ECOG-ACRIN
cancer research group
Reshaping the future of patient care

EAQ162CD

Longitudinal Assessment of Financial Burden in Patients with Colon or Rectal Cancer Treated with Curative Intent

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STUDY PARTICIPANTS	***ACTIVATION DATE***
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SWOG / SWOG – NCORP SITES ONLY	

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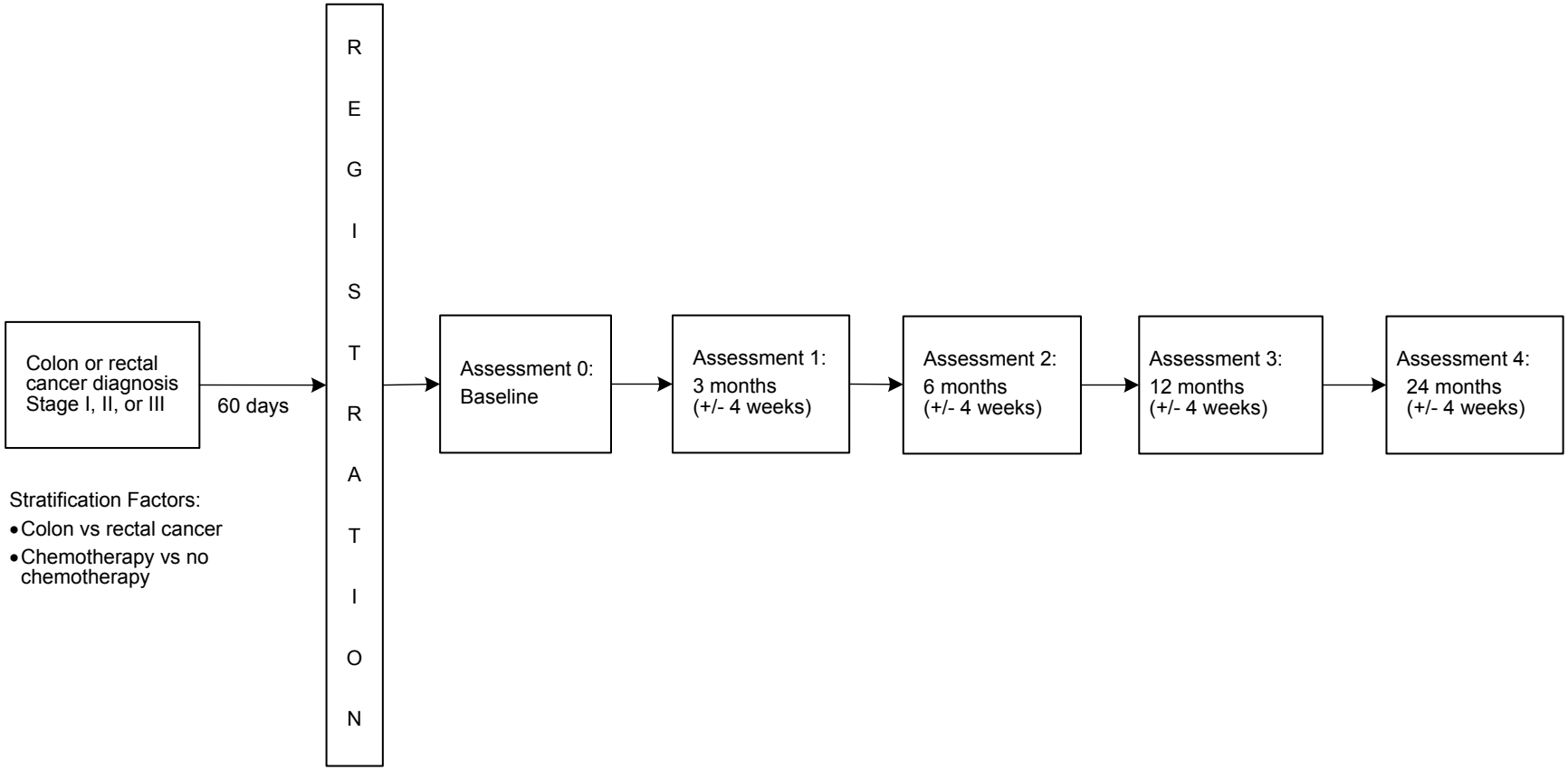
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done through Medidata Rave and the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) system. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Schema


Colon or rectal cancer diagnosis Stage I, II, or III
60 days
R E G I S T R A T I O N
Assessment 0: Baseline
Assessment 1: 3 months (+/- 4 weeks)
Assessment 2: 6 months (+/- 4 weeks)
Assessment 3: 12 months (+/- 4 weeks)
Assessment 4: 24 months (+/- 4 weeks)
Stratification Factors:
• Colon vs rectal cancer
• Chemotherapy vs no chemotherapy

1. Introduction

1.1 Study Foundation

The impact of a cancer diagnosis on employment and financial burden is poorly understood but is increasingly important to patients and families as the cost of cancer diagnostics and therapeutics increase. Understanding the longitudinal impacts of a cancer diagnosis and treatment on patient's financial distress, employment, and quality of life will be essential in developing interventions to address the financial consequences of a cancer diagnosis.

1.2 Background

1.2.1 Rising Cost of Cancer Care and Impact on Patients

The number of cancer treatment options has significantly increased over the past two decades leading to improvements in patient outcomes in many malignancy types (1). These advancements, however, have come with a high cost and cancer is now the second most expensive disease in the United States, after heart disease, with an annual estimated cost of $124 billion dollars in 2010 and a projected rise to $157 billion dollars in 2020, a 27% increase (2). As the cost of cancer diagnostics and therapeutics escalate, financial concerns of patients and families, physicians, health systems, and payers are increasingly common (3, 4). Little is known about the impact of cancer treatment costs on an individual patient, but it has been increasingly the focus of study.

Previous reports demonstrate that cancer patients are at particular risk for financial burden when compared to persons without cancer (5). In a study using pooled data for 1997 through 2007 from the Medicare Current Beneficiary Survey linked to Medicare claims, 50% of elderly patients with a diagnosis of cancer paid at least 10% of their income towards out-of-pocket, cancer-related expenses (6). In a sample from the 2001 to 2008 Medical Expenditure Panel Survey (MEPS), non-elderly patients with cancer reported higher out of pocket cost burden (defined as spending more than 20% of their income on health) when compared to patients with and without other chronic illnesses (13.4%, 9.7%, and 4.4% respectively) (7). Cost sharing for cancer patients can lead to the inability to afford basic needs such as food and clothes (8-12), non-adherence (8, 9, 11, 13), spending savings (10), and even bankruptcy (8, 14, 15). Previous studies have explored predictors of increased financial burden, and those that appear to be vulnerable subgroups include racial and ethnic minorities (16, 17), younger age (17, 18), lower annual household income (17, 18), less than a college degree (17), unemployment (17), and Medicaid insurance (17). In a study from the National Health Interview Survey (NHIS), increased financial burden as a result of cancer care costs was the strongest independent predictor of poor quality of life among cancer survivors (19).

Rising costs for patients are unlikely to reverse as researchers and physicians continue to develop innovative, and expensive cancer

therapies and also observe changing trends in health insurance coverage. According to an analysis by the National Center for Health Statistics, between 1984 and 2013, there was an overall decrease in private insurance obtained through the workplace (20). For those with employee-based insurance, health insurance premiums for family coverage increased 69% between 2004 and 2014 (from $9,950 to $16,834) and there was an 81% increase in the worker's contribution of the premium cost (from $2,661 to $4,823) (21). Further adding to out of pocket cost for patients, annual deductible amounts have increased from $584 in 2006 to $1,217 in 2014 (21) and there are many additional costs in the forms of co-payments and co-insurances. The 2010 Affordable Care Act (ACA) was intended to ensure access to affordable health care, and specific provisions would have either helpful or harmful effects on cost sharing for patients. Provisions that have the potential to lower out of pocket costs include annual out of pocket limits, Medicaid expansion, expansion of parents' insurance coverage to 26 years of age, and mandatory primary care and preventative service coverage requirements. Despite these provisions, the degree to which an individual's out of pocket spending varies by plan and how much health care they utilize. For example, those with lower income and high-utilization of services will likely experience the greatest reduction in cost sharing (22). With the new administration, however, it is expected there may be some changes to this policy.

