Foundation in 659 German and Austrian patients. The researchers assessed HgA1c, blood pressure, blood lipids, nutritional status (BMI, BMI standard deviation score [BMI-SDS], weight-SDS and height SDS), microvascular complications, diabetes education courses, and self-monitoring of blood glucose (SMBG).

Just over half (54.2%) of individuals in the Scheuing et al. (2014) study were younger than 20 years old. Under half (44.9%) of participants had at least one structured diabetes education program after diagnosis. The researchers found that the yearly number of HgA1c, blood pressure, lipid, and nutritional status measurements was less than

recommended, and not all participants performed SMBG. Pediatric patients went to clinics significantly more than adults, and they had more medical audits.

Over one-third (36.5%) of patients had a weight below the third percentile for age and sex. Only 6.7% of patients were being treated with oral anti-diabetic drugs only (OADs), whereas 77.2% were using a combination of OADs and insulin. Overall, the researchers noted a lack of adherence to the current international guidelines for CFRD, including a lack of structured diabetes education program sessions. Similarly, less than 20% of patients had a BMI equal to or above the target (Scheuing et al., 2014).

The Scheuing et al. (2014) study also identified a large time gap between diagnosis of CFRD and initiation of insulin therapy. There was a substantial delay in the initiation of insulin in both the pediatric population (0.9 years after diagnosis) and the adult population (2.7 years). The researchers noted that the reasons for this delay were unclear. Suggested reasons included the burden of starting this type of therapy and social challenges. Although insulin was recommended therapy for patients with CFRD, OADs may be less complex and less likely to create hypoglycemia. Suboptimal adherence to CFRD guidelines creates challenges such as hyperglycemia and body weight below recommended levels, and these guidelines are followed less frequently in the adult population.

Although not an inherent disadvantage, a limitation of this study with regards to this literature review is that the study focused on patients >5 years and older, and so did not distinguish adults. The study also included only patients in Germany and Austria, so it is difficult to determine how these results could be translated to other countries. However, this study did include the largest number of participants of any study examined

in this literature review. This study contributes to overall knowledge of adherence to current CFRD therapies.

Treatments for CFRD

Moran et al. (2009) examined the impact of diabetes therapy on the BMI of adult CF patients. Specifically, the researchers focused on those individuals who had a diagnosis of CFRD but did not exhibit fasting hyperglycemia (CFRD FH-) to determine whether they required standard insulin therapy as they typically do not have the usual microvascular and macrovascular complications as seen in those with fasting hyperglycemia (CFRD FH+). This was a three-arm multicenter randomized trial that included individuals with CF who were considered CFRD FH- or having severe impaired glucose intolerance (IGT).

During the study by Moran et al. (2009), the participants were randomized into three groups: receiving 0.5 units of insulin per 15 grams dietary carbohydrate, 2.0 mg repaglinide (an oral anti-hyperglycemic), or oral placebo three times per day before meals. In comparison, a typical dose of repaglinide, which is a part of the meglitinide class of type 2 diabetes medications, is 0.5 mg to 4 mg with meals (Food and Drug Administration, 2008). The primary study endpoint was BMI, which the researchers reported they chose due to its correlation with survival in CF. Eighty-one participants completed the study, including 61 with CFRD FH- and 20 with IGT. In the one year of study participation, those with CFRD FH- and receiving insulin therapy gained 0.39 ± 0.21 BMI units. Those who received repaglinide had a weight gain of 0.53 ± 0.19 BMI units within the first six months of the study. However, this effect was not sustained after six months, and by 12 months there was no significant difference in BMI as compared to

the year prior to the study. Those in the IGT groups did not show a significant difference in BMI between insulin or repaglinide treatment after one year compared to the year before the study.

Moran et al. (2009) concluded that insulin therapy significantly reversed weight loss in CF patients without fasting hyperglycemia. This study was one of the first that directly studied the impact of various treatments and their impacts on BMI. A strength of this study was the duration because it demonstrated that repaglinide did not have a sustained effect, while insulin treatment did have a sustained effect. This is an important contrast that demonstrates prolonged efficacy of insulin over oral medications. Unfortunately, the study did not include longer-acting insulin and meal-time insulin and compare that to pre-meal short-acting insulin only. Another weakness to the study was that those using insulin were unable to be blinded to the treatment. Overall, this study contributes to current knowledge of two CFRD treatment options and how they contribute to BMI (Moran et al., 2009).

Similarly to the Moran et al. (2009) study, an ongoing multi-national, multicenter, randomized, prospective controlled parallel trial is currently being conducted by Ballmann et al. (2014) to determine whether oral therapy with repaglinide is as effective as insulin in CFRD. The study included subjects with diagnosed CFRD who are over the age of ten. One group in the trial was assigned to use repaglinide before meals. Dose was adjusted individually based on blood glucose levels two hours after the previous meal. The second group received insulin therapy using regular insulin, injected by pen. There was no designated control group. Doses were adjusted based on postprandial blood glucose levels. All participants in the study received basic diabetes education, including

hyper- and hypo- glycemia management, macronutrient composition of foods, and effect of carbohydrates on blood glucose. All participants in the study were followed for two years. The primary endpoint was HgA1c, and secondary endpoints were mean blood glucose levels, changes in BMI-Z-score, changes in FEV1% predicted, and various hypo- and hyper- glycemic complications. Once these results are published, the authors hope to determine if an OAD is as effective as insulin at controlling HgA1c and BMI. Once the results are compiled, this study will likely be used in conjunction with Moran et al (2009) to compare the results of insulin versus OADs (Ballmann et al., 2014).

A similar study conducted by Onady and Langdon (2006) examined the differences in various outcomes in patients with CFRD using insulin and three different oral diabetes medications: sulfonylureas, metformin, and thiazolidinediones. A total of 20 participants from the Dayton Adult Cystic Fibrosis Program in Dayton, Ohio, elected to participate in the study during a ten-year period from 1992-2002. All participants were able to select which form of treatment they preferred. Eight participants chose insulin (NPH insulin ranging from 0.3-0.5 units/kg body weight), five patients chose sulfonylureas, four patients chose metformin, and three patients chose thiazolidinediones. Outcomes in the study included changes in HbA1c, weight, FEV1, and alanine aminotransferase which is a clinical monitor for liver disease.

In the study by Onady and Langdon (2006), the participants were started on the lowest dose of each treatment. At the three-month mark, HgA1c values were obtained, and any participant with an A1c >7 had a dose increase at the next recommended level. None of the 20 participants changed treatment as a result of complications of the

treatment. However, four patients did choose to discontinue insulin and begin an oral agent due to inadequate control of HgA1c.

The Onady and Langdon (2006) study found no significant differences between treatments in achieving glycemic control, however the researchers noted that this was likely due to the small number of participants in each group. The researchers also agreed that those with CFRD may require more strict glycemic control due to the tendency of HgA1c to be underestimated in this population, although they did use this parameter as a primary outcome. The study demonstrated an average weight gain of 1.8 kg in those taking metformin, with one patient in this group having a 27% weight gain. The authors proposed that this may have occurred due to proteolysis suppression of metformin, thus optimizing nitrogen balance and discouraging insulin degradation.

The authors reported several conclusions to their prospective, case-based study. With respect to this literature review, the authors reported that a consideration to use a sulfonylurea or thiazolidinedione should be made to attempt to wean off insulin after initial use of insulin as a therapy. They also conclude that in those with HgA1c >7 and preserved lung function (>60%) with no documented liver dysfunction, metformin should be considered in the outpatient setting. Overall, the researchers suggested that insulin may not be the only beneficial therapy for CFRD. They recommend further studies with a randomized design be conducted to determine effectiveness of oral agents with potential anti-inflammatory activity to improve clinical outcomes in this population.

A limitation of the study was the small sample size and the uneven number of patients in each treatment group due to patients electing their own treatment. The study

was therefore unblinded and non-randomized. The authors chose to use HgA1c as a primary study outcome, although the Cystic Fibrosis Foundation does not recommend use of this parameter as an accurate assessment of CFRD severity. A strength of the study was the examination of various oral anti-diabetic agents. This contrasts with the Moran et al. (2009) study and the Ballmann et al. (2014) study, which focus only on one agent as compared to insulin treatment. This study expands the knowledge surrounding treatment for CFRD and its impact on nutritional status by exploring unconventional therapies that have yet to be used routinely in this population.

In addition to the Moran et al. (2009) and Onady and Langdon (2006) studies, a study conducted by Frost et al. (2018) examined the use of insulin and outcomes on weight and pulmonary lung function in participants. In contrast to the Moran et al. (2009) study, the researchers used continuous glucose monitoring (CGM) rather than an OGTT test as their guide to initiating insulin therapy. The study was conducted at the Liverpool Adult CF Center in Liverpool, United Kingdom. Continuous glucose monitoring was conducted for a minimum of 72 hours. The participants also completed a food and exercise diary during the CGM. The researchers used a cutoff of >7.8 mmol/L (equivalent to a blood glucose of 140 mg/dL) that was present for >4.5% of the entire CGM period as an indication of significant hyperglycemia. For those participants who had clear triggers as a reason for their hyperglycemic readings (i.e., sugary beverages or insufficient pancreatic enzyme supplementation), dietary modification suggestions were made. For those individuals in which no clear dietary modification could be suggested, insulin therapy was initiated.

