Protocol 18-380
Tumor Markers, Liquid Biopsies, and Patient Reported Outcomes in Metastatic Colorectal, Pancreatobiliary, and Esophagogastric Cancers
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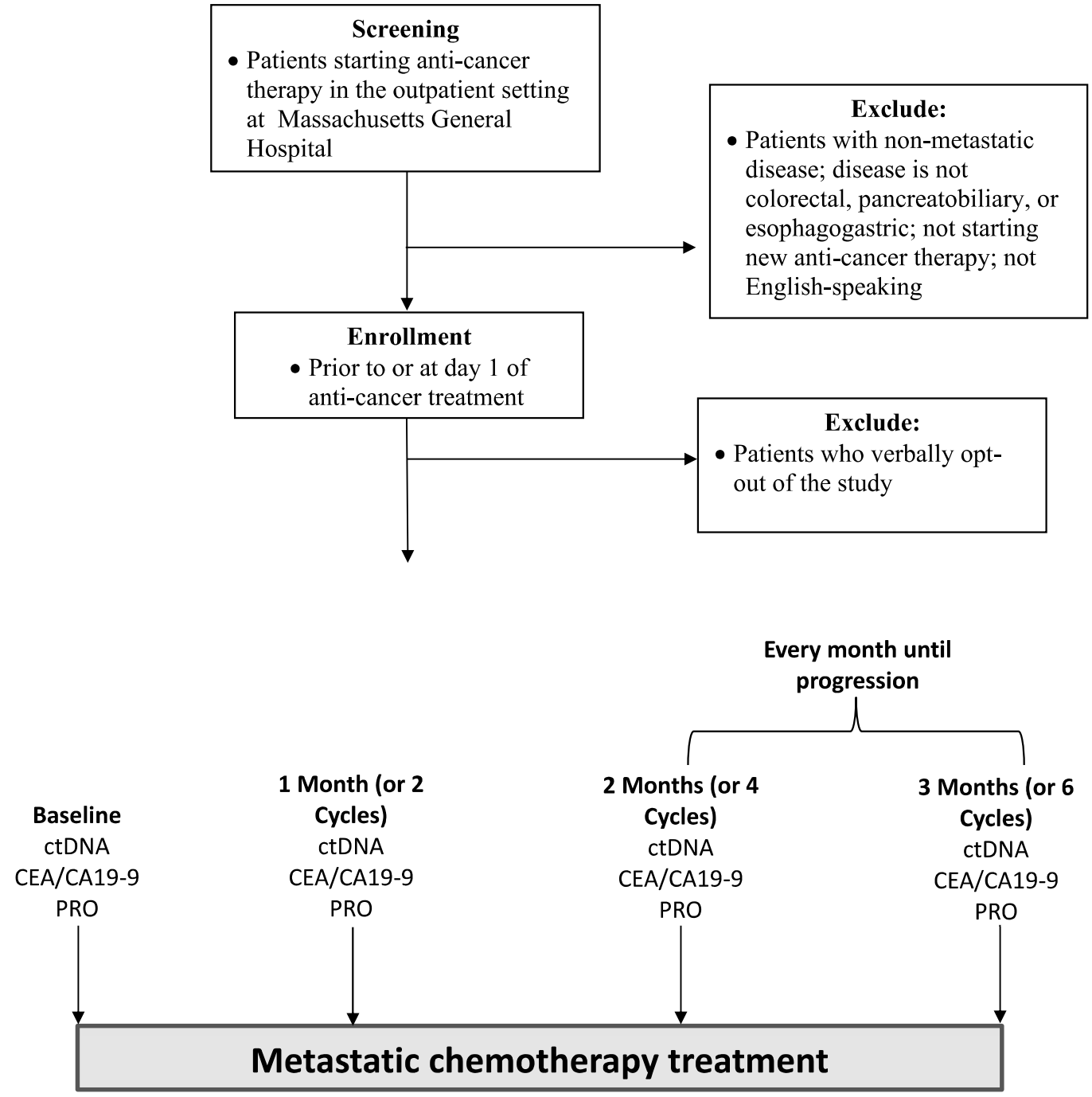
SECTION 1: Protocol Schema



SECTION 2: Body of the Protocol

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1.0 INTRODUCTION

1.1 Overview

This is a prospective study addressing the challenge of predicting disease progression and/or recurrence in patients diagnosed with metastatic colorectal, pancreatobiliary, or esophagogastric cancer that are receiving anti-cancer therapy.

1.2 Background and Rationale

Patients with cancer experience many physical and psychological symptoms that are often underrecognized by the clinicians caring for them.[1-6]Symptoms such as pain, dyspnea, fatigue, and nausea lead to poor quality of life (QOL) and psychological distress for patients and their family.[7-9] However, research demonstrates that clinicians often fail to reliably detect their patients' symptoms and frequently underestimate their severity.[10-13]Also, studies suggest that patients may underreport their symptoms to their cancer clinicians, often resulting in worse symptom management.[6, 14-16] Further, seminal data by Ethan Basch et al in 2017 demonstrated that integrated patient reported outcomes (PROs) into clinical care for metastatic disease are associated with survival.[17-18]Additionally, data in patients with lung cancer has shown that self-reported outcomes may predict overall survival due to early relapse detection.[19] Additional work also suggests that symptoms, mood and QOL can predict patient outcomes, including survival.[20-24] Thus, these data support that PROs may predict for disease progression and survival among patients with cancer.

