RESEARCH PROTOCOL OUTLINE

Title of Project: **Leveraging mHealth to deliver integrated pain-CBT, opioid monitoring, and self-management support for advanced cancer patients coping with chronic pain**

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Abstract

The primary purpose of this project is to determine feasibility and acceptability of a novel mobile health application focused on integrating behavioral coping tools with medication management for pain for patients with advanced cancer and pain. The majority of patients with advanced cancer experience pain, which is extremely psychologically and physically distressing. Current pain management strategies include the use of opioid and nonopioid medications in combination with other analgesics. However, many patients who take opioids experience inadequate relief. Strong evidence suggests that psychological interventions, namely cognitive behavioral therapy for pain (pain-CBT), lead to significant improvement in pain. The STAMP+CBT app (Smartphone Technology to Alleviate Malignant Pain + Cognitive Behavioral Therapy**)** seeks to provide education about pain medications alongside cognitive behavioral therapy techniques for pain to patients with advanced cancer. The application uses multi-media educational materials and survey algorithms assessing pain, medication usage, mood, stress, and sleep to improve pain management in this population. In this study, patients with advanced cancer at OU (n=60) will participate in a single-arm, 6-week study of STAMP+CBT (4-week intervention period and a 2-week post intervention period).

A. Specific Aims

The purpose of this study is to pilot test a novel mHealth intervention that harmonizes psychological and pharmacological support for advanced cancer pain. I adapted core components of pain-CBT and integrated them into STAMP (Smartphone Technology to Alleviate Malignant Pain), an existing NINR-funded cancer pain mHealth intervention. STAMP enables patients with advanced cancer to track their pain, opioid use, and side effects (R21 NR017745, PI, Enzinger; IRB #18-504 at Dana Farber Cancer Institute). It delivers tailored education and self-management advice while facilitating clinician monitoring and patients' proactive outreach. We developed an extensive suite of multi-media cancer pain psycho-education covering core pain psychology principles. We refined and integrated pain-CBT treatment with medically oriented self-management support in STAMP (OUHSC IRB #13-725). Capitalizing on mHealth technology, this app strives to destigmatize pain psychology through a potentially scalable model that disseminates behavioral treatments for advanced cancer pain paired with their palliative care pain management plan.

Aim 1 (App Feasibility and Acceptability): Determine feasibility and acceptability of the STAMP+CBT app: up to 60 patients with advanced cancer pain will be recruited from Stephenson Cancer Center outpatient supportive care clinics at a major cancer center to participate in a single-arm, 6-week study of STAMP+CBT (4-week intervention period and a 2-week post intervention period). Surveys at baseline, 4 weeks (end of intervention period), and 6 weeks (end of 2-week post intervention period) will explore trends in pain specific intensity, self-efficacy, and catastrophizing, physical function, opioid use, and quality of life. End-of-study interviews with up to 30 patients will identify facilitators and barriers to usability, acceptability, and satisfaction of the app. The primary outcome will be feasibility evaluating 1) app retention rates and 2) completion of app exercises.

Outcomes and accomplishments

ENDPOINT 1: The primary objective is to determine the feasibility and acceptability of the STAMP+CBT app. Specifically, we will evaluate patients' adherence to daily and weekly comprehensive symptom self-assessments within the STAMP+CBT app. We will calculate patients' overall adherence rate and 95% confidence interval. Defined using precision analysis, we will consider the intervention to be **feasible** if ≥70% of subjects complete any activity on the app at least 50% of days on study. The intervention will be considered **acceptable** if >80% of the sample rate the app as satisfactory and useful (4 or higher/5); lower ratings will lead to app and content refinements. Other feasibility measures will assess time to accrual participation rates, and study retention and completion rates. Other acceptability outcomes will be assessed through qualitative debriefing interviews with patients evaluating the perceived benefits, usefulness, and satisfaction of the app, and quantitative acceptability ratings of the app's functionality, perceived utility, ease of use, and content relevance. Power calculation: with 35 evaluable patients, we will be able to estimate these proportions with margins of error (half of a 95% confidence interval) of approximately 18% or less assuming that the feasibility threshold of 70% is reached. This margin of error is small enough so that proportion estimates relevant to study feasibility will be accurate and provide informative guidance for future, larger studies. Using qualitative framework analysis methods, we will explore barriers/facilitators, suggested changes to content, acceptability of intervention engagement, and whether app use continues after completion. Although power is not sufficient in this pilot, we will explore associations between levels of engagement and changes in pain severity/interference, opioid use, catastrophizing, sleep, mood, and pain self-efficacy.

The study team will use qualitative and quantitative results to determine the comprehensive feasibility and acceptability of the pain CBT mobile health app for patients with cancer. This feasibility study will inform final modification to the application and study procedures in preparation for a future efficacy study of the STAMP+CBT mobile health app.

