ACCESS Study

Protocol #: LCI-GI-NOS-NAV-001

A Randomized, Controlled ProspeCtive Trial Evaluating The Impact Of A NurSe Navigation Program on Patients with GastrointeStinal Cancers Undergoing Oncological Treatment

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The study will be conducted in compliance with the protocol, ICH/GCP and any applicable regulatory requirements.

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PROTOCOL SIGNATURE PAGE

PROTOCOL TITLE: A Randomized, Controlled ProspeCtive Trial Evaluating The Impact Of A NurSe Navigation Program on Patients with GastrointeStinal Cancers Undergoing Oncological Treatment

~~THE ACCESS TRIAL~~

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

_____ _____

Signature of Investigator Date

MOHAMED SALEM, MD
Investigator Name (printed)

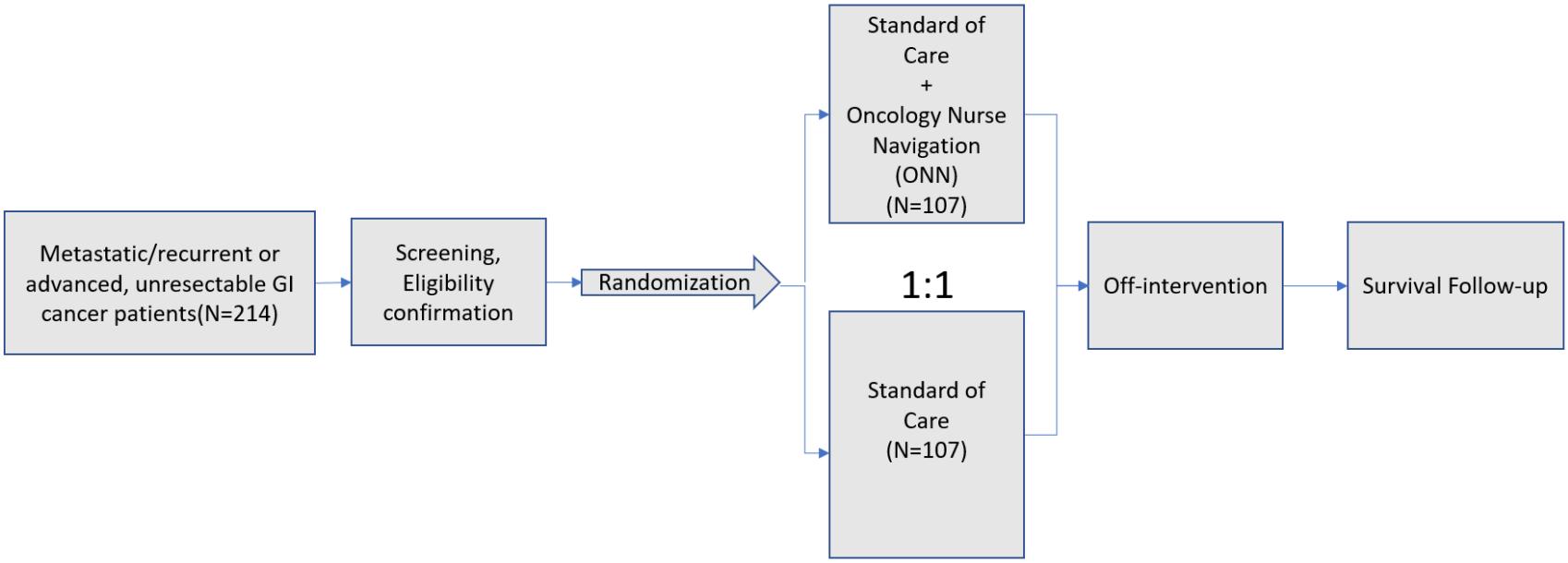
SYNOPSIS

TITLE	A randomized controlled prospective trial evaluating the effectiveness of a nurse navigation program for gastrointestinal cancer patients undergoing oncological treatment.
STUDY POPULATION	Gastrointestinal cancer patients who are receiving oncologic treatments at LCI.
SUMMARY OF STUDY RATIONALE	We hypothesize that the prompt and effective coordination of care provided by Oncology Nurse Navigation (ONN) service will reduce the number of avoidable, unplanned ED visits and hospitalizations, as well as adding measurable value to cancer care, and improve patient overall survival.
STUDY DESIGN	This trial is designed to evaluate the impact of ONN together with standard care (compared to standard of care alone) in terms of clinical outcomes in gastrointestinal cancer patients. Enrollment of subjects onto this study will not affect the course of their cancer treatment in any way; however, we aim to examine if those randomized to ONN will potentially have less utilization of acute care services, better experience and improved survival than those receiving standard care alone. Subjects will be on the study until the criteria for the final analyses have been met or meet any of the other criteria for off study (consent withdrawal, death, etc). Patient overall survival (OS) and other patient-related outcomes (listed below) will be assessed.
OBJECTIVES	**Primary Objective**: The co-primary objectives of this study are to assess the impact of Oncology Nurse Navigation service on: A) patient acute care utilization (defined as unplanned in-patient admissions, emergency room encounters, and/or urgent care visits), and B) overall survival (OS) rate at 6 months. **Secondary Objectives:** Secondary objectives are to compare patients with and without ONN for o Overall survival o Rate of OS at 12 months o Length of hospital stay o 30 days readmission rate o Referral rate to Palliative Care, Hospice, Nutrition Services, and Social Work Services o Adherence to clinical care (the number of no-shows as a percent of all scheduled within Atrium Health, regardless of visit type) o Subject satisfaction as assessed by a EORTC IL109 customized questionnaire
KEY INCLUSION CRITERIA	~~Subjects must meet all of the following applicable inclusion criteria to participate in this study:~~ • Aged ≥ 18 years at the time of consent, capable of providing written informed consent and HIPAA authorization for the release of personal health information. • Treatment naïve OR adjuvant greater than 6 months ago (except metastatic colorectal or small bowel cancer; which may have progressed on or be intolerant to fluorouracil/capecitabine, oxaliplatin and irinotecan-based therapy), histologically or cytologically confirmed metastatic/recurrent or locally advanced GI cancers (metastatic/recurrent fact can be radiologically confirmed) • Enrollment no later than 30 days after initiation of the systemic therapy

	• Ability of the subject to understand and comply with study procedures for the entire length of the study • Life expectancy is > 3 months
KEY EXCLUSION CRITERIA	• Subjects have previously received or are currently receiving LCI Patient Navigation Program services • Subjects with colorectal cancer enrolled in the Empower Program • • Subjects with low grade neuroendocrine tumors
STATISTICAL CONSIDERATIONS	Study is designed with co-primary objectives to evaluate the acute care utilization and 6-month OS rate; the study is primarily powered based on the OS landmark objective. The overall type I error rate for this study is alpha = 0.05, and the co-primary endpoints were both powered at the 2-sided alpha = 0.025 significance level. It is estimated that treatment with standard therapy results in median survival of 8 months, and when assuming an exponential distribution, this corresponds to a 6-month survival rate of approximately 60%. The primary OS objective of this study is designed to test the null hypothesis that the 6-month OS survival rate is ≤ 60%. Thus, 300 evaluable subjects, randomized in a one-to-one fashion, will provide 80% power, assuming the true 6-month OS rate with Nurse Navigation is 80% (a 20% improvement in the 6-month OS rate is considered clinically relevant). This sample size will also provide at least 93% power to detect a 20% reduction in acute care visits (assuming there will be 6 acute care utilization visits per year in the control arm).
NUMBER OF SUBJECTS	Up to 347 subjects may need to be enrolled to reach 300 evaluable subjects

SCHEMA

Table 1.