In total, 37 participants required insulin and 15 participants had clear nutritional triggers and did not begin using insulin. A majority of the participants who used insulin (35/37) began therapy with a long-acting insulin once daily. The remaining two participants began treatment with a short-acting, meal-time insulin. The 37 individuals using insulin had a significantly lower mean BMI (61.2 kg) at the start of the study as compared to the dietary modification and normoglycemia groups (74.1 kg and 69.0 kg respectively, $p < 0.01$). The insulin group had significant improvements in both FEV1 percentage and weight after three months of treatment (+4.27% and +1.2 kg, respectively, $p = 0.01$). The individuals who did not require insulin or dietary modification had no significant changes from baseline. The dietary modification group had no changes in weight from baseline. Of the 37 individuals commenced on insulin during the study, 32 (86.5%) had improvements in weight and/or lung function at the three-month mark.

The authors of the study reported that this was one of the first studies to examine the outcomes of insulin usage on early detectable glucose abnormalities diagnosed using CGM for a minimum of 72 hours in individuals with CFRD. They concluded that insulin therapy can produce significant benefits in both weight and lung function. The authors reported that because those who were advised to make dietary modifications continued to have weight loss, it may be beneficial to proactively start those individuals on insulin as well. However, they stated that the number of individuals in this group was small and it is unclear if the dietary suggestions were adhered to because compliance data was not collected for those in the dietary modification group. A limitation of the study is the single-center design and the lack of true controls or a comparison group.

An additional study was conducted by Mohan et al. (2008) at the same facility in Liverpool, United Kingdom. The researchers were interested in the long-term effects of insulin use in the adult CF population, as they reported the research that was available was limited to a short time after insulin initiation. The primary outcomes examined were pulmonary function via FEV_1 and FVC, BMI, and number of hospital admissions.

Mohan et al. (2008) found that of the 215 patients attending the Liverpool center, 65 had diagnoses of CFRD (30%). Only 42 participants had complete data for five years before and up to three years after insulin initiation, which was the specified date collection period. Thirty-one patients received short-acting insulin with meals, nine received both bolus, meal-time insulin three times per day and basal, intermediate-acting insulin injected once daily, and a further two patients took intermediate-acting insulin once daily. BMI was calculated an average of four times per year (quarterly). Patients acted as their own controls in the study, as their data was compared from five years prior.

Mohan et al. (2008) found a mean annual reduction in FEV_1, FVC, and BMI before participants were diagnosed with CFRD. Annual BMI reduction was -0.07% on average. At baseline, the mean BMI was 19.5 kg/m^2, which is below the recommended BMI for both men and women with CF. After three months on insulin, there was a significant improvement in FEV_1, FVC, and BMI ($p < 0.0001$ for all three variables). These improvements were maintained at one year for each primary outcome ($p < 0.002$, $p < 0.001$, $p < 0.0001$, respectively). BMI was sustained for three years.

Mohan et al. (2008) concluded that long-term insulin use produced significant improvements in pulmonary function and nutritional status in this population. Limitations

include the absence of a control group and the lack of insulin adherence measurement. The study was not able to account for changes in CF treatments over the eight-year period and their influence on CFRD clinical outcomes. The researchers knew of seven participants who were not entirely compliant with their insulin regimens, and a sub-group analysis demonstrated that their lung function and BMI benefits were restricted to three months after insulin commencement.

Hardin et al. (2009) conducted a study in Texas on nine adult patients with known CFRD. Unlike the Moran et al. (2009) study, all individuals had fasting hyperglycemia. Individuals were included if they were being treated with a minimum of three insulin injections daily for at least six months on a basal/bolus insulin regimen, recorded blood glucose readings at least four times per day, were competent in carbohydrate counting, and were overall compliant with CF and diabetes therapies. Participants were converted to CSII in a single visit.

Hardin et al. (2009) asked participants to record blood glucose levels and to contact researchers if more than 20% of recorded levels were outside of specific ranges as set by the study researchers. Doses were corrected if this occurred. Total body lean mass was measured at baseline and again at the six-month mark. Body weight was measured at each study visit. Glycated hemoglobin (HgA1c) was also measured at baseline and at every three months. Similarly to the Mohan et al. (2008) study, each participant served as their own control.

There were no instances of hypoglycemia in the study by Hardin et al. (2009). In contrast, prior to the study, participants reported several episodes of hypoglycemia per

month while on their basal/bolus insulin regimens. After the study, blood glucose and HgA1c both improved significantly, and there were also significant improvements in body weight and lean body mass. The researchers also found a decrease in protein catabolism and a lower rate of endogenous hepatic glucose production.

Hardin et al. (2009) concluded that the metabolic benefits were likely present due to the CSII more closely approximating physiologic insulin secretion. They also concluded that the use of CSII over basal and bolus insulin demonstrated better glycemic control and improvements in overall weight and preservation of lean body mass. Sample size was a limitation. A strength of this study was that the researchers used blood samples to objectively determine protein turnover and hepatic glucose production. This study demonstrates that the use of CSII is another potential option for patients with CFRD, as it demonstrated improvements in weight and lean body mass.

While the Moran et al. (2009) study examined the influence of MDIs on BMI, Hardin et al. (2009) focused instead on using CSII with examinations of body weight and lean body mass changes. Similarly to the Hardin et al. (2009) study, three case reports described by Sulli et al. (2006) demonstrated an improvement in metabolic control and nutritional status with the use of CSII when compared to MDIs. Only two of the case reports involved adults over the age of 18 years and will be discussed here. One female individual was diagnosed with CFRD at 23.2 years old and was started on an oral diabetes agent. After two years, she started multiple insulin injections four times per day. At 28.2 years old, the patient began using CSII. The individual's hemoglobin A1c prior to CSII use was 7.6%. One and two years after pump initiation, the A1c readings were reduced to 6.2% and 6.4%, respectively. At the start of CSII, her BMI was 20.0 kg/m^2.

One and two years after starting CSII, her BMI increased to 21.9 and 22.1 kg/m^2, respectively.

The case report by Sulli et al. (2006) also discussed a male patient who was 23.1 years old at the time of the study. He was diagnosed with CFRD at 14.2 years of age and was also started on four insulin injections daily. This individual began using CSII at the age of 21 years. Prior to use of the CSII pump, A1c readings were 9.8% and 8.8% after 3 months. After 1 and 2 years of using the pump, the individual's A1c was 7.2% and 7.1% respectively. BMI also increased in both the first and second year of pump use. Prior to using CSII, the individual's BMI was 21.2 kg/m^2. It increased to 22.8 kg/m^2 after one year and was 22.6 kg/m^2 after 2 years.

Besides the improvement in BMI and A1c readings, Sulli et al. (2006) also indicated that flexibility with the number and timing of meals without increasing the number of insulin injections was a benefit to using CSII. This is especially important for the cystic fibrosis population because of their high calorie needs and their need to snack frequently throughout the day. Unfortunately, this study included only three patients, and only two were adults. This was a case report and so it cannot be used to define a cause and effect relationship. The authors concluded that studying a larger number of patients using the CSII will provide a broader idea about the differences between MDIs and CSII.

Conclusions

Summary of Evidence

The literature review evidence points to the importance of management of CFRD and its impact on BMI and weight status. BMI and weight are directly linked with outcomes in the CF population. There is a small body of evidence indicating that insulin

is more effective than oral anti-diabetic drugs in the management of blood glucose levels, however studies are still ongoing, including the study by Ballmann et al. (2014). Most studies demonstrated that insulin was an effective treatment for increasing BMI in this population. There are limited studies examining whether MDIs are a superior strategy compared to CSII for improving nutritional status.

Comparison of Articles

Moran et al. (2009), Onady and Langdon (2006) and the ongoing study by Ballmann et al. (2014) all focus on the use of oral antihyperglycemics in contrast to insulin. While the Moran et al. (2009) study showed a sustained effect of up to one year with insulin use, it did not show this same sustained effect with the use of repaglinide. In contrast, Onady and Langdon (2006) focused on three different oral antihyperglycemics and found no significant difference between insulin and these medications during the 10-year period of investigation. Indeed, they concluded that insulin may not be the only beneficial therapy for those with CFRD. However, as noted earlier, this study had a very small sample size and an uneven number of participants in each treatment group. This likely influenced the results of the study. The Ballmann et al. (2014) study is still ongoing, but similarly to the Moran et al. (2009) study, it will examine differences in the effects of using repaglinide versus insulin.

Several studies of various designs investigated the use of insulin and its benefits on nutritional status. Frost et al. (2018) used CGM instead of the OGTT to determine the need for insulin in CFRD. The participants in this study used either long-acting insulin, meal-time insulin, or dietary strategies alone for their treatment. Those using insulin reported a beneficial outcome in both lung function and weight. In contrast, those in the

dietary modification group demonstrated continued weight loss, leading to the question of whether dietary modification alone in CFRD is an adequate intervention. Similarly, Mohan et al. (2008) studied four different insulin regimens and their long-term effects on BMI. They compared clinical outcomes both before insulin initiation and after initiation. The participants showed a significant improvement in BMI after starting insulin, and this effect was sustained for three years after insulin therapy started (the end of the study period).