Current modalities of treatment response include radiographic surveillance and standard tumor markers, such as CEA and CA19-9. Several studies have shown that ctDNA levels fluctuate with tumor response and disease progression, suggesting that ctDNA may be an effective measure of disease burden. Indeed, data by Corcoran et al in BRAF mutant colorectal cancer patients treated with a BRAF inhibitor combination demonstrated that the magnitude of the decrease in BRAF V600E mutant fraction in ctDNA at week 4 of therapy relative to day 0 displayed a striking and statistically significant correlation with tumor response, while the standard serum tumor marker CEA showed no correlation.[25] Data has shown that tumor markers are an imperfect measure of disease progression and/or recurrence. In an initial stage II colorectal cancer patients who did not receive chemotherapy showed that a positive post-operative ctDNA after surgical resection correlated with recurrence. Patients with a positive ctDNA versus a negative ctDNA post-operatively were 18 times more likely to have recurrence of their cancer even in the stage 2 setting whereas tumor markers did not predict recurrence.[26]

Given the imperfections of tumor markers, emerging data around ctDNA and importance of symptom and quality life assessment, we propose to look at how PROs compare with not only standard of care clinical assessment such as imaging and tumor markers but with ctDNA which may be a better blood based biomarker than tumor markers.

2.0 OBJECTIVES

2.1 The primary objective is:
To compare tumor markers, ctDNA, and PROs (symptoms, mood, and QOL) in predicting disease progression.

2.2 The secondary objective is:
To compare tumor markers, ctDNA, and PROs (symptoms, mood, and QOL) in predicting overall survival.

In order to analyze ctDNA, tissue will be sequenced in order to identify somatic mutations. If a mutation is identified that can be found in the ctDNA using digital PCR or next generation sequencing, then it will be followed throughout the patient's treatment. In ctDNA, we will be looking at the percent change in mutant allele fraction at each timepoint from baseline. We hypothesize that at least a 20% decrease in ctDNA mutant allele fraction at 1 month on treatment will predict stable disease or response and an increase in ctDNA mutant allele fraction at 1 month on treatment will predict progression. For PROs, we will be looking at the change in symptom, mood, and quality of life scores at each timepoint from baseline. For tumor markers (CEA and/or CA19-9), we will be looking at the change in tumor markers at each timepoint from baseline. Additional information in Section 5.7.

3.0 RESEARCH SUBJECT SELECTION

3.1 Eligbility Criteria

3.1.1 Patients must have histologically confirmed colorectal, pancreatobiliary, or esophagogastric cancer.

3.1.2 Diagnosed with metastatic disease

3.1.3 Age > 18 years.

3.1.4 Patients must be starting new line of anti-cancer therapy.

3.1.5 Patient must be English-speaking.

3.2 Exclusion Criteria

3.2.1 Unwilling or unable to participate in the study

3.2.2 Non-metastatic disease

3.2.3 Not starting new anti-cancer treatment

3.2.4 Cognitive issues interfering with ability to participate.

3.2.5 Active, unstable, untreated serious mental illness interfering with ability to participate.

3.2.6 Patient does not speak English.

4.0 RESEARCH SUBJECT ENTRY

We will recruit patients over a 3 year period from Massachusetts General Hospital Cancer Center only. The PI or RA will identify all patients with a diagnosis of cancer beginning anti-cancer treatment through the electronic medical record by querying the infusion schedule on a daily basis. The RA will approach patients who are identified as having a colorectal, pancreas, biliary, or esophagogastric cancer diagnosis with metastatic disease prior to their new anti-cancer treatment start. The study staff will obtain informed consent from eligible patients using a written consent form. Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC SOP REGIST-101.

5.0 STUDY DESIGN AND PROCEDURES

5.1 Study design

This is a prospective serial biomarker and questionnaire collection study of patients with metastatic esophagogastric, colorectal, or pancreatobiliary malignancies who receive anti-cancer therapy at Massachusetts General Hospital.

5.2 Selection of instruments

5.2.1 Symptoms: We will use the self-administered revised PRO-CTCAE and ESAS-r quesionnaires to measure patients' symptoms. The revised PRO-CTCAE consists of 12 items assessing common symptoms in patients with cancer. The revised PRO-CTCAE items are scored on a scale of (0 reflecting no reported presence of symptom and 3 reflecting the worst possible severity of the symptom). For each individual symptom assessed, a revised PRO-CTCAE score of 3 indicates severe symptom burden.**[Appendix A]** The revised ESAS consists of 12 items assessing common symptoms in patiens with cancer. The tems are scored on a scale of 0 reflecting no reported presence of symptom and 10 reflecting the worst possible severity of the symptom. **[Appendix E]**

5.2.2 Mood: We will also use the PHQ-4 to assess depression and anxiety in study patients. The PHQ-4 is a valid, brief tool for detecting both anxiety and depressive disorders**. [Appendix B]**

5.2.3 Quality of Life: We will use the FACT-G to assess health-related quality of life in study patients. **[Appendix C]**

5.2.4 ctDNA: We will use ctDNA as a molecular biomarker to assess tumor burden in study patients.

