RESEARCH PROTOCOL OUTLINE

Title of Project: Mobile Health Study and Enhanced Symptom Monitoring to Prevent Severe Illness from COVID-19 in Cancer Patients

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Abstract
The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) outbreak in late 2019 has resulted in over 4.28 million confirmed cases of novel coronavirus disease (COVID-19), with over 292,000 confirmed deaths worldwide (as of May 13, 2020). Severe disease occurs in ~10% of cases overall. However, risk for severe disease and mortality is greater in immunocompromised cancer patients, requiring scarce ventilation resources and intensive care unit space to address rapid clinical deterioration in this population. We propose to use the established Insight™ mHealth Platform, a component of the Stephenson Cancer Center (SCC) mHealth Shared Resource, to create the "Symptom Tracker" app. The Symptom Tracker (Insight™) app will enable real-time monitoring of cancer patient symptoms that are consistent with early signs of SARS-CoV-2 infection in this high-risk population by automatically (and securely) transferring this information to health care providers. The primary aim of this study is to determine the feasibility, ease of use, and perceived utility of this app to monitor symptoms and health risk behaviors among cancer patients currently receiving chemotherapy. Health risk behaviors, standard COVID-19 screening questions, and a single chemotherapy risk question will be assessed daily through the smartphone app. Specific responses will automatically trigger an alert to clinic nurses AND provide app-based access to contact the clinic for triage to home care or emergency assessment. When/if study participants screen positive for COVID-19, they will receive a device to measure their pulse and blood oxygen levels daily. This information and COVID-19 symptoms will be monitored daily via the Symptom Tracker (Insight™) app. This study will determine if an app can be used to rapidly report COVID-19 symptoms and quickly intervene to reduce morbidity and mortality in immunocompromised cancer patients. Further, data from this study will be used to inform the development of future mHealth interventions that will be tested in fully powered randomized control trials.

A. Specific Aims

The primary objective of this research is to use innovative mHealth technology to monitor symptoms in real-time and facilitate medical triage of high-risk patients. The current study will obtain data on the feasibility of an innovative mHealth application to track symptoms and automatically intervene upon reported high-risk symptoms among cancer patients who are receiving cytotoxic chemotherapy or immunotherapy treatments. This objective will be attained by pursuing the following specific aims:

1. Determine the feasibility, ease of use, and perceived utility of the Symptom Tracker (Insight™) mHealth app to monitor symptoms and health risk behaviors for up to 500 patients who are receiving chemotherapy to treat cancer.
    a. On average, participants will complete >50% of all prompted daily phone based ecological momentary assessments (EMAs).

   b. Most participants will report that the app is easy to use, and provides useful information (assessed quantitatively and qualitatively during the 24-week phone based or RedCap follow-up interview).
2. Examine participant characteristics and outcomes of those who do and do not test positive for COVID-19 during the 24-week monitoring period.
   a. Among those who undergo enhanced monitoring, we will use descriptive statistics to summarize the proportion of patients experiencing the following outcomes: manifestations of severe disease, treatment related toxicity, need for hospitalization, and SARS-CoV-2 related mortality.
   b. We will also compare outcomes and tolerability of enhanced self-monitoring for severe infection and compare rates of disease related morbidity and mortality to baseline rates published in the literature.
   c. We will use quantitative and qualitative methods to evaluate participant satisfaction with the app among those who test positive for COVID-19 and are asked to report vital signs each day.
3. Collaboratively document and share lessons learned regarding the impact of the COVID-19 pandemic on cancer care delivery via telemedicine and mHealth technology. We commit to a collegial collaboration with other cancer centers funded to study the use of telemedicine through the COVID-19 CCSG supplement mechanism.

This study will also explore the potential reduction of severe COVID-19 mediated disease through: 1) reducing time from symptom detection to treatment initiation (i.e., comparing treatment initiation times among those who test positive for COVID-19 in this study to published literature), and 2) closely monitoring COVID-19 symptoms among those who contract the virus (i.e., again, comparing participants in this study to published literature). COVID-19 is a novel virus and we do not fully understand its impact on our patient population. This study will provide useful, granular information about the daily symptoms of and recovery from COVID-19 in cancer patients. Data from this study will be used to pursue NIH R01 funding to formally evaluate the effects of using mHealth technology to monitor symptoms and health risk factors and intervene in real-time.

B. Background and Significance

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) outbreak in late 2019 has resulted in approximately 4.28 million confirmed cases of novel coronavirus disease (COVID-19), with over 292,000 confirmed deaths worldwide (as of May 13, 2020)[1]. The United States has reported the greatest number of cases across the world, with a total of 1.4 million new cases and over 83,000 attributable deaths as of May 13, 2020. Severe disease accounts for approximately 10% of cases and adds tremendous burden on limited medical resources and medical personnel.

Risk factors for severe disease are largely unknown, but clinical experience suggests that persons over age 65 with co-morbid conditions, such as immunosuppression from cancer or chemotherapy, place cancer patients in the “high-risk” group for severe manifestations of COVID-19 mediated disease [2]. Therefore, cancer patients are likely at increased risk for COVID-19 infection and may have a poorer prognosis. According to recent data, the risk of severe infection in cancer patients approaches 40% with up to a 20% mortality rate [3]. Thus, there is increased need for invasive ventilation and intensive care unit admission to circumvent rapid clinical deterioration in this population. Novel methods are needed to remotely monitor for SARS-CoV-2 infection and rapidly intervene to reduce morbidity and mortality in cancer patients exhibiting symptoms of the virus. Given evidence of poor outcomes in cancer patients, early intervention may significantly improve outcomes.