B. Background and Significance

Between 39% to 75% of patients with cancer suffer from pain, with the highest burden of symptoms occurring among those with advanced disease.[1] Poorly managed pain can be devastating to patients' psychological health, physical functioning, social connectedness, and quality of life.[2, 3] Opioids are the cornerstone of treatment;[4] however, up to 60% of patients experience inadequate relief.[5, 6]Effective non-pharmacologic treatments are greatly needed to mitigate the burden of advanced cancer pain.[7]

The most efficacious psychological treatments for chronic non-cancer pain address both emotional and evaluative aspects of pain while teaching pain coping skills.[8-11] Cognitive behavioral therapy for pain (pain-CBT) is the most widely utilized psychological treatment for chronic pain, with meta-analyses demonstrating small to moderate improvements in pain severity and daily functioning.[12]

While the broad goals of pain-CBT are highly relevant to advanced cancer pain, its mode of delivery and certain emphases require modification to be suitable for advanced cancer patients. A few studies have sought to modify pain-CBT for general cancer populations, in part by using telehealth to overcome barriers to delivery.[13-15] Early data suggest these programs are feasible and acceptable to patients;[13-15] however, to our knowledge, none tailor pain-CBT specifically for advanced cancer patients, and none integrate pharmacologic management, which would complement patient-centered pain-self management strategies.[16]

Mobile health technology (mHealth) is a promising strategy to overcome access barriers and tailor, deliver, and disseminate psychological interventions for advanced cancer pain.[17, 18] Developing a smartphone intervention that combines medical and pain self-management support has great potential for scalability to advanced cancer populations.

To our knowledge, this will be the first adaptation of pain-CBT specifically for advanced cancer pain. STAMP+CBT will adapt critical components of pain-CBT to address common concerns of advanced cancer patients, while ensuring a realistic level of engagement for this population.

Traditional interventions using tablets and/or videoconferencing do not fully employ the unique capabilities of mHealth to tailor psychological treatments[19] and present content in engaging, empathic ways[20, 21] (e.g., through gamification, quizzes). STAMP+CBT will leverage mHealth tailored software to integrate engaging media (e.g., audio, videos, graphics), and user-centered design (e.g., positive aesthetics, playful interface).

C. Preliminary Studies/Progress Report

Using iterative content development procedures, I led a multidisciplinary team that reviewed and refined pain-CBT psycho-education materials and adapted them for advanced cancer pain and mobile health delivery through DFCI protocols (IRB #20-453 and OUHSC IRB# 13-725); See Appendices A, B, J, & L. Initial content development occurred in Boston, MA at DFCI – patients with advanced

cancer (n=14, our target population, DFCI IRB #20-453), reviewed and provided feedback on all content leading to modifications. We then had patients with advanced cancer (n=14, our target population) from Oklahoma, OK at the SCC (OUHSC IRB # 13-725) review this modified content and provide feedback on the literacy, acceptability, useability, relevance, and clarity, leading to further iterations. Patients at both sites also reviewed survey items, survey algorithms, app-based feedback, and wireframes to ensure app clarity, legibility, and acceptability.

We developed survey schedules and programmed STAMP+CBT on the Insight ™ platform through the SCC mHealth Shared Resource housed within the Health Promotion Research Center. Daily surveys assess pain, stress, mood and related symptoms (e.g. pain, opioid use, pain interference, stress, mood, and sleep) using adaptive survey logic and alternating schedules to minimize survey burden. Patients receive feedback and tailored education based upon their reported symptoms (e.g. advice on pain, mood, stress, and sleep), including advice to contact their care team for concerning symptoms. The app also houses links to an extensive suite of multi-media cancer pain education covering medication support (e.g. using short and long-acting opioids, managing side effects, opioid safety); pain psychology (e.g. pain perception, pain and the stress response); health behaviors and pain (e.g. sleep hygiene); and skills training (e.g. activity pacing/ relaxation recordings). Content is presented in multiple engaging formats (e.g. written texts with paired illustrations, 2-D animated videos, audio-recordings, games), using real-world examples, everyday language (7th grade reading level), and metaphors to support important concepts.

We have completed initial user acceptability testing of the app with patients from our target population (n=6) at the SCC (OUHSC IRB # 13-725) testing the app at home for 2-4 weeks. We are also currently completing pilot testing of the app with patients with advanced cancer at the DFCI in Boston, MA (DFCI IRB #21-719). Study procedures outlined in this protocol parallel those approved in DFCI IRB #21-719 protocol (currently enrolling). At this time, 5 patients have been enrolled in the study, we are recruiting 10 more patients to complete testing of the app at home for 4 weeks, in addition to completing survey assessments – similar to those outlined in this protocol. Patients who have tested the app to date (DFCI pilot, n=3; SCC pre-pilot, n=5) have reported finding the app easy to use (5-Point Likert scale for all items: DFCI=4.33; SCC=4.80), understandable (DFCI=5; SCC=4.8), and enjoyable (DFCI=4.33; SCC=3.80). They reported feeling that it took an appropriate amount of time to use the app (DFCI=4.33; SCC=4.20) and were satisfied with the app overall (DFCI=4.33; SCC=4.60). Patients at DFCI who tested the app for 4 weeks took an average of 57.14% of the surveys pushed by the app (median=62.50%). Patients at SCC who had tested the app for 2 weeks took an average of 54.76% of surveys pushed to them (median=64.29%). **This specific study outlined in this protocol will enable pilot testing of the application in Oklahoma, allowing for comparison between patient samples between Boston and Oklahoma.**

D. Research Design and Methods (What, When, How, Where)

STUDY PROCEDURES:
Patients in the Pilot Cohort will pilot the application for 4 weeks (4-week intervention period) and remain on study through the 2-week post-intervention period (6-weeks on study total). The onboarding and monitoring protocol are available in Appendix S. A study team member will contact participants after 4 weeks (end of intervention period), and 6 weeks (end of 2-week post-intervention period). The purpose of these contacts would be to schedule the end of intervention interview and confirm completion of survey assessments (end of 4-week intervention period), as well as the final survey assessments at 6 weeks (end of 2-week post intervention period).

