PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activation Date October 15, 2019

SWOG CANCER RESEARCH NETWORK

FEASIBILITY OF A DIGITAL MEDICINE PROGRAM IN OPTIMIZING OPIOID PAIN CONTROL IN CANCER PATIENTS

STUDY CHAIRS:

Dawn L. Hershman, M.D., M.S. (Medical Oncology)
Columbia University
161 Fort Washington Ave
10-1068
New York, NY 10032
Phone: 212/305-1945
FAX: 212/305-0178
E-mail: dlh23@cumc.columbia.edu

Sherry Shen, M.D. (Medical Oncology)
Columbia University
161 Fort Washington Ave
10-1068
New York, NY 10032
Phone: 212/305-1945
FAX: 212/305-2913
E-mail: shs7028@nyp.org

Scott D. Ramsey, M.D., Ph.D. (Medical Oncology)
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, M3-B232
PO Box 19024
Seattle, WA 98109
Phone: 206/667-7846
FAX: 206/667-5977
E-mail: sramsey@fredhutch.org

Mina S. Sedrak, M.D., M.S. (Digital Engagement)
City of Hope
1500 E. Duarte Rd.
Duarte, CA 91010
Phone: 626/218-4173
FAX: 626/301-8233
E-mail: msedrak@coh.org

AGENTS:

Percocet®
(Oxycodone hydrochloride/Acetaminophen 5 mg/325 mg) used within the Proteus Digital Medicine Program (DMP)
(Device Number K150494)

BIOSTATISTICIANS:

Riha Vaidya, Ph.D.
Joseph M. Unger, Ph.D.
Amy Darke, M.S.
SWOG Statistics and Data Management Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, M3-C102
Seattle, WA 98109 – 1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: rrvaidya@fredhutch.org
E-mail: junger@fredhutch.org
E-mail: adarke@fredhutch.org

PATIENT ADVOCATE:

Barbara Segarra-Vazquez, D.H.Sc.

PARTICIPANTS

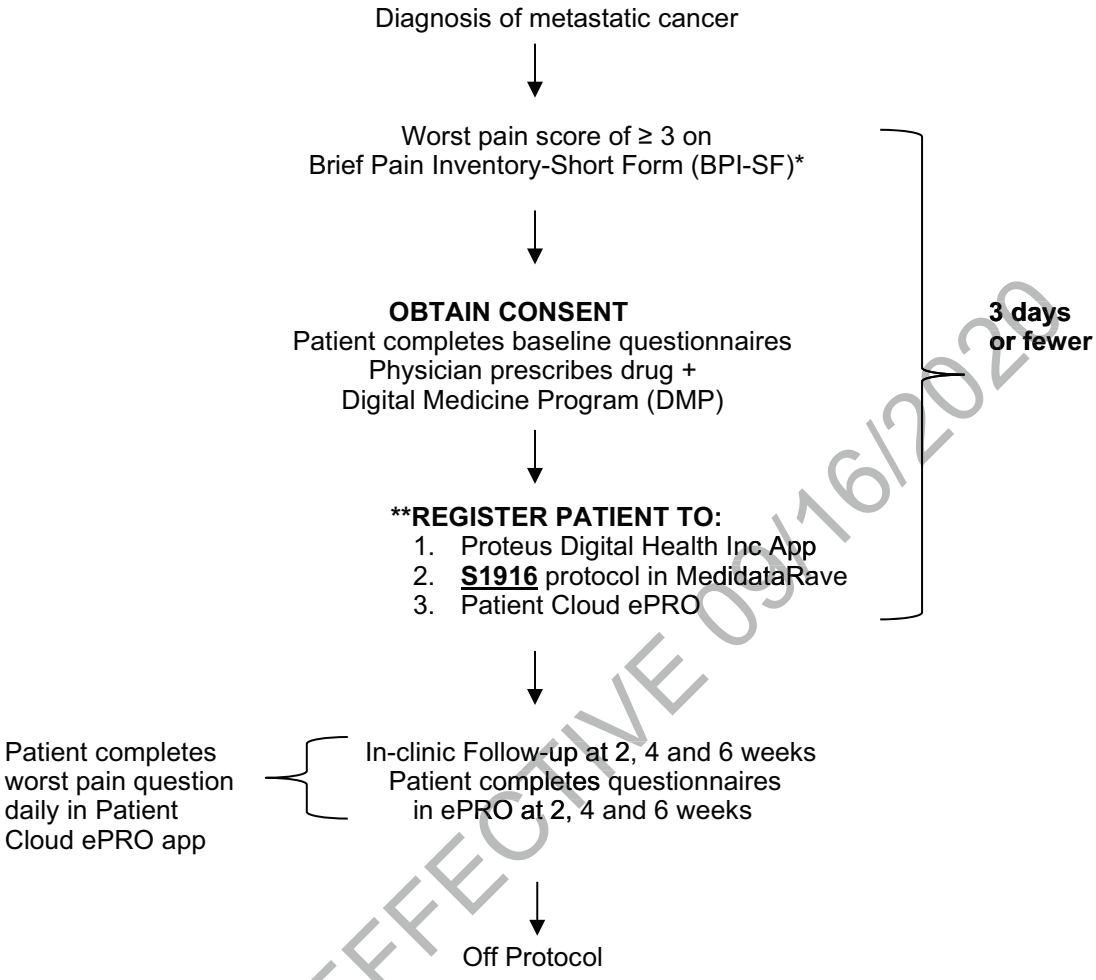
This study is limited to the following sites:

IL CARLE/Carle Cancer Center NCORP
IL HEARTLAND/ Heartland NCORP
IL094/Decatur Memorial Hospital
MT MONTANA/ Montana NCORP
MT002/Billings Clinic
NY024/ Columbia MU-NCORP
Columbia University-Herbert Irving Cancer Center
SC GREENVILLE/Greenville NCORP
SC045/Greenville Memorial Hospital
UT003/University of Utah (Huntsman Cancer Institute)

TABLE OF CONTENTS

STUDY CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
IRB approvals must be submitted by participating sites to SWOG Operations Office: IRBapprovals@swog.org Along with IRB approval, submit the completed contact information sheet located in Appendix 18.4 to IRBapprovals@swog.org Please indicate "S1916 IRB Approval" and SWOG institution name in the subject line. If you need assistance contact: member@swog.org	Enrollment to this study will be conducted via Medidata Rave© at the following url : https://loginimedidata.com/selectlogin If you need assistance, contact the SWOG Statistics and Data Management Center: cancercontrolquestion@crab.org	Data collection for this study will be done exclusively through Medidata Rave©. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions as this is not a CTSU supported study. Protocol, study documents, tools and reports: Protocol, consent, forms, and all study related documents are accessible to participating sites via the SWOG website (www.swog.org).
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the SWOG Member Web site located at https://www.swog.org. Access requires user log on with CTEP-IAM username and password.		
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center by phone or email: 206/652-2267 cancercontrolquestion@crab.org **For treatment or toxicity related questions** contact the Study Chair by phone or email: Dawn Hershman, M.D. at 212/305-1945, e-mail: dlh23@columbia.edu or Sherry Shen, M.D. at shs7028@nyp.org.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact SWOG Statistics and Data Management Center by phone or email: 206/652-2267, cancercontrolquestion@crab.org		

SCHEMA



* For screening purposes, the patient need only answer the single question related to worst pain on the BPI-SF. This is collected on the **S1916** Enrollment form and at study registration.

** Patients must be registered no more than 5 calendar days prior to planned start date of treatment.

1.0 OBJECTIVES

1.1 Primary Objective

a. To assess the feasibility of using a Digital Medicine Program (DMP) in cancer patients with metastatic disease experiencing uncontrolled pain. Feasibility will be determined in terms of study accrual, adherence to the DMP, and patient retention during follow-up.

1.2 Secondary Objective(s)

a. To assess the potential impact of the DMP on:

1. Pain level, as measured by the Brief Pain Inventory (BPI) pain and interference scores over time,

2. Opioid medication consumption,

3. High consumption of opioid medication,

4. Unplanned hospital or emergency department visits due to pain.

b. To assess the frequency of changes in pain management regimen.

c. To assess physical activity (steps, rest, movement) levels over time.

d. To profile patients' symptom burdens and health-related quality of life using PROMIS-29, Edmonton Symptom Assessment System (revised version)(ESAS-r), and Patient Health Questionnaire-4 (PHQ-4).

e. To describe the feasibility of using ePRO in a multi-center clinical trial setting.

f. To evaluate patient and provider satisfaction with the DMP and pain control.

2.0 BACKGROUND

2.1 Background / Rationale

For patients with cancer, pain can be a debilitating symptom that is distressing and interferes with daily life. A recent systematic review found that 66.4% of patients with advanced, metastatic, or terminal cancer, 55% of patients undergoing anticancer treatment, and 39.3% of patients after curative treatment reported living with pain. (*1*) Various studies show that despite its high prevalence, cancer pain is often undertreated. In a European study that screened over five thousand cancer patients, 69% of the patients reported that their pain interfered with their daily activities, and 50% believed that their healthcare professionals did not prioritize their quality of life. Despite high rates of opioid and analgesic use, 63% of the patients still experienced breakthrough pain.(*2*) In the last decade, the pharmacologic management of cancer pain has improved but around one-third of cancer patients still report undertreatment of their pain.(*3)*

2.2 Barriers to adequate pain control

There are various barriers that prevent successful use of opioid analgesics for cancer pain, which can be categorized into patient, physician, and systems barriers, or some combination of these. A study of 270 patients with cancer pain showed that the most

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.

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

problems that are often overlooked by clinicians in routine practice.(*30*) A systematic review found that PRO measures may be associated with increased patient satisfaction, symptom control, and use of supportive care measures.(*31*) A randomized controlled trial of symptom monitoring showed that use of a web-based system for collecting PROs and generating reports for physicians resulted in improved quality of life, fewer ER visits, and fewer hospitalizations compared with those who received usual care.(32) After a median follow-up of 7 years, those who had used the electronic PRO measure system had improved overall survival as well.(*33*) This type of system in which PROs are reported to physicians, who then view the data and in turn make changes to treatment regimens, facilitates improved patient-physician communication and promotes a partnership in managing the patient's symptoms.

2.8 Digital medicines as an innovative way to monitor medication adherence patterns

Proteus Discover® is a digital medicine program (DMP) consisting of an FDA-approved ingestible sensor made of dietary minerals embedded or co-encapsulated with patients' medications, a small wearable sensor patch, and a mobile device app that enables patients to share their medication adherence patterns as well as other parameters such as vital signs and physical activity with their physicians and care teams (*Proteus Digital Health, Redwood City, CA).(34)* When the digital medication is swallowed, the tiny ingestible sensor (size of a grain of sand) is activated by fluid in the stomach and sends a tiny heart beat-like signal which is detected by the patch. The patch also measures physical activity, rest, step count, and heart rate. Both the ingestible sensor and the wearable patch were approved as Class II medical devices in 2012 by the FDA.

