BMJ Open

Active Surveillance of Treatment-Related Symptom Burden in Ambulatory Cancer Patients via the Implementation of Electronic Patient Reported Outcomes and Biometric Monitoring Technologies for Vital Signs – A Randomized Controlled Trial Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057693
Article Type:	Protocol
Date Submitted by the Author:	28-Sep-2021
Complete List of Authors:	Offodile, Anaeze ; The University of Texas MD Anderson Cancer Center, Institute for Cancer Care Innovation; The University of Texas MD Anderson Cancer Center, Department of Plastic and Reconstructive Surgery DiBrito, Sandra; The University of Texas MD Anderson Cancer Center, Division of Surgical Oncology Finder, Janice; The University of Texas MD Anderson Cancer Center, Patient Experience Clinical Programs Shete, Sanjay; The University of Texas MD Anderson Cancer Center, Department of Biostatistics Jain, Sanchita; The University of Texas MD Anderson Cancer Center, Office of the Chief Delgado, Domenica; The University of Texas MD Anderson Cancer Center, Office of the Chief Miller, Christopher; The University of Texas MD Anderson Cancer Center, Department of Behavioral Science Davidson, Elenita; The University of Texas MD Anderson Cancer Center, Department of Behavioral Science Overman, MJ; The University of Texas MD Anderson Cancer Center, Department of Gastrointestinal Medical Oncology Peterson, Susan; The University of Texas MD Anderson Cancer Center, Department of Behavioral Science
Keywords:	CHEMOTHERAPY, Adult oncology < ONCOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Active Surveillance of Treatment-Related Symptom Burden in Ambulatory Cancer Patients via the Implementation of Electronic Patient Reported Outcomes and Biometric Monitoring Technologies for Vital Signs – A Randomized Controlled Trial Protocol

Anaeze C. Offodile II MD MPH[1,2] Sandra R. DiBrito MD PhD,[3] Janice P Finder MSN,[4] Sanjay Shete PhD MPhil,[5] Sanchita Jain MBA,[6] Domenica Delgado MBA,[6] Christopher Miller,[7] Elenita Davidson,[7] Michael J. Overman MD,[8] Susan Peterson PhD MPH[7]

Affiliations:

1. Institute for Cancer Care Innovation, The University of Texas MD Anderson Cancer Center, Houston TX
2. Department of Plastic and Reconstructive Surgery, The University of Texas MD Anderson Cancer Center, Houston TX
3. Division of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston TX
4. Patient Experience Clinical Programs, The University of Texas MD Anderson Cancer Center, Houston TX
5. Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston TX
6. Office of the Chief, Data and Technology Office, The University of Texas MD Anderson Cancer Center, Houston TX
7. Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, Houston TX
8. Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston TX

Corresponding author:

Anaeze C. Offodile II MD MPH

University of Texas MD Anderson Cancer Center, Houston TX

1400 Pressler Street, Unit #1488

Houston, TX 77030

Email: acoffodile@mdanderson.org

ABSTRACT

Introduction: Remote patient monitoring (RPM) has emerged as a potential avenue for optimizing the management of symptoms in patients undergoing chemotherapy. However, RPM is a complex, multi-level intervention with technology, workflow, contextual and patient experience components. The purpose of this pilot study is to determine the feasibility of protocol implementation with respect to recruitment, patient retention, adherence to reporting recommendations, RPM platform usability and patient experience in ambulatory cancer patients at high risk for chemotherapy-related symptoms.

Methods and Analysis: This protocol describes a single-arm feasibility pilot study of technology-enhanced outpatient chemotherapy symptom management in patients with gastrointestinal or thoracic cancer receiving care at a single site (MD Anderson Cancer Center). An anticipated total of 25 patients will be recruited prior to the initiation of chemotherapy and provided a set of validated questionnaires at enrollment and after our one-month feasibility pilot trial period. Our intervention entails the self-reporting of symptoms and vital signs via a HIPAA-compliant, secure tablet interface that also enables: a) the provision of self-care materials to patients, b) generation of threshold alerts to a dedicated call-center, and c) video-conferencing. Protocolized triage and management of symptoms will occur in response to the alerts. Feasibility and acceptability metrics will characterize our recruitment process, protocol adherence, patient retention, and usability of the RPM platform. We will also document the perceived effectiveness of our intervention by patients.