Two studies were identified as including the use of CSII. Case reports from Sulli et al. (2006) involved two adults converting from MDIs to CSII and examined differences in outcomes. Both the adult male and adult female cases showed improvement in BMI after converting their insulin regimens. After switching to CSII, both the male and female gained weight to the extent that their BMIs were near the recommended BMIs as outlined by the Cystic Fibrosis Foundation. Hardin et al. (2009) included participants with CFRD and fasting hyperglycemia. The nine individuals converted to CSII in a single clinic visit. Using each patient as their own control, significant improvements in both weight and lean body mass were identified as compared to the MDI regimens used previously by the patients. Overall, there were few controlled trials that compared the use of MDIs and CSII. Unlike in type 1 diabetes, use of CSII in CF is currently limited.

White et al. (2009) and Scheuing et al. (2014) both investigated the impact and adherence of various nutritional interventions on this population. White et al. (2009) demonstrated a correlation between the use of enteral nutrition and oral nutritional supplements and diagnosis of CFRD. They identified insulin use as especially important in children and adolescents, who have elevated needs due to growth. Scheuing et al.

(2014) examined compliance to CFRD guidelines. The researchers identified a gap of 2.7 years between diagnosis and initiation of insulin therapy. The authors suggested this delay may be due to the burden of treatment or to social factors. Overall, the study found that adults were less likely to follow CFRD guidelines compared to children.

Gaps in the Literature

There are evident gaps in the literature. A question remains about oral anti-diabetic medications and whether they are as effective as insulin in the management of CFRD as it relates to weight and BMI. Studies are ongoing in this area. Another question that remains is the optimal insulin regimen - MDIs versus the use of CSII. Overall, there is a lack of comparative, controlled trials of sufficient size to draw conclusions about one regimen being more beneficial than another. Finally, more research is needed to investigate the role of oral nutrition supplements (ONS) and enteral nutrition (EN) in the development of CFRD.

Implications for Dietetic Practice

This research has significant implications for dietetic practice. CF is the most common fatal genetic disorder in the Caucasian population, and 40-50% of individuals with CF will develop CFRD (Yen & Leonard, 2015). As life expectancy increases, this complication of CF will become more common and present an additional burden to the complex treatment regimen that patients with CF follow. It is more difficult for those with CFRD to maintain their weight and their BMI at or above recommendations which will compromise their pulmonary function. A treatment protocol that manages the CFRD and improves nutritional status, pulmonary function and ultimately life expectancy is

needed. The review of the literature surrounding these topics has identified shortcomings in the treatment of this population and has also raised additional questions that need to be answered in order to be able to provide the best medical and nutritional therapy for CFRD.

Methods

This chapter will describe a potential study design to examine the impact of MDIs versus CSII on nutritional status in adults with CFRD. This study will follow a pilot design. According to the NCCIH (2017), pilot studies are used to test the feasibility of the study design. They are useful to determine if the procedures and treatments will be acceptable for a larger-scale study. The NCCIH (2017) article provided examples of questions that pilot studies may answer, including "Can I recruit my target population?," "Can I keep participants in the study?," Will participants do what they are asked to do?," and "Are the treatment conditions acceptable to participants?". The proposed pilot study will attempt to answer these questions to determine if a larger-scale version would be feasible. It may also reveal aspects of the study design that need to be modified. Pilot studies are notable for not being hypothesis-testing studies.

Overall Pilot Trial Feasibility Research Question:

- In adults with a new diagnosis of CFRD, how feasible is a trial examining the effectiveness of multiple daily injections of insulin compared to the use of a continuous subcutaneous insulin infusion in improving nutritional status?

Feasibility Subquestions:

There are several questions that can be answered using a pilot trial. A list of feasibility subquestions chosen for this pilot trial can be found in Table 3.1 with information from the NCCIH (2017).

Table 3.1

Review of Feasibility Subquestions

Feasibility Question	Measure of Success or Failure
Can the study design recruit enough participants for the trial?	- Ability to recruit the recommended sample size in a three-month period
Can the study design keep participants in the pilot study?	- Dropout rate (measured as a percentage) will be used to assess retention.
Will participants do what they are asked to do?	- Attendance at clinic visits (measured as a percentage) - Completion of a three-day food record - Completion of two phone calls with the RD, discussion of three-day food record and 24-hour diet recall. - Medication compliance assessed by the CDE.
Are the treatments safe and effective?	- Number of blood glucose readings outside of target ranges as defined by Brunzell et al. (2015)
Are the treatment protocols acceptable?	- Those who dropout will be asked to discuss their reason for leaving the study.

Setting and Sample:

Sample size:

The NCCIH (2017) noted that pilot studies do not test hypotheses, and thus inferential statistics are not performed. For this reason, power analyses cannot be conducted to determine minimum sample size. Leon, Davis, and Kraemer (2011) noted determining sample size for a pilot study should be based on patient flow, budgetary constraints, and other pragmatics. A total sample size of 10-15 participants was determined to be sufficient to answer feasibility questions. This sample size, along with ongoing recruitment, will be useful to determine the amount of work for RDs and CDEs

as well. The ability to recruit the appropriate number of participants will be a focus of the feasibility study.

Population:

A convenience sample will be used to recruit the sample population. The study population will include adult (age 18+ years) CF patients without known CFRD who are followed by Froedtert Hospital's Cystic Fibrosis Clinic in Milwaukee, Wisconsin. Patients will be eligible for the study if they screen positive for CFRD based on their annual OGTT during their clinic visit. Because CFRD affects those with pancreatic insufficiency, those with pancreatic sufficiency will be excluded.

Recruitment:

Individuals who complete their annual OGTT at Froedtert Hospital's Cystic Fibrosis Clinic and are determined to have CFRD based on the criteria by Brunzell et al. (2015) listed in Table 3.2 will be recruited for the study.

Table 3.2

Review of Various Diagnoses During the Oral Glucose Tolerance Test

Blood Glucose Value	Diagnosis
2-hour glucose > 200 mg/dL	CFRD
2-hour glucose 140-199 mg/dL	Impaired glucose tolerance (IGT)
Mid-OGTT glucose ≥ 200 mg/dL, with OGTT otherwise normal	Indeterminate glycemia (INDET)
2-hour glucose < 140 mg/dL	Normoglycemia

Only those individuals who consent to the study will be included. The consent form can be found in Appendix A.

Instrumentation:

Weight will be taken by the RD at the beginning and end of each treatment period in Froedtert Hospital's Cystic Fibrosis Clinic. The Cystic Fibrosis Foundation uses BMI as its measure of nutritional status. Specifically, the Foundation notes that a higher BMI typically correlates with a higher lung function, and recommends that women maintain a BMI ≥ 22 kg/m^2, while men should maintain a BMI ≥ 23 kg/m^2 (Cystic Fibrosis Foundation, n.d.-c). For this reason, BMI will also be calculated based on the individual's height and weight. A Dexcom G6 Continuous Glucose Monitor (CGM) will be used to collect blood glucose data throughout the day for each participant, with the participant also being asked to keep track of blood glucose levels at various time points (see "Study Design" below).

A three-day food record will be required from each participant during both trial periods. Use of food records may increase the likelihood of underreporting actual consumption, however Shim et al. (2014) stated that this food intake assessment tool has benefits, such as minimal to no recall bias and real-time data collection. In addition to the three-day food record, the RD will also complete a 24-hour food recall during the participant's visit to CF Clinic at the end of periods 1 and 2. A food record combined with a 24-hour food recall will provide a balanced dietary overview, which will allow the RD to calculate typical daily calorie and carbohydrate intake with more accuracy.

Study Design:

The study will include two treatments in succession - MDIs for two months via insulin pens, followed by CSII for two months. A chronological timeline of the pilot study is shown in Table 3.3.

Table 3.3.