GLOSSARY OF TERMS

Abbreviation	Definition
COVID-19	Coronavirus disease 2019
CTMS	Clinical Trial Management System
DMP	Data Management Plan
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
ED	Emergency Department
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council of Harmonisation
IRB	Institutional Review Board
ITT	Intent To Treat
LCI	Levine Cancer Institute
LPNP	LCI Patients Navigation Program
MDT	Multidisciplinary Care Team
NN	Nurse Navigator
ONN	Oncology Nurse Navigation
OS	Overall Survival
OS6	Overall Survival at 6 months
QALY	Quality-adjusted life-year
SOP	Standard Operating Procedure
UAP	Unanticipated Problems

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1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Multidisciplinary Cancer Care

In 2019, an estimated 1,762,450 new cancer cases will be diagnosed in the United States and 606,880 people will die from the disease (1), having a major impact on society in the United States and across the world.

The diagnosis and treatment of cancer is a complex process that requires many different clinical specialists to collaborate over a prolonged period. The multidisciplinary care team (MDT) model has become the standard approach for cancer care delivery. The introduction of MDTs has improved survival (2) and reduced the variability in survival rates between hospitals (3). When an MDT functions efficiently, patients are referred for appropriate medical interventions in a timely manner, individual patient needs are more likely to be met, and care is coordinated (4-6). Uncoordinated care can significantly hinder effective cancer care delivery; it is associated with poor symptom management (7), medication errors (8), missed follow-up diagnostic tests (9), and delays in the initiation of therapy. Coordination of care is particularly important for patients with poor prognosis to ensure that they are treated in a timely manner, their symptoms are well managed, and necessary interventions are provided on time.

1.1.2 Management Of Gastrointestinal Cancers

Gastrointestinal cancer patients are very complex to treat, with specific prognosis (10, 11). The 5-year relative survival rates for stage IV disease – 3% for pancreatic cancer, 5-10% for gastroesophageal cancer and 14% for colorectal cancer – are among the lowest of all cancer types (12). Pancreatic cancer is the fourth most common cause of cancer death. The only potentially curative intervention, surgical resection, is not an option for most patients because most are diagnosed at a late stage due to paucity of early symptoms. Likewise, surgery is the only curative option for other gastrointestinal cancer, and because of the vague nature of early symptoms of disease, many patients are diagnosed at a late stage. Therefore, prolonging life and maximizing the quality of life are the main treatment goals for most patients with these diagnoses. A large MDT is typically needed to provide optimal treatment and care for these patients, which ideally comprises gastroenterologists, oncologists, radiologists, radiation oncologists, specialized surgeons, nutritionists, palliative care clinicians, social workers, and many others. The sheer volume of providers required makes the coordination of effective care for these patients extremely challenging; however, this essential coordination is the pivotal point of the highest quality of care for these patients.

1.1.3 Healthcare Disparities

In an ideal situation, all patients would receive an equally high level of quality cancer care, but healthcare disparities exist between privileged and under-resourced patient populations. Social variables such as income level, racial and ethnic background, and insurance status affect access to care and the quality of cancer care received by patients (13-15). These disparities affect almost every aspect

of the cancer care experience. Several studies showed that sociodemographic variables influence the likelihood of experiencing a delay in the initiation of adjuvant chemotherapy for breast cancer (16), a delay in the time from diagnosis to treatment initiation for head and neck cancers (17) and advanced bladder cancers (18), and surgery wait times for many cancer types (19). In a study of early-stage pancreatic cancer patients, sociodemographic variables appeared to determine how likely a patient was to undergo tumor resection, and geographic location was independently associated with disease-specific survival after resection (20). In a study of gastric cancer patients, racial background was found to influence treatment decisions and survival rates (21).

1.1.4 Acute Care Utilization

Certain populations are more likely than others to use acute care services for cancer-related symptoms. A 2018 study showed that pancreatic and gastric cancer patients were more likely than not to be frequent emergency department (ED) attenders (22). In addition, a study of advanced cancer patients showed that those who missed their first appointment were more likely than patients who kept their appointment to have an ED visit within two weeks of the missed appointment (23). These studies suggest that certain patient groups especially need additional support to ensure that they get appropriate care when they need it, outside of the acute care setting. Initiatives to enhance care coordination and easy access to care may help to keep patients out of the ED, improve the quality of cancer care, and alleviate the high economic burden of ED attendance and frequent hospitalization on the healthcare system.

1.1.5 Strategies to Improve Care Coordination

The MDT model improved the quality of cancer care even though coordinating care for all patients within this model is challenging. Several strategies have been applied in an effort to improve care coordination. For instance, a centralized phone call reminder system in 10 clinics at a Houston-based hospital reduced the number of missed appointments (24). Conversely, a complementary ride sharing program in Philadelphia did not reduce rates of missed primary care appointments (25). In a 2018 review, Handley and colleagues outlined several approaches to reduce acute care utilization among cancer patients. Strategies included increasing early access to palliative care, creating standardized approaches to symptom management, and enhancing care coordination through programs such as patient navigation (26). Improving the coordination of care for vulnerable patient populations is critical for reducing healthcare disparities and maximizing the quality of life for patients with a poor prognosis.

1.1.6 Patient Navigation Program

There is a large body of evidence to support the positive impact of patient navigation on many aspects of cancer care delivery. Patient navigation was first introduced in 1990, in New York, to address the disparities in breast cancer survival for minority populations (27). Since then, oncology patient navigation has expanded to many healthcare systems, and this patient-centered service was introduced as a new standard by the Commission on Cancer in 2015 with the hope of remedying the apparent inequality in cancer care (28). Patient navigation programs aim to identify and address individual barriers to care. The scope of work varies widely between different patient navigation programs, most notably by the type of navigators employed, which included lay navigators, social workers, or nurse

navigators. In the oncology setting, experienced registered nurses that carry out patient navigation programs are often referred to as Oncology Nurse Navigators, and the program involving these experienced, registered oncology nurse navigators is termed Oncology Nurse Navigation (ONN). Nurse navigators serve to provide supportive and coordinated care; they bridge the gap between clinical providers in MDTs and patients and ensure that patients have the resources they need to complete the recommended series and courses of treatment. In other words, the role of a nurse navigator is to support patients as they go through the many stages of their cancer journey.

Many studies demonstrate that patient navigation increases cancer screening (29-31) and shortens the time to treatment initiation (32-38).

A few studies have addressed the impact of navigation programs on different aspects of cancer care beyond treatment initiation. A secondary analysis of geriatric cancer patients within The University of Alabama at Birmingham Health System Cancer Community Network showed that patients in a lay navigator program had fewer hospitalizations and ED admissions than a matched cohort; moreover, this reduction in resource utilization translated into a sharp decline in treatment costs (39). A nurse navigation program for oncology pain management at two German hospitals improved adherence to pain medication, reduced pain, and increased quality of life (40). Furthermore, to test the hypothesis that navigation increases access to palliative care services for Latino adults with advanced cancer, a randomized clinical trial was conducted across multiple healthcare facilities in Colorado. Researchers found that navigation increased advance care planning and improved physical symptoms (41).

1.1.7 Oncology Nurse Navigation at Levine Cancer Institute

A nurse navigation program was introduced at Levine Cancer Institute (LCI) in 2011. LCI Patients Navigation Program (LPNP) has expanded to all 28 LCI locations and currently employs approximately 40 Oncology Nurse Navigators – registered nurses with a BSN and two or more years of nursing experience, preferably in oncology. LPNP stops active navigation at the time the patient completes active treatment and transitions into survivorship. Metastatic/recurrent or advanced, unresectable patients are navigated through end of their life.

To assess the potential impact of nurse navigation on clinical outcomes at LCI, several retrospective observational studies were conducted. Patients diagnosed with one of eight cancer types associated with a poor prognosis (acute myeloid leukemia, esophagus, liver, lung, myeloma, ovary, pancreas, stomach), who were assigned oncology nurse navigators were compared to a matched cohort who were not assigned navigators. Navigated patients had improved overall survival (OS). The strongest survival benefit was observed for patients insured by Medicaid, which suggests that the nurse navigation program may reduce disparities in cancer care(42). The impact of nurse navigation on acute care utilization was investigated in a separate cohort of patients, each with an advanced-stage cancer including bladder, breast, colon, kidney, lung, pancreas, prostate, thyroid, or uterine cancer or melanoma. Acute care utilization was significantly reduced for navigated patients compared to those who were not navigated (43).