Participants will fall into only one eligibility category:

Table 1: Brief description of pilot cohort activities

Description	Components of Participation
Participants will include OUHSC-SCC patients presenting to outpatient supportive care clinics with ongoing chronic cancer pain management issues. Participants will meet with the study team in person, over the phone, or via a compliant and secure video chat/screen-share platform (i.e. Zoom). We will conduct the pilot cohort with up to 60 patients. Each participant will receive a $50 gift card upon completion of the 4-week intervention period survey, and another $25 gift card upon completion of the 2-week post intervention survey.	• Use the STAMP+CBT mobile app for 4 weeks • Engage with pain CBT content including a goal-setting module, relaxation exercises, and educational content • Daily and weekly reporting of pain, catastrophizing, mood, and sleep symptoms and painkiller usage and satisfaction through the app (Appendix B) • Complete survey assessments at baseline, 4 weeks (end of 4-week intervention period), and 6 weeks (end of 2-week post intervention period) assessing pain severity, self-efficacy and catastrophizing, physical function, opioid use, and quality of life outcomes. (Appendices P, Q, R) • End-of-intervention interview assessing usability and acceptability (Appendix T) • Medical Record Abstraction (Appendix O)

Survey Assessments
A study team member will ask the patient to complete 3 surveys in total, a baseline survey assessment after consenting (to confirm their enrollment in the study), at the end of the 4-week intervention study period, and at the end of the 2-week post intervention period to assess key outcomes (app acceptability, pain severity/interference,[22] QOL[23]), potential mediators of intervention effects (catastrophizing[24], self-efficacy[25], perceived stress[26], anxiety/depression[27], sleep[28]), acceptability,[29] and usability[30]. These surveys will be completed

remotely through a REDCap link.

The Baseline survey will assess socio-demographics, baseline technology use, current comorbidities, current pain management, pain severity, opioid use, pain and psychological symptoms, and quality of life, with metrics shown in Table 4. The end of 4-week intervention period survey will largely replicate the baseline survey; additionally, patients will rate their satisfaction with STAMP+CBT using the 6-item Acceptability E-scale. Surveys will be used to assess pain and psychological symptom trajectory, medication use, and quality of life. See **Appendix P** for the Baseline survey items, **Appendix Q** for 4-week (end of 4-week intervention period) survey items, and **Appendix R** for 2-week (post intervention period) follow-up survey items. Additionally, a subset of patients (up to 15) will be invited for a qualitative interview focused on study burden, facilitators/barriers to app use, satisfaction, and perceived utility in order to guide future refinements to the app (see Appendix T) when they complete use of the app at 4 weeks (end of intervention study period).

Intervention

After the patient completes the baseline survey, a study team member will meet with the patient (in person or virtually), to assist in either 1) downloading the application onto participants' mobile device or 2) providing/mailing the study phone to the participant. The study team member will help to register the patient to the app and help set up any preferences. The study team member will then conduct a 20-30 minute tutorial on the STAMP+CBT app and its intended use (Appendix S). The study team member will also input the patient's pain medications from the EMR, reconciling this list with the patient. The participant will also input their desired goal to work towards for the duration of the trial. During the trial, there is also a survey item that if selected notifies the research team whether a patients' medication or goal needs to be changed and reflected in the app.

Participants will utilize the STAMP+CBT app for 4-weeks (intervention study period). The 4 weeks will consist of all content introductions. STAMP+CBT hosts and organizes patients' opioid/non-opioid analgesics. It has an extensive multi-media library of education content related to pain management (Appendix A) and pain specific CBT concepts (Appendices A, L, and G). Content will be delivered on a schedule to ensure that patients receive all pain CBT and medication education available (Appendix B). STAMP+CBT prompts patients to take daily surveys to report their pain, pain catastrophizing, mood, opioid/pain medication use, and sleep symptoms and progress towards individualized goals (Appendix B). At the end of each survey, patients receive feedback according to their symptom severity, with links to tailored educational content about pain and psychological symptom management (Table 2, Appendix B). Patients also complete weekly surveys for reporting symptoms listed above as well as goal progress.

If patients report any severe symptoms (Table 3), they are instructed to contact their care team immediately, with a telephone number included on the application screen, see table 2, or to go the Emergency room/call 911 for a true medical emergency. If patients' pain is poorly controlled but not severe enough to be prompted to immediately contact their care team (for example if their average pain is above a 4 and not acceptable), they are reminded to contact their care teams if their symptoms worsen or if they are concerned about it.