1.2.2 Financial Burden and Employment

In addition to direct cost of care, a cancer diagnosis can impact a patient's employment status or increase work limitations due to symptoms, treatment, or any medical complications (23-27). Previous literature has reported that in early stage breast and prostate cancer, the greatest work limitations (defined as weekly hours worked) occurred at 6 months, and by 12-18 months, most patients had returned to work (28). An estimate of lost work time was studied in pooled data from the 2000-2005 MEPS, where working-aged participants (age range, 25-64 years) (n = 89,520) with a diagnosis of cancer were included and estimates were made for the probability of being employed and the annual number of workdays missed because of illness or injury (29). Four respondent groups for comparison were constructed during the analysis period: (1) respondents with no cancer, and (among those who reported having cancer) (2) respondents with active cancer care, (3) respondents with follow-up cancer care, and (4) respondents with no cancer care. This analysis showed that, compared with those without cancer, patients undergoing active cancer care have a 3.3% absolute (4.5% relative) decrease in the probability of employment. Among respondents who were employed, those undergoing active cancer care missed 22.3 more workdays per year than those without cancer. Follow-up cancer care is associated with about 1 more workday missed per year compared with those without cancer.

At this point, we do not know the interaction between perceived financial burden and changes in employment status or limitations.

Understanding the timing of employment changes and limitations is important in designing optimal interventions and this study will prospectively follow employment changes and its interactions with perceived financial burden.

1.2.3 Challenges to Addressing Cost of Cancer Care

In response to this unsustainable cost burden, The Institute of Medicine (IOM) has emphasized the urgent need to address multiple strategies to deliver more efficient, coordinated, and high quality care that is still affordable. As part of this challenge, the IOM recommends that providers improve communication about value and cost of treatment options and incorporate this information in decision making (30). There are many recognized challenges, however, to discussing costs with patients that stem from barriers at the systems level, interpersonal level between the provider and patient, and individual patient level (31). From a health system's level, patients are not systematically screened for financial burden, there is a lack of price transparency to both the patients and providers, and oftentimes institutions do not have adequate financial resources (i.e. social worker, financial counselors) to address a need if identified. From an interpersonal standpoint, there is evidence that patients desire to talk about the cost of their therapy (32), however there is discomfort and lack of training in conducting these sensitive conversations both among physicians and patients (33). From an individual patient perspective, patients are often unprepared and unaware of costs and resources. They are overwhelmed with a new diagnosis and cost discussions become neglected by both patients and providers as other issues quickly dominate clinic time. Because of these challenges, better characterization of the optimal population, timing, and content of an intervention for financial burden is still unknown.

1.2.4 Preliminary Data for Assessing Financial Burden in Cancer Patients

Our study team has experience studying financial burden in cancer patients (5, 11, 12, 17, 34-42), and has specifically developed and utilized the COST measure (17, 42). In order to further test the validity, feasibility, and acceptability of longitudinally measuring financial burden using a validated measure of financial burden in cancer patients, our group completed a pilot study at Robert H. Lurie Comprehensive Cancer Center at Northwestern University (36). In this study, 96 patients with either a gastrointestinal, sarcoma, or lung cancer were longitudinally assessed over three months for both level financial burden (using COST, Incharge (43), and EORTC financial question) and health related quality of life. The COST score (described in more detail below) ranges from 0 to 44 with a score of 0 representing the highest financial toxicity and a score of 44 representing the lowest financial toxicity. In a population of both early and advanced stage disease, the mean COST score was 25.5 (SD 11.8) at baseline and there was no change in any of the financial burden measures at Assessment 2 (3 months after baseline). It is possible that no change was seen because this study did not follow patients long enough to see an increase in burden. Feasibility was

demonstrated with a 35% attrition rate. When accounting only for those that were alive to complete Assessment 2, attrition was 24%.

Acceptability of asking patient's questions regarding their financial situation were assessed in this pilot study with results summarized in Table 2. The majority of participants answered that they were either "somewhat" or "a lot" comfortable with answering questions about their financial situation and cost of treatment.

Table 2: Acceptability of answering financially related questions.

Acceptability question	Not at all (%)	A little bit (%)	Somewhat (%)	A lot (%)
How comfortable did you feel answering questions about your general financial situation?	6	12	29	53
How comfortable did you feel answering questions about how the cost of your treatment has affected your finances?	6	12	24	59
How comfortable do you feel discussing your finances and insurance with your physician?	12	24	35	29
How comfortable do you feel discussing your finances and insurance with a counselor?	0	24	24	53

Factors affecting employment have been evaluated by Tevaarwerk et al (26, 27, 44) (co-investigator on this proposal) using data from the ECOG-ACRIN Symptom Outcomes and Practice Patterns study in both the early and advanced stage. The analysis of those with non-metastatic disease found that 24% reported a change in employment. Participants with at least moderate symptom interference were more likely to report no longer working than their less effected counterparts (odds ratio (OR) = 8.0, 95 % CI, 4.2–15.4), as were minority participants compared with their non-Hispanic white counterparts (OR = 3.2, 95 % CI, 1.8–5.6) (26). We will build on this observational data to determine the association of perceived financial burden and employment factors in a longitudinal period over both active therapy and surveillance.

1.2.5 Feasibility and Motivation for Proposed Study through the NCI Community Oncology Research Program (NCORP)

The overarching goal of this study is to reliably measure the changes in financial burden and its interaction with access and utilization of financial services over a period of a cancer patient's treatment schedule. Once we gain a better understanding of the "life cycle" of financial burden and access/utilization of financial services, we can more effectively study the educational content, timing, and quality of cost discussions with patients that can lead to effective implementation studies. The NCORP is an ideal mechanism to accrue a diverse population of patients being treated at a community setting. Specifically, the minority/underserved sites within NCORP provide a

unique opportunity to include patients that may be at most risk of financial distress.

1.2.6 Description of the Patient Population and Assessment Time Points in Proposed Study

This study will focus on patients receiving curative-intent treatment for colon or rectal cancer specifically for several reasons. Colon and rectal cancer were chosen because these are common malignancies that are most frequently diagnosed in the curative-intent setting (45). Because these patients typically have longer survival than those with metastatic disease, they potentially have a longer period of time to be impacted by the costs of their cancer and changes in employment. Previous studies have largely focused only on patients receiving chemotherapy and/or with metastatic disease (18, 42, 46). The recently opened SWOG trial investigating financial burden (PI: Veena Shankaran) focuses on metastatic disease, and our proposed study of early stage disease will synergize with her work and will contain some common variables to allow for cross-study analysis.

There remain many unanswered questions about the financial burden that our study will address. We hypothesize that those who receive chemotherapy may have higher burden than those who do not, however this is currently unknown and will be prospectively studied in this study. We will stratify by both disease type and receipt of chemotherapy to allow for robust comparisons between these groups, which has not been previously reported in a prospective study. These comparisons may be important as we develop implementation studies and education to focus on malignancy types and treatment settings that demonstrate the highest level of burden.