1.1.8 The Role of Oncology Nurse Navigators at LCI

Oncology Nurse Navigators are usually "tumor site-specific". At LCI GI clinics, they are currently employed to care exclusively for patients with gastrointestinal cancers (GI NN). Regional sites with lower volumes have General Nurse Navigators working with all types of cancers (General NN).

Oncology Nurse Navigators at LCI play many roles such as:

1. Care Coordinator. This encompasses expediting care and facilitating communication between providers, the patient, and the family. LCI Navigators communicate across treatment modalities and expedite referrals. They oversee the coordination of appointments and ensure that they are made in a timely manner.
2. Patient-centered assessor of barriers to care. This includes assisting patients in overcoming the challenges encountered throughout their treatment. These barriers can be logistical, health literacy-related, psychosocial, financial, transportation-related, etc.
3. Patient educator. This involves communicating with the patient to ensure that they understand their disease, their care plan, their treatment, and how to manage their symptoms and treatment side-effects.
4. Patient referral specialist. Referral of patients to appropriate resources helps the patients to overcome identified barriers related to finances, treatment logistics, psychosocial health, transportation, and health literacy, for example. These resources may be within the healthcare system or the community.
5. Patient advocate. Navigators serve as patient advocates and provide a central point of contact for the patient as issues and concerns related to their care arise.

Navigation begins at the time of diagnosis and continues throughout active treatment. LCI navigation has a standardized patient intake process and all new patients that are referred for navigation are promptly assessed to identify any potential barriers to care. Navigators assess each patient's needs, either in person at the patient's first visit or over the telephone. On the basis of this assessment, navigators assign each patient an acuity score that grades the level of support needed. With this grading system, Oncology Nurse Navigators can prioritize patient needs and assist with resource management at an administrative level. Patient assessments are repeated and reevaluated throughout treatment. All assessments are documented in the patient's Electronic Medical Record using Patient Navigation Acuity Grading Scale (See Appendix A).

1.2 Study Rationale

As discussed above, our preliminary results from retrospective analyses demonstrated the potential impact of our nurse navigation program on survival, enhancement of care coordination and quality of care (43). Furthermore, navigated patients were shown to have improved overall survival (OS) compared to those who were not navigated (42). Consistently, these data are supported from studies in other centers as well (29-31).

However, it remains unclear whether the improved outcomes are a result of nurse navigation program or case selection bias, notwithstanding the propensity matching of our previous study. To this end, we propose a prospective, randomized controlled trial to formally examine the effectiveness of nurse navigation on cancer patients undergoing oncological treatment. This study particularly aims

prospectively to assess the impact of ONN on acute care utilization and clinical outcomes. This study is critical to rationalize the continued fiscal support of nurse navigation programs in oncology and is likely to affect health care policy and reimbursement strategies if a positive outcome is proven for nurse navigation. It is not our intention to address the differences between nurse navigation and non-nurse navigation.

1.3 Study Design

In this study, we plan to recruit 300 patients with gastrointestinal cancers, who are receiving care at LCI. Upon accrual, patients will be randomized 1:1 to receive standard of care plus ONN service (n = 150) or standard of care only (without ONN service; n = 150). Patients in both arms will be assessed for acute care utilization and overall survival (OS) rate at 6 months as primary objectives.

Anticipated accrual period will be 48 months.

We hypothesize that the implementation of a prompt and effective coordination of care provided by ONN will reduce the number of avoidable, unplanned ED visits and hospitalizations, reliance on acute care utilization, and may result in an improvement of patient overall survival.

2. STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

- The co-primary objectives of this study are to examine the impact of Oncology Nurse Navigation program on patient **Acute Care Utilization**, defined as unplanned inpatient admissions, emergency room encounters, and/or urgent care visits, and **overall survival rate at 6 months**.

2.1.2 Secondary Objectives

- Secondary objectives are to compare patients with and without ONN for
    - Overall survival
    - Overall survival rate at 12 months
    - Length of hospital stay
    - Time from hospice referral to death
    - 30 days readmission rate
    - Referral rate to Palliative Care, Hospice, Nutrition Services, and Social Work Services
    - Adherence to clinical care (the number of no-shows as a percent of all scheduled within Atrium Health, regardless of visit type)
    - Subject satisfaction as assessed by a EORTC IL109 customized questionnaire

2.1.3 Exploratory objectives

- To compare outcomes within the ONN arm for subjects navigated by GI specialists versus subjects navigated by general oncology nurse navigators.

- To describe the distribution of the timing from enrollment to initiation of systemic therapy.
- To evaluate outcomes within the ONN arm as a function of the time from enrollment to initiation of systemic therapy in those evaluable subjects initiating systemic therapy on study.

3. SUBJECT SELECTION

3.1 Subject Identification and Recruitment

Subjects will be recruited at LCI sites where ONN performed under the LCI Patient Navigation Program is available. Patients with the diagnosis of GI cancers (as defined in the inclusion criteria) who are not previously or currently receiving navigation service in LCI will be identified and enrolled into the study. Patients will not be excluded from recruitment based on their gender, race, or ethnic origin.

3.2 Inclusion Criteria

~~Patients~~ Subjects must meet all the following applicable inclusion criteria to participate in this study:

1. ~~Capable of providing written I~~informed consent and HIPAA authorization for the release of personal health information
2. Aged ≥ 18 years at the time of consent
3. Subject is planning to receive their cancer care at LCI at the time of consent
4. Histologically or cytologically confirmed one of the following diagnoses (metastatic/recurrent status can be radiologically confirmed):
    a. Treatment naïve* or adjuvant greater than 6 months ago:
        i. Metastatic/recurrent or locally advanced, unresectable or borderline resectable (as defined per NCCN, Alliance or other acceptable guidelines criteria) pancreatic cancer
        ii. Metastatic/recurrent or locally advanced, unresectable esophageal, gastroesophageal junction (GEJ) or gastric cancer patients or those who are not eligible for surgery
        iii. Metastatic/recurrent or locally advanced, unresectable hepatocellular carcinoma (HCC)
            - radiographic confirmation of the HCC diagnoses is acceptable
            - prior locoregional treatment for subjects with HCC is allowed, but no prior systemic therapy is allowed
        iv. Metastatic/recurrent or locally advanced, unresectable biliary cancers (e.g. gall bladder cancer, cholangiocarcinoma)
            - prior locoregional treatment for subjects with biliary cancers is allowed, but no prior systemic therapy is allowed
    b. Disease progression on or are intolerant to fluorouracil/capecitabine, oxaliplatin, and irinotecan-based therapy (e.g. FOLFOX, FOLFIRI, or FOLFOXIRI)
        i. Metastatic colorectal or small bowel cancer

**Subjects can be enrolled within, but no later than 30 days after initiation of their systemic therapy, however every effort will be made to enroll subjects prior to the initiation of*

systemic therapy. Subjects who have completed or undergoing a current palliative radiotherapy are allowed

5. Ability to read and understand the English or Spanish language
5.6. As determined by the enrolling physician, ability of the subject to understand and comply with study procedures for the entire length of the study. However, refusal to complete a patient satisfaction questionnaire IL109 should not refrain a subject from being enrolled.
6.7. Life expectancy is >3 months

3.3 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Subjects have previously received or are currently receiving LCI Patient Navigation Program services
1.2. Subjects with colorectal cancer enrolled in the Empower Program
2.3. Subjects with low grade neuroendocrine tumors

3.4 Screen Failures

A consented subject who, for any reason (e.g., fails to satisfy the eligibility criteria or withdraws consent ~~for study participation~~), terminates his/her study participation prior to randomization is regarded as a "screen failure." All screen failures will be tracked. Reasons (e.g. specific inclusion/exclusion criteria) for screen failure will be recorded in the CTMS.

