1 COVER PAGE

Research Protocol - 2018-0297

Fresh Food Farmacy: A Randomized Controlled Trial

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TABLE OF CONTENTS

2 ABBREVIATIONS USED IN THE PROTOCOL

Abbreviation	Term
AE	Adverse Event
BMI	Body Mass Index
ED	Emergency Department
EHR	Electronic Health Record
FFF	Fresh Food Farmacy
GIRB	Geisinger IRB
HbA1c	Hemoglobin A1c
HEDIS	Healthcare Effectiveness Data and Information Set
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
J-PAL	Jameel Poverty Action Lab at MIT
MTM	Medically-Tailored Meals
PHI	Protected Health Information
RCT	Randomized Controlled Trial
SAE	Serious adverse event
T2DM	Type II Diabetes Mellitus

3 ABSTRACT

We propose an Interventional Study of the effects of Geisinger's Fresh Food Farmacy program on patient health. In particular, we will conduct a pragmatic, prospective, randomized-controlled trial of Geisinger's Fresh Food Farmacy (FFF) program.[1]

In July 2016, Geisinger began piloting the "Fresh Food Farmacy" (FFF) program for diabetic, food insecure patients in northeastern Pennsylvania. Fresh Food Farmacy brings a "food-as-medicine" approach to communities to combat high rates of obesity, pre-diabetes, and diabetes. The program evolves over time, but the key elements include the following. Participants receive a referral to the Fresh Food Farmacy dietitian who provides a diet prescription for fresh food for themselves and their household, enough for 5 days a week, 2 meals a day. Participants also receive medication management services from a pharmacist, and receive case management services from a health manager or other health care professional. Their biometric measures (HbA1c, fasting glucose, weight, BMI, blood pressure, total cholesterol, LDL cholesterol, and triglycerides) and medication usage are tracked on a regular basis. In addition, participants receive a comprehensive suite of services, including diabetes wellness classes; dietary

consultations; workshops to discuss challenges to healthy eating and diabetes management; self-management training (including monthly group classes); cooking expos; and a welcome kit with measuring cups/spoons, recipes, and nutritional and program information.

FFF has received considerable attention, as it uses a holistic approach to address a key "social determinant of health" and providers, public health officials, and payers are increasingly willing to consider innovative approaches to improve the health of patients. While the potential to benefit patients is high, there is a need for randomized-controlled trial evidence for such programs to establish their effectiveness.

Geisinger plans to expand the program in the coming months, first in Scranton and then in Lewistown. The program faces capacity constraints such that the program cannot be offered to all eligible participants on the first day. We propose a pragmatic, randomized controlled trial as a way to implement the expansion of the program by randomizing eligible participants to receive the program at the start of the expansion, while those randomized to control will receive the program six months later. Such a structured roll out will allow a rigorous examination of the effects of the program for outcomes at 6 months, and for longer-term outcomes to the extent that effects take time to become apparent. The advantage of this approach is that we can rigorously test the effects of the program to learn whether it should be further expanded at Geisinger, attempted at other healthcare systems, or whether new approaches should be considered instead.

4 BACKGROUND AND SIGNIFICANCE

Diet, Chronic Disease, and Food Insecurity

In the past century, changes in diet and lifestyle have led to a dramatic increase in chronic diet-related disease; today, almost half of all American adults have one or more preventable chronic diseases that are related to poor diet, such as cardiovascular disease, high blood pressure, and Type 2 diabetes.[2] These chronic diet-related diseases are collectively the #1 cause of death in the US, with over 800,000 deaths annually.[3]

One diet-related chronic disease of particular concern is Type II diabetes, the prevalence of which has increased from less than 1% in 1958 to 7.4% in 2015.[4] In 2015, 23.3 million

Americans were diagnosed with diabetes, and an estimated 7.2 million have diabetes but remain undiagnosed; diabetes is the #7 cause of death in the U.S. (24.7 per 100,000 persons), and treatment of diabetes was estimated to cost $245 billion in 2012.[5]

Another consequence of the American diet is that obesity has risen at an unprecedentedly rapid rate. Since 1980, the prevalence of adult obesity in the United States has more than doubled,[6] and as of 2015–2016, 39.8% of adults are obese,[7] a level that the U.S. Surgeon General described as "epidemic".[8] Obesity represents a serious public health problem, raising the risk of Type II diabetes, cardiovascular disease, cancer, and asthma.[9] Obesity raises health care costs by $2,741 annually per obese adult; for the U.S. as a whole, this amounts to $190.2 billion per year, or 20.6% of national health expenditures.[10] Obesity is responsible for roughly 365,000 deaths per year in the U.S.[11]

The problem with the modern, Western diet is that it includes too much saturated fat, cholesterol, added sugars, sodium, and refined grains, and too little fresh fruits and vegetables and whole grains.[12] It is estimated that following a healthy diet could more than halve mortality from diet-related chronic diseases and could improve other measures of health in clinically meaningful ways.[13] For example, Sacks et al. (2001) find that the "DASH" diet (which contains large amounts of fresh fruits and vegetables) and low-sodium intake reduced systolic blood pressure by 11.5 mm Hg in participants with hypertension.[14] LDL cholesterol can be expected to fall by 10% with a healthier diet.[15] Sargrad et al. (2005) find that high-protein or high-carbohydrate diets that lead to weight loss among type 2 diabetic patients are associated with a 1.3% reduction in Hemoglobin A1c concentrations.[16]