Ethics and Dissemination: This study has been granted approval by the institutional review board of MD Anderson Cancer Center. We anticipate dissemination of our pilot and subsequent effectiveness trial results via presentations at national conferences and peer-reviewed publications in the relevant medical journals. Our results will also be made available to cancer survivors, their caregivers and hospital administration.

Trial Registration number: NCI-2021-07464; pre-results

Strengths and Limitations of This Study

- The present pilot study will allow us to delineate the feasibility of recruitment, acceptability, and implementation of a remote patient monitoring platform for the active surveillance of and early intervention for chemotherapy-related symptoms.
- The associated results will also provide plausible estimates for the sample size calculation and design of a non-blinded, 2-arm (1:1) pragmatic randomized controlled trial that will compare usual care to RPM plus usual care for a cohort of solid-tumor cancer patients.
- This care delivery paradigm holds considerable promise for reducing acute care utilization, improved quality-of-life, and symptom control.
- To the best of our knowledge, there is no published clinical trial assessing the effectiveness of remote patient monitoring of real-time biometrics and symptom burden on clinical outcomes in cancer.

INTRODUCTION

The motivation for applying telemedicine and digital health tools in oncology has been evident for several years.[1] However, their potential to transform clinical care is now beginning to be realized, partly due to the unparalleled scope of the SARS-CoV2 pandemic and need to maintain continuity of care within the context of quarantine and self-isolation.[2] Technologies now in use include remote patient monitoring (RPM), apps, wearables, and chatbots among others.[3] RPM characterizes the real-time acquisition and transmission of health-related data using home-based, sensor-enabled digital monitoring devices and mobile applications to assess vital signs, symptoms and other health-related outcomes.[3] RPM has been successfully leveraged for the outpatient management of several chronic conditions including diabetes, heart failure, chronic wounds and chronic obstructive pulmonary disease.[4–7] RPM implementation in these clinical settings have been associated reduced emergency room (ER) utilization, improved quality-of-life, reduced healthcare spending and better symptom control. [7–10]

Although overall mortality from cancer is declining,[11] patients with cancer still face debilitating physical and psychosocial treatment side-effects including fatigue, myalgias, pain, shortness of breath, sleep disturbance and depression.[12,13] Unfortunately, clinicians often fail to recognize the incidence and severity of chemotherapy-induced symptoms, even in instances that mandate the reporting of treatment toxicities.[14–16] Poor symptom management is associated with increased healthcare spending, and worse quality of life, clinical outcomes, and overall survival.[9,17–19] This has led to considerable interest in leveraging symptom self-reporting during ambulatory cancer care. Pioneering work by Basch et al. identified statistically significant reductions in ER utilization, chemotherapy disruptions, and gains in quality-adjusted survival.[20] However, despite compelling evidence, systematic approaches for symptom assessment, patient-provider communication, and early intervention are still lacking.[21] This is largely because the full integration of ePROs with a health system's medical record and clinical informatics platform has not been widespread.[22] As a result, clinicians do not have "real time" access to patient generated- health data (e.g. vitals signs and ePROs) and the prevailing care model for

treatment-toxicities is largely patient-initiated and reactive i.e. unable to proactively monitor and mitigate symptom burden before they escalate.[23] RPM-enabled *digital touch points* can reassure patients that their treatment team is connected to them and informed about all aspects of their disease course. Furthermore, the American Society of Oncology (ASCO) has strongly advocated for the increased integration of information technology into patient care.[24]

We posit that the implementation of a RPM platform that facilitates electronic patient-reported outcomes (ePRO) capture and protocolized, point-in-time vital sign measurements has the potential to enhance real-time clinical decision-making, improve health related quality-of-life, lower symptom burden, mitigate treatment delays, and engender greater patient engagement. Additionally, moving from an episodic care model to a more continuous care model has the potential of improving patient experience. At MD Anderson Cancer Center (MDACC), we have developed a technology and operational infrastructure for remotely monitoring chemotherapy symptoms in-between clinic visits. It entails the active surveillance of patient-reported biometrics (heart rate, blood pressure, temperature, oxygen saturation, and weights) and adverse events (PRO-CTCAE) by advanced care practitioners (i.e. nurse practitioners), guided by backend threshold alerts for both vitals and ePROs. Automated self-care advice for patients and care-givers is also delivered across the platform. In this work, we articulate our framework for the development and pilot-testing of our RPM platform, intended for the active surveillance of treatment-related symptoms, in patients with gastrointestinal and thoracic cancers who are receiving chemotherapy in the ambulatory setting.[25]