The potential for smartphone-based treatments has only recently become evident due to the substantial increase in smartphone ownership and use. Most Americans (i.e., 81% in 2018) have active smartphones;[4] thus smartphone-based intervention apps could play a significant role in improving cancer treatment symptom reporting and treatment adherence, and thereby improve overall treatment outcomes. Smartphone apps could offer easily accessible, highly tailored, and intensive interventions at a fraction of the cost of traditional counseling, thereby, overcoming many of the barriers that have hampered use of traditional empirically supported treatments.[5, 6]

Mobile technology can assist in overcoming many barriers to mental health care among cancer patients by offering immediate access to clinical information and support from any location using a low-cost, patient-driven interface. Existing studies have already identified the value and effectiveness of personal technology devices in monitoring symptoms and improving adherence during and after primary cancer treatments.[7-9] Recent studies also reveal cancer patient satisfaction with information delivered through smartphone applications, even when frequent, daily assessments were required.[10, 11] Yet to date, few studies have tested mHealth technology that identifies and automatically intervenes upon reported symptoms in real-time to address the needs of cancer patients. The Advanced Symptom Management System (ASyMS), however, is an exception and is a well-studied mHealth program for monitoring systems and providing automated feedback among both adult and youth cancer patients in the UK.[7, 12-17] ASyMS has demonstrated good feasibility of mHealth to manage physical symptoms and has received positive feedback from both patients and providers.[13, 15, 16] Further research is needed to examine mHealth interventions that specifically target symptom monitoring in cancer patients. The current study will use ecological momentary assessments (EMAs) to collect information about symptoms, exposure to coronavirus, and health risk behaviors among a sample of adults undergoing chemotherapy treatments for cancer at the Stephenson Cancer Center.

Our research team and others have demonstrated that smartphones can be used to capture moment-to-moment experience, allowing for the measurement of phenomena in real-time within natural settings.[18, 19] In addition, many studies have indicated that smartphone prompts can be used to increase targeted behaviors (e.g., [20, 21]·[22, 23]). Few studies, except our recent pilot work [24], have used a participant's responses to EMAs to automatically prompt tailored interventions in real-time. This feasibility study will test a novel smartphone application that will assess symptoms and automatically provide information and referrals when needed.

C. Preliminary Studies/Progress Report

Our team has used smartphones in 11 previous and ongoing studies to collect data and influence health behavior in high-risk samples for up to 6 months, including homeless[25, 26] and other socioeconomically disadvantaged adults.[27-31] In *Project Prevail*, EMA data were collected from smokers seeking treatment at a safety-net hospital tobacco cessation clinic (*N*=146).[27, 29, 31] Participants completed 83% of all EMAs. Using just 6 EMA variables (i.e., urge, stress, cigarette availability, alcohol use, motivation to quit, proximity to others smoking), we created a smoking lapse risk estimator that identified 80% of all smoking lapses within 4 hours of the lapse (false positive rate = 17%; see a detailed description of the development of the risk estimator here [30]). In another study, we developed the *Smart-T* app that includes on demand features (e.g., tips on coping with stress) and incorporates the Prevail lapse risk estimator to deliver tailored messages based on a person's momentary risk for smoking lapse. We examined the feasibility of the Smart-T app among smokers recruited from an urban safety-net hospital tobacco cessation clinic (n=59). In that study, socioeconomically disadvantaged

participants completed 87% of all EMAs and received an intensive level of tailored smoking-cessation treatment messages (102 messages on average) over a 3-week intervention period. We found that the on demand app functions were used regularly and the app was well-liked (e.g., 97% would like to use the app in the future if they were to relapse, and 85% would refer their friends who smoke to use the app).[30] Analyses of EMA data revealed that urges to smoke were significantly reduced when tailored urge messages were delivered by the app, as compared to instances where other types of messages were delivered (p<.001).[32] We also found reductions in stress (p=.021) and cigarette availability (p<.001) following tailored stress and cigarette availability messages, compared to other types of messages.[32] A total of 20% of participants were biochemically-confirmed abstinent 12 weeks post-quit, [24] which is better than many interventions conducted with low SES smokers.[33-38] We recently completed a 3-armed pilot randomized clinical trial (i.e., Project Smart-T2; OUHSC IRB #7195) that compared the Smart-T2 app to standard in-person smoking cessation clinic care and the free NCI QuitGuide app. Smokers who attended a clinic based tobacco cessation program were randomized to groups and followed for 13 weeks (1 week pre-quit through 12 weeks post-quit). All participants were asked to complete EMAs on study-provided smartphones for 5 weeks. 84 participants were enrolled and 22% of Smart-T, 15% of QuitGuide, and 15% of in-person participants achieved biochemically verified 7-day point prevalence abstinence 12 weeks post-quit. Smart-T3 (R01CA221819; the 3.0 version of Smart-T) was recently funded by the NCI. Smart-T Alcohol (i.e., R34AA024584) is an ongoing alcohol use reduction app for homeless adults) and Link2Care (i.e., R01MD010733) is an ongoing smartphone-based case management intervention for homeless adults. These studies demonstrate the utility, feasibility, versatility, and high compliance rates of our innovative smartphone apps.