The effectiveness of this type of digital medicine has been tested in several studies. In a randomized controlled trial of the digital medicine offering vs. usual care in patients with hypertension and diabetes, those in the digital medicine arm who were taking their medications co-encapsulated with a sensor and detected via the wearable patch had significantly greater reductions in their systolic blood pressure and A1c at 12 weeks when compared to those in the usual care arm.(*35*) Average medication adherence for the digital medicine cohort was 87%; the most commonly reported adverse event was a self-limiting skin irritation at the site of the wearable patch. The digital medicine system was also studied as a way to replace directly observed therapy in the setting of tuberculosis treatment. Coined "wirelessly observed therapy" (WOT) by UCSD researchers in a study of 61 tuberculosis patients, randomized 2:1 WOT vs. DOT: the system confirmed 98.4% detection accuracy. WOT confirmed a significantly greater percentage of prescribed doses taken (by more than 50%) than DOT over 7 and 5-day analysis periods within highly funded US TB DOT programs. WOT is highly accurate and was a superior alternative to DOT for confirming adherence to TB medications. (*36*)

While this type of digital medicine system generates a large quantity of data, modern methods of visual analytics can be applied to represent the data and can reveal interesting individual patterns of medication adherence. (*37*) The cost of wirelessly observed therapy was estimated to be only 36% of the cost of directly observed therapy. (*38*) Finally, the digital medicine system has also been studied in psychiatric patients. In a study of 67 patients with schizophrenia taking aripiprazole co-encapsulated with the ingestible sensor across 6 U.S. sites, 82% of the patients were able to use the wearable patch independently or with minimal assistance, wore the wearable patch for a mean of 71% of the time, and 78% of the patients reported satisfaction with the system. (*39)*

2.9 Difficulty assessing the timing of medication consumption

Differences in individual drug-taking behavior such as timing of medication ingestion and use of "as needed" medications can make it difficult for providers to adjust pain medication regimens, and can lead to unnecessary changes in dosing, scheduling, switches to other opioid medications, and possibly increased toxicity. Usage patterns of as-needed

medications are difficult to measure; possible methods include directly observed therapy, patient questionnaires, performing pill counts, and verifying refills with pharmacies, but these strategies often depend on patient reliability. (*40*)

2.10 Need for monitoring methods that feed back to physicians

Technology-based methods of monitoring have been developed, such as Medication Event Monitor Systems that use micro-processors to record each time a pill bottle is opened or eyedrop bottle monitors that can detect each time the cap is removed and the bottle inverted. (*41, 42*) These methods aim to generate real-time information regarding medication use patterns in the form of data that is accessible to physicians. However, these methods are often inaccurate and non-specific resulting in patient disengagement and have not shown significant impact on clinical outcomes. (*43*)

They also cannot detect whether the patient actually ingested the medication or when, as patients can open pill bottles but not take the medications, take an incorrect dose, or time doses incorrectly. Additionally, patients may perceive these monitoring methods as surveilling for "good behavior" rather than assessing individual patients' needs and responses to medication. Clearly, a more unique, accurate, and timely approach to monitoring medication use is needed.

2.11 An easily usable form of monitoring that promotes patient-physician partnership

Proteus Digital Health, Inc. has developed a novel platform that provides patients and physicians with specific, timely, and accurate feedback by logging medication ingestions, known as the Digital Medicine Program (DMP), which consists of a unique tiny ingestible sensor and an adhesive patch worn on the torso that together can register the exact time and dose of medication ingested. (*44*) The medication of interest can be co-encapsulated with the ingestible sensor, which is FDA-approved, within a gelatin capsule. The patch receives a signal when the medication has been ingested. The data are transmitted wirelessly via Bluetooth to a personal mobile device and can be shared with physicians via a secure web portal. This relatively new technology will allow for more personalized monitoring and has demonstrated improvements in medication adherence and clinical outcomes. (*45*, *46, 47*) Additionally, it may promote more communication between patients and their physicians and demonstrated increased medical decision making.

2.12 Incorporating physiologic feedback into pain control strategies

In addition to medication ingestion, the biometric patch also measures various other parameters such as activity, rest time, step count, heart rate, and soon respiratory rate. These data can help physicians make treatment decisions regarding adverse effects or sedation from opioid medications and adjust patients' regimens accordingly.

2.13 Summary

In patients with cancer, pain is a widely prevalent symptom that is often under-recognized and undertreated. It has been estimated that up to 66% of patients with advanced or metastatic disease live with pain, but nearly 43% of patients report undertreatment of their pain as measured on Pain Management Indices.(*48, 49)* Physicians often have difficulty judging the severity of their patients' pain and may minimize the importance of pain management at office visits; minorities and the elderly are at even higher risk for inadequate pain management.(*50, 51)* Other barriers include under-reporting of pain severity by patients, non-adherence to prescribed medication, difficulty accessing pain medications and pain specialists, and concerns regarding abuse particularly in the setting of a national opioid epidemic.(*52*) As more patients with active cancer are living longer,

efforts aimed at increasing adequacy of pain management, monitoring of pain medication use, and surveillance for the development of misuse behavior are needed.(*53)*

The Proteus Digital Medicine Program (DMP) was developed to introduce pharmaceutical biofeedback to patients and providers and accurately time-stamp medication consumption.(*54*) It has been studied in hypertension, diabetes, tuberculosis, HIV, hepatitis C, mental illness, etc., but has not been previously studied in patients with chronic cancer pain requiring opioid analgesics.(*55, 56, 57)* For this current proposal, we aim to test the feasibility of the DMP consisting of an FDA-approved ingestible sensor co-encapsulated with the medication of interest, a small wearable patch, and a mobile application for monitoring patterns of medication ingestion, medication titrations, and adverse effects of an opioid analgesic in patients with metastatic cancer and baseline moderate to severe pain.

Given the high prevalence of cancer pain and issues with undertreatment and opioid misuse, focused efforts to improve monitoring of medication ingestion patterns are needed. Data collected from this study (such as information on patterns of DMP usage by patients and physicians and changes to medication dosage based on the reported symptoms) will inform the design of a randomized controlled trial of the DMP vs. usual care to control cancer pain and increase quality of life. If successful, this DMP could be a new way for physicians to evaluate patients' pain medication use patterns and titrate for adequate pain control while concurrently monitoring for adverse effects or abusive/addictive behavior. It will also promote improved communication between patients and their physicians and potentially address and ease some of patients' concerns and hesitancies regarding opioid medications.

2.14 Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	0	0	0	1
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	3	2	0	0	5
White	21	21	3	3	48
More Than One Race	1	1	0	0	2
Total	27	27	3	3	60

3.0 DRUG AND DEVICE INFORMATION

Investigator Brochures

Oxycodone/acetaminophen (Percocet®)

The oxycodone/acetaminophen (5 mg/325 mg) used for this study is commercially available; therefore, Investigator Brochure is not applicable to this drug. Information about the commercial drug is publicly available in the prescribing information and other resources.

Digital Medicine Program

The ingestible sensor and the wearable sensor are FDA approved and are not considered investigational. However, in cases where the IRB insists on having the official Investigator's Brochure from the company, further information may be requested by contacting the SWOG Operations Office at protocol@swog.org.

3.1 Oxycodone hydrochloride/Acetaminophen (5 mg/325 mg)(Percocet®)

a. PHARMACOLOGY

Oxycodone hydrochloride/Acetaminophen (5 mg/325 mg) is a C-II controlled substance as labeled by the DEA.

Mechanism of Action: Oxycodone hydrochloride binds to opiate receptors in the central nervous system (CNS), causing inhibition of ascending pain pathways, altering the perception of and response to pain, and produces generalized CNS depression. The analgesic effects of acetaminophen (APAP) are believed to be due to activation of descending serotonergic inhibitory pathways in the CNS. Interactions with other nociceptive systems may be involved as well. Antipyresis is produced from inhibition of the hypothalamic heat-regulating center.

b. PHARMACOKINETICS

1. Absorption and Distribution:

a. *Oxycodone*:
The oral bioavailability of oxycodone is 60% to 87%. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. Single- or multiple-dose bioavailability of extended-release oxycodone hydrochloride/acetaminophen is similar to that of the immediate-release products containing oxycodone or acetaminophen. Given the short elimination t½ of oxycodone (5.6hrs), steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing. Oxycodone has been shown to be 45% bound to human plasma proteins in vitro. The volume of distribution after intravenous administration is 211.9 ±186.6 L.

b. *Acetaminophen*
Absorption is rapid and almost complete from the gastrointestinal (GI) tract after oral administration. With overdosage, absorption is complete in 4 hours. Binding of the drug to plasma proteins is variable; only 20% to 50% may be bound at the concentrations encountered during acute intoxication.

2. Metabolism:

a. *Oxycodone*
In humans, oxycodone is extensively metabolized to noroxycodone by means of CYP3A-mediated N- demethylation, oxymorphone by means of CYP2D6-mediated O-demethylation, and their glucuronides. Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone. Noroxycodone is oxidated to form noroxymorphone, which does not significantly cross the blood brain barrier. Oxymorphone's contribution to analgesia following oxycodone administration is thought to be clinically insignificant.

b. *Acetaminophen*
Acetaminophen is metabolized in the liver via cytochrome P450 microsomal enzyme. About 80-85%of the acetaminophen in the body is conjugated principally with glucuronic acid and to a lesser extent with sulfuric acid and cysteine. About 4% of acetaminophen is metabolized via cytochrome P450 oxidase to a toxic metabolite which is further detoxified by conjugation with glutathione, present in a fixed amount. It is believed that the toxic metabolite NAPQI (N acetyl-p-benzoquinoneimine, N-acetylimidoquinone) is responsible for liver necrosis. High doses of acetaminophen may deplete the glutathione stores so that inactivation of the toxic metabolite is decreased. At high doses, the capacity of metabolic pathways for conjugation with glucuronic acid and sulfuric acid may be exceeded, resulting in increased metabolism of acetaminophen by alternate pathways

3. Elimination:

a. *Oxycodone*
Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. Following a single, oral dose of oxycodone, the mean ± SD elimination half-life is 3.51 ± 1.43 hours. The total plasma clearance was approximately 1.4 L/min in adults.

b. *Acetaminophen*
After hepatic conjugation, 90 to 100% of the drug is excreted via the kidney (<5% unchanged; 60%-80% as glucuronide metabolites; 20% to 30% as sulphate metabolites; ~8% cysteine and mercapturic acid metabolites)

c. ADVERSE EFFECTS

1. Possible Side Effects:

a. *Oxycodone*

As an opioid, oxycodone exposes users to the risk of addiction, abuse, and misuse.