There are many possible explanations for the low-quality Western diet, but for lower-income individuals a possible contributing factor is food insecurity, which is defined as the limited or uncertain availability of nutritionally adequate food.[17] This could be due to low income or low access/availability of healthy food sources. Historically, food insecurity was associated with being underweight or stunted, but in the modern food environment, food insecurity can cause

and/or coexist with obesity and Type II diabetes.[18] Approximately 1 in 4 Americans with cardio-metabolic conditions that lead to cardiovascular-related death, such as hypertension, hyperlipidemia, and diabetes, experience "food insecurity" (i.e. difficulty accessing or affording nutritious food).[19]

Despite the consensus that addressing diet and food insecurity is an important way to improve health, there remains considerable uncertainty over the effectiveness of various approaches. We propose to conduct an RCT to evaluate the "Fresh Food Farmacy," an innovative approach that addresses food insecurity through the health care system. This is in line with other programs that are being studied that follow a food-as-medicine approach.[20]

Specific Details:

Disease/diagnosis: Type II diabetes

Population to be studied: Food-insecure patients of Geisinger

Endpoints: HbA1c; fasting glucose; weight, BMI; blood pressure; total cholesterol, LDL cholesterol, triglycerides (lipid panel); and healthcare utilization.

Rationale for the proposed project

In July 2016, Geisinger began piloting the "Fresh Food Farmacy" (FFF) program for diabetic, food insecure patients in central Pennsylvania. The program brings a "food-as-medicine" approach to address a key social deterimant of health for these patients. Patients are eligible for the Fresh Food Farmacy program if they meet the following criteria:

1. Type II Diabetes and an HbA1c $\geq$ 8.0% as determined in Geisinger EMR
2. Food insecure based on a two-question survey instrument
3. Age $\geq$ 18 and age $\leq$ 85
4. Living within geographic reach of the program

A Fresh Food Farmacy dietitian prescribes fresh food for meals five days per week for each patient's family. Prescriptions are filled at no charge at a local clinic. Complementary services include case management, wellness and cooking classes, recipes to use the fresh food, medication management, self-management training (including monthly group classes), and

biometric tracking. Fresh Food Farmacy staff collaborate with the patient's primary care provider to request and collect biometric measurements regularly (HbA1c and Lipid panel every 6 months). The full program is described here: https://www.geisinger.org/freshfoodfarmacy

Through random assignment to the start-date of the intervention, we plan to study the impact of the FFF program on these biometrics and downstream utilization.

FFF has received considerable attention, as it uses a holistic approach to address a key "social determinant of health" and providers, public health officials, and payers are increasingly willing to consider innovative approaches to improve the health of patients. While the potential to benefit patients is high, there is a need for randomized-controlled trial evidence for such programs to establish their effectiveness.

Geisinger plans to expand the program in the coming months, first in Scranton and then in Lewistown. The program faces capacity constraints such that the program cannot be offered to all eligible participants on the first day. We propose a pragmatic randomized controlled trial as a way to implement the expansion of the program by randomizing eligible participants to receive the program at the start of the expansion (treatment group), while those randomized to the control group will receive the program approximately six months later. Such a structured roll out will allow a rigorous examination of the effects of the program for outcomes at 6 months, and for longer-term outcomes to the extent that effects take time to become apparent. The advantage of this approach is that we can rigorously test the effects of the program to learn whether it should be further expanded at Geisinger, attempted at other healthcare systems, or whether new approaches should be considered instead.

Existing evidence

Medically-tailored Meals

There is related research on "medically-tailored meals" (MTM) that are typically delivered to patients. This dramatically lowers the cost of consuming a nutritious diet, both in terms of time cost for acquisition and preparation as well as the direct monetary cost of healthy ingredients. The provision of nutritious food by health care providers is becoming increasingly common.[21] These programs typically do not deliver a patient's entire nutritional intake. Rather, they are

designed to provide a significant supplement each week, roughly half of the patient's intake. Meals are typically prepared under the supervision of a registered dietitian, so they are closely tailored to the nutritional recommendations for a patient's medical condition.

Little research has been conducted on the impact of such meal delivery to test whether the program improves health and is potentially cost effective. Gurvey et al. 2013 report an observational study that found reductions in costs among Medicaid managed care beneficiaries with life-threatening illnesses on the order of 31%.[22] Berkowitz et al. 2017 conducted an observational study of the Community Servings program in Massachusetts that provides medically-tailored meals to patients with life-threatening illnesses resulting in large reductions in ED usage and inpatients stays and a 16% reduction in healthcare spending overall.[20]

5 HYPOTHESIS AND SPECIFIC AIMS

5.1 Hypothesis

Our primary hypothesis is that the Fresh Food Farmacy program will improve patient health; specifically, we expect the program to result in significantly reduced levels of HbA1c, lower blood pressure, and fewer emergency department visits and inpatient admissions.

5.2 Specific Aim 1: Measure Effectiveness of FFF on clinical measures

Our first specific aim is to evaluate the effectiveness of FFF on clinical measures of health including HbA1c, fasting glucose, weight, BMI, blood pressure and lipid panel. HbA1c is glycated hemoglobin, a long-term measure of glucose in the blood that is used to classify individuals' diabetes status and to track management of diabetes. We will collect this information from the treatment and control groups in follow-up visits described below.

5.3 Specific Aim 2: Measure Effectiveness of FFF on healthcare utilization

Our second specific aim is to evaluate the effectiveness of FFF on healthcare utilization including ED visits and a combination of ED visits and inpatient admissions, as well as costs to Geisinger Health Plan. Direct utilization as part of the program will be considered as a

comparison to reductions in utilization after enrolling in the program. We plan to study program participants as well as their family members who are expected to benefit from the healthy food.