We chose the time points, baseline at diagnosis, 3, 6, 12, and 24 months because they correlate with important landmarks in the treatment of colorectal cancer. At three months after diagnosis, most patients are in the initial phase of their therapy (either surgery for colon cancer or chemo-radiation for rectal). By 6 months, most patients are approaching the end of their planned therapy, and by 12 months most patients are typically done with therapy. The 24 month time point is an opportunity to collect data related to adherence to follow-up guidelines, more specifically either a colonoscopy, sigmoidoscopy, or barium enema. By analyzing data at each of these time points, there is hope to gain better understanding of the timing of changes in employment and financial burden to inform when in the cancer continuum would a future intervention be optimal.

2. Objectives

2.1 Primary Endpoints

2.1.1 Evaluate the change in level of self-reported financial burden from baseline (within 60 days of diagnosis) to 12 months after diagnosis of colon or rectal cancer treated with curative-intent.

2.2 Secondary Endpoints

2.2.1 Evaluate reported access and utilization of financial services (i.e. financial counselor, navigator, social workers) and its association to financial burden in the first 12 months after diagnosis of colon or rectal cancer treated with curative-intent.

2.2.2 Evaluate the change in level of self-reported financial burden and employment limitations from baseline (within 60 days of diagnosis) to 3, 6, and 12 months after diagnosis of colon or rectal cancer treated with curative-intent.

2.2.3 Evaluate long term outcomes at 24 months after diagnosis including financial burden, employment limitations and adherence to clinical follow-up guidelines.

2.2.4 Evaluate the change of quality-of-life outcome (QoL) from baseline to 12 months and its association with predictors.

2.2.5 Evaluate the change in level of self-reported financial burden from baseline to 12 months using alternate measures of financial burden (i.e. impact of cost questions and single item from EORTC Q30)

3. Selection of Sites

All interested NCORP sites will be invited to participate. There will be no specific exclusion criteria (i.e. minimum number of cases) because we would like to include a wide variety of different systems to better understand the variability in available financial resources and patient experiences. To ensure patient diversity in this study, all Minority/Underserved National Cancer Institute Community Oncology Research Programs (MU NCORP) sites will be specifically invited to participate.

4. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 4.1 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 4.1 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

4.1 Eligibility Criteria for Patient Participants

_____ 4.1.1 Age ≥ 18 years.

_____ 4.1.2 Patients must have a life expectancy of ≥ 24 months

_____ 4.1.3 ECOG PS 0-3

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_____ 4.1.4 Patients must have a newly diagnosed colon or rectal cancer or rectosigmoid junction (initial diagnosis, either a biopsy or curative surgery, whichever is most recent) within 60 days of registration and have either not yet received radiation or chemotherapy or are starting radiation or chemotherapy on the same day as registration.

_____ 4.1.5 Patients must have Stage I, II, or III disease at the time of enrollment and will be treated with curative-intent. This can be defined either clinically or pathologically if they have already undergone surgery. For staging of both colon and rectal cancer, the definition of stage I-III is based on the seventh edition (2010) or an updated version of the TNM staging system.

_____ 4.1.6 Patients are not eligible if they are already enrolled on a **treatment** clinical trial at the time of registration. They can remain on the study if they subsequently enroll on a treatment clinical trial during the study time period.

_____ 4.1.7 Patients are not eligible if they are to receive treatment at an outside facility throughout the duration of the trial.

_____ 4.1.8 Patients who choose to not receive radiation and/or chemotherapy after a curative-intent surgery are eligible to participate.

_____ 4.1.9 Patients with a history of previous malignancy (except non-melanoma skin or cervical in-situ cancer) treated (with either surgery, chemotherapy, and/or radiation) within the last 3 years are not eligible because it is possible that their employment and burden due to cancer care may be impacted by their previous malignancy and therefore add heterogeneity to the study.

_____ 4.1.10 Patients with two primary cancers that consist of colon, rectal or colorectal are not eligible.

_____ 4.1.11 Patients must be able to complete questionnaires in English.

_____ 4.1.12 Patients must sign and give written informed consent in accordance with institutional and federal guidelines

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. Add1 **5. Registration Procedures**

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>.

For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Rev. Add1 **IRB Approval:**

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number

- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the EAQ162CD protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **EAQ162CD**
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For EAQ162CD Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted.)

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Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:

   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

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Patient Enrollment

Patients must not start protocol treatment prior to registration.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check <https://ctepcore.nci.nih.gov/iam/>) and a 'Registrar' role on either the LPO or

participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.1 Protocol Number

5.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

5.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID
- Patient demographics
  - Sex
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

5.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 4.1.

5.5 Stratification Factors

- Rectal or colon cancer
- Chemotherapy or no chemotherapy

5.6 Additional Requirements

5.6.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

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5.6.2 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system and the EASEE-PRO system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam/>) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

6. Methodology Plan

6.1 This is a single arm, prospective, longitudinal cohort study.

6.2 Setting

This study will be conducted through NCORP community sites and minority/underserved sites across the NCI network. Enrollment will be limited to these sites in order to explore the financial experiences of those treated for cancer in the community setting. The infrastructure of resources (i.e. social workers, navigators, financial counselors) may be different at NCORP community sites when compared to large comprehensive cancer centers. Because most patients with these types of common malignancies are treated in the community setting, utilizing NCORP sites will provide a more representative picture of the financial experience of cancer patients in the United States.

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6.3 Screening, Consent and Patient Registration

Patients from a gastroenterology, surgical oncology, radiation oncology, or medical oncology clinic with newly diagnosed colon or rectal cancer are potential candidates for the study. Participants must enroll within 60 days of their diagnostic biopsy or curative-intent surgery and prior to any chemotherapy and/or radiation (participants may enroll on the first day of chemotherapy and/or radiation).

Institutions will identify a clinical research nurse (CRN) or clinical research associate that will be responsible for all aspects of this study. The designated CRN/CRA from each institution will be available to work with physicians during the clinical session to identify and recruit patients. The CRN/CRA or other members of the research team will discuss the details of this study with appropriate care and thoughtfulness as patients have recently received the diagnosis of a cancer. Because of the sensitive nature of a new diagnosis of cancer as well as financial questions, a script with talking points will be provided that address common concerns. Talking points will include: ensured privacy of financial information and sensitivity to new diagnosis. If the patient agrees, they will be screened for study eligibility at that time or at a subsequent visit as deemed appropriate by study personnel. This person will also be available to answer any questions regarding the study and obtain written informed consent.

6.4 Data Collection

Patients will be followed for the duration of the study and all questionnaires will be administered as described in Section 8.

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6.4.1 Patients will be assessed at baseline (following consent and registration), and at subsequent time points (3, 6, 12 and 24 months) following registration. See Section 7 for a description of the questionnaires administered at each time point). Questionnaires are self-administered and require approximately 45-60 minutes to complete at each time point.

6.4.2 Patients will receive survey instrument at 5 time points over a 24-month period of time. A0 (baseline) assessment will occur after registration and within 60 days after initial diagnosis. A1 will be completed at 3 months after baseline (+/- 4 weeks), A2 at 6 months

after baseline (+/- 4 weeks), A3 12 months after baseline (+/- 4 weeks), and A4 24 months after baseline (+/- 4 weeks).

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6.4.3 Participants will be asked at the time of registration if they would like to complete the surveys online or on paper. The time points were chosen with 4-week flexibility as they typically correlate with scheduled clinic visits.

6.4.4 It is acceptable to have a caregiver assist the participant with completing the questionnaires.

6.4.5 Criteria for Removal of Patient from Protocol Participation

6.4.5.1 Patient completes 24 months of study participation.

6.4.5.2 The patient may withdraw from the study at any time for any reason. Research staff should only submit the End of Study Clinical Form if the patient refuses all future direct and indirect follow-up on the study.