As a practicing oncologist within Stephenson Cancer Center, Dr. Bethany Hannafon, Ph.D. is knowledgeable about the medical needs of the population that is being recruited for this study, and she regularly uses evidenced-based interventions to treat cancer. Her research and clinical experience complement Dr. Businelle's experience with research using mobile technology for health improvement. Additional study investigators include Dr. Summer Frank-Pearce (biostatistician) and Dr. Bethany Hannafon (basic and translational scientist) have agreed to assist with study recruitment and follow-up procedures.

D. Research Design and Methods

Study Design: A total of 500 treatment-seeking males and females will be asked to complete daily monitoring of symptoms and weekly monitoring of health risk factors weekly via smartphone app (Aim 1). Those who screen positive for COVID-19 will be triaged to emergency or non-emergency medical treatment. COVID-19 positive patients identified for non-emergent medical treatment will receive a study-supplied device to measure their oxygen level and heart rate and be instructed in the device's use. They will be prompted to enter vital signs data daily (such as body temperature, oxygen level, and heart rate) and questions from the app will change to assess the severity of COVID-19 related symptoms and inform changes in level of care, to emergency or non-emergency medical management as indicated by self-reporting. The proposed study will assess the impact of heightened symptom and vital sign monitoring on the early identification of severe manifestations of COVID-19 in this high-risk population (Aim 2). It is hypothesized that this will significantly improve COVID-19 related morbidity and mortality compared to the national and international rates currently reported in the literature. Figure 1 displays the participant flow through this 24-week study.

The SCC mHealth Shared Resource has created the versatile and reusable Insight™ mHealth Platform. Insight™ is HIPAA compliant and data are encrypted within the app. There will be 4 sources of data for the current study: 1) in-person data collected in a private room at the SCC

(i.e., Baseline visit) in REDcap, 2) smartphone based EMA survey data collected on study-provided or personal smartphones via the encrypted Insight™ smartphone application "Symptom Tracker", 3) qualitative interview data (e.g., opinions about the app, ways the app can be improved for future patient monitoring) collected over the phone (or via RedCap if a medical condition prevents them from being able to speak for long periods of time) at the conclusion of the study, and 4) data extracted from the electronic health record.