5.2.5 Tumor Markers: We will use standard of care tumor markers (CEA, CA19-9) as biomarkers to assess tumor burden in study patients.

5.2.6 Imaging: Scans will be ordered by the physician according to standard of care. The results will be used to determine treatment response and for body composition analysis.

5.3 Description of Intervention

There is no intervention component of this study. Results of the PHQ-4, FACT-G, ESAS-r, and ctDNA will not be reported back to the clinical staff to impact clinical care as the administration of these measures is not part of routine care. PRO-CTCAE and tumor markers are being used clinically as part of standard of care and thus will be reported to clinical staff.

5.4 Description of Study Process

5.4.1 Description of Study Participation

Eligible patients with metastatic esophgagogastric, colorectal, or pancreatobiliary malignancies receiving anti-cancer therapy who consent to participate in the study will have blood draws for tumor markers and ctDNA and PROs administered. Trained study staff will also collect clinical information from the electronic medical record (see Data Collection). Blood samples will be obtained and questionnaires will be self-administered on day (+7/-7) of treatment or every 2 cycles of chemotherapy as described in the study calendar. Patients will resume on planned schedule once they re-start anti-cancer therapy. When a patient is permanently taken off treatment they will be taken off study. A patient that changes anti-cancer therapy may stay on study and is followed as a new treatment start.

5.4.2. Study Schedule

Trial Period	Screening	On Anti-Cancer Therapy			Progression
Treatment Cycle/Title	Screening[1]	Baseline	1 Month or 2 cycles	2 Months or 4 cycles[2]	Progression
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Demographics and Medical History	X				
PRO-CTCAE		X	X	X	X
PHQ-4		X	X	X	X
FACT-G		X	X	X	X
ESAS-r		X	X	X	X
Tumor Imaging	X				X[5]
ctDNA		X	X	X	X
Tumor Markers[3]		X	X	X	X

5.5 Questionaire Administration

5.5.1 PRO-CTCAE: PRO-CTCAE is administered as a standard of care to all patients receiving anti-cancer therapy at MGH Cancer Center. On days that study participants are scheduled to receive anti-cancer treatment, they will either complete the PRO-CTCAE questionnaire over Patient Gateway prior to coming to clinic or when they arrive to clinic, they will be asked to complete the PRO-CTCAE questionnaire using a tablet computer. Their responses are logged into their electronic medical chart. The study team will extract the PRO-CTCAE responses from their electronic medical chart and enter the data electronically using REDCap. If questionnaire administration on the tablet is not feasible at a given study visit, it will be given on paper or over the phone. If a study participant does not answer the PRO-CTCAE questionnaire on a day that it should be administered for the study, a member of the study team may prompt the patient to complete the questionnaire. If study participants fail to complete the questionnaire within the given timeframe, we will report the data as missing and document the reason for incompletion.

5.5.2 PHQ-4, FACT-G, and ESAS-r: PHQ-4, FACT-G, and ESAS-r questionnaires will be administered either on paper or over the phone during the day of anti-cancer treatment (+7/-7). The study team will enter the data electronically using REDCap. If a study participant does not answer the PHQ-4, FACT-G, or ESAS-r questionnaire on a day that it should be administered for the study, a member of the study team may prompt the patient to complete the questionnaire. If study participants fail to complete the PRO within the given timeframe, we will report the data as missing and document the reason for incompletion. If participants do not complete the PROs, study staff may approach them.

5.6 Specimen Collection

5.6.1 Blood Samples: Blood will be collected serially throughout study treatment as specified in study calendar. 20 mL of blood will be collected at each time point into two 10 mL Streck cfDNA tubes. The two 10 mL Streck cfDNA tubes will be centrifuged to separate cell pellet from plasma,

and each component will be aliquoted and frozen for subsequent analysis. Blood samples in Streck tubes will be shipped at room temperature (within 5 days of draw) to:

Corcoran Laboratory
Massachusetts General Hospital Cancer Center
149 13th St, Room 7330
Charlestown, MA 02129

5.6.2 Tissue Samples: Tissue may be obtained by the following methods for next-generation sequencing. DNA extracted from formalin-fixed or frozen primary tumor tissue will need to be sequenced to identify somatic mutations across all or a subset of the coding regions for at least 50 genes.

5.6.2.1 Fixed Tissue

All new patients currently seen in the MGH Cancer Center routinely have their archival tumor tissue reviewed using an organized approach to identify and obtain fixed tissues. MGH pathologists review the H&E slide and/or available pathology reports to determine which paraffin-embedded blocks contain the most representative tumor and normal tissue. For patients from outside institutions, the study team will contact the institution from which the original biopsy was obtained and request the appropriate tissue block. Upon arrival at MGH, tissue sections will be obtained for any routine pathological evaluation and or archival tissue collection as mandated by the corresponding treatment protocols. If there is a sufficient amount of archival tissue available and there is no risk of exhausting the tumor block, tumor sections will be cut and adhered to poly-lysine coated glass slides, catalogued, and stored in the Corcoran Lab for future analysis. The remaining tissue blocks will be returned to the referring institution. Insufficient amount of tumor tissue will not constitute a deviation. This cannot be assessed until the analysis phase, so no participant will be taken off-study for insufficient tumor tissue.