Adverse effects reported in >20% to 100% of subjects treated with oxycodone include constipation, nausea, somnolence

Adverse effects reported in 6% to 20% of subjects treated include dizziness, pruritis, vomiting, headache, dry mouth, asthenia, decreased appetite, pyrexia

Adverse effects reported in 1% to 5% or less of subjects include hypotension, sweating, adrenal insufficiency, anaphylaxis, respiratory depression, dyspnea, hiccups, febrile neutropenia, neutropenia, tachycardia, abdominal pain, diarrhea, dyspepsia, gastritis, anorexia, gastroesophageal reflux disease, fatigue, twitching, pain, chills, fever, procedural pain, seroma, oxygen saturation decreased, alanine aminotransferase increased, hemoglobin decreased, platelet count decreased, neutrophil count decreased, red blood cell count decreased, weight decreased, hypochloremia, hyponatremia, pain in extremity, musculoskeletal pain, hypoesthesia, lethargy, paresthesia, insomnia, anxiety, depression, abnormal dreams, confusion, dysphoria, euphoria, nervousness, thought abnormalities, agitation, dysuria, urinary retention, oropharyngeal pain, hyperhidrosis, rash, drug withdrawal syndrome in neonates of a dependent mother.

Adverse effects reported in less than 1% of patients include: lymphadenopathy, tinnitus, abnormal vision, dysphagia, eructation, flatulence, increased appetite, stomatitis, withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema, accidental injury, ST depression, dehydration, syncope, migraine, abnormal gait, amnesia, hyperkinesia, hypoesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perversion, depersonalization, emotional lability, hallucination, dysuria, hematuria, polyuria, urinary retention, impotence, cough increased, voice alteration, dry skin, exfoliative dermatitis

b. *Acetaminophen*
Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death.

Adverse effects reported in >3% of subjects treated with APAP include nausea, vomiting, headache, insomnia, pruritis, constipation

Adverse effects reported in 3% or less of subjects include anemia, fatigue, infusion site pain, edema peripheral, aspartate aminotransferase increased, abnormal breath sounds, hypokalemia, muscle spasms, trismus (lockjaw), anxiety, dyspnea, hypertension or hypotension, acute generalized

exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), hepatic failure

2. Pregnancy and Lactation:

a. *Pregnancy:* Category C.
Animal reproduction studies have not been conducted with this combination. [US Boxed Warning] Prolonged use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts.

b. *Breast-feeding considerations*
Oxycodone and acetaminophen are present in breast milk. Due to the potential for serious adverse reactions in the breast feeding infant, breastfeeding is not recommended by the manufacturer.

3. Drug Interactions:

a. *Drug/Drug Interactions with Oxycodone*
Opioid analgesics may enhance the neuromuscular-blocking action of skeletal muscle relaxants and produce an increase in the degree of respiratory depression.

Interactions with Other CNS Depressants
Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, centrally-acting anti-emetics, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with oxycodone may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics
Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients

b. *Drug/Drug Interactions with Acetaminophen*
Alcohol, ethyl: Hepatotoxicity has occurred in chronic alcoholics following various dose levels(moderate to excessive) of acetaminophen.

Anticholinergics: The onset of acetaminophen effect may be delayed or decreased slightly, but the ultimate pharmacological effect is not significantly affected by anticholinergics.

Oral Contraceptives: Increase in glucuronidation resulting in increased plasma clearance and a decreased half-life of acetaminophen.

Charcoal (activated): Reduces acetaminophen absorption when administered as soon as possible after overdose.

Beta Blockers (Propanolol): Propranolol appears to inhibit the enzyme systems responsible for the glucuronidation and oxidation of acetaminophen. Therefore, the pharmacologic effects of acetaminophen may be increased.

Effects of Other Substances on Acetaminophen
Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

Anticoagulants
Chronic oral acetaminophen use at a dose of 4,000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of acetaminophen in patients on oral anticoagulants, more frequent assessment of INR may be appropriate in such circumstances.

c. *Avoid concomitant use*
Avoid concomitant use of Oxycodone and Acetaminophen with the following: Azelastine (nasal), Bromperidol, Conivaptan, Eluxadoline, Fusidic Acid (Systemic), Idelalisib, Opioids (Mixed Agonist/Antagonist), Orphenadrine, Oxomemazine, Paraldehyde, Thalidomide, ethanol, imatinib, isoniazid, lamotrigine, and other potentially hepatotoxic drugs.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

The maximum human daily dosage of acetaminophen is 4,000 mg/day.

In patients treated with oxycodone hydrochloride/acetaminophen tablets for more than a few weeks who no longer require therapy, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

e. HOW SUPPLIED

Oxycodone/acetaminophen (5 mg/325 mg tablet) is commercially available. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

Participating site pharmacies will purchase commercially available oxycodone/acetaminophen (5 mg/325 mg) tablets from their regional drug distributor.

Many sources are too large to co-encapsulate, therefore pharmacies must use one of the following National Drug Codes (NDCs) products for encapsulation:

Manufacturer Name	NDC	Recommended Capsule Size
Purdue Pharma/Rhodes Pharmaceuticals	42858-0102	AAA
PD-Rx	43063-653	AAA
Proficient Rx	63187-824	AAA
Mayne Pharma	68308-0841	AAA

The participating site pharmacies will co-encapsulate the oxycodone/acetaminophen (5 mg/325 mg) tablets with the Proteus ingestible sensors. See Section 3.2b.2 for description of encapsulation.

Co-encapsulated study drug will be provided to patients at no cost and will be distributed at baseline, and at the Week 2 and Week 4 clinic visits.

f. DRUG ACCOUNTABILITY

Participating site pharmacies must maintain a careful record of the receipt, dispensing, and return of study drugs. For SWOG auditing purposes, the study requires use of the NCI DARF. (Electronic accountability systems may be used as long as the template mirrors the NCI DARF).

3.2 Digital Medicine Program

The Proteus Digital Medicine Program (DMP) consists of a mobile application (app), Ingestible Sensor (IS) and Wearable Sensor (WS) (also known as Patch which consists of a data Pod and adhesive Strip). For complete product information, please visit www.proteus.com/instructions.

a. Wearable Sensor (WS) “Patch”

1. Device Description

The patch is a body-worn sensor that collects and stores date- and time-stamped physiological and behavioral metrics, such as heart rate, activity, and body angle. The patch collects and stores date- and time-stamped ingestions of the Ingestible Sensor (IS). The patch may be used with or without the IS.

The patch adheres to the torso like an adhesive bandage. The data collected by the patch are processed, compressed, and stored in the non-volatile memory of the patch. The patch periodically connects to a general-purpose computing device, such as a mobile phone, using encrypted wireless communication. The stored data are transmitted over this link and the memory of the patch is cleared subsequently to free space for further data collection. The process of data upload could be configured as

automatic, or user-initiated. The patch contains electrodes that sample biopotentials of the subject.

This study will utilize the Reusable Wearable (RW2) Sensor which includes a Pod and a disposable adhesive Strip. The Strip uses skin-friendly biocompatible adhesive to adhere onto an individual's skin for up to 7 days. The Strip contains two electrodes used to detect the signals emitted by the IS, as well as to measure a patient's heart rate, skin impedance, etc.; a battery to supply power to the Pod; and a fixture to secure the Pod. After use (up to 7 days), the Strip is disposed of in regular waste.

The electronic module portion of the RW2 is called the Pod and is designed for up to 360 days of usage. The Pod contains a printed circuit board (PCB) surrounded with a plastic cover designed with features that facilitate attachment and detachment to the Strip. The PCB has sensors and other electronic components to record physiological information and to transfer the data. The Pod connects to the Strip via connectors on the Strip. The electronic components on the Pod are sealed against water ingress. After up to 7 days, the Strip is removed from the torso. The Pod is disconnected from the old Strip and connected to a new Strip, to form a new patch.

2. Mobile Computing Device and Patch Pairing

The capabilities of a commercially available mobile computing device (e.g., smartphone or tablet computer) can be used to relay and display information collected by the Proteus DMP Pairing of the patch with the mobile computing device allows relay and display of DMP information. Pairing the mobile computing device to a patch can be performed easily in an ambulatory setting as needed. (It is expected that study staff will help patients with the device and patch pairing).

3. Biocompatibility

The patch that is in contact with the skin consist of one or more of the following materials: hydrogel or conductive gel; hydrocolloid; and skin adhesive.

4. Safety

Patch anticipated adverse events

Patch-Anticipated Adverse Events
Previously encountered (judged as *related or possibly* related to the patch)
At patch location: Skin rash, redness, macular rash, papular rash, macular papular rash, erythema, non-erythematous skin discoloration, pruritis.

5. Recommended Use

Activities while wearing the patch: Bathing, rigorous physical activity, and swimming are allowed while wearing the patch. Physical activities which

represent a risk of forceful contact with the patch (e.g., boxing, karate) should be avoided.

Roentgenography (X-Ray Imaging), Computerized Tomography (CT), and Patch Visualization: The patch is radiopaque and should be removed during roentgenography or other diagnostic imaging utilizing X-rays (e.g., computerized tomography) should more comprehensive roentgenographic imaging be desired. A new adhesive strip should be applied after imaging is completed.

Magnetic Resonance Imaging (MRI) : The patch should be removed before magnetic imaging. A new patch should be applied after imaging is completed.

Please note that any IS that is ingested during the imaging procedure will not be detected/recorded should the patch be removed before the ingestion. As well, the new patch that is applied after the procedure will not record any ingestion that occurred prior to its application.

6. Cautions

- DO check the component expiration dates before use.
- DO keep components out of reach of children
- DO NOT store components in extremely hot, cold, humid or bright conditions.
- DO NOT use for medication treatment decisions. Accuracy is less than 100%. Contact your physician with any questions or concerns regarding medication use.
- DO NOT continue use until further instructed by a physician if your skin is irritated or inflamed around the Patch.
- DO NOT place in locations where skin is scraped, cracked, inflamed or irritated.
- DO NOT place in a location that overlaps the area of the most recently removed Patch.
- DO NOT use if you are allergic to adhesive tape.
- DO NOT wear the same adhesive Strip for longer than one week.
- DO NOT dispose of the data Pod when changing the adhesive Strip
- DO NOT drop or bump the Patch with excessive force.
- DO NOT use to diagnose heart-related conditions.
- DO NOT wear during magnetic resonance imaging (MRI), cautery, or external defibrillation procedures.

7. Adhesive Strip disposal

Patients are to replace the adhesive strip weekly or as prompted by their mobile app. The adhesive strip contains a battery and should be disposed of the same way a household battery or electronic device is disposed of.

Instruct patients NOT to throw the data Pod away as it is to be used again with each new adhesive strip.

8. Supply: Kits (consisting of multiple adhesive strip patches and single pod) will be provided by Proteus and distributed to patients by the local pharmacy.

b. Ingestible Sensor (IS) also known as Ingestible Event Marker (IEM),

1. Device Description

The IS is a very small ingestible device comprised of an Integrated Circuit (IC), that is coated with thin layers of minerals and metals that are consumed in the human diet, and a cellulose-based disc. The IS has low levels of extractable copper (Cu), magnesium (Mg), chloride (Cl), and ethyl citrate (triethylcitrate) in the gastrointestinal (GI) tract. The cellulose-based disc consists of ingredients that are procured from reputable vendors. These are commonly used pharmaceutical excipients that are considered as GRAS (Generally Recognized as Safe) materials and used as common food additives.