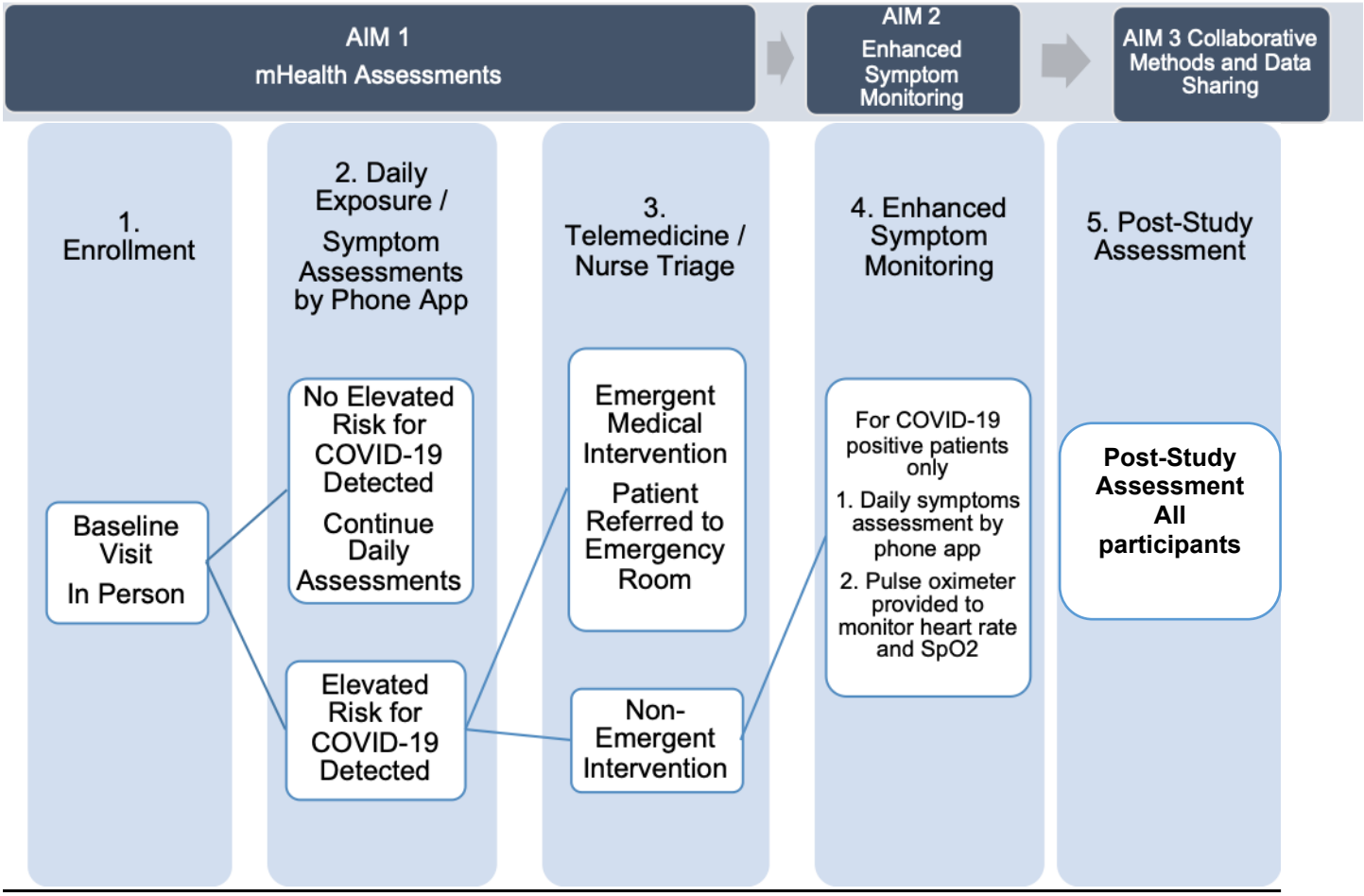

Figure 1. Study Participant Flow.

Measures

Baseline (in person) Measures. Baseline measures will assess demographic characteristics, health risk behaviors, and health related quality of life (See Table 1 and Appendix). The Baseline visit will take approximately 30 minutes to complete and data will be collected via RedCap (i.e., study screener) and Symptom Tracker app (i.e., baseline assessment items will be completed on study provided smartphones or the participant's personal phone). Each baseline questionnaire item will appear on the smartphone screen (participants touch the screen to select answers). Staff will be available to help participants who may have difficulty during the baseline assessment.

EMA (phone based) 24 Week Follow-Up Measures. The 24-week follow-up assessment, which includes a Treatment Improvement Survey, will be completed over the phone and via EMA and will take 15-30 minutes to complete. EMA enables measurement of phenomena in real-time, natural settings.[18, 19] EMA items will identify fluctuations in key variables that

predict study outcomes with less bias than traditional in-person assessments. EMA data will be used to identify and report COVID-19 symptoms to SCC medical staff, assess health risk factors, and collect other health related data that may be used to guide future intervention development with this population. All participants will download the assigned smartphone app to their personal smartphone or receive a smartphone at the baseline visit and will be asked to carry it with them at all times for 24 weeks. Participants will be trained to use the smartphone app for data collection purposes. Participants will be instructed to click the “call staff” button to speak with study research staff in the event that they have difficulty with the phone app. In addition, participants will be instructed that they can click the “Call Clinic Staff” button in the app to speak with medical professionals about their symptoms. In weeks 1-24, participants will be asked to complete one daily survey that will be automatically prompted and administered through an encrypted and secure smartphone app. All participants will be asked to self-initiate a survey (by clicking a button labeled “Report Symptoms” in the app) in the event that any new symptoms arise after the morning survey is completed. Participants will respond to survey questions by using the touch screen.

EMA types. The EMA methodology used in this study will be similar to what has been used in our previous studies, and by other researchers.[24, 25, 28, 30, 39-45] Each EMA will ask about current mood, medication use, perceived social support, pain, and symptoms consistent with COVID-19. This daily survey will take approximately 2 minutes to complete (see Table 1 and Appendix). Every Monday, participants will complete additional items focused on health risk factors, depression, anxiety, and medication use. The phone will ring and vibrate to cue these EMAs for 30 seconds. If the participant has not responded after 5 prompts, the EMA will be recorded as missed. Participants may also initiate a survey by clicking a Report Symptoms button in the app when COVID-19 symptoms arise later in the day (see Table 1 and Appendix). All EMAs will be date and time stamped for future analyses.

Table 1: Study Measures

MEASURE	ITEMS	FULL BATTERY ASSESSMENTS			Chart Review	EMA ASSESSMENTS
		Screen	Base	24-W		Daily Phone Survey (Aim 1)
Descriptive Variables						
Screening Questionnaire	11	X				Sleep
Rapid Estimate of Adult Literacy in Medicine-Short Form	9	X				Social Support
						Affect (3 items)
Demographic/Background Questionnaire	10		X			Medication
Smoking Questions	6		X	X		Pain
Health Questions	10		X	X		COVID-19 (8 items)
Health Related Quality of Life	4		X	X		
Patient Health Questionnaire + GAD7	15		X	X		**Weekly EMA**
Alcohol Questions	1		X	X		Health Behaviors
Treatment Improvement Interview	13			X		Alcohol (2 items)
App Quality Questions	3			X		Depression (2 items)
Chart Review	16				X	Anxiety (2 items)
						Emotion
Total number of items	--	20	46	52	15	App evaluation
Time needed to complete assessment (minutes)	--	8	10	25		Chemo (7 items)

Note. *Event EMA's only. Screen = Screening (in person); Base = Baseline (via Insight app); 24-W = 24-Week Follow-Up (via Insight app and phone call).

