commonly reported concerns about pain management included fear of addiction and fear of side effects such as nausea or constipation.(*4*) Another study of hospice patients found that patients were also concerned that pain signifies disease progression.(*5*) Some patients may be reluctant to report pain due to concerns that it may limit treatment options, fear of "bothering" caregivers, or assuming that pain is an expected symptom of cancer.(*6*) Physicians and other caregivers often cite poor pain assessment as an important barrier to adequate pain control (76% of physicians in a study by the Eastern Cooperative Oncology Group).(*7*) In fact, providers are often inaccurate when assessing patients' pain levels, particularly when patients are in severe pain.(*8*) Other provider concerns include lack of sufficient knowledge and skill with regard to pain control, worries about patients' development of tolerance, management of patients' side effects, and an overall reluctance to prescribe opioids due to believing that opioids should only be used in terminal cancer, concerns about reimbursement or need for prior authorization, and fears about regulatory oversight.(*9*) Finally, systems-wide barriers may also be at play, such as limits placed on acquisition of opioid medications and poor availability of palliative care and pain specialists, particularly in low-resource areas. (*10*)

2.3 Metastatic cancer pain

Patients with advanced, metastatic, or terminal disease have higher rates of pain compared with those who have received curative treatment or those undergoing active anticancer treatment; 55.1% of those with advanced, metastatic, or terminal disease report moderate to severe pain.(*11*) While mild-to-moderate pain can be treated with nonopioid analgesics and adjunctive therapies, those with moderate-to-severe pain often require initiation of opioid therapy and uptitration.*(12)* Particularly among patients with bone metastases, which can cause significantly debilitating pain, strong opioids are the mainstay of treatment.(*13*) Thus, patients with metastatic cancer are most likely to have severe enough pain warranting initiation of opioid therapy and are most likely to benefit from close monitoring and titration of their pain medication regimens.

2.4 Current recommendations for control of cancer pain

Evidence-based guidelines on the skilled use of opioids to adequately treat cancer pain exist but may not be comprehensive enough in guiding day-to-day practice. The WHO analgesic ladder has been validated and adopted worldwide, and provides a general schematic on escalation of analgesics.(*14*) The CDC also has guidelines for prescribing opioids, recommending that providers establish treatment goals, consider how to discontinue opioids if benefits do not outweigh risks, start with the lowest effective dose, monitor every 3 months or sooner, and review prescription drug monitoring data regularly.(*15*) ASCO has similar guidelines, recommending the early identification of need for referral to other healthcare professionals to manage complex pain needs, starting with nonopioid and adjuvant analgesics, carefully selecting patients as candidates for opioid therapy, and taking universal precautions in minimizing risk of abuse and addiction.(*16*) However, clinicians often do not find these guidelines helpful in conversations with patients regarding pain management.(*17)*

2.5 Standardized interventions may improve management of cancer pain

Standardized pain assessment tools can aid physicians in identifying cancer pain early and guide future research in this field. Several single-item scales have been validated in the assessment of cancer pain, including the Visual Analogue Scale, Numerical Rating Scale of pain intensity, and Verbal Rating Scale of pain intensity; the most widely used validated multiple-item assessment is the Brief Pain Inventory pain intensity scale. (*18*) However, despite being frequently used in research, these scales have yet to become part of common practice.

8.3 Adverse Event Monitoring

Patients will complete the **S1916** Opioid Adverse Event Survey (See Section 14.4) at the 2, 4, and 6-week follow-up visits to report the frequency with which they experience severl potential adverse effects. Sites will collect side effect data at the same interval on the **S1916** Adverse Events form and code using CTCAE 5.0. The rare adverse effects associated with the Digital Medicine Program (ingestible sensor and patch) will be collected on **S1916** Follow-Up form.

Data on the changes made to patients' pain regimens at the 2, 4, and 6-week visits will be collected on the **S1916** Follow-Up form. Clinic or emergency room visits during the 6-week study period will be reported on the **S1916** Health Care Utilization form.

8.4 Serious Adverse Event Reporting Requirements

Please Note: This protocol utilizes Rave® for expedited reporting of serious adverse events. To initiate an expedited report you must first enter the event information on the appropriate adverse event reporting form in Rave®. If you have questions about this process, please contact the SAE Program Manager 210-614-8808 or email adr@swog.org.

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. For this study, adverse events are reported on the **S1916** Adverse Events form (as described in Sections 8.3 and 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events use the Medidata Rave® System

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event as specified in Table 8.4e.