6.4.5.3 If a patient cannot or refuses to complete the patient questionnaires for a study time point, this is not a criterion for discontinuation of protocol participation. Submit the Baseline Clinical Form and Follow-up Clinical Form and document the reason the questionnaires were not completed at the time point and administer questionnaires to the patient at the next study time point.

6.4.6 Follow-up Period

There is no further follow up required once the patient completes 24 months of study participation.

7. Questionnaires

7.1 Financial Measures

7.1.1 Financial burden

7.1.1.1 **COST-** This instrument assesses the degree of financial distress experienced by cancer patients and will be used at each time point. The Comprehensive Score for Financial Toxicity (COST) measure is the primary outcome and has undergone validation, and was created via a robust development process (42). The COST is an 11-item PRO measure of financial toxicity that uses a 7-day time window and a 5-point Likert response scale ranging from 0 (“not at all”) to 4 (“a lot”). Higher COST scores (range: 0-44) represent better Financial Well-Being. Negatively valenced items are reverse coded so that higher scores indicate greater financial wellbeing, which is assessed as a uni-dimensional construct. Development of the COST included literature review, iterative qualitative interviews with patients and providers (informing item generation and selection), selection of candidate items based on factor analyses and other psychometric properties (e.g., inter-item correlation, IIC). The COST has demonstrated excellent internal consistency (Cronbach alpha coefficient = 0.9), item non-redundancy (mean IIC = 0.47, range, 0.22-0.69), and good construct validity (mean item-total correlation = 0.71, range, 0.62-0.79) (Appendix B). Further, a financial toxicity grading scale has been developed for the COST based on clinically meaningful changes in health-related quality of life as measured by the FACT-G measure (17). Based on previous cross-sectional studies (36, 42, 47), we assume that the baseline COST score follows a normal distribution with the mean 25 and standard deviation 12.

7.1.1.2 **Impact of Cost-** Patients will be asked questions about their insurance status at each assessment. They will be asked about insurance denials in addition to specific out of pocket costs related premiums, deductibles/co-pays for doctor visits, prescription and over the counter drug costs, and other services related to their cancer treatment at each time point. We will assess various lifestyle coping strategies to help pay for cancer care such as asking about cutting back on leisure activities, reducing spending on basic needs (food or utilities), spending savings, selling possessions, or borrowing money (18). We will ask questions related to communication preferences with their health care team about the cost of cancer care.

7.1.2 **Access and Utilization of Financial Resources-** The Consumer Based Cancer Care Value Index (CCVI) was developed in collaboration with The Patient Advocate Foundation and measures

the aspects of care patients value most and the degree to which these aspects of care were experienced during their treatment. The CCCVI is a patient-centric, value-based tool that reflects the patients' vision and experience in defining the value of the care they seek. We modified items from this measure that reflect access and utilization of financial resources and experience of paying for their cancer care. This is an 8-item measure.

7.1.3 **Employment**- We will use items from both the Work Productivity and Activity Impairment Questionnaire (WPAI:SHP) (49), Work Ability Index (WAI) (50), and Work after cancer survey (WACS) (44). The WPAI:SHP evaluates effects of disease on employment status, hours missed due to health problems, hours worked, and the degree to which health problems affect productivity and regular activity. This scale has been utilized previously in breast cancer patients (51). The Work Ability Index (WAI) is an instrument used in occupational health care and it reveals how well a worker is able to perform his or her work. The WAI and all its items reliably predicted work disability, retirement and mortality in a Finnish population (50). The measure has been used in patients with a variety of cancers (52-54), including early stage colon and rectal cancer (55). We will use items from the WAI that represent data not captured by other surveys (items can stand alone). The item regarding employment benefits (i.e. disability, sick leave) is from the WACS, a survey utilized in patients (including colon cancer) receiving curative intent therapy (44). The Baseline Employment Questionnaire will include 18 items and Follow up will include 14 items.

7.1.4 **Quality of Life (FACT-G7) -** The Functional Assessment of Cancer Therapy- General (FACT-G) is a validated measure that incorporates many prevalent symptoms and functional domains (56). This measure has been further developed into a rapid version (FACT-G7) that includes 7 items which we will utilize to reduce survey burden (57). Quality of life is an important domain to include in relation to financial burden. Fenn et al. reported data from the National Health Interview Survey where increased financial burden was the strongest independent predictor of poor quality of life among cancer survivors (68).

7.1.5 **Self-Efficacy-** The 6-item Stanford Self-Efficacy for Managing Chronic Disease measures self-efficacy of patients with chronic illnesses. The instrument consists of several domains including symptom control, role function, emotional functioning, and communication with physicians (66). Self-efficacy measure may be an important predictor or moderator of financial well-being. In previous studies, self-efficacy was found to play a moderating role for the relationship between depression and distress in cancer patient. We hypothesize that patients with high self-efficacy may be a predictor of improved financial well-being (67).

7.1.6 **Baseline Questionnaire and Sociodemographic Follow up-** Patients will be asked information about their sociodemographics (i.e. sex, ethnicity, marital status, income, comorbities etc.) at baseline. At

both the baseline and follow up, we will ask participants details about their insurance plan and coverage. Because we hypothesize that the site will collect more accurate insurance information when compared to patient knowledge of insurance information, when there is a discrepancy, we will use the response from the site in analysis.

7.1.7 Study Measures and Objectives Table

Patient Questionnaires	Objectives
Baseline Questionnaire	Sociodemographics, comorbities, insurance information. Used as predictor variables for all objectives
Sociodemographic Follow-up	Sociodemographics and insurance information. Used as predictor variables for all objectives
Baseline Employment	Secondary Endpoint (2.2.2)
Follow-up Employment	Secondary Endpoint (2.2.2). Employment asked at baseline, 6, 12, and 24 months as these are time points in cancer continuum that we hypothesize change and we want to understand longitudinal change. We omitted 3 month due to patient burden. We include a 24 month time point to understand long term survivorship employment limitations.
FACT-G7	Secondary Endpoint (2.2.4). QOL asked at baseline, 6, 12, and 24 months as these are time points in cancer continuum that we hypothesize change. We omitted 3 month due to patient burden. We include a 24 month time point to understand long term survivorship QOL
Self-Efficacy	This will be used as predictor variable for all objectives. To limit burden we omitted 3 and 12 month
COST	Primary Endpoint (2.1.1)- needed at all time points to understand changes at diagnosis (baseline), beginning of tx (3), end of therapy (6), short term survivorship(12), and long term survivorship(24).
Impact of Cost	Secondary Endpoint (2.2.5)- needed at all time points to understand changes at diagnosis (baseline), beginning of tx (3), end of therapy (6), short term survivorship(12), and long term survivorship(24).
Access and Utilization of Financial Resources	Secondary Endpoint (2.2.1)- needed at all time points to understand changes at diagnosis (baseline), beginning of tx (3), end of therapy (6), short term survivorship(12), and long term survivorship(24).
Acceptability	Because of sensitive nature of questions will include these questions to assess acceptability at the 12 month time point.
Site Completed Forms	
Site Survey	Assesses available resources for financial assistance. Will be used as predictor variable
Baseline Clinical Form	Clinical information collected at all time points to correlate with primary endpoint of financial burden
Follow-up Clinical Form	Clinical information collected at all time points to correlate with primary endpoint of financial burden
24-month Follow-up Clinical Form	Clinical information and adherence variables collected for Secondary Endpoint (2.2.3)
End of Study Clinical Form	Completed if the patient has completed 24 months of study participation and refuses all future direct and indirect follow-up on the study.

