# PROTOCOL COVER PAGE

## Title: Optimizing Delivery of Diabetes Management During Cancer Care

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**TITLE:** Optimizing Delivery of Diabetes Management During Cancer Care

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## Statement of Compliance

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

**Confidentiality Statement**

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

**List of Abbreviations**

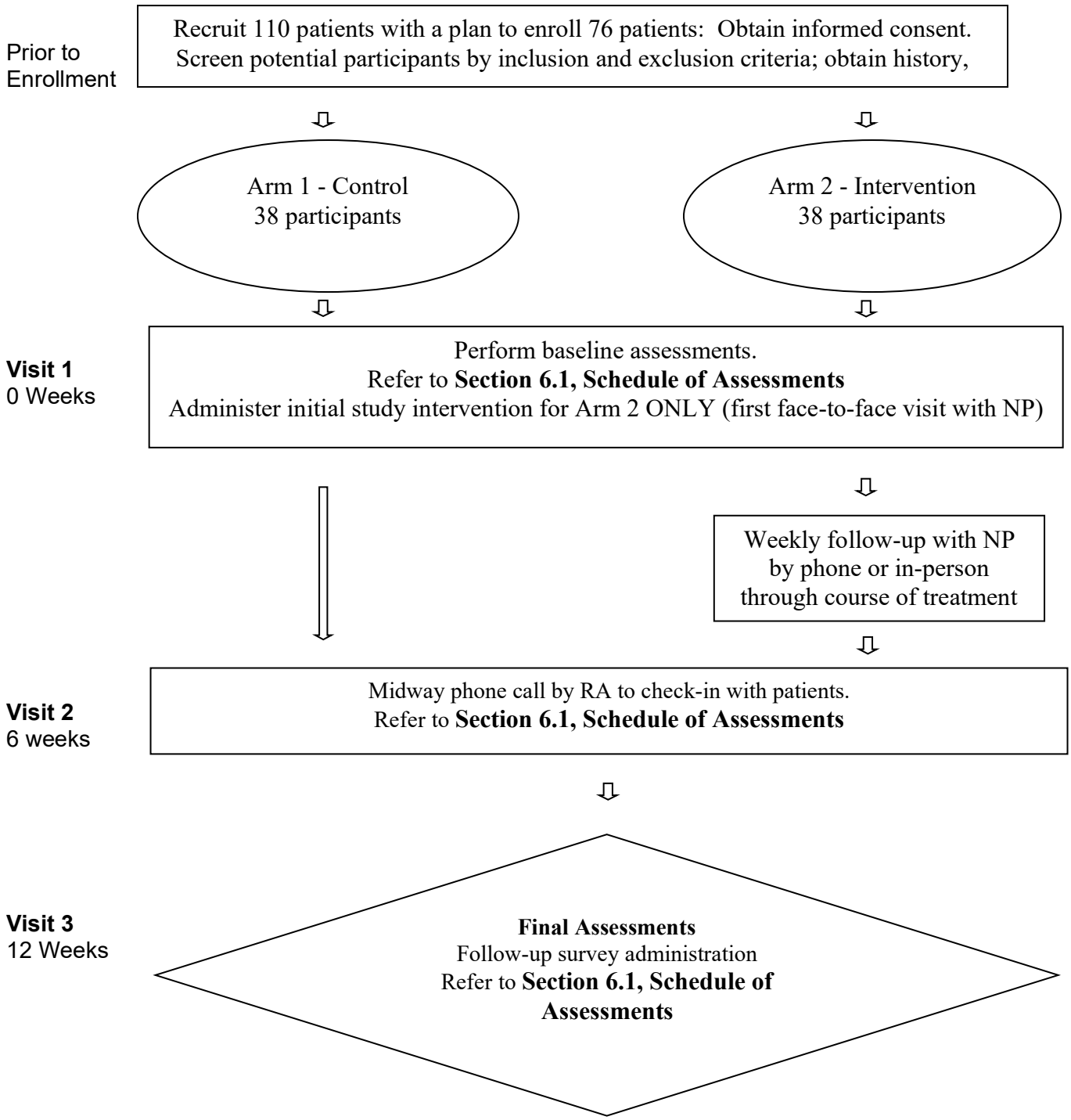
| | |
|---|---|
| **AE** | Adverse Event |
| **CFR** | Code of Federal Regulations |
| **CRF** | Case Report Form |
| **CTSC** | Clinical Translational Science Center |
| **DSMB** | Data Safety Monitoring Board |
| **DSMP** | Data Safety Monitoring Plan |
| **DM** | Diabetes Mellitus |
| **FDA** | Food and Drug Administration |
| **GCP** | Good Clinical Practice |
| **HIPAA** | Health Insurance Portability and Accountability Act of 1996 |
| **HRBFA** | Human Research Billing Analysis Form |
| **ICF** | Informed Consent Form |
| **IRB** | Institutional Review Board |
| **HUD** | Humanitarian Use Device |
| **ICF** | Informed Consent Form |
| **IDE** | Investigational Device Exemption |
| **IND** | Investigational New Drug |
| **IRB** | Institutional Review Board |
| **NP** | Nurse Practitioner |
| **RA** | Research Assistant |
| **PALS** | Patient Activated Learning System |
| **PHI** | Protected Health Information |
| **PI** | Principal Investigator |
| **PRO-CTCAE** | Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events |
| **REDCap** | Research Electronic Data Capture |
| **SAE** | Serious Adverse Event |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **UIRTSO** | Unanticipated Problem Involving Risks to Subjects or Others |
| **WCM** | Weill Cornell Medicine |

## 1. Protocol Summary

| | |
|---|---|
| **Full Title:** | Optimizing the Delivery of Diabetes Management During Cancer Care |
| **Short Title:** | Diabetes care for cancer patients |
| **Clinical Phase:** | /// |
| **Principal Investigator:** | Laura Pinheiro, PhD, MPH |
| **Study Description:** | The present study aims to develop a stakeholder-engaged nurse practitioner (NP)-led intervention to improve diabetes care for patients with cancer and diabetes who are ongoing cancer treatment. We will use a quasi-experimental pre-post design with non-randomized intervention and control groups, to test if an NP embedded in the oncology team who is trained in diabetes management may successfully manage diabetes for these patients. |
| **Sample Size:** | Control group (N = 38); Intervention group (N = 38) |
| **Enrollment:** | In total, this study will enroll 76 subjects and screen up to 200 subjects. |
| **Study Population:** | We will recruit 110 male or female patients with cancer and pre-diabetes or type 2 diabetes who plan to receive cancer treatment at Weill Cornell Medicine.<br><br>Additionally, we will make a concerted effort to recruit at least 30% racial/ethnic minorities. |
| **Enrollment Period:** | January 2023 – June 2025 |
| **Study Design:** | This is a pilot feasibility study, in which we will use a quasi-experimental pre-post design with non-randomized intervention and control groups. |
| **Description of Sites/ Facilities Enrolling Participants:** | We will recruit participants from NYP/Weill Cornell Medical Center, NYP Brooklyn Methodist Hospital, and NYP Queens Hospital. |
| **Study Duration:** | The entire study duration will be a maximum of 24 months from baseline enrollment to final follow-up. |

