Phase II Study of Low-Dose Ibuprofen for Cognitive Problems in Patients with Cancer
URCC16092
NCT #: NCT03186638

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Participating Sites: Open to all NCORPs affiliated with the URCC NCORP Research Base

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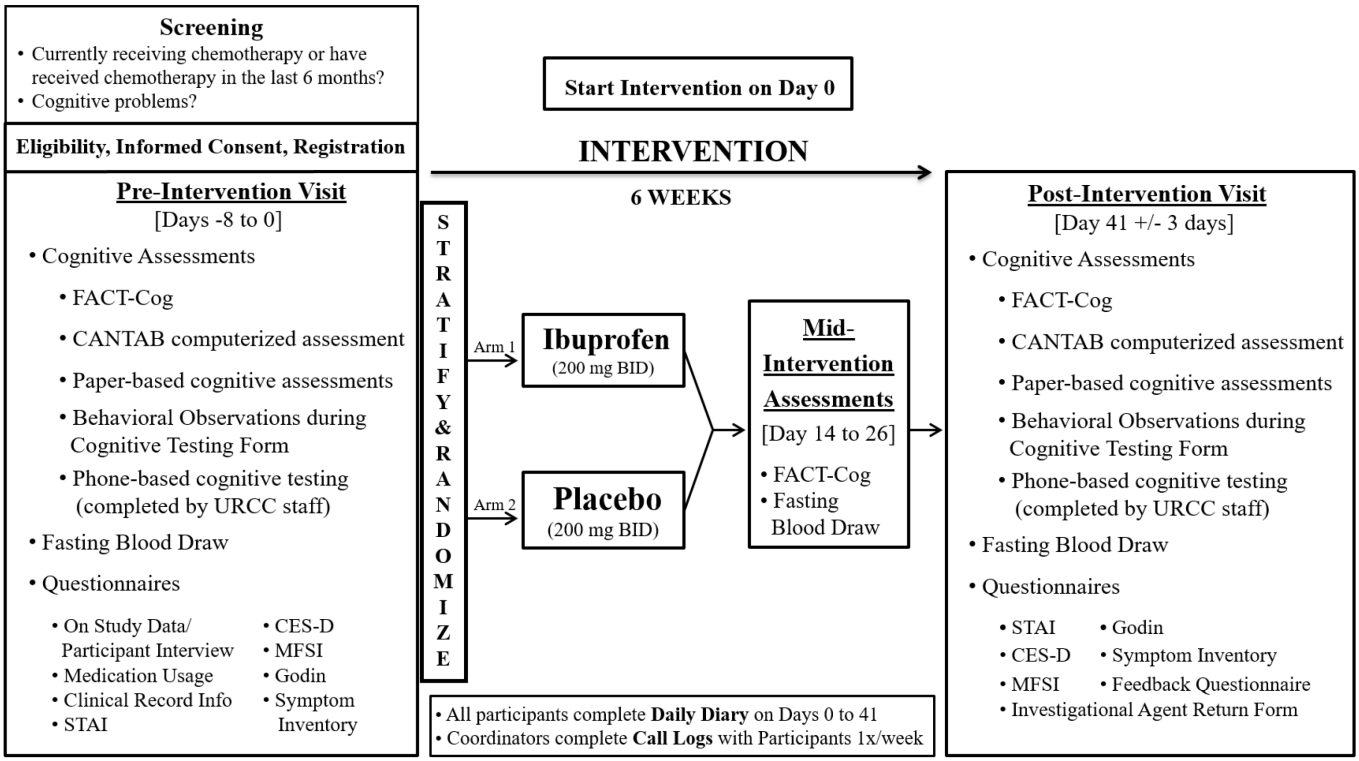
Appendix:

A. Study Calendar

Schema


Screening
• Currently receiving chemotherapy or have received chemotherapy in the last 6 months?
• Cognitive problems?
Eligibility, Informed Consent, Registration
Pre-Intervention Visit
[Days -8 to 0]
• Cognitive Assessments
• FACT-Cog
• CANTAB computerized assessment
• Paper-based cognitive assessments
• Behavioral Observations during Cognitive Testing Form
• Phone-based cognitive testing (completed by URCC staff)
• Fasting Blood Draw
• Questionnaires
• On Study Data/ Participant Interview
• Medication Usage
• Clinical Record Info
• STAI
• CES-D
• MFSI
• Godin
• Symptom Inventory
Start Intervention on Day 0
INTERVENTION
6 WEEKS
STRATIFY&RANDOMIZE
Arm 1
Ibuprofen
(200 mg BID)
Arm 2
Placebo
(200 mg BID)
Mid-Intervention Assessments
[Day 14 to 26]
• FACT-Cog
• Fasting Blood Draw
• All participants complete Daily Diary on Days 0 to 41
• Coordinators complete Call Logs with Participants 1x/week
Post-Intervention Visit
[Day 41 +/- 3 days]
• Cognitive Assessments
• FACT-Cog
• CANTAB computerized assessment
• Paper-based cognitive assessments
• Behavioral Observations during Cognitive Testing Form
• Phone-based cognitive testing (completed by URCC staff)
• Fasting Blood Draw
• Questionnaires
• STAI
• CES-D
• MFSI
• Godin
• Symptom Inventory
• Feedback Questionnaire
• Investigational Agent Return Form

1. Table of Contents

1. INTRODUCTION AND BACKGROUND

1.1. Rationale and Literature Review

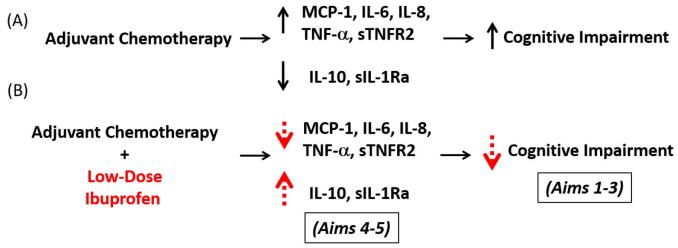
Clinical Relevance. Chemotherapy-related cognitive impairment (CRCI) is characterized by difficulty in memory, attention, concentration and executive function. CRCI is most pronounced and severe during chemotherapy (in up to 80% of cancer patients); however, it can last for many years following treatment (up to 20 years) in up to 35% of survivors.[1-3] With over 13 million cancer survivors in the US, up to 4 million could be living with long-lasting CRCI.[4] CRCI is independent of other symptoms (e.g., anxiety, depression)[5] and has a negative impact on quality of life (e.g., activities of daily living, work performance).[6-10] CRCI influences treatment adherence; 80% of participants state that they would not choose a treatment if they knew it could interfere with their mental capacity.[11] It is critically important to help participants with CRCI, by testing interventions to alleviate this burdensome side effect.

CRCI affects patients with many different cancers. A majority of the research on CRCI has been conducted in breast cancer showing that CRCI is a pervasive problem during chemotherapy; however, CRCI affects patients with multiple cancer types that receive chemotherapy including those with colorectal cancer, prostate cancer, lymphoma, testicular cancer, multiple myeloma, and ovarian cancer.[2,9,12-23] Of note, Dr. Janelsins has collected pilot data to indicate that, as *Preliminary Study # 1* demonstrates, 78% of colorectal cancer patients report memory difficulty during chemotherapy. Recruitment of patients with colorectal cancer will be one of the key understudied groups included in this research.

While studies have focused on developing CRCI interventions for breast cancer patients and survivors[24-26], we are interested in studying interventions for CRCI more broadly; therefore, this study is novel and of potential clinical impact with more broad scope by addressing CRCI in those with different disease types.

The preliminary link between CRCI and Inflammation forms the basis for testing ibuprofen intervention. Inflammatory processes play a role in a number of neurocognitive diseases.[27-37] Dr. Janelsins and others have shown that chemotherapy increases production of pro-inflammatory cytokines including MCP-1, IL-6, IL-8, TNF-α, and receptor TNFR2 and these are correlated with CRCI (*Preliminary Study # 2*).[38-42] Elevated peripheral blood levels of these molecules can cause reduced neuronal plasticity and neuronal cell death which ultimately lead to cognitive impairments,[27,30,37,43-50] and are thought to contribute to cognitive diseases including Mild Cognitive Impairment.[39,51-53] Chronic expression of these pro-inflammatory cytokines leads to a cytokine cascade that may become chronic and contribute to and exacerbate CRCI, and may occur via similar neuronal degenerative pathways initiated by inflammation as in other cognitive disease settings.[69,70] Conversely, anti-inflammatory cytokines are associated with neuroprotection (IL-10, sIL1Ra). Therefore, interventions that reduce inflammation, such as ibuprofen, that are associated with improved cognitive function in other disease settings and in healthy adults may reduce CRCI-induced inflammation and improve cognitive function in cancer patients receiving chemotherapy with CRCI (Fig. 1).

Figure 1: Theoretical Framework of CRCI (A) and Study Hypotheses (B)



Ibuprofen is an FDA-approved non-steroidal anti-inflammatory (NSAID) for treatment of conditions that involve pain, fever, and inflammation.[54] Ibuprofen inhibits cyclooxygenase 1 and 2 activity, thereby inhibiting the synthesis of prostaglandins and consequently down-regulating inflammatory pathways involving IL-1β, MCP-1, IL-6, CRP and TNF-α [54-56] the same pathways involved in CRCI. NSAIDs, even at low doses, are neuroprotective among healthy female adults with long-term use.[57] Additional studies have shown the benefits of NSAIDs, including ibuprofen, on slowing cognitive decline in those with Alzheimer's or Mild Cognitive Impairment (MCI).[58-60, 61] Most recently, a protective effect of

ibuprofen in Parkinson's risk was observed.[62] Since low-dose ibuprofen is effective in these settings, we hypothesize that it may be beneficial for CRCI.[63] Because CRCI develops quickly after chemotherapy, and because of the rapid effect of ibuprofen on inflammation, we hypothesize that noticeable improvements may occur with a brief (6-week) administration of low-dose ibuprofen. We observed benefits in a study where an NSAID was delivered to alleviate pegfilgrastim-induced bone pain (proposed inflammation mechanism); in that randomized clinical trial (RCT;N=510), we found a significant improvement with a 1-week delivery of a low-dose NSAID on chemotherapy-related bone pain showing that it is feasible and safe to give an NSAID of 1000 mg/day during chemotherapy.[64,65] *Preliminary Study # 3* suggests that ibuprofen (200 mg twice a day for 6 weeks), is preliminarily safe and feasible for cancer patients receiving chemotherapy, and may be beneficial for CRCI. We arrived at the dosage of 200 mg twice a day for 6 weeks and each dose 8 hours apart based on safety considerations.

CRCI is a significant problem for cancer patients during chemotherapy and interferes with QOL. Dr. Janelsins also has preliminary data that participants on chemotherapy perform worse on the CANTAB memory task compared to similar age- and gender-paired controls (*Preliminary Study # 5*). If our hypothesis that intervening during chemotherapy may prevent post-treatment CRCI by reducing inflammation, the goal of future research is to follow participants for longer post-treatment times.

1.2. Preliminary Data

Study 1: In a secondary analysis on 69 colorectal cancer patients from a completed nationwide CCOP study originally designed to assess the effect of modafinil for cancer-related fatigue (URCC2901), we found that 78% of these participants experience memory difficulty during chemotherapy Cycle 3 (Fig. 2). Difficulty at cycle # 3 also predicts interference in quality of life items at cycle # 4 (mood, work, general activity, enjoyment of life; OR Range=2.16-3.43, $p<0.05$; Janelsins et al., Society for Behavioral Medicine Abstract). Colorectal cancer patients are one of the important groups we will recruit as they are underrepresented in CRCI intervention research.