5.6.2.2 Frozen Tissue

The following methods will be used to collect frozen specimens. Tissue will be obtained by routine interventional radiation (IR) or surgical procedures performed at MGH. Technical support to facilitate the organization of collection and processing these specimens is available at MGH. Specimens collected and processed at the MGH will then be available for use by the study team. The specimens collected will include both tumor and normal tissue in surgical samples and tumor alone in biopsy specimens.

Following removal of the tissue, the interventional radiologist or surgeon, working with the study team, will select appropriate portions of the tumor for routine pathological review and all trial-mandated tissue procurement. Any tissue not required for routine pathological review or trial mandated procurement will be snap-frozen and stored on dry ice to preserve high molecular weight DNA and RNA. This additional tissue will be stored in the Corcoran Lab for future analysis.

5.7 Analysis of Variables

5.7.1 Tumor Sequencing & Circulating tumor DNA (ctDNA) analysis

If molecular profiling on the tumor tissue has not already been done through standard of care, tumor tissue will be profiled with a targeted sequencing panel in a CLIA-certified laboratory. One or more clonal mutations specific to each patient's tumor will be identified. DNA extracted from plasma will be assessed for the presence of the pre-selected mutations. The Corcoran lab has an extensive library of ddPCR probes for the most commonly found clonal events in GI cancers that is being used currently for routine analyses of ctDNA. Testing may be performed using digital PCR or next generation sequencing, but must also reliability identify genomic alterations (including copy number changes or fusions) at or below a minimum allele frequency of 0.2%. ctDNA Analysis would be looking at the mutant allele fraction in the blood at baseline and then over the course of treatment and specifically the change in ctDNA over the course of treatment. If a patient lacks any clonal mutation in their tumor, they will remain on study.

5.7.2 Patient Reported Outcomes analysis

Patient reported outcomes will be analyzed individually as well as a composite score. PRO-CTCAE symptom variables include fatigue, insomnia, general pain, decreased appetite, nausea, vomiting, constipation, diarrhea, shortness of breath, numbness and tingling, rash, and fever. The PHQ-4 mood variables include 1) feeling nervous, anxious, or on edge 2) not being able to stop or control worrying, 3) little interest or pleasure in doing things, and 4) feeling down, depressed or hopeless. FACT-G quality of life variables include 1) physical well-being, 2) social/family well-being, 3) emotional well-being, and 4) functional well-being.

5.8 Data Collection

5.8.1 Demographic data: Demographic data will be obtained from the medical record (e.g. age, sex, ethnicity, race, religion, education, relationship status, and insurance coverage).

5.8.2 PROs: The following PROs will be administered at baseline and throughout treatment (1) PRO-CTCAE; (2) the PHQ-4; (3) the FACT-G; (4) the ESAS-r. The time required to complete these PROs is approximately twenty to thirty minutes. If participants do not complete the PROs, they will be approached again within 1 week and asked if they are willing to complete them. If the patient does not verbally opt-out of the study, he or she will be asked to complete identical PROs at timepoints specified in the study calendar. If a participant opts out of completing a questionnaire at one time point, the data will be marked as missing and the reason will be documented. However, if a participant decides to opt out of completing the questionnaires indefinitely, they will continue to be monitored for clinical outcomes.

5.8.3 Medical record abstraction: Study staff will obtain clinical information including, but not limited to, the date of diagnosis of cancer, specific cancer diagnosis, age, gender, and treatment history, from the electronic medical record.

5.8.4 Data Storage: All patient information will remain confidential and stored in a data-entry database and in REDCap. The data-entry database is HIPAA compliant and password protected. REDCap

(Research Electronic Data Capture) is a free, secure, HIPAA compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. Vanderbilt University, with collaboration from a consortium of academic and non-profit institutional partners, has developed this software toolset and workflow methodology for electronic collection and management of research and clinical study data. Access to the database will only be granted to the study team who are responsible for maintaining the database.

5.9 Specimen Storage

5.9.1 Biologic specimens: Biologic specimens will be coded using numeric identifier and dated prior to processing and storage, and the key will be kept in the data-entry database. Specific identifiers will then have been removed from the samples.

5.10 Research Use of Collected Specimens and Data

5.10.1 Blood Analyses

Cell free DNA will be isolated from serial plasma aliquots. For each patient, one to two specific clonal mutations identified by sequencing of tumor tissue will be used to track circulating tumor DNA (ctDNA) levels throughout treatment using custom mutation specific droplet digital PCR probes as a personalized measure of tumor burden.This method will allow accurate monitoring of the response of overall tumor burden to treatment and can be correlated with radiologic endpoints. As new ctDNA technologies emerge they may be utilized for analyses.