One protocol-mandated study staff outreach to patients will occur within a week of enrollment. A study team member will call to assess any technical or usability problems with the app (e.g., how to access the app on their phone, where to find certain study areas). These technical discussions will be optional for the patient and more can be scheduled if requested. Thereafter, the study team member will monitor the STAMP+CBT dashboard twice daily (Mon-Fri) to assess app engagement and survey completion rates (Table 3). If a patient reports one of these severe symptoms, the app sends an automated email to the research team listing patients concerning symptoms. (See Table 3). A member of the research team will then forward a copy of the patients concerning symptoms to their study nurse for evaluation or follow-up. As an additional safety measure, the application always prompts the patients to contact their care team or 911 for any severe symptoms they report and there is no expectation for proactive clinician outreach. These procedures have been approved by participating clinic nurses. The application provides a direct link to call the Outpatient Supportive Care Clinic at OUHSC.

To minimize the burden of the intervention on clinicians, patients are prompted to call their care teams or 911 (emergency services) if they report severe symptoms (Table 3). Patients are reminded during onboarding to the app that the research portal is not monitored around the clock and therefore they should reach out for urgent needs. Reports (with summarized pain and psychological symptoms; opioid use data; side effects; patients' goals and reported goal attainment) will be sent from a study team member to nurse managers, supportive care providers, and oncologists to enable effective communication, opioid titration, and other management changes when alerted by a patients red flag symptom email via in-app algorithms.

During the study, patients will be asked to complete 3 survey assessments, one at baseline, one at the end of the 4-week intervention period, and another at the end of the 2-week post intervention period. Patients will also be invited to complete a short semi-structured interview about their experiences using the application (See Appendix T). See below for description of the surveys (Table 4).

Table 2: Algorithms used to provide feedback to patients

Relief with opioids	No relief OK Unsure

	Good relief
Pain Control	Poor Suboptimal Good
Other Severe Symptoms	Number of severe symptoms on Table 2
Opioids need updating	Yes No
Mood	IF Patient responds to mood questions 17-20 with a total score of ≥12: Low Mood IF Patient responds to mood questions 17-20 with a total score of <12: High Mood
Catastrophizing	IF Patient responses to catastrophizing questions 12-16 with a total score greater than ≥10: High Stress IF Patient answers catastrophizing items 12-16 with a total score <10: Low Stress
Sleep	If sleep item 23 on the survey score ≥3 : Poor If score <3: Good
Goals need updating	IF Patient answers "No, it needs to be changed" in goal-setting section of weekly survey: Goal needs updating

Table 3. Severe Symptoms that trigger an email alert to the research team

Pain	• Worst pain = 9-10 • Worst pain = 7-10 and new pain
Red Flag Symptoms	• Severe weakness or fatigue • Lightheadedness or feeling like I was going to pass out • No gas or stool from my bottom (or ostomy) in the last 2 days • Vomiting 2 or more times in the last 24 hours • Fever of 100.5 or greater • New or worsening chest pain • New or worsening shortness of breath • New or worsening back pain • New numbness and weakness in one or both of your legs • Severe difficulty eating or drinking • Hallucinations/nightmares
Opioid Side Effects	• Hallucinations

STUDY TIMELINES

Patients in this Pilot Cohort will be in the research study for 6 weeks total including: a 4-week intervention period and 2-week post intervention period. Patients will use the app for a total of 4 weeks and remain on study through the 2-week post intervention period. They will complete surveys at baseline, 4 weeks (end of intervention period), and at 6 weeks (end of 2-week post intervention period).

We anticipate enrolling 1-2 patients per week during the pilot period, and should this complete the study within 6-8 months.

The study timeline may change due to unforeseen circumstances. The estimated date for the investigators to complete this study (complete primary analysis) is July, 2024.

E. Chart Review

The study team will complete a limited structured chart abstraction at baseline and at end-of-study to collect basic non-identifiable clinical/demographic information (See appendix O). Chart abstraction will assess clinical actions responding to STAMP+CBT data and healthcare utilization related to pain and symptom management (e.g., hospitalization, ER visits, urgent clinic visits for symptom management, psychosocial oncology social work, psychology, or psychiatry visits). As people with cancer have variable prognoses, they may pass away during a study; therefore, we want to be able to abstract and record if/when a patient passes away during or recently after their involvement. Should this situation arise, it can negatively influence outcomes of the study evaluation (feasibility/acceptability).

Chart abstraction information collected will include the following:

- **Demographics**: Gender, age, ethnicity, race
- **Cancer**: Patient's date of diagnosis, diagnosis (cancer type), stage at diagnosis, status of active curative or palliative treatment, history and date of surgery related to cancer, and whether patient has seen palliative care (yes/no)
- **Pain**: patient's last pain rating, type of pain, location of pain, surgeries or operations for pain, documented calls about pain.
- **Prescribed Pain Medicines**: Patient's prescribed short-acting opioid, long-acting opioid, and non-opioid pain medications, and length of time taking opioids.
- **Prescribed Anxiolytics**: Patients' prescribed anxiolytics and whether this was prescribed before or during the study
- **Prescribed Antidepressants**: Patients' prescribed antidepressants and whether this was prescribed before or during the study
- **Medication/Opioid side effects**: Constipation or related symptoms.
- **Clinic visits**: Unplanned or urgent clinic visits that include pain 6 months prior, during, and 6 months post-intervention, and social work, psychology, or psychiatry visits during study period
- **Mental Health Diagnoses**: Whether the patient has a mental health diagnosis and what mental health diagnosis the patient has

F. Biospecimens

This study does not involve any specimen collection/banking of any kind. Personal health information will be collected as part of the study. The consent

form informs the participants that data collected for this study may be used in the future. By consenting, participants agree. Participants will not be asked to provide additional informed consent for the use of de-identified information in future research. There is no scheduled date on which the information and data that is being used or shared for this research will be destroyed because research is an ongoing process. Patients will not provide any data on their personal symptoms reports; no specific patient symptom data will be collected.