AIMS

Primary aims **-** The primary aim of this external pilot study is to investigate the feasibility of protocol implementation (i.e. recruitment process, evaluation of eligibility criteria, assessment of usability of technology platform) prior to a non-blinded, randomized controlled trial of the effectiveness of technology-enhanced (i.e. RPM with ePRO capture) outpatient management of treatment-related symptoms. Our *a priori* specified feasibility objectives are as follows:

1) Patient eligibility and recruitment – Defined as an approach-to-consent rate of > 60% among eligible patients (i.e. enrollment rate). 2 patients per month, on average, should be consented into the program.

2) Adherence – Defined as > 70% adherence with PRO-CTCAE surveys $\geq$ 4 days per week and > 80% adherence to biometrics reporting $\geq$ 4 days per week.

3) Implementation outcomes – The feasibility, acceptability, and appropriateness of our intervention will be assessed via the following validated 4-item psychometric tools: FIM ("Feasibility of Intervention Measure"), AIM ("Acceptability of Intervention Measure"), and IAM ("Intervention Appropriateness Measure").[26] Each item is scored on a 5-point Likert scale (completely disagree to completely agree) and our pilot will be considered successful if the calculated mean scores for each of the implementation measures is > 3.[26]

4) Feasibility outcomes – We will monitor the generation of an alert (red or yellow) after an abnormal vital sign or self-reporting of a severe symptom burden. We will also record the number of adverse events related to the use of the biometric devices i.e. blood pressure cuff, weight scale, thermometer etc. Lastly, we will track the clinical action that is associated with an alert generation e.g. phone consultation, video visit, care escalation to the emergency room.

Secondary aims – Following completion of the one-month pilot reporting period, participants will also be invited to share their experiences with our RPM platform through the use of questionnaires.

1) Perceived effectiveness – Participating patients will be asked to respond to the following two questions: "I found the remote monitoring system helped me manage my symptoms" and "I found that this remote monitoring system helped me better communicate with my care team".[16] Responses will be graded according to a Likert scale (1-5) based on these responses: "strongly disagree", "disagree", "neither agree nor disagree", "agree", "strongly agree".

2) Usability – The validated symptom usability scale (SUS) will be provided to patients to assess usability of the RPM platform.[27] The scale is a reliable tool that consists of 10-questions regarding the usability of an electronic

or technology system. Responses are on a 5-point Likert scale (1-5) and our RPM platform will be considered usable if the mean score is greater than 68, concordant with published work.

METHODS AND ANALYSIS

Setting, Patient Population and Eligibility Criteria

This will be a single-arm, single-institution feasibility pilot study in the gastrointestinal and thoracic medical oncology clinics at MDACC, Houston-Texas. We will approach adult English-fluent adults (≥18 years) with gastrointestinal (esophagus, stomach, liver, pancreas, small bowel, colon, and rectum) or thoracic cancers who are scheduled to initiate or continue outpatient chemotherapy. There will be no exclusions applied on the basis of underlying tumor histology. Patients on combination chemotherapy and immunotherapy or combination chemotherapy and biologics will also be eligible for inclusion. We plan to recruit a diverse sample of patients (n = 25), reflecting at least three patients of age > 65 years, at least three patients from racial/ethnic minority groups and a balanced gender distribution.[16] Patients will be invited by their oncologist providers to participate in the study based on the following published clinical criteria: 1) baseline co-morbidities that increase risk of chemotherapy adverse events, 2) provider-identified social barriers to care, 3) inability to tolerate oral intake or ailment sufficient, 4) high tumor burden, 5) high levels of psychosocial distress or multiple symptomatic complaints, 6) recent emergency room visits or hospitalizations, defined as within the preceding six months, 7) recent dose reduction with initial antineoplastic treatment, and 8) combined modality therapy e.g. chemoradiation.[28]