Figure 2	% Colorectal Cancer Pts. with Difficulty		
Problem Area	Cycle 2	Cycle 3	Cycle 4
Memory difficulty	75%	78%	74%
Difficulty thinking	55%	52%	48%
Unable to concentrate	62%	44%	58%

Study 2: We assessed levels of cytokines, MCP-1, IL-6 and IL-8, at two time-points during adriamycin-based chemotherapy in breast cancer patients (n=54), and found that all three increased (IL-6 was significant, $p<0.05$).[53]

Study 3: In preparation for the proposed Phase II RCT in cancer patients, we have collected feasibility data on an RCT conducted at Wilmot Cancer Institute which included Ibuprofen (200 mg twice a day for 6 weeks) and EXCAP®© (tailored walking and resistance training program for 6 weeks) and in cancer patients receiving chemotherapy and reporting a least a mild/moderate level of CRCI via self-report score of 3 or higher on a MDASI CRCI question at cycles 3-5. These data have been collected as part of Dr. Janelsins' ongoing NCI K07 Award and has an accrual closure date set for October 31, 2020. The feasibility data are based on 33 consented participants with 28 providing full evaluable pre/post data (67% breast cancer and 33% gastrointestinal (GI) cancer with 15% colorectal cancer). A majority of the patients with colorectal cancer received FOLFOX while one received Capecitabine. The goal of this feasibility phase of Dr. Janelsins' K Award was to assess the feasibility of the interventions in a similar protocol design and procedures to help inform the proposed Phase II study.

- Outcome Assessment: All randomized GI participants (to EXCAP©® or ibuprofen) completed the validated FACT-Cog, CANTAB neuropsychological tests, aerobic testing (6-minute walk test), strength testing (rep. max testing), symptom measures, diaries, and provided blood at pre- and post-intervention. Note: EXCAP©® can lead to improvements in 6-minute walk test and rep. max testing over 6 weeks.[66] In this pilot, we observed similar improvements with our study participants.

- Adherence: Pill compliance was greater than 90% from all participants with the exception of one. Those in the EXCAP©® group had a 2,553 pedometer step increase moving participants from a sedentary to low-active level, and a 375 step increase in those not in EXCAP©®; those participants remained sedentary. 75% of participants reported using resistance bands with an average of 3 days/week for 20 minutes at an average moderate RPE of 4.
- Adverse Events: No study-related AEs occurred.
- Satisfaction: 100% highly recommended the study.
- Preliminary effect estimates of 0.4-0.7 on the Delayed Match to Sample CANTAB Task suggesting that exercise and ibuprofen are trending in the right direction; these are based on a very small number of patients and we only calculated these to get an idea of the sample size needed for the current Phase II study.
- Beyond the feasibility phase of data collection highlighted above, Dr. Janelsins and colleagues are currently continuing her work with these interventions as part of her NCI K Award and this Phase II study at Wilmot Cancer Institute primarily in breast cancer patients. Eleven physicians worked with her and 10 allowed their patients to participate reaching an accrual of 110 patients to that study. We focused on recruiting from breast cancer and GI clinics and have also recruited from lung and prostate clinics. Of the 110 patients accrued to the study, 82 had breast cancer (including metastatic and non-metastatic cancer), 26 had GI cancers (16 colorectal cancer, 4 pancreatic, 2 esophageal, 2 bile duct, 1 appendix, 1 liver), 1 prostate cancer patient, and 1 with lung cancer.
- The current study will focus on the low-dose ibuprofen intervention for CRCI within the NCORP network.

Study 5: In a large observational study (URCC10055) lead by Dr. Janelsins and conducted through the URCC NCORP Research Base and affiliates, we found that the FACT-Cog was a robust measure of CRCI, detecting clinically and statistically meaningful changes from pre- to post-chemotherapy as well as up to 6 months post-chemotherapy.[67] Using objective neurocognitive testing, Dr. Janelsins and colleagues showed that CRCI was a significant problem from pre- to post-chemotherapy and up to 6 months post-chemotherapy.[68]

Summary: Given the significance and innovation presented and our original preliminary data, the next logical step of investigating ibuprofen (200 mg twice a day—for cancer patients receiving chemotherapy or who have received chemotherapy within the last 6 months and are experiencing CRCI, is a Phase II pilot RCT. The Phase II RCT, if promising, would support an eventual Phase III study.

1.3. Feasibility

NCORP Community Sites and Minority/Underserved Community Sites have been involved in developing and reviewing this study concept. NCORP Investigators on this protocol played a role in reviewing and refining this protocol.

The pilot study for this protocol was presented at the 2015 Annual NCORP Meeting by Dr. Janelsins with a majority of respondents indicating a high level of interest in this study. Conference attendees were given opportunities to discuss the concept with Dr. Janelsins, to provide written comments on the study concept, and to indicate their level of interest. A high level of participation from NCORP sites is anticipated based on data collected at the 2015 Annual NCORP Meeting. Representatives of nine of the NCORP community sites in attendance at the conference indicated a willingness to participate in this study.

a. This study underwent peer review as part of an NCI study section and Dr. Janelsins was awarded funding under an NCI R21. Feasibility was assessed as part of the peer review.
b. The preliminary data in Section 1.2 solidifies study feasibility.

2. OBJECTIVES

2.1. Primary Objective

2.1.1. To provide preliminary data on the effect of ibuprofen on alleviating CRCI in cancer patients receiving chemotherapy or who have received chemotherapy within the last 6 months compared to a placebo control, as assessed by the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog).

2.2. Exploratory Objectives

2.2.1. To provide preliminary data on the effect of ibuprofen on alleviating CRCI in cancer patients receiving chemotherapy or who have received chemotherapy within the last 6 months compared to a placebo control by objective assessments of cognitive function. These are measured by validated neuropsychological assessment of verbal memory, attention, and executive function via CANTAB (computerized DMS, VRM, and RVP) and paper-based measures (CTMT and COWA).

2.2.2. To provide preliminary data on the effect of ibuprofen on alleviating CRCI in cancer patients receiving chemotherapy or who have received chemotherapy within the last 6 months compared to a placebo control on phone-based cognitive function measures (digit span, word recall, digits backward, CALVT, category fluency; all from BTACT).

2.2.3. To provide preliminary data on the effect of ibuprofen on alleviating CRCI in cancer patients receiving chemotherapy or who have received chemotherapy within the last 6 months compared to a placebo control on serum pro-inflammatory (MCP-1, IL-6, IL-8, TNF-α, sTNFR2, sTNFR1, IL-1β) and anti-inflammatory (sIL-1Ra, IL-10) cytokines/receptors in cancer patients receiving chemotherapy.

2.2.4. To provide preliminary data on the mediating effects of cytokine/receptor concentrations on the CRCI changes due to ibuprofen in cancer patients receiving chemotherapy or who have received chemotherapy within the last 6 months compared to placebo control.

3. CHARACTERISTICS OF STUDY POPULATION

3.1. Inclusion Criteria

Study participants must:

3.1.1. Be ≥ 18 years of age

3.1.2. Have a diagnosis of cancer and are now receiving cytotoxic chemotherapy or have received cytotoxic chemotherapy within the last 6 months (i.e. are within a 6 month window of completion of chemotherapy).

3.1.3. Report cognitive difficulties or respond YES to the question: "Have you noticed any problems in your memory, attention, concentration, multi-tasking, or other cognitive functions?"

NOTE: If a participant does not report cognitive difficulties or answers NO, they should be re-approached multiple times. Patients should be re-screened at all subsequent chemotherapy treatments and multiple times during the six months following completion of chemotherapy via phone and in person.

3.1.4. Be able to swallow medication.

3.1.5. Be able to read English.

3.1.6. Be able to give written informed consent.

3.2. Exclusion Criteria

Study participants must not:

3.2.1. Have a confirmed brain tumor or confirmed brain metastases.

3.2.2. Be taking regular daily doses of an NSAID. Note: Daily doses of 81 mg aspirin are permitted and higher doses of an NSAID on an 'as needed' basis are permitted.

3.2.3. Be diagnosed with dementia or severe neurodegenerative disease that would prohibit the ability to complete cognitive testing.

3.2.4. Have a contraindication to ibuprofen per physician or physician's designee (e.g., allergy, worsening of ongoing medical problem due to NSAID, very low platelet count from chemotherapy, full-dose anti-coagulation/high risk of bleeding, as well as uncontrolled conditions such as hypertension, asthma, or peptic ulcer disease).

3.2.5. Have a hospitalization for treatment of a major psychiatric illness within the last five years.

3.2.6. Be pregnant.

3.2.7. Have a serum creatinine above 1.5 ULN. ULN is per institutional definition. If currently receiving chemotherapy, lab test must be collected within the 4 weeks prior to study enrollment. If not currently receiving chemotherapy, most recent labs tests may be used.

3.2.8. Be colorblind.

3.2.9. Have active substance abuse (e.g. alcohol, drugs) that would interfere with participation in this study per self-report or medical record.

3.3. Source of Study Participants

Data will be gathered from patients, 18 years of age or older, undergoing chemotherapy treatment for cancer or have received chemotherapy within the last 6 months at participating sites. Pediatric patients will be excluded from this study. Women and members of minority groups and their subpopulations will be included in the study.

Planned Accrual:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	1	0	0	1
Asian	2	2	0	0	4
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	5	7	1	0	13
White	32	33	0	1	66
More Than One Race	1	0	0	0	1
Total	40	44	1	1	86

3.4. Process of Consent

3.4.1. Prior to study initiation, the informed consent document will be reviewed and approved by the NCI Central IRB (CIRB). Any subsequent changes to the informed consent will be approved by the NCI CIRB prior to utilization.

3.4.2. All potential study participants will be given a copy of the CIRB-approved Informed Consent to review. The investigator/investigator's designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the potential participant decides to participate in the study, s/he will be asked to sign and date the Informed Consent document. The study documents or interventions will not be released to a potential participant who has not signed the Informed Consent document. Potential participants who refuse to participate or participants who withdraw from the study will be treated without prejudice.

3.4.3. Participants will be provided the option to allow the use of blood samples for future research purposes. Statement of this option will be included within the informed consent document.

3.4.4. The eligibility checklist must be signed by the treating physician prior to study registration and initiation of any study procedures.

3.5. Recruitment and Retention Plan

3.5.1. Study personnel at participating NCORP sites with appropriate human subject protection certification and study-specific training will monitor patient visit schedules and inform treating physicians when a patient is potentially eligible for a study. If the treating physician deems the study appropriate for the potential participant, and, if the potential participant agrees to hear about it, the treating physician will introduce study personnel to the potential participant. Study personnel will then explain the project to the potential participant and answer all questions. Treating physicians can also identify and approach potential participants about this study.

3.5.2. Retention of participants will be supported by flexible scheduling of study assessments and weekly phone contacts. Also, participants will be compensated a total of $100.00 for their time and travel upon the completion of study assessments. This is dispensed as follows: $25 upon completion of Pre-Intervention requirements, $30 ($5/week x 6 weeks for completing

daily diaries/Mid-Intervention assessments) upon completion of the intervention and assessments on study, and $45 for completion of the Post-Intervention requirements. See Section 5.12.

4. REGISTRATION AND RANDOMIZATION

4.1. Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located 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.