The IS can be combined with an oral solid formulation of an active drug or a placebo. After ingestion, the IS is powered by the conductive environment of the stomach and a unique identifying code is communicated by modulating the current through the IS. The modulated current propagates through the body tissues to a cleared compatible medical device on the skin surface. The code is communicated to cleared compatible medical device by the IS for several minutes, after which the IS becomes inactive.

The main function of the ingestible disc is to augment the quality and strength of the information communicated by the IS by forcing current to take a longer path from one side of the chip to the other. The ingestible disc retains its rigidity for several minutes and then gradually softens within the gut for ultimate excretion within the feces. By the time the IS reaches the large intestine, the ingestible disc portion will have become mechanically soft. The IC will remain largely unchanged by its passage through the gut, except for the depletion of the mineral layers, and is excreted in the feces. Excretion of the IS and ingestible disc will generally occur in 24 to 72 hours, depending upon individual transit time.

2. Dosage Form Factors

Co-encapsulation (CoE) provides a vehicle to combine any solid-dosage drug product inside a capsule with an IS tablet dose form. A drug product of various form factors (for example a tablet, a capsule, or a powder) can be placed inside the capsule along with the IS tablet dose form. The capsule is then closed and locked by inserting and pushing the capsule cap over the capsule body. With the CoE method, the IS, the drug product, and the standard excipient materials are completely contained within the capsule. Co-encapsulation provides an IS-enabled dosage form with a familiar appearance to patients or consumers.

The commercially available capsules that are used for co-encapsulation include the following ingredients:
hard gelatin or hydroxypropylmethylcellulose (HPMC), and colorant.

3. Safety

IS-Anticipated Adverse Events
Previously encountered (judged as *related or possibly* related to the IS Device)
Abdominal cramping, asthma exacerbation, bitter taste in mouth, constipation, nausea/vomiting non-cardiac chest pain

Pregnancy and Lactation

The doses from ingestion of excipients and extractable components (individually and in combination with each other) in 30 IS tablet dose forms per day are below the levels determined to be safe for pregnant women and their fetuses, and lactating women and their nursing infants.

4. Recommended Use of the IS

Dosage: Excipient doses in 30 IS tablet dose forms per day do not exceed, and are well below, doses determined to be safe in humans.

Food and IS Co-Ingestion: A clinical study has demonstrated that food and beverages including alcohol do not affect IS function in any clinically significant manner.

Medication and IS Co-Ingestion: ISs have been ingested in clinical studies with no limitations placed upon the co-ingestion of capsules, tablets, or gelatin tabs. **There have been no reported losses of drug efficacy associated with the co-ingestion of any medication and an IS**.

Gastrointestinal Absorption of Materials in the IS and GI Safety: The IS has been deliberately developed to consist of minute amounts of materials already consumed in the human diet. The IS's extractable materials are present in quantities well below acceptable daily levels, even if 100% absorption is assumed. The size of a single IS at the time of ingestion is similar to a single grain of sand. The size of the IS decreases as after it comes into contact with gastric and intestinal fluids.

Magnetic Resonance Imaging (MRI) and the IS: The IS does not represent a magnetic imaging risk as there are no ferrous metals (such as nickel, iron, cobalt) or other magnetic materials in the IS. **The Wearable Sensor, however, should be removed before magnetic imaging.**

Roentgenography (X-Ray Imaging), Computerized Tomography (CT), and IS Visualization: The IS is not radiopaque. Please note that any IS that is ingested during the imaging procedure will not be detected/recorded should the cleared compatible medical device on the skin surface be removed, and the replaced cleared compatible medical device after the imaging procedure will similarly not detect/record this ingestion.

5. Cautions

- DO check the component expiration dates before use.
- DO keep components out of reach of children and pets.

- DO take with a sufficient amount of water.
- DO NOT store components in extremely hot, cold, humid or bright conditions.
- DO NOT use for medication treatment decisions. Accuracy is less than 100%. Contact your physician with any questions or concerns regarding medication use.
- DO NOT chew.
- DO NOT tamper with or place in water before ingestion.

6. Supply: Ingestible sensors will be provided by Proteus. Encapsulation of the study drug with the ingestible sensor will occur at designated pharmacies at each participating site. Co-encapsulation will be performed by pharmacists who have completed the Proteus training. Proteus will supply pharmacies with bottles, caps, AAA gel capsules and desicant packets.

7. Expiration of ingestible sensor: **Once the bottle of ingestible sensors is opened for co-encapsulation, the sensor's integrity is maintained for 30 days. It is recommended that the bottle of sensors be unsealed at the point of co-encapsulation and that the co-encapsulation prescription be dispensed immediately to the patient**.

c. Product numbers for Starter Kit Supplies

Part Number	Description
SPC- 2329	Starter Kit
SPC-2006	Adhesive strips
SPC-2008	Pod
SPC-2032-A22-B50	Ingestible Sensor Pill for oxycodone/acetaminophen (15 bit)
SPC-2232-D22-B50	Ingestible Sensor Pill for oxycodone/acetaminophen (30 bit)
SPC-2346-05	Universal Capsule

d. Mobile application:

The mobile application "Proteus Discover." is to be downloaded by the patient onto his/her phone or tablet at no cost. See Section 7.4.

e. Inventory Records: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all products received from Proteus. For SWOG auditing purposes, the study requires use of the NCI DARF. (Electronic accountability systems may be used as long as the template mirrors the NCI DARF).

f. Product and Drug Returns: Unused drug supplies must NOT be returned. After final accountability is performed, unused patches, sensors and study drug must be disposed of per local institutional guidelines

g. Questions related to the Proteus Digital Medicine Program should be e-mailed to cancercontrolquestion@crab.org.

4.0 STAGING CRITERIA

Staging is not applicable to this study.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration in Medidata Rave®. Section 5 may be printed and used by the site, but is not to be uploaded in RAVE (unless specifically stated). For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG SDMC in Seattle at 206/652-2267 or cancercontrolquestion@crab.org prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have a diagnosis of metastatic cancer.

NOTE: Patients with brain metastases, known human immunodeficiency virus (HIV) infection, chronic hepatitis B virus (HBV), or history of hepatitis C virus (HCV) are eligible.

5.2 Prior/Concurrent Therapy Criteria

a. Patients currently on oxycodone/acetaminophen are eligible as long as they are on the 5 mg/325 mg dose. Patients currently on another opiate, who have been prescribed or will be prescribed oxycodone/acetaminophen as an addition to their therapy are also eligible.

5.3 Clinical/Laboratory Criteria

a. Patients must have a worst pain score of at least 3 (on a scale of 0-10) on the Brief Pain Inventory (BPI)* within 3 days prior to registration and be deemed by their physician to require initiation, continuation, or uptitration of opioid therapy with oxycodone/acetaminophen 5mg/325mg.

NOTE: Patients requiring only "as-needed" therapy (PRN) are also eligible.

*For screening purposes, the patient need only answer the single question related to worst pain within the last 24 hours on the BPI, Question #3. This is collected on the **S1916** Enrollment Form.

b. Patients must be ≥ 18 years of age.

c. Patients must complete the baseline PRO questionnaires prior to registration.

d. Patients must be able to read English, as the ePRO questionnaires are in English and patient instructions on the Proteus Discover mobile application are in English.

e. Patients must be willing to participate in electronic data collection and must have an iPhone, Android phone, or tablet with cellular connectivity in order to download the Patient Cloud and Proteus Discover mobile applications onto his/her device.

f. Patients must have successfully downloaded the Proteus Discover App

g. Patients must not have a known allergy to adhesive tape, hydrogel or conductive gel, or hydrocolloid. (The adhesive strip for the Wearable Sensor Patch does **not** contain natural latex rubber).

h. Women must not be pregnant or nursing due to the potential obstetric and neonatal complications of opioid therapy. Patients of reproductive potential must have agreed to use an effective contraceptive method. All men are considered to be of reproductive potential unless they have had a vasectomy or orchiectomy. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal

ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

5.4 Regulatory Criteria

a. Patients ***must*** be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the registration process (see Section 13.0 for instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

There are no stratification factors for this study.

7.0 TREATMENT PLAN

For study procedure related questions, please contact the SWOG Statistics and Data Management Center in Seattle at 206/652-2267 or cancercontrolquestion@crab.org. For questions related to the study treatment, please contact the Study Chair, Dawn Hershman, M.D. at dlh23@cumc.columbia.edu. If Dr. Hershman is not available, email Sherry Shen, M.D. at shs7028@nyp.org.

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

7.1 Site Requirements and Study Flow

See Appendix 18.3 for pre-study site, provider, staff and pharmacy requirements.

See Appendix 18.4 for a flow diagram of study activities for patients.

7.2 Prescription

At baseline and the 2- and 4-week follow-up visits, patients will be given a prescription for an initial 2-week supply (168 pills) of oxycodone/acetaminophen 5mg/325mg - DMP by their treating physician to be filled by the site's designated pharmacy. These are co-encapsulated pills of oxycodone/acetaminophen 5mg/325mg with FDA approved ingestible sensor. Co-encapsulation of the study drug with the ingestible sensor will occur at participating pharmacies prior to patient registrations. Patients will receive dosing instructions from their physician.

Example of Prescription for digital medication:

If patient kits (which include the adhesive Strips and Pod) will be distributed by the pharmacy, SIG should read:

Oxycodone/acetaminophen 5/325 mg tab

SIG/label: Medication with Proteus Sensor *with adherence packaging.*
Take 1-2 tablets every 4-6 hours as needed.

Quantity: 14 day supply
Number of refills: 2

If patient kits will be distributed by the clinical research staff/office, SIG should read:

Oxycodone/acetaminophen 5/325 mg tab

SIG/label: Medication with Proteus Sensor
Take 1-2 tablets every 4-6 hours as needed.

Quantity: 14 day supply
Number of refills: 2

7.3 Treatment

a. *Example* of Study treatment

Agent	Dose	Route	Schedule	Duration
Oxycodone / acetaminophen-DMP with ingestible sensors**	5 mg / 325 mg	oral	1-2 capsule every 4-6 hours as needed*	6 weeks

*Not to exceed 3 pills in a 4 hour period
**Patients receive study medication at baseline, Week 2 and Week 4 clinic visit.

While the pharmacist fills the prescription, patients will return to the clinic to work with staff on mobile application download, patch placement and device. (See Section 7.4).

b. After 6 weeks

After 6 weeks of oxycodone-acetaminophen-DMP protocol treatment, the patient will be removed from protocol therapy and treatment will be at the discretion of the treating investigator.