G. Banking/Repository/Database

All data collected during this study will be stored and used for future research. Any personal identifiers will be removed so that information cannot be linked back to a patient. Data will be destroyed as soon as analysis is complete.

Investigators can request the data collected from this study for new research. Data may also be shared with outside non-profit academic investigators as well as with for-profit pharmaceutical investigators or commercial entities with whom the University of Oklahoma collaborates. Requests must be sent to the study chair (Desiree Azizoddin) and must be approved by the University of Oklahoma IRB as well as the NIH prior to sharing.

Data to be collected:

Interview Data: Audio and video recordings of feedback will be collected from all interview participants regarding their perceived feasibility and acceptability of the mobile application, as well as their experience with the app.

E-Acceptability (Survey) Data: Participants will complete an acceptability survey following review of finalized content (see Appendix F).

Chart Abstraction: Baseline demographic and clinical data will be collected from all patient participants via chart abstraction. Data will also be collected at the end of the pilot intervention. Data will include non-identifiable clinical/demographic information, including the following:

- Gender
- Age
- Ethnicity
- Race
- Cancer type
- Cancer stage
- Opioid medications
- Pain score during last visit (see Appendix O)
  Health service utilization (e.g. ED visits, hospitalizations, unplanned urgent clinic visits, changes to opioid medications, psychosocial oncology visits, psychology and psychiatry visits)

Survey Assessment Data: Demographic, disease, medication, pain, quality of life, mood, stress, and sleep data will be collected at baseline before the intervention, at end of the 4-week intervention, and at the end of the 2-week post intervention period (see Appendices P, Q, R). T1 and T2 of Table 4.

Symptom Reporting: Individual pain, pain interference, pain medication use, stress, mood, and sleep symptoms as well as pain management data will be recorded for each participant over the course of the pilot intervention (Appendix B). Participants will report their symptoms and management daily.

Long Term Follow-up: Participants in the Pilot Cohort will complete survey assessments assessing quality of life, pain, psychological measures, healthcare utilization, and app use at the end of the 2-weeks post-intervention period (T3 of Table 4).

Table 4: Measures collected from patients at each of the three survey timepoints

Measures collected via patient assessments		Survey			App data	Chart review
Assessment	**Measure**	**T1**	**T2**	**T3**		
Socio-demographics	Standard	x				
Clinical characteristics	Standard					x
Baseline cellphone use	MTUAS	x				
Pain severity/interference	BPI	x	x	x		
Opioid use/adherence	Self-report	x	x	x		
Quality of life	FACT-G	x	x	x		
Satisfaction	Novel metric		x			
Use of STAMP+CBT	-		x	x	x	
Usability	SUS		x			
Management changes	-					x
Healthcare utilization	-		x	x	x	x
Self-efficacy in managing symptoms	PROMIS	x	x			
Self-efficacy in managing medications	PROMIS	x	x			
Pain catastrophizing	PCS	x	x	x		
Stress	PSS	x	x	x		
Patient reported outcomes	PRO-CTCAE	x	x	x		
Depression and Anxiety	PROMIS	x	x	x		
Sleep Disturbance	PROMIS	x	x	x		

H. Inclusion / Exclusion Criteria

Pilot Cohort Inclusion Criteria:

- Age ≥ 18 years
- Patient diagnosed with an active cancer diagnosis (locally advanced solid tumor malignancy, multiple myeloma, or other advanced hematologic malignancy), either undergoing active treatment or receiving treatment for an advanced cancer or are receiving supportive care
- Chronic pain related to cancer or treatment (≥ pain score of 4)
- Has an active prescription for at least one opioid medication to treat their cancer pain (i.e. not for post-surgical pain)
- Completed baseline survey

Pilot Cohort Exclusion Criteria:

- Patients in survivorship: patients who have completed their treatment regimens, are not actively receiving treatment for an advanced cancer, or have a cancer that is in remission
- Cognitive impairment that would interfere with study participation, as judged by treating clinician
- Inability to speak English (the intervention has not yet been translated to Spanish)
- Enrolled in hospice
- Currently hospitalized
- Use of transmucosal fentanyl, given safety concerns and ongoing risk mitigation program required to prescribe these (TIRF REMS)
- Pain primarily related to a recent surgery (within the last 2 weeks)

We will exclude adults who are unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women, and prisoners.

WITHDRAWAL OF SUBJECTS

Subjects who do not complete the baseline assessment within 4 weeks of study enrollment will be withdrawn from the research study without their consent and considered non-evaluable for the primary endpoint. Non-evaluable subjects will be replaced until the total evaluable subject accrual of 35 participants is met.

These patients will be informed of their withdrawal from the study by study staff. The study PI, Dr. Desiree Azizoddin, will make all decisions regarding early termination of the study. The study team will then notify all participants accordingly.

Patients will be notified by study staff if they will be partially withdrawn from the research, as reviewed in their consent form (Appendix AD) as well.