Chronological Overview of Study Treatment Periods

Pilot Study Event	Description of Event
Visit to CF Clinic	- Diagnosis of CFRD and participant consent
Visit CF Clinic (approx. 2 weeks after initial visit)	- Carbohydrate counting education - Begin using CGM at home
Visit CF/Endocrine Clinics (1-2 months after diagnosis)	- Obtain starting weight - Carbohydrate counting review - Begin MDIs treatment with education completed by the CDE
Period 1 begins (MDIs treatment period)	- CDE calls participant one week into treatment to make adjustments (if applicable) - Participant uses MDIs for 2 months - Participant completes 3-day food record during first month - Phone call with RD to discuss food record
Visit CF/Endocrine Clinic	- Obtain Period 1 ending weight - Review of carbohydrate counting with the RD - Complete 24-hour diet recall with the RD - Begin CSII treatment with education completed by the CDE
Period 2 begins (CSII treatment period)	- CDE calls participant one week into treatment to make adjustments (if applicable) - Participant uses CSII for 2 months - Participant completes 3-day food record during first month on this therapy - Phone call with RD to discuss food record
Visit CF Clinic	- Obtain Period 2 ending weight - Complete 24-hour diet recall with the RD

After diagnosis of CFRD in CF clinic, the individual will meet with the CF RD to discuss calorie and protein goals. During this visit, they will also receive education regarding carbohydrate counting. Due to the high calorie needs of individuals with CF, variable carbohydrate counting will be taught so calorie intake is not limited. Thus, the participant is able to eat variable amounts of carbohydrates at meals and snacks and correctly administer the appropriate amount of insulin. The participant will be provided with a Dexcom CGM which tracks blood glucose levels every five minutes, 24 hours per day and wirelessly transmits the data to a smartphone. The individual will be instructed to note their blood glucose readings at the suggested times by Ode et al. (2019): before breakfast, two hours after breakfast, before lunch, two hours after lunch, before supper, and before bed. They will be instructed to note when blood glucose levels are outside of target range. This information will be useful for the participants because they can use this data to see how various meals and snacks affect their blood glucose levels. Specifically, the researchers will be focusing on blood glucose readings outside of target range obtained by the CGM at the timepoints used by Brunzell et al. (2015):

- Fasting and pre-meal: 80-130 mg/dL (4.4-7.2 mmol/L)
- 2-3 hours after eating: < 180 mg/dL (< 10.0 mmol/L)
- Bedtime: 90-150 mg/dL (5.0-8.3 mmol/L)

A referral to the Endocrine Clinic will be placed. During the visit to Endocrine Clinic (about 1-2 months after diagnosis in CF Clinic), the individual will receive education regarding MDIs from the CDE. Initial insulin dosing will follow the guidelines as set by the American Diabetes Association's 2010 CFRD Consensus Statement (Moran et al., 2010):

- For those with CFRD and fasting hyperglycemia, initial bolus insulin dosing should be 0.5 units rapid-acting insulin per 15 grams of dietary carbohydrate. Basal insulin should be dosed with an approximately 50:50 basal:bolus insulin ratio.
- For those with CFRD without fasting hyperglycemia, insulin dose should be 0.5 units of rapid-acting insulin per 15 grams of dietary carbohydrate. No basal insulin is needed.

When blood glucose levels are above the treatment range, participants will adjust their insulin dose using a correction factor. Moran et al. (2010) observed that a typical correction dose or "sensitivity factor" starts at one unit of rapid-acting insulin to lower blood glucose by approximately 50 mg/dL.

During the MDIs period, the Humalog U-100 KwikPen (containing 100 units of insulin lispro) will be used for meal-time boluses, while the Lantus SoloStar pen (containing 100 units of insulin glargine) will be used as long-acting insulin. Long-acting insulin will only be used in the MDIs period if the participant has fasting hyperglycemia as determined by their OGTT. In period 2, the t:slim X2 Insulin Pump with Control IQ Technology will be used because of its interface with the Dexcom G6 Continuous Glucose Monitor (Dexcom, 2020). Pumps use only rapid-acting insulin because the pump method of administration delivers insulin every few minutes, essentially acting as the "basal" dose (Diabetes Teaching Center at the University of California, San Francisco, 2020). This makes longer-acting insulin (such as the Lantus used in period 1) unnecessary. Meal-time boluses will also be given via the insulin pump with the participant's authorization of the Humalog dose. During period 2, the insulin pump will

use Humalog U-100 (indicating 100 units of Humalog insulin in the pump at one time). Humalog U-100 insulin was chosen for use with the insulin pump so it will match the insulin used in period 1. Those participants who required Lantus in period 1 will not use a long-acting insulin in period 2, due to the mechanism of action of the pump using Humalog to create their "basal" dose.

Immediately following the Endocrine Clinic visit, the individuals will again meet with the CF registered dietitian and obtain a period 1 starting weight in kilograms. They will receive additional education on carbohydrate counting. The RD will use sample menus and food labels to assess the participant's knowledge of carbohydrate counting prior to initiation of period 1. Once the patient demonstrates to the RD that they are proficient in carbohydrate counting, the first trial period will begin.

The CDE will follow up with the patient via phone one week following initiation of the MDIs method to determine if any insulin adjustments need to be made based on the readings from the CGM. Dosing would be addressed during this phone call and any relevant changes will be made to the insulin dosages. This step is necessary to ensure that the insulin dosages are stable and blood glucose levels are within goal range during the majority of treatment period.

After the first two-month period, the individual will come back to CF and Endocrine Clinics. There will be a one-day "washout" period in which frequency of blood glucose levels outside of target goal range would not be collected. In CF Clinic, an "ending" weight for period 1 will be obtained. To begin period 2, participants will transition to CSII and receive education on the use of the insulin pump provided by the CDE in Endocrine Clinic. The CDE will again call the participant one week into their use

of CSII to make any adjustments to dosing and answer any further questions from the participants. After two months on this therapy, they will again come in to CF Clinic, and their "ending" weight will be obtained.

In addition to clinic visits, dietary compliance will be assessed with phone calls from the CF dietitian one month after each treatment initiation (two calls per participant for the duration of the study). The participants will be instructed to complete a three-day food record prior to these scheduled phone calls (one three-day food record per treatment period). The individuals will be requested to complete the three-day record on three "typical" days (for example, not on holidays). They do not necessarily need to complete this on three consecutive days, but they should be completed during the weekdays. These food records will be compared to a 24-hour diet recall at the end of periods 1 and 2, completed by the RD. The RD will use the information from the food records and recall to assess whether patients are meeting calorie and protein goals. Participants' caloric intakes will be documented based on their caloric intake relative to their calorie goal as calculated by the RD. Carbohydrates are not restricted for these patients; however, the RD will use these calls to assess understanding of carbohydrate counting and to answer any further questions. This is a crucial step of the study to assist the participant with keeping their blood glucose levels within the target range for as long as possible. These calls would also be used to assess whether the participants had experienced any acute illnesses that would have affected their blood glucose control, such as a pulmonary exacerbation leading to a hospitalization. Additionally, the calls will be used to determine if any new medications were started during the treatment period, such as steroids, which may impact blood glucose control. These instances would be noted by the researchers,

but the participant would not be excluded from the trial. The number of new medication or hospital occurrences will be used to assess whether these individuals would need to be excluded from a larger-scale trial in the future.

Data Analysis Plan:

Descriptive Statistics:

Descriptive statistics will be used to answer the feasibility questions:

"Can the study design recruit enough participants for the trial?"

- This will be assessed by the ability to recruit the recommended sample size in a three-month period
- Researchers will also document the number of participants asked to participate and the number that are actually recruited

"Can the study design keep participants in the pilot study?"

- This question will be assessed by the percentage of participants who drop out of the trial at any time point before the ending of period 2.

"Will participants do what they are asked to do?"

- Attendance at clinic visits will be assessed for each participant as a percent of the total.
- It will be documented whether or not the participant completed a three-day food record for each period and a phone call with the RD, along with the completion of a 24-hour diet recall in CF Clinic.
- Medication compliance will be assessed by the CDE, using the number of empty insulin containers.

"Are the treatments safe and effective?"

- This question will be assessed by the number of blood glucose readings outside of target ranges as defined by Brunzell et al. (2015).

"Are the treatment protocols acceptable?"

- Those who drop out of the trial early will be asked to discuss their reason for leaving the study.

This pilot trial will not be focusing on the specific treatment outcomes of change in weight or BMI. However, to simulate how a larger-scale trial would be measuring these outcomes, the RD will document weight change and change in BMI.

Inferential Statistics:

No inferential statistics will be performed in this pilot study.

Threats to Validity:

Threats to External Validity:

Threats to external validity exist in this proposed pilot study that may prevent researchers from generalizing the results to the CF population as a whole. Convenience sampling will be used to recruit participants, thus creating a sampling bias. The group of participants who join the study may be those who are more compliant with clinic visit attendance and may not be representative of all adult CF patients. Additionally, the exclusion criteria lists pancreatic sufficient individuals, meaning that any results seen in the pilot study will not be generalizable to this small percentage of individuals with CF. Another threat to external validity is the Hawthorne effect, in which participants change their behavior because they know they are being studied. They may be more vigilant in their carbohydrate counting and therefore have better blood glucose levels than they would if they were not a part of the pilot trial.

Threats to Internal Validity:

There also exists concerns surrounding internal validity. One of the biggest concerns is maturation, in which the participant may develop additional knowledge or skills and affect the results. For example, the participant may become better at carbohydrate counting as the study goes on. This could create a potential confounding factor in which the participant has better blood glucose control in period 2. However, the study was designed to begin period 1 only after the participant can demonstrate that they are efficient in carbohydrate counting. This is to cushion the effect of maturation on blood glucose control and to hold the two treatments responsible for fluctuations in blood glucose levels as much as possible.

Instrumentation is another potential threat to internal validity. To avoid the effect of differing results due to instrumentation, the same weight scale will be used for all appointments when obtaining weight during the study. The same RD and CDE will conduct clinic visits and phone calls during the course of the study as well. The three-day food records and 24-hour diet recall may also be potential causes of a threat to internal validity through instrumentation. Both assessment methods have limitations. Food records may cause participants to erroneously estimate consumed amounts, and participants may not eat their usual food items if they know their intakes are being documented and assessed. Similarly, food recalls may encourage participants to eat foods that do not necessarily reflect their average daily intake. Food recalls also have the disadvantage of being only a small snapshot of long-term overall intake (David Geffen School of Medicine, UCLA, 2003).