4.2. CTSU Registration Procedures

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

4.2.1.IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the

institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *URCC* and protocol number *URCC-16092*
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2. Submitting Regulatory Documents

Submit your CIRB-approved Annual Signatory Institution Worksheet and Annual Principal Investigator Worksheet URCC_Regulatory@URMC.rochester.edu for the URCC Research Base study records

4.2.3. Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3. Enrolling Participants

To enroll a participant who meets the eligibility criteria and who has signed the informed consent document, log on to the URCC NCORP Research Base website at http://www.urcc-ncorp.org/, enter your NCORP's username and password and enter the information outlined below. An email confirmation of registration will be forwarded by the URCC. Participants can be registered up to 3 weeks prior to their initiation of study procedures. If you are unable to log on, contact Kari Gilliland by phone at 585-275-6303 or by email at URCC_16092@URMC.*rochester.edu*.

The following information will be requested:

a. NCORP name
b. NCORP component name and CTEP#
c. Enrolling physician name
d. Enrolling physician CTEP Investigator ID
e. Name and telephone number of person following study participant
f. Verification that participant has met all inclusion and exclusion criteria listed in Section 3.
g. Verification that consent form has been signed
h. Participant's identification
   - First name and last initial
   - Birth date (MM/DD/YYYY)
   - Gender
   - Race

- Five-digit zip code
- Payment code
- Other protocol-specific information, including:
    - Phone number
    - Best time to call
    - Permission to leave voicemail
    - Anticipated Intervention Start Date (i.e. Day 0 date)
    - Currently Receiving Chemotherapy? (Yes or No)
    - Date of first chemotherapy received while on this study (If currently receiving chemotherapy)
        - Note: must match day 0 date

An email confirmation of registration will be forwarded by the URCC NCORP Research Base. Participants can be registered up to 3 weeks prior to their initiation of study procedures. The Eligibility Checklist must be signed and dated by the treating physician prior to registration.

4.4. Randomization

Randomization will occur at the time of registration. A computer-generated randomization schedule will be used to assign participants in equal numbers to the two arms, stratified by NCORP site and gender with a block size of 4. The schedule will be prepared and maintained by the URCC NCORP Research Base biostatistician.

The 2 study arms are as follows:

Arm 1: Participants assigned to Treatment Arm 1 will receive a 6-week supply of ibuprofen (200 mg), which consists of 84 capsules of ibuprofen to be taken twice daily.

Arm 2: Participants assigned to Treatment Arm 2 will receive a 6-week supply of placebo, which consists of 84 capsules of placebo to be taken twice daily. The placebo contains trace amounts of lactose (Approximately 0.32 grams per capsule).

A total enrollment of 86 participants is planned, with 43 participants in each treatment group. Accounting for a 30% rate of incomplete data, we estimate 30 participants in each intervention group will yield fully evaluable data. It should take approximately 12 months to accrue all participants if 8 participants are accrued per month across NCORP sites.

Treatment Arm	N	Evaluable
Arm 1: Ibuprofen	43	30
Arm 2: Placebo	43	30
Total	86	60

5. RESEARCH PROTOCOL/STUDY PROCEDURES

5.1. Overview of Study Plan and Coordinator Training

5.1.1. Overview of Procedures and Study Timelines:

This will be a phase II, multi-center, double-blind, placebo-controlled, 2-arm randomized clinical trial of an intervention examining the preliminary efficacy of the 2 treatment arms on perceived cognitive function. Participants in the study must have a diagnosis of cancer, be

currently receiving cytotoxic chemotherapy or have received chemotherapy treatment within the last 6 months, and report cognitive difficulties or respond yes to the question: "Have you noticed any problems in your memory, attention, concentration, multi-tasking, or other cognitive functions any time after initiation of cytotoxic chemotherapy cycle 1 (i.e. first infusion). Participants can receive other concurrent treatments (e.g. radiation, biologics) with cytotoxic chemotherapy or after cytotoxic chemotherapy. Therapeutic trial participants are also allowed as long as they are known to be receiving a cytotoxic chemotherapy agent. Participants can be enrolled up to 6 months after of completion of cytotoxic chemotherapy.

Coordinators should provide an introduction to the concept of "chemo brain" and then ask the question above. An example introduction is below:

> Some patients experience changes in cognitive abilities during chemotherapy and within 6 months following chemotherapy treatments. These can be mild or more severe. Some examples of cognitive problems could include things like:
>
> - Feeling overall general "fogginess"
> - Trouble with details like names, events, dates
> - Trouble with learning new things
> - Trouble remembering common words - word is on the 'tip of the tongue.'
> - Trouble remembering things you usually have no trouble recalling, like directions
> - Trouble focusing on tasks and taking longer to accomplish a task
> - Trouble with multi-tasking at work or home

If a caregiver is present at the time of screening they may be consulted during the discussion about changes in the participant's cognitive function. However, to be eligible the participant themselves must agree to participate and report cognitive difficulties or respond yes to the screening question. Caregiver should be a person at least 21 years of age that provides support in any way to the participant. It is acceptable to ask a caregiver to provide input on the cognitive function of the participant and the participant's problems with memory, attention, concentration, or multi-tasking.

Participation in the study intervention will span 6 weeks (42 days) and participants will be evaluated at three time points during the study: Pre-Intervention (within Days -8 to 0), the study midpoint (Mid-Intervention; within Days 14-26), and Post-Intervention (Days 41 +/-3).

Participants will complete brief daily diaries which include questions about symptoms, daily exercise, study agent use, and non-study agent drug usage. All participants will complete the Daily Diary on study Days 0 to 41. Time on this study could go up to approximately 7 weeks to allow for flexibility in scheduling the Pre-Intervention and Post-Intervention study visits. The intervention will begin on study Day 0. All Pre-Intervention visit assessments will be completed by participants within 8 days prior to or on Day 0. If Pre-Intervention visit occurs on Day 0 the assessments should be completed before the initiation of the study intervention. For participants currently receiving chemotherapy Day 0 will occur on the day of the first chemotherapy received while on the study. If Pre-intervention assessments are collected on the same day chemotherapy is given assessments must be completed prior to the chemotherapy infusion. The Post-Intervention visit will occur most often on Day 41 of the intervention. However, as scheduling issues can occur, the Post-Intervention visit may occur within Days 38 to 44. For participants currently receiving chemotherapy the Post-Intervention visit must occur **BEFORE the next administration of chemotherapy and not after**. If Post-intervention assessments are collected on the same day chemotherapy is given assessments must be completed prior to the chemotherapy infusion.

All participants will be given a measure of cognitive functioning (Functional Assessment of Cancer Therapy with Cognition (FACT-Cog)) and other self-report measures evaluating depression (CES-D), fatigue (MFSI-SF), anxiety (STAI), Godin Exercise Leisure-time Questionnaire (Godin) and a symptom inventory (SI) to complete at the Pre-Intervention visit and Post-Intervention visit. **Note: FACT-Cog is completed prior to computerized and paper-based testing.** Participants will complete a FACT-Cog questionnaire at the Mid-Intervention time point at home.

At Pre-Intervention and Post-Intervention, all participants will be evaluated for cognitive performance on the CANTAB computerized neuropsychological assessment of memory performance on a delayed matching to sample task. This assessment measures memory across delay times (0, 4, 12 seconds) as well as reaction time. This assessment is non-invasive and only requires touching a computer screen. It takes less than 10 minutes to complete. Two other CANTAB tests will be included for exploratory analyses: Verbal Recognition Memory (Immediate and Delayed Memory; ten minutes) and Rapid Visual Information Processing (a short 10 minute test of attention and working memory). Paper-based assessment consisting of the WRAT-4 Reading (Pre-Intervention only), COWA, and CTMT will also be conducted. Study coordinators will complete the Behavioral Observations During Cognitive Testing form at the Pre-Intervention visit and Post-Intervention visit.

After the cognitive testing, a follow-up call for a brief cognitive assessment (no more than 15 min) with the Brief Test of Adult Cognition by Telephone (BTACT) will be conducted by research staff at the URCC NCORP Research Base for Pre-Intervention and Post-Intervention. For all participants, the Pre-Intervention BTACT will be completed BEFORE the initiation of the study intervention. If the Pre-Intervention BTACT cannot be completed before the initiation of the study intervention, the assessment will be completed within 7 days after the in-person cognitive assessments completed at the Pre-Intervention visit.

For participants currently receiving chemotherapy, Pre-Intervention BTACT should also be completed BEFORE the first administration of chemotherapy they receive while they are a participant on the study. If the Pre-Intervention BTACT cannot be completed before the first chemotherapy administered while on the study (for those receiving chemotherapy), the BTACT assessment may be completed within 7 days after the in-person cognitive assessments completed at the Pre-Intervention visit.

For all participants, the Post-Intervention BTACT assessment will be collected AFTER the Post-Intervention in-person cognitive assessments have been completed. If the Post-Intervention BTACT cannot be completed before the in-person cognitive assessments, the assessment may be completed within 7 days after the in-person cognitive assessments completed at the Post-Intervention visit.

For participants currently receiving chemotherapy, Post-Intervention BTACT should be completed BEFORE the last administration of chemotherapy received while they are a participant on the study. If the Post-Intervention assessments are completed on the same day as the final chemotherapy administered while on study (for those receiving chemotherapy), the BTACT phone assessment will be performed AFTER in-person cognitive testing has been completed but before chemotherapy infusion, when possible. For participants receiving chemotherapy, the anticipated date of the last chemotherapy received while on the study will be communicated to the URCC Research Base by email when sending Post-Intervention CANTAB data files.

Ibuprofen and placebo will be provided by the University of Rochester Medical Center Investigational Drug Service. Instructions for the study agent will be reviewed with all participants by the study coordinator at the Pre-Intervention visit. Participants will be given

one bottle containing 84 capsules. The placebo contains trace amounts of lactose (approximately 0.32 grams per capsule). Participants will take study agent (1 capsule twice a day separated by at least 8 hours) for approximately 42 days starting on Study Day 0. At sites, study agent is stored in a secured location that is locked at all times and only accessible by approved study personnel. Study pills will be over encapsulated in opaque gelatin capsules so that participants will not know whether they have ibuprofen or placebo.

Fasting blood draws (6-8 hours) at three time-points will be done to measure cytokine, chemokine and receptor levels by appropriate ELISA/multiplex methods. These time-points coincide with Pre-Intervention (Day 0), Mid-Intervention (Day 14 to 26), and Post-Intervention assessment (Days 41 +/- 3 days) time windows. Pre-Intervention blood will be collected prior to or on Day 0.

For participants currently receiving chemotherapy, blood can be collected with pre-chemotherapy labs but must be collected before the initiation of the first chemotherapy received while on study. Participants currently receiving chemotherapy must complete the Post-Intervention blood draw prior to the last administration of chemotherapy received while on study.

Blood will still be collected if not fasted and this will be noted on the blood requisition form. Additionally, every effort should be made to make the Mid- and Post-Intervention blood draws the same time of day as the Pre-Intervention blood draw. Time of day is noted on the Blood Requisition Form. Blood will be drawn and processed using standardized kits supplied by URCC NCORP Research Base and using the standard processing procedure. All blood draws will occur at the NCORP sites and affiliated laboratories if blood is drawn off-site.

If collected, blood counts measured by standard CBC with differential procedures will be abstracted from the participant's medical record and entered into the Laboratory Data Form at Pre-Intervention and Post-Intervention time-points. Blood counts entered into the Laboratory Data form should be collected within 10 days of the associated time-point. If blood tests have not been completed within 10 days of the Pre-Intervention or Post-Intervention visit the coordinator will document this on the Laboratory Data form.