| | |
|---|---|
| **Participant Duration:** | Individual participants will be expected to complete all study activities at the end of their treatment plan, with an additional 4 weeks after to collect final data (approximately 20 weeks). |
| **Study Agent/Device Name Intervention Description:** | Include a nurse practitioner (NP) who is trained in diabetes on the oncology team to manage diabetes for cancer patients undergoing cancer treatments. |
| **Primary Objective:** | To conduct a pilot study to implement the NP-led intervention and assess implementation outcomes (e.g., reach, acceptability, appropriateness, feasibility, fidelity) among individuals undergoing treatment for cancer and their providers. |
| **Secondary Objectives:** | To assess the effectiveness of the NP-led intervention. |
| **Exploratory Objectives:** | To determine a link between improved diabetes control and cancer treatment completion. This will have implications for large-scale interventions to improve glycemic control, thereby increasing the likelihood of cancer treatment completion and improving patients' cancer outcomes. |
| **Primary Endpoints:** | **Reach, Adoption,** and **Implementation**. To determine **R**each, we will calculate recruitment success and data completion ratios; and for intervention participants, an intervention completion ratio. Among intervention participants and their providers, I will assess **A**doption using psychometrically validated measures of acceptability, feasibility, and appropriateness. **I**mplementation will be assessed by fidelity (degree to which the intervention was implemented according to protocol). |

**1.1 Schema**




**Note:** This is a quasi-experimental pre-post design with non-randomized intervention and control groups. We will recruit 110 participants (55 per group) to ensure that we meet our goal of enrolling 76 participants (38 per group, 70% participation).

## 1.2 Study Objectives and End Points

### 1.2.1 Primary Objectives

To conduct a pilot study to implement the NP-led intervention and assess implementation outcomes (See **Table 1** e.g., reach, acceptability, appropriateness, feasibility, fidelity) among individuals undergoing treatment for cancer and their providers.

### 1.2.2 Secondary Objectives

To assess the effectiveness (see **Table 1**) of the NP-led intervention.

### 1.2.3 Exploratory Objectives

To determine a link between improved diabetes control and cancer treatment completion. This will have implications for large-scale interventions to improve glycemic control, thereby increasing the likelihood of cancer treatment completion and improving patients' cancer outcomes.

### 1.2.4 Primary Endpoints

**Reach, Adoption,** and **Implementation**. To determine **R**each, we will calculate recruitment success and data completion ratios; and for intervention participants, an intervention completion ratio. Among intervention participants and their providers, I will assess **A**doption using psychometrically validated measures of acceptability, feasibility, and appropriateness. **I**mplementation will be assessed by fidelity (degree to which the intervention was implemented according to protocol).

**Table 1: Study Outcomes Guided by the RE-AIM Framework[1]**

| RE-AIM Domain | Measure | Measure Description | Type of Data | Baseline Collection | Follow-up Collection |
|---|---|---|---|---|---|
| **R -Reach*** | Recruitment Success Ratio | # participants recruited/# of participants approached | Study data collection | **X** | |
| | Intervention Completion Success Ratio | # of participants who completed intervention/# of participants who enrolled | Study data collection | | **X** |
| | Data Collection Success Ratio | # of participants who completed both surveys/# of participants who enrolled | Study data collection | | **X** |
| **E -Effectiveness** | Patient Satisfaction | Diabetes Treatment Satisfaction Questionnaire (8 items, | Patient Self-report | **X** | **X** |

| | | | | | |
|---|---|---|---|---|---|
| | | α=0.92)[2] | | | |
| | Patient Distress | Diabetes Distress Scale (17 items, α=0.93) | Patient Self-report | **X** | **X** |
| | Patient cancer QoL | Functional Assessment of Cancer Therapy. (44-items, α=0.90) | Patient Self-report | **X** | **X** |
| | Neuropathy | PRO-CTCAE (2 items) | Patient Self-report | **X** | **X** |
| | Hospitalizations | # of inpatient stays since cancer diagnosis | Medical record/patient self-report | | **X** |
| | ED visits | # of ED visits since cancer diagnosis | Medical record/patient self-report | | **X** |
| | Missed cancer treatment appointments | total # planned appointments-# of appointments attended | Medical record | | **X** |
| | Delayed cancer treatment | # of days treatment was delayed from schedule date | Medical record | | **X** |
| | Chemotherapy dose reduction | Indication if chemo dose was reduced | Medical record | | **X** |
| **A -Adoption*** | Feasibility | Feasibility of Intervention Measure (4 items, α=0.89)[3] | Patient and Provider Self-report | | **X** |
| | Acceptability | Acceptability of Intervention Measure (4 items, α=0.85)[3] | Patient and Provider Self-report | | **X** |
| | Appropriateness | Intervention Appropriateness Measure (4 items, α=0.91)[3] | Patient and Provider Self-report | | **X** |
| **I -Implementation*** | Fidelity | # of patients who receive DSME/# of patients with baseline visit; # of patients who received summary | Study data collection | **X** | **X** |

| | | | | | |
|---|---|---|---|---|---|
| | | document/# patients with follow-up visit; # of NP contacts | | | |
| **M -Maintenance** | Assessed in Future R01 | N/A | N/A | N/A | N/A |

***** primary outcomes; QoL (quality of life), DSME (Diabetes self-management education); # of (number of), α refers to Cronbach's α (measure of a scale's internal consistency with values >0.80 indicating high reliability[4]

## 2. Background

### 2.1 Disease

**Concurrent diabetes increases risk of poor outcomes in patients with cancer.**

Twenty percent of cancer patients have diabetes.[5] Comorbid diabetes puts cancer patients at increased risk for infections,[6] hospitalizations,[7] and mortality.[8, 9] Insufficient attention to diabetes during active cancer care may explain why diabetic cancer patients have worse outcomes compared to their non-diabetic cancer counterparts.[10, 11]

In the US, there are 3.5 million breast cancer survivors, 20% of whom had diabetes at the time of their cancer diagnosis.[5, 12, 13] With an aging population and rising prevalence of obesity, the number of patients with cancer and diabetes is expected to grow. Among patients with cancer, those with diabetes have a 50% increased risk of all-cause and cancer-related mortality compared with those without diabetes.[7, 14] Racial/ethnic minorities may be at increased risk as they tend to have more aggressive cancer,[15, 16] a higher prevalence of diabetes,[17] and poorer glycemic control compared with their White counterparts.[18]