Attrition may also be a threat to internal validity if participants choose to dropout of the study early. This may potentially create a biased sample of participants who are more motivated or who have more time to complete the protocol of the trial compared to those who dropout. Consequently, the results of the feasibility questions could lean more towards the characteristics of those who stayed in the trial versus those who were not able to complete it.

Ethical Procedures:

All participants' data will be kept in a secure, central online database at Froedtert Hospital. Consent forms with personal data will be locked in a secure drawer in the Cystic Fibrosis Clinic at Froedtert Hospital. Data will be de-identified and analyzed by researchers. Researchers will discuss consent and individuals will be asked to sign the consent form found in Appendix A if they choose to participate in this trial. Participants will be informed that they can drop out of the pilot trial at any time without consequences. This study will be approved by the Institutional Review Board at Mount Mary University. The IRB application for the study can be found in Appendix B.

Summary:

This proposed pilot study will focus on the feasibility of a trial comparing MDIs to CSII in the CFRD population and their effects on nutritional status The proposed pilot study is an important step to determine if the suggested design is feasible and worth exploring with a larger sample size. It may also suggest areas of the study that need to be modified for a larger version to be successful. In the future, a study of this design may provide critical information regarding the management of uncontrolled blood glucose levels in a population that is at risk for malnutrition. In Chapter 4 the anticipated results

are discussed, and Chapter 5 provides a discussion and concluding statements on the topic.

Anticipated Results

The overarching research question for the pilot trial is, "*In adults with a new diagnosis of CFRD, how feasible is a trial examining the effectiveness of multiple daily injections of insulin compared to the use of a continuous subcutaneous insulin infusion in improving nutritional status?"* Although the trial has not yet been completed, anticipated data of the pilot study participants are shown in Table 4.1, with a predicted enrollment of 12 participants during an ongoing three-month recruitment period. A rationale for each of the anticipated values shown can be found in chapter 5, Discussion.

Table 4.1.

Description of Potential Participants

Subject Traits	Subjects (n=12)
Gender	
Male	6 (50%)
Female	6 (50%)
Age (years)	
18-24	6 (50%)
25-30	4 (33%)
30+	2 (17%)
Initial BMI (kg/m^2)	
<18.5	2 (17%)
18.5-22	9 (75%)
>22	1 (8%)
Fasting Glycemia Status during OGTT	8 (67%)
FH+	4 (33%)
FH-	

Descriptive statistics and subjective participant data will be used when addressing the feasibility subquestions. Inferential statistics cannot be performed for a pilot trial (NCCIH, 2017). Table 4.2 lists each feasibility subquestion and its anticipated outcome at

the end of the pilot trial. A rationale for each of the anticipated results can be found in chapter 5, Discussion.

Table 4.2.

Anticipated Results of Feasibility Subquestions

Feasibility Subquestion	Anticipated Result
Can the study design recruit enough participants for the trial?	
Ability to recruit recommended sample size in three-month period	Yes, anticipate 10-15 participants
Percentage of participants who are asked to join the study and provide consent (recruitment rate)	≥75%
Can the study design keep participants in the study?	
Percentage of participants who drop out of the trial before the end of period 2	<20%
Will participants do what they are asked to do?	
Average percentage of attendance at clinic visits (total of 5 visits)	>80% (>4/5 visits)
Completion of three-day food record and 24-hour recall for each period (total of 4 dietary assessments for each participant for entire study)	≥80% will complete 4/4 assessments
Medication compliance, assessed by percentage of insulin prescribed and used, assessed by CDE	≥80% compliance
Are the treatments safe and effective?	
Percentage of blood glucose readings outside of recommended target ranges	≤20% for each treatment
Are the treatment protocols acceptable?	Subjective information– participants asked to provide reasoning for leaving the study early

The subquestion “Are the treatment protocols acceptable?” will be answered subjectively by participants, and thus will direct researchers to aspects of the study which were not tolerable or were too demanding. For example, some participants may not be able to attend all clinic visits. Other participants may not be able to complete diet records or diet recalls with the RD. Chapter 5 will conclude with a discussion of the proposed pilot study.

Discussion

As the life expectancy for those with CF continues to increase, so will the number of these individuals with additional complications. CFRD is just one of these additional complications. It is well known that those individuals with CF who maintain a BMI above 22 kg/m^2 for women and 23 kg/m^2 for men tend to have better outcomes (Cystic Fibrosis Foundation, n.d.-c). Uncontrolled blood glucose levels in CFRD can lead to glucosuria and subsequently, weight loss; therefore, normoglycemia is an important clinical goal (Pencharz & Durie, 2000). Currently, the only recommended treatment for CFRD is insulin therapy (Ode et al., 2019). The most common regimen is MDIs. Unlike in type 1 diabetes, CSII is still an uncommon form of treatment for the CF population. There are currently no large-scale studies comparing the use of MDIs and CSII in this population, the impact on blood glucose levels and ultimately their effects on nutritional status (Ode et al., 2019).

A pilot study design was chosen for this project to determine the feasibility of a larger trial. Pilot studies guide researchers on various aspects of the study that need to be addressed before a larger trial can be initiated. The goal for this study is not to assess the outcomes of each treatment periods; instead, the goal is to determine if the protocol is sound and to identify limitations and areas for improvement. The NCCIH (2017) notes that pilot studies can answer questions surrounding recruitment, retention of participants, and acceptability of study protocols. These questions can be answered with this study. If the results of the pilot study determine that a larger-scale trial is feasible, this larger study could be conducted to answer the hypothesis question "*In adults with a new diagnosis of*

CFRD, how do multiple daily injections of insulin compare to a continuous subcutaneous insulin infusion in improving nutritional status?"

Conducting a large-scale trial to answer this hypothesis question will be important for RDs and other healthcare professionals who care for patients with CFRD. It is imperative that these professionals have the best information to help determine the most successful treatments for managing the nutritional side effects of CFRD. By providing the best treatment, it is anticipated that the life expectancy for those with CF will continue its trend upward. Marshall et al. (2017) noted that the median life expectancy for those with CF in 2017 was 46.2 years, which is an increase of nearly 20 years compared to three decades earlier. This increase in life expectancy means that more individuals with CF will be diagnosed with CFRD during their lifetime.

Rationale for Anticipated Participants Statistics

There are currently only two major adult CF care clinics in southern Wisconsin. At any given time, the Cystic Fibrosis Clinic at Froedtert Hospital follows between 150-200 patients with CF. These patients are seen quarterly in clinic and so have the opportunity to be a part of the proposed pilot trial because of the ongoing three-month recruitment. The Cystic Fibrosis Clinic at Froedtert Hospital is also a main care center for those individuals who have previously been cared for by Children's Wisconsin (CW). Once an individual with CF turns 18 years of age, they will be referred to the clinic at Froedtert Hospital. Many of the patients from CHW choose Froedtert Hospital for their CF care due to the similar location in Milwaukee, Wisconsin. The ongoing recruitment also means that those being referred from CW will also have the opportunity to join the pilot if they are screened positive for CFRD. Yen and Leonard (2015) note that on

average 40-50% of individuals with CF will develop CFRD during their lifetime, which indicates a large number of potential participants based on the current size of the clinic and the continuous admittance of new patients from CHW. If the pilot trial is successful, a larger trial could include those individuals with CFRD who get their care from the other major CF care center in Wisconsin, at the University of Wisconsin campus.

An individual must inherit one copy of a mutated CFTR gene from each parent in order to have CF, and it is equally likely to affect males and females (Cystic Fibrosis Foundation, n.d.-a). For this reason, I anticipated to recruit an equal number of males and females for the trial. Because the trial focuses on new diagnoses of CFRD, I anticipated that the majority of those in the trial would be younger (<40 years old), since it is more likely for older patients to have already been diagnosed. Additionally, a review of the literature in Chapter 2 demonstrates that most of the participants at baseline in the reviewed studies were under the age of 30 years (Frost, et. al, 2018; Moran et. al, 2009; Onady & Langdon, 2006). As expected, multiple studies that provided baseline BMI for their participants (some studies included weight rather than BMI) demonstrated that at baseline, average BMIs were below the recommended targets from the Cystic Fibrosis Foundation (Mohan et. al, 2008; Moran et. al, 2009). In an additional study by Frost et al. (2018), participants who started on insulin therapy had an average BMI of 22.1 kg/m^2, which is only 0.1 kg/m^2 above the recommended BMI for women and is 0.9 kg/m^2 below the recommended BMI for men. These factors were used to estimate the number of participants in each age and BMI category. Because individuals with CFRD have traits of both type 1 and type 2 diabetes (Brunzell et al., 2015), I anticipated participants to have

issues with fasting glycemia more often than not because they will likely have some amount of insulin dependence.