8. Patient Reported Outcomes (PRO) and Quality of Life (QOL) Administration

Rev. Add1

8.1 Data Collection Approach

We will use a combination of EASEE-PRO and mailed questionnaires for this study. A proxy or family member can complete the questionnaires on behalf of the patient as long as they can speak English. The questionnaires are only available in English. See Appendix III for a Participant Retention-Focused Communication Calendar.

8.2 Questionnaire Administration Process

Rev. Add1

8.2.1 Participant Contact Information Form

At the time of recruitment into this study, patients will be asked to complete the Participant Contact Information Form. This form collects information used to maintain contact with the participant over the course of the study, including their name, home address, phone number, and e-mail (if available). Additionally, information for one contact person (the participant's spouse, next of kin or close family member), and a primary (or other) physician is collected to assist with requests for patient location (if necessary).

This form is retained in the study participant's chart at the site and is not submitted to the ECOG-ACRIN master database. The completed form is faxed to the central ECOG-ACRIN Outcomes and Economic Assessment Unit (OEAU) located at Brown University so that the participants can be contacted for the Patient Reported Outcomes (PRO) portion of the study. The contact information is stored in a dedicated SQL database and IS NOT linked to the master ECOG-ACRIN database. The OEAU RA will not have access to the main ECOG-ACRIN database that contains screening results.

On the Participant Contact Information Form, patients will be asked to express a preference for on-line or paper administration of patient reported outcome (PRO) forms. Patients may choose to complete questionnaires using a web-based application (see Section 8.3 for a description) or by mail. Administration of questionnaires, both web-based and paper will be coordinated by the OEAU. Administration of the questionnaires will be triggered based on completion of study milestones marked by submission of forms in RAVE.

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8.2.2 Web-based questionnaire completion

Patients will be prompted to complete web-based forms via an email prompt. These emails will include a link to the web site for questionnaire completion. Questionnaires will be completed on line using a unique patient account. The web site will reference a study-specific toll-free phone number that patients can use to reach the OEAU staff should they have questions or need assistance. All data will be stored on a secure server. Patients who do not complete the web questionnaires within 3 working days of the initial request e-mail will receive up to 3 additional e-mail reminders, each 3 days apart. These reminder e-mails, like the initial e-mail, will provide a link to the

current surveys, ask the participant to confirm that they have been able to access the web site, and provide both the e-mail address and the toll free help number for support.

If patients still have not responded within 12 days of the original e-mail, the OEAU Research Associate may attempt to telephone the patient and administer the questionnaire over the telephone. If questionnaires are telephone-administered, they will be marked as such in the database. Up to five attempts will be made to contact the participant over the telephone. All surveys, while desired within 3 days of the event, will remain available for participants until either the surveys are completed or they are off-study. Since the completion date is recorded for all surveys, the study team will be able to make relevant determinations for inclusion of this data in specific analyses. However, after telephone follow-up, no additional or extraordinary means will be employed to collect overdue/missing questionnaires

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8.2.3 Mailed questionnaire completion

Mailed questionnaire packets will include a letter introducing the study and include a study-specific toll-free phone number that patients can use to reach the OEAU staff should they have questions or need assistance, questionnaires, and pre-addressed, stamped envelopes for return mailing to the OEAU. If patients do not complete the paper questionnaire within 10 working days of the date of the mailing, the OEAU RA will attempt to telephone the patient. If the patient has not received the paper questionnaires, additional questionnaires will be sent after confirming the correct mailing address. If the questionnaire is available to the patient, the OEAU RA will urge the study patient to complete and return the questionnaire. If the patient has still not responded within 20 working days of the original mailing, the OEAU will attempt to telephone the patient and telephone administer the questionnaire. Up to five attempts will be made to contact the participant over the telephone. If questionnaires are telephone-administered, they will be marked as such in the data base.

8.2.4 Evaluation of patient survey burden

We will provide the NCI an interim report providing the range and median time to completion of the totality of the baseline questionnaires. This will be reported to the NCI within 90 days of the first 50 patients completing this questionnaire.

8.3 ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) System:

Access to the study in EASEE-PRO is granted to all participants registered to the study through the OPEN registration system with a valid participant email address. Upon registration, an account verification email will be sent to the user with a link to activate their account. The user will be required to enter some verification information (e.g. DOB) in order to activate their EASEE-PRO account. Additionally, site persons with the appropriate roles in RSS will be granted access after IRB approval is obtained. In some studies, this access may allow

CRAs to assist the participant accessing baseline surveys, educational materials, or other EASEE-PRO materials.

EASEE-PRO Participant Access:

To access EASEE-PRO, the participant must have an active EASEE-PRO user account. Upon registration to the study in OPEN, an account activation email will be sent to the address entered for the participant in OPEN eligibility checklist. This email address must be a valid email address for the participant. (If the patient email address were entered incorrectly in OPEN, the CRA must contact the OEAU (pro-help@stat.brown.edu to manually correct the error.) To activate their account, users must click the link in the email and verify their account before they can login and complete surveys or view web education materials. Once the account is activated, participants may login to the EASEE-PRO system through the OEAU-PRIDE web portal (https://pride.stat.brown.edu/Participant-Login). Upon login, users will be presented with a list of available surveys and materials they can view.

EASEE-PRO CRA Access:

To access EASEE-PRO, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of ECOG-ACRIN must have the mapped ECOG-ACRIN roles or explicit Rave roles (Rave CRA) in RSS at the enrolling site. Site users that are not members of ECOG-ACRIN must have the Rave roles on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website. To login, CRAs will use their CTSU(IAM) credentials on the OEAU-PRIDE web portal (https://pride.stat.brown.edu/CRA-Login) using the familiar IAM interface. No e-learnings are required for use of this site.

The ECOG-ACRIN Outcomes and Economics Assessment Unit can be contacted for Patient Reported Outcome Questions via email at pro-help@stat.brown.edu. An EASEE-PRO instructional guide for both sites and patients can be found on both the E-A and CTSU websites.

Please see below for additional details on the EASEE-PRO system.

1) A secure environment for control of user records, information, and transactions (SECURIT): Provides a secure – limited access point for entering data into the restricted secure PII Database, for management of user data, creating user accounts, and reporting. The SECURIT web management interface requires the secure hypertext transfer protocol (HTTPS) to ensure encryption of transmitted data.
    a) PII database: is a dedicated secure limited access database, used to store protected PII.
        i) Secure: All communications to the PII database through SECURIT are encrypted. The database resides behind a firewall and cannot be reach from outside the OEAU.
        ii) Limited access: this database is restricted not only by username and password but is also restricted to specified internal OEAU computers by IP address, so that only authorized users logging in at the OEAU

from pre-specified computers may access/enter PII. At no time is outside access allowed to this database.

iii) Protected restricted PII (e.g. SSN) are encrypted at the time of data entry and double data entered for verification. All users regardless of their security level are blinded to this protected data, and it cannot be decrypted without the encryption key, housed in a safe, in a location separate from the OEAU. This type of data is generally collected for long term follow-up where it may be needed to be decrypted for select patients in order to search registries like the national death index to determine survival status of lost participants. In these instances, with appropriate approvals, the Database Administrator will decrypt this data in accordance with the approved retrieval specification.

b) User records: This functionality allows OEAU personnel, using specific computers within the OEAU, to create user records, enter user information into the PII database, and establish user web accounts in the separate user database. Allows the management of users and their data, including the ability to update a participant's preferred contact method, address, and participation status (e.g. no longer wishes to be contacted with respect to the PRO component of the study).

c) Information: This functionality allows the OEAU to record all participant contact, document any changes to the participant, and make any important notes related to the participant.

d) Transactions: SECURIT provides a reporting and monitoring interface to the PRO database, which is used to store non-PII patient reported survey responses.

i) Allows OEAU to monitor per patient form completion status using the tracking management facility. This facility reports on what data is currently expected from participants, CRAs, and the OEAU interviewers.

ii) Aggregate reporting: this series of reports allows the OEAU to monitor the distribution of patients over data completion methods and form completion methods (both overall and by site).