We will collect this information from administrative data from electronic health records and Geisinger Health Plan claims. These are additional health outcome measures and provide a way to consider the cost effectiveness of the program. Program data on the use of services by participants will be included for the full comparison of utilization. Our cooperation with Geisinger, which not only conducts the FFF program but also maintains records of medical care utilization, is a strength of this proposal. FFF also provides services for patients who are not Geisinger Health Plan members. Highmark (another local insurer) may share utilization data for their patients that are participating in the program in the future. As with Geisinger data, any Highmark data would be shared with MIT researchers under a DUA that would be submitted to the IRB under an amendment.

6 PRELIMINARY DATA

As proof of concept that was part of a quality improvement initiative at Geisinger led by PI Andrea Feinberg and analyzed by researchers at MIT, existing electronic health records of Fresh Food Farmacy participants were compared to diabetic patients living in Northumberland and Lackawanna counties. Outcomes included changes in HbA1c, blood pressure and weight for patients as well as ED and inpatient admissions to Geisinger facilities.

Because participation in the Shamokin pilot program was not randomly assigned, there is no pre-existing control group. Instead, each FFF participant was matched to other Geisinger patients (who did not participate in FFF) based on age, sex, payer type, and baseline HbA1c, as well as the timing of HbA1c measurements. Estimates of regression models based on these matched data imply that participation in FFF was associated with a reduction in A1C of roughly one point 60-180 days after enrollment. This non-randomized data suggests that the FFF program may be beneficial on these dimensions, but the non-randomized nature of the data and limited power underscore the importance of studying the question with a randomized controlled experiment.

This preliminary analysis has several limitations: a small sample of participants in Shamokin, the lack of random assignment, measurements of HbA1c and weight at different periods of time. However, despite the small sample and limited power there is a statistically significant reduction in A1c, which suggests that the FFF is a credible program and worth investigating further through a field RCT.

We intend to continue to work with this historical data to provide context for the RCT. Details below.

7 STUDY DESIGN- RETROSPECTIVE STUDY

7.1 Description

A retrospective analysis component will be included in this study to allow historical data already collected in the EHR to provide context for the prospective, RCT.

7.2 Study Population

7.2.1 Approximate Number of Subjects

For the historical data analysis for context, we will compare approximately 200 FFF participants in Shamokin to similar diabetic, non-FFF participant patients in Lackawanna, Mifflin, Juniata, and Northumberland counties. We will also study household members: those who share the same residential address. For this data-only portion of the research, approximately 20,000 patients are considered to find the matches and test robustness to the ways the matching is conducted.

There are 2 groups of subjects identified in this retrospective protocol:

- Group 1- Past and Current participants in the Shamokin FFF program.
- Group 2- Diabetic, non-FFF participant patients in Lackawanna, Mifflin, Juniata, or Northumberland counties. Patients will be matched based on observable characteristics including HbA1c, age, sex, and ZIP code with Group 1 participants (FFF Participants).

7.2.2 Inclusion Criteria

Inclusion criteria for the retrospective study is consistent with the current FFF inclusion criteria:

1. Type II Diabetes and an HbA1c ≥ 8.0% as determined in Geisinger EMR
2. Food insecure based on a two-question survey instrument
3. Age ≥ 18 & age ≤ 85
4. Living within geographic reach of the program (Shamokin) or comparison areas: Lackawanna, Mifflin, Juniata, or Northumberland counties.

7.2.3 Exclusion Criteria

In general, patients who satisfy the following criteria are excluded from the FFF program; however, some may be allowed to enroll on a case-by-case basis:

1. Not English speaking
2. On active chemotherapy
3. On hospice or palliative care
4. Active psychiatric disorder that would preclude participation in the program
5. Active medical disorder that would preclude participation in the classes, weekly clinic visits, and/ or result in a limited diet, including:
    - Severe asthma
    - Severe COPD
    - Colitis requiring steroid therapy
    - Moderate to severe kidney dysfunction with metabolic disorders
    - Celiac disease
6. Resides in a facility which provides meals.

Inclusion and exclusion criteria applicable to program participants only; these criteria are not applicable to household members.

7.3 Study Date Range

Data are analyzed from January 1, 2015 to December 31, 2019.

7.4 Study Timeline

Planning and analysis will occur this year. We aim to prepare a manuscript this year and seek publication through the following year. Ongoing analysis in parallel with the prospective trial will augment the analysis of the RCT through 2021 as described below.

8 STUDY DESIGN- PROSPECTIVE STUDY

8.1 Description

This is a pragmatic, randomized, prospective research study. Qualifying subjects will be randomized 1:1 to receive either early participation in the FFF program (treatment group) or later participation (control group).

8.2 Study Population

8.2.1 Approximate Number of Subjects

Approximately 500 Geisinger subjects will participate in this study with about half assigned to the treatment group and about half to the control group. Approximately 2000 household members will be included in the data-only portion of the research.

There are 3 groups of subjects identified in this prospective protocol.
Group 1- Will be randomized to the treatment ("Begin Now") group for the FFF program. Subjects will be consented to join the FFF study prior to learning their program start date. They will join the FFF program right away when the program opens in their geographic area. Data will be collected during the first 12 months of subject participation and EHR and claims data may be analyzed for an additional 12 month follow-up period (24 months in total).

Group 2- Will be randomized to the control ("Begin Later") group for the FFF program. These subjects will be consented to join the FFF study prior to learning their program start date. They will join the FFF program approximately 6 months after the program opens in their geographic area. Data will be collected during the first 6 months of subject participation and used as control data for the study. EHR and claims data may be analyzed for an additional 12 month follow-up period (24 months in total from the start of the trial).

Group 3- Household Member data. Consented subjects will be asked for the names and dates of birth (DOB) of individuals living in their household who will be consuming food and benefiting from the FFF program. A waiver of consent is being requested in order to access health

information from the household members' medical records. EHR and claims data may be analyzed 24 months from the start of the trial by a household member.