Rationale for Anticipated Results

Because of the high rate of CFRD diagnosis in the CF population (Yen & Leonard, 2015), we expect to be able to recruit our recommended sample size. It is estimated that >75% of those who are asked to join the trial will consent. This percentage is expected because insulin is currently the only recommended therapy for the management of CFRD (Ode et. al, 2019), and because I believe the extra protocol measures (three-day diet record, 24-hour diet recall) to be feasible for most participants. It is unclear if participants will be able to attend all study clinic visits, which is why the anticipated number of clinic visits attended was set at 80%, or an average of four out of five visits attended. However, these visits will all be scheduled at the beginning of the trial, with the anticipation that this will promote better attendance.

I do not expect a high number of participants to drop out of the trial. The rationale for the low anticipated dropout rate is the same as the recruitment rate - participants will be encouraged to use insulin regardless of trial participation. CF patients are accustomed to taking multiple medications (pancreatic enzymes, vitamin and mineral supplements, antibiotics, etc.) and completing breathing treatments throughout the day. For this reason, we expect good compliance with insulin administration. Education on the benefits of consistent insulin administration will be discussed with the participants at the start of the trial.

The CGM was chosen specifically for this trial because of the benefit of real-time blood glucose readings. As the individual becomes more familiar with their typical blood

glucose readings after eating certain food items, I anticipate better blood glucose control and a fewer number of blood glucose readings outside of target ranges. This is also the reason for beginning to use the CGM prior the start of period 1. The CDE and the participant will use this data to identify individual trends in their levels and to make any necessary adjustments. For this reason, I anticipate only a few number of blood glucose readings outside of target range (<20%) which would be equivalent to less than one to two readings per day because the recommended number of blood glucose readings for individuals with CFRD is six times daily (Ode et al., 2019). Acceptability of treatment protocol will be subjective and based on information provided by participants who drop out of the study, if applicable. Because the pilot trial will have a small sample size, this amount of data should be small enough to be assessed subjectively.

The RD will be collecting information regarding calorie intakes through the use of food records and diet recall. This information will be assessed during the pilot to determine if participants have been meeting their prescribed calorie goals or falling short, which will be defined as <80% of prescribed goal intake. Diagnosis of CFRD does not inherently necessitate an increase in caloric goals; therefore, it is expected that participants will have a good understanding of their goals since these are discussed at all CF visits and will be emphasized during visits with the RD during this pilot. However, this information does not fall within one of the feasibility subquestions. Additionally, the RD will document any relevant medication changes, including medications that may affect blood glucose levels, and any instances of pulmonary exacerbations. These instances will be noted; however, this information again does not fall into any one of the feasibility subquestions.

Strengths and Limitations of the Proposed Study

This study has strengths and weaknesses related to its pilot design, as well as strengths and weaknesses inherent to the proposed study plan. One of the most beneficial aspects of a pilot study is its ability to answer multiple feasibility questions at once and identify which features of the study will need to be modified prior to initiating a larger-scale trial. Specifically, this pilot study will help to answer multiple feasibility subquestions which were chosen to address the overarching hypothesis question. By assessing the outcomes of the study related to questions of recruitment, retention, and acceptability of protocol, features of the design can be modified to save time and resources in a larger study. Participants will be able to provide feedback regarding design and tolerability of the protocol. Subjective participant data will be manageable with the small sample size of participants. This feature may prompt researchers to develop more realistic or achievable approaches in a future larger-scale trial.

Recruitment will be ongoing, so individuals will not all start Period 1 at the same time. This will be a useful approach to determine the amount of work needed from both the RD and the CDE for each participant. Additionally, the pilot's chosen intervention (insulin) is the only treatment currently recommended for the treatment of CFRD (Ode et. al, 2019). For this reason, we expect to recruit a sufficient number of participants with the understanding that they will be encouraged to start insulin therapy regardless of participation in the trial. If the pilot study is not able to recruit the recommended number of participants, a different strategy could be explored, such as including other CF centers in the study. Including multiple CF centers is a strategy used by various studies in the Chapter 2 Literature Review and could be helpful to recruit more participants.

The participants in the pilot study will have one-on-one visits with both the RD and the CDE at Froedtert Hospital. Their insulin dose and education will be individualized based on their needs. Carbohydrate education is a necessary component of proper CFRD treatment. Because of the close association of nutritional status and CF outcomes, many CF patients are already familiar with carbohydrate counting and monitoring of food and beverage intake. Therefore, I do not foresee this being an issue with most participants.

Participants will also have the unique opportunity to try both methods of insulin administration, which will allow them to decide which method is most beneficial for their lifestyle once the trial is over. As previously mentioned, individuals newly diagnosed with CFRD are encouraged to begin using insulin regardless of participation in the trial, and I believe the additional requests of food and drink documentation will be tolerable and achievable for the majority of participants. Therefore, this will likely be an advantage to the study and will support the retention rate. The within-subject design also requires a fewer number of participants. This type of design reduces the amount of error that can develop during a between-subject study design with confounding natural variance between participants.

There are limitations to conducting a pilot study. No inferential statistics can be conducted at the completion of a pilot study. For this reason, researchers will not be able to make a determination about which of the two treatments was more effective. In the future, a larger trial comparing the two treatments could use ANCOVA analysis to make inferences about the efficacy of the treatments. Based on the proposed pilot design, a larger-scale trial could use dietary compliance and glucose control measured via number

of blood glucose levels outside of target range as its covariates while using ANCOVA for its analysis. This type of analysis would control for the two covariates and subsequently allow for the comparison of the average change in weight between the two periods. However, the proposed pilot study will only be able to use descriptive statistics and subjective participant data to answer the feasibility subquestions.

Another limitation to the study is the use of convenience sampling to recruit participants for the trial. Participants must come in for their annual oral glucose tolerance test and test positive for CFRD in order to be considered for the trial. This type of sampling may be biased and may not be representative of the entire population. For example, the participants who may come in for the oral glucose tolerance test may be those who would be more inclined to come to other clinic visits during the trial. Although this would be beneficial for study retention rate, it may not be representative of the entire population to accurately answer the feasibility subquestion, “Will participants do what they are asked to do?”, since attendance at clinic visits will be collected. This method of convenience sampling also means that recruitment will be ongoing, and each participant will be initiating the study at various time points.

An additional limitation to the study is that insulin adjustments may be made during the beginning of both insulin treatment periods. I anticipate that any and all changes that need to be made will be caught by this point after participants have been using insulin and tracking blood glucose levels with their CGM for one week. Although not a main outcome studied during this pilot trial, this may affect weight results at the end of a larger-scale trial. For participant’s safety, they will be instructed to contact the Endocrine Clinic if they have any unresolving issues with hypo- or hyper- glycemia at

any point during the trial. However, this is an expected result of insulin therapy, as changes in insulin needs may happen for anyone experiencing illness, change in exercise habits, stress, or other changes in their environment. Tracking the number of blood glucose levels outside of target range during the pilot trial will help researchers determine if more frequent calls with the CDE are warranted during a larger trial.

Alignment with Previous Studies

After completion of this pilot, a larger study of similar design examining MDIs and CSII will be one of the first of its kind in adults. Previous studies with the two methods either had a small sample size or were case reports only. For this reason, it will be difficult to compare this study to others. A similar study conducted by Hardin et al. (2009) examined the effects on nutritional status after participants switched from MDI to CSII. This study examined changes in weight and lean body mass. However, this study recruited only nine participants. The proposed pilot study will help to determine if a larger study can be conducted, and this would be one of the first of its kind to compare the two insulin methods in this population.

Suggestions for Future Studies

Future studies are needed to examine how nutritional support, with either enteral nutrition or parenteral nutrition, affects nutritional status for those diagnosed with CFRD. These individuals likely need individualized insulin administration regimens, but it is unclear if these patients would benefit from the use of CSII for weight maintenance or weight gain. Additional studies are also needed to identify any differences between those with CFRD FH+ and CFRD FH- and their responses to MDIs and CSII.

Maintenance of weight and BMI at or above the recommendations by the Cystic Fibrosis Foundation is crucial for reducing morbidity and mortality (Yen & Leonard, 2015). Multiple studies (Barni et al., 2017; Panagopoulou et al., 2013) have found associations between lower BMI and forced expiratory volume in 1 second (FEV_1) in patients with CF. Those with the additional complication of CFRD are at an increased risk for malnutrition due to glucosuria and subsequently a net negative caloric balance (Pencharz and Durie, 2000).

Currently, there is a paucity of research examining various insulin programs in the adult CF population. Specifically, there are no large-scale trials involving the use of CSII in this population. It is unclear if any one insulin approach has more beneficial impacts to weight and BMI. This pilot study provides a potential design for a study comparing MDIs and the use of CSII with regards to nutritional status and will be a stepping-stone towards creating a larger study. Advancement in CFRD research is a necessary step for RDs and other healthcare providers to support those with CF and reduce morbidity and mortality in this population.