4. SUBJECT ALLOCATION

4.1 Randomization

Following informed consent and eligibility check per standard operating procedures, subjects will be randomized in a 1:1 fashion to either Arm A (standard of care plus ONN service) or Arm B (standard of care only) ~~and assigned a Sequence Number~~. This will be accomplished utilizing the CTMS whereby a list of Sequence Numbers and associated treatment arm assignments randomly generated prior to study activation will be uploaded by a member of the Levine Cancer Institute Data Coordinating Center. The Sequence Number will be a four digit randomly generated ID number, ranging from 0001 to 9999. A stratified block randomization will be utilized including the following stratification factors to reduce confounding of comparisons between the treatment arms:

- COVID-19 study period:
  - Time from study activation to end of pandemic* (Study Period A)
  - End of pandemic to end of study (Study Period B)
  - Note: The time of the start of the post-pandemic era will be determined by a declaration from World Health Organization, Center for Disease Control (or other United States federal agency), or LCI, whichever comes first.

    *On January 30, 2023, the Biden Administration announced its plan to end the COVID-19 national emergency and public health emergency in the United States on May 11,

2023. The end of the pandemic will be defined by the United States declaration of the end of the COVID-19 national emergency and public health emergency.

- Disease diagnosis:
  - Metastatic pancreatic
  - Locally advanced unresectable pancreatic
  - Metastatic or unresectable esophageal, gastroesophageal junction (GEJ) or gastric cancers
  - Metastatic or unresectable hepatocellular carcinoma
  - Metastatic or unresectable biliary cancer
  - Colorectal cancer patients who had disease progression on or are intolerance to fluorouracil, oxaliplatin, and irinotecan-based therapy

5. STUDY PLAN

See Schema (Table 1).

This trial is designed to evaluate the impact of ONN in addition to standard care (compared to standard care alone without ONN) on GI cancer patients' acute care utilization as well as clinical outcomes. Subjects enrolled to this study will be patients presenting to the GI clinic.

Enrollment of patients onto this study will not affect the course of their cancer treatment in any way; however, we hypothesize that those randomized to ONN will have less utilization of acute care and an improved survival compared to those receiving standard care only.

Target accrual period is anticipated to be 48 months.

5.1 Study Intervention

The study intervention is providing the patient with the service of navigation (ONN) performed under LCI Patient Navigation Program (LPNP), led by a registered oncology nurse. When the patient is diagnosed with cancer, and after successfully enrolled on the study, subject(s) who are randomized to the ONN will be assigned an ONN. Subjects can be enrolled within, but no later than, 30 days after initiation of their systemic therapy, however every effort will be made to enroll subjects prior to the initiation of systemic therapy. This ONN`s first role will be to assess the subject's needs either in person at the subject's first visit, over the telephone or utilizing virtual care. The subsequent services may be continued the same way.

The ONN will aim to perform the following: expedite care, facilitate communication between the subject and providers, assist the subject in overcoming challenges throughout their treatment, ensure the subject understands their care plan, disease, and treatment, and most importantly, serve as the subject's central point of contact when questions or concerns arise.

For subject randomized for the control arm intervention will be defined as data collection only, per section 5.43.

5.2 Duration of Subject Intervention Status

Subject on intervention status will begin on the day of randomization and continue until criteria for off-intervention is met (Section 8.1).

5.3 Patient satisfaction survey

Patient satisfaction will be assessed through EORTC IL109 customized questionnaire. Subjects will be offered the option to provide patient satisfaction survey responses electronically or during a clinic visit. Completion of EORTC IL109 questionnaire can be declined by a subject at any time-point. Refusal to complete a survey will not be a protocol deviation or refrain a subject from being enrolled, and will NOT be a criterion for study discontinuation by the Investigator. If subject is not able to complete a survey during the study window, they will be asked to complete at the next scheduled in-person visit. This will NOT be considered as a protocol deviation.

5.4 Duration of Data Acquisition

Underlying primary data needed to support study endpoints will be acquired by trained study conduct research staff. For each subject, this will be done starting at the day of randomization and then on an every 3-month basis.

The duration of data acquisition will be as follows:

- For ACU, readmissions, adherence to clinical care, and subject satisfaction, the duration of data acquisition will be until the subject meets the criteria for off-intervention (see Section 8.1)
- For survival data, the duration of data acquisition will be until the subject becomes off study (see Section 8.2).

6. STUDY CALENDAR

Table 2. Study Procedures and assessments

Study Procedures	Registration	Baseline[2]	During the Intervention[8]		Off-intervention[9]	Survival Follow-up
Informed Consent	X					
Demographics[1]		X				
Medical History[3]		X				
Adherence to clinical care[4]			*Continuously throughout the study from Randomization to Off-intervention every **3 months**[11]*			
Acute Care Utilization[5]						
Collection of subject`s hospital admission and discharge dates[6]						
Survival assessment			X[10]			
Subject satisfaction survey			X[7]	X[7]		

Key to Footnotes

[1] Demographic information will include: DOB, sex, race, live-in caregiver status, income, insurance status, education level, zip code.
[2] Screening window is at most 28 days prior to enrollment.
[3] The following baseline medical history information will be manually collected from EMR: smoker status, diabetes, ETOH use, BMI, weight, clinically significant pre-existing conditions, and treatment and procedure history.
[4] Collect the number of visits scheduled for the subject and the number of no-shows, to include all visits scheduled within Atrium Health, not just oncology related.
[5] Collect unplanned inpatient hospital admissions, emergency room encounters, and urgent care visits.
[6] Hospitalization encounter is temporally defined as a difference between date of discharge and subtracted date of admission.
[7] Assessed by a EORTC IL109 customized questionnaire ~~(Appendix B)~~. It will be collected in two time points. 1st survey will be collected at 4 weeks +2 weeks after the randomization, 2nd survey at 10-14 weeks from the randomization. Subjects will be offered the option to provide survey responses electronically or during a clinic visit. If subject is not able to complete a survey during the study window, they will be asked to complete at the next scheduled in-person visit. This will NOT be considered as a protocol deviation.
[8] If subject remains on study after the relocation from one LCI site to another LCI site, subject will remain on their original arm he/she was randomized to.
[9] Subject will become off-intervention and enter the survival follow-up after meeting the criteria for off-intervention, Section 8.1.
[10] Survival will be continuously assessed for subjects who are On Intervention (at least every 3 months ± 2 weeks). For subjects who are Off Intervention, best effort will be made to obtain survival information approximately every 6 months ±4 weeks either by phone or during a clinic visit until the off-study criteria are met (Section 8.2).
[11] Research designee will contact the subject by phone every 3 months ± 2 weeks, or during a clinic visit.

7. DETAILS ON STUDY ASSESSMENTS

Please also refer to the Study Calendar (Table 2 in Section 6.)

7.1 **Screening procedures**

Prior to enrollment, subjects will undergo standard screening procedures to confirm whether the subject meets eligibility criteria:

- **Informed Consent:** No protocol-related assessments may be performed prior to obtaining informed consent.
- **Medical History:** A complete relevant medical history should be obtained, including: smoker status, diabetes, ETOH use, BMI, weight, clinically significant pre-existing conditions, and treatment and procedure history.
- **Subject demographics** (DOB, sex, race, live-in caregiver status, income, insurance status, education, zip code) should be recorded.

7.2 During the Intervention

- **Subject satisfaction survey:** a EORTC IL109 customized questionnaire ~~(Appendix B)~~ will be collected at two time points.
  1st survey at 4 weeks +2 weeks after the randomization,
  2nd survey at 10-14 weeks from randomization. Patients will be provided with the option to provide survey responses electronically or during a clinic visit.