5.10.2 Imaging Data- Body Composition Analyses

Patients with cancer experience body composition changes (e.g. loss of skeletal muscle) that are associated with worsening symptom burden and quality of life, poor treatment tolerability and decreased survival.[27-30] As an exploratory analysis we will use CT scans collected as part of routine clinical care to assess body composition and its' associations with clinical outcomes. We will use thoracic and lumbar vertebral bodies as a landmark and will quantify skeletal muscle and fat at these levels using threshold-based segmentation. Hounsfield units -29 to +150 will identify muscle and Hounsfield units -190 to -30 will identify adipose tissue. Tissue cross-sectional area (in cm2) will be computed by summing the given tissue's pixels and multiplying the sum by the absolute unit pixel surface area. Skeletal muscle at L3 indexed to height will be used to categorize patients as sarcopenic based on previously defined cutoff values (<38.5 cm2/m2 for females and < 52.4 cm2/m2 for males).[31] We will also assess the skeletal muscle density (SMD) (obtained via Hounsfield units) as a potential variable of interest based upon previous studies that determined SMD as an important factor in body composition analyses.[32-34] We will correlate the body composition data obtained with clinical outcomes including symptom burden, quality of life, radiologic response, and survival.

5.11 Deidentification and Patient Confidentiality

5.11.1 Breach of confidentiality is a concern in all studies with human subjects. We will put safeguards in place to ensure that participant information is kept private and confidential. We will store all

data in locked cabinets located in the PI's office as well as password-protected computer files, accessible only to trained study staff. Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept in a separate file under lock and key.

5.12 Adverse Events, Adverse Reactions, and Their Management

5.12.1 Reporting Adverse or Unanticipated Events: We do not anticipate any adverse reactions as a result of study participation. The PI will be responsible for ensuring that any adverse events are reported to the DF/HCC IRB, as necessary. The PI will be responsible for cataloguing and tallying adverse events, and will report these events to the DF/HCC IRB as well as review the report in the biannual meeting with the advisors of the proposed study. Study staff will report serious adverse events to the DF/HCC IRB within 24 hours of their detection using the necessary written forms provided by the DF/HCC IRB.

5.12.2 Expected Toxicities: One expected toxicity related to this study is the minor discomfort related to venipuncture for blood collection. Efforts will be made to collect the blood through a pre-existing intravenous access, or at the time of clinically indicated phlebotomy. The expected blood loss will be minimal and of no clinical consequences. All other patient materials related to this protocol will occur only in the setting of already scheduled procedures. No specific adverse events are expected from collection of these materials.

5.12.3 Anticipated Reactions: We do not anticipate any serious adverse reactions as a result of study participation. Participants may find some questionnaire items to be emotionally upsetting. Study staff will assure participants that they may skip any questions they wish.

5.12.4 Reaction Management: If study participants become distressed while completing the study questionnaires, the PI will be available to discuss the patient's concerns. If distressed patients request services for anxiety or depression, we will inform the oncology team. The inpatient social worker for the oncology service will also be available to offer any further counseling, if needed.

5.13 Special concerns: None

5.14 Compensation: We will not provide compensation to study participants.

6.0 STATISTICAL ANALYSIS

Primary Outcome and Analyses:

The primary outcome is treatment response (RECIST 1.1) at first scan (≥1 month post-treatment start). Both response status (PR vs SD or PD [including death]) and clinical benefit status (PR or SD vs PD [including death]) will be examined. Primary analyses will compare one month change from baseline in tumor markers, MAF of the selected clonal mutation in ctDNA, and PROs (symptoms, mood, and QOL) individually and a composite score in predicting response and clinical benefit (CB) at first scan.

Each variable (tumor markers [CEA, CA19-9], ctDNA, and PROs [symptoms, mood, QOL]) will be evaluated individually as a predictor of response and CB at first scan. Logistic regression models will be used to assess the relationship between change from baseline in each variable and response/CB outcomes. We will evaluate the impact of adjusting for baseline values and use interaction terms between baseline values and change values to explore how the relationship between change values and outcome is affected by baseline values, in particular to determine the impact of ceiling/floor effects that restrict change values based on minimum and/or maximum baseline values. ROC curves based on both univariate and adjusted logistic regression models will be generated for each variable and the area under the ROC curve will be compared between variables to evaluate the predictive ability of each. Threshold values associated with clinically meaningful levels of specificity and/or sensitivity will be identified from ROC curves. Additional analyses will investigate predictive performance of tumor markers, ctDNA, and PROs within disease-specific subgroups (pancreatobiliary, colorectal, and gastroesphageal).

Historically, the area under the ROC curve has been 0.70 for CEA and CA 19-9 in predicting disease progression in gastrointestinal malignancies.[35,36] We will enroll 630 patients in order to have 600 evaluable patients (assuming 5% may transfer care and not have complete data at first scan) , and this gives us >80% power both overall and within disease-specific subgroups to detect an improvement of the area under the ROC curve from 0.70 to 0.85 using ctDNA and/or PROs using two-sided test with an alpha of 0.05. In combined analyses (i.e. those including all cancer types), we will only consider differences in AUC of 5% or greater to be clinically meaningful.

Secondary outcomes and analyses: Secondary outcomes will include percent change from baseline to first scan in tumor measurements (continuous outcome) via RECIST 1.1 criteria, progression-free survival (PFS) and overall survival (OS).