Exclusions

Patients receiving investigational new drug treatments (i.e. not yet FDA approved) or concurrently enrolled in a phase 1 clinical trials will be excluded due to the associated structured reporting and regulatory requirements. Patients with a requirement for inpatient infusion (i.e. CAR-T cell therapy), living in institutional settings (i.e. prison), with a history of dementia, physical disability or neurological deficits that prohibit their

ability to report symptom burden will also be excluded. Patients may participate if they do not have a caregiver or if their caregiver declines participation. Caregivers will participate only with consent of the patient.

RPM Intervention

Consenting patients will be asked to use the Vivify platform for RPM (VivifyHealth, Plano, TX). The Vivify platform is HIPAA-compliant, FDA-registered as a Class 1 Medical Device Data System that is commercially available and allows for transmission of biometric data to a centralized team of health care providers. The Vivify platform includes a set of wireless, Bluetooth-connected biometric devices that are provided to patients, including a scale, blood pressure cuff, pulse oximeter, thermometer, and tablet computer loaded with the Vivify mobile application and a measure of frequency and severity of twelve treatment-related symptoms (i.e., appetite loss, nausea, vomiting, cough, constipation, hot flashes, diarrhea, dyspnea, pain, neuropathy, fatigue, and dysuria).[18,29,30] Furthermore, if necessary, an internet hot-spot will also be provided. Patients will be provided with these devices directly by mail from Vivify. The MDACC research staff will be responsible for troubleshooting technical problems. Patients will return kits, postage-paid, at end of study. Prior to receiving the kits, patients will be instructed with a video conference training protocol on how to use each device, which are comparable to commercially available devices that can be purchased by consumers, as well as on the use of the tablet computer.[31,32] The "teach-back" method will be used to ensure patient understanding.[33] Patients will be asked to take one reading per day with each device, and to complete one symptom assessment per day via the tablet. As part of the informed consent and study onboarding process, patients will be asked to follow instructions for proactively seeking medical care that have been provided as part of patient education and by their health care team, and not to rely on any feedback received as a result of data submitted through the Vivify platform.

The Vivify platform supports the creation of algorithms to detect vital signs or symptom PROs that exceed predetermined threshold values. Biometric data that exceed pre-specified threshold values specified (self-reported biometrics: heart rate > 120, heart rate < 55, systolic blood pressure < 90, oxygen saturation <

90%, temperature > 101F) will generated an alert email to the patient call center staffed by advanced care practitioners.[18] Our self-reporting system for symptom burden will be adapted from the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) pertaining to the following common symptoms encountered during chemotherapy: constipation, diarrhea, fatigue, dry mouth, decreased appetite, difficulty swallowing, nausea, pain, vomiting. These symptoms are graded on a 0 (non-present) to 4 (very severe) and the corresponding alert will be triggered by absolute values of greater than or equal to 2.

The alerts, based on biometric and/or ePRO data, will be transmitted in near real-time to MDACC's patient call center, ***askMDAnderson***, which is staffed by a dedicated team of oncology advanced care practitioners (i.e. nurse practitioners, physician assistants) and registered nurses. These clinicians have received additional training in the assessment and management of advanced cancer symptoms as well as the Vivify platform used in this study. The *askMDAnderson* staff will access and review these data elements through a secure, Web dashboard at least once daily. Upon receipt of an alert email, the *askMDAnderson* staff will review the data via the Vivify dashboard and will provide follow-up and referral as clinically appropriate, using National Comprehensive Cancer Network (NCCN) symptom management guidelines as a point of reference for non-pharmacologic recommendations.[34,35] Biometric information captured on the Vivify platform is integrated with MDACC's electronic medical record (EMR) (Epic, Madison, WI), allowing the primary clinical team to also have access to the patient-reported data. Lastly, the end-user license agreement (EULA) associated with the Vivify device and study consent documents will reinforce that patients should not substitute the RPM program with the need to notify their care team if they are experiencing concerning symptoms. Following the initiation of a severe symptom alert, this message will appear on the Vivify platform: "*The Chemo Remote Monitoring Program hours are 8 a.m. to 8 p.m., Monday through Friday. If you are concerned, need assistance after hours, or feel that the symptoms are worsening, please contact askMDAnderson, your primary oncologist office or go to your local emergency room. In case of an emergency, call 911".*