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2) Database utility and control environment (PRO-DUCE): This utility interfaces with the main clinical database containing CRF/trigger data (Medidata RAVE), monitors the clinical database for events (eg., participant registrations, scheduled procedures, and other triggers) and establishes event scheduling. The system sets up e-mail reminders to CRAs, participants and OEAU personnel to ensure timely completion of surveys.

3) Web entry systems (PROWESs): a Web site where participants complete online surveys

a) PROWESs provides a front facing web portal for participants to complete questionnaires and have those results stored in the PRO database.

b) Secure site using HTTPS and requiring a username and password login.

c) On login, user is presented with brief instructions; including approx. time for completion, number of questions to be completed in this session, any important information regarding this survey (including help and contact information)

d) PROWESs is a one-way interface, data cannot be returned from the PRO-DB to the user.

4) Valet Interface and data entry system (PROVIDES).
   a) The PROVIDES system is a web interface that allows site CRAs to act as a valet and enter a participant's responses to a survey into the PRO database should the survey be completed on paper. This allows Site CRAs to enter forms completed by the patient on site.
   b) Secure site using HTTPS and requiring a username and password login.
   c) Which forms can be entered is restricted by username, site affiliation, and role, thus Sites RAs can only enter surveys predesignated as on-site data collection surveys and only for their own patients.
   d) On login, user is presented with brief instructions; is requested to select the protocol, case number, timepoint and verify the case Id by providing the participant birthdate.

   PROVIDES is a one-way interface, data cannot be returned from the PRO-DB to the user.

9. Site completed forms and administration

Rev. Add1 9.1 Data Collection Approach

The principal investigators of the participating NCORP sites with CCDR components or subcomponents will be instructed to identify points-of-contact (CCDR leaders) who will be responsible for completing the site completed forms. Each participating NCORP site will complete forms including one Site Survey, Baseline Clinical form, Follow-up form at 3, 6, 12, and 24 months, and End of Study form. One Site Survey is filled out per site and should be completed within 30 days of the first participant enrollment. The Baseline, Follow-up, and End of Study form are participant-specific and contain data collection from the medical records. The designated site research coordinator will be responsible for data abstraction. Specifics about where in the medical record to locate each variable will be generally described within the form. Further questions and trouble-shooting for finding these variables will occur in personal communication with the study team.

Rev. Add1 9.2 Questionnaire Administration Process

Rev. Add1 9.2.1 Site Survey

At the time the NCORP site opens the study, the CCDR leader will complete the “Site Survey” which asks analytic numbers for colorectal cancer at their site, resources available at their institution (i.e. social worker, financial counselor, navigator), and institutional practice regarding referrals for financial concerns. Details of where the data for of these variables can be found are included in the form. Each site with an individual CTEP ID is required to fill out one “Site Survey” within 30 days of the first participant enrollment.

Rev. Add1 9.2.2 Baseline Clinical Form

This form should be completed within 14 days of registration. For participants who choose paper surveys, the date the survey was completed (date signed) must be within 14 days of starting radiation or chemotherapy. It contains questions related to type of malignancy (colon versus rectum) and if chemotherapy is planned. These two variables (malignancy type and chemotherapy use) will be used for stratification. In the case that it is uncertain if chemotherapy is planned, the site research coordinator will choose the option “uncertain”, and this question will again be asked in the 3 month follow-up form. This form will also ask about the insurance status of participant. Because we hypothesize that the site will collect more accurate insurance information when compared to patient knowledge of insurance information, when there is a discrepancy, we will use the response from the site in analysis.

9.2.3 Follow-up Clinical Form

This form will be completed by the research coordinator at 3, 6, 12, and 24 month time points. It contains questions regarding vital status (dead/alive), chemotherapy use, performance status, stage, status of

treatment, if there was any insurance changes, and if the participant required help from a caregiver from their knowledge.

9.2.4 24 Month Clinical Form

This form is completed once the participant has completed 24 months of study. This form contains questions on vital status, reasons for being off study, and questions regarding adherence to guidelines.

9.2.4.1 Adherence to guidelines questions

There are questions contained within the "24 Month Assessment" that ask if the patient has received a colonoscopy, sigmoidosocpy, and barium enema since completing therapy (and how many months this test was performed after surgery). These adherence questions also include how often the patient has been examined by their oncologist and had a serum CEA performed. We will define adherent versus non-adherent according to below questions and responses.

Considered ADHERENT if they answer the following (must have ALL) in bold.

Has the patient received a colonoscopy, sigmoidoscopy, or barium enema at some point since their initial surgery (if applicable)?

- Yes
- If yes, how many months since surgery was it completed
- No
- Unsure

How many times has the patient been seen by their oncologist for a history/physical since ending treatment?

- The patient has not been seen by their oncologist since ending treatment
- Once
- Twice
- More than twice
- I don't know the reason

How many times has the patient had a carcinoembryonic (CEA) serum checked since ending treatment?

- The patient has not had a CEA checked since ending treatment
- Once
- Twice
- More than twice
- I don't know

9.2.5 End of Study Clinical Form

The patient may withdraw from the study at any time for any reason. Research staff should only submit the End of Study form if the patient refuses all future direct and indirect follow-up on the study.

10. Study Calendar

See below for a schedule of study assessments

	Baseline[1]	3 month	6 month	12 month	24 month
Patient questionnaires (min/max # questions based on skip pattern)					
Baseline Questionnaire (32/44)	X				
Sociodemographic Follow-up (3)		X	X	X	X
Baseline Employment (18)	X				
Follow-up Employment (14)			X	X	X
FACT-G7 (7)	X		X	X	X
Self-Efficacy (6)	X		X	X	
COST (11)	X	X	X	X	X
Impact of Cost (31/41)	X	X	X	X	X
Access and Utilization of Financial Resources (8)	X	X	X	X	X
Acceptability (2)				X	
Minimum/Maximum number of items at each time point	113/144	56/66	83/93	85/95	77/87
Site Completed Forms					
Site Survey[2]	X				
Baseline Clinical Form	X				
Follow-up Clinical Form		X	X	X	X
24-month Follow-up Clinical Form					X
End of Study Clinical Form					X

Rev. Add1 [1] Baseline study assessments must be completed within 14 days of registration. For participants who choose paper surveys, the date the survey was completed (date signed) must be within 14 days of starting radiation or chemotherapy.

[2] Each site with an individual CTEP ID is required to fill out one Site Survey within 30 days of the first participant enrollment.

11. Statistical Considerations

11.1 Sex and Ethnicity

Based on previous CDC data of 2009-2013 Colon and Rectum by Cancer Type and Race (age-adjusted) (66) the anticipated accrual in subgroups defined by sex and race is:

Ethnic Category	**Sex**		
	Females	**Males**	**Total**
Hispanic or Latino	20	23	43
Not Hispanic or Latino	252	268	520
Ethnic Category: Total of all subjects	**272**	**291**	**563**

Racial Category			
American Indian or Alaskan Native	2	2	4
Asian	9	10	19
Black or African American	35	34	69
Native Hawaiian or other Pacific Islander	0	0	0
White	223	242	465
More than one race	3	3	6
Racial Category: Total of all subjects	**272**	**291**	**563**

11.2 Study Design and Objectives

This is a single-armed longitudinal study and the measurements of financial burden (COST score) will be collected at 5 time points over a 24-month follow-up time. The primary endpoint of this study is the change of COST score from baseline to the 12-month follow-up (FU) measurements.