Change from baseline in each variable (tumor markers [CEA, CA19-9], ctDNA, and PROs [symptoms, mood, QOL]) will be evaluated individually as a predictor of secondary outcomes.

Linear regression models will be used to explore the associations between percent change in tumor measurements at first scan and change in each variable at 1st scan.

We will estimate distributions of PFS and OS using the Kaplan-Meier method. We will also use Cox proportional hazards models to obtain hazard ratios for PFS and OS for change in tumor markers, ctDNA and PROs. We will adjust these models for variables known to be associated with PFS and OS (e.g., age, sex, race, etc).[37] We will evaluate change in variables at different timepoints (e.g. first scan, 3 months, etc) and models will account for left truncated data to account for the fact that participants must survive without progression to a given timepoint in order to be included in the analysis for the timepoint. We will compare the predictive ability of change in tumor markers, ctDNA, and PROs in these models using time-dependent ROC curves evaluated at specific timepoints including 6 and 12 months.

As additional secondary outcomes, we will run multivariable Cox proportional hazards regression with purposeful selection of covariates to explore combinations of variables (change in tumor markers [CEA, CA19-9], ctDNA, and PROs [symptoms, mood, QOL]) as predictors of PFS and OS. We will also look at association between baseline ctDNA levels, baseline tumor markers and baseline PRO asssesments and tumor response, 6-month PFS and 6-month OS.

Subgroup Analyses:

Given that for metastatic colorectal cancer, pancreatobiliary cancer, and gastric cancer, we expect over 90% of patients to have progression within one year and that we hope to have a tumor agnostic prediction model, we will not stratify our analyses based on tumor type and line of therapy.[38-40] The primary outcomes is prediction of response at 6 months irrespective of tumor type and line of treatment.

Body Composition Analyses:

As an exploratory outcome we will compare differences (e.g. demographic and clinical characteristics, PROs, clinical outcomes) between patients with and without sarcopenia, as well as by skeletal muscle and SMD. Univariate tests will include logistic regression, chi-squared and Fischer's exact tests for categorical outcomes; linear regression, t-tests and ANOVA for normally distributed continuous outcomes; and non-parametric tests (Wilcoxon rank sum, Kruskal-Wallis) for non-normally distributed outcomes.

To examine the association between sarcopenia (and ranges of body composition/SMD) and survival, we will use a censored time-to-event analysis. We will measure survival as time from diagnosis of cancer to death (measured in months), censoring patients still alive at the time of their last follow-up. We will use the Kaplan-Meier method to describe the distributions of time-to-event for patients with and without sarcopenia, as well as by skeletal muscle and SMD. We will then use Cox proportional hazards regression models to assess the effects of sarcopenia (and ranges of body composition/SMD) on patients' survival while adjusting for variables likely related to survival (e.g. patients' age, comorbidity and cancer type).

7.0 REFERENCES

1. Davis MP, Dreicer R, Walsh D, et al: Appetite and cancer-associated anorexia: a review. J Clin Oncol 22:1510-7, 2004
2. Miovic M, Block S: Psychiatric disorders in advanced cancer. Cancer 110:1665-76, 2007
3. Teunissen SC, Wesker W, Kruitwagen C, et al: Symptom prevalence in patients with incurable cancer: a systematic review. J Pain Symptom Manage 34:94-104, 2007
4. Lage DE, Nipp RD, D'Arpino SM, et al: Predictors of Posthospital Transitions of Care in Patients With Advanced Cancer. J Clin Oncol:JCO2017740340, 2017
5. Nipp RD, El-Jawahri A, Moran SM, et al: The relationship between physical and psychological symptoms and health care utilization in hospitalized patients with advanced cancer. Cancer 123:4720-4727, 2017
6. Nekolaichuk CL, Maguire TO, Suarez-Almazor M, et al: Assessing the reliability of patient, nurse, and family caregiver symptom ratings in hospitalized advanced cancer patients. J Clin Oncol 17:3621-30, 1999
7. Cooley ME, Short TH, Moriarty HJ: Symptom prevalence, distress, and change over time in adults receiving treatment for lung cancer. Psychooncology 12:694-708, 2003
8. Chang VT, Hwang SS, Feuerman M, et al: Symptom and quality of life survey of medical oncology patients at a veterans affairs medical center: a role for symptom assessment. Cancer 88:1175-83, 2000
9. Brown LF, Kroenke K, Theobald DE, et al: The association of depression and anxiety with health-related quality of life in cancer patients with depression and/or pain. Psychooncology 19:734-41, 2010
10. Fromme EK, Eilers KM, Mori M, et al: How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol 22:3485-90, 2004
11. Laugsand EA, Sprangers MA, Bjordal K, et al: Health care providers underestimate symptom intensities of cancer patients: a multicenter European study. Health Qual Life Outcomes 8:104, 2010
12. Atkinson TM, Li Y, Coffey CW, et al: Reliability of adverse symptom event reporting by clinicians. Qual Life Res 21:1159-64, 2012
13. Di Maio M, Gallo C, Leighl NB, et al: Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol 33:910-5, 2015
14. Bernabei R, Gambassi G, Lapane K, et al: Management of pain in elderly patients with cancer. SAGE Study Group. Systematic Assessment of Geriatric Drug Use via Epidemiology. JAMA 279:1877-82, 1998
15. Breetvelt IS, Van Dam FS: Underreporting by cancer patients: the case of response-shift. Soc Sci Med 32:981-7, 1991
16. Ward SE, Goldberg N, Miller-McCauley V, et al: Patient-related barriers to management of cancer pain. Pain 52:319-24, 1993
17. Basch E, Deal AM, Kris MG, et al: Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol 34:557-65, 2016
18. Basch E, Deal AM, Dueck AC, et al: Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA 318:197-198, 2017
19. Denis F, Lethrosne C, Nicolas P, et al: Randomized trial comparing a web-mediated follow-up to routine surveillance in lung cancer patients. Journal of the National Cancer Institute, 2017
20. Giese-Davis, J. et al: Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: A secondary analysis. J Clin Oncol 29(4): 413-420, 2011
21. Pirl, WF., et al: Depression and survival in metastatic non-small-cell lung cancer: Effects of early palliative care. J Clin Oncol 30(12): 1310-1315, 2012.
22. Luoma, M, et al: Prognostic value of quality of life scores for time to progression (TTP) nad overall survival time (OS) in advanced breast cancer. Eur J Cancer 39(10): 1370-1376, 2003
23. Maisey, N.R, et al: Baseline quality of life predicts survival in patients with advanced colorectal cancer. Eur J Cancer 38(10): 1351-1357, 2002
24. Stukenborg, G, et al: Longitudinal patterns of cancer patient reported outcomes in end of life care predict survival. Support Care Cancer 24(5) 2217-2224, 2016