Among patients with cancer, those with diabetes are 12% less likely to receive surgery, 27% less likely to receive radiation, and 34% less likely to receive chemotherapy compared with those without diabetes.[19] A possible reason for this disparity is that among patients with cancer, those with diabetes are at greater risk for treatment-related infections and hospitalizations during and after cancer care compared with those without diabetes.[6, 8, 13, 20] For example, among patients with breast cancer receiving chemotherapy, those with diabetes have a 32% increased risk of being hospitalized (43% for infection/fever) compared with those without diabetes.[13] As such, oncologists may reduce chemotherapy doses for those with diabetes to avoid adverse outcomes and hospitalizations.[13] Dose reduction is a problem, however, because cancer prognosis declines when fewer than 85% of planned doses are given.[21]

### 2.2 Investigational Agent/Device, or Surgical Treatment/Method

**Nurse practitioners (NP) have been successful at managing diabetes in other settings.**

NPs have successfully managed diabetes in ambulatory,[22, 23] inpatient,[24] and community[25] settings. No study, however, has examined the ability of an NP to manage diabetes in an oncology setting. NPs have been successfully integrated into many oncology care teams.[26] We hypothesize that an NP embedded in the oncology team who is trained in diabetes management can successfully manage diabetes during active breast cancer care. NPs can prescribe and adjust diabetes medications quickly in response to fluctuating blood-glucose levels and anticipated responses to chemotherapy (e.g., glucocorticoid-induced hyperglycemia). Furthermore, NPs can communicate effectively with oncologists and PCPs regarding a patient's diabetes management. The individualized nature of diabetes and cancer co-management responds to the national call for improved diabetes and cancer co-management.[27] Although an NP may be able to manage diabetes in this context, there is no consensus on how to best

deliver diabetes care during active cancer treatment.

### 2.3 Rationale

**Cancer care supersedes diabetes management during active cancer treatments.**

Less attention than usual to diabetes management (e.g., decreased adherence to antidiabetic medical therapy, lifestyle, or blood-glucose monitoring) during active cancer care has been hypothesized as an explanation for poorer outcomes among those with diabetes versus those without diabetes.[28] Diabetes is difficult to manage in general,[29] and when cancer is diagnosed, the patient may feel overwhelmed, rendering diabetes care even more difficult.[10, 30] Patients with cancer and diabetes may deprioritize diabetes management while receiving cancer treatment because of cancer care demands.[10] Additionally, diabetes management is not the clinical priority of oncologists.[11, 30] Furthermore, the high-dose glucocorticoids included in many chemotherapy regimens can lead to hyperglycemia;[31] and conversely chemotherapy-induced nausea and vomiting can lead to hypoglycemia.[31] Patients with cancer and diabetes may not know how to adjust their diabetes medications during this time of unstable blood-glucose levels. As patients increase the frequency of visits to their oncologists during active cancer care, they may see their primary care physicians (PCPs) less often, limiting the PCP's ability to manage their diabetes.[32] Finally, PCPs have limited knowledge of rapidly changing chemotherapies[33] and may not know how to manage diabetes while patients receive chemotherapy or other targeted therapies.

**Improved diabetes management during active cancer treatment may increase cancer treatment completion.**

A recent study in patients with colorectal cancer found that that adherence with antidiabetic oral medication was associated with a 24% reduced risk of hospitalization.[34] Another study showed that adherence with antidiabetic oral medication improved glycemic control and subsequently reduced risk of hospitalization.[35] As such, if an NP facilitates good glycemic control in a patient with breast cancer and diabetes during active cancer treatment, then the patient may experience fewer adverse outcomes, such as hospitalization or infection, thus reducing the likelihood of chemotherapy delays or dose adjustments. In turn, by receiving more timely and more complete cancer treatment, the patient with breast cancer and diabetes may experience better cancer and overall health outcomes.

### 2.4 Risk/Benefit Assessment

#### 2.4.1 Known Potential Risks

There are minimal risks involved with participating in this study (completing two surveys, having a one-on-one educational session with a NP, receiving weekly follow-up contacts, receiving an endocrinology referral, and receiving a summary document describing diabetes management during cancer treatment). However, exposure to the intervention could lead to tighter glucose control. The primary risk associated with increased diabetes mellitus (DM) management is tighter glucose control, which could lead to hypoglycemia. This may result in a hospitalization or emergency department visit. Below, we describe potential risks for control and intervention participants, separately.

<u>Control Participants:</u>

a. Risks associated with a 45-minute baseline and 30-minute follow-up survey: Emotional distress related to answering questions about treatment satisfaction, self-efficacy, and quality of life; breach of confidentiality.

b. Increased patient attention to DM management may lead to tighter glucose control, which could potentially lead to hypoglycemia, which may result in a hospitalization or emergency department visit. In the follow-up survey (end of cancer treatment), we plan to document these potential visits (since baseline) among control participants.

Intervention Participants:

a. Risks associated with a 45-minute baseline and 30-minute follow-up survey: Emotional distress related to answering questions about treatment satisfaction, self-efficacy, and quality of life; breach of confidentiality.
b. Risks associated with a 60-minute in-person consultation with nurse practitioner: Emotional distress related to discussing diabetes management during cancer care; hypoglycemia related to tighter glucose control (adverse event), which may result in a hospitalization or emergency department visit.
c. Risks associated with weekly phone/email follow-ups with nurse practitioner: Emotional distress related to increased awareness of diabetes management, hypoglycemia related to tighter glucose control (adverse event), which may result in a hospitalization or emergency department visit.
d. Risks associated with receiving an endocrinology referral: None
e. Risks associated with receiving a summary document about diabetes management during cancer treatments: None.

#### 2.4.2 Known Potential Benefits

There is no guarantee that the patients' diabetes will improve as a result of their participation in this study. It may stay the same or worsen. However, the information learned from this study may help other people with this disease in the future.