11.3 Sample Size Considerations and Monitoring Plan

11.3.1 Stratification to be considered

The type of disease (colon versus rectal cancer) and the chemotherapy status (getting chemotherapy versus not getting chemotherapy) will serve as the stratification factors. Chemotherapy for these strata includes all intravenous and oral cytotoxic chemotherapy. For those with rectal cancer, those receiving chemotherapy combined with radiation will be considered in the “chemotherapy” strata. For the chemotherapy stratification, some patients may not know their chemotherapy plan at the time of registration. For this group of patients, the stratification will be implemented at the time of the 3-month follow-up. In addition, based on the stage distribution (Table 3 below), stratifying by receiving chemotherapy or not shouldn’t be a bottleneck on patient’s enrollment.

As illustrated in Table 3, it's expected the patients with colon and rectal cancers will be enrolled into the study at a ratio of 2:1 and the group of patients receiving chemotherapy versus patients not receiving chemotherapy will roughly equal to each other in the enrollment. Therefore, the accrual thresholds would be set up according to these ratios (Table 3), after the overall sample size is determined in the next section.

NOTE: Based on the actual enrollment as of 4/1/2019, the ratio of rectal cancer patients receiving chemotherapy versus not receiving chemotherapy is around 1:4. Thus, we accordingly changed the thresholds of these two strata.

Table 3: Stage distribution of colon and rectal cancer from SEER data (82).

Disease Type	Stage	Proportion*	Receiving Chemotherapy	Accrual Thresholds
Colon cancer (70%)	1 and 2	38%	Likely not	180-190
	3	37%	Getting Chemo	180-190
	4	21%	Excluding from study	None
Rectal cancer (30%)	1 and 2	44%	Likely not	36-38
	3	33%	Getting Chemo	144-152
	4	18%	Excluding from study	None

* The relative proportion of new cancer cases in US, 2016 (www.cancer.org).

11.3.2 Sample Size

Based on the data from previous cross-sectional studies (42, 50), we assume that the baseline COST score follows a normal distribution with the mean 25 and the standard deviation 12 and the 12-month FU score follows a normal distribution with the mean 22.5 and the standard deviation 12. Thus, the effect size of change is assumed to be 10%. The correlation between the baseline and the 12-month FU scores is assumed to be 0.2. Based on these assumptions, a sample size of 394 cancer patients will be needed to achieve a 90% power to detect the 2.5 difference (i.e., 10% change) at the 0.05 significance level using a two-sided Wilcoxon Signed-rank Test. These results are based on 20,000 Monte Carlo samples for the sample distributions under the null and the alternative hypothesis. The sample size will be 296 if the power remains at 0.90 and the correlation is assumed to be 0.4. A pilot study assessing financial burden among patients with advanced cancers had a 24% attrition rate between baseline and 12 month assessments, excluding those who died before the 12 month time point (36). An ongoing study on employment among cancer patients across the stage spectrum had a 30% attrition rate at the 12-month follow-up (Tevaarwerk, personal communication). Therefore, we assume a 30% attrition rate at the 12-month follow-up and expect to enroll 563 patients into the study. *Note: The imputation was based*

on Monte Carlo samples in simulations, which caused slight fluctuations in the sample size. However, with 20,000 simulations, the fluctuation rate is only about 1%.

With these sample sizes, we will have the power of 1.0 to detect a difference of 5 (i.e., 20% change) from the baseline to the 24-month FU score, while the latter is assumed to follow a normal distribution with mean 20 and standard deviation 12. The above computations were done using PASS 14 (83).

Table 4: Power Analysis. Power: 0.80 and 0.90. Correlation: 0.20 and 0.40.

Power	N	H0 Diff0	H1 Diff1	Corr R	Target Alpha	Actual Alpha	Beta
0.797 (0.006) [0.791	292 0.802]	0.0	2.5	0.200	0.050	0.050 (0.003) [0.047	0.203 0.053]
0.803 (0.006) [0.798	218 0.809]	0.0	2.5	0.400	0.050	0.049 (0.003) [0.046	0.197 0.052]
0.900 (0.004) [0.896	**394 0.904]**	**0.0**	**2.5**	**0.200**	**0.050**	**0.051 (0.003) [0.048**	**0.100 0.054]**
0.904 (0.004) [0.900	296 0.908]	0.0	2.5	0.400	0.050	0.051 (0.003) [0.048	0.096 0.054]

11.3.3 Accrual and Attrition Monitoring

It is expected that the monthly accrual for this trial will be approximately 15 to 16 cases, excluding the first 6 months as institutions obtain IRB approval. Therefore, we anticipate that 563 participants will be enrolled in about 3 to 3.5 years.

After assessing the preliminary data in Tevaarwerk's employment study (still ongoing), we didn't observe an obvious pattern of the dropout that associates with cancer type, stage, or employment status. Thus, we will not implement the adaptive design in our study. However, we will closely monitor the patient's attrition and then determine if the attrition rate will be significantly different among various groups. Accordingly, the protocol may be amended and the sample size may need to be adjusted to oversample patients for the groups with high attrition rates.

Rev. Add1 11.3.4 Recruitment and Retention Plan

We will learn from the experiences of the ongoing SWOG 1417CD trial investigating financial burden in metastatic disease.

In addition to site visits and available phone and email support, as outlined above, the EASEE-PRO system will send email notifications and up to 3 follow-up reminders to notify web-based participants to complete surveys. Mail-based participants will receive surveys in the US mail as well as follow-ups for delinquent surveys. With both types of delivery, excessively delinquent participants may receive a phone call from the OEUA to determine if there is a problem completing the surveys. In the event that participants are unreachable by the OEAU,

the OEAU will coordinate with the site CRA in an effort to contact and retain participants.

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11.3.5 Interim Analysis

To assess the survey burden, we will provide the NCI an interim report to analyze the range and median time to completion for the totality of the baseline questionnaires. Survey completion time will be determined from the meta-data collected form patients who opt to complete the survey online. This will be reported to the NCI within 90 days of the first 50 patients completing the questionnaire.

11.4 Statistical Analysis Plan

11.4.1 Primary Objective

The primary aim is to evaluate the change in the level of self-reported financial burden from baseline (within 60 days of diagnosis) to 12 months after diagnosis of colon or rectal cancer treated with curative-intent.

We will calculate the difference of COST measurements from baseline to 12-month FU for the completers who provide data at both time points, and use the paired t-test to assess if the mean difference is significantly different from zero. In case the data are not normally distributed, nonparametric methods (e.g., Wilcoxon signed-rank test) will be used instead to assess the difference. For the participants with missing measurements at one time point, we will implement the methods as described in Section 11.4.3 to handle the missing values. The two results will be compared as a sensitivity analysis.

In addition, linear regression models with the change of COST from baseline to 12-month FU as the response variable will be fit to investigate the impact of other factors, including demographics variables (e.g., age, sex, marital status), clinical variables (e.g., stage of disease, malignancy type, chemotherapy status), baseline questionnaire variables (e.g., self-efficacy,). The three-level treatment status (IV chemotherapy, chemotherapy without IV, and no chemotherapy) will also be evaluated as a predictor. The impact of system level variables (including being designated a minority/underserved site or not, availability of financial resources for patients) will be examined in the regressions as well. Since pregnant women may have higher health-care related costs, the response will be compared between pregnant women and the others; if significant, the subset analysis may be performed in this population.

11.4.2 Secondary Objectives

11.4.2.1 Evaluate reported access and utilization of financial services (i.e. financial counselor, navigator, social workers) and its association to financial burden in the first 12 months after diagnosis of colon or rectal cancer treated with curative-intent.