In the rare event when internet connectivity is disrupted notification is made to SWOG by telephone at 210-614-8808 or by email adr@swog.org. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug/device companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 8.4e. The commercial agent/device used in this study is Percocet (oxycodone-acetaminophen) with Proteus Ingestible Sensor. If there is any question about the reportability of an adverse event or if on-line Medidata Rave® cannot be used, please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 8.4e. Expedited reporting requirements for adverse events experienced by patients within 30 days of the last administration of the combination commercial agent/ingestible device.

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			Medidata Rave®	Medidata Rave®
Possible, Probable, Definite	Medidata Rave®		Medidata Rave®	Medidata Rave®

Medidata Rave®: Indicates an expedited report is to be submitted via Medidata Rave® within 10 calendar days of learning of the event[b].

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

b Along with submission of the on-line Medidata Rave® SAE report plus any necessary amendments, supporting documentation must be submitted to SWOG. Supporting documentation should be sent to SWOG within 5 calendar days by fax to 210-614-0006.

c A malfunction of the ingestible device (the failure of the device to meet its performance specifications or otherwise perform as intended) should be reported to SWOG SAE Program 210-614-8808 or by email adr@swog.org.

j. ePRO feasibility will be defined by: 1) the extent of missing data at each assessment time for those items or instruments required to be completed using the Patient Cloud ePRO app; 2) assessing the patient experience of using the Patient Cloud ePRO app with a one-time questionnaire at the conclusion of the study.

10.3 Patient Reported Outcomes

a. Patient-Completed Questionnaires

NOTE: Patient-completed questionnaires will continue to be collected even if the patient discontinues the study intervention prior to Week 6.

Brief Pain Inventory (Short Form) (BPI-SF) - The BPI-SF is nine-item pain assessment tool that contains subscales for worst pain, average pain, and pain interference rated on scales of 0-10 with 10 signifying the worst symptoms; this scale has been validated for use in patients with cancer pain.(*58*)

Edmonton Symptom Assessment System (revised version) (ESAS-r) - The ESAS-r consists of nine items regarding somatic symptoms such as nausea, drowsiness, lack of appetite, shortness of breath, and psychological symptoms such as depression, anxiety, and distress, that was developed for use in the palliative care setting. Questions are rated on scales of 1-10 with 10 being “worst possible”. (*59)*

Patient Health Questionnaire-4 (PHQ-4) - The PHQ-4 is a combination of a 2-item depression and 2-item anxiety screen for psychological distress. Questions are rated on a scale of 0-3 with 0 being “not at all” and 3 being “nearly every day”. (*60)*

PROMIS-29© - The PROMIS-29© consists of 29 questions to measure global quality of life, including four questions from each of the following domains: anxiety, depression, fatigue, pain interference, physical function, sleep disturbance, satisfaction with participation in social roles, and ability to participate in social roles and activities; it includes a single pain intensity item. Questions are scaled 1 to 5. (*61*)

Participant Survey – Satisfaction with Proteus – This survey consists of 11 items that measure patient experience with the Proteus DMP and the Proteus Discover app in the following domains: satisfaction, patient engagement, and communication with providers. The survey also includes 2 items for patients to describe what they liked about the Proteus DMP and suggestions for improvement.

Patient Cloud Feasibility Questionnaire – The Patient Cloud Feasibility Questionnaire consists of 13 questions that assess patient experience using the Patient Cloud app. These questions measure ease of use, reasons for non-completion, frequency of completing the daily pain question, and preferences regarding use of mobile devices and paper forms for completing PRO questionnaires.

b. Provider-Completed Questionnaire

DMP HCP Satisfaction Survey – The DMP HCP satisfaction survey consists of 10 items to rate physician experience with the DMP, its value in providing actionable data and informing treatment approach, their likelihood of recommending the DMP to other physicians, and likelihood of prescribing the DMP to patients.

10.4 Performance Status

Patient performance status will be graded according to the Zubrod performance status scale.

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

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Endpoint

The primary endpoint is feasibility, which will be determined by the following criteria.

a. Adherence to the use of the digital medicine program: This will be measured by the percentage of the time patients wear the sensor patch. Adherence feasibility will be achieved if at least 66% (e.g., 33 out of 50 patients who complete the 6-week pilot) wear the sensor patch for at least 28 out of 42 days (≥66% of time). Out of 60 recruited patients, it is assumed that 10 patients will drop out of the study or have incomplete 6-week data, leading to 50 patients with complete data that can be analyzed. The lower bound of the 95% confidence interval for 33/50 patients is 51%, allowing the investigators to rule out use of the offering by less than 50% of enrolled patients.

b. Patient retention: at least 50 out of 60 recruited patients complete the 6-week pilot, assuming that 10 patients will not complete the study or will be ineligible.

c. Accrual: Full accrual of 60 patients within 6 months of IRB approval at all participating sites.