#### 2.4.3 Assessment of Potential Risks and Benefits

The survey questions are designed to help understand the ability of a stakeholder-engaged NP-led intervention to improve diabetes care for patients with cancer and diabetes who are undergoing cancer treatment. All psychological risks will be minimized by protecting subjects' rights and emphasizing that participation in this study is voluntary and subjects have the right to stop at any time

### 2.5 Correlative Studies Background

*Not applicable*

## 3. Study Design

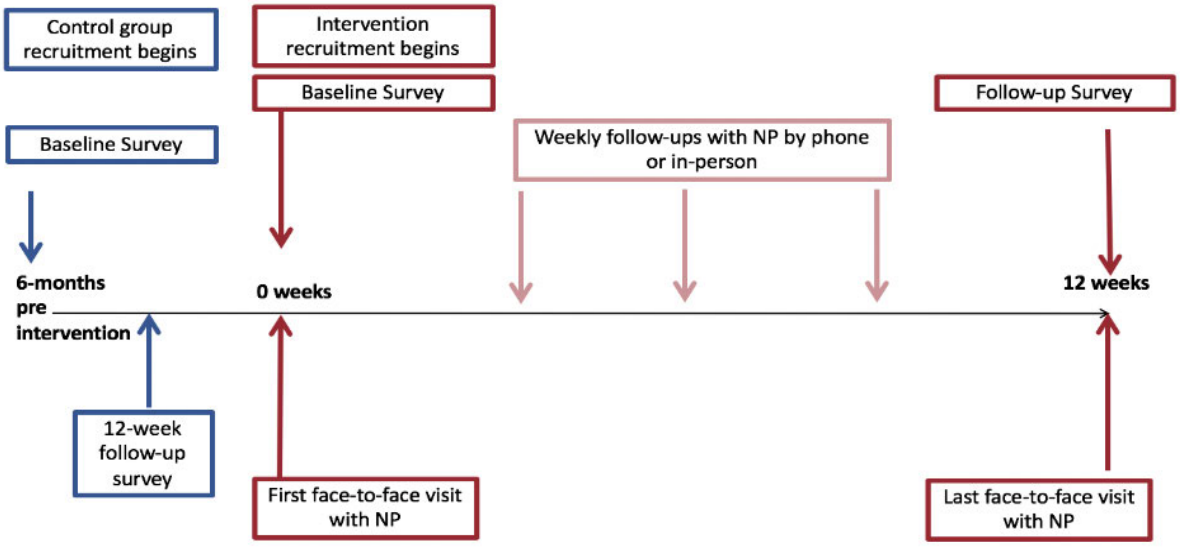
### 3.1 Overall Design

This is a pilot feasibility study, in which we will use a quasi-experimental pre-post design with non-randomized intervention and control groups (Figure 1). In this feasibility study, we will first enroll 38 eligible patients for the control group and collect effectiveness measures at baseline and follow-up (end of cancer treatment ~4-20 weeks) (Table 1). Through chart review, we will document cancer treatment regimen completion at follow-up. We will then

enroll 38 patients for the intervention group, collecting the effectiveness and implementation outcomes at the end of cancer treatment (~4-20 weeks).

The main hypothesis that will be tested in this pilot study is that an NP embedded in the oncology team who is trained in diabetes management may successfully manage diabetes during active cancer care for patients undergoing cancer treatment.

**Figure 1. Proposed Timeline of the Workflow of the Study**




### 3.2 Scientific Rationale for Study Design

As the study takes place at a clinic where oncologists often see each other's patients, randomization at the patient or provider level is not feasible. Thus, for this pilot study we will use a quasi-experimental pre-post design with non-randomized intervention and control groups (Figure 1). For this feasibility study, we will enroll 38 control adults (see section 12.2 for sample size calculation) and collect effectiveness measures at baseline and follow-up (end of cancer treatment, ~4-20 weeks), to capture usual care. At follow-up, we will use the EHR to document cancer treatment regimens. After 6 months, we will enroll 38 intervention women, collecting the same effectiveness measures, health services use, and the implementation outcomes described above.

### 3.3 Justification for Dose

*Not applicable*

### 3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed their treatment regimen and completed the follow-up survey (**Schedule of Assessments (SoA), Section 6.1***)*

## 4. Subject Selection

**4.1 Study Population**

Female and male patients with a diagnosis of invasive cancer who meet the inclusion and exclusion criteria will be eligible for participation in this study.

**4.2 Inclusion Criteria**

- Invasive cancer
- Plan to receive neo-adjuvant or adjuvant cancer treatment at Weill Cornell Medicine (WCM)
- Age 18+ years
- Pre-diabetes OR type 2 diabetes.
    - Treatment with antidiabetic medication OR
        - HbA1c >=5.7 OR
        - Random glucose >=140 OR
        - Fasting blood glucose >=100

**4.3 Exclusion Criteria**

1. Patients receiving hospice care
2. Type 1 diabetes

**4.4 Lifestyle Considerations**

*Not applicable.*

**4.5 Screen Failures**

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

**4.6 Strategies for Recruitment and Retention**

i. Sampling strategy**:** We will identify potentially eligible patients from the EHR prior to initiation of cancer treatment. Then we will ask their oncologist for permission to approach the patient for recruitment. We will over-sample racial/ethnic minorities with the goal of recruiting ≥30% minorities.

ii. Participants will be consented remotely using an electronic version of the informed consent form that follows federal, state, and local regulations, as applicable. We will implement the following procedures for electronic informed consent.

   a. The informed consent document(s) will be sent to the subject or their Legal Authorized Representative (LAR), if applicable, via secure email sent by REDCap prior to the scheduled consent discussion. The subject or LAR will be asked to review the consent document prior and during the consent discussion with a study staff member via phone or approved teleconferencing service (i.e., Zoom). The study staff member will confirm the subject or LAR

has read and has the capacity to appreciate all aspects of the information presented in the consent process for the research study. The subject or LAR will be encouraged to ask questions. If agreeing to participate, the subject or LAR will sign the consent form using electronic informed consent (eConsent) via REDCap. A computer, tablet or touch screen phone will be used to capture digital signatures. If applicable, the person conducting consent will also sign the electronic informed consent (eConsent) document in a contemporaneous manner. Subjects will be provided with a digital copy of the completed form via email. The informed consent discussion and process will be documented by the study team in the subject's medical record or study record.

If a subject does not have access to a touch screen phone, computer or tablet, cannot work with remote electronic informed consent, or the remote electronic informed consent cannot be obtained for any other reasons, the consent may be conducted and documented at an in-person visit prior to study activities via paper consent form or through REDCap on an ITS tagged device.

iii. Recruitment and incentives: Among patients approved for recruitment by their oncologist, the research assistant (RA) will coordinate with the NP about approaching patients at their first cancer treatment visit using the recruitment script (included in this application). Among patients willing to share, we will document reasons for refusal and collect aggregate demographic and clinical information to compare participants with non-participants. Among patients who are interested in participating, the RA will review the informed consent form (see ICF attached to the application) and obtain written informed consent. After signing the ICF, the RA will give them the baseline survey to complete on paper or using an iPad. The baseline survey is estimated to take 45 minutes to complete. Participants will receive a $25 gift card at baseline and a $50 gift card at follow-up once they complete the 30-minute follow-up survey. Our team will also make a phone call to the patient halfway through their cancer treatment to check how they are doing.