*The following assessments will be performed throughout the study from the Randomization to Off-intervention every **3 months:***

- **Acute Care Utilization:** unplanned inpatient admissions, emergency room encounters, and urgent care visits should be collected continuously throughout the study from the randomization.
  Hospital admission and discharge dates should be tracked.
- **Adherence to clinical care:** Collect the number of visits scheduled for the subject and the number of no-shows, to include all visits scheduled within Atrium Health, not just oncology related, continuously throughout the study from the randomization.
- **Survival assessment:** Subjects will be assessed during the ONN services continuously throughout the study from the randomization.

7.3 Survival Follow-up

- **Survival assessment:** The best effort will be made to obtain survival information after the subject comes off-intervention until the off-study criteria are met (Section 8.2).

8. OFF INTERVENTION AND OFF STUDY

8.1 Off Intervention

Subjects will be removed from Intervention Status when at least one of the following criteria are met:

- Subject on either arm who permanently discontinues all active anti-cancer therapy
- Subject on either arm who relocates to a non-LCI institution
- Subject on either arm who relocates to an LCI site without LPNP
- Subjects randomized to the ONN arm withdraws consent to participate in the LPNP

8.2 Off Study

Subjects may stop their participation in this study at any time if they no longer wish to participate, or if the investigator believes this to be in the best interest of the subject.

When subjects are removed from the study, the reason for study removal and date the subject was removed should be documented.

Subjects will remain on study until the criteria for final analysis have been met (Section 11.5). Reasons a subject may be removed from study prior to meeting the criteria for final analysis include, but are not limited to:

- The subject or legal representative (such as a parent or legal guardian) withdraws study consent or study participation
- Study is terminated early (Section 12)
- Investigator's decision to withdraw the subject
- Subject death

Subjects that are Off Study will not participate in any study related procedures, including data collection. The completion of this study is not related to the continuance of cancer care.

8.3 Special Considerations

Subject Relocation: At any point during the conduct of the trial, the subject may desire to relocate from their present LCI study site to another LCI facility with LPNP due to travel feasibility or other circumstances. If subject relocates away from the study site, the present study site Sub-Investigator will consult with relocation-site Sub-Investigator to determine if subject should continue study participation. If subject remains on study, subject will remain on their original arm he/she was randomized to.

9. DATA AND SAFETY MONITORING PLANS

Data will be collected in electronic case report forms (eCRFs). ~~The database uses fully validated secure web-enabled software that conforms with 21CFR Part 11 requirements.~~ Study personnel will be trained on data entry by the sponsor and provided protocol-specific eCRF guidelines.

This protocol will be monitored according to the processes in effect for all LCI investigator-initiated studies and the protocol-specific monitoring plan~~, the protocol-specific Data Management Plan (DMP)~~

and will abide by applicable regulations and guidelines (e.g. Good Clinical Practice [GCP]). It is the responsibility of the Sponsor-Investigator to monitor the study safety data for this study. The Sponsor-Investigator and other sponsor-level team members will meet regularly to monitor subject consents, enrollment and retention, study safety data, and timeliness/validity/integrity of the data. Documentation of these meetings will be kept with study records. The Sponsor-Investigator will submit reports to the LCI Data and Safety Monitoring Committee according to the institutional Data and Safety Monitoring Plan.

This study will be monitored to ensure the study is conducted in compliance with the study protocol, SOPs of the LCI and Atrium Health Office of Clinical and Translational Research (and/or other participating institutional SOPs), the FDA, and other applicable regulations and guidelines (e.g. GCP).

Investigators and/or their delegated study personnel will be required to be available during the monitoring visits.

10. POTENTIAL RISKS/UNANTICIPATED PROBLEMS

10.1 Potential Risks

10.1.1 Subject Confidentiality

We do not anticipate any breach of confidentiality as no records will be shared with any personnel outside the research team. All medical information including assessments and other medical records will be recorded and stored in a database. The database will exist on a password protected secured server. Medical records data will be abstracted by the Research Designee. All records will be kept confidential.

~~All data and records generated during this study will be kept confidential in accordance with Institutional policies on subject privacy and HIPAA; the investigators and other site personnel will not use such data and records for any purpose other than conducting the study. No breach of confidentiality is anticipated because no records will be shared with any personnel outside the research team. All medical information including assessments and other medical records will be recorded and stored in a database. The database will exist on a password protected secured server. All records will be kept confidential.~~

~~To minimize risks to confidentiality, data will only be monitored by Sponsor-Investigator and trained research staff. At a minimum, research staff will have completed basic human subject protection research training.~~

10.1.2 Emotional Distress

Some questions in the questionnaires could create emotional distress or confusion. If a subject experiences distress or confusion, the questionnaire process will be interrupted or discontinued, and the Research Designee will follow up with the Sponsor-Investigator.

10.2 Unanticipated Problems (UAP)

10.2.1 Definition

A UAP is any incidence, experience or outcome that is unexpected (e.g., a lost or stolen laptop computer that contains sensitive study information) given the information provided in research-related documentation (e.g., informed consent) and the study population characteristics, that is related or possibly related to participation in the research study and places the participant at an increased risk.

10.2.2 Reporting

All UAPs occurring during the conduct of a protocol and meeting the definition of a UAP will be reported to the Sponsor-Investigator and IRB per IRB reporting requirements.

11. STATISTICAL CONSIDERATIONS

11.1 Milestones

11.1.1 Registration Date

The date the subject signs the informed consent.

11.1.2 Enrollment Date

The date that the subject is randomized.

11.1.3 Intervention Discontinuation Date

The date when S-I becomes aware of the subject meeting any of the criteria in Section 8.1.

11.1.4 Off Study Date

The date the subject terminates participation on the study or is removed from the study per the criteria in Section 8.2.

11.2 Sample Size

This study is designed with co-primary objectives to evaluate the acute care utilization and 6-month OS rate. Power and sample size calculations were primarily calculated based on the OS landmark objective. The overall type I error rate for this study is alpha = 0.05. Therefore, the co-primary endpoints were both powered at the 2-sided alpha = 0.025 significance level. We estimate that treatment with standard therapy results in median survival of 8 months. Assuming an exponential distribution, this corresponds to a 6-month survival rate of approximately 60%. Therefore, the primary OS objective of this study is designed to test the null hypothesis that the 6-month OS survival rate is ≤ 60%. A total of 300 evaluable subjects enrolled in a one-to-one fashion will provide 80% power, assuming the true 6-month OS rate with Nurse Navigation is 80%. A total of 347 subjects may need to be enrolled to achieve 300 evaluable subjects. A 20% improvement in the 6-month OS rate is considered clinically relevant. This sample size will also provide at least 93% power to detect a 20% reduction in acute care visits (assuming there will be 6 acute care utilization visits per year in the control arm).

11.3 Endpoints

11.3.1 Definition of Primary Endpoints

Overall survival at 6 months (OS6) will be determined as a binary variable indicating whether or not the subject was alive at 6 months following randomization.

Acute care utilization visits will be calculated for each subject as the total number of acute care visits normalized to an annual basis. Acute care visits will include unplanned hospital admissions, ED visits, and urgent care visits.

11.3.2 Definition of Secondary Endpoints

- Overall Survival (OS)

OS is defined as the duration from enrollment to the study (randomization) to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

- Overall survival at 12 months (OS12) will be determined as a binary variable indicating whether or not the subject was alive at 12 months following randomization.

- Length of hospital stay (LOS)

Length of stay will be calculated for each subject and for each unplanned in-patient admission as the difference between the admission date and the discharge date (plus 1).

- Time from hospice referral to death

Time from hospice referral to death is defined as the duration from hospice referral to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive. This endpoint will only be calculated for subjects referred to hospice.

- 30-day readmission

The 30-day readmissions will be calculated for each subject as the total number 30-day readmissions. This endpoint will only be calculated for subjects with at least one in-patient admission.

- Referral to Supportive Oncology services

Referral to Supportive Oncology will be binary variables determined for each subject indicating whether or not the patient received referrals to Palliative Care, Nutrition Services, and Social Work Services offered by the Levine Cancer Institute Department of Supportive Oncology.