I. Gender/Minority/Pediatric Inclusion for Research

Potential participants will not be excluded based on gender or race/ethnicity, though note that English fluency will be required as many assessments that will be used in the present study are not available in other languages. We will exclude

adults who are unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women, and prisoners.

J. Recruitment and Enrollment

Identifying potential subjects: Potentially eligible patients will be identified by 1) referrals from clinic staff, and 2) by pre-screening the EMR for outpatient solid tumor, hematology disease center clinics, or the supportive care clinic schedules. Once the study team identifies a potentially eligible patient, the team will reach out to the treating clinician for permission to approach and offer engagement in the study. If the provider does not approve that the study staff approach a patient, the study staff with NOT approach the patient to offer engagement in the study. Patients will provide written consent on the consent form and HIPAA forms after reviewing the consent and HIPAA forms with a study staff member according to IRB procedures (see Appendices AD, X, and Y).

Recruitment of potential subjects: Under a HIPAA waiver, study staff will look in the electronic medical record, scheduling systems, and inpatient lists to pre-screen and identify potentially eligible patients who meet the eligibility criteria. Study staff may also accept potential patient referrals from site clinicians. Purposive sampling based on data from the electronic medical record (e.g., demographics, cancer stage, number of recent hospitalizations, number of prescription drugs) will be used to ensure that perspectives of diverse patients are included.

Patient approaches can occur through the following mechanisms dependent upon COVID-19 related research regulations and clinic operations at the time.

- In person approach: A study team member will approach the patient in clinic to explain the study and offer participation. Interested participants will then review the study letter, consent and HIPAA forms with a research team member (Appendices AD, W, and X) and if interested provide signed consent. The patient and a study team member will then set up a time to onboard to the application.
- Remote approach: The clinician can introduce the study to the patient during a clinic visit and the study team member will follow up by phone to explain the study and offer participation. The study team member will attempt to contact the patient three times. The study letter, consent and HIPAA forms will be sent electronically through a secure and personalized link in REDCap (Appendices AD, W, and X). If no contact is established, the study team member will email the participant a copy of the recruitment letter (Appendix AC). The recruitment letter introduces the study and encourages the patient to contact the study team if they are interested in participating. If the patient contacts a study team member after the recruitment letter, the study team member will review the study letter and consent form before obtaining signed consent.

  See study letter Appendix X, recruitment letter Appendix AC, consent form Appendix AD, and HIPAA form Appendices W and Y for the Pilot Cohort.

A $50 incentive will be provided upon completion of the 4-week intervention period survey, and another $25 incentive will be provided when patients complete the 2-week post intervention period survey. Clinicians will not receive compensation for their engagement.

K. Risks and Benefits

Risks and Risk Mitigation:

There are risks to taking part in any research study. The primary risk of this study is loss of privacy or confidentiality. The risk of loss of privacy or confidentiality by using the STAMP+CBT app or taking part in this study is minimal. The study team has taken many steps to prevent any loss of privacy or confidentiality on the Insight platform developed at OUHSC/HPRC, including training of all clinic and research staff in best practices, rules, and regulations surrounding privacy and confidentiality, collecting research data using unique study ID numbers instead of names or other identifying information, and use of data collection systems that meet the NIH's data security standards.

As such, the only adverse event that will be monitored and reported is psychological distress as determined by the treating clinician. For any patient who exhibits severe distress as result of the study procedures, the study research assistant will notify the patients' clinician and social worker for appropriate response, including possible mental health referral if necessary. Patients' scores on self-administered assessments (e.g., pain score, mood) within the app will be used to determine if an adverse event has occurred. In these instances, an email alert will be automatically sent to the study team describing the patient's severe symptoms. Study staff will report the patient's symptoms by forwarding the email to the patient's care team, who will then contact the patient for further information. The alert will also instruct patients to contact their care team or call 911. Patients have immediate access to study staff through a call button on the app's home screen and will be advised to call research staff for any severe adverse events or other study-related needs, which will then be communicated with the clinical team when necessary and reported to the IRB. Any severe adverse event that is related to the physical and psychological risks described below and that results from participation in the study will be reported to the IRB within 2 business days and to the NIH within 5 business days. Furthermore, participants will be reminded that participation is voluntary and can be stopped at any time for any reason.

Recruitment and Informed Consent: Participants will only be approached if approval is received by their treating clinician. If the physician deems them unsuitable for the study, they will not be approached. Participants will be approached in clinic or by phone by a study team member in a private and confidential manner. If the patient is eligible and interested in participation, the study letter, consent and HIPAA form (Appendices AD, W, and Y) will be reviewed with the participant.

In the case of remote approach by phone, a study team member will attempt to contact the patient 3 times. If the patient contact cannot be established, the study team member will email a copy of the recruitment letter to the patient (Appendix AC). The recruitment letter encourages the patient to reach out to the study staff if they are interested in participating. If a patient reaches out to the study staff then the study letter, consent form, and HIPAA authorization form (Appendix W) will be reviewed before the patient provides written consent. During remote approaches by phone the study letter, consent and HIPAA forms will be sent by email through a secure and personalized link in REDCap. While discussing the study letter and consent the study staff will emphasize that participation is voluntary and the participant may stop participating at any time. Consent discussions may take place over the phone or HIPAA-compliant Zoom.