Study coordinators will complete weekly phone contacts. During phone contacts, coordinators will provide study reminders and participants will be questioned regarding compliance with the study interventions, completion of diaries, and occurrence of any adverse events. Information collected during weekly phone contacts will be recorded on the weekly Call Logs.

5.1.2. Coordinator Training

All NCORP coordinators and staff must complete mandatory training conducted by URCC NCORP Research Base staff for this study.

The training will be conducted via live video conference (or by watching a recorded training session followed by a short Q&A); content and training requirements vary by role. NCORP site staff members must complete the appropriate URCC NCORP Research Base training prior to conducting study assessments and delivering study interventions. All phone-based cognitive assessment coordinators will also receive training at URCC. Coordinators must be trained on all study procedures (cognitive assessment, study data management, blood procedures) prior to conducting study procedures.

All cognitive assessments must be conducted on a colleague prior to administering to a study participant and these documents should be sent to URCC_16092@URMC.rochester.edu for

review. A certification email will be sent to the coordinator from the Research Base after review.

5.2. Schedule of Activities

Time-point	Screening	Pre-Intervention Visit	Day 0	Mid-Intervention Visit	Post-Intervention Visit
Time window		Day -8 to 0	Intervention Start	Day 14 to 26	Day 41[2]
Screening	X				
Informed Consent	X				
Confirm eligibility/Register	X				
Randomization	X				
Adverse event review		Weekly	Weekly	Weekly	Weekly
Medication Usage		X			
Questionnaires		X		X	X
Cognitive Assessments (CANTAB and Paper-based Cognitive Tests)		X			X
Brief Test of Adult Cognition by Telephone (BTACT; URCC Staff)			X[1]		X[3]
Blood Draw		X		X	X
Laboratory Data (from medical record)		X			X
Study Agent dispensed			X		
Study Agent returned					X
Phone Contact		Weekly	Weekly	Weekly	Weekly
Daily Diaries			Daily	Daily	Daily

1. For participants receiving chemotherapy, this will ideally be completed prior to first chemotherapy received while on study (Day 0) but can be completed within 7 days after the in-clinic cognitive assessments.
2. If a participant cannot complete the Post-Intervention visit on Day 41 the visit may be completed on Days 38-44 as long as it is prior to the next administration of chemotherapy for participants currently receiving chemotherapy.
3. Must be completed after computerized and paper-based cognitive tests are administered and before the participant receives the final chemotherapy while on the study if currently receiving chemotherapy.

5.3. Screening and Pre-Intervention Assessment

5.3.1. Screening and Consent

All potentially eligible cancer patients that are currently receiving cytotoxic chemotherapy or have received cytotoxic chemotherapy treatment within the last 6 months and have been treated at NCORP communities affiliated with the URCC NCORP Research Base in the U.S. will be screened using an eligibility checklist. All screening data of potentially approached patients must be entered on the URCC screening log submitted monthly to the research base including those not eligible and those who declined to participate. If the person meets all eligibility criteria, study personnel will go over the study in detail using the consent form. Both parties must sign the full study consent form, if the person agrees to be on study. The eligibility checklist must be reviewed and signed by the participant's oncologist prior to registering the participant. Contact Kari Gilliland at 585-275-6303 or email URCC_16092@URMC.rochester.edu with any questions regarding participant eligibility.

5.4. Study Agent

5.4.1. Study Agent IND Exemption

This clinical investigation of ibuprofen meets all criteria for an exemption from the IND requirements outlined in § 312.2(b). The study agent is a non-prescription oral medication lawfully marketed in the United States. The investigation is not intended to be reported to the FDA in support of a new indication, there is no intent to use this study to support any other significant change in ibuprofen labeling or to promote or commercialize the drug. This investigation does not involve any factors that significantly increase the risk associated with the use of ibuprofen. This investigation will be conducted in compliance with IRB regulations and policies.

5.4.2. The treatment arms will follow the guidelines listed below:

5.4.2.1. The University of Rochester Investigational Drug Service (IDS) will supply the ibuprofen 200 mg in the form of pills over-encapsulated into opaque-colored capsules. A full six week supply of capsules will be given to the participants in a plastic vial by the study coordinator. Research participants will be instructed to take the ibuprofen once in the morning and once in the evening, where the doses are at least 8 hours apart. Participants will take 2 capsules /day for a total of 6 weeks. They will be instructed to take capsules whole and not open the capsule. The IDS will keep all regulatory information regarding packaging of the study agent.

5.4.2.2. The placebo capsule, which contains trace amounts of lactose (approximately 0.32gm per capsule), will be supplied by the UR IDS and will be over-encapsulated into opaque-colored capsules to match the ibuprofen. A full six week supply of capsules will be given to the participants in a plastic vial by the study coordinator. Research participants will be instructed to take the capsules once in the morning and once in the evening, where doses are at least 8 hours apart. Participants will take 2 capsules/day for a total of 42 days (study Day 0 to Day 41).

5.4.2.3. The study coordinator will contact each participant weekly to remind participants to take the study agent as directed. Review of diaries will occur at this time. The study coordinator will use this opportunity to assess any potential complications or toxicities due to the intervention and if any occur, they will be reported per the Adverse Events section (Section 11) of this protocol. Adherence and compliance is further detailed in Section 6.3

5.4.3. Obtaining Study Agent (Additional Study Agent Information in Section 8)

Study agent will be shipped from the URCC NCORP Research Base to each participating site. In order for the sites to have interventions available upon enrollment, the URCC NCORP Research Base will ship study agent for each arm to each NCORP. Bottles will be shipped to the designated pharmacy or investigator, who will be responsible for the receipt of the study agent from the Research Base, storage, and distribution to participants. Distribution and supply will be monitored and recorded using a modified version of the standard NCI Investigational Agent Accountability Record. Study agent can be requested by contacting Kari Gilliland at the URCC NCORP Research Base:

PREFERRED CONTACT is e-mail:
URCC_16092@URMC.rochester.edu
Otherwise, call 585-275-6303

When ordering, the number of bottles of each arm and the study protocol number are required. Orders will be express mailed from the URCC within 2 working days unless notified otherwise.

5.4.4. Agent Disposal

Any study agent returned by participants must be recorded on the Investigational Agent Accountability Record form and destroyed at the NCORP site per their institution's guidelines. At the completion of this investigation, any study agent left in stock (i.e., not dispensed to a study participant) will be destroyed at the NCORP site per their institution's guidelines and recorded on the DARF. Investigational agents are NOT returned to URCC Research Base.

5.5. Pre-Intervention Visit

5.5.1. Questionnaires and Forms

The On-Study Data/Participant Form is used to record demographic information (e.g., age, race, ethnicity, education). Other clinical information (e.g., KPS or ECOG, diagnostic, planned and previous treatment (e.g., surgery, chemotherapy regimens, radiation, and hormone therapies)) will be abstracted from the participant's chart and recorded on the Clinical Record Information form. The Laboratory Data form will be completed by the study coordinator using test results abstracted from the participant's medical record. Lab values entered into the Laboratory Data form for the Pre-Intervention assessment should be collected within 10 days of the Pre-Intervention visit. If blood tests have not been completed within 10 days of the Pre-Intervention visit the coordinator will document this on the Laboratory Data form.

The Medication Usage form, completed at the Pre-Intervention visit, will track the participant's use of all prescription and non-prescription medications (e.g., stimulants, anti-depressants, NSAIDs, vitamins; as cognitive aids or for other conditions) used at the time of enrollment. Participants will be asked about specific medications such as anti-depressants, stimulants, NSAIDs, and vitamins they may be taking. This form will also specifically ask participants to report the use of any complementary and alternative medicine (CAM) modalities for any reason.

All participants will complete the Daily Diary, which includes questions about symptoms, exercise, and drug usage, on Days 0 to 41.

5.5.2. Cognitive Functioning Assessments

All coordinators must complete study-specific training in cognitive assessment prior to the conduct of assessments on study participants. Coordinators administering the cognitive assessments should use only the cognitive assessment manual and study-specific training provided by Dr. Janelsins' team. After completing training, each coordinator will conduct at least one mock cognitive assessment. Results of the practice assessment should be submitted to the URCC Research Base for review at the study email URCC_16092@URMC.rochester.edu. A certification email will be sent to the coordinator from the Research Base after review. **Participants will first complete the FACT-Cog questionnaire and then all of the subsequent cognitive assessments.**

5.5.2.1. Computerized Testing

Participants will complete three cognitive tests using Cambridge Neuropsychological Test Automated Battery (CANTAB), an objective and validated computerized testing tool for various cognitive functioning domains in the setting of multiple disorders, including cancer.[69-78] All testing will be completed in a quiet, well-controlled environment at a flat workstation using a portable computer with a 20 inch touchscreen monitor provided to sites by the URCC NCORP Research Base. Cognitive tests will be administered in the following order: MOT, DMS, VRM (Immediate), RVP, CTMT (paper-based), COWA (paper-based), and VRM (Delayed), and WRAT-4 (Pre-intervention only) (paper-based). The VRM (Delayed) computerized cognitive test should be administered AFTER the completion of paper-based cognitive tests to meet the requirement for an approximate 20 minute delay following the administration of the VRM (Immediate) test. The trained coordinator will describe each task to the participant prior to testing and provide scripted instructions throughout each task. All computerized testing is anticipated to take about 30 minutes to complete.

5.5.2.1.1. Participants will first complete a three-minute motor screening task (MOT) to confirm normal motor control and to get accustomed to using the computer.

5.5.2.1.2. Short-term visual memory will be assessed by the Delayed Matching to Sample (DMS) task. This test takes approximately 10 minutes to complete, and a total of three data points is obtained (at 0, 4, and 12 seconds). A participant is shown a complex visual pattern and then, after a brief delay (4 and 12 seconds), is shown four similar patterns. The participant is instructed to touch the pattern on the computer screen which exactly matches the sample. Speed to complete the task (latency in ms) is also assessed within the same measure which may indicate attention/motivation contributions to performance on the task.

5.5.2.1.3. Memory (verbal) will be assessed by the Verbal Recognition Memory (VRM) Task. In this task, the participant is asked to remember a list of words (presented to them on a screen) and then immediately recall them verbally. The participant is then asked to recall from a list if they previously saw the word (pressing yes or no). Following the next three tasks (i.e., the attention task, CTMT and COWA) approximately 20 minutes later, the participant is then asked to recall whether or not they recognize the word (pressing yes or no) from the original list of words.

5.5.2.1.4. Attention will be assessed by the Rapid Visual Information Processing (RVP) task. Errors will be recorded. A white box is displayed in the center of the computer screen, inside which digits, from 2 to 9, are displayed in a pseudo-random order, at the rate of 100 digits per minute. The participant must detect consecutive odd or even sequences of digits (for example, 2-4-6) and respond by pressing the touch pad.

5.5.2.1.5. The coordinator will fill out a Brief Behavioral Observations During Cognitive Testing sheet about each study participant after each CANTAB assessment. This one page form will be used to determine the validity of the results.

5.5.2.1.6. Details for saving files are provided in the Cognitive Testing Manual. Upon completion of the computerized testing, data files (i.e., CANTAB files (html) and EXCEL files (.csv)) will be saved onto the CANTAB computer in the following format: STUDY ID_Assessment #. Assessment 1 is Pre-Intervention and Assessment 2 is Post-Intervention. Back-ups will occur on each computer at 2 week intervals; CANTAB will automatically ask you to back up the data, and the coordinator will follow the computer prompts as indicated.