All participants will be prompted to complete EMAs once per day during the 24-week study time period. If a participant contracts COVID-19, they will click the "COVID-19 Positive" button in the app. This action will cause to app to ask a different set of questions focused on enhanced monitoring COVID-19 symptoms for the next 21 days. At the end of 21 days, the app will return to daily prompts of the pre-COVID-19 EMAs. At the conclusion of the 24-week EMA period, participants will gain access to a new button in the app that will initiate the 24-week follow-up assessment (see Appendix). Participants will receive a daily alert from the app to click the "Final Survey" button in the app to complete the end of study assessment. The 24-week phone interview (or RedCap interview if a medical condition prevents them from being able to speak for long periods of time) will be scheduled at the baseline visit and the date/time of the call will appear at the top of the app home screen. A maximum of five phone call/text attempts and one mailed letter will occur over two-week period, before data from phone interview (or RedCap interview if a medical condition prevents them from being able to speak for long periods of time) will be considered unattainable. Those participants who were loaned a mobile phone to use during the study will be mailed a stamped envelope to return the phone and charger, or will be approached by study staff to reclaim the mobile device during a routine follow-up visit in the SCC chemo infusion clinic. Upon receipt of the smartphone and charging equipment, all equipment will be sterilized with alcohol-based sanitizer in accordance with current practice guidelines put forth by the Centers for Disease Control at the time it is returned by the study subject.

EMA completion rates, participant dropout, and feedback on the participant satisfaction survey will be used to evaluate feasibility of this type of mobile intervention in this population.

Qualitative interview data. A qualitative interview will be conducted at the end of the 24-week study period via a brief phone call (or RedCap if a medical condition prevents them from being able to speak for long periods of time). This interview will assess opinions about the app, ways the app could be improved for future patient monitoring, etc. The follow-up phone call will be recorded for transcription and analyzed using NVivo. Recordings will be transcribed by internal staff, Microsoft Transcribe, or by approved contractors with whom a Business Associates Agreement has been made. When using Microsoft Transcribe, all transcriptions will be reviewed by study staff.
De-identified information will be shared with collaborators and colleagues at other NCI Designated Cancer Centers (see Aim 3).

Data from the electronic health record. Relevant data from the EHR will be extracted as needed to address any discrepancies or omissions surrounding specified study outcomes that have been collected through the smartphone EMA surveys. This supplemental information will be collected and stored in REDcap.

Private identifiable data (e.g., participant names, study assessment dates, and contact information) will be required for participant contact and thus will be collected in this study. Private identifiable data will be used to contact participants and will be saved in compliance with university storage of PHI (e.g., encryption). All printed private identifiable data will be stored in a locked filing cabinet in Dr. Hannafon's research office when not in use and will destroyed 12 months after data collection is completed.

Smartphone programming. The mHealth Shared Resource at the OUHSC and Stephenson Cancer Center (SCC) has developed the Insight™ mHealth Platform that empowers researchers to build, test, and launch technology-based assessment and intervention tools. The mHealth resource employs a program manager, four senior programmers, and two research technicians, who develop and maintain web and mobile applications and relational databases. Applications are developed using state-of-the-art cross-platform design tools. The Resource is located within the Oklahoma Tobacco Research Center (OTRC), where Dr. Businelle's office is located. Dr. Businelle is the Scientific Director of the mHealth Shared Resource, which will provide the programming services for the proposed project.

Smartphone training. Participants will receive brief systematic instructions (created by the researchers) at the baseline visit that demonstrates use of the app features. Instructions will be loaded into the app home screen so they may view it at any time. The instructions will describe how to use each of the app features ("Call Staff", "Call Clinic Staff", "Report Symptoms", "COVID-19 Positive", and "Update Contact Details" button/options; See Appendix). We have achieved high EMA compliance rates (i.e., 82%-87% of all EMA's completed) using similar protocols in multiple studies.

Data loss prevention. In order to overcome potential loss of data if participants lose their phone (less than 1% of phones have been lost in most studies), phones will be programmed to connect to our secure server each day to upload encrypted data. This will ensure that no collected EMA data are lost. This tactic will also allow the researchers to remotely monitor each participant's EMA completion rate and intervene (e.g., call the participant) when this rate is low (calls will be noted in the dataset and this variable may be used as a covariate in study analyses). Importantly, EMA data are password protected and encrypted on the phone and only encrypted data are transmitted to our secure server. Thus, study data are ONLY accessible by the research team. If a phone is lost, the app and all study data will be remotely wiped and only one

replacement phone will be provided to each participant.

EMA alert settings. At the baseline visit, a phone set-up wizard is used to set participant sleep and wake times for each day of the week (Note: sleep/wake times can be changed for those with variable schedules). This practice reduces the likelihood that the phone will ring when participants are sleeping. Prompted EMAs will be automatically rescheduled 30 minutes later (four times) if a participant does not respond to the prompt.

Compensation. Participants will not be compensated for completing study surveys. Those who are loaned study phones and do not complete the 24-week follow-up assessment, will be contacted to reschedule and request that loaned phones be returned in person or by mail.