## 5. Registration Procedures

### 5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

### 5.2 Subject Registration (Sub-sites)

We will recruit participants from NYP/Weill Cornell Medical Center

## 6. Study Procedures

### 6.1 Schedule of Assessments

**Table 2. Schedule of trial events**

| | Baseline | Follow-up |
|---|---|---|
| **Demographics** | | |
| Age, race, ethnicity, marital status, educational attainment, health insurance, zip code (7 items) | X | |
| **Medical History** | | |
| Any other comorbid conditions (1 item) | X | |
| **Surveys** | | |
| DM data (4 items) | | |
| Patient Satisfaction - DM Treatment Satisfaction Questionnaire (8 items) | X | X |
| Patient Distress - DM Distress Scale (17 items) | X | X |
| Patient Breast Cancer QoL - Functional Assessment of Cancer Therapy-Breast (44 items) | X | X |
| Neuropathy – PRO-CTCAE (2 items) | X | X |
| | | |
| **EPIC Review** | | |
| Cancer data | X | X |
| DM data | X | X |
| | | |
| **Intervention Evaluation** | | |
| Feasibility (4 items) | | X |
| Acceptability (4 items) | | X |
| Appropriateness (4 items) | | X |
| | | |
| **Patient/Provider Interviews** | | X |

#### 6.1.1 Screening Visit (*-X days before start of treatment*)

**Sampling strategy:** We will identify potentially eligible patients from the EHR prior to initiation of cancer treatment (using inclusion/exclusion criteria described above). Then we will ask the oncologist for permission to approach the patient for recruitment. Among patients approved for recruitment by their oncologist, the research assistant (RA) will coordinate with the NP about approaching patients at their first treatment visit using the recruitment script (included in this application). Among patients who are interested in participating, the RA will review the informed consent form (see ICF attached to the application) and obtain written informed consent. After signing the ICF, the RA will give them the baseline survey to complete on paper or using an iPad. The baseline survey is estimated to take 45 minutes to complete. Participants will receive a $25 gift card at baseline and a $50 gift card at follow-up.

Data collection: The RA will collect baseline data either before or during their first treatment visit. As infusions last ~2-4 hours, participants will have sufficient time to complete the 45-minute survey. Typically, patients do not feel sick when they are receiving chemotherapy infusions, as symptoms/side effects present themselves after infusion ends. As such, the infusion time is considered a good time to complete surveys according to the oncologists and nurses. The survey can be completed on paper or using a tablet (online). If the patient does not want to complete the survey in clinic, they can complete it at home electronically or on paper (bringing the copy to the next visit). Follow-up data will be collected at the last infusion or treatment visit

and will inquire about health services use since baseline, (e.g., ED visits, hospitalizations, urgent care). Similarly, this survey can be completed on paper or using a tablet and should take up to 30 minutes. If the patient does not want to complete the survey in clinic, they can complete it at home electronically or on paper (bringing the copy to the next visit or mailing it to the study team). All intervention patients will provide suggestions for improvement for the intervention at the follow-up survey. We will invite up to 15 intervention participants to participate in brief, semi-structured interviews by phone or in-person so that we can collect more granular information about the intervention's implementation process (see interview guide). We will review medical records of all participants after the follow-up survey to record number of cancer treatment visits such as, chemotherapy infusions, planned and received, and if any dose adjustments or missed doses occurred (described below).

EPIC review at baseline

1. ***Cancer data*** (tumor stage at diagnosis, surgeries received since cancer diagnosis, radiation received since cancer diagnosis, hormone therapy received since cancer diagnosis);
2. ***DM data*** (most recent HbA1c, most recent glucose lab values, name, dose, and frequency of DM medications currently being taken)

EPIC review at follow-up

1. ***DM data*** (most recent HbA1c, most recent glucose lab values, name, dose, and frequency of current DM medications being taken, number of visits with PCP and/or endocrinologist since baseline, episodes of hypoglycemia since baseline, # of ED visits since baseline, # of hospitalizations since baseline, number and types of infection since baseline)
2. ***Cancer data*** (surgeries, radiation, hormone therapy, # planned chemo doses, # doses of chemo given, chemo dose reduction, # days chemo delayed, pauses/interruptions to chemo);

For our EPIC chart review, we will have a second team member re-abstract 20% of the charts and conduct a quality control analyses to determine inter-rater reliability

### 6.1.2 Treatment Phase

#### 6.1.2.1 Visit 1 (baseline; Cycle 1 Day 1)

Baseline survey: 81 items

1. ***Demographics*** (age, race, ethnicity, marital status, educational attainment, health insurance, zip code);
2. ***Medical history*** (any other comorbid conditions);
3. ***DM data*** (DM medications currently being taken, number and type of DM self-care behaviors, type and frequency of glucose self-monitoring, relationship with an existing endocrinologist, relationship with an existing PCP)
4. Patient Satisfaction: DM Treatment Satisfaction Questionnaire (8 items, $\alpha$=0.92)[2]
5. Patient distress: DM Distress Scale (17 items, $\alpha$=0.93)[36]
6. Patient breast cancer QoL: Functional Assessment of Cancer Therapy (44-items, $\alpha$=0.90)[37]

7. Neuropathy –PRO-CTCAE (2 items)

#### 6.1.2.2 Visit 2 (± 3 day(s))

Our team will make a phone call to the patient halfway through their treatment plan to check how they are doing (see phone script for controls and intervention participants).

### 6.1.3 Follow-up Phase

Follow-up survey: 93 items

1. ***DM data*** (name, dose, and frequency of DM medications currently being taken, number and type of DM self-care behaviors, type and frequency of glucose self-monitoring, number of visits with PCP and/or endocrinologist since baseline, episodes of hypoglycemia since baseline, # of ED visits since baseline, # of hospitalizations since baseline, number and types of infections since baseline)
2. Patient Satisfaction: DM Treatment Satisfaction Questionnaire (8 items, α=0.92)[2]
3. Patient distress: DM Distress Scale (17 items, α=0.93)[36]
4. Patient breast cancer QoL: Functional Assessment of Cancer Therapy - (44-items, α=0.90)[37]
5. Neuropathy –PRO-CTCAE (2 items)
6. Feasibility of the intervention (4 items)
7. Acceptability of the intervention (4 items)
8. Appropriateness of the intervention (4 items)

## 7. Study Intervention

### 7.1 Study Intervention/Device Description

**Proposed Intervention Overview**:

i. Integration of a certified DM educator NP on oncology team.

ii. Face-to-face or virtual consultation with NP during chemotherapy infusion or other cancer treatment with individualized recommendations/medications AND patient education through the Patient Activated Learning System (PALS).

iii. Weekly follow-ups from NP via phone, Zoom, or in-person (patient directed) for 12 weeks/course of chemotherapy or other cancer treatment.

iv. Check in call from study team week 6 (halfway) through chemotherapy regimen or other cancer treatment to check on patient (this can enhance study retention for the final data collection)

v. Glucose target guidance for patients undergoing chemotherapy or other cancer treatment
   - If capillary glucose is >400, patients should be called by phone and potentially sent to ER
   - During chemotherapy or other cancer treatment, target levels: fasting blood sugar: <150, random glucose <200

vi. Endocrinology consultation if needed at the discretion of the NP.

vii. Summary of diabetes care over the course of chemotherapy or other cancer treatment to be shared with patient, PCP, oncologist, and endocrinologist at the end of 12 weeks (or end of chemotherapy regimen). This will include starting glucose/HbA1c levels, DM medications taken during the course of treatment, cancer treatments received, and final glucose/HbA1c levels.