URCC will provide USB flash drives that belong with each computer. The coordinator will transfer each of the files onto the flash drive to be transferred and saved on a HIPAA-compliant, regularly backed up network storage or computer. The EXCEL file (5 pages) will be printed and saved in the participant's record, the CCLAR file will be uploaded to the URCC NCORP Research Base via Box.com. For participants receiving chemotherapy, the anticipated date of the last chemotherapy received while on the study will be communicated to the URCC Research Base by email when sending Post-Intervention CANTAB data files. **CANTAB data must be submitted within 24 hours of each assessment.** The CANTAB data file will be emailed to:

URCC_16092@URMC.rochester.edu

URCC will send an email response confirming receipt of the data.

5.5.2.2. Standard Paper-based Neuropsychological Testing

All coordinators will be trained to administer and score neuropsychological tests as part of the computerized testing training and must submit a practice test for review prior to certification.

Administration of the test battery takes approximately 20 minutes total.

5.5.2.2.1. Basic academic skills/cognitive reserve will be measured with the Wide Range Achievement Test-Fourth Edition (WRAT-4). The WRAT-4 Reading test involves the recognition and naming of letters and the pronunciation of words out of context. Participants are provided with the Green Wording list to read from. The administrator checks pronunciation carefully and scores the participant's responses. This test will take approximately five minutes to complete.

5.5.2.2.2. Attention/scanning, speed/sequencing, and executive function will be assessed by the Trail Making Test (Comprehensive Trail Making Test Trails 1 and 5).[79,80] In part A/Trail 1, participants draw a line connected to each number in sequential order. In part B/Trail 5, participants draw a line to connect numbers and letters in sequential order. Time to complete the test (in seconds) is recorded for both parts A and B. Part A is stopped after 3 min, and Part B is stopped after 5 minutes.

5.5.2.2.3. Verbal fluency/executive function will be assessed by the Controlled Oral Word Association Test (COWA).[81] Designed by Benton and colleagues, this test assesses fluency with naming words with C, F, and L. Participants are asked to tell the administrator as many words as possible beginning with the letter C, excluding proper nouns and the same word with a different suffix. The participant has 60 seconds to list as many words as possible. The number of correct words will be recorded. This test takes less than five minutes to administer. Trials are repeated for the letter F and L.

5.5.3. Phone-based Cognitive Testing

All phone-based cognitive testing will be conducted by trained research study staff at the URCC NCORP Research Base. Research study staff will contact participants by email or text messaging to schedule the phone-based cognitive testing if necessary. The adapted Brief Test of Adult Cognition by Telephone (BTACT) will be used and was originally developed at the Lifespan

Developmental Psychology Lab by Drs. Margie Lachman and Patricia Tun. This adapted telephone test battery was developed to be brief (taking no more than 20 minutes to administer), to cover important domains of adult cognitive functioning, and to be easily administered by trained personnel. BTACT testing has resulted in similar cognitive scores as in-person testing. [82]

5.5.3.1.1. Each participant will be asked to verify a short string of numbers (3,8,5) at the beginning of the call.

5.5.3.1.2. Memory will be assessed by the Rey Auditory-Verbal Learning Test[81]. One trial is administered at the beginning of the session and a second delayed trial is administered at the end of the session. One word per second is read aloud, and the participant recalls back as many of the words as possible within one minute. At the end of the session, participants are asked to recall as many words as possible from the list. The number of correct responses (one point) is totaled for the scoring of both immediate and delayed recall. The number of incorrect responses is also recorded for each.

5.5.3.1.3. Working memory/attention will be assessed with the backward digit span test from the WAIS-III (1997).[83] The participant hears an increasingly longer series of digits read by the interviewer (starting with 2 digits leading up to 8 digits), and attempts to repeat them in reverse order. Two chances are given to complete each level. The test is stopped when the participant cannot get either trial for a particular number of digits. The score is the longest string (maximum of 8) that the participant can read in reverse order.

5.5.3.1.4. Executive function (verbal fluency) will be assessed by category fluency. Participants will be asked to list as many items in the category "animals" as they can within 60 seconds. The second executive function test is the Number Series test which involves a number series of increasing or decreasing length and pattern of numbers where the participant has to state what the next number would be. This is a 5-item measure.

5.5.3.1.5. Speed of Processing will be assessed by backward counting. Each participant will be asked to count backwards from 100 by one unit, and has 30 seconds to get as far as they can. The score is the total number of correct numbers reported. Skipped numbers and number of errors are also recorded.

5.5.4. Self-Reported Outcomes

Note: FACT-Cog is completed prior to computerized and paper-based testing.
After completion of computerized and paper-based cognitive assessments, all participants will complete the remaining questionnaires including the CES-D, Symptom Inventory, STAI, MFSI-SF, and Godin. Based on previous studies, we anticipate that these forms will take participants approximately 15 minutes to complete.

5.5.4.1. Self-reported cognitive functioning will be assessed by the Functional Assessment of Cancer Therapy with Cognition (FACT-Cog, ver 3). This measure includes 37-items. The FACT-Cog addresses a wide range of cognitive functioning domains which allows one to separate specific domains of cognition. It was developed by Wagner and colleagues[84] and is currently undergoing validation in studies with cancer patients.[85]

5.5.4.2. Depressive symptoms will be measured with the Center for Epidemiological Studies Depression Scale (CES-D). The CES-D is a 20-item depression scale developed and validated for use with a variety of populations. It is in a format similar to that of the Beck Depression Inventory, but with less emphasis on physical symptoms of depression that may be confounded with disease symptoms or treatment side effects. It has been shown to reliably and validly measure depression in cancer populations,[86] and we have successfully used this measure in previous studies.

5.5.4.3. General symptomatology will be measured with a Symptom Inventory, a list of symptoms modified from measures created at M.D. Anderson and Memorial Sloan-Kettering Cancer Centers. It is a series of uniscales where the severity of each symptom is indicated on an 11-point scale, anchored by 0 = "Not Present" and 10 = "As Bad as You Can Imagine."

5.5.4.4. Anxiety will be measured using the Spielberger State/Trait Anxiety Inventory (STAI Form). In order to reduce the overall participant burden, we will use only the state portion of the questionnaire. This one-page, self-administered questionnaire consists of 20 short statements which people may use to describe their feelings. Participants are asked to fill in a numbered circle to indicate the degree to which they generally experience the particular feeling, ranging from 1 = "Not at all" to 4 = "Very much so" at that time. It is one of the most widely-used assessments of anxiety. Internal consistency coefficients > 0.90 have been shown, along with test/retest reliability coefficients > 0.70. Concurrent, construct, convergent and divergent validity have also been demonstrated.[87] We have successfully implemented this measure in previous studies.

5.5.4.5. Fatigue will be assessed via the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF). The MFSI-SF is a 30-item fatigue scale developed specifically for documenting cancer-related fatigue. In addition to a fatigue total score, the instrument includes subscales for assessing general, physical, emotional, mental and vigor domains of fatigue. The self-report instrument was psychometrically validated among a sample of 304 cancer patients and has been shown to have good fit via confirmatory factor analysis, reliability and validity.[88]

5.5.4.6. The Godin is a brief two-part questionnaire used for assessing changes in leisurely exercise behavior over time and for assessing the impact of a physical activity program**.** [89]

5.5.5. Blood Draw

5.5.5.1. Blood samples will be collected as part of the Pre-Intervention, Mid-Intervention, and Post-Intervention assessments. All study coordinators must perform training prior to any study procedures. Training can be organized by sending an email to the study mailbox (urcc_16092@URMC.rochester.edu).

5.5.5.2. Cytokines (i.e., MCP-1, IL-1 β, IL-6, IL-8, IL-10, sTNFR2 and sIL1Ra) can be reliably measured in the blood serum using a Luminex Multiplex Assay. Blood will be collected for banking of serum and plasma and whole blood for future protein, DNA and RNA analyses. An 8-hour fasting blood draw will be performed on all participants for the Pre-Intervention, Mid-Intervention, and Post-Intervention assessments. Six tubes of blood (approximately 50ml) will be collected including: two red top tubes for serum, two purple top EDTA tubes (1 for plasma and 1 for DNA) and 2 Paxgene tubes for RNA. All NCORPs will

handle all human biological materials and disposal of biohazard waste in accordance with biosafety level II guidelines at their respective institutions for blood collection, handling, disposal, storage and shipping. All NCORP personnel handling human biological materials and laboratories used by NCORPs must have received appropriate biosafety certifications and meet routine inspection guidelines.

5.5.5.3. All requisitions, blood tubes, microfuge tubes, freezer boxes, pipettes, and labels for blood draws are provided by the URCC NCORP Research Base in the form of barcoded and pre-labeled participant kits. All participant kits are study specific.

DO NOT MIX REQUISITIONS, BLOOD TUBES, MICROFUGE TUBES OR PIPETTES ACROSS PARTICIPANT BLOOD DRAW KITS EVEN IN THE SAME STUDY BECAUSE THE BARCODES AND LABELS ARE KIT SPECIFIC.

DO NOT MIX THE FREEZER BOXES, LABELS OR EXTRA SUPPLIES PROVIDED ACROSS STUDIES EVEN URCC NCORP RESEARCH BASE STUDIES BECAUSE THEY ARE STUDY SPECIFIC.

All study coordinators will fill in the appropriate participant information on the requisition form in each kit when it is assigned to the participant. Every time a blood draw is performed a separate new kit is used and assigned to the study participant. Each NCORP is responsible for designating an individual that is certified by URCC and a lab or facility that meets the biosafety level II criteria to perform the blood draws and to handle, dispose, store and ship the blood samples appropriately. The individual designated to coordinate the blood draws, handle, dispose, store and ship the samples must participate in the training provided by the URCC NCORP Research Base, and be approved by the study PI, Dr. Janelsins, prior to any blood collection at each NCORP site.

5.5.5.4. Serum will be extracted from the two red top tubes for estimation of cytokines (MCP-1, IL-1 β, IL-6, IL-8, IL-10, sTNFR2 and sIL1Ra). Plasma will be extracted from one of the purple top EDTA tubes for estimation of cytokines (MCP-1, IL-1 β, IL-6, IL-8, IL-10, sTNFR2 and sIL1Ra). To extract the serum and plasma, the tubes will first sit upright for 30 minutes at room temperature after blood collection. Second, the tubes will then be put into a centrifuge (4°C if available) and spun for 15 minutes at 1600 x g. After 15 minutes, there should be a clear separation of the serum or plasma (yellowish liquid on top) from the other cells. If this is not evident, then centrifuge for 15 additional minutes. The upper layer of serum (red top tubes) and plasma (purple top tube) is then gently aliquotted into the 2.0ml microfuge tubes provided in each URCC NCORP participant blood draw kit. Serum from the red top blood tubes is to be placed into the pre-labeled pink microfuge tubes. Plasma from the purple top tube is to be placed in the pre-labeled purple microfuge tubes. All microfuge tubes are then placed in the pre-labeled freezer boxes provided by the URCC NCORP Research Base and the freezer box is then placed in either a -20°C freezer or a -80° C degree freezer (-80°C is preferred if available but not required) for storage until shipped to URCC NCORP Research Base. Cytokines (MCP-1, IL-1 β, IL-6, IL-8, IL-10, sTNFR2 and sIL1Ra) will be assessed using Multiplex and ELISA methods as appropriate. The remaining serum and plasma will be stored and banked for use in future research by Dr. Janelsins and her research team if participants have given permission.