Study application. All patients will receive standard cancer treatment as prescribed by SCC health professionals plus baseline, follow-up, and daily EMA assessments relevant to this study. Participants who own an Android smartphone (OS version 6.0 or higher) will be encouraged to download and use the study app on their own phone. Those who do not own this type of smartphone and those who do not have a data plan will be loaned a Samsung smartphone (or equivalent) for 24 weeks so that they may complete EMAs. Participants will navigate through the EMA program and enter data simply by touching the screen. The study app includes a "Call Staff" function/button that automatically calls study staff (e.g., if they have problems completing EMAs). Participants will also be asked to self-initiate "Report Symptoms" EMAs when they experience new symptoms consistent with COVID-19. Smartphones will automatically collect data when on demand features are accessed. Use of personal vs. study provided phones will be examined as a covariate in all analyses.

When participants provide a pattern of responses that are suggestive of heightened risk for COVID-19 (See algorithm in Appendix), they will receive a suggestion to contact SCC staff, and the app will send an encrypted email containing this information to Dr. Hannafon and other SCC staff with a request to contact the participant to assess symptoms (see Appendix) and whether urgent medical attention is indicated. Should urgent medical attention be warranted, the patient will be instructed to the clinical unit most appropriate to the symptoms they reported through the app algorithm or discussed with the clinical nursing or physician staff. Non-emergent patients who screen positive for COVID-19 will begin an enhanced symptom and vital sign monitoring period that will continue until the participant reports that they are no longer symptomatic and/or a medical professional informs them that they no longer need to self-quarantine, which is expected to be approximately 21 days. These patients will receive a pulse oximeter (provided by the study) and the app questions will change to include daily prompts requesting that the patient input morning vital signs (temperature, heart rate, blood oxygen levels (SpO2)) and answer questions specific to the severity of symptoms and/or emergence of new symptoms of COVID-19. If a patient is hospitalized, they can continue to complete the daily assessments if they are willing and able to do so. The app will also support check-ins with SCC staff and after-hours medical staff as needed after diagnosis of COVID-19 or until the patient has been medically released from self-quarantine. Once the participants have completed the enhanced symptom and vital sign monitoring portion of the study, the pulse oximeter will be returned to the research team at the time of their next scheduled appointment. These devices will then be sterilized with both alcohol-based sanitizing products as well as ultraviolet light exposure in accordance with practices endorsed by the Centers for Disease Control.
Participants will continue to use the app to complete a final 24-week follow-up survey and will be contacted by phone (or RedCap if a medical condition prevents them from being able to speak for long periods of time) to complete a brief qualitative interview 24 weeks after study enrollment. Relevant demographic, cancer-specific and COVID-19 related data will be extracted

from electronic health records at the conclusion of the study.

E. Chart Review

Study staff will conduct a chart review on OUHSC campus computers using OU Medicine's electronic medical record. Chart review will be conducted after completion of the EMA period. Initial evaluation, treatment plan, and follow-up notes will be searched for the following data points:

a) Cancer Stage at Initial Presentation
b) Type of Cancer – text field
c) History of Previous Cancer Diagnosis
d) Previous Cancer Treatment
e) History of Previous Cancer Treatment with Surgery
f) History of Previous Cancer Treatment with Chemotherapy
g) History of Previous Cancer Treatment with Endocrine Therapy
h) History of Previous Cancer Treatment with Radiation
i) History of Previous Other Types of Cancer Treatment
j) Receiving concurrent chemotherapy and radiation
k) Body Mass Index at start of treatment
l) Body Mass index at end of treatment
m) Number of no-show and cancelled office visits
n) Referral to Supportive Care
o) Distance in miles from the participant's home to the SCC?
p) Does the participant reside in a rural county?

All data collected during the chart review will be assigned to the corresponding participant ID number and entered into study electronic databases in accordance with the data and safety-monitoring plan outlined below. See Appendix for a full list of data that will be collected via chart review.

F. Biospecimens

No biospecimens will be collected as part of this study.

G. Banking/Repository/Database

No biospecimens will be banked for future use. All data will be stored and accessed on OUHSC devices/computers.

H. Inclusion / Exclusion Criteria

Individuals will be included in the study if they:
1) Demonstrate > 6th grade English literacy level (i.e., phone based EMAs require >6th grade literacy)
2) Present for care at the Stephenson Cancer Center at the University of Oklahoma Health Sciences Center
3) Are currently receiving cytotoxic chemotherapy or immunotherapy by intravenous infusion or by orally delivered medication
4) Are greater than or equal to 18 years of age
5) Are willing and able to complete surveys on their personal smartphone or a study provided smartphone
6) Are willing and able to provide informed consent

There are no early termination criteria; however, individuals can elect to stop participation in

mobile app monitoring at any time.

I. Gender/Minority/Pediatric Inclusion for Research

This sample will consist of up to 500 male and female cancer patients. Individuals under the age of 18 (pediatric population) will be excluded from this study. Minorities will also be included, as this study seeks to adequately capture the diversity of patients receiving treatment at the SCC. There are no known additional risks for women or minorities.