- Adherence to clinical care

Adherence to clinical care will be calculated for each subject in terms of the rate of subject compliance with scheduled visits. For each subject, the number of no-shows will be calculated as a percent of all scheduled within Atrium Health visits, regardless of visit type.

- Patient satisfaction

Patient satisfaction will be assessed through the EORTC IL109 customized questionnaire. The EORTC IL109 customized questionnaire was compiled in the EORTC web-based library system and combined selected items from the PATSAT-C33 and OUT-PATSAT7 questionnaires. The selected scales and individual items included in the IL109 questionnaire are shown in Table 11.3.2

Table 11.3.2 **Scoring the IL109 customized questionnaire ~~(Appendix B)~~**

Scoring the PATSAT IL109	Number of items (*n*)	Item range*	item numbers (*I1*, *I2*, …, *In*)
Scales			
D/Technical Skills *from PATSAT-C33*	3	4	1 – 3
D/Information Exchange *from PATSAT-C33*	3	4	4 – 6
D/Affective Behaviour *from PATSAT-C33*	4	4	7 – 10
N Information *from PATSAT-C33*	3	4	11 – 13
N Affective Behaviour *from PATSAT-C33*	4	4	14 – 17
Coordination *from PATSAT-C33*	4	4	18 – 21
Single items			
Interaction with HCP *from PATSAT-C33* altered**	3	4	22,23,24
Family involvement *from PATSAT-C33*	1	4	25
Access/parking *from PATSAT-C33*	1	4	26
Access/way *from PATSAT-C33*	1	4	27
Continuity *from Out-PATSAT7*	1	4	28
Convenience *from Out-PATSAT7* altered**	2	4	29,30
Transition *from Out-PATSAT7* altered**	3	4	31,32,33
Overall care *from PATSAT-C33*	1	4	34

D = Doctors; N = Nurses; HCP = health care professional
* "Item range" is the difference between the possible maximum and the minimum response to individual items. All items are scored 1 to 5, giving range = 4.
** Altered means selected a subset of items from an multi-item scale and are included as single items in the IL-109 questionnaire.

Scores derived from the IL109

Raw scores and standardized scores will be derived for each patient for each single-item measure and multi-item scale based on the following:

- **Raw score**

For each multi-item scale (captured in Table 11.3.2), the responses of the corresponding items will be averaged using the following formula:

$Raw\ Score = RS = \frac{\sum_1^n I}{n}$, where n represents the number of items in the multi-item scale. For each single-item measure, the score of the concerning item corresponds to the raw score.

- **Linear transformation**

Raw scores will be standardized to a 0 – 100 range to obtain the score *S* using the following transformation:

$$S = \frac{(RS - 1)}{range} * 100$$

The following guidance will be observed to derive the above endpoints for subjects with missing response data:

Single-item measures will not be imputed; raw scores and standardized scores for unanswered single-item measures will be considered as missing values.

Within a multi-item scale, if at least half of the items have been answered, it will be assumed that the missing items have values equal to the average of those items which are present for that respondent. This is algebraically equivalent to using all the items completed and applying the formulas above to calculate the raw scores and standardized scores (i.e., the missing items are ignored when making the calculations). If at least half of the items from the scale have not been answered, the raw scores and standardized scores will be considered as missing values.

- **Average overall standardized score**

It is acknowledged that the following is not endorsed by the EORTC Data Center:

The average overall standardized score across the six multi-item measures and 13 single-item measures will be calculated for each subject as the sum of the nonmissing standardized scores divided by the number of measures contributing to the sum.

11.3.3 Definition of Exploratory Endpoint

Time to initiation of systemic therapy will be calculated as the difference (in days) between the dates of enrollment and initiation of systemic therapy (this difference is 0 when treatment initiation occurs on the date of enrollment). A binary variable indicating if the time to initiation of systemic therapy is less than 0 (i.e., systemic therapy was initiated prior to date of enrollment) will be determined for each subject.

11.4 Analysis Populations

The intent to treat (ITT) population will consist of all randomized subjects. This population will be used to summarize the CONSORT diagram, subject disposition, and baseline subject and disease

characteristics. The evaluable population will consist of all enrolled subjects who meet both of the following criteria:

- Receive at least one dose of standard of care systemic anti-cancer therapy on or after the enrollment date
- Die within six months of enrollment or otherwise are on study for at least 6 months.

The evaluable population will be used for the analyses of all primary, secondary, and exploratory endpoints and interim analyses. Select analyses of time to initiation of systemic therapy will be conducted on the subset of the evaluable population initiating systemic therapy on study only (Section 11.5.6). Additionally, an intervention-compliant population will be defined as all subjects in the evaluable population who meet all of the following criteria:

- Subjects received intervention they were randomized to:
    - Subjects randomized to the ONN arm who have at least one LPNP encounter within 2 weeks from randomization.
    - Subjects randomized to the control arm who do not have any LPNP encounters within 6 months from randomization.

11.5 Analysis Methods

11.5.1 Timing of Analysis

An interim analysis will occur after 100 subjects have been enrolled in the evaluable population. A second interim analysis will occur after 85 deaths have occurred in the evaluable population. A third interim analysis will occur after 120 deaths have occurred in the evaluable population. Analyses of the primary objectives will occur after 300 subjects have been enrolled in the evaluable population. A final analysis will occur when the OS censoring rate reduces to 20% or when all surviving subjects (who remain on study) are on study for at least 30 months (whichever occurs first).

11.5.2 Subject Disposition

A summary of all consented subjects will be provided. This will include a summary of subjects who consented, were enrolled, treated, completed study participation, discontinued study participation (including reasons), died, were lost to follow-up or withdrew consent. These summaries will be presented in the form of a CONSORT diagram.

11.5.3 Baseline Subject Characteristics

A summary of subject demographic, socioeconomic, and disease-related factors will be completed and selected subject medical history will be assessed.

11.5.4 Primary Analysis

The frequency and proportion of subjects alive at 6 months or better will be calculated for each study arm. Corresponding 95% confidence intervals will be estimated using the Clopper-Pearson method. A

two-sided test for binomial proportions will be carried out, testing the null hypothesis that there is no difference in the OS6 rate between the arms.

Poisson regression analyses will be used to analyze acute care utilization visits. Treatment arm will be included in the model as the primary covariate and an asymptotic test of significance will be carried out to compare acute care utilization between the arms.

11.5.5 Secondary Analysis

Overall survival will be analyzed using Kaplan-Meier techniques. Tests of statistical significance between the arms will be carried out using the log-rank test. The 12-month survival rate will be estimated for each study arm based on the Kaplan-Meier estimates. A statistical test of significance will be carried out to compare the 12-month survival rates between the arms. This will be accomplished by pooling the standard errors of the 12-month OS rates and performing a Chi-Square test. Additional survival analyses and analysis of time from hospice referral to death will be conducted using Cox-proportional hazards models. Thirty-day readmissions will be analyzed using Poisson regression. Length of stay and adherence to clinical care will be analyzed using analysis of variance techniques. The frequencies and proportions of subjects referred to Supportive Oncology services will be calculated, alongside corresponding 95% confidence intervals estimated using the Clopper-Pearson method.

The following models will be estimated for each of the six multi-scale measures, thirteen single-item measures, and one average overall standardized score: Linear mixed models for repeated-measures will be used to analyze subject-level satisfaction as assessed through the derived endpoints of the EORTC IL109 customized questionnaire. Fixed factors included in the models will be treatment arm, sampling time (T1 and T2) and the treatment by time interaction. A random factor for subject will be included in the models to account for repeated observations on the same subject. For single-item measures, mixed-effects models for repeated ordinal outcomes will be estimated for the thirteen single-item measures using ordinal logistic regression. The response outcome may be treated as a 5-level raw score or a collapsed version (e.g., 2-level factor as raw scores 1-3 versus 4-5) as appropriate. Similarly, fixed factors included in the models will be treatment arm, sampling time (T1 and T2) and the treatment by time interaction, and a random factor for subject will be included in the models to account for repeated observations on the same subject.