8.2.2 Inclusion Criteria

The inclusion criteria for the RCT will mirror the FFF program's eligibility criteria:

1. Type II Diabetes and an HbA1c ≥ 8.0 as determined in Geisinger EMR. The most recent HbA1c value within the past 12 months will be used to determine eligibility.
2. Food insecure based on a two-question survey instrument
3. Age ≥ 18 and age ≤ 85
4. Living within geographic reach of the program
    a. Lewistown, PA
    b. Scranton, PA

If the study is unable to reach its enrollment goal within 1 year, the HbA1c inclusion criteria for the study and program may be reduced to ≥7.5%.

Patients should meet the above clinical criteria and be of able mind and body to participate with the educational, consultative and food provisional services. In addition, patients should understand and speak English.

8.2.3 Exclusion Criteria

Patients who satisfy the following criteria will be excluded from the proposed trial, although some may be allowed to enroll in the program itself on a case-by-case basis:

1. Already enrolled in FFF in Shamokin
2. Not English speaking
3. On hospice or palliative care
4. Acute or chronic psychosis
5. Active medical disorder that would preclude participation in the classes, weekly clinic visits, or result in a limited diet, including:
    - Cancer; active treatment
    - Steroid dependent asthma/ COPD/ emphysema
    - Steroid dependent Colitis
    - Chronic Kidney Disease with GFR< 30 mg/mmol
    - Celiac disease
    - Cirrhosis
    - Steroid dependent arthritis
6. Resides in a facility which provides meals

Inclusion and exclusion criteria are applicable to program participants only; these criteria are not applicable to household members.

8.2.4 Recruitment

Step 1. Subject identification

In consultation with the investigators, study staff will coordinate the outreach, which is similar to outreach planned for the program. With assistance from a Geisinger data broker, we intend to screen the EMR for eligible patients meeting criteria for age, diagnoses, HbA1c elevation $\geq$ 8.0%, and food insecurity, which is expected to be included in the EHR by the time of program enrollment. In the event that this is not yet completed, we will screen patients for food insecurity digitally by MyGeisinger outreach, by phone or in person at a clinic visit.

Step 2. Outreach and Informed Consent

Once the patient is identified as eligible via EMR data pull, a study staff member will review the patient's chart to ensure that the patient does not have any exclusionary criteria and contact the patient via phone to determine whether the patient is willing and capable of participating. Study staff will describe the FFF program that is being introduced to their area and how participation will begin on a rolling basis over the coming months. Study staff will then describe the study and determine if the patient is interested in hearing more about it. For those interested in participating, the study will be explained in more detail and verbal informed consent will be requested. A recruitment script has been developed to ensure information regarding the program and study is conveyed accurately and consistently by research staff. Study staff will be aware of diabetes-related resources and usual care for diabetics in case questions arise. For patients who provide verbal consent, an information sheet describing the FFF study will be sent to the patient via mail.

Step 3. Randomization and program initiation

After the study enrollment procedures described in Step 2, study staff will consult a pre-determined treatment group/control group assignment for the subject ID number. Study staff will schedule patients' initial program visit.

Those who decline consent to be in the study will enter the program in the (non-study) manner used by FFF. To distribute entry into the program in an equitable way, this continues to entail randomizing the start dates to begin at the time of initial intake or approximately six months later. These patients will be excluded from the data analysis, except for a comparison of their eligibility variables to place the study population in context.

8.3 Study Duration

8.3.1 Approximate Duration of Subject Participation

We expect subjects will participate in the study for up to 24 months. Currently, participants do not graduate from the program, but this may change as the program evolves.

8.3.2 Approximate Duration of Study

This study will be completed in three years, defined as the last period when electronic medical records will be consulted for utilization outcomes.

We expect the effects of the program will be detectable at 6 months, with some convergence at 12 months as the control group enters the program and begins treatment; we expect the treatment group to still exhibit benefits relative to the control group at 12 months given that they will have participated in the program for twice as long and had more time to change their dietary habits and for the effects of such changes to be felt. Utilization, such as ED usage, may be noticed in this later period.

8.4 Procedures

Baseline biometric measures (HbA1c, fasting glucose, weight, BMI, blood pressure and lipid panel) will be collected utilizing the most recent values available in the subjects' medical records within the year prior to enrolling in the FFF study. These biometric measures will be used to determine eligibility for the study and during data analysis.

A set of blood tests (HbA1c, fasting glucose and lipid panel) will be collected for research immediately prior to the subject beginning the FFF program (month 0 for treatment group or approximately month 6 for the control group). In addition, research participants will complete a baseline survey upon entry into the FFF program. This survey will be completed on site at the FFF program clinic.

A set of research biometric measurements (HbA1c, fasting glucose, weight, BMI, blood pressure and lipid panel) will be collected at approximately the 6 and 12 month time points (plus or minus

1 month) for the treatment group. A set of research biometric measurements (HbA1c, fasting glucose, weight, BMI, blood pressure and lipid panel will be collected at approximately the 12 month time point (plus or minus 1 month) for the control group.

In addition, all research participants will complete a survey after 6- and 12-months of participation (similar to the baseline survey) during FFF program visits. For those who do not enroll in the study, we will not continue to investigate their outcomes at these intervals.

Protocol required lab draws will be paid for by the study. Patients will be compensated with a $50 gift card for the time and effort to complete the lab work and the patient surveys.

Based on our experience with the FFF program, we expect nearly all the patients to continue with the study. For the few who do drop out of the study but remain in the program, we will contact these subjects and collect outcome information, including clinical lab results and the ongoing survey. For those who drop out of the FFF program, but remain in the study the lab work will be covered by the research study and the surveys will be completed by phone or e-mail. The patients will be offered a $50 gift card as compensation.