Data Collection

Using a combination of data abstraction from the electronic medical record by the study team and patient feedback via surveys, we hope to collect the following information:

1) Patient demographics - age, race, sex, presence of caregiver, and marital status

2) Clinical information – cancer histology, stage, location, chemotherapy regimen, line of chemotherapy, Eastern Cooperative Oncology Group (ECOG) status

3) Implementation and feasibility measures as outlined above i.e. consent rate, AIM, FIM, IAM, perceived effectiveness rating, and SUS score.

All data points will be collated and stored on a REDCap (Research Electronic Data CAPture) database. REDCap is a secure web application that is widely used in health services research. It is able to support the administration of surveys, data export from external sources such as an EMR, and provides a user-friendly interface for data entry.[36]

Data analysis plan

Descriptive statistics (e.g., means, medians, numbers, percentages, ranges, and standard deviations) for demographic and clinical characteristics of participants will be reported. Response rates (i.e. completion of required assessments), most frequent symptoms, proportion of actioned alerts will also be described. Graphical methods (e.g., boxplots and histograms) will also be employed to examine the distributions of outcome measures. By design, the present pilot study is not intended or powered to determine the efficacy of RPM in the outpatient management of treatment-related symptoms. This important scientific question will be addressed with our planned RCT. Our anticipated sample size of 25 will allow us to be relatively precise in our conclusions with respect to continuous implementation outcomes (FIM, AIM, IAM) and also facilitate preliminary estimates for our larger trial. All data analysis will be carried out with SAS statistical software (SAS Institute Inc, Cary, NC, USA).

Patient and Public Involvement

The research team has engaged with the Patient and Family Advisory Council (PFAC) during the conceptualization and design phase of our pilot. PFAC is a unique program comprised of patients, survivors, and caregivers, it serves as the patients' "voice" for institutional committees, operational projects and department-level initiatives. Specifically, we gathered formative data on the design of the proposed RPM pilot with respect to the perception among PFAC attendees (n =78) about the acceptability of daily symptom assessments, potential burden of our RPM platform, and whether phone-based communication is appropriate within the context of escalating treatment-related symptoms. We also received feedback on the prevalence of smartphone use. The PFAC will be retained in an advisory capacity for the duration of both the pilot and subsequent RCT. The study leadership team (Drs Offodile and Peterson) plan to meet with the PFAC two to three times a year to review and iterate study plans and seek feedback with respect long-term sustainability and implementation of RPM at MDACC. Meeting notes will be shared along with regular project updates and related professional communication. Patients will not be involved in the recruitment and dissemination of the results for this pilot study.

Patient Experience

We utilized a human-centered design thinking approach to anticipate the needs of our patients and created end-to-end experiential touchpoints that would enable a seamless experience on the program.

ETHICS AND DISSEMINATION

All study documents (i.e. protocol, consent, educational materials) have been approved by the MDACC Institutional Review Board. Patients will be informed that their participation is completely voluntary and that there will receive no compensation. They will also be assured that they will receive standard-of-care and shall be exposed to no negative consequences as a result of either their participation or refusal. All patients will be able to opt out of the study at any time and for any reason. We anticipate dissemination of our pilot and subsequent effectiveness trial results via presentations at national conferences and peer-reviewed publications in the

relevant medical journals. No patient identifying information will be used in the publication of findings.

PROTECTION AGAINST RISKS TO PATIENT SAFETY

The present pilot study is of minimal risk to patients. We will use validated survey questionnaires, the content of which are not sensitive in nature. It is possible that our remote monitoring devices may incite anxiety, annoyance or distress in patients. However, we believe that the possibility of such adverse events is minimal. To reduce this risk of distress, during the onboarding and consent process, patients will be instructed to a) not substitute routine medical care with the device readings and b) contact their primary oncology care team if at any point they feel concern or worry. Furthermore, all patients will receive standard chemotherapy education, which includes explicit guidance as to when to seek urgent medical care. The Vivify devices are FDA approved, HIPAA-compliant, commercially available, and meet the highest standards of protecting patient privacy. All data transmission will leverage standard encryption and security protocols. Vivify will not participate in the study design, patient recruitment, data interpretation, analysis, or dissemination of results. Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