Protection against physical risks: The study team has placed extensive protections against the aforementioned physical risks of the app which have been approved in the initial app protocol (DF/HCC #18-504). These protections significantly exceed the level of support and guidance that patients would receive with usual care. Finally, the patient-facing app always instructs patients to contact their care teams and reminds them that the research portal is not monitored continuously.

The STAMP+CBT application sets a low bar for instructing patients to contact their care teams for reported symptoms. This includes reporting any new pain, fever, new or worsening back pain, new or worsening chest pain, any pain rated $\geq$ 8 out of a 0 to 10 scale (See table 3 for the detailed list). Moreover, if patients report moderate to severe pain levels that do not meet the previous criteria, in addition to receiving education about their pain management, they are also reminded that their care team wants to hear from them if they are concerned about their symptoms or if their symptoms are not improving. A link to their care team's number is included in the application. This level of support is much greater than what patients have usually with routine care.

Participants may feel reassured that their symptoms are being monitored and be less likely to call their care team. We have sought to mitigate this possibility in multiple ways. First, study staff emphasize and reiterate that the study platform is not monitored continuously during onboarding. Staff tell participants to contact their care team or call 911 should any concerning symptoms arise. Second, when patients report potentially serious symptoms, they are specifically instructed by the application to notify their care team by calling or paging after hours (the clinic number is included in the application). See Table 3 for the list of symptoms that prompts phone contact.

Protection against psychological risks: If in the course of their participation patients raise significant emotional distress, the appropriate care team members (i.e. nurse navigator, physician, mid-level provider) will be contacted to make appropriate social work or mental health referrals. Similar to that of physical

risks, this app provides closer monitoring than what is provided for usual care for psychosocial needs.

Benefits and knowledge to be gained: Using the STAMP+CBT app and taking part in this research study may or may not benefit participants. We hope that by reviewing the content in the STAMP+CBT app, patients are able to better manage their symptoms and the increased flow of information between a patient and their care team improves their experiences. We also hope the information learned from this research study will provide more information about how patients' pain management experience varies between clinic visits, as at-home app management will allow for increased monitoring of system and therefore increased access to daily symptom data. Lastly, we hope this will help patients and their care team work together during and between visits to achieve better symptom management in cancer patients.

L. Statistical Methods

Statistical analyses will be utilized in this pilot intervention to ascertain feasibility and acceptability of the STAMP+CBT app. We will measure time spent on the app per day and per week, completion rates for surveys and content review, and frequency of app interactions over the course of the pilot. Defined using precision analysis, we will consider the intervention to be **feasible** if ≥70% of subjects complete any activity on the app at least 50% of days on study. The intervention will be considered **acceptable** if >80% of the sample rate the app as satisfactory and useful (4 or higher/5); lower ratings will lead to app and content refinements. Other feasibility measures will assess time to accrual participation rates, and study retention and completion rates. Other acceptability outcomes will be assessed through qualitative debriefing interviews with patients evaluating the perceived benefits, usefulness, and satisfaction of the app, and quantitative acceptability ratings of the app's functionality, perceived utility, ease of use, and content relevance. Power calculation: With 35 evaluable patients, we will be able to estimate these proportions with margins of error (half of a 95% confidence interval) of approximately 18% or less assuming that the feasibility threshold of 70% is reached. This margin of error is small enough so that proportion estimates relevant to study feasibility will be accurate and provide informative guidance for future, larger studies. Although power is not sufficient in this pilot, we will explore associations between levels of engagement and changes in pain severity/interference, opioid use, catastrophizing, sleep, mood, and pain self-efficacy.

Because interviews produce qualitative results, statistical analyses will not be employed for a portion of this study. The study team will review qualitative feedback from patients and find common themes related to app feasibility and acceptability. The study team will use the common themes derived from qualitative thematic analysis of the interview that review this feasibility study to guide further iterations of the application and study procedures for future larger, efficacy study of the STAMP+CBT app.

M. Data and Safety Monitoring Plan

SCC Clinical Trials Office (CTO) study coordinators will assist in pre-screening, recruiting, and consenting patients. Once patients have consented, the principal investigator's study team will complete app onboarding and study procedures, except completing documentation on clinicaltrials.gov.

For this study, we will utilize the SCC CTO for registering human subjects for trials via the clinical staff, including registration in Oncore; ensuring high-quality standards are used for data collection; ongoing management of clinical trials, auditing, and data and safety monitoring; and coordinating quality assurance efforts related to clinical research.

The following Data and Safety Monitoring Plan (DSMP) will ensure that our OU/SCC project will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements, and applicable OU/SCC Guidelines.

The OU/SCC will:

- Ensure that the investigators and study team members are qualified and appropriately resourced to conduct the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training prior to enrolling participants and throughout trial's conduct as needed. The Principal Investigator will ultimately be responsible to make sure that required personnel have completed their training.
- Monitor progress and overall conduct of the study by Dr. Azizoddin's team.
- Ensure all OU Institutional Review Board (IRB), OU/SCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable OU/SCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the OU/SCC Sponsor.
- Monitor accrual and address problems meeting accrual requirements.
- Maintain documentation of Adverse Event reports and deviations/violation the OU/SCC study team for timely review.
- Maintain Regulatory documents which includes: IRB approvals/notifications, AE submissions, IRB approved consents.