11.2 Secondary Endpoints

All secondary endpoints – including PRO responses (on validated and non-validated measures) at baseline and at each assessment time, opioid medication consumption, high consumption, number of unplanned hospital or emergency department visits, frequency of changes in pain management regimen, and physical activity levels – will be examined descriptively using summary statistics. Exploratory correlation analyses will be conducted to examine the relationship between pain and activity levels.

Additionally, exploratory longitudinal analyses of the PROs (BPI-SF, ESAS-r, PHQ-4, and PROMIS-29©) will be conducted using baseline and follow-up times of 2, 4, and 6 weeks

post-registration using linear mixed models (with patient as the random effect) to estimate the trajectories of PRO responses over time.

11.3 Data and Safety Monitoring

There is no formal Data and Safety Monitoring Committee for this study. Accrual reports are generated weekly and study-specific accrual is monitored by the Study Chair, Study Statistician and the Disease Committee Chair. Reports summarizing adverse events, serious adverse events (SAEs), and treatment administration are provided monthly to the Study Chair and Study Statistician for monitoring. In addition, all SAEs which by definition require expeditious reporting are reviewed and processed by the Adverse Event Coordinator at the SWOG Operations Office and a physician reviewer based on data provided via in Medidata Rave®. (Note that SAEs will not be reported through CTEP-AERS). Cumulative study-specific SAE reports are provided to the Study Chair and Study Statistician upon occurrence of an event. Formal reports summarizing the study are prepared for all SWOG members every 6 months.

12.0 DISCIPLINE REVIEW

There is no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of study treatment (no more than 5 calendar days prior to planned start of treatment).

13.2 Investigator Requirements

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Registration Procedures

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

2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members website and OPEN.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1916 Onstudy Form
On Treatment Vital Status Form
S1916 Cover Sheet for Patient-Completed Questionnaires
Brief Pain Inventory (Short Form)
Edmonton Symptom Assessment System (revised version)
PHQ-4
PROMIS-29© Profile V2.1

b. DAILY, FROM REGISTRATION THROUGH THE 6-WEEK ASSESSMENT:

Patient submits the following using the Patient Cloud ePRO app:

Worst pain rating

c. WITHIN 15 DAYS AFTER THE 2 AND 4-WEEK ASSESSMENTS:

Study site submits the following:

On Treatment Vital Status Form
S1916 Follow-Up
S1916 Adverse Events
S1916 Health Care Utilization
S1916 Cover Sheet for Patient-Completed Questionnaires (See Section 15.2d)
Brief Pain Inventory (Short Form)

Patient submits the following using the Patient Cloud ePRO app:

Edmonton Symptom Assessment System (revised version)
PHQ-4
S1916 Opioid Adverse Effects Survey
PROMIS-29© Profile V2.1

d. WITHIN 15 DAYS AFTER THE 6-WEEK ASSESSMENT:

Study site submits the following:

On Treatment Vital Status Form
S1916 Follow-Up
S1916 Adverse Events
S1916 Health Care Utilization
S1916 Off Treatment Notice (If patient is on treatment at the time of the 6-week assessment)
S1916 Cover Sheet for Patient-Completed Questionnaires (See Section 15.2d)
Brief Pain Inventory (Short Form)
S1916 Patient Cloud Feasibility Questionnaire

Patient submits the following using the Patient Cloud ePRO app:

b. Registration of Patient to Patient Cloud ePRO

To minimize patient burden and streamline patient visits, most patient reported outcome data for the 2, 4 and 6 week timepoints will be submitted directly by the patient through the ePRO Patient Cloud app. Daily pain evaluation will also be completed through the ePRO application. A paper copy of the Brief Pain Inventory (Short Form) will be completed in person by the patient at each clinic visit. A paper copy of the **S1916** Patient Cloud Feasibility Questionnaire will be completed in person by the patient at the 6-week clinic visit.

During the first clinic visit, the site staff will complete a registration for the patient to the Patient Cloud ePRO through iMedidata (see Section 18.1). The registration to the Patient Cloud ePRO will create a unique patient registration code that the site staff will provide to the patient. The CRA will instruct the patient to download the Patient Cloud ePRO app onto his/her own device (iPhone, Android smartphone, or tablet with cellular connectivity).