5.5.5.5. One purple top EDTA tube and two Paxgene tubes will be prepared and stored for future DNA and RNA extraction. The EDTA tube will be rocked 10 times and then placed upright in a -20° C freezer for a minimum of 24 hours. After 24 hours, the EDTA tube can then be transferred to a -80° C freezer if available. The two Paxgene tubes will be rocked 10 times, stored upright for minimum of 2 hours and a maximum of 24 hours at room temp and then placed upright in a -20° C freezer for a minimum of 72 hours. After 72 hours, the Paxgene tubes can be transferred to a -80° C freezer if available. After the tubes have been frozen upright for their designated time above, they can then be placed on their side in the pre-labeled freezer boxes provided by the URCC NCORP Research Base. (Storage in a -80° C freezer after 4 days is preferred if available but not required.)

5.5.5.6. Shipping Supplies to NCORPs and Inventory Tracking:

When the URCC NCORP Research Base receives notification that the NCORP has received CIRB approval, a starter blood drawing package, Blood Procedures Operations Manual, and an initial supply of barcoded and pre-labeled blood draw kits will be shipped to the NCORP for distribution and use.

Each NCORP site will be responsible for designating someone on the research staff to be responsible for receiving the blood draw supplies and kits. The staff member will verify that the shipment contains the correct number of supplies and kits and that the supplies and kits are in good condition. The identification numbers need to be verified for accuracy and recorded. The Investigational Device Accountability Record (DARF) will be used to track supplies and kits arriving from the URCC NCORP Research Base, kits given to participants, samples stored, and samples shipped to the URCC NCORP Research Base.

5.5.5.7. Shipping Frozen Blood Samples to URCC NCORP Research Base:

THE URCC NCORP RESEARCH BASE MUST BE NOTIFIED AND ARRANGEMENTS MADE TO RECEIVE SAMPLES AT THE URCC NCORP RESEARCH BASE 24 HOURS IN ADVANCE PRIOR TO SHIPPING ANY SAMPLES

WE WILL NOT ACCEPT PACKAGES TO BE RECEIVED ON A FRIDAY.

To arrange shipping samples, refer to the provided URCC16092 Blood Procedures Operations Manual.

Ship Samples To:
ATTN: Cancer Control
University of Rochester Medical Center
CCPL Laboratory (2-3155)
601 Elmwood Avenue
Rochester, NY 14642

NCORPs must ship the frozen samples to the URCC NCORP Research Base CCPL Lab every 3 months. Samples cannot be kept at the NCORP location for longer than 3 months total. Samples can be shipped sooner if storage space is limited.

The NCORPs are responsible for shipping all samples to the URCC NCORP Research Base. All samples must be shipped **priority overnight** and frozen on dry

ice. Each NCORP is responsible for adhering to URCC NCORP Research Base biosafety level II guidelines (outlined in the Blood Procedures Operations Manual provided), their NCORP institutional biosafety level II guidelines and the shipping company guidelines when packing and shipping the frozen blood samples to the Research Base.

5.6. Mid-Intervention Assessments

Between study Days 14 and 26 participants will complete Mid-Intervention assessment. At Mid-Intervention, the study coordinator will collect and process blood samples and complete the Blood Requisition form, and store samples until shipping is required. Participants will complete a FACT-Cog questionnaire between study Day 14 and 26 on their own.

5.7. Post-Intervention Visit

Ideally, the Post-Intervention visit will occur on Day 41. However, if a participant cannot complete the Post-Intervention visit on day 41, the participant can complete the visit on Days 38-44. For participants that are currently receiving chemotherapy, the Post-Intervention visit can occur on the same day as a chemotherapy treatment if assessments are completed prior to chemotherapy.

At the Post-Intervention visit, participants will complete study questionnaires including the FACT-Cog, CES-D, MFSI-SF, STAI, and Symptom Inventory (SI), Godin, and feedback questionnaire. Study staff will complete the Investigational Agent Accountability Form after the participant returns unused study agent.

Cognitive assessments to be performed at the Post-Intervention visit include the CANTAB computerized assessment, paper-based cognitive testing (COWA and CTMT), and phone-based Cognitive Testing administered by URCC staff. Note: FACT-Cog is to be completed prior to computerized and paper-based testing. For participants receiving chemotherapy, the anticipated date of the last chemotherapy received while on the study will be communicated to the URCC Research Base by email when sending Post-Intervention CANTAB data files. Phone based-testing will be completed within 7 days of the in-clinic Post-Intervention assessments.

Blood samples will be collected during the Post-Intervention visit period, the Blood Requisition form will be completed, and processed samples will be shipped to the URCC NCORP Research Base when required per shipping requirements in Section 5.5.4.

The Laboratory Data form will be completed using test results abstracted from the participant's medical record. Lab values entered into the Laboratory Data form for the Post-Intervention time point should be collected within 10 days of the Post-Intervention visit. If blood tests have not been completed within 10 days of the Post-Intervention visit the coordinator will document this on the Laboratory Data form.

All cancer treatment records (e.g., chemotherapy, any biologic/targeted therapies, radiation) prior to going on study through the duration of the study must be submitted with protected health information redacted and labeled with Participant ID and NCI protocol number.

Study coordinators will collect unused study agent and completed diary pages from study participants at the Post-Intervention visit.

5.8. Potential Risks

5.8.1. Ibuprofen

The potential risks and side effects of ibuprofen can include headaches, dizziness, drowsiness, rash, abdominal pain, nausea, diarrhea, constipation, renal insufficiency, and heartburn. Since ibuprofen reduces the ability of blood to clot, bleeding may be increased after injury. Studies of high doses of ibuprofen (800 mg 3 times per day) have been associated with low incidence of gastroduodenal and gastric ulcers.[90,91] The low dose for the proposed studies is not likely to cause ulcers; as a precaution, we are excluding those who have a history of ulcer disease during the past year. A full list of potential side effects of ibuprofen are located in the consent form and will be reviewed with the potential participant. Additionally, lactose is not an exclusion criteria due to trace amounts found in the placebo capsules (approximately 0.32 grams); however, this information is included in the consent form and will be reviewed with the potential participant and any concerns should be addressed with the provider.

NSAIDs (e.g., ibuprofen) have been used in clinical studies in cancer patients receiving chemotherapy and have been safe and have not altered chemotherapy pharmacokinetics.[92] The doses of ibuprofen and time-frame of ibuprofen that we have chosen are similar to other ongoing studies of NSAIDs given in combination with chemotherapy (clinicaltrials.gov identifiers: NCT00520091, NCT00300729, NCT00064181, NCT00135018).

5.8.1.1. Ibuprofen Toxicity Monitoring

Participants should be removed from the study for any of the following reasons:

1. Any grade ≥ 4 toxicity probably or definitely related to the study agent.
2. Any grade ≥ 2 toxicity that persists for more than 2 weeks that is probably or definitely related to study agent.
3. Any grade ≥ 2 GI bleeding.
4. Primary treating physician deems it is unsafe for the patient to continue on the study for any reason.
5. Withdrawal of consent.

5.8.1.2. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for adverse events (CTCAE), version 5.0 as described in Section 11.

5.8.2. Blood Collection

There is a chance of bruising and a very slight chance of infection with blood collection. This will be minimized through the use of standardized hospital procedures for blood collection, use of a trained phlebotomist and sterile materials.

5.9. Participant Withdrawal

If a participant decides to withdraw from the study, the study staff should clarify whether the participant wishes to withdraw entirely from the study or only from a component of the study. If a participant requests to be withdrawn from the study agent, research activities involving other components of the clinical trial, such as follow-up data collection activities, for which the participant previously gave consent, may continue. The study site staff may continue to follow the study participant for assessment data if the participant agrees and medical monitors feel it is safe for the participant to complete study assessments. Study participants may resume the study intervention if the participant agrees and medical monitors feel it is safe for the participant to receive study intervention. All communication (e.g., emails) with study medical monitors must be documented and recorded in the research record. Any withdrawals or partial withdrawals are documented on a Withdrawal and Study Status Form via REDCap with a physical copy of the form

filed in the participant binder. The REDCap Withdrawal and Study Status Form can be found on the URCC NCORP Research Base website.

5.10. Data & Specimen Storage for Future Research Use

All human blood samples collected for the current study will be used in post hoc analyses as appropriate by Dr. Janelsins' and her colleagues. The participant indicates on the consent form whether their blood is allowed to be used for future research. If a participant does not allow their blood to be used for future research, their blood will not be stored. Human samples collected for future research are stored in locked and alarmed freezers within Dr. Janelsins' labs that are accessible by electronic card swipes or card swipe and key.

5.11.Costs to the Participant

All study materials are provided without cost to participants.

5.12.Payment for Participation

Participant Payment: In order to improve study retention and compliance, participants will be compensated for their participation and completion of study procedures. Participants that complete all assessments will receive a total payment of $100.00. Participants will receive $25.00 after completing the Pre-Intervention assessment, $30.00 after completing the Mid-Intervention assessments ($5/wk x 6 weeks), and $45.00 after completing the Post-Intervention assessment. Compensation has been pro-rated for participants that do not complete the full study. Participants are only paid for the study assessments they actually complete. Each NCORP will be responsible for dispersing the payments to study participants using methods appropriate for their sites. Each NCORP will invoice the URCC Research Base monthly for payment expenses. URCC will only reimburse for the cash value per assessment; no gift card or other fees will be reimbursed if NCORPs choose to use methods of payment that incur extra fees in lieu of cash. Contact Christine Lanceri to obtain an NCORP-specific invoice.

Send invoices by email to:
Mrs. Christine Lanceri
Email: Christine_Lanceri@URMC.rochester.edu

6. INTERVENTION/STUDY AGENT ADMINISTRATION AND INFORMATION

6.1. Contraindications

Participants must have approval of their treating physician to take the study agent. Participants should not take a regular daily NSAIDs in addition to their study agent during the intervention period. Higher doses of an NSAID on an 'as needed' basis are permitted. Daily doses of 81 mg aspirin are permitted.

6.2. Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the Medication Usage form at the Pre-Intervention visit. Medications taken for a procedure (*e.g.*, surgery) should also be included.

6.3. Adherence/Compliance

6.3.1. Intent to treat analysis will be used. All participants enrolled into the study will be included in the analysis.

6.3.2. Adherence and compliance of participants to the study agent will be monitored via the Daily Diary. Also, during weekly phone calls, study coordinators will question participants on their study agent compliance and address any questions. Participants are also asked to return unused study agent at the end of the intervention period for an evaluation of study agent compliance. The Investigational Agent Accountability Form will be used to capture the number of capsules dispensed to and returned from participants.

7. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

7.1. Primary Endpoint

The primary aim is to provide preliminary data on the effects of ibuprofen on alleviating cancer-related cognitive impairment in cancer patients that have received chemotherapy compared to placebo control, as assessed by the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog).

7.2. Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, adverse event or serious adverse event, inadequate agent supply, noncompliance, concomitant medications, or medical contraindication. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events.

The participant will stop the study medication at the Post-Intervention visit (if visit occurs Days 38-41). If participants are 100% compliant with the study agent use instructions, there will be no capsules left in the bottle at the end of Day 41. Because there is flexibility in scheduling the post-intervention visit, the participant could end prior to Study Day 41 (i.e. 42 days of medication). In this case, the number of pills left will be noted on the Investigational Agent Accountability Form. If a participant is withdrawn or partially withdrawn from the study, coordinators will record the study day on which the study agent is stopped on the REDCap Withdrawal and Study Status Form.