7.4 Mobile application download, Patch/Pod placement and device Bluetooth pairing

While prescriptions are being filled, the research staff will instruct the patient to initiate the Proteus Discover app download to the patient's cellular service-enabled device and registration to the Discover app. Research staff must record the patient ID number provided by the app as it will be collected during the SWOG study registration. The mobile application contains thorough self-help instructions for connecting the Patch to the patient's phone and placing the Patch on the torso. Research staff must assist with Patch placement and device pairing. The adhesive strip on the Patch should be replaced on a weekly basis, which can be done by the patient at home. The patient should be reminded not to throw away the Pod. The data Pod is to be used again with each new adhesive strip. Patients will be provided with two adhesive strip Patches in their start-up kit and a 6-pack of

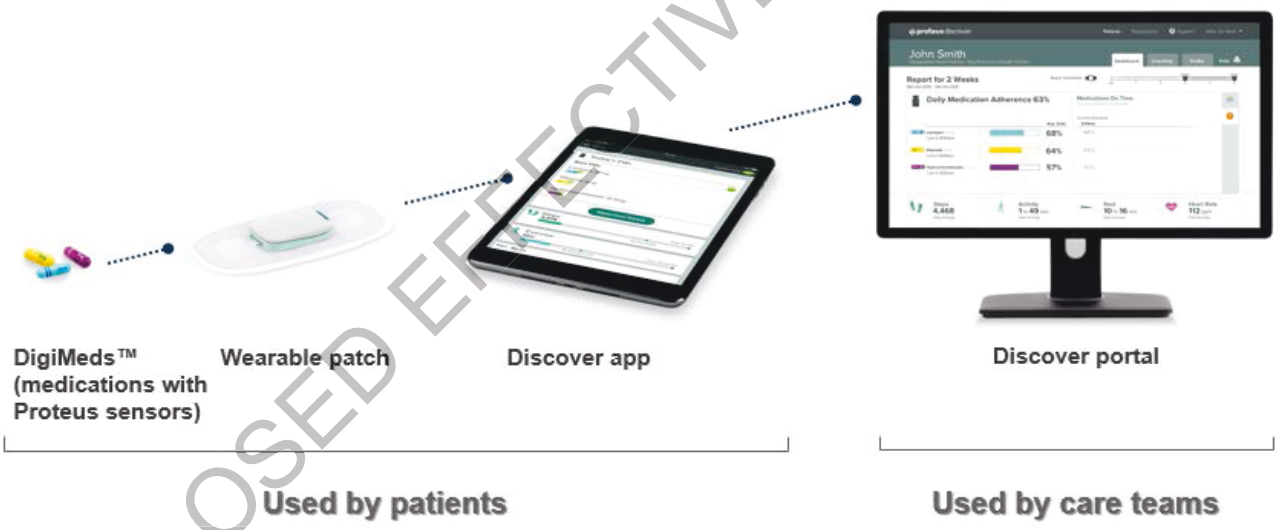
adhesive strip Patches for the study duration. **Patches are not MRI or electrocautery-compatible and need to be removed prior to MRI or surgery and replaced afterward**. In the event that the patient needs more than 8 adhesive strip/Patches for the duration of the study, strips can be ordered by the study site and refilled from Proteus. Ordering information is available on the Discover app. Patients will be instructed to take the co-encapsulated medication as per their physicians' recommendations for pain control. Additional instructions regarding skin care, and appropriate patch removal and replacement are provided through the mobile application.

The Proteus Discover app is available in the App Store for iOS and in Google Play for android

Proteus Discover

7.5 Description of the Digital Medicine Program (DMP)

Medication ingestion and vital signs: Data generated by the digital medicine program include the number of pills and frequency taken, vital signs including heart rate, amount of time spent in activity and at rest, and total number of steps taken daily. A schema for data generation by the digital medicine program is displayed below:



Data from the patch are transmitted via Bluetooth to a mobile device app and uploaded to a secure server, allowing the patients to share this data with their study physician. The study physician can therefore access patient data in near real-time through a secure web portal/EMR. Data from the patient's patch are transmitted wirelessly every 15 seconds to a HIPAA compliant cloud and are stored separately from patient identifiers. An abnormal average daily resting heart rate <60 or >100) detected by the patch will generate a notification for the physician via the web portal. Physicians will be expected to access the data via web portal during scheduled visits, but the patch data are not intended to function as "emergency alert systems," as physicians will only see the data when they choose to access the portal. When data cannot be detected via the wearable sensor, suggesting that the patient may have removed it, the patient will receive a reminder via text message and push notification within the mobile application to replace the wearable sensor.

7.6 Review of Patch Data

***Providers must review patch data prior to their patient's clinic visit.** Note that the Providers are to use the patient ID that Proteus assigned to the patient when the patient performed the app download. Do not use the SWOG patient ID to view patch data.

If patient patch data indicates that pain is not being controlled despite optimal dosing of the study medication, provider is to start the patient on additional long acting agent. Study drug should be continued as long as the patient is not experiencing serious adverse events.

7.7 Adherence and Refills

Patients will be asked to bring bottles with unused study drug back at each clinic visit. Staff will collect unused study medication before the pharmacy dispenses the refill. Unused study drug should not be carried forward due to short expiration of the ingestible sensor. Unused study drug will be destroyed per local procedures.

7.8 Criteria for Removal from Protocol Treatment

a. Completion of 6 weeks of follow-up after registration.

b. Unacceptable toxicity (patient cannot tolerate the oxycodone/acetaminophen-DMP or wearable patch).

c. The patient may withdraw from the study at any time for any reason.

7.9 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented on the **S1916** Off-Treatment Notice.

NOTE: Patient-completed questionnaires and site-completed forms will continue to be collected even if the patient discontinues protocol intervention prior to the completion of the 6 weeks of protocol defined therapy.

7.10 Follow-Up Period

All patients will be followed for 6 weeks from **S1916** registration.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 Dose Modifications

There are no dose modifications for this study.

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.

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.

9.0 STUDY CALENDAR

REQUIRED	Baseline	2 weeks[1] +/- 4 days	4 weeks[1] +/- 4 days	6 weeks[1] Or end of study visit +/- 4 days	Daily through week 6
Vital Status	X	X	X	X	
History, Physical Exam, Height, Weight, Performance Status	X				
Dispense study drug[2]	X	X	X		
Adverse Event monitoring		X	X	X	
Provider reviews patient's patch information on the Proteus provider web portal prior to each clinic visit		X	X	X	
Patient-reported Questionnaires:					
Brief Pain Inventory (Short Form) (BPI-SF)[3]	X[4]	X	X	X	
Edmonton Symptom Assessment System (revised version) (ESAS-r)	X[4]	X[5]	X[5]	X[5]	
Patient Health Questionnaire (PHQ-4)	X[4]	X[5]	X[5]	X[5]	
PROMIS-29	X[4]	X[5]	X[5]	X[5]	
S1916 Participant Survey - Satisfaction with Proteus				X[5]	
S1916 Opioid Adverse Effects Survey		X[5]	X[5]	X[5]	
S1916 Patient Cloud Feasibility Questionnaire				X	
Daily worst pain rating					X[6]
Provider-completed Form:					
S1916 Digital Medicine Program HCP Satisfaction Survey				X[7]	

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Click here for footnotes. Forms submission guidelines are found in Section 14.0.

NOTE: See Section 14.4 for site-completed forms.

Footnotes

1 Target dates for 2, 4 and 6 weeks are calculated from the date of registration.
2 Instruct patients to bring bottles with unused study drug back at each clinic visit. Staff is to collect unused study medication before the pharmacy dispenses the refill. See Section 7.7.
3 Paper copies of the BPI-SF will be administered at each clinic visit. All other PRO questionnaires *after baseline* are collected via Patient Cloud ePRO.
4 Patient-reported *baseline* questionnaires are to be completed by the patient on paper PRIOR to registration. See Section 15.0 for patient-completed forms requirement.
5 Completed via Patient Cloud ePRO on the patient's mobile phone or tablet.
6 Patients provide a pain rating daily through Week 6 via the Patient Cloud ePRO.
7 The DMP Health Care Provider Satisfaction Survey will be distributed at the end of the study through a separate data collection mechanism. It will not be collected in Medidata Rave®. See Section 14.4g.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Primary endpoint:

a. Feasibility will be defined independently according to the following factors:

1. Complete accrual within 6 months after study activation at all participating sites.

2. Adherence to the use of the digital medicine program (DMP), as measured by the percentage of the time that patients wear the biometric patch; successful adherence is defined as ≥ 66% of patients (i.e., ≥ 33 out of 50) wear the sensory patch for at least 28 out of 42 days

3. Patient retention, defined as percentage of enrolled patients who complete the 6-week surveys and evaluation; successful retention is defined as ≥ 50 of 60 patients completing the study

10.2 Secondary endpoints:

a. Pain levels are measured by average pain score and pain interference with daily activity score at 2, 4, and 6 weeks on the BPI-SF. Additionally, pain in the last 24 hours is measured daily using the worst pain item from the BPI-SF.

b. Opioid medication consumption is assessed as the number of pills taken over the number of study pills prescribed.

c. High consumption is assessed as the number of time patients consumed more than 3 pills in a 4 hour period.

d. Unplanned hospital and emergency department visits assessed as any reported unplanned visits because of pain between the date of registration and the 6-week follow-up timepoint.

e. Frequency of changes in pain management regimen is measured as any change in the dosage, frequency, or the pain medication between baseline and 6-week follow-up.

f. Activity levels are measured as active time and rest time in minutes and total daily step count.

g. Patient reported outcomes include measurement of overall symptom burden and development of adverse effects from opioids using the Edmonton Symptom Assessment System, PHQ-4 questionnaire for psychological distress, and PROMIS-29 questionnaire on quality of life at baseline and 2, 4, and 6-week follow-up.

h. Patient satisfaction with the DMP is assessed using the **S1916** Patient Survey - Satisfaction with Proteus at 6 weeks.

i. Provider satisfaction with DMP is assessed using the **S1916** Digital Medicine Program HCP Satisfaction Survey when all patients at the provider's site have completed follow-up. The survey will be distributed by a separate mechanism. It will not be collected in Medidata Rave©.

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.

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

SWOG Operations Office at IRBapprovals@swog.org. You will not need to submit other version approvals or copies of the consent

b. Contact Information Sheet

Along with the IRB approval, submit the **S1916** Contact Information Sheet provided in Appendix 18.4 to IRBapprovals@swog.org. Participating sites must submit the contact information for the PIs, CRAs and pharmacists who will be involved with the study at their site. The contact information will be used for Proteus to initiate contact with your site for the training necessary for study participation.

c. Access requirements for Medidata Rave®

Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.

To perform registrations, the site user must submit S1916 Contact Information Sheet (see Appendix 18.4) to IRBapprovals@swog.org. The contact sheet collects the name and e-mail of person(s) doing data entry into Medidata Rave®. SWOG Membership will issue an invite and site users must accept the invitation within 30 days. If invite is not accepted within 30 days, contact SWOG membership (member@swog.org) to re-issue the invite.

Staff must perform the required training in Rave if necessary.