J. Recruitment and Enrollment

Participants (N=500) will be recruited through the OU Medical Stephenson Cancer Center Infusion Clinic which is located at 800 NE 10th Street, Floor 3, OK 73104. The SCC Infusion Clinic provides chemotherapy services for approximately 1200 patients per month. Based upon the treatment regimens provided, we anticipate that 250-300 cancer patients will be accrued to the trial every quarter. The clinic is staffed by oncologists, pharmacists, and advanced practice professionals. Patients will be given a verbal description of the study during a clinic visit, and those interested will be screened for study eligibility. Individuals who provide informed consent and meet the study inclusion criteria will complete the baseline assessment in the Infusion Clinic space. Participants will use study phones or personal smartphones to complete the baseline and follow-up assessment and phone-initiated and self-initiated surveys for the entire duration of the study. At the time of consent, patients will be provided with a copy of the informed consent to keep and will be encouraged to contact the investigators should they have further questions. The assessment questions are presented through the Insight™ mHealth platform. No incentive or cost reduction for care will be provided to the patient in order to minimize the risk of coercion. Several strategies will be utilized to retain study participants. Survey responses are automatically uploaded to the secure server every day; thus, study staff can closely monitor participant completion of daily surveys, and attempt to make contact with participants who do not complete them. Figure 1 displays the participant flow through the study.

K. Risks and Benefits

Participation in this study poses minimal risk to participants. Potential risks include consenting process and loss of confidentiality. Each of these risks are discussed below. The consent form will clearly describe the potential risks of this study. Thus, participants who feel uncomfortable with such assessments or intervention programs are not likely to agree to participate.

Consent process. The patient risk in this clinical study is minimal. As part of the informed consent process, patients will be made aware of how their data will be collected. Subjects who choose not to take part in the proposed study, will not be penalized or lose benefits to which they are entitled.

Loss of confidentiality. One potential risk is loss of confidentiality. The severity of harm in the case of loss of confidentially may range from mild to severe depending upon the individual and the specific circumstances. However, the risks of participation in the study are similar to that of participation in usual in person or phone-based treatments, as loss of confidentially may be experienced in each case. Other possible adverse events might include compromised data security and discomfort related to being asked study questions. The research team will monitor risk and report adverse events immediately to the IRB.

Intervention. Risk to subjects from the proposed intervention research is minimal. There is no known harm from the use of standard thermometers or pulse oximetry units or daily monitoring and automated reporting of symptoms to medical professionals.

Alternative Treatments. The consent form will explain that, rather than participating in this study, individuals may choose to continue treatment in accord with their oncology treatment plan at the SCC.

General Procedures to Reduce Risk. Each participant will be assigned an identification number that will be utilized in place of names in all electronic and print data files. The sheet containing the links between participant names and identifiers will be kept in locked filing cabinet when not in use and will be destroyed 12 months after data collection has been completed. All print information, including informed consent and screening questionnaires, will be stored in a separate locked filing cabinet in Dr. Hannafon's research offices. All electronic data (with names omitted) will be maintained on the investigators' computers and all computers, electronic files will be encrypted, and password protected. Participant information will not be released to any party outside the research team at any time.

In-person data. Participants will complete all assessments on their personal smartphone or a study provided smartphone using the Symptom Tracker (Insight™) mHealth platform app and/or the REDcap program. Participants will be instructed that they may elect to not answer questions that make them feel uncomfortable. All questionnaire data is automatically saved and password protected. To ensure that research staff are adequately trained in data collection, confidentiality, and the protection of human subjects, all project staff will complete extensive training focused on each of the following topics: 1) project rationale and objectives; 2) the informed consent process; and 3) general data collection procedures (e.g., computer data collection, privacy). They will also complete all confidentiality, conflict of interest, and HIPAA training programs as required by the University of Oklahoma Health Sciences Center.

EMA data. Participant responses to study questions will be encrypted and stored on the study/personal smartphone. Encrypted data will be automatically uploaded to our secure server each day. When/if the app determines that risk for COVID-19 infection is high, or COVID-19 symptoms are worsening (in those who contract the virus), an encrypted email will be sent from our secure server to clinical study staff that includes the participant name, date of birth and phone number. The following features are designed to ensure the security of this data: 1) the data stored on the smartphone device are in a SQLite database in a sandbox environment, where read/write operations are only available through the programming application (i.e., no file or output is readable to end users); 2) a 10-12 character password (only known to researchers) is required to authenticate the current user before data can be manually accessed; 3) the web browser application linking the investigator's computer to the database is on HTTPS protocol (SSL certificate with encryption) which will guarantee the data transfer from web browser to the backend database is well protected; and, 4) the backend database is hosted by Microsoft Azure and the University of Oklahoma Health Sciences Center. These steps will ensure the security of EMA data. Software will be downloaded onto each study phone so that study data can be remotely wiped if phones are lost or stolen.

Beyond the above noted issues, the following step will be taken to minimize the likelihood of an adverse reaction to the study: The consent form will clearly describe the nature of the assessments and intervention. Thus, participants who feel uncomfortable with such assessments or intervention programs are not likely to agree to participate.

Potential Benefits. Potential benefits to participants include the use of study phones during the intervention period (at the current time, this benefit is estimated to be unlimited voice and text messages and 2 GB high speed data for the duration of their involvement in the study [i.e., 24 weeks]). Participants may also directly benefit from early detection of and immediate intervention upon presentation of COVID-19 symptoms. Finally, participants may also benefit from the enhanced symptom monitoring that is proposed.

Risks in Relation to Benefits. The current study involves very minimal risk to participants, and the risks of study participation are similar to that of participation in standard care (e.g., loss of confidentiality). All participants will be already seeking standard care before they are provided with any information about the research study. In addition, the knowledge gained from this study may be utilized to improve our understanding of symptom monitoring, health risk factors, and general experiences of individuals who undergo chemotherapy treatments to treat cancer.