Using the models described above, univariate and multivariable modeling will be conducted to identify baseline prognostic factors and to estimate adjusted between-arm treatment effects. All models will be stratified including the stratification factors used in the randomization. Univariate models will be used to identify baseline factors (including subject demographic, socioeconomic, and clinical characteristics) that are individually prognostic. Statistically significance factors identified from the univariate models will then be jointly included in a multivariable model. Backwards elimination will be used to identify baseline factors that are independently prognostic. If it is determined that the sample sizes in some stratification strata are too sparse, then strata will be combined prior to analyses. This will result in a smaller number of strata, each with larger sample sizes.

11.5.6 Exploratory Analysis

Descriptive statistics (including, but not limited to, mean and standard deviation, median and range, interquartile range) will be calculated to describe the distribution of time to initiation of systemic therapy. The frequency and proportion of subjects initiating treatment on study will be calculated for each study arm; corresponding 95% confidence intervals will be estimated using the Clopper-Pearson method and these proportions will be compared between the arms using Fisher's Exact tests.

The following will be performed in the subset of evaluable subjects initiating treatment on study only:

Time to initiation of systemic therapy will be compared between the arms using analysis of variance techniques. If the distribution is highly skewed, a log transformation may be performed.

Time to initiation of systemic therapy may be summarized as a categorical variable (e.g., time to treatment initiation is between 0 and 6 days versus 7+ days) based on the observed distribution in this subset of evaluable patients. Outcomes may be evaluated and compared within the ONN arm with regards to time to initiation of systemic therapy. Time from enrollment to initiation of systemic therapy may assessed separately as both a continuous and categorical measure where appropriate. These analyses will be conducted on the primary and secondary endpoints as described above; time from enrollment to initiation of systemic therapy may be the comparison/covariate of interest.

11.5.7 Subset Analysis

Subset analyses within the ONN arm comparing outcomes for subjects receiving navigation services from GI specialist versus general navigation services will be performed. These analyses will be conducted on the primary and secondary endpoints as described above.

11.5.8 Interim Analysis

After 100 subjects have been enrolled in the OS evaluable population, a formal interim analysis will be conducted. The interim analysis is designed primarily to assess futility regarding the 6-month OS rate objective and will be based on the conditional power. If the conditional power falls below 50%, the OS6 objective may be removed from the co-primary objective. If this occurs, the primary objective will be based only on the acute care utilization objective. With this revised design, 158 evaluable subjects would provide 90% power to detect a 20% reduction in acute care utilization from 6 visits per year in the non-navigation arm based on a 2-sided alpha = 0.05 significance level.

If the OS6 conditional power is greater than 50% but less than 80%, the sample size may be increased so that the power for the revised sample size is maintained at 80%. As discussed in Chen et al, 2004, this sample size re-estimation will not inflate the type I error.

Sample size re-estimation

As per protocol, the interim futility analysis occurred on 9/22/2022. Based on the results of the interim analysis and on the initial statistical design, the trial will proceed with OS6 and ACU as co-primary

endpoints. In order to retain 80% power for the OS6 objective, the sample size will be increased from 107 evaluable subjects per arm to 150 evaluable subjects per arm.

In order to achieve a total of 300 evaluable subjects, it is estimated that approximately a total of 347 subjects may be enrolled.

Additionally, ~~an~~ interim efficacy ~~analysis~~ analyses will be performed after 85 and 120 deaths in the evaluable population have occurred (Interim Efficacy Analysis I and II). This will be conducted under the auspices of the LCI DSMC and will be blinded to the Sponsor-Investigator and the study conduct trial site. If, in the clinical judgement of the LCI DSMC, there are impelling favorable OS trends, the study may be terminated due to ethical considerations. No formal statistical stopping rules will be utilized, and no alpha spend will be incurred due to this interim efficacy evaluation.

As per protocol, Interim Efficacy Analysis I occurred on 1/23/2022. Based on the results of the blinded survival analysis and the updated statistical design (following the interim futility analysis on 9/22/2022), the trial will continue and Interim Efficacy Analysis II will be performed after 120 deaths in the evaluable population have occurred.

12. STUDY COMPLETION OR TERMINATION

12.1 Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects have withdrawn from the study
- All subjects have discontinued from the study
- The IRB, LCI DSMC, or Sponsor-Investigator discontinues the study because of safety considerations
- The Sponsor-Investigator defines an administrative or clinical cut-off date

12.2 Termination

The study will be terminated when one or more of the following conditions occur:

- If risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study
    - Results of parallel clinical studies
    - If the study conduct (e.g., recruitment rate, drop-out rate, data quality, protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame
- The Sponsor-Investigator has decided to close the trial at any site and at any time

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.

- In case of a partial study closure, ongoing subjects, including those in follow- up, must be taken care of in an ethical manner.

13. STUDY MANAGEMENT

13.1 IRB Approval

The study protocol, the informed consent(s) and any other necessary documents must be approved by the Sponsor IRB and site(s) IRB of record in accordance with federal regulations and obtained prior to implementation.

The Sponsor IRB and sites(s) IRB of record will be informed of any amendment to the protocol, informed consent(s), and any other necessary documents in accordance with IRB reporting requirements. The study protocol will undergo continuing IRB review based on the level of risk as assessed by the IRB no less than annually, or as applicable, in accordance with IRB requirements.

13.2 Informed Consent

Before recruitment and screening/enrollment onto this study, the subject will be given a full explanation of the study, the opportunity to review each consent form, and the opportunity to have all their questions answered. Prior to a subject's participation in the trial, the written informed consent(s) will be reviewed, signed and personally dated by the subject and by the person who conducted the informed consent discussion. Written informed consent may include electronic signatures when use of electronic informed consent is obtained from the subject on site or remotely. A copy of each informed consent will be given to the subject and each original will be placed in the subject's research record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

13.3 Protocol Adherence

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

13.3.1 Amendments to the Protocol and Informed Consent

If it is necessary for the study protocol to be amended and/or the informed consent revised, the amendment or a new version of the study protocol and/or revised informed consent must be approved by the Sponsor-Investigator and the Sponsor IRB.

13.4 Other Protocol Deviations

If a deviation occurs, the event should be reported ~~promptly~~ to the Sponsor-Investigator promptly. Any IRB reportable event that occurs must be reported to the IRB per IRB reporting requirements~~ and to the Sponsor-Investigator as soon as possible but no later than 10 business days of awareness~~.

Protocol deviations that, in the Investigator's judgment, potentially caused harm to participants or others or indicates that the participants or others are at an increased risk of harm, or has adversely impacted data integrity will be reported promptly to the IRB per IRB reporting requirements.

Planned protocol deviations should be submitted to the Sponsor for approval prior to the anticipated deviation occurring. After Sponsor approval has been obtained, planned deviations should be submitted to the IRB prior to the anticipated deviation occurring. IRB approval must be obtained prior to deviation occurrence. No exceptions for eligibility criteria are not allowed.

13.5 Retention of Records

Essential documentation (e.g., source documents, Sponsor-Investigator correspondence, monitoring reports, and regulatory documents), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

13.6 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by GCP guidelines. The study will also be carried out in full conformity with Regulations for the Protection of Human Subjects of Research codified in the ICH E6 and in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies will be obtained for all participating centers before the start of the study, according to GCP, local laws, regulations and organizations.

Strict adherence to this protocol is required for all aspects of study conduct; the investigators may not modify or alter the procedures described in this protocol.

The Sponsor-Investigator is responsible for the conduct of the trial at the sites in accordance with the Declaration of Helsinki. The Sponsor-Investigator is responsible for overseeing all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

13.7 Confidentiality of Records

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

13.8 Compliance with ClinicalTrials.gov

The Sponsor-Investigator is solely responsible for determining whether the trial and its results are subject to the requirements for submission to ClinicalTrials.gov (http://www.clinicaltrials.gov).