25. Corcoran, R.B. et al. Efficacy and circulating tumor DNA (ctDNA) analysis of the BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E–mutated (BRAFm) metastatic colorectal cancer (mCRC) ESMO 2016, Oct 9, 2016.
26. Tie, J. et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Sci Transl Med 8(364): 346ra92, 2016
27. Nipp RD, Fuchs G, El-Jawahri A, et al. Sarcopenia Is associated with quality of life and depression in patients with advanced cancer. *Oncologist*. 2018;23:97-104. doi:10.1634/theoncologist.2017-025
28. Deluche E, Leobon S, Desport JC, Venat-bouvet L, Usseglio J, Tubiana-mathieu N. Impact of body composition on outcome in patients with early breast cancer. *Support Care Cancer*. 2018;26:861-868. doi:10.1007/s00520-017-3902-6
29. Bruggeman AR, Kamal AH, Leblanc TW, Ma JD, Baracos VE, Roeland EJ. Cancer cachexia: Beyond weight loss. *Am Soc Clin Oncol*. 2016;12(11):1163-1172. doi:10.1200/JOP.2016.016832
30. Morishita S, Kaida K, Tanaka T, et al. Prevalence of sarcopenia and relevance of body composition, physiological function, fatigue, and health-related quality of life in patients before allogeneic hematopoietic stem cell transplantation. *Support Care Cancer*. 2012;20(12):3161-3168. doi:10.1007/s00520-012-1460-5
31. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology. 2011;12(5):489-95.
32. Brown JC, Caan BJ, Prado CM, et al. Body composition and cardiovascular events in patients with colorectal cancer: A population-based retrospective cohort study. *JAMA Oncol*. 2019;70808(7):967-972.
33. Caan BJ, Cespedes Feliciano EM, Prado CM, et al. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. *JAMA Oncol*. 2018;4(6):798-804.
34. Kroenke CH, Prado CM, Meyerhardt JA, et al. Muscle radiodensity and mortality in patients with colorectal cancer. *Cancer*. 2018;124(14):3008-3015.
35. Shinkins B, Nicholson BD, Primrose J, et al. The diagnostic accuracy of a single CEA blood test in detecting colorectal cancer recurrence: Results from the FACS trial. *PLoS One*. 2017;12(3). doi:10.1371/journal.pone.0171810.
36. Dong Q, Yang X, Zhang Y, et al. Elevated serum CA19-9 level is a promising predictor for poor prognosis in patients with resectable pancreatic ductal adenocarcinoma: a pilot study. *World Journal of Surgical Oncology*. 2014;12:171. doi:10.1186/1477-7819-12-171.
37. Nipp R, Tramontano AC, Kong CY, et al. Disparities in cancer outcomes across age, sex, and race/ethnicity among patients with pancreatic cancer. *Cancer Med*. 2018;7(2). doi:10.1002/cam4.1277.
38. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335-2342. doi:10.1056/NEJMoa032691.
39. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817-1825. doi:10.1056/NEJMoa1011923.
40. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376(9742):687-697. doi:10.1016/S0140-6736(10)61121-X.

8.0 APPENDICES

APPENDIX A: PRO-CTCAE

PRO-CTCAE QUESTIONNAIRE

Domain #1: Fatigue

1.In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?

○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

2. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?

○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

Domain #2: Insomnia

3. In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?

○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

4. In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?

○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

Domain #3: General Pain

5.In the last 7 days, how OFTEN did you have PAIN?