All information extracted from the medical record will be entered onto coded data sheets which will be maintained on stored in approved locations. Each patient will be assigned a unique study identification number by MDACC research staff which will be programmed into the Vivify tablet and devices. Electronic data will be strictly stored only on password-protected Institutional computers; accessible only to the PI and collaborators. Only the PI and the collaborators will be participating in the collection and analysis of data. No patient identifying information will be used in presentation or publication of this material. Upon study termination, all data, questionnaires and remaining identifiers will be banked indefinitely in REDCap according to institutional policy for future use only in IRB-approved research settings. Lastly, all study personnel will undergo the requisite human subjects research training which includes procedures for maintaining patient confidentiality.

DISCUSSION

The present pilot study will allow us to delineate the feasibility of recruitment, acceptability and

implementation of an RPM platform for the active surveillance of and early intervention for chemotherapy-related symptoms. The associated results will also provide plausible estimates for the sample size calculation and design of a non-blinded, 2-arm (1:1) pragmatic randomized controlled trial that will compare usual care to RPM plus usual care for a cohort of solid-tumor cancer patients. This care delivery paradigm holds considerable promise for reducing acute care utilization and improving quality-of-life in this patient population. To the best of our knowledge, there is no published clinical trial assessing the effectiveness of remote patient monitoring of real-time biometrics and symptom burden on clinical outcomes in cancer.

Trial status: Pilot study is now open and recruiting patients.

A. Contributorship statement: ACO: Study design, manuscript drafting, and final approval of version to be published. SD: Study design, manuscript drafting, and final approval of version to be published. JPF: Study design, critical revision of the manuscript for important intellectual content, and final approval of version to be published. SS: Study design, critical revision of the manuscript for important intellectual content, and final approval of version to be published. SJ: Study design, critical revision of the manuscript for important intellectual content, and final approval of version to be published. DD: Study design, critical revision of the manuscript for important intellectual content, and final approval of version to be published. CJM: Study design, critical revision of the manuscript for important intellectual content, and final approval of version to be published. ED: Study design, critical revision of the manuscript for important intellectual content, and final approval of version to be published. MJO: Study design, critical revision of the manuscript for important intellectual content, and final approval of version to be published. SP: Study design, critical revision of the manuscript for important intellectual content, and final approval of version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the integrity of any part of the work are appropriately resolved.

B. Competing interests: The authors declare that they have no competing interests

C. Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Acknowledgments: We wish to thank the members of the MDACC Patient and Family Advisory Council for their contributions to the present work.

REFERENCES

1. Sirintrapun SJ, Lopez AM. Telemedicine in Cancer Care. *Am Soc Clin Oncol Educ B*. 2018; 38: 540-545

2. Hollander JE, Carr BG. Virtually Perfect? Telemedicine for Covid-19. *N Engl J Med*. 2020; 382(18): 1679-81

3. Andreu-Perez J, Leff DR, Ip HMD, Yang GZ. From Wearable Sensors to Smart Implants-Toward Pervasive and Personalized Healthcare. *IEEE Trans Biomed Eng*. 2015; 62(12): 2750-62

4. Barnett TE, Chumbler NR, Vogel WB, Beyth RJ, Qin H, Kobb R. The effectiveness of a care coordination home telehealth program for veterans with diabetes mellitus: A 2-year follow-up. *Am J Manag Care*.2006: 12(8): 467-74

5. Louis AA, Turner T, Gretton M, Baksh A, Cleland JGF. A systematic review of telemonitoring for the management of heart failure. *Eur J Heart Fail*. 2003; 5(5): 583-90

6. Rasmussen LM, Phanareth K, Nolte H, Backer V. Internet-based monitoring of asthma: A long-term, randomized clinical study of 300 asthmatic subjects. *J Allergy Clin Immunol*. 2005; 115(6): 1137-42

7. Bartoli L, Zanaboni P, Masella C, Ursini N. Systematic review of telemedicine services for patients affected by chronic obstructive pulmonary disease (COPD). *Telemed e-Health*. 2009; 15(9): 877-83