Please refer to Section 18.1 for the Patient Cloud ePRO Registration Process and Instructions.

c. PROs for the 2, 4, and 6 Week Timepoints

The following data will be completed by the patient on paper and submitted by the study site in Medidata Rave® at the 2, 4, and 6 week visits (+/- 4 days):

S1916 Patient Cloud Feasibility Questionnaire (6 weeks only)
Brief Pain Inventory (Short Form)

The following data will be self-reported by the patient via the Patient Cloud ePRO app at 2, 4, and 6 weeks (+/- 4 days) after registration:

Edmonton Symptom Assessment System (revised version)
PHQ-4
S1916 Opioid Adverse Effects Survey
PROMIS-29© Profile V2.1
S1916 Participant Survey – Satisfaction with Proteus (6 weeks only)

NOTE: *The patient will self-report pain on daily basis via the Patient Cloud ePRO app.*

d. Timepoints for Site-Completed **S1916** Cover Sheet for Patient-Completed Questionnaires

The **S1916** Cover Sheet for Patient-Completed Questionnaires is completed and submitted by the site each time paper-based PROs are expected to be done (baseline, 2 weeks, 4 weeks, and 6 weeks). **The Cover Sheet is used to report the PROs completed on paper only.** Data directly entered by the patient using the Patient Cloud ePRO app at weeks 2, 4 and 6 **are not reported** on the Cover Sheet.

e. Administration

Questionnaires will be self-administered and are anticipated to require 15-20 minutes to complete at each study time point. When a patient is registered to **S1916**, a calendar may be made by the local site with dates of upcoming patient-completed questionnaires noted and provided to the patient. A copy of the planned

Interventions aimed toward patient education may improve patient attitudes toward cancer pain and medication regimens. A Taiwanese study of cancer patients in the outpatient setting found that negative beliefs toward opioids was associated with lower adherence to opioid regimens whereas greater feelings of self-efficacy, the belief in one's ability to enact certain behaviors in order to achieve the desired result, was associated with both increased adherence to opioid regimens and increased pain relief.(*19)* These results suggest that interventions to improve patient knowledge and attitudes toward opioid use may result in better pain control. A meta-analysis that included 15 studies found that educational interventions, defined as behavioral instructions or advice dispensed by a healthcare provider or peer through verbal, written, or technology-aided modalities, decreased the intensity of average and worst pain, although there was no significant improvement in medication adherence. (*20*)

The American Pain Society has issued recommendations to improve standardization in the way physicians treat cancer pain, including early recognition of pain, involving patients in the treatment plan, improving treatment patterns by using a multimodal approach, regularly adjusting the pain regimen for the patient's needs, and monitoring outcomes of pain management. (*21*)

2.6 Monitoring and adverse effects of opioid medications

There are various side effects of opioid medication that require monitoring by physicians. Constipation is often underestimated because patients may assume fewer bowel movements is normal when they have decreased oral intake and are less active than previously. Nausea and sedation can both be managed by trying other opioids or maintaining a rotation of opioid medications. Two more potentially serious adverse effects include respiratory depression and neurotoxicity, both of which may be due to drug interactions and are important to identify early and address.

The opioid epidemic in the United States has become a public health crisis and efforts to control opioid use may have unintended consequences on cancer patients. A more standardized method for recognizing opioid use disorders is needed. An integrative review of the literature on opioid misuse found that based on screening questionnaires and drug toxicology urine tests, at least one in five cancer patients may be at risk of opioid misuse.(*22*) In another, 29% of the cancer patients assessed with the Screener and Opioid Assessment for Patients with Pain – short form had high-risk scores for misuse.(*23)* Risk factors for opioid misuse include younger age, prolonged survival, comorbid health conditions (especially psychiatric conditions such as anxiety and depression), limited financial resources, and pre-existing substance use disorders.(*24, 25, 26)* Physicians need to cautiously evaluate patients in whom they suspect opioid misuse because opioid-seeking behavior may also simply be a reflection of inadequate analgesia or difficulty understanding the treatment plan such as the use of "as needed" medications. On the other hand, failure to recognize opioid misuse can result in patients' long-term addiction and even criminal activity.

The American Society of Interventional Pain Physicians found good evidence to support routine monitoring including via prescription monitoring programs and urine drug testing, and to establishing treatment goals prior to initiation of opioid therapy with respect to expectations regarding pain relief and improvement in functional status.(*27*) Other ways to detect opioids misuse include contacting pharmacies regarding prescriptions, since overlapping opioid prescriptions written by multiple different prescribers and filled at multiple different pharmacies suggests "shopping" behavior.(*28, 29)*

2.7 Importance of feedback and communication

Patient-reported outcome (PRO) measures, which are measurements of patients' health status that are directly reported by the patient, are vital in identifying symptoms and

f. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via Medidata Rave® System as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via Medidata Rave® System at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.**

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, to ensure the event is not seen as study participant death.