**Control Group**

i. Baseline survey and access to patient education (PALS) modules

ii. Check in call from study team halfway through chemotherapy regimen or other cancer treatment to check on patient

iii. Follow-up survey at the conclusion of cancer treatment

Intervention delivery: After baseline data collection, the NP will meet with each intervention participant and begin the first 30-minute session. She will use a structured form to record provision of elements of the intervention for this and subsequent sessions. Additional contacts (by phone or secure message) outside of scheduled contacts will be recorded using a similar form. The NP will record start and end times spent with patients to estimate human resources/workforce needs for the future R01 trial. Dr. Pinheiro will meet with the NP bi-weekly to debrief about the delivery process and discuss modifications and improvements, as necessary. These ongoing discussions will allow me to monitor to the intervention's delivery and fidelity.

- Additionally, patients should be evaluated for neuropathy symptoms using the two PRO-CTCAE items at every encounter with NP.
- Glucose levels should be asked about during each NP visit – glucose in the morning, after meals, etc.

### 7.2 Availability

*Not applicable*

### 7.3 Acquisition and Accountability

*Not applicable*

### 7.4 Formulation, Appearance, Packaging, and Labeling

*Not applicable*

### 7.5 Product Storage and Stability

*Not applicable.*

### 7.6 Preparation

*Not applicable*

### 7.7 Dosing and Administration

*Not applicable*

#### 7.7.1 Dosing Delays/Dose Modifications

*Not applicable*

### 7.8 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on subject medication log throughout the course of the study and saved in subject binder, if applicable.

### 7.9 Duration of Therapy and Criteria for Removal from Study

Study Termination Guidelines: A subject's follow-up in the study will end after one of the follow applies:

- Subject's voluntary withdrawal
- Subject lost to follow-up
- Subject death
- Completion of all scheduled study follow-up appointments
- Any other rules specific to your study

### 7.10 Duration of Follow Up

Subjects will be followed for up to 24 months after removal from study or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

### 7.11 Measures to Minimize Bias: Randomization and Blinding

As the study takes place at a clinic where four oncologists see each other's patients, randomization at the patient or provider level is not feasible. Thus, for this pilot study I will use a quasi-experimental pre-post design with non-randomized intervention and control groups. We will complete data collection for controls before enrolling the first intervention participant to avoid any contamination of exposure.

### 7.12 Study Intervention/Follow-up Compliance

*Not applicable*

## 8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

### 8.1 Discontinuation of Study Intervention

Discontinuation from the nurse practitioner intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will

determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

3. ***DM data*** (episodes of hypoglycemia since baseline, # of ED visits since baseline, # of hospitalizations since baseline, number and types of infection since baseline)

4. ***Cancer data*** (# of scheduled cancer treatments, changes to any cancer therapies, pauses/interruptions to treatment regimen);

**8.2 Participant Discontinuation/Withdrawal from the Study**

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention for more than 4 weeks consecutively
- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

**8.3 Lost to Follow Up**

A participant will be considered lost to follow-up if he or she fails to return for 4 scheduled visits with the NP and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing

address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 9. Correlative/Special Studies
*Not applicable*

### 9.1 Laboratory Correlative Studies
*Not applicable*

#### 9.1.1 Title – Laboratory Correlative Study #1
##### 9.1.1.1 Collection of Specimen(s)
##### 9.1.1.2 Handling of Specimen(s)
##### 9.1.1.3 Shipping of Specimen(s) (if multicenter)
##### 9.1.1.4 Site(s) Performing Correlative Study (if multicenter)

### 9.2 Special Studies
*Not applicable*

#### 9.2.1 Title – Special Correlative Study #1
##### 9.2.1.1 Assessment
##### 9.2.1.2 Method of Assessment
##### 9.2.1.3 Timing of Assessment

## 10. Measurement of Effect

This is a Hybrid Type 3 implementation study, which evaluates implementation outcomes and collects information about the intervention's effectiveness (e.g., patient satisfaction, cancer treatment completion, quality of life. However, we are not powered to detect an effect, as our primary outcomes are implementation outcomes.

There are three main outcomes for this pilot study: *1) Reach; 2) Adoption; and 3) Implementation* (**Table 1)**. Effectiveness is a secondary outcome. These outcomes are grouped by the RE-AIM domains[1]. The RE-AIM framework will be used to determine **R**each (how many people received the intervention), **E**fficacy (effectiveness of intervention), **A**doption (feasibility, acceptability, appropriateness), **I**mplementation (fidelity), and **M**aintenance (to be assessed in future studies).[1] In the present study, we will focus on the first 4 constructs[1].

Qualitative patient feedback: We will invite 15 intervention participants to participate in brief (~15 minute), semi-structured interviews by phone or in-person so that we can collect more granular information about the intervention's implementation process (see interview guide).

Qualitative provider feedback: We will also conduct brief (~15 minute) semi-structured interviews to assess provider (oncologists, NPs, and nurses) impressions about the intervention's implementation and opportunities for protocol improvement. During these interviews, we will ask specific questions about their impressions about the intervention's implementation process. Following these interviews, we will assess feasibility, acceptability, and appropriateness using the previously mentioned measures.

### 10.1 Response Criteria

***Reach***

To determine Reach, we will calculate recruitment success ratio and data completion ratio, and, for intervention participants, intervention completion ratio.

***Adoption***

To assess Adoption among intervention group participants and their providers, we will use psychometrically-validated measures of acceptability, feasibility, and appropriateness.[3]

Implementation Questions for patients.[3]

**Acceptability of the intervention**

| | Completely disagree | Disagree | Neither agree nor disagree | Agree | Completely agree |
|---|---|---|---|---|---|
| This NP-led intervention to co-manage my diabetes/pre-diabetes and cancer treatment meets my approval. | | | | | |
| This NP-led intervention is appealing to me. | | | | | |
| I like this NP-led intervention. | | | | | |
| I welcome this NP-led intervention to co-manage my diabetes/pre-diabetes and cancer treatment. | | | | | |

**Appropriateness of the intervention**

| | Completely disagree | Disagree | Neither agree nor disagree | Agree | Completely agree |
|---|---|---|---|---|---|
| This NP-led intervention seems fitting for co-managing my diabetes/pre-diabetes and cancer treatment. | | | | | |
| This NP-led intervention seems suitable for co-managing my diabetes/pre-diabetes and cancer treatment. | | | | | |
| This NP-led intervention seems applicable for co-managing my diabetes/pre-diabetes and cancer treatment. | | | | | |
| This NP-led intervention seems like a good match for co-managing my diabetes/pre-diabetes and cancer treatment. | | | | | |

**Feasibility of the intervention**

| | Completely disagree | Disagree | Neither agree nor disagree | Agree | Completely agree |
|---|---|---|---|---|---|
| This NP-led intervention for co-managing diabetes/pre-diabetes and cancer seems implementable. | | | | | |
| This NP-led intervention for co-managing diabetes/pre-diabetes and cancer seems possible. | | | | | |
| This NP-led intervention for co-managing diabetes/pre-diabetes and cancer seems doable. | | | | | |
| This NP-led intervention for co-managing diabetes/pre-diabetes and cancer seems easy to carry out. | | | | | |

*Implementation*

The Implementation of the intervention will be assessed by fidelity (degree to which the intervention was implemented according to protocol[38]). We will report the number of patients who access the PALS content, the number of patients who receive a summary document at the end of the intervention, the number of in-person, virtual or phone contacts with the NP over the course of the study.