We do not anticipate harm to research participants, but the principal investigators will monitor unanticipated problems (including serious and non-serious adverse events) and protocol deviations. Potential unanticipated problems for this project are all non-medical in nature. Unanticipated problems will be submitted within five University business days to the IRB using the Unanticipated Problem Report Form. The following information will be included in an adverse event report: date of event, attribution to data collection, and outcome of adverse events. All adverse events will also be reported in the annual report to the IRB along with a Summary of Participant Harms.

L. Multiple Sites

This is a single-site study.

M. Statistical Methods

Aim 1. We will examine the percentage of prompted daily surveys that are completed throughout the 24-week intervention period and the percentage of participants who report they are satisfied with monitoring and use of mHealth application at the end of the 24-week study period. We will compare participant characteristics (e.g., demographics, health behaviors) and outcomes between those who are satisfied with the app and monitoring versus those who are dissatisfied. We will observe via mHealth app patient health risk factors and readiness to change health risk behaviors in SCC cancer patients. We will compare participant characteristics using chi-square test or independent t-test, as appropriate. The follow-up phone call based qualitative interview (or RedCap interview if a medical condition prevents them from being able to speak for long periods of time) will access participant perceptions of each app feature and be recorded for transcription and analyzed using NVivo. Recordings will be transcribed by internal staff, Microsoft Transcribe, or by approved contractors with whom a Business Associates Agreement has been made. When using Microsoft Transcribe, all transcriptions will be reviewed by study staff. This information will be used to improve this type of symptom monitoring apps in future studies and interventions.

Aim 2. We will examine participant characteristics among those who are and are not transitioned to an Aim 2 monitoring of vital signs and severity of COVID-19 symptoms. We will also examine participant characteristics and outcomes for those that require emergent intervention versus non-emergent intervention. Among those who undergo enhanced monitoring, we will use descriptive statistics to summarize the proportion of patients experiencing the following outcomes: manifestations of severe disease, treatment related toxicity, need for hospitalization, and COVID-19 related mortality. We will also compare outcomes and tolerability of enhanced self-monitoring for severe infection and compare rates of disease related morbidity and mortality to baseline rates published in the literature. We will evaluate participant satisfaction with the app and identify ways to improve this novel patient monitoring technology. We will perform logistic regression to determine the odds of experiencing primary outcomes, based upon baseline characteristics (e.g., sex, race/ethnicity, cancer stage/type). Kaplan-Meier survival curves and log-rank tests of homogeneity will be used to identify the survival functions, describing the time to resolution of symptoms based upon

demographic characteristics. Because COVID-19 is a novel virus and we do not fully understand its impact on our patient population, this study will provide useful, granular information about the daily symptoms of and recovery from COVID-19 in cancer patients.

Aim 3. No analyses proposed, as this is a collaboration aim.

N. Data and Safety Monitoring Plan

Data quality and integrity will be held to the highest standard to ensure accurate reporting and documentation of the objectives outlined in the proposal. The Institutional Review Board and the Office of Clinical Research will monitor data and safety monitoring. The institutional plan for data and safety monitoring for all trials funded by the NCI has been adopted by the University and will be utilized for conduct of our planned proposal.

Procedures to minimize the risk, including of loss of confidentiality, are described in the Protection against Risks section. The study poses minimal risk to participants, therefore the principal investigators (Drs. Hannafon and Businelle) and co-investigators (Drs. Hannafon and Frank-Pearce) will undertake continuous monitoring and reporting of events. Although unlikely given our experience, any unanticipated problems will be promptly reported to the IRB. The NIH will be informed of any actions taken by the IRB as a result of its continuing review. Breach of confidentiality is highly unlikely because all data will be encrypted, identified only by numeric code, and/or stored in locked file cabinets/online-secure server. A master list of names and numbers will be kept in a separate location and is used to facilitate the collection of follow-up data. All staff will be fully trained in relevant ethical principles and procedures, particularly around confidentiality.

O. Data Sharing

De-identified summary information about the feasibility of using mHealth technology to assess risk for COVID-19 and interventions to address risk will be shared with the other 2 cancer centers that received CCSG funding on a similar topic. We plan to publish the outcomes of this study and present findings at local and national conferences.

P. Confidentiality

Each participant will be assigned an identification number that will be utilized in place of names in all electronic and print data files. The sheet containing the links between participant names and identifiers will be kept in locked filing cabinet when not in use and will be destroyed 12 months after data collection has been completed. All print information, including informed consent and screening questionnaires, will be stored in a separate locked filing cabinet in the investigators' research offices. All electronic data (with names omitted) will be maintained on the investigators' computers and all computers and electronic files will be encrypted and password protected. When/if the app determines that risk for COVID-19 infection is high, or COVID-19 symptoms are worsening (in those who contract the virus), an encrypted email will be sent from our secure server to clinical study staff that includes the participant name, date of birth and phone number. Participant information will not be released to any party outside the research team at any time.

University IT Security has fully vetted and approved the Insight mHealth Platform that will be used to collect data on participant and study provided smartphones. University IT has also approved the Insight data storage procedures described above.

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