8.4.1 Study Time and Events Table

Study timeline (calendar time, H1=January-June, H2=July-December):

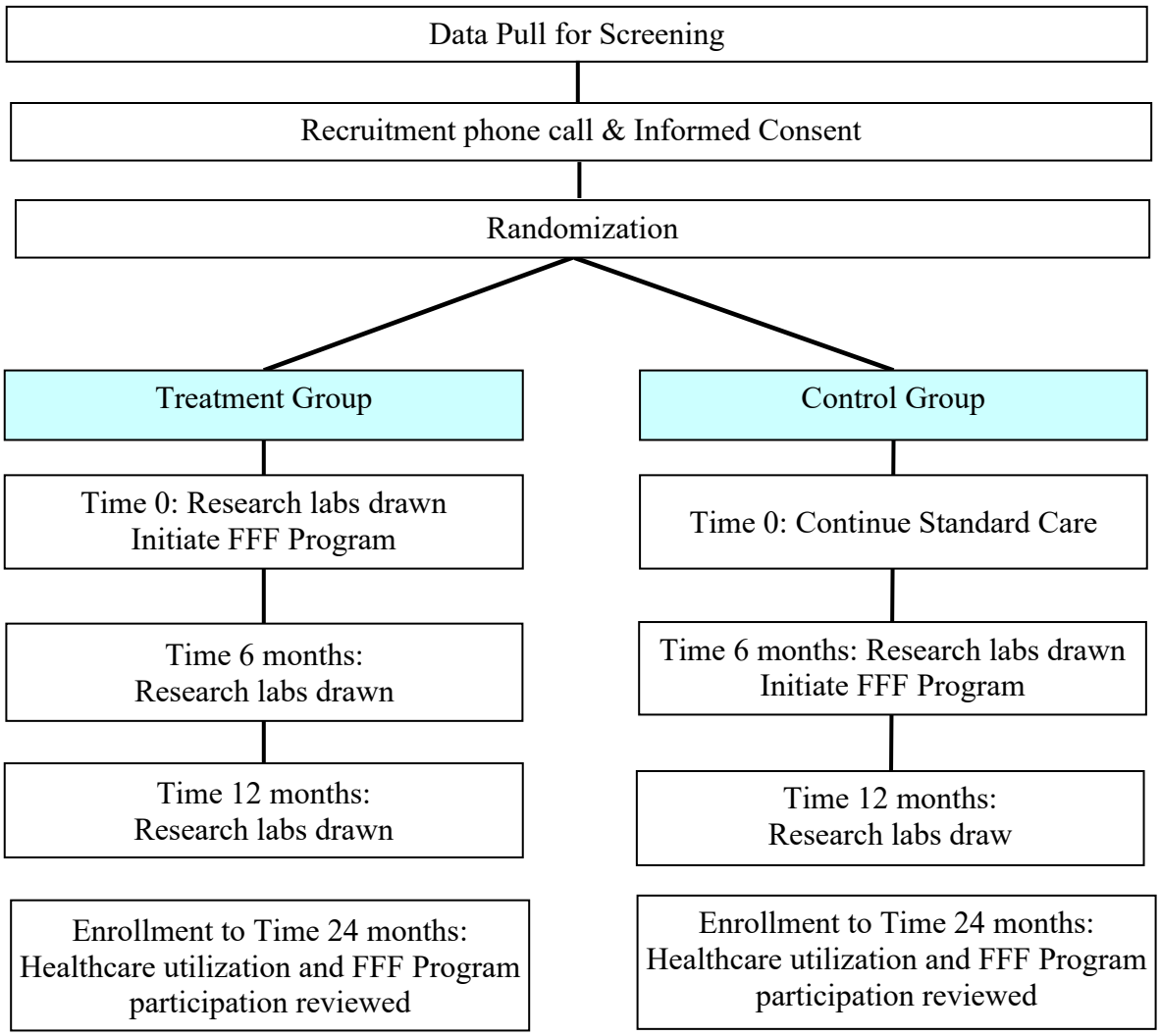
	2018 H1	2018 H2	2019 H1	2019 H2	2020 H1	2020 H2	2021 H1	2021 H2	2022 H1
Planning									
Enrollment									
Outcome tracking									
Analyze impact									
Manuscript preparation									

Study timeline (subject point of view):

Treatment				
Study Activity	**Enrollment**	**Month 6**	**Month 12**	**Month 24**
Informed Consent [1]	X			
Randomization	X			
FFF Program Initiation [5]	X			
Survey [3]	X	X	X	
Research Labs [4]	X	X	X	
Health Care Utilization Review (EMR)	X			

Control				
Study Activity	**Enrollment**	**Month 6**	**Month 12**	**Month 24**
[1] Patients will be asked to provide verbal consent over the phone. [2] FFF program start will occur approximately 6 months after consent for *Control patients*. [3] Redcap surveys will be administered by FFF staff during program visits. [4] Research labs include: HbA1c, Fasting Glucose, lipid panel [5] FFF program start will occur within 1 month after consent for *Treatment patients.*				
Research Labs [4]		X	X	
Health Care Utilization Review (EMR)	X			

8.4.2 Study Flow Diagram



8.5 Primary Endpoints

The primary endpoint will be HbA1c at 6 months. HbA1c is the primary measure for diabetes diagnosis and disease progression. We explored the existing literature on the link between A1c and spending. The literature is largely a set of correlations: reductions in A1c are associated with lower costs in patients with diabetes. In summary, improving A1c from poor to fair is associated with savings on the order of $1000 per year (sustained over time). As expected, the effects are nonlinear so that larger cost savings are achievable for those with A1c > 9 compared to those between 7 and 8.