Patient Registration: To register a participant, we will send the study letter with signed informed consent document/ HIPAA authorization form (if separate from the informed consent document) and eligibility checklist to SCC Clinical Trials Office. At the time of registration, SCC Clinical Trials Office requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number that will be used on all de-identified subsequent communication and documents. Participation may not begin without confirmation from the Coordinating Center that the participant has been registered.

Safety Monitoring:

The study and all research activities will be monitored by the study team and the PI. The PI and project manager will work closely with SCC Clinical Trials Office to implement the Data and Safety Monitoring Plan that is consistent with SCC Clinical Trials Office. All members of the research team will be responsible for immediately reporting breaches to confidentiality or data security, or adverse reactions, to the PI, and the study tracking database will provide tools for tracking and reporting any of these issues.

The PI and project manager will be responsible for timely submission of any necessary reports of adverse events, revisions to the protocol that indicate a change in risk for participants, or actions taken by the IRBs regarding the research. The project manager will be responsible for submission of the final approved protocol and any subsequent amended protocols to the OUHSC IRB. The CTO regulatory team will maintain a copy of the master regulatory binder in eREG, documenting IRB approved versions of the study protocol and consent forms for, correspondence with the IRB, and general human subjects and study-specific staff training.

The PI will monitor participant accrual monthly. A data submission and processing timeline will be developed for each data element. The PI and the project manager will monitor data submission and processing monthly.

The PI will be responsible for assessing external factors or relevant information (e.g., developments in the literature) that may impact the safety or participants or ethics of the research study.

It is unlikely that the intervention will cause any clinically significant AE's, as the intervention is predominantly a system by which patients can self-report symptoms, and receive education/coaching around symptom self-management. All adverse events will be reported to the OUHSC IRB and study investigators in accordance with usual procedure. Any serious adverse event (SAE), defined as an adverse event that results in death, is life threatening, results in hospitalization, or results in another important medical event, will be reported to the IRB and to the study investigators within 2 working days of occurrence.

Although a DSMB is not required for this small pilot study of a behavioral intervention, any SAE's related to study participation will be immediately reported to the PI and study team (Dr. Azizoddin). All SAE's will be reviewed by the study staff within 2 working days of occurrence. All SAEs will also be reported to the NIH within 5 business days. The NIH will not be directly involved in the review of these SAEs, but they will be notified to maintain transparency during the trial. If the SAE's are determined to be likely related to the intervention, the protocol and consent forms will be amended as necessary.

Data Management: PHI data will be collected using REDCap and the STAMP+CBT app.

REDCap: For this study, data will be collected using the REDCap platform. REDCap (Research Electronic Data Capture) is a free, secure, HIPAA-compliant web-based application. Data collection is customized for each study or clinical trial by the research team with guidance from REDCap administrators. REDCap is built around HIPAA guidelines and is 21 CFR Part 11 capable.

STAMP+CBT app: The final application will be HIPAA compliant and compliant with OU security and privacy standards through the Insight app platform developed at the OUHSC/HPRC.

Study specific procedure to maximize data security:

Controlled access: The REDCap and STAMP+CBT app administrators will set up all user accounts so that each user only has access to their own relevant participant data in a prototype model only.

Use of unique study ID numbers: REDCap automatically assigns unique study ID numbers to each new case.

Extensive training: All personnel involved in this study are required to complete and document completion of extensive protocol training. Furthermore, all research personnel are required to have valid certification of human subjects research training.

Storage of Patient Research Data: All patient research data is subject to HIPAA regulations at the host institution.

Note: Interviews will be audio and video recorded using the HIPAA-compliant platform, Zoom. The recordings will be stored in a password protected dropbox business account and destroyed once the data analysis is complete. The audio recordings will be transcribed analysis of feedback. The entire interview will not be conducted in a group setting. It is important to keep the facial features of patients in the videos as this provides important sociobehavioral analysis.

The staff at University of Oklahoma will be responsible for monitoring the data for completion, accuracy, and compliance. All personnel involved in this study are required to complete and document completion of extensive protocol training.

Furthermore, all research personnel are required to have valid certification of human subjects' research training.

N. Data Sharing

As noted elsewhere, data collection for this project will take place at the TSET Health Promotion Research Center, Stephenson Cancer Center at the University of Oklahoma Health Sciences Center.

De-identified data will be shared with co-investigators at Dana-Farber Cancer Institute and Brigham and Women's Hospital in Boston, MA.

O. Confidentiality

Protection against privacy risks: To monitor the risk of loss of confidentiality/privacy, the study team has ensured that the STAMP+CBT app is HIPAA compliant and meet the privacy and security standards set by University of Oklahoma Health Sciences Center. In addition, all collected study data will be maintained in a secure location and personal identifiers will be removed.

To maximize data security, both REDCap and STAMP+CBT employ:

- User Privileges - To ensure that users have access only to data and information that they are supposed to have within the application, user privileges are utilized within the software. Each user has their own account, and their user account will only have access to information that they themselves have created or to which administrators have granted them access.
- Password-protection & Authentication - Both systems are password protected and implement authentication to validate the identity of end-users that log in to the system.
- Logging and Audit Trail - Both systems maintain built-in audit trails that log all user activity and all pages viewed by every user.

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