O Never O Rarely O Occasionally O Frequently O Almost constantly

6. In the last 7 days, what was the SEVERITY of your PAIN at its WORST?

O None O Mild O Moderate O Severe O Very severe

7. In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?

O Not at all O A little bit O Somewhat O Quite a bit O Very much

Domain #4: Decreased appetite

8. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?

O None O Mild O Moderate O Severe O Very severe

9. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?

O Not at all O A little bit O Somewhat O Quite a bit O Very much

Domain #5: Nausea

10. In the last 7 days, how OFTEN did you have NAUSEA?

O Never O Rarely O Occasionally O Frequently O Almost constantly

11. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?

O None O Mild O Moderate O Severe O Very severe

Domain #6: Vomiting

12. In the last 7 days, how OFTEN did you have VOMITING?

O Never O Rarely O Occasionally O Frequently O Almost constantly

13. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?

O None O Mild O Moderate O Severe O Very severe

Domain #7: Constipation

14. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?

O None O Mild O Moderate O Severe O Very severe

Domain #8: Diarrhea

15. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?
    O Never O Rarely O Occasionally O Frequently O Almost constantly

Domain #9: Shortness of Breath

16. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?
    O None O Mild O Moderate O Severe O Very severe
17. In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?
    O Not at all O A little bit O Somewhat O Quite a bit O Very much

Domain #10: Numbness and Tingling

18. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?
    O None O Mild O Moderate O Severe O Very severe
19. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with
your usual or daily activities?
    O Not at all O A little bit O Somewhat O Quite a bit O Very much

Domain #11: Rash

20. In the last 7 days, did you have any RASH?
    O Yes O No
21. In the last 7 days, what was the SEVERITY of your RASH at its WORST?
    O None O Mild O Moderate O Severe O Very severe

Domain #12: Fever- *domain edited from SHIVERING AND SHAKING CHILLS*

24. In the last 7 days, how OFTEN did you have FEVER?
    O Never O Rarely O Occasionally O Frequently O Almost constantly
25. In the last 7 days, what was the SEVERITY of your FEVER at their WORST?
    O None O Mild O Moderate O Severe O Very severe

APPENDIX B: PHQ-4

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Little interest or pleasure in doing things	0	1	2	3
4. Feeling down, depressed, or hopeless	0	1	2	3

Appendix C: FACT-G

FACT-G QUESTIONNAIRE

Below is a list of statements that other people with your illness have said are important**.**
Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.* ☐					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

APPENDIX D: ESAS-r

ESAS-r QUESTIONNAIRE

Please circle the number that best describes how you have been feeling over the past 24 hours:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
No Insomnia *(Insomnia = trouble sleeping)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Insomnia
No Constipation	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Constipation
No Diarrhea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Diarrhea

APPENDIX E: Data Usage Agreement

DATA USE AGREEMENT FOR A LIMITED DATA SET

Part A – Study Information

1. **Protocol Title**: Symptom Assessment for Hospitalized Patients with Cancer

2. **The Limited Data Set contains the following elements of Protected Health Information** [list all such information and data elements in a specific and meaningful fashion (e.g., data from survey, radiology and lab results, related medical conditions, information on cancer treatments)]:

3. **Recipient-Investigator agrees to use the Limited Data Set solely for conduct of the following research entitled** (provide complete title of the research project):

4. **The purpose of this research is to** (provide complete description of the purpose of the research project):

5. **Recipient-Investigator agrees to use the Limited Data Set solely in the following manner** (provide complete description of all proposed uses of the data set):

6. **Recipient-Investigator agrees to limit access to the Limited Data Set to the following individuals or classes of individuals** (provide complete list of all individuals, or classes of individuals, who will access the Limited Data Set):

7. **Recipient-Investigator agrees to take the following actions and/or institute the following controls to prevent unauthorized use or disclosure of the Limited Data Set** (provide complete description of such measures):

Part B – Conditions and Stipulations

Recipient-Investigator further agrees to the following conditions and stipulations:

1. The Limited Data Set information will not be used or further disclosed other than as permitted by this Agreement or as otherwise required by law.
2. Appropriate safeguards will be implemented as described above to prevent use or disclosure of the Limited Data Set information other than as provided for by this Agreement.
3. The Limited Data information set will not be re-identified.
4. Individual(s) whose information is contained in the Limited Data set will not be contacted.
5. The Protected Health Information contained in the Limited Data set represents the minimum necessary for the research purposes described above.
6. Upon learning of any use or disclosure of information not provided for by this Agreement, such unauthorized use or disclosure will be reported to the covered entity releasing the information.
7. Any individuals or organizations, including subcontractors, to whom the Limited Data Set is provided, must first agree to the same restrictions and conditions set forth in this Agreement.

Part C - Signatures

The parties signing below agree to the conditions enumerated above.

Recipient of the Limited Data Set:

_____ _____

Signature of Recipient-Investigator **Date**

Name of Recipient-Investigator:

Recipient-Investigator's Institution:

Phone(s): **Email:**

Address: **Fax:**

Authorized Representative of the Facility releasing the Limited Data Set:

_____ _____

Signature of Authorized Representative of the Facility releasing the Data Set **Date**

Name of Authorized Representative:

Title of Authorized Representative:

Name of Facility:

Phone(s): **Email:**

Address: **Fax:**