The 8-question CCVI measure as described in Section 7.1.2 will be analyzed to evaluate the change from

baseline to 12-month FU. For the continuous item variable, we will conduct the paired t test to examine the difference if the distribution is normal. If not normally distributed, Wilcoxon signed rank test will be used. For the categorical item variable, the paired proportion test (e.g., McNemar test) will be used instead. The association between CCVI and COST measures will be evaluated using the Pearson or Spearman correlation coefficient.

Because we are aware that there is not a "gold standard" financial burden measure, we will include two other measures that have been used previously; (1) a series of items (Impact of cost questions) that are being used in the ongoing S1417CD; and (2) a single item in EORTC Q30 as our secondary endpoints. We acknowledge potential discrepancy between measures. Therefore we will conduct sensitivity analyses around the primary endpoint using the other measures and explore potential sources of discrepant outcomes.

11.4.2.2 Evaluate the change in level of self-reported financial burden and employment limitations from baseline (within 60 days of diagnosis) to 3, 6, and 12 months after diagnosis of colon or rectal cancer treated with curative-intent.

The measurements of employment limitation by WPAI: SHP, WAI and WACS as described in Section 7.1.3 will be analyzed as continuous variables to evaluate the change from baseline to 3, 6, and 12-month FU. If the distributions are normal, we will conduct the paired t tests to examine the differences of these variables. If not normally distributed, Wilcoxon signed rank tests will be used. The association with COST measures will be evaluated using the Pearson or Spearman correlation coefficients.

11.4.2.3 Evaluate long-term outcomes at 24 months after diagnosis including financial burden, employment limitations and adherence to clinical follow-up guidelines.

To evaluate the change of financial burden from baseline to the other time points (i.e., 3-month, 6-month, and 24-month), the similar approaches described for the primary objective's assessment will be implemented. In addition, longitudinal data analysis will be conducted to estimate the measurements' trajectory across all five times points. Specially, linear (or generalized linear) mixed model will be fit to study the change in the mean response over time and also the effects of cancer type, stage, treatment plan and demographics, etc. on financial burden. In case the changes in the mean response over time are not linear, the quadratic trends or non-linear trends via spline may be considered in the modeling (61). Interactions will be

evaluated as well. The above analyses may be repeated to explore the categorized COST measures (63, 64).

Logistic regressions will be fit to study whether or not the level of financial burden will impact the patient's adherence to clinical follow-up guidelines, which is defined as follows: "adherent" is defined as completing all of the follow up guidelines within the 24 month study period and includes an endoscopic evaluation of their colon or barium enema, routine history and physical at least twice, and serum carcinoembryonic (CEA) level checked at least twice. The details of adherence questions can be found in Section 9.2.4.1.

11.4.2.4 Evaluate the change of quality-of-life outcome (QoL) from baseline to 12 months and its association with predictors

FACT-G7, as described in Section 7.1.4, will be analyzed to evaluate the change of QoL from baseline to 12 months. The sum of the 7-item scores will be modeled as a continuous variable in the linear regressions (57). The predictors will include demographics (age, sex, marital status), clinical variables (stage of disease, malignancy type, chemotherapy status), and financial variables (COST score). Similar to the primary aim assessment, the impact of the baseline questionnaire variables (e.g., self-efficacy) and the system level variables (including being designated a minority/underserved site or not, availability of financial resources for patients) will be examined in the models as well. FACT-G7 at 6 months will be included as an adjustment covariate. Similar analysis will be conducted to evaluate the change of FACT-G7 from baseline to 24 months as well.

11.4.2.5 Evaluate the change in level of self-reported financial burden from baseline to 12 months utilizing alternate measures of financial burden (i.e. impact of cost questions and single item from EORTC Q30)

Because there is not a "gold standard" financial burden measure, we will include two other measures that have been used previously; (1) a series of items (Impact of cost questions) that are being used in the ongoing S1417CD; and (2) a single item in EORTC Q30 assessing the impact of medical treatment on finances. We acknowledge potential discrepancy between measures. Therefore we will conduct sensitivity analyses around the primary endpoint using the other measures and explore potential sources of discrepant outcomes.

Similar approaches as used in the primary aim will be conducted to evaluate the changes of these two measures from baseline to 12 months.

11.4.3 Handling Missing Data

As stated in the Section 11.3.3, we will closely monitor the patient attrition and determine whether the dropout is informative or not. If the missing is random, we may implement the method like multiple imputation to impute the missing values. In case the missing is not random (e.g., patients who are lost to follow up may experience more financial burden), we will implement various methods for the adjustment in our analysis, e.g., Bayesian modeling with informative priors. Analysis under different scenarios will be conducted to explore sensitivity to different missing data assumptions (65).

Since the COST is an 11-item PRO measure of financial toxicity, it is likely that partial data might be collected from some patients. According to the FACIT guidelines (www.facit.org), the patients who answer less than 6 out of 11 items will be excluded from the analysis. For patients who answer more than 6 but less than 11 items, the normalized score will be recorded according to the following formulae:

(sum of individual item scores)* 11 / the number of items answered.

12. Electronic Data Capture

Please refer to the EAQ162CDForms Completion Guidelines for the forms submission schedule. Data collection will be performed in Medidata Rave and EASEE-PRO.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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Longitudinal Assessment of Financial Burden in Patients with Colon or Rectal Cancer Treated with Curative Intent

Appendix I

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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Appendix II

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Longitudinal Assessment of Financial Burden in Patients with Colon or Rectal Cancer Treated with Curative Intent

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Appendix III

Participant Retention-Focused Communication Calendar

Based on the participants' preferred method of communication, they will receive either an email or phone call.

For those whose preferred method of communication is e-mail.

Assessment 0, 1, 2, 3, 4	Prompted when assessment due	If the participant wants to do the assessments online, a link to the survey will be sent. After completion of each assessment, participants taking survey online are immediately thanked on their screen for participating and provided with name and phone number of contact at their site.
Assessment 0-4 (if needed)	No survey response – 3 days after target date or appointment	Participants will receive up to 3 additional e-mail reminders, each 3 days apart. These reminder e-mails, like the initial e-mail, will provide a link to the current surveys, ask the participant to confirm that they have been able to access the web site, and provide both the e-mail address and the toll free help number for support.
Assessment 0-4 (if needed)	No survey response – 12 days after target date or appointment	If participants still have not responded within 12 days of the original e-mail, the central ECOG-ACRIN Outcomes and Economic Assessment Unit Research Associate may attempt to call the patient and administer the questionnaire over the telephone. Up to five attempts will be made to contact the participant over the telephone.
Assessment 4	After completion of all surveys – using preferred communication	After completion of all assessments, participants taking survey online are immediately thanked on their screen for completing the study and provided with name and phone number of contact at their site.

For those whose preferred method of communication is mail.

Assessment 0, 1, 2, 3, 4	Prompted when assessment due	If the participant wants to do paper surveys, these will be sent via mail. After completion of each assessment, a customized thank you letter will be sent.
Assessment 0-4 (if needed)	No survey response – 10 days after target date or appointment	If paper was requested, participant will receive a telephone call from the site research coordinator. If the patient has not received the paper questionnaires, additional questionnaires will be sent after confirming the correct mailing address. If the questionnaire is available to the patient, the OEAU RA will urge the study patient to complete and return the questionnaire.
Assessment 0-4 (if needed)	No survey response – 20 days after target date or appointment	If the patient has still not responded within 20 working days of the original mailing, the OEAU will attempt to call the participant and telephone administer the questionnaire. Up to five attempts will be made to contact the participant over the telephone. If questionnaires are telephone-administered, they will be marked as such in the data base.

Assessment 4	After completion of all surveys – using preferred communication	For mail participants, a customized thank you letter will be sent.