13.4 Medidata Rave® Registration Procedures

a. This study will **not** be utilizing OPEN. Enrollments to this study will be conducted via Medidata Rave© at the following url: https://login.imedidata.com/selectlogin

- If prompted, select the "CTEP-IAM IdP" link.
- Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members website and OPEN.
- Click the link for "Add Subject" located just below subject search.
- Enter each data item required using the **S1916** Enrollment form as outlined in Section 13.5.
- Clicking "save" will run applicable edit checks. Once a successful submission is made, Medidata Rave© will generate a Subject Enrollment Form confirming the registration and displaying treatment information. Please print this confirmation for your records.

b. Prior to accessing Medidata Rave® site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the **S1916** Enrollment form has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

13.5 Medidata Rave® Registration Requirements

The individual registering the patient must have completed the **S1916** Enrollment form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Proteus ID Number

e. Registrar's SWOG Roster ID Number

f. SWOG Treating Investigator Number

g. Credit Investigator

h. Patient Initials

i. Patient's Date of Birth

j. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

k. Country of Residence

l. ZIP Code

m. Gender (select one):
- Female Gender
- Male Gender
- Unknown

n. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

o. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

p. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare

- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

13.6 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the **S1916** Enrollment Form) must be submitted on-line via the Web; see below for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons who have requested access on the **S1916** Contact Sheet in Appendix 18.4.

b. Once IRB approval is received by SWOG Membership department, the designated registrar(s) will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

c. SWOG institutions will submit data electronically via Medidata Rave® at the same url: https://login.imedidata.com/selectlogin

1. If prompted, select the "CTEP-IAM IdP" link.

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:

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

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

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).

Product Accountability

The study site will maintain a full product accountability log with an inventory of all components of the Proteus products distributed to patients. Site staff must document the number of kits received, dispensed, and returned on a NCI DARF (or electronic version of the NCI DARF that is modified for product dispensation). All discrepancies must be accounted for and documented.

Drug Accountability

Participating site pharmacies must maintain a careful record of the receipt, dispensing, and return of study drugs. For SWOG auditing purposes, the study requires use of the NCI DARF. (Electronic accountability systems may be used as long as the template mirrors the NCI DARF).

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

SAE Reporting

See Section 8.4 for Serious Adverse Event Reporting Requirements.

17.0 BIBLIOGRAPHY

1. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage.* 2016;51(6):1070-1090 e1079.

2. Breivik H, Cherny N, Collett B, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol.* 2009;20(8):1420-1433.

3. Greco MT, Roberto A, Corli O, et al. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. *J Clin Oncol.* 2014;32(36):4149-4154.

4. Ward SE, Goldberg N, Miller-McCauley V, et al. Patient-related barriers to management of cancer pain. *Pain.* 1993;52(3):319-324.

5. Wilkie DJ, Ezenwa MO, Yao Y, et al. Pain Intensity and Misconceptions Among Hospice Patients With Cancer and Their Caregivers: Status After 2 Decades. *Am J Hosp Palliat Care.* 2017;34(4):318-324.

6. Paice JA. Cancer pain management and the opioid crisis in America: How to preserve hard-earned gains in improving the quality of cancer pain management. *Cancer.* 2018.

7. Von Roenn JH, Cleeland CS, Gonin R, Hatfield AK, Pandya KJ. Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. *Ann Intern Med.* 1993;119(2):121-126.

8. Grossman SA, Sheidler VR, Swedeen K, Mucenski J, Piantadosi S. Correlation of patient and caregiver ratings of cancer pain. *J Pain Symptom Manage.* 1991;6(2):53-57.

9. Paice JA. Cancer pain management and the opioid crisis in America: How to preserve hard-earned gains in improving the quality of cancer pain management. *Cancer.* 2018.

10. Kwon JH. Overcoming barriers in cancer pain management. *J Clin Oncol.* 2014;32(16):1727-1733.

11. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage.* 2016;51(6):1070-1090 e1079.

12. Levy MH. Pharmacologic treatment of cancer pain. *N Engl J Med.* 1996;335(15):1124-1132.

13. Kane CM, Hoskin P, Bennett MI. Cancer induced bone pain. *BMJ (Clinical research ed).* 2015;350:h315.

14. Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer.* 1987;59(4):850-856.

15. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *JAMA.* 2016;315(15):1624-1645.

16. Paice JA, Portenoy R, Lacchetti C, et al. Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2016;34(27):3325-3345.

17. Chang JS, Kushel M, Miaskowski C, et al. Provider Experiences With the Identification, Management, and Treatment of Co-occurring Chronic Noncancer Pain and Substance Use in the Safety Net. *Subst Use Misuse.* 2017;52(2):251-255.

18. Jensen MP. The validity and reliability of pain measures in adults with cancer. *J Pain.* 2003;4(1):2-21.

19. Liang SY, Yates P, Edwards H, Tsay SL. Factors influencing opioid-taking self-efficacy and analgesic adherence in Taiwanese outpatients with cancer. *Psychooncology.* 2008;17(11):1100-1107.

20. Bennett MI, Bagnall AM, Jose Closs S. How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. *Pain.* 2009;143(3):192-199.

21. Gordon DB, Dahl JL, Miaskowski C, et al. American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. *Arch Intern Med.* 2005;165(14):1574-1580.

22. Carmichael AN, Morgan L, Del Fabbro E. Identifying and assessing the risk of opioid abuse in patients with cancer: an integrative review. *Subst Abuse Rehabil.* 2016;7:71-79.

23. Koyyalagunta D, Bruera E, Aigner C, Nusrat H, Driver L, Novy D. Risk stratification of opioid misuse among patients with cancer pain using the SOAPP-SF. *Pain Med.* 2013;14(5):667-675.

24. Bruera E, Paice JA. Cancer pain management: safe and effective use of opioids. *Am Soc Clin Oncol Educ Book.* 2015:e593-599.

25. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain.* 2007;129(3):355-362.

26. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res.* 2006;6:46.

27. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. *Pain Physician.* 2012;15(3 Suppl):S67-116.

28. Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Assessing opioid shopping behaviour: a large cohort study from a medication dispensing database in the US. *Drug Saf.* 2012;35(4):325-334.

29. Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Opioid shopping behavior: how often, how soon, which drugs, and what payment method. *J Clin Pharmacol.* 2013;53(1):112-117.

30. Valderas JM, Alonso J. Patient reported outcome measures: a model-based classification system for research and clinical practice. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2008;17(9):1125-1135.

31. Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *J Clin Oncol.* 2014;32(14):1480-1501.

32. 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.* 2016;34(6):557-565.

33. 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.* 2017;318(2):197-198.

34. Browne SH, Peloquin C, Santillo F, et al. Digitizing Medicines for Remote Capture of Oral Medication Adherence Using Co-encapsulation. *Clin Pharmacol Ther.* 2018;103(3):502-510.

35. Frias J, Virdi N, Raja P, Kim Y, Savage G, Osterberg L. Effectiveness of Digital Medicines to Improve Clinical Outcomes in Patients with Uncontrolled Hypertension and Type 2 Diabetes: Prospective, Open-Label, Cluster-Randomized Pilot Clinical Trial. *J Med Internet Res.* 2017;19(7):e246.

36. http://www.croiconference.org/sites/default/files/uploads/croi2018-abstract-ebook.pdf

37. Browne SH, Behzadi Y, Littlewort G. Let Visuals Tell the Story: Medication Adherence in Patients with Type II Diabetes Captured by a Novel Ingestion Sensor Platform. *JMIR Mhealth Uhealth.* 2015;3(4):e108.

38. Au-Yeung KY, DiCarlo L. Cost comparison of wirelessly vs. directly observed therapy for adherence confirmation in anti-tuberculosis treatment. *Int J Tuberc Lung Dis.* 2012;16(11):1498-1504.

39. Peters-Strickland T, Pestreich L, Hatch A, et al. Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. *Neuropsychiatr Dis Treat.* 2016;12:2587-2594.

40. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353(5):487-497.

41. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA.* 1989;261(22):3273-3277.

42. Kass MA, Meltzer DW, Gordon M. A miniature compliance monitor for eyedrop medication. *Arch Ophthalmol.* 1984;102(10):1550-1554.

43. Choudhry NK, Krumme AA, Ercole PM, et al. Effect of Reminder Devices on Medication Adherence: The REMIND Randomized Clinical Trial. *JAMA Intern Med.* 2017;177(5):624-631.

44. Browne SH, Peloquin C, Santillo F, et al. Digitizing Medicines for Remote Capture of Oral Medication Adherence Using Co-encapsulation. *Clin Pharmacol Ther.* 2018;103(3):502-510.

45. Frias J, Virdi N, Raja P, Kim Y, Savage G, Osterberg L. Effectiveness of Digital Medicines to Improve Clinical Outcomes in Patients with Uncontrolled Hypertension and Type 2 Diabetes: Prospective, Open-Label, Cluster-Randomized Pilot Clinical Trial. *J Med Internet Res.* 2017;19(7):e246.

46. Belknap R, Weis S, Brookens A, et al. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. *PLoS One.* 2013;8(1):e53373.

47. Peters-Strickland T, Pestreich L, Hatch A, et al. Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. *Neuropsychiatr Dis Treat.* 2016;12:2587-2594.

48. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage.* 2016;51(6):1070-1090 e1079.

49. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol.* 2008;19(12):1985-1991.

50. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med.* 1994;330(9):592-596.

51. Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. *CA: a cancer journal for clinicians.* 2018;68(3):182-196.

52. Portenoy RK, Lesage P. Management of cancer pain. *Lancet.* 1999;353(9165):1695-1700.

53. Glare PA, Davies PS, Finlay E, et al. Pain in cancer survivors. *J Clin Oncol.* 2014;32(16):1739-1747.

54. Browne SH, Peloquin C, Santillo F, et al. Digitizing Medicines for Remote Capture of Oral Medication Adherence Using Co-encapsulation. *Clin Pharmacol Ther.* 2018;103(3):502-510.

55. Frias J, Virdi N, Raja P, Kim Y, Savage G, Osterberg L. Effectiveness of Digital Medicines to Improve Clinical Outcomes in Patients with Uncontrolled Hypertension and Type 2 Diabetes: Prospective, Open-Label, Cluster-Randomized Pilot Clinical Trial. *J Med Internet Res.* 2017;19(7):e246.

56. Belknap R, Weis S, Brookens A, et al. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. *PLoS One.* 2013;8(1):e53373.

57. Peters-Strickland T, Pestreich L, Hatch A, et al. Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. *Neuropsychiatr Dis Treat.* 2016;12:2587-2594.

58. Jensen MP. The validity and reliability of pain measures in adults with cancer. *J Pain.* 2003;4(1):2-21.

59. Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. *Cancer.* 2000;88(9):2164-2171.

60. Lowe B, Wahl I, Rose M, et al. A 4-item measure of depression and anxiety: validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. *Journal of affective disorders.* 2010;122(1-2):86-95.

61. PROMIS Scoring Guideline: Overview https://www.assessmentcenter.net/documents/PROMIS%20Scoring%20Manual-%20CATs,%20Profiles,%20Short%20Forms.pdf. Accessed September 1, 2016.