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Appendix A

Research Participant Information and Consent Form

Mount Mary University

Title of Study: A Pilot Study Involving Two Insulin Programs in Cystic Fibrosis-Related Diabetes

Invitation to Participate and Purpose of the Research

You are invited to participate in a research study that seeks to examine the benefits of different types of insulin administration on nutritional status in the adult cystic fibrosis population. At the beginning and throughout the study, participants will receive education on carbohydrate counting and its relationship to blood glucose control. Participants will be asked to begin using insulin with multiple injections of insulin throughout the day for two months once they are proficient with carbohydrate counting and their insulin regimen is stable. Weights will be taken at the beginning and end of the two-month period. After this period, participants will be transitioned to using a continuous subcutaneous insulin infusion. Weights will be taken at the beginning and end of this two-month period as well. Participants will be asked to monitor their blood glucose levels at certain times throughout the day using a Dexcom continuous glucose monitor. They will also be asked to complete a three-day food record one time during each period. Data will be de-identified and analyzed by researchers. Participants must be 18 years of age or older.

Benefits and Risks

This research is designed to benefit the dietetics profession, and other professions involved in the care of cystic fibrosis patients, by providing information about how two different forms of insulin administration affect nutritional status in this population. Although participants may not benefit personally from being in this research study, findings generated by this research may add new knowledge to the dietetics field in general. There will be no monetary compensation. There are no known potential risks associated with participating in this study. There may be minor discomfort when using insulin therapy, because it does involve the use of small needles. However, participants will be provided with education from a certified diabetes educator on insulin administration. Withdrawal from the study will not jeopardize or otherwise affect any treatment or services the participant is currently receiving or may receive in the future. Please address any questions or issues of concern to the researchers using the contact information provided above.

Confidentiality

All information obtained will be kept confidential by the researchers who will be the only people with access to the data. Information obtained will be stored electronically and will be password protected. Per the U.S. Office of Human Research Protections (code §46.115), all data will be destroyed 3 years after the end of data collection. Paper files will be shredded, and electronic files will be deleted. Should a participant wish to withdraw from the study, their data will be destroyed. Individual participants will not be identified in any report or publication about this study.

Contact Information

If you have questions about this research study, your rights as a research subject, or would like to know the outcome of the research, please contact Dr. Dana Scheunemann (supervising faculty member, email: scheuned@mtmary.edu) and Caitlin Guell (primary investigator, email: guellc@mtmary.edu). If you have any questions regarding your rights or privacy as a participant in this study, please contact Dr. Tammy Scheidegger, Mount Mary University Institutional Review Board Chair, 2900 North Menomonee River Parkway, Milwaukee, Wisconsin, 53222-4597, telephone (414) 930-3434 or email schediet@mtmary.edu.

Consent

By signing below, you are indicating that you have read this consent form, have been given the opportunity to ask questions, and have agreed to voluntarily participate. You may withdraw from participation at any time, or refuse to answer any question herein, without penalty or loss of benefits to which other participants are entitled.

You may request a copy of this page for your records. Thank you for your participation.

Signature of participant_____ Date _____

Appendix B

Office use only: IRB Approval #: _____

Mount Mary University
Institutional Review Board (IRB)
for the Protection of Human Subjects

Application for IRB Review

DATA COLLECTION CANNOT BEGIN
UNTIL THE IRB HAS APPROVED THIS PROJECT

Directions:

- Faculty and student researchers, as well as student research advisors, should **read all relevant information on the University IRB page in My Mount Mary before initiating an application**. This includes full knowledge of the US Department of Health and Human Services Code of Federal Regulations Title 45 (Public Welfare), Part 46 (Protection of Human Subjects). http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
- All applicants must verify completion of Human Subjects Training. See http://www.citiprogram.org
- The IRB application must be filed and approved by the IRB **prior** to any Mount Mary University faculty, staff, or student (undergraduate or graduate), initiating a research project/study.
- If there is a cooperating institution, attach a copy of their IRB approval.
- In the case of a student research project, the student may complete the IRB application but the student's research advisor must sign and submit the application to the IRB for approval. It is the responsibility of the faculty research advisor to ensure that student applications and all attachments (e.g., informed consent forms and survey instruments) are in their final edited form. Even though a student research project may qualify as **exempt** from full IRB review, the research advisor may request the student to complete and submit a full IRB application.
- Complete this application using your word processing program (ex. Word), then print it out and obtain signatures from all investigators and advisors. (**Handwritten applications will not be accepted**.) For your benefit, save the completed application on your computer in case it needs to be revised and resubmitted.
- This is a professional document; please check spelling, grammar and punctuation.
- Submit an electronic copy, via email, of the completed application with required signatures and attachments, **in a single pdf**, to Tammy Scheidegger, IRB Chair, scheidet@mtmary.edu . You will receive an email verifying receipt of the application from the IRB Board Chair.

- Allow a **minimum of 30 working days** to process your application. Make sure this timeframe is accounted for when considering initiation of data collection and due dates for student projects. Please be aware that if, upon completion of the application, you find that ***no exemptions apply to your research, your application will need to go through a full IRB Committee review which can take as many as 60 days to be completed.***
- For class projects you must submit IRB applications to the IRB Chair by October 31st of the fall semester and March 31st for the spring semester. For summer classes, please consult with the IRB Chair.
- Upon receipt of the IRB letter of approval, data collection may begin.

I. Required Documentation - No action will be taken without these attachments.

Are the following attached to the IRB application?

Informed Consent Document	X Yes	Informed Consent Documents should include an explanation of procedures, risk, safeguards, freedom to withdraw, confidentiality, offer to answer inquiries, third party referral for concerns, signature and date. See Appendix.A and use the **MMU Informed Consent Template** to avoid delays in the process.
Questionnaire/Survey Instrument(s)	☐ Yes	If a survey is being administered in any written format (e.g., survey monkey, qualtrics), a copy of that survey must accompany this application. If a survey is being conducted verbally, a copy of the introductory comments and survey questions being asked must be attached to this application. If survey includes focus group questions, a complete list of the question must be attached. For research using a published/purchased instrument, a photocopy of the instrument will suffice.
Verification of Human Subjects Training	X Yes	Copy of transcript, certificate or other evidence that ALL members of the research team have completed the required training. .
Copy of cooperating institution's IRB approval.	X Yes	Not required if there is no cooperating institution. .

II. Investigator(s):

Name: Caitlin Guell Phone: (920) 539-9419
Affiliation with Mount Mary University (e.g. faculty, student, etc.): student
Email: guellc@mtmary.edu

Signature: _Caitlin Guell_____ Date: 7/5/2020

Name: Phone:
Affiliation with Mount Mary University:
Email:

Signature: _____ Date:

If student, list Research Advisor and complete the application. Research Advisor must provide requested information and verify.

Department: Dietetics
Research Advisor's Name: Dana Scheunemann
Email: scheuned@mtmary.edu Phone:

Research Advisor: Have you completed Human Subject's Training? ☐ Yes ☐ No

Research advisor's signature indicates responsibility for student compliance with all IRB requirements.

Signature: Date:
_____
Research Advisor

III. Project Description – Required by all applicants

Instructions: Briefly describe the proposed project including the sample and methodology (e.g. human subjects, data collection, data analysis and instruments).

1) Objectives (purpose of project):

The purpose of the project is to determine the feasibility of a larger-scale trial comparing the use of multiple daily injections of insulin versus the use of a continuous subcutaneous insulin infusion in adult cystic fibrosis patients with a new diagnosis of CFRD.

2) Relevance to practice/body of knowledge:

Cystic fibrosis is the most common genetic disorders in Caucasians. The disease creates a variety of issues that affect nutritional status, including increased energy expenditure and malabsorption of nutrients. A common complication of cystic fibrosis is cystic fibrosis-related diabetes, which is a unique form of diabetes. There is currently no consensus on which treatment for cystic fibrosis-related diabetes will produce the most beneficial results related to nutritional status. Insulin therapy is used to maintain blood glucose levels, however there is limited research on the use of the continuous subcutaneous insulin infusion in this population. This research study will be a beginning step towards conducting a larger-scale trial comparing the use of multiple daily injection of insulin and the use of a continuous subcutaneous insulin infusion and their relative effects on weight. This will be a feasibility pilot study to assess recruitment rates, compliance, and dropout rates.

3) Describe the research design (e.g. subject/participant selection and assignment, design, intervention, data analysis):

The study would recruit participants using convenience sampling. Since this a pilot trial, researchers would aim for 10-15 participants. Individuals would be recruited if they come into adult CF Clinic at Froedtert Hospital for their oral glucose tolerance test. This test determines if the patient has a diagnosis of cystic fibrosis-related diabetes. Those with a new, positive test for CF- related diabetes would be asked for consent to complete the trial.

The study would include two treatments in succession - multiple daily injections of insulin (MDIs) for two months, followed by continuous subcutaneous insulin infusion (CSII) for two months. Primary outcome would be weight after two months of each treatment. A secondary outcome that would be examined is frequency of blood glucose levels outside of a specified target range. The participant would receive education regarding their protein and calorie goals, as well as carbohydrate counting education, with the registered dietitian prior to starting the pilot study. The participant would be provided with a continuous glucose monitor to monitor their blood glucose levels throughout the day.