3. **Death Neonatal** "Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth." A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal" under the General disorders and administration SOC.**

   Neonatal death should NOT be reported as a Grade 5 event under the General disorders and administration SOC to ensure the event is not seen as study participant death.

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

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

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

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, must be rostered at the enrolling site with a participating organization (i.e., SWOG).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

b. For this study, investigators writing the prescription for the oxycodone-acetaminophen-DMP may need to have DEA license as part of the IRB regulatory review. This requirement varies by State. Investigators should follow their State and local IRB directives.

13.3 Site Requirements

a. IRB Approval

This study will **not** be using the NCI CIRB. Each site must obtain local IRB approval for this protocol and submit IRB approval and supporting documentation including a list of all enrolling sites covered by the IRB approval to the SWOG Operations Office only:

SWOG Operations Office
4201 Medical Drive, Suite 250
San Antonio, TX 78229
FAX: 210: 614-0006
E-mail: IRBapprovals@swog.org

Please indicate “S1916 IRB Approval” and SWOG institution name in the subject line.

Do not submit IRB approvals to the CTSU Central Regulatory Office in Philadelphia, PA. You will only need to submit the initial Approval, annual re-approvals, and any amendments that require submission of IRB approvals to the

Edmonton Symptom Assessment System (revised version)
PHQ-4
S1916 Participant Survey – Satisfaction with Proteus
S1916 Opioid Adverse Effects Survey
PROMIS-29© Profile V2.1

e. WITHIN 15 DAYS OF DISCONTINUATION OF CO-ENCAPSULATED OXYCODONE-ACETAMINOPHEN-DMP PROTOCOL TREATMENT:

Submit the following:

On Treatment Vital Status Form
S1916 Off Treatment Notice

f. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the On Treatment Vital Status form, Notice of Death and the **S1916** Off Treatment Notice (if the patient was on protocol treatment) documenting death information.

g. AT THE END OF STUDY:

Providers submit:

S1916 Digital Medicine Program HCP Satisfaction
(This survey will be sent to providers by e-mail when all patients at the provider's site have completed follow-up. The survey will not be collected in Medidata Rave©.)

15.0 SPECIAL INSTRUCTIONS

15.1 Site Training

Site staff (pharmacist, site PI and/or CRA) must participate in training provided by Proteus prior to study activation. Sites submit contact information to IRBapprovals@swog.org using the Contact Information Form in Appendix 18.4 to initiate training conducted by Proteus. Proteus will notify the SWOG Operations of training completions via e-mail.

15.2 Administration of Patient-Reported Outcome Measures

a. Baseline PROs

Baseline PROs will be paper-based as the expectation is that sites will administer the forms at the time of consent. Patients can be registered to Patient Cloud ePRO after the patient is registered in Medidata Rave® (a SWOG Patient ID number is required).

The following data will be self-reported on paper forms by the patient PRIOR to registration:

Brief Pain Inventory (Short Form)
Edmonton Symptom Assessment System (revised version)
PHQ-4
PROMIS-29© Profile V2.1

questionnaire administration time points should be kept in the patient's research record.

f. Follow-Up Assessments – PROs completed by paper

Target follow-up assessment dates should be based on the date of registration. A window of ± 4 days is allowed for each assessment to provide more flexibility in scheduling. If the patient visit and form completion are not within the target window, all attempts should be made to complete the next assessment within the target follow-up assessment schedule per Sections 15.2c and 14.0.

g. Follow-Up Assessments – ePRO

Target follow-up assessment dates are based on the date of registration. A window of ± 4 days is allowed for each assessment to provide more flexibility in scheduling. Study sites are not required to monitor patient completion of ePRO forms at follow-up.

NOTE: Patient-completed forms will continue to be collected even if the patient discontinues the study intervention prior to Week 6.

15.3 Additional Quality Control Procedures

a. Anyone involved in the collection of PRO data in SWOG trials should review the Patient Reported Outcome Questionnaires Training Module available from this link on the SWOG CRA workbench

https://crawb.crab.org/TXWB/TrainingYouTube.aspx

b. A CTEP IAM user ID and password is required.

c. For questions regarding the patient-reported outcome assessments, contact SWOG Statistics and Data Management Center at cancercontrolquestion@crab.org.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).