18.0 APPENDIX

18.1 Instructions for Patient Cloud ePRO

18.2 Pre-Study Requirements for Sites

18.3 Study Flow for Patients

18.4 Contact Information Sheet

18.1 Instructions for Patient Cloud ePRO

a. Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata Patient Cloud ePRO will be used for this study. The ePRO application allows patients to report clinical trial information patient reported outcomes (PROs) directly from their mobile devices into the Medidata Clinical Cloud. Paper submissions of the ePRO forms designated for this study will not be accepted. Patients will submit PRO data via the Patient Cloud app and must be registered to Patient Cloud ePRO by an authorized site user after the patient has been registered to the clinical trial.

For this study, it is required for patients to use their personal device as they will have to enter daily pain evaluations.

b. CRA/Site Staff Users

Site staff require access to the Patient Cloud ePRO application. This access is granted through the Medidata, and is similar to the process of obtaining access to Rave studies. Site staff will receive an invitation to the Patient Cloud application which they must accept in order to begin registering patients. Staff that have not previously activated their Medidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from Medidata to activate their account. Medidata Account Activation and Study Invitation Acceptance instructions are located on the CTSU members' website under Data Management > Rave Resource Materials. Site staff will not be able to access the study in the Patient Cloud application until all required Rave and study specific trainings (eLearnings assigned in Medidata) are completed.

Additional information on Medidata/Rave is available on the CTSU members' website under the Data Management tab and further under the Rave subtab or by contacting the SWOG SDMC by e-mail at cancercontrolquestion@crab.org.

c. Site Staff Patient Registration Instructions for ePRO

Site staff must complete the required eLearnings (assigned in Medidata) for the Patient Cloud ePRO before registering a patient to the Patient Cloud. Reference materials on Patient Cloud ePRO for site staff is available on the Medidata Learning Tool website.

Subject registration process for the Patient Cloud ePRO starts in Medidata. To register a patient:

1. Select the Patient Cloud ePRO Registration link for your study.

2. From the Patient Management app, select your STUDY and SITE from the drop downs and click Launch.

3. Register your patient. Select the S1916 patient ID and then select a Country / Language from the drop down (required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.

4. The subject will be added to the Patient Management grid and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient, linked to the S1916 patient ID and it is not interchangeable between patients. Provide the patient with his/her unique activation code and instruct the patient to complete the Patient Cloud ePRO app registration. In the Patient Management grid, there is also a status section which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

d. Patient Users

The patient (with assistance from the site staff) should be instructed to download the Patient Cloud ePRO app onto his/her own device (iPhone, Android phone, or tablet with cellular connectivity). The patient will use the unique patient authorization code to create an account on the Patient Cloud app. Once the patient's account is set up in the app, the patient will be able to complete the submission of patient reported outcomes electronically for the trial via the app.

There are multiple versions of the Medidata Patient Cloud ePRO Application. Patients should be instructed to download the version of the app called Patient Cloud (shown below). The patient will receive an error if the wrong version is downloaded.

To use the Patient Cloud ePRO app, patients will need to use their own device (iPhone, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

e. Patient Instructions for Accessing the Patient Cloud Using Your Personal Device

NOTE to research staff: The following section can be copied and provided to patients.

Downloading the Patient Cloud App: Information for Study Participants

If you do not have the Patient Cloud app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud app is already on your device, you can skip this section. There are multiple versions of the app available. Make sure that you download the version of the app called Patient Cloud (shown below):

Patient Cloud

You will need an e-mail address that you agree to use for this purpose. The e-mail address is needed to uniquely identify you on the Patient Cloud Application and to reset your password if needed. Your e-mail address will only be used for this study, and will not be used for mail or marketing purposes.

If you do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites commonly used that will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud app
2. Tap the *App Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Note: Patient Cloud is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud app
2. Tap the *Play Store* icon.
3. Search for the appropriate Medidata Patient Cloud ePRO application and follow the installation instructions.

Registering

You must register to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud application.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your study staff.

There are two ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud app.

1. If registering from the Patient Cloud app, tap *Register* on the bottom of the log in page. If registering on the web, open the URL *shield.imedidata.com* on a web browser.
2. Enter your activation code and tap *Activate*.
3. On the next page, read the instructions and tap *Next*.
4. Read the privacy notice and tap *I agree*. Then tap *OK* to confirm.
5. Enter and confirm your email address. Tap *Next*.
6. Enter and confirm your password. Tap *Next*.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap *Create my account* to complete your registration.

If you registered on the Patient Cloud app on your device, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap *Log in*.

Note: If you do not remember your password, tap *Forgot Password*, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the Patient Cloud app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap *Yes* when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting *Set PIN*.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap *Forgot PIN* and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap *Reset Password*.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. Select a form, and complete and submit the form. New forms can appear on the Tasks page at any time, depending on how the study is designed.
There may be two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

To complete and submit form(s):

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you may be given the opportunity to review and change your responses prior to submitting.
3. If you are given the opportunity to review and update, review your responses by scrolling down the list. If you need to change an answer, tap the question to go back and change the answer.
4. When you are ready to submit, tap *Submit Your Data.*

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

END OF PATIENT CLOUD INFORMATION FOR STUDY PARTICIPANTS

f. Patient Compliance

The patient data imports directly from a device into the study database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

g. Security

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks "Submit," the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The patient's email links the device (used) and Patient Cloud) account to where the data is stored. The patient's email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave© Electronic Data Capture (EDC) and the patient accounts are hidden in iMedidata from sites and Lead Protocol Organizations (LPOs).

The Patient Cloud application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud are encrypted and therefore this information cannot be read if intercepted while in transit.

h. Site checklist for Patient Cloud activities

☐ Accept study invitation at iMedidata.com
- Site staff must be rostered in RSS and have received an invitation to Patient Cloud

☐ Site staff must have already completed required eLearnings for the Patient Cloud ePRO before gaining access to the study in Rave. See last bullet with hyperlink to training video library. Contact the LPO (IRBapprovals@swog.org) to request appropriate Rave access to register patients in Patient Cloud.

☐ Verify the patient's iPhone, Android phone or tablet operating system is the most current version and that the patient has cellular service on the device.

☐ Verify the patient downloads the correct Patient Cloud app as follows:

Patient Cloud

☐ Refer to Review Quick Reference Guides for videos and other procedural information (https://learn.mdsol.com/patient-cloud/patient-cloud-central-144614299.html)

If sites have questions about setting up ePRO app for patient, contact cancercontrolquestion@crab.org.

Note: Sites should consider copying this site checklist and placing it in the clinic or area where site is consenting patients to ePRO and also copy the correct image and name of the ePRO app version with it to help remind staff and patients the correct version being used in the protocol.

Patient Cloud

18.2 Pre-Study Requirements for Providers, CRAs and Site Pharmacies

a. Site IRB approvals and Contact Sheet

1. Sites obtain local IRB approval for **S1916** and submit to IRBapprovals@swog.org per Section 13.3

2. Complete the Contact Information Sheet for Sites Participating in **S1916** in Appendix 18.4 and submit to IRBapprovals@swog.org along with the IRB approval documentation. Provide the names and e-mails of the Principal Investigators (PIs) that will be registering patients on the trial, the CRAs/site staff that will be doing data entry into Medidata Rave©, and the pharmacists who will be performing encapsulation.

3. For this study, PIs writing the prescription for the oxycodone-acetaminophen-DMP may need to have Drug Enforcement Administration (DEA) license as part of the IRB regulatory review. This requirement varies by state. Investigators should follow their state and local IRB directives.

b. Training by Proteus

1. PI and CRA: Training on how to log into the Proteus web portal and view patient data transmitted by the Proteus Discover patient app will be provided by Proteus.

   Proteus will notify the SWOG Operations Office when sites' PI and CRA training is complete.

2. Pharmacists: Training on encapsulation process will be provided via webinar by Proteus.

   Proteus will notify the SWOG Operations Office when the site's pharmacy training is complete.

c. Access to Medidata Rave®

1. Access to Medidata Rave will be granted to CRAs who have requested access on the **S1916** Contact Sheet. (See Section 18.3a above). SWOG Membership Department will send the designated CRAs an invitation to **S1916** in Medidata Rave®. Site registrars must accept the invite within 30 days. (If invite is not accepted within 30 days, contact membership department at (IRBapprovals@swog.org) to reissue the invite. If there is a change in registrar, contact SWOG membership to perform an update in Medidata Rave®.

d. Patient Cloud ePRO

1. CRA(s) must have completed required eLearnings for the Patient Cloud ePRO application so that they can assist patients with access and registration to the Patient Cloud app per protocol Section 18.1.

18.3 Study Flow

Sites screen for patients with diagnosis of metastatic cancer

↓

Sites further screen for patients who have a "worst pain" score of at least 3 on the Brief Pain Inventory (Short Form) (BPI-SF)*, completed within 3 days prior to registration, warranting initiation, continuation, or uptitration of opioid therapy with oxycodone/acetaminophen 5mg/325mg as determined by the patient's physician

↓

Site Confirms S1916 Eligibility
Patient Provides Consent and completes the following *paper* baseline questionnaires in the clinic:
Brief Pain Inventory (Short Form)
Edmonton Symptom Assessment System (revised version)
Patient Health Questionnaire (PHQ-4)
PROMIS-29© Profile V2.1

↓

Physician prescribes oxycodone/acetaminophen 5mg/325mg – DMP (digital medicine program)

↓

Prescription is filled
(This includes encapsulated medication with sensors, adhesive patches and pod)

↓

Registration to Proteus Discover app

Research staff oversees patient download of Proteus Discover app to smartphone or cellular-enabled tablet and helps patient register in the app.

↓

Patient views tutorial, staff oversees patient initial patch/pod placement

↓

Registration to S1916 Protocol

Site staff registers the patient to **S1916** protocol in Medidata Rave®

↓

Registration of patient to Patient Cloud

Staff completes a registration for the patient to the Patient Cloud through Medidata®
Research staff oversees patient download of Patient Cloud app to smartphone or cellular-enabled tablet

↓

Patient submits pain evaluation *daily* via the Patient Cloud app on smartphone or cellular-enabled tablet

↓

Patient follow-up at Weeks 2, 4 and 6 (+/- 4 days):

Patients will be evaluated in clinic:
Physician reviews patch data using the web portal prior to each clinic visit

Physician reviews patch placement with patient
Site collects additional pain medication use, health care utilization, and adverse events data
Site collects unused capsules of oxycodone/acetaminophen-DMP dispensed at previous visit
Site prescribes additional oxycodone/acetaminophen-DMP (2 and 4 weeks only)

Patient pain assessment is conducted via BPI-SF (paper copy)
S1916 Patient Cloud Feasibility Questionnaire (paper copy, 6 weeks only)

Patients complete the following surveys via Patient Cloud ePRO:
Edmonton Symptom Assessment Scale (ESAS-r)
PHQ-4
PROMIS-29©V2.1
S1916 Participant Survey - Satisfaction with Proteus (6 weeks only)
S1916 Opioid Adverse Effects Survey

↓

Study follow-up is complete at 6 weeks after **S1916** registration

*For screening purposes, the patient need only answer the single question(Question #3) related to worst pain on the BPI; this is included on the **S1916** Enrollment Form.