*Effectiveness*

To assess Effectiveness, we will compare measures of effectiveness listed in Table 1 between the control and intervention groups. The following effectiveness measures are included as *secondary outcomes*: 1) patient satisfaction, 2) diabetes-related distress, 3) quality of life, 4) hospitalizations, 5) emergency care, and 6) treatment regimens.

### 10.2 Duration of Response

*Not applicable*

### 10.3 Progression-Free Survival

*Not Applicable*

### 10.4 Other Response Parameters

*Refer to section 10.1*

## 11. Data Reporting / Regulatory Considerations

## 11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all survey, treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

The RA will collect baseline data either before or during the time of the first treatment . As infusions last ~2-4 hours, participants will have sufficient time to complete the 45-minute survey. Typically, patients do not feel sick when they are receiving chemotherapy infusions, as symptoms/side effects present themselves after infusion ends. As such, the infusion time is considered a good time to complete surveys according to the oncologists and nurses. For radiation therapy, the RA will ask the patient to complete the survey before or after the treatment according to patient preference. The survey can be completed on paper or using a tablet (online). If the patient does not want to complete the survey in clinic, they can complete it at home electronically or on paper (bringing the copy to the next visit). Follow-up data will be collected at the last treatment visit and will inquire about health services use since baseline, (e.g., ED visits, hospitalizations, urgent care). Similarly, this survey can be completed on paper or using a tablet and will take up to 30 minutes to complete. If the patient does not want to complete the survey in clinic, they can complete it at home electronically or on paper (bringing the copy to the next visit or mailing it to the study team). All intervention patients will provide suggestions for improvement for the intervention at the follow-up survey. We will invite 15 intervention participants to participate in brief, semi-structured interviews by phone or in-person so that we can collect more granular information about the intervention's implementation process (see interview guide). We will review medical records of all participants after the follow-up survey to record number of cancer treatments planned and received, and if any pauses or interruptions to their treatment occurred.

### 11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

## 11.2 Regulatory Considerations

### 11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all

relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

### 11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

### 11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

### 11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

### 11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

## 12. Statistical Considerations

*All investigator-initiated trials **must** include a study statistician assigned by the Division of Biostatistics and Epidemiology or approval to use alternate biostatistician personnel. Please contact Dr. Paul Christos (pac2001@med.cornell.edu) for additional information and assignment of a study statistician.*

*Describe the statistical methods that will be used to analyze the data (chi square, t-test, correlation, etc.)*

### 12.1 Study Design/Endpoints

We will use a quasi-experimental pre-post design with non-randomized intervention and control groups. We will enroll 38 control adults (see section 12.2 for sample size calculation) and collect effectiveness measures at baseline and follow-up (end of cancer treatment and/or ~20 weeks), to capture usual care. At follow-up, we will use the EHR to document cancer treatment plan. After 6 months, we will enroll 38 intervention adults, collecting the same effectiveness measures, health services use, and the implementation outcomes.

**Reach, Adoption,** and **Implementation**. To determine **R**each, we will calculate recruitment success and data completion ratios; and for intervention participants, an intervention completion ratio. Among intervention participants and their providers, we will assess **A**doption using psychometrically validated measures of acceptability, feasibility, and appropriateness. **I**mplementation will be assessed by fidelity (degree to which the intervention was implemented according to protocol). **Effectiveness** measures are *secondary outcomes*: patient satisfaction, self-efficacy, distress, quality of life, hospitalizations, emergency care, and cancer treatment regimens.

## 12.2 Sample Size/Accrual Rate

We plan for 30 control and 30 intervention patients to **complete** the study (60 patients total). Conservatively anticipating 20% attrition, we will enroll 38 patients for each group or 76 patients in total (31% of eligible number of patients), a sample size sufficiently large to assess the study's primary outcomes. We anticipate recruiting ~55 eligible patients per group in order to enroll 38 patients (70% participation). As the primary outcomes are implementation process measures, the study is not powered to test effectiveness. However, with 30 patients per group, we will be able to detect differences as small as 4.68 points (assuming power of 0.80, one-sided alpha=0.025) in differences in patient satisfaction, as measured by the DM Treatment Satisfaction Questionnaire (range 0-36; standard deviation 6.5).[2] This difference is considered clinically significant.[2, 39, 40] The analyses will not be controlled for multiplicity given the pilot nature of this study.

For the controls, we will enroll approximately 38 subjects over a period of six months ~6-7 subjects per month. For the intervention group, we plan to enroll over a 12-month period with ~3-4 subjects per month.

## 12.3 Stratification Factors

*Not applicable*

## 12.4 Analysis of Endpoints

### 12.4.1 Analysis of Primary Endpoints

We will first compare characteristics between the intervention and control groups using chi-square tests for categorical variables and t-tests for continuous ones. For **R**each outcomes, we will report ratios overall and by intervention year. For **A**doption and **I**mplementation outcomes, we will report proportions, frequencies, and means for patients and providers, separately. For preliminary **E**ffectiveness outcomes, we will test differences between groups using chi-square tests for categorical variables, t-tests for normally distributed continuous and Wilcoxon signed rank test for non-normal continuous ones. Given the pre-post design with nonrandomized control and intervention groups, we will use a difference-in-difference (DID) approach to examine changes in **E**ffectiveness outcomes from baseline to follow-up.[41] We will add potential confounders (e.g., age, race/ethnicity, insurance, education) to DID models, recognizing that the modest sample size will allow limited covariance adjustment. DID models are used to estimate intervention effects by comparing changes in outcomes over time between intervention and control groups.[41] We will also use DID models to examine changes in DM data over time. As an exploratory analysis, we will examine associations between better DM control and treatment delays, interruptions and changes. If sample size permits, we will examine differences in effectiveness outcomes across racial and ethnic groups, preliminarily exploring the intervention's potential differential effect on minority patients.