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APPENDIX A

Patient Navigation Acuity Grading Scale

I. **PURPOSE:** To assess patient acuity level as they are navigated through the cancer continuum. To assist the navigator in developing an appropriate plan of care and the ability to prioritize patients with the greatest barriers to care. To document and track the level of care and effort required based on the level of patient need.

II. **POLICY:** The navigator will perform an assessment of the patient acuity level and document in the patient record. This assessment will be made using the "Acuity Grading Scale" and will be performed at the time the intake form is completed. The acuity level of a patient may increase or decrease at any time during care due to a change in patient circumstances. If a change occurs, it should be documented accordingly in the patient record.

III. **PROCEDURE:**

A. The navigator will assess the patient's level of acuity using the Acuity Grading Scale at the time the intake form is completed.
B. The acuity level will be recorded in the patient's medical record.
C. The navigator will develop a plan of care based on the patient acuity level.
D. If the patient acuity changes at any time, the navigator will update the acuity level in the patient record.
E. If the patient has any urgent issues at the time of the assessment, the navigator will contact the appropriate staff immediately.

Patient Navigation Acuity Scale

Level I-Initial patient contact when referral received
--Initial guidance/education/coordination as needed
--Typically no follow up required

Level 2-Initial patient contact when referral received
--Initial guidance/education/coordination
--Basic needs identified*
--Ongoing guidance/education throughout treatment as needed

Level 3-Initial patient contact when referral received
--Coordination of multimodality treatment
--Moderate intensity needs identified*
--Ongoing guidance/education provided throughout treatment

Level 4-Initial patient contact when referral received
--Coordination of multimodality treatment
--High intensity needs*
--Difficulty coping with diagnosis or treatment
--Ongoing guidance/education/support provided throughout the patient's treatment

*Please refer to the provided reference guide (next page)

Reference Guide for Acuity Scale

Basic needs: (including, but not limited to)
--Survivorship programs
--Educational needs

--Assistance expediting appointments
--Genetics referral

Moderate intensity needs: (including, but not limited to)

--Supply needs
--Nutritional support
--Transportation issues
--Fertility Services
--Emotional needs
--Absence of support

High intensity needs: (including, but not limited to)

--Language barrier
--Uninsured or under insured
--Illegal status
--Low health literacy
--Psychological issues
--Unresolved symptoms
--Frequent hospitalization
--Coordination with outside facilities
--Child/elder care

Carolinas HealthCare System
Levine Cancer Institute

Patient Navigation Acuity Grading Scale

Reviewed: 6/17

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II. **POLICY:** The navigator will perform an assessment of the patient acuity level and document in the patient record. This assessment will be made using the "Acuity Grading Scale" and will be performed at the time the intake form is completed. The acuity level of a patient may increase or decrease at any time during care due to a change in patient circumstances. If a change occurs, it should be documented accordingly in the patient record.

III. **PROCEDURE:**

A. The navigator will assess the patient's level of acuity using the Acuity Grading Scale at the time the intake form is completed.
B. The acuity level will be recorded in the patient's medical record.
C. The navigator will develop a plan of care based on the patient acuity level.
D. If the patient acuity changes at any time, the navigator will update the acuity level in the patient record.
E. If the patient has any urgent issues at the time of the assessment, the navigator will contact the appropriate staff immediately.

Jeffrey Kneisl, MD and Co-Chairman of the Cancer Committee

~~APPENDIX B~~

ENGLISH

EORTC IL109

Please answer the following questions only if you are currently receiving outpatient care.

Please answer all the questions yourself by circling the number that best applies to you. There are no 'right' or 'wrong' answers. The information that you provide will remain strictly confidential.

Please indicate the hospital service or clinic you are assessing (select only one of them):

If inpatient care: ☐

If outpatient care: **X**

In the course of your current illness or its treatment, not only the past week:

In this hospital, how would you rate doctors, in terms of:	**Poor**	**Fair**	**Good**	**Very good**	**Excellent**	**Not applicable**
1. Their awareness of the care and treatment you received previously?	1	2	3	4	5	
2. The attention they gave to your physical symptoms?	1	2	3	4	5	N/A
3. Their thoroughness in treating your physical symptoms?	1	2	3	4	5	N/A
4. The information they gave you about your illness?	1	2	3	4	5	N/A
5. The information they gave you about your medical tests and treatment?	1	2	3	4	5	N/A
6. The attention they gave to your opinion about the choice of your treatment (in case of possible choices)?	1	2	3	4	5	N/A
7. The interest they showed in you as a person?	1	2	3	4	5	N/A
8. The comfort and support they gave you?	1	2	3	4	5	N/A
9. The frequency of their visits/consultations?	1	2	3	4	5	
10. The time they devoted to you?	1	2	3	4	5	N/A

Please go on to the next page

In this hospital, how would you rate nurses or radiotherapy technicians, in terms of:	**Poor**	**Fair**	**Good**	**Very good**	**Excellent**	**Not applicable**
Please indicate the professional(s) you evaluate: ☒ Nurse(s) ☐ Radiotherapy technician(s)						
11. The attention they paid to your physical comfort?	1	2	3	4	5	N/A
12. The information they gave you about your care and treatment?	1	2	3	4	5	N/A
13. The advice they gave you on managing your physical symptoms?	1	2	3	4	5	N/A
14. The interest they showed in you as a person?	1	2	3	4	5	N/A
15. The comfort and support they gave you?	1	2	3	4	5	N/A
16. Their promptness in answering your specific requests?	1	2	3	4	5	N/A
17. The time they devoted to you?	1	2	3	4	5	N/A
In the outpatient setting of this hospital, how would you rate services and care organisation, in terms of:	**Poor**	**Fair**	**Good**	**Very good**	**Excellent**	**Not applicable**
18. The ease of recognizing the roles and responsibilities of the different caregivers (doctors, nurses, physiotherapists, psychologists, etc.) involved in your care?	1	2	3	4	5	
19. The exchange of information between the different caregivers (doctors, nurses, physiotherapists, psychologists, etc.)?	1	2	3	4	5	
20. The way doctors, nurses and other caregivers involved in your care seem to work together as a team?	1	2	3	4	5	
21. The exchange of information with other care services in the community (general practitioner, home care, nursing house, social services, etc.)?	1	2	3	4	5	N/A
22. The information provided on the scheduling of medical tests, treatment or care?	1	2	3	4	5	
23. The information provided on the overall supportive services available (social, psychological, physiotherapy, dietitian services, support group, etc.)?	1	2	3	4	5	
24. The information provided by doctors, nurses and other caregivers on things you could do to improve your health or prevent illness?	1	2	3	4	5	
25. The opportunity for your family or those close to you to be involved in your care (talking to doctors, receiving disease and care information, etc.)?	1	2	3	4	5	N/A

Please go on to the next page

ENGLISH

In the outpatient setting of this hospital, how would you rate services and care organisation, in terms of:	**Poor**	**Fair**	**Good**	**Very good**	**Excellent**
26. The ease of access (parking, means of transport, etc.)?	1	2	3	4	5
27. The ease of finding your way to the different departments in the hospital?	1	2	3	4	5
28. The opportunity to see the same caregivers when you come to the outpatient clinic?	1	2	3	4	5
29. The ease of arranging medical appointments at convenient times?	1	2	3	4	5
30. The ease of communicating with the hospital services from home?	1	2	3	4	5
31. The information on who to contact if you are worried after you leave your hospital appointment?	1	2	3	4	5
32. The information provided about what you should/ should not do after you leave your hospital appointment?	1	2	3	4	5
33. The provision of follow-up by the different caregivers (doctors, nurses, physiotherapists, psychologists, etc.) after treatment?	1	2	3	4	5
In general,					
34. How would you rate the care received in this hospital?	1	2	3	4	5