Justification

HbA1c is meaningfully related to health and healthcare utilization. Elevated levels are often noted to increase healthcare costs by $4000. Menzen et al. (2010) controlled for a number of characteristics and estimated healthcare costs were $4000 higher over five years for those with A1c>10 compared to those with A1c <7.[23] Juarez et al. (2013) used propensity score matching to control for differences across patients and found that having an A1c>=7 was associated with $2700 higher medical costs per year compared to those with A1c<7. Importantly, the relationship is nonlinear with larger savings for patients with the higher levels of HbA1c considered here.[24]

In Canada, McBrien et al. (2013) also find that, among diabetics, annual medical costs rise in a nonlinear fashion with A1c: C$27,064 for those with A1c <=7%, C$26,736 for those with A1c of 7.1 – 7.9%, C$28,687 for those with A1c of 8-9%, and C$32,629 for those with A1c>9%.[25]

Where many studies compare utilization across patients with different levels of A1c and control for patient characteristics in various ways, Wagner et al. (2001) took the approach of comparing changes in utilization with changes in A1c at the individual level. This controls for fixed characteristics of the person that would otherwise be difficult to control, such as education level, stable attitudes toward health.[26] They define an improvement as a 1 percentage point reduction that is sustained for 2 years. Among those who achieved this improvement, healthcare costs were approximately $900 lower each of the following two years (or approximately $1440 in

2017 dollars). This included a 2-percentage point reduction in hospitalization rates each year, compared to a 15% hospitalization rate overall.

Other studies look at disease management impacts on A1c and costs or drug adherence programs on costs. One relatively large observational study is Oglesby et al. (2006), where direct medical costs attributable to type 2 diabetes were 16% lower for individuals with A1c<7 compared to those with A1c >7 and < 9, and 20% lower for those with A1c <7 compared to those with A1c > 9.[27]

8.6 Secondary Endpoints

We will also examine HbA1c at 12 months, where we can compare 12 months of exposure to the program compared to 6 months of exposure to the program. This difference will be smaller if the gains in A1c improvement are greater during the initial 6 months, as expected. The comparison will help us learn the rate of improvement over time. In addition to 6- and 12- month results, we will also consider interim lab results in the patient's EHR record to trace out the timing of effects.

In addition, related measures that may be affected by the program: Fasting glucose, weight, BMI, blood pressure, and lipid panel. Reductions in BMI among patients with diabetes are associated with lower health care costs (Cawley et al., 2015). [28]

Utilization is also an important secondary input. This will be measured using EHR data and claims data from Geisinger Health Plan for those participants who are members. Highmark (another local insurer) may share utilization data for their patients that are participating in the program as well. In particular, ED visits, inpatient care, and outpatient visits will be considered. In addition, the EHR data will allow us to determine whether a subject completes wellness visits in terms of PCP and endocrinologist visits along with diabetes Healthcare Effectiveness Data and Information Set (HEDIS) measures, as another set of healthy behaviors that may be improved as a result of program participation. We will measure

clinical measures and utilization measures for subjects' household members as well to measure spillover effects.

A third set of secondary outcome measures will come from the patient surveys conducted. Each question will be analyzed and compared across treatment and control groups similar to the lab results. The categories are food choices, healthy behaviors, self-assessed health, and patient satisfaction.

Additionally, we will include program participation outcomes to measure treatment intensity: visits to pick up the food, use of dietician services, and food choices.

9 STATISTICS

Statistical analysis will be conducted by our co-investigators: Marcella Alsan, MD, PhD; John Cawley, PhD, and Joseph Doyle, PhD. This academic team is supported by the Jameel Poverty Action Lab (J-PAL) at MIT, which specializes in randomized-controlled trials in healthcare delivery.[29]

9.1.1 Statistical Analysis Plan

For both specific aims, we will estimate intent-to-treat models using Ordinary Least Squares regression. Consider an outcome, Y_i, such as HbA1c, for each subject i. The estimating equation is:

$$Y_i = \beta_0 + \beta_1 1(\text{Treatment})_i + \beta_2 X_i + \varepsilon_i$$

For the historical data analysis, $1(\text{Treatment})_i$ is an indicator variable equal to one if the subject participated in the FFF program, and zero otherwise. For the prospective trial analysis, $1(\text{Treatment})_i$ is an indicator equal to one if the subject was randomized to the treatment group and zero if the subject was randomized to the control group; X_i is a vector of control variables. These control variables should be uncorrelated with the treatment indicator, but they can aid in

the precision of the estimate. We propose standard demographic and prior-utilization controls: age (5-year age bins), sex (indicator that the patient is male), race/ethnicity (indicators for African American and Hispanic), as well as the most recent outcome recorded prior to enrollment (HbA1c at the baseline visit). We will also include controls for the timing of the tests, including the number of days from baseline to the test and the month-year of enrollment in the study.

The coefficient $\beta_1$measures intent-to-treat: the causal effect of being randomized into the treatment group. This can differ from the effect of the program if there is non-compliance: some subjects in the treatment group may decide not to join the program or join for a very short time. At the initial pilot site, 17% of those who begin the program are no longer in the program at 6 months. We plan to record outcomes for all subjects regardless of program participation and will estimate the equation using Two Stage Least Squares (2SLS), with the initial treatment assignment used as an instrumental variable for ultimate assignment. The 2SLS estimate measures the average causal effect of the program for those who choose to remain in it as a complementary parameter to the intent-to-treat analysis. In addition, if there is differential attrition from the study across treatment and control groups—despite our efforts to obtain outcomes from each subject including obtaining multiple forms of contact information for subjects and their family members and compensation for subjects' time, we will explore bounding estimates under a range of assumptions about effect sizes for those not observed.