Study medication may be stopped at any time as determined by the treating physician if there is a reason they deem the intervention is unsafe for the participant as mentioned in the toxicity monitoring plan in Section 5.8.1.1.

There are no dose modifications of the study agent.

7.3. Off-Study Criteria

Participants may go 'off-study' for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, adverse event/serious adverse event, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, death, physician request, or pregnancy.

8. STUDY AGENT/DEVICE DISTRIBUTION – IBUBROFEN/PLACEBO

8.1. Availability

Ibuprofen and matching placebo will be manufactured by the UR IDS and supplied by URCC NCORP Research Base. Both ibuprofen and placebo capsules will be packaged in bottles containing 84 capsules.

8.2. Distribution

The ibuprofen and placebo capsules will be supplied by the UR IDS and will be over-encapsulated. Agents will only be released by URCC NCORP Research Base affiliates approved to participate. URCC-supplied agents must be requested by the Investigator (or their authorized designees) at each site. URCC does not automatically ship agents; the site must make a request. Agents are requested by emailing the URCC NCORP Research Base and should include complete shipping and contact information):

Kari Gilliland
URCC_16092@URMC.rochester.edu
585-275-6303

8.3. Agent Accountability

The NCORP site, and responsible party designated at the site, must maintain a careful record of the inventory and disposition of all agents received from the URCC NCORP Research Base using the Investigational Agent Accountability Record. All receipt and dispensation of study agent should be recorded, including date, quantity and batch or lot number.

8.4. Packaging and Labeling

UR IDS, under the direction of Steve Bean, PharmD, will package, label and oversee the distribution of ibuprofen and placebo to participating NCORP sites. Each bottle of study agent will contain 84 capsules. Each bottle will be labeled with a two-part label identifying study specific information, including study title, URCC protocol number, dosing instructions, recommended storage conditions, the name and address of the distributor, randomization number, and a caution statement indicating that the agent is limited by United States law to investigational use only and the agent should be kept out of reach of children.

8.5. Storage

Store ibuprofen and placebo at room temperature, between 59°F and 86°F (15°C and 30°C). Store study agents away from heat, moisture, and light. Study agents should be stored in a secured location that is locked at all times and only accessible by approved study personnel.

8.6. Blinding and Unblinding Methods

Participants, study coordinators, and investigators will be blinded to ibuprofen/placebo group assignments. The active study agent supplied to participants entered into arm 1 will be indistinguishable from the placebo supplied to participants entered into arm 2. Active agent and placebo treatments will be self-administered by participants at the same dose and frequency (200 mg twice a day). Study agents supplied to sites will be labeled with a letter code that will be used to identify the assigned treatment arm for unblinding purposes.

Unblinding of the study agent is ONLY permitted in the case of serious and unexpected adverse events that are definitely associated with the use of the study agent AND if knowledge of the study treatment arm received is necessary for interpreting the medical event and related treatment of that medical event. In this situation, only the treating physician will be made aware of the study agent dispensed and no other staff members will be notified. Research staff at NCORP sites can request unblinding of a participant's study agent treatment group by emailing the URCC NCORP Research Base and should include participant ID number, site investigator, and reason for unblinding in the message:

Kari Gilliland
URCC_16092@URMC.rochester.edu
585-275-6303

URCC Research Base staff will contact sites regarding unblinding requests within 24 hours of notification. Participants that require emergency study agent disclosure will discontinue the study agent. The research team may continue to follow the study participant for assessment data with participant and medical monitor approval.

Any unblinding will be communicated to the CIRB in accordance with its reportable events policy.

9. CORRELATIVE/SPECIAL STUDIES

9.1. Rationale for Methodology Selection

We will use standardized Millipore Luminex kits that have been used to analyze these or similar targets in hundreds of samples from NCORP samples in Dr. Janelsins' laboratory. These are industry standard kits that have undergone R&D and validation at Millipore.

9.2. Comparable Methods

Luminex kits are industry standard and well validated. We can replicate our results with ELISA in a subset of participants.

10. SPECIMEN MANAGEMENT

10.1.Laboratories

All samples will be analyzed by the University of Rochester Medical Center Cancer Control and Psychoneuroimmunology Laboratory using the same Luminex machine with the same assay kits and reagents. This will limit biases in data output. The lab will conduct stability and selectivity analyses for our samples to assure data quality before running all samples. Any remaining samples will be stored in the URCC NCORP Research Base secure and alarmed -80C freezer.

10.2.Specimen Storage

After processing, the remaining blood samples will be stored for use in future research by Dr. Janelsins and her research team. Only specimens where participants have consented to future research will be used in any future research not included in this protocol.

11. REPORTING ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by federal regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's common terminology criteria for adverse events (CTCAE), version5.0. The CTCAE is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.html.

CTCAE term (AE description) and grade: CTCAE version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The relationship to the study agent and the severity of each adverse event as judged by the investigator must be recorded. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

11.1.Definitions

Adverse event (AE) is any untoward medical occurrence associated with the use of a medical product, which does not necessarily have a causal relationship with its use. An adverse event can be any unfavorable and unintended sign (including abnormal laboratory test results), symptom, or disease temporally associated with the use of the study product or not considered related to the study product. The relationship of each adverse event to the study interventions must be recorded as one of the choices on the scale described below.

Attribution: An assessment of the relationship between the adverse event and study agent/intervention, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is clearly NOT related to the study agent
Unlikely	The AE is doubtfully related to study agent
Possible	The AE may be related to study agent
Probable	The AE is likely related to study agent
Definite	The AE is clearly related to study agent

Serious Adverse Event (SAE): A serious adverse event is defined as any adverse medical event (experience) that results in at least one of the outcomes listed below:

1) Death
2) Life-threatening
3) Requires inpatient hospitalization or prolongation of existing hospitalization.
4) Results in persistent or significant disability/incapacity with substantial disruption of the ability to conduct normal life functions.
5) Congenital anomaly/birth defect.
6) A medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon medical judgment, it may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Hospitalization (or prolongation of hospitalization): For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.

11.2.Reporting

At each participant visit the site study staff will assess adverse events by recording all voluntary complaints of the participant and by assessment of clinical and laboratory features. At each study visit and weekly phone contact, the participant should be questioned directly regarding the occurrence of any adverse experience since his/her last contact with the study staff.

All adverse events, whether observed by study staff or investigator, elicited from or volunteered by the participant, should be documented. Each adverse event will include the date of onset, date of resolution, severity, and the relationship to the study agent or intervention, and any action taken with respect to the study agent or intervention.

Recording of the adverse events will occur once the participant signs the consent form.

Adverse events will be reported to the URCC NCORP Research Base using REDCap, which can be accessed from the URCC NCORP website. The following table will be utilized to report adverse events:

Adverse Event					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**

Unrelated		URCC-GI Bleed Only	URCC	URCC	URCC
Unlikely		URCC-GI Bleed Only	URCC	URCC	URCC
Possible	URCC	URCC	URCC	URCC	URCC
Probable	URCC	URCC	URCC	URCC	URCC
Definite	URCC	URCC	URCC	URCC	URCC

Adverse events Grades 1 and 2 that the treating physician determines are unrelated or unlikely related to study participation do NOT require reporting with the exception of grade 2 gastrointestinal (GI) bleeding which will need to be reported to URCC via REDCap Adverse Event Reporting. All other adverse events will be reported to the URCC NCORP Research Base using REDCap Adverse Event Reporting. Serious adverse events requiring expedited reporting via CTEP-AERS are described below in Section 11.3. Serious adverse events not requiring expedited reporting through CTEP-AERS should be entered into REDCap and URCC notified within 10 calendar days of learning of the event.

All recorded adverse events reported to the URCC Research Base will be reported to the Data Safety Monitoring Committee.

All adverse events that in the opinion of the investigator are clinically significant will be documented and followed according to good medical practices.

11.3.Responsibilities for Expedited Reporting

URCC NCORP Research Base affiliates are required to notify the URCC Research Base if a participant has an adverse event requiring expedited reporting. All SAEs that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task

Commercial reporting requirements are provided in the table below. The commercial agent used in this study is ibuprofen.

Expedited reporting requirements for adverse events experienced by participants who have received study agent/intervention within 30 days of the last administration of commercial study agent/intervention.

Attribution	Grade 4		Grade 5(a)	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			CTEP-AERS	CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS	CTEP-AERS

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event (b).

a) This includes all deaths within 30 days of the last dose of study agent with a commercial agent/intervention, regardless of attribution. Any death that occurs more than 30 days after the last dose of study commercial agent/intervention and is attributed (possibly, probably or definitely) to the agent/intervention and is not due to cancer recurrence must be reported according to the instructions above.

b) Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Research Base in order to complete the evaluation of the event.

For more information see:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

Contact Information for NCI Safety Reporting:

Website for submitting expedited reports	http://eapps-ctep.nci.nih.gov/ctepaers
AEMD Help Desk (for CTEP)*	301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Fax for expedited report supporting Medical Documentation for CTEP Trials	301-230-0159 (Back-up FAX: 301-897-7404)
AEMD Help Email:	aemd@tech-res.com
Technical (E.G., IT or computer issues ONLY) Help Phone *	1-888-283-7457 or 301-840-8202
CTEP-AERS Technical Help Email	ncictephelp@ctep.nci.nih.gov
CTCAE v 5 Help/Questions Email	ncicctcaehelp@mail.nih.gov
CTEP-AERS FAQs link	https://eapps-ctep.nci.nih.gov.ctepaers/help/webhelp/CTEP-AERS%20FAQ.htm
CTEP-AERS Computer based training link	https://ctep.cancer.gov/protocolDevelopment/electronic applications/adverse_events.htm

Office phone and fax are accessible 24 hours per day 7 days a week (The AEMD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.

12. STUDY MONITORING

12.1. Data Management Summary

All participant data will be identified in the database by a study ID assigned by sequential numbering. This project will collect data in multiple formats: paper documents, CANTAB csv files, electronic questionnaires (REDCap), and biospecimens (blood).

All data forms must be sent to URCC within 30 days of completion from the participant.

When paper data are received at the URCC NCORP Research Base, they are processed as follows:

1. Data are visually checked line by line for missing, duplicate, ambiguous or unreasonable responses and if found, the originating site is queried for such data.
2. When a query response is received, the form is amended per Good Clinical Practice, and the change is documented or the sites amend the form and submits it to the URCC Research Base.
3. All paper forms are scanned via Teleforms software into tables in an Access database. Again, any missing, duplicate or ambiguous data found at this step generates a query to the originating site.
4. The electronic database tables are visually checked, line by line, against the corresponding forms for accuracy.
5. Queries are also generated if data are not received per the protocol timeline.
6. When all data have been received on any given case, a chart audit is performed to ensure receipt and accuracy of all necessary data.
7. All paper documents are stored in locked file cabinets or in locked, limited access file rooms. The electronic Access databases of those scanned documents are on password protected drives located behind University of Rochester firewalls, with limited access.

Data submitted through REDCap are reviewed for accuracy and stored, protected by the University of Rochester firewalls with limited access. Queries are generated for any questionable or late data.

Biospecimens: Blood kits sent from URCC have bar-coded tubes for collecting samples. One kit is used for one data collection time point of one participant. Samples are frozen on site and shipped frozen to URCC where they are stored in locked -80^{o} freezers in Dr. Janelsins' lab with limited access.