8. Cleland JGF, Louis AA, Rigby AS, Janssens U, Balk AHMM. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: The Trans-European Network-Home-Care Management System (TEN-HMS) study. *J Am Coll Cardiol*. 2005; 45(10): 1654-64

9. Noel HC, Vogel DC, Erdos JJ, Cornwall D, Levin F. Home telehealth reduces healthcare costs. *Telemed e-Health*. 2004; 10(2): 170-83

10. Santamaria N, Carville K, Ellis I, Prentice J. The Effectiveness of Digital Imaging and Remote Expert Wound Consultation on Healing Rates in Chronic Lower Leg Ulcers in the Kimberley Region of Western Australia. *Prim Intent Aust J Wound Manag*. 2004; 12(2): 62-70

11. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019; 69(1): 7-34

12. Rhondali W, Yennurajalingam S, Chisholm G, et al. Predictors of response to palliative care intervention for chronic nausea in advanced cancer outpatients. *Support Care Cancer*. 2013; 21(9): 2427-35

13. Tookman AJ, Jones CL, DeWitte M, Lodge PJ. Fatigue in patients with advanced cancer: A pilot study of an intervention with infliximab. *Support Care Cancer*. 2008; 16(10): 1131-40

14. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. *J Clin Oncol*. 2004; 22(17): 3485-90

15. Di Maio M, Gallo C, Leighl NB, et al. Symptomatic toxicities experienced during anticancer treatment: Agreement between patient and physician reporting in three randomized trials. *J Clin Oncol*. 2015: 33(8): 910-15

16. Wright AA, Raman N, Staples P, et al. The HOPE Pilot Study: Harnessing Patient-Reported Outcomes and Biometric Data to Enhance Cancer Care. *JCO Clin Cancer Informatics*.2018; 2:1-12

17. Kirkova J, Walsh D, Rybicki L, et al. Symptom severity and distress in advanced cancer. *Palliat Med*. 2010; 24(3): 330-9

18. Basch E, Deal A, Kris M, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine

Cancer Treatment: a Randomized Controlled Trial. *J Clin Oncol*. 2016;34(6):557-565. doi:10.1200/JCO.2015.63.0830

19. Basch EM, Delal AM, Dueck AC, et al. Overall survival results of a randomized trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA*. 2017; 318(2): 197-98

20. Judson TJ, Bennett A V., Rogak LJ, et al. Feasibility of long-term patient self-reporting of toxicities from home via the Internet during routine chemotherapy. *J Clin Oncol*. 2013; 31(20): 2580-5

21. Maguire R, Fox PA, McCann L, et al. The eSMART study protocol: A randomised controlled trial to evaluate electronic symptom management using the advanced symptom management system (ASyMS) remote technology for patients with cancer. *BMJ Open*. 2017 Jun 6: 7(5):e015016. doi:10.1136/bmjopen-2016-015016

22. Basch E, Bennett A, Pietanza MC. Use of patient-reported outcomes to improve the predictive accuracy of clinician-reported adverse events. *J Natl Cancer Inst*. 2011; 103(24): 1808-10

23. Richards HS, Blazeby JM, Portal A, et al. A real-time electronic symptom monitoring system for patients after discharge following surgery: A pilot study in cancer-related surgery. *BMC Cancer*. 2020; 20(1): 543. doi: 10.1186/s12885-020-07027-5

24. Meropol NJ, Kris MG, Winer EP. The American Society of Clinical Oncology's blueprint for transforming clinical and translational cancer research. *J Clin Oncol*. 2012; 30(7): 690-1

25. Moore CG, Carter RE, Nietert PJ, Stewart PW. Recommendations for planning pilot studies in clinical and translational research. *Clin Transl Sci*. 2011; 4(5): 332-7

26. Weiner BJ, Lewis CC, Stanick C, et al. Psychometric assessment of three newly developed implementation

outcome measures. *Implement Sci*. 2017; 12(1): 108. doi:10.1186/s13012-017-0635-3

27. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. *Int J Hum Comput Interact*. 2008; 24(6): 574-94