For survey responses, we will consider answers in the top and bottom categories as separate outcomes and will test robustness to using nonlinear estimators. For patient satisfaction, we will calculate the net promoter score as an outcome as well. To avoid concerns about multiple hypothesis testing, each category of questions will be compiled into an index and we will report p-values corrected for the multiple tests when presenting results for each question individually.

In addition to outcome comparisons across all of the participants, we will consider heterogeneous treatment effects in three ways. First, a priori we are interested in whether the program is

especially effective for different levels of baseline HbA1c to help target the program going forward. For example, if effect sizes decrease with the baseline, we may want to expand the program into those with A1c > 7.5. Next, we are interested in whether the program has different effects across the two locations where the expansions are planned to begin to investigate the external validity of the estimates. Third, we plan to consider whether machine-learning techniques to allow the data to shed light on the types of patients where the effects are particularly large are feasible with the given sample size and statistical power. This will likely entail normalizing the outcomes so that we measure effects relative to each participant's baseline rather than absolute differences.

Interim results from the trial will be monitored on an ongoing basis by the MIT/J-PAL researchers (Drs. Alsan, Cawley and Doyle), while the clinician team will be blinded from these interim results so that such do not affect program management in a way that would not be feasible outside of the study setting. Such blinding adds credibility to the results so that they are more likely to apply to other programs in the future that are not part of a study.

9.1.2 Statistical Power and Sample Size Considerations

Using data for current (i.e. self-selected, non-randomized) FFF participants, we conducted parametric power calculations. These take into account the increase in power from controlling for baseline characteristics, but qualitatively results were found when we did not include controls and when we used nonparametric (simulation) methods to estimate power. Similar results were also found when we based the calculations on similar patients in the counties where the two new sites (Lewistown and Scranton) will be located. All power calculations were conducted using STATA Version 15.

The table below shows that with the expected sample size of 500 we will have substantial power to detect small minimal detectable effects (MDE), as well as the ability to conduct heterogeneity

analyses for the clinical outcomes. For utilization outcomes, we will have power to detect the (albeit) large reductions in utilization found in the observational literature.

Table 2: Statistical Power to Detect Targeted Minimal Detectable Effects (MDE)

Variable	Mean	Std.Dev.	$\sqrt{1-R^2}$	Target MDE	Required N for MDE
HbA1c after 180 days	8.58	1.74	0.66	10%	55
HbA1c after 365 days	8.56	1.67	0.66	10%	56
Weight after 180 days	228	64	0.96	10%	228
Weight after 365 days	228	64	0.96	10%	228
Hospital Visit (Inpatient or ED) 0-180 days	0.39	0.49	0.85	30%	397
Hospital Visit (Inpatient or ED) 0-365 days	0.48	0.50	0.87	30%	278
Hospital Visit (Inpatient or ED) 90-365 days	0.40	0.49	0.92	30%	447

9.2 Data Management

9.2.1 Data Collection and Storage

Only approved study staff will have access to data collected for this research.

Administrative data are collected by Geisinger's data broker. For the prospective RCT, under a Data Use Agreement reviewed by the Privacy Office/ISO, a limited dataset stripped of personal identifiers will be transferred securely to MIT.

For the retrospective data exploration, PHI will be de-identified in accordance with a limited data set as allowed by the Research Collaboration Agreement between Geisinger and MIT. The historical data includes diabetic subjects and their household members from Northumberland,

Mifflin, Juniata, and Lackawanna counties where our goal is to compare program participants to non-participants as described above.

Once the data set is sent to MIT, the research team will review it for analysis. The resulting analytic file will be stored in a password-protected database on MIT's secure network. Only research team members can access the data files. The research team members will review the charts and gather all the needed information.
The limited dataset for the prospective portion of the study will also include dates of service and ZIP codes.
It will also include information relevant to all encounters:

- Admissions/discharges, clinical procedures, medications administered, problem list entries, and lab values
- Baseline demographic variables of patients (age, sex, ethnicity, payer, comorbidities)
- FFF Program participation

Paid claims summed over various categories of care and timeframes around program entry are requested from Geisinger Health Plan as well.

The FFF program provides food for the entire household. As a result, we are requesting data on household members as well. For the prospective study, household members are identified by the subject to ensure an accurate listing of household members who are actively benefiting from the program. Pulling data using the same address may lead to including household members who are not actively living in the residence (e.g. college student who is not living at home). FFF plans to ask members about their family members in the future, and this will be used to check the household record extraction as well. Data will be provided to MIT with an encrypted household identifier. While we will not have follow-up visits with family members, we aim to observe clinical measures as they appear in the electronic health record. Household IDs will facilitate this analysis.

The retrospective data analysis will include the same data as the prospective study; however, household members will be identified by a shared home address due to no patient contact.

9.2.2 Records Retention

Records of data generated in the course of the study shall be retained for at least 6 years and could be used for future research studies submitted and approved by the IRB.

10 SAFETY MONITORING

10.1 Adverse Event Reporting

This is a minimal risk study and there is no intervention apart from obtaining blood samples. The adverse event reporting and the reporting of unanticipated problems related to research will be limited to events directly related to the study procedures (venipuncture and breach of privacy/loss of confidentiality). All study-related unanticipated problems or adverse events will be recorded and reported.

11 SAMPLE COLLECTION AND RETENTION

11.1 Collection

As outlined in Section 8.4 of this protocol, subjects in the treatment group will provide a blood sample for research purposes prior to beginning the FFF program, at 6 months and 12 months. Subjects in the control group will provide a blood sample for research purposes prior to the beginning the FFF program (6 months into the study) and again after 6 months in the program (12 months in the study). Processing will be completed in a Geisinger Laboratory and testing completed according to institutional policy.