## 12.5 Interim Analysis

*Not applicable*

### 12.6 Reporting and Exclusions

#### 12.6.1 Evaluation of Toxicity

Not applicable

#### 12.6.2 Evaluation of Response

Not applicable

## 13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

### 13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

#### 13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

Refer to section **2.4.1**

#### 13.1.2 Adverse Event Characteristics and Related Attributions

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

#### 13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be

maintained by the research staff and kept in the subject's research chart.

#### 13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

#### 13.1.5 Reporting Events to Participants

*Not applicable*

#### 13.1.6 Events of Special Interest

*Not applicable.*

#### 13.1.7 Reporting of Pregnancy

*Not applicable*

### 13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. *(Modify as necessary)*

#### 13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

#### 13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

Not applicable

#### 13.2.3 Reporting of SAE to Pharmaceutical Company

Not applicable

### 13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

### 13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The research assistant will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

## 14. Unanticipated Problems Involving Risks to Subjects or Others

### 14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.

## 15. Data and Safety Monitoring Plan (DSMP)

In this section, please include a written plan of the measures that will be taken to ensure the safety of clinical research subjects and protect the validity and integrity of research data. The following questions should be addressed as a part of the DSMP and must be incorporated into your WCM eIRB application:

### 1. Brief Summary

The proposed pilot feasibility study will implement the nurse practitioner (NP)-led intervention and assess key implementation outcomes (e.g., reach, acceptability, appropriateness, feasibility, fidelity) among women, with Type 2 diabetes, undergoing treatment for cancer at Weill Cornell Medicine (WCM). To achieve this goal, the proposed quasi-experimental pre-post design with non-randomized intervention and control groups will enroll 76 adults (38 in the intervention group and 38 in the control group). This innovative pilot study will lay the groundwork for a future, multi-site, cluster-randomized trial testing the developed NP-led model. Given the national interest in optimizing outcomes for individuals with multiple comorbidities, findings from this study have tremendous potential to improve cancer outcomes for cancer patients with comorbid conditions, such as diabetes, who receive their primary and oncology care in a broad range of health systems and settings.

To ensure study participant safety, below are details of the data and safety-monitoring plan for

this proposed study. Notably, Dr. Pinheiro will work with WCM's Office of Research Compliance to constitute a Data Safety Monitoring Board (DSMB) to monitor the study's progress. Dr. Pinheiro will present the study's completed protocol and provide summary tables as requested every 3 months.

**2. Oversight Responsibilities**

Oversight of the pilot study will be conducted by the Principal Investigator Dr. Laura Pinheiro, Primary Mentor (and Co-Investigator) Dr. Monika Safford, and Dr. Jonathan Tobin (Scientific Advisor and the President of Clinical Directors Network).

**3. Safety Monitoring Procedures**

Dr. Pinheiro will ensure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Study data will be accessible at all times to Dr. Pinheiro to review. Dr. Pinheiro will review the study conduct on an ongoing, weekly basis.

All data collected from this study will be stored safely and securely. Patients will complete informed consent forms and baseline/follow-up surveys using paper/pen. This data will be collected by the study's research assistant (RA) and entered into the Research Electronic Data Capture (REDCap), a web-based, secure, data storage program at Weill Cornell Medicine, which is managed by the Clinical and Translation Science Center (CTSC). REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

Drs. Pinheiro, Safford, and Tobin will ensure that any protocol deviations, adverse events (AEs), and serious adverse events (SAEs) are reported to the DSMB, the NIH, and the IRB according to their respective requirements. Dr. Pinheiro will review AEs and SAEs individually in aggregate every 3 months. The DSMB will also conduct an unblinded review of the study AE's in the control and intervention groups every 3 months. As such, the control group will be reviewed twice and the intervention group will be reviewed 6 times.

Drs. Pinheiro, Safford, and Tobin will perform continuous close monitoring of all subjects and closely adhere to all NIH, IRB, and DSMB reporting requirement for AEs, unanticipated problems, and protocol deviations.

The study protocol will be reviewed annually by the BRANY IRB.

**4. Expected Potential Risks**

There are minimal risks involved with participating in this study (completing two surveys, having a one-on-one educational session with a NP, receiving weekly follow-up contacts, receiving an endocrinology referral, and receiving a summary document describing diabetes management during cancer treatment. However, exposure to the intervention could lead to tighter glucose control. The primary risk associated with increased diabetes mellitus (DM) management is tighter glucose control, which could lead to hypoglycemia. This may result in a hospitalization or emergency department visit. Below, we describe potential risks for control and intervention participants, separately.

<u>Control Participants:</u>

c. Risks associated with a 45-minute baseline and 30-minute follow-up survey: Emotional distress related to answering questions about treatment satisfaction, self-efficacy, and quality of life; breach of confidentiality.
d. Increased patient attention to DM management may lead to tighter glucose control, which could potentially lead to hypoglycemia, which may result in a hospitalization or emergency department visit. In the follow-up survey (end of cancer treatment), we plan to document these potential visits (since baseline) among control participants.

Intervention Participants:

f. Risks associated with a 45-minute baseline and 30-minute follow-up survey: Emotional distress related to answering questions about treatment satisfaction, self-efficacy, and quality of life; breach of confidentiality.
g. Risks associated with a 60-minute in-person consultation with nurse practitioner: Emotional distress related to discussing diabetes management during cancer care; hypoglycemia related to tighter glucose control (adverse event), which may result in a hospitalization or emergency department visit.
h. Risks associated with weekly phone/email follow-ups with nurse practitioner: Emotional distress related to increased awareness of diabetes management, hypoglycemia related to tighter glucose control (adverse event), which may result in a hospitalization or emergency department visit.
i. Risks associated with receiving an endocrinology referral: None
j. Risks associated with receiving a summary document about diabetes management during cancer treatments: None.

**5. Adverse Events**

Potential adverse events related to tighter glucose control could be hypoglycemia, which could lead to hospitalization and emergency department visits. We plan to monitor AEs in aggregate every 3-months for control and intervention groups, separately. However, if participants, staff or the intervention NP report any AEs between visits, Dr. Pinheiro will immediately report the AEs to the WCM IRB and/or federal agencies, as appropriate.

**6. Data and Safety Monitoring Board (DSMB)**

The WCM DSMB is available to aid WCM principal investigators and the Institutional Review Board (IRB) in providing an independent means of data and safety monitoring for clinical trials that involve significant risk to research subjects. The WCM DSMB reviews interim data on a schedule commensurate with the needs of a given protocol to evaluate research subject safety, rates of accrual, and efficacy of experimental intervention. After each evaluation, the Board provides the principal investigator with recommendations for protocol modification, continuation or termination. Upon funding, Dr. Pinheiro will work with WCM's Office of Research Compliance to establish the DSMB for this study. The DSMB will ultimately determine the frequency of AE monitoring.

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**Appendix A**