In addition to clinic visits, dietary compliance would be assessed with phone calls from the dietitian one month after each treatment initiation (two calls per participant for the duration of the study). The participants would be instructed to complete a three-day food record prior to these scheduled phone calls (one three-day food record per treatment period). Participants' caloric intakes would be documented based on their caloric intake relative to their calorie goal as calculated by the dietitian. The goal for these phone calls would be to assess the participant's dietary compliance and accurate carb counting. These calls would also be used to assess whether the participants had experienced any acute illnesses that would have affected their blood glucose control, such as a pulmonary exacerbation leading to hospitalizations. Additionally, the calls would be used to determine if any new medications were started during the treatment period, such as steroids, which may also impact blood glucose control. These instances would be noted.

The pilot study would begin after the participant has been diagnosed with CFRD and provides their consent to join the study. Within one to two months after diagnosis, the participant would visit CF and Endocrine Clinics at Froedtert Hospital and begin using multiple daily injections of insulin for their diabetes treatment. Education would be provided by the Certified Diabetes Educator (CDE) in Endocrine Clinic. An initial weight in kilograms will be taken at initiation of this treatment, and they would review carbohydrate counting with the dietitian. This is treatment period one, and it will last two months. One week into period one, the CDE from Endocrine Clinic would call the participant to ensure appropriate blood glucose control, and to make any adjustments to insulin dosing if needed. The participant would also be instructed to conduct a three-day food record during period one to ensure he or she is taking in adequate calories and protein. This food record would be discussed on the phone with the RD.

After two months, the individual would come back to CF and Endocrine Clinics at Froedtert Hospital. The RD would obtain an "ending" weight for period one. The individual would transition to using a continuous subcutaneous insulin infusion in Endocrine Clinic with education provided by the CDE. A review of carb counting would be provided with the RD, and a 24-hour diet recall would also be completed to compare calorie and protein amounts to the three-day food records.

During period two, the participant would use CSII at home. They would again complete a three-day food record to discuss during a phone call with the RD and also complete a phone call with the CDE to determine if any dosing changes need to be made. CSII therapy would also be conducted for a total of two months. An "ending" weight would be obtained at the end of period two, and the RD again would complete a 24-hour diet recall to compare calorie and protein intake during period two with their three-day food record.

4) What measurement/data collection tools are being used?

This is a pilot trial that will focus on the feasibility of completing a larger-scale version of the study. Weight will be the primary outcome used in this pilot trial. A three-day food record will also be used during each trial period (a total of twice during the study) along with a 24-hour diet recall during clinic visits. Documentation of blood glucose levels will be tracked with the continuous glucose monitor. At the end of the study, recruitment rates, dropout rates, and clinic attendance will be reported as percentages of the total. If any participant drops out of the study, they will be asked to explain their reasoning for leaving the study, to provide researchers information about treatment protocol acceptability.

IV. Additional Project Information – Required by all applicants

1) What human subjects training has the researcher completed (e.g. course work, online certification)?
CITI Human Subjects online training

2) What process is used for obtaining informed consent (attach the informed consent application)? See Appendix for consent application.
Informed consent application in Appendix A

3) Does the research include special populations?

Minors under 18 years of age?	☐ Yes	X No
Persons legally incompetent?	☐ Yes	X No
Prisoners?	☐ Yes	X No
Pregnant women, if affected by research?	☐ Yes	X No
Persons institutionalized?	☐ Yes	X No
Persons mentally incapacitated?	☐ Yes	X No

4) If **YES,** describe additional precautions included in the research procedures.

5) Does the research involve any of the following procedures?

False or misleading information to subjects?	☐ Yes	X No
Withholds information such that their informed consent might be questioned?	☐ Yes	X No
Uses procedures designed to modify the thinking, attitudes, feelings, or other aspects of the behavior of the subjects?	☐ Yes	X No

6) If **YES**, describe the rationale for using procedures, how the human subjects will be protected and what debriefing procedures are used.

7) Does the research involve measurement in any of the following areas?

Sexual behaviors?	☐ Yes	X No
Drug use?	☐ Yes	X No
Illegal conduct?	☐ Yes	X No
Use of alcohol?	☐ Yes	X No

8) If **YES**, describe additional precautions included in the research procedures.

9) Are any portions of the research being conducted online?

Survey posted on a website?	☐ Yes	X No	If yes, assure anonymity
URL for survey includes information that could identify participants?	☐ Yes	X No	If yes, assure anonymity
Invitation to participate sent by email?	☐ Yes	X No	If yes, assure anonymity
Items use drop-down box?	☐ Yes	X No	If yes, assure that items allow choice of "no response"

10) If **YES**, describe additional procedures.

11) Describe the methods used to ensure confidentiality of data obtained.
All information, including consent forms, will be kept confidential by the primary researchers at Froedtert Hospital in a secure, locked location. Collected data will be held on a secure, online database that will be accessed only by the primary researchers. All data will be destroyed 3 years after the end of data collection.

Risks and Benefits

1) Describe risks to the subjects and the precautions that will be taken to minimize them. (Risk includes any potential or actual physical risk of discomfort, harassment, invasion of privacy, risk of physical activity, risk to dignity and self-respect, and psychological, emotional or behavioral risk.)

This study will include the use of insulin therapy, which is a medication used to manage blood glucose levels. Currently, this is the standard therapy for individuals with CFRD. When using insulin, there is a risk for hypoglycemia (low blood glucose levels). All participants will be education on the correct method for correcting low blood glucose levels prior to initiation of the first trial period. Participants have the opportunity to drop out of the study at any time. There are no other known risks to the study.

2) Describe the benefits to subjects and/or society. (These will be balanced against risk.) This pilot study will be conducted to determine if a larger-scale trial is feasible. The study will provide information to researchers about the nutritional benefits of using various forms of insulin therapy.

V. Is the proposed project "research" as defined by Institutional Review Board requirements? - Required by all applicants

- Research is defined as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
- A human subject is defined as a living individual about whom an investigator obtains either 1) data through intervention or interaction with the individual; or 2) identifiable private information.

Does the research involve human subjects or official records about human subjects?

X Yes
☐ No

***If NO STOP here, and SUBMIT application*.**

If the results will be available in the library, presented at a professional conference (includes any presentation to group(s) outside of the classroom), or published, please check the Yes box:

X Yes
☐ No

If the YES box is CHECKED, proceed to SECTION VI.

***If the NO box is CHECKED, STOP here, and SUBMIT application*.**

VI. Exemptions - Required by all applicants

Are you requesting exemption from IRB review in one of the federally approved categories?

If yes, please reference OHRP website http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html and continue with application.

1) Does the research meet the criteria for exempt category 1 (education)? [45 CFR 46.101 (b) (1)]

Is the research conducted in established or commonly accepted educational settings (e.g. schools, Universities or other sites where educational activities regularly occur)?	☐ Yes X No
Does the research study involve only normal education practices (e.g. instructional strategies, techniques, curricula, or classroom management techniques)?	☐ Yes X No

*If **both** questions are answered **"yes"**, stop here, and **submit** application.*

2) Does the research meet the criteria for exempt category 2 (specific procedures)? [45 CFR 46.101 (b) (2)]

Does the research involve only the use of educational tests, survey procedures, interview procedures or observation of public behavior?	☐ Yes X No
Is the information obtained recorded in such a manner that human subjects cannot be identified directly or through identifiers linked to the subjects? (See Appendix B)	X Yes ☐ No

*If **both** questions are answered **"yes"**, stop here, and **submit** application.*

3) Does the research meet the criteria for exempt category 3 (public officials)? [45 CFR 46.101 (b) (3)]

Does the research involve only the use of educational tests, survey procedures, interview procedures or observation of public behavior?	☐ Yes X No
Are the human subjects elected or appointed public officials or candidates for public office? **If no, proceed to Category 4.**	☐ Yes X No
Does any federal statute require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter? (See Appendix B)	X Yes ☐ No

*If **all** questions are answered **"yes"**, stop here, and **submit** application.*

4) Does the research meet the criteria for exempt category 4 (existing data/specimens)? [45 CFR 46.101 (b) (4)]

Does the research involve only the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens?	☐ Yes X No
Will the information be recorded by the investigator in such a manner that the subjects cannot be identified directly or through identifiers linked to the subjects? (See Appendix B)	X Yes ☐ No

*If **both** questions are answered **"yes",** stop here, and **submit** application.*

5) Does the research meet the criteria for exempt category 5 (federal program research)? [45 CFR 46.101 (b) (5)]

Does the research involve studying, evaluating or examining federal public benefit or service programs?	☐ Yes X No
Is the research conducted through a federal agency?	☐ Yes X No

*If **both** questions are answered **"yes"**, stop here, and **submit** application.*

6) Does the research meet the criteria for exempt category 6 (taste and food quality)?
[45 CFR 46.101 (b) (6)]

Does the research involve a taste and food quality evaluation or consumer acceptance study?	☐ Yes X No
Does the food consumed contain no additives, or a limited amount of food additives at or below a level approved by the FDA or EPA or the Food Safety and Inspection Service of the U.S. Department of Agriculture?	☐ Yes X No

*If **both** questions are answered **"yes"**, stop here, **submit** application.*

If no exemptions apply, your application will need to go through a full IRB Committee review. Be advised that this process can take as many as 60 days to be completed.