CANTAB files are electronically sent to URCC by uploading to the URCC NCORP Research Base secure file servers via the University of Rochester's Box.com system.

1. The files are opened to confirm that the data in the file agrees with the site's label of the file.
2. These data are stored on password protected drives located behind University of Rochester firewalls, with limited access.

Forms can also be emailed to the study email:
URCC_16092@URMC.rochester.edu

(Pages sent by email must be straight with all four Teleform brackets visible on the page).

On-site audits are conducted by the Research Base at least every three years in accordance with NIH/NCI CTMB Guidelines. The primary objective of an on-site audit is to document compliance of the NCORP site with protocol and regulatory requirements, verify accuracy of data by comparing submitted data to source documents at the NCORP site, and to provide information on good clinical practice in study conduct and data management. 10% of cases accrued at each component site are audited. The on-site pharmacy is visited and investigational agent records are reviewed at that time.

12.2.Records to be Kept

Evaluation/ Procedure	Screening	Pre-Intervention	Day 0	Mid-Intervention	Post-Intervention
Eligibility Checklist	X				
Informed Consent Form	X				
Screening Data on all approached subjects (Submitted electronically)	X				
Clinical Trial Patient Registration	X				
Clinical Record Information*		X			
On Study Data/Participant Form		X			
Medication Usage		X			
Investigational Agent Accountability Form					X
Behavioral Observations During Cognitive Testing		X			X
WRAT-4 Reading		X			
CTMT		X			X
COWA		X			X
Laboratory Data		X			X
Blood Requisition Form		X		X	X
BTACT Phone Interview Tests (URCC Conducts)		X			X
FACT-COG		X		X	X
CES-D		X			X
STAI		X			X
MFSI-SF		X			X
Symptom Inventory		X			X
GODIN		X			X
Feedback Questionnaire					X
Daily Diary			Daily	Daily	Daily
Call Logs		Weekly	Weekly	Weekly	Weekly
Receipt for Participation		X		X	X
Withdrawal and Study Status Form (Completed as needed in REDCap)					

* All cancer treatment records (e.g., chemotherapy and other biologic therapy-radiation summary) prior to going on study through the duration of the study must be submitted with the Post-Intervention forms (with protected health information redacted).

12.3.Data and Safety Monitoring Plan

All adverse events reported to URCC are per Section 11.

The James P Wilmot Cancer Center Data Safety Monitoring Committee (DSMC) will serve as the DSMC of record for this study. The DSMC provides oversight of study progress and safety by review of accrual and events at regularly scheduled meetings.

Study investigators conduct continuous review of data and patient safety. The Wilmot Cancer Center Peer Review Committee has determined that progress reports of these data will be submitted annually to the DSMC for review. These reports will include: the number of participants enrolled, withdrawals, any

significant toxicities, and serious adverse events both expected and unexpected. The study chair maintains a database of all adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. A copy of the AE spreadsheet is submitted with the annual progress report to the DSMC for review. Actual review dates will be assigned when the 1st patient is accrued.

- Any adverse event that is serious, related AND unexpected must be reported within 10 calendar days from notification to the DSMC safety coordinator and DSMC chair. The NCORP sites will report to the URCC NCORP Research Base in REDCap and if applicable CTEP AERS per Section 11 of the protocol. The NCORP Research Base will be responsible for reporting to the DSMC. The DSMC Chair will determine whether further action is required, and when patient safety is of concern, may call an interim meeting.

- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the Committee for review at the annual meeting. SAE reports are expected to include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Unless otherwise specified in the protocol, serious adverse events that require reporting (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5. See Section 11 for specific reporting requirements for this protocol.

The DSMC Safety Coordinator administratively coordinates reports and data collection and prepares documents for the DSMC Chair and committee review. The Safety Coordinator will administratively monitor adverse event rates utilizing the report from the study database. If the study has had two or more of the same SAE's reported in a month or more than six of the same SAE's in six months, the DSMC will review the summary of SAEs, discuss events with Study Chair, and conduct a more detailed review with the Study Chair. The Data Safety Monitoring Chair will determine if further action is required.

The URCC will notify the NCORP sites immediately of any serious safety concerns identified by the DSMC. DSMC reports will be available for download on the research base website.

12.4. Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the originating NCORP site in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidance, and NCI/DCP requirements, unless the standard at the site is more stringent. Records will be retained at the NCORP site for at least five years after the completion of the research. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration.

13. STATISTICAL CONSIDERATIONS

13.1. Study Design

This is a phase II, multi-center, double-blind (based on ibuprofen), placebo-controlled, two-arm randomized clinical trial of an intervention to determine the preliminary efficacy of the two treatment arms on perceived cognitive function using intent to treat principles.

13.1.1. Data Handling

Data will be analyzed as intent-to-treat. Since this is phase II trial all individual tests will be performed at the two tailed 10% significance level.[93,94] The assumptions underlying all statistical analyses will be thoroughly checked. In the

case of serious violations of distributional assumptions, appropriate nonparametric methods or transformations will be attempted. If outliers or influential data are detected, the accuracy of the data will be investigated; analyses may be done without these cases to evaluate their impact on the results. We will also conduct exploratory analyses on a subset of participants that provided data for both Pre- and Post-Intervention and will also conduct analyses of the outcomes based on compliance.

13.1.2 Missing Data

Every effort will be made to avoid dropout, but dropout is inevitable. In keeping with intent to treat, we will apply multiple imputation to all our analyses, thereby including all randomized subjects irrespective of whether they has post-intervention data. These results will be compared with the complete case results. If they are similar, we will report the complete case results. If we believe that the mechanism for missing data is missing not at random (MNAR), we will perform a sensitivity analysis using pattern-mixture models.[95]

13.1.3 Sample Size and Power

We do not know what the possible effect sizes of the interventions might be which is the reason for conducting this RCT; this is, therefore, not a fully powered study. We will target 43 per group to account for 30% dropout and anticipate 30 evaluable per group. We have used this N per group for several similar 2 year R21/Phase II-level studies in the past. This sample size will be sufficient for informing the design of a possible Phase III study. Assuming a correlation of 0.65 between the pre- and post- treatment measures of FACT-Cog (calculated using the data in Study 5), this sample size allows for detecting effect sizes ≥ 0.5 comparing each individual arm with control at the two-sided 10% type I error with 80% power. These calculations are based on contrast estimates from an ANCOVA.

13.2.Primary Objectives and Analysis Plans

Primary Objective: To provide preliminary data on the effect of ibuprofen on alleviating CRCI in cancer patients who have received chemotherapy compared to a placebo controls as assessed by the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog).

Primary Hypothesis: Ibuprofen will lead to more improvement in FACT-Cog scores from Pre- to Post-Intervention in cancer patients who have received chemotherapy compared to the control group (placebo).

Primary Statistical Analyses: Means, standard deviations, and 95% confidence intervals will be determined in order to estimate preliminary population variances and effect sizes in preparation for a larger R-01 investigator-initiated efficacy trial for cognitive scores as described in the measures. These statistical measures will be calculated by group for the Pre and Post measures of the FACT-Cog scores as well as the change (Post-Pre) in the scores using the subjects that completed the study (complete case estimation). The complete case estimates will be compared to multiple imputation estimates based on all subjects that completed Pre-Intervention as outlined in 13.1.2 above.

Additional Primary Aim Analyses: In addition to the above descriptive statistics, an ANCOVA will be run using FACT-Cog Post-Intervention as the response with group (ibuprofen/placebo) as the fixed effect and baseline FACT-Cog as a covariate. NCORP Site will also be entered in the model initially as a fixed effect and removed if not statistically significant. The mean Post-Pre changes in Fact-Cog for Ibuprofen vs. placebo will be estimated from the model (the main effect). The ANCOVA results including the main effect estimate will be used to inform the design of the future R-01 study. We will also construct models controlling for relevant covariates (e.g., age, gender, education, menopausal status, medications, WRAT-4 Reading score, chemotherapy type, fatigue, anxiety, and depression, number of cycles of prior

chemotherapy, treatment regimen and cycles, and expectancy/beliefs); non-significant factors will be removed. We will also conduct ANCOVA analyses stratified by 1) cancer type (i.e. colorectal, breast, other), and 2) by treatment status (i.e. completed chemotherapy (yes/no)) to compare the main effect estimates across cancer types and treatment status, respectively.

13.3. Exploratory Objectives and Analysis Plans

1. To provide preliminary data on the effects of ibuprofen on alleviating CRCI in cancer patients who have received chemotherapy compared to placebo controls by objective assessments of cognitive function as measured by validated neuropsychological assessment of verbal memory, attention, and executive function via CANTAB (computerized DMS, VRM, RVP) and paper-based measures (CTMT and COWA) respectively.

2. To provide preliminary data on the effects of ibuprofen on alleviating CRCI in cancer patients who have received chemotherapy compared to placebo controls on phone-based cognitive function measures (digit span, word recall, digits backward, CALVT, category fluency; all from BTACT).
For 1 and 2, ANCOVA will be used as with the primary aim analyses to assess mean differences between cognitive function assessed by the remaining objective total scores at Post-Intervention.

3. To provide preliminary data on the individual effects of ibuprofen on alleviating CRCI in cancer patients who have received chemotherapy compared to placebo controls on serum pro- (MCP-1, IL-6, IL-8, TNF-α, sTNFR2, sTNFR1, IL-1β) and anti-inflammatory (sIL-1Ra, IL-10) cytokines/receptors. We will also assess the effects of the interventions on cytokines, hypothesizing that each intervention will reduce pro-inflammatory cytokines and increase anti-inflammatory cytokines using the same ANCOVA analysis as 1.

4. To provide preliminary data on the mediating effects of cytokine/ receptor concentrations on the CRCI changes due to ibuprofen, in cancer patients who have received chemotherapy compared to placebo controls.

To assess these aims, we will use the techniques of mediation analysis, popularized by Baron and Kenny[96], described by Kraemer[97] in clinical trials contexts, and methodologically updated by MacKinnon et al.[98] Specifically, we will use path modeling to estimate indirect (mediation) effects, and bootstrapping to estimate the 95% confidence intervals. We will use the MPlus software.[99] We will evaluate whether cytokines mediate the effect of the intervention on cognitive scores. This will involve a separate analysis for each cytokine, using linear models with Arm, Pre-Intervention cognitive score and with/without cytokine post-pre change scores as model predictors (to be used for hypothesis-generation/aid in the R01 design). In addition, we will attempt to do a structural equation model (SEM) where the mediator is a latent variable measured by changes in all the cytokines, and the response is a latent variable representing CRCI using the FACT-Cog subscales.

5. We will also verify adherence to the study medication (pill counts) and determine if it was similar between all groups. In addition, we will review non-study NSAID medication usage (tracked on the Daily Diary) and determine if there is a difference between arms. Specifically, we will assess total counts and differences between groups on number of days of non-study medication on the Daily Diary and number of days a week of ibuprofen and other NSAID use on the Medication Usage Form.

13.4.Interim Analysis

There will be no interim analysis for this protocol.

13.5.Ancillary Studies

Ancillary studies could include exploratory data analyses and use of blood samples for future research.

14. **FINANCING, EXPENSES, AND/OR INSURANCE**

This study is supported by the URCC NCORP Research Base grant UG1CA189961 and NCI R21CA187500. There are no expenses to the participant for participating in this study. Compensation for participants is described in Section 5.15.

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