18.4 Contact Information Sheet

Contact Information for Sites Participating in S1916

Site Instructions: Submit this completed form along with IRB approval via email to IRBapprovals@swog.org. CRA registrar information is required in order for site to submit data in Medidata Rave®.

Additionally, this contact information will be used to initiate training of PIs, pharmacists and CRAs by Proteus.

Site Name	State	SWOG Institution #	NCI Code

PI Name (first and last) **Email address:**

(These PIs will be contacted by Proteus to receive training in the use of the Proteus Discover portal where they will view their patient's Patch data).

CRA(s) that will be doing data entry for this study - Registrar(s): *(Membership will use this list as a trigger to issue the invite to S1916 in Medidata Rave®).*

CRA Name (first and last) **Email address:**

Additional CRAs or research staff that would like to be contacted by Proteus to receive training about the DMP: *(This includes research staff that will be assisting patients with the app download, or placement of the Patch).*

Name (first and last) **Email address:**

Pharmacists that will be doing encapsulation:

Name (first and last) **Email address:**

Informed Consent Model for S1916

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This is a pilot study being conducted in the SWOG Cancer Research Network. Each participating site must obtain IRB approval of the study and informed consent document. The information provided on this model consent reflects SWOG's minimum requirements. Changes to this document are allowed in order to meet the standards of the IRB of record.

Readability Statistics:	
Flesch Reading Ease	63.3 (targeted above 55)
Flesch-Kincaid Grade Level	8.6 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes any companies or grantors that are providing study support. "SWOG" must be listed as one of the parties that may inspect the research records.
- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent,

review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/

- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Consent Form

Study Title for Study Participants:

Practicality of Using a Digital Health Feedback Device to Improve Pain Control with Opioids in Cancer Patients

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
S1916, Feasibility of a Digital Medicine Program in Optimizing Opioid Pain Control in Cancer Patients

Summary and Overview

What am I being asked to do?

You are being asked to take part in a research study. We are doing this research study to try to answer questions about how to treat cancer pain. We are asking you to take part in this research study because you have metastatic cancer with uncontrolled pain and your doctor feels you would benefit from opioid treatment, you are willing to provide responses to questionnaires through your phone, and you speak English.

(Metastatic means cancer has spread to other parts of the body. Opioids are a class of drugs that include pain relievers that are available by prescription only.)

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

Many patients with cancer suffer from significant pain that can cause worry and interfere with normal life. Studies have shown that cancer pain is often undertreated because doctors have a hard time judging their patient's pain level. Also, patients sometimes do not tell their true pain level because they are afraid of side effects or of becoming addicted to the pain medication.

This study is being done to find out if using a digital health feedback device with a pain medication (oxycodone/acetaminophen, also known as Percocet) is a practical way for patients and physicians to monitor and communicate about cancer pain.

The digital health feedback device will allow your doctor to see if you are taking your pain medication regularly and will help your doctor adjust your pain medication if needed.

The Proteus Digital Medicine Program (DMP) consists of a mobile application (app), a patch worn on the body, and ingestible sensors.

- The tiny ingestible sensor is made from ingredients found in the human diet and will be placed with the pain medication in a gelatin capsule. The ingestible sensor sends a signal to the patch after it reaches your stomach.
- The patch is an adhesive strip that sticks to your body, and a clip in data pod. The patch is usually placed on the trunk of the body. The patch records the time the medication (with the embedded sensor) is taken. The pod stores your data and regularly sends it to the mobile app for display on your phone or tablet. It records when medication is taken, heart rate, activity, body position, and rest.
- The mobile app will instruct you how to put the patch together, how to connect it to the mobile app and how to place it on your body. These instructions will also be explained to you in person.

What is the usual approach to treating pain?

Patients who are experiencing significant pain may receive regular pain medication such as Percocet (oxycodone-acetaminophen) for pain.

A different approach to control pain is to use Percocet with the Digital Medicine Program (DMP).

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach as described above.
- You may choose to take part in a different research study, if one is available.

What will happen if I decide to take part in this study?

If you decide to take part, you will be given a prescription for Percocet (5 mg oxycodone with 325 mg acetaminophen)-DMP. The "DMP" means that your supply of Percocet contains ingestible sensors. Along with the medication, you will be given a supply of adhesive strips (also called "patches") and a data pod. The study staff will help you download the mobile app to your phone or tablet. The app will tell you how to place the patch with data pod on your body and how to connect it to your app. It will also tell you about skin care, how to take off the patch and to replace the strip weekly.

You will be asked to complete questionnaires before you begin the study (these will be paper questionnaires), and at Weeks 2, 4 and 6 (some will be on paper; others will be done through your phone or tablet). You will also be asked to complete a daily question about your pain through your phone or tablet.

You will have follow-up visits at the clinic scheduled at 2, 4, and 6 weeks.

You will be on the study for 6 weeks from the time you start treatment with Percocet-DMP.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. These risks include side-effects from the pain medication, skin irritation from the adhesive patch and stomach irritation from the ingestible sensor. We give you more information in the "What risks can I expect from taking part in this study?" section.

Benefits

This study may or may not help you. However, it may help the study doctors learn new ways to manage your cancer pain.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.
If you decide to stop, let your study doctor know as soon as possible. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- The study is stopped by the Institutional Review Board (IRB), or study sponsor SWOG Cancer Research Network, the organization who oversees the study.

This is the end of the study summary. It is important that you understand the information in the informed consent before making your decision. Please read further, or have someone read to you, the rest of this document for detailed information about the study. If there is anything you don't understand, be sure to ask your study doctor or nurse.

****

What is the purpose of this study?

You will be getting pain medication to treat pain associated with your cancer. We will be using a digital device inside the medicine and a sensor patch worn on your body to track when and how often you take your pain medication. This device will also provide feedback to your doctor. We want to see if this device is a good way for patients and doctors to communicate about pain. We also want to see if patients will continue to use the sensor patch for the length of the study which is 6 weeks.

There will be about 60 people taking part in this study.

What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will look at your health information to see if you can take part in the study. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have exams, tests, and procedures to closely check your pain. Most of these are included in the usual care you would get even if you were not in a study.

Some questionnaires are a necessary part of the research study and would not be part of usual care.

If you choose to take part in this study, you will be asked to fill out questionnaires about your pain level, physical and emotional well-being, and quality of life.

Since these questionnaires are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

The first set of questionnaires (see below) will be given to you after you agree to take part in the study. All of these questionnaires will be on paper. It may take about 10-20 minutes to answer all of the forms the first time.

The following will take place at study entry (first clinic visit):

- History and physical examination (performed by your study doctor)
- You will fill out forms that collect information about your pain, symptoms, mood, anxiety, and quality of life.
- Information such as age, gender, race, ethnicity, employment status will be collected.

Also, at this clinic visit, the research staff will help you to download an app, called "Patient Cloud", to your smart phone or tablet with a cellular connection. You can view the questionnaires and enter your responses on your phone or tablet the next time. It will take about 10-20 minutes to answer all of the questions.

At 2 and 4 weeks:

- Before your clinic visit, your doctor will review the information that was sent electronically from the sensor on your body. This information includes your heart rate, activity, and medication usage.
- In the clinic, you will fill out a paper questionnaire that asks you to rate your pain.
- You are expected to go to the Patient Cloud app on your phone or tablet to provide responses to the study questionnaires. The questionnaires will collect information about your pain, symptoms related to the pain medication and ingestible sensor and patch, questions about your mood, anxiety and quality of life.

At 6 weeks:

- Before your clinic visit, your doctor will review the information that was sent electronically from the sensor on your body. This information includes heart rate, activity, and medication usage.
- In the clinic, you will fill out a paper questionnaire that asks you to rate your pain. You will also fill out a questionnaire that asks how you liked the Patient Cloud app and whether you found it easy to use.
- You are expected to go to the Patient Cloud app to provide responses to the study questionnaires. The questionnaires will collect information about your pain, symptoms related to the pain medication and ingestible sensor and patch, questions about your mood, anxiety and quality of life.
- There will be an additional questionnaire regarding satisfaction with the digital medicine program (ingestible sensor and wearable patch).

Daily on your mobile device:

- Answer one question regarding your pain level in the last 24 hours.

Throughout the study, the research staff will review your medical chart to collect information such as:

- Changes to your pain medication
- Visits to the hospital or emergency room due to pain.

What risks can I expect from taking part in this study?

Possible side effects of the pain medication – oxycodone-acetaminophen

Less Likely

- Pain in belly
- Diarrhea
- Nausea
- Vomiting
- Constipation

Unlikely

- Flu-like symptoms: watering eyes, runny nose, sneezing, increased sweating, chills
- Fast heartbeat
- Worry
- Difficulty sleeping
- Restlessness
- Abnormal body movement
- Dry mouth
- Yawning
- Loss of appetite
- Dizziness
- Muscle pain
- Joint pain
- Leg cramps

Possible risks associated with the wearable sensor patch

Less Likely

- Rash at the site where the patch was placed
- Skin changes where the patch was placed
- Itching where the patch was placed

The patch should not be worn during MRI imaging, during any procedures involving electric cautery (burning skin or blood vessel to stop bleeding), or external defibrillation (device which delivers electric shock to the heart).

Possible risks associated with the ingestible sensor:

Less Likely

- Bitter taste in mouth

Unlikely

- Nausea
- Vomiting
- Constipation
- Pain in the belly
- Increase in shortness of breath, chest tightness or coughing for patients who have asthma

General Risks

If you choose to take part in this study, there is a risk that the different approach may not be as good as the usual approach for managing your pain.

When filling out forms, you may feel uncomfortable being asked about your physical and emotional health, and quality of life. You may skip any questions that make you feel uncomfortable.

What are my responsibilities in this study?

If you choose to take part in this study, you will need to:

- Keep your study appointments. Cancelled appointments should be rescheduled as soon as possible.
- Tell your doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.
- Adhere to the DO and DON'T list for the ingestible sensor and patch communicated through the app

For women: Do not get pregnant or breastfeed while taking part in this study. Tell your study doctor right away if you think that you have become pregnant during the study.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer pain.

This includes:

- the costs of tests, exams, and procedures, and drugs that you get during the study to monitor your safety and prevent and treat side effects.
- your insurance co-pays and deductibles.

The study drug (Percocet, co-encapsulated with the ingestible sensor), the adhesive strips and the data pod are provided to you at no cost by the study.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, medicines you took, and responses to questionnaires will be kept by the study sponsor in a

central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor, SWOG Cancer Research Network
- Proteus Digital Health, Inc.
- The Institutional Review Board (IRB), which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number)***.**

(Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

Please initial YES_____ NO_____

My Signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the study.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____