11.1.1 Total Volume of Blood Collected

The total volume of blood collected from each subject will be approximately 30 mL.

11.2 Retention

Records of data generated in the course of the study shall be retained for at least 6 years and could be used for future research studies submitted and approved by the IRB.

Identifiable samples can be destroyed at any time at the request of the subject.

12 PROTECTION OF HUMAN SUBJECTS

12.1 Informed Consent and HIPAA Authorization

We are requesting a waiver from written informed consent and HIPAA authorization for subjects consented to FFF study. Instead, we will request verbal consent from study participants. The study will be described during the initial outreach prior to the patient's initial visit. A follow-up information sheet will be sent via mail reiterating the FFF study details, the fact that a study is occurring, and that the participant may choose to end study participation at any time.

We are requesting this verbal consent with follow-up information instead of an in person written consent for three reasons. First, this is a pragmatic trial in that the program is being rolled out to new participants in a randomized way to smooth the onboarding process. This process is largely done by phone and our study staff will not be in the areas where the subjects are being recruited. Second, written consent in this context could undermine the program. For written consent we would need subjects to go to the FFF clinic, as home visits would not be feasible. Such a visit would expose both the treatment and control group to the information campaigns hosted there and may dampen the enthusiasm for the program for anyone not beginning the program until a later date.

Third, the study represents minimal risk to patients because the treatment is the offer of healthy, fresh food, and the main risks are data confidentiality. These risks will be dealt with by sending only a limited data set to researchers at MIT under a data use agreement complete with review by Geisinger's Information Security/Privacy Office. Furthermore, the program is being rolled out regardless of whether a study occurs or not. Last, the patient will not incur a cost to enroll in the program or have their outcomes measured.

For those who decline consent to be in the study, they will still enter the program based on their control or treatment status as determined by the pre-randomization, as this is the way the program is being rolled out in an equitable fashion: if we were to allow those who

do not consent to enter the program sooner, this would delay the entry of others. In addition, allowing earlier entry to those who do not participate could lead to sample attrition from the control group, rendering the trial infeasible.
Data for those who refuse consent will not be analyzed as part of the study, except for the eligibility variables that will be compared to those who did consent so that the study population can be placed in context.

We also stress that given the lack of randomized controlled trial evidence for this type of program, there is scientific equipoise as to whether this program is effective.

Household members of study participants

Household members may benefit from the program and we would like to measure effects for this group using administrative data. Study subjects will be informed of this as part of the consent process.

Household members are secondary subjects, however, and we are requesting a waiver of consent and HIPAA authorization. Household members are identified by the subject to ensure an accurate listing of household members who are actively benefiting from the program. Pulling data using the same address may lead to including household members who are not actively living in the residence (e.g. college student who is not living at home). Our request for the waivers are due to:

1. The study represents minimal risk to the household members because we will only analyze secondary data and will not contact them. The main risks are data confidentiality. These risks will be dealt with by sending only a limited data set to researchers at MIT under a data use agreement complete with review by Geisinger's Information Security/Privacy Office.

2. It is not practical to carry out the research if each of these secondary research subjects needed to be contacted.

Retrospective data analysis

The retrospective data analysis will use previously existing data to compare program participants to similar patients. We are requesting a waiver of consent and HIPAA authorization for this analysis because consenting 20,000 patients is infeasible given the retrospective nature of the research. We propose that this portion of the research carries minimal risks to patients, as the primary risk is data breach, the risk of which is minimized as described above and below.

12.2 Protection of Human Subjects Against Risks

The program provides nutrition advice and fresh food to recipients. The main risk to subjects is data confidentiality. As a result, we take a number of steps to protect subjects' private data.

Identifiable data will remain on Geisinger's internal servers. A deidentified study ID will be assigned to each participant and the table matching patient identifiers with the study IDs will be stored on a password-protected, encrypted file on Geisinger's internal server. Only key data study personnel will have access to this linked file.

A limited data set will be constructed that will be stripped of name, address, medical record number, and social security number. Dates of service and zip code of residence will be present. It will include the unique, scrambled identifiers for subject ID.

The limited dataset set will be transferred securely to MIT under a Data Use Agreement with Geisinger, complete with review by the Information Security/Privacy Office.

Data at MIT will be stored on an institutional stationary server restricted to authorized hosts and users using IP-based host lists and Kerberos credentials. Kerberos credentials are assigned to specific individuals who are associated with MIT. All computations and analytical work will be performed exclusively on these servers. File based permissions will be set to restrict data access

to the research team. Remote access to this server will be provided using the encrypted SSH protocol and require strong passwords. The data security at MIT is managed by a dedicated staff of IT professionals. This support includes account management, security patching, software installation and host monitoring. Data is backed-up to a secondary NAS device which is accessible only by IT personnel.

No attempts by members of the MIT team will be made to identify or contact individual patients. Any publications of analysis or data will include only aggregated data not linked to any individual.

12.3 Data Monitoring Plan

PI, Dr. John Bulger, will oversee overall data safety and monitoring for the project. The Geisinger and MIT teams will continually assess the potential risks and participant safety throughout the study period and report to the PI. Further, the GIRB will review progress of the study per GIRB policy. Any protocol changes will be submitted to the IRB via a modification request and no changes will be implemented without IRB approval.

13 PUBLICATION PLAN

We plan to apply for grant funding to supplement the enrollment and oversight at Geisinger and publish a manuscript in a peer-reviewed journal.

One year after the initial publication, we will seek to publish fully-deidentified data as is common for NIH-funded studies.[30] The contents of such data will be governed by a Data Use Agreement between MIT and Geisinger.

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