28. Daly B, Kuperman G, Zervoudakis A, et al. InSight Care Pilot Program: Redefining Seeing a Patient. *JCO Oncol Pract*. 2020; 16(10): e1050-e1059

29. Daly B, Gorenshteyn D, Nicholas KJ, et al. Building a Clinically Relevant Risk Model: Predicting Risk of a Potentially Preventable Acute Care Visit for Patients Starting Antineoplastic Treatment. *JCO Clin Cancer Informatics*. 2020; 4: 275-289

30. Daly B, Nicholas K, Gorenshteyn D, et al. Misery Loves Company: Presenting Symptom Clusters to Urgent Care by Patients Receiving Antineoplastic Therapy. *J Oncol Pract*. 2018; 14(8): e484- e495

31. Peterson SK, Shinn EH, Basen-engquist K, et al. Identifying early dehydration risk with home-based sensors during radiation treatment: A feasibility study on patients with head and neck cancer. *J Natl Cancer Inst - Monogr*. 2013; Dec 2013(47): 162-68

32. Peterson SK, Shinn EH, Garden AS, et al. Identifying dehydration risk in head and neck cancer patients undergoing radiation therapy using remote, sensor-based monitoring: A randomized controlled trial. *J Clin Oncol*. Published online 2016. doi:10.1200/jco.2016.34.3_suppl.152

33. White M, Garbez R, Carroll M, Brinker E, Howie-Esquivel J. Is “teach-back” Associated with knowledge retention and hospital readmission in hospitalized heart failure patients? *J Cardiovasc Nurs*. 2013; 28(2): 137-146

34. Vidall C, Dielenseger P, Farrell C, et al. Evidence-based management of chemotherapy-induced nausea and vomiting: A position statement from a European cancer nursing forum. *Ecancermedicalscience*. 2011; 5:211. doi:10.3332/ecancer.2011.211

35. National Comprehensive Cancer Network (NCCN) Guidelines for Supportive Care. Accessed April 1, 2021. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#supportive.

36. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42(2): 377-81

BMJ Open

Active Surveillance of Chemotherapy-Related Symptom Burden in Ambulatory Cancer Patients via the Implementation of Electronic Patient Reported Outcomes and Sensor-enabled Vital Signs Capture – Protocol for a Decentralized Feasibility Pilot Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057693.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Feb-2022
Complete List of Authors:	Offodile, Anaeze ; The University of Texas MD Anderson Cancer Center, Institute for Cancer Care Innovation; The University of Texas MD Anderson Cancer Center, Department of Plastic and Reconstructive Surgery DiBrito, Sandra; The University of Texas MD Anderson Cancer Center, Division of Surgical Oncology Finder, Janice; The University of Texas MD Anderson Cancer Center, Patient Experience Clinical Programs Shete, Sanjay; The University of Texas MD Anderson Cancer Center, Department of Biostatistics Jain, Sanchita; The University of Texas MD Anderson Cancer Center, Office of the Chief Delgado, Domenica; The University of Texas MD Anderson Cancer Center, Office of the Chief Miller, Christopher; The University of Texas MD Anderson Cancer Center, Department of Behavioral Science Davidson, Elenita; The University of Texas MD Anderson Cancer Center, Department of Behavioral Science Overman, MJ; The University of Texas MD Anderson Cancer Center, Department of Gastrointestinal Medical Oncology Peterson, Susan; The University of Texas MD Anderson Cancer Center, Department of Behavioral Science
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Patient-centred medicine, Health informatics, Health services research
Keywords:	CHEMOTHERAPY, Adult oncology < ONCOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

Active Surveillance of Chemotherapy-Related Symptom Burden in Ambulatory Cancer Patients via the Implementation of Electronic Patient Reported Outcomes and Sensor-enabled Vital Signs Capture – Protocol for a Decentralized Feasibility Pilot Study

Anaeze C. Offodile II MD MPH[1,2,3] Sandra R. DiBrito MD PhD,[4] Janice P Finder MSN,[5] Sanjay Shete PhD MPhil,[6] Sanchita Jain MBA,[7] Domenica Delgado MBA,[7] Christopher Miller,[8] Elenita Davidson,[8] Michael J. Overman MD,[9] Susan Peterson PhD MPH[8]

Affiliations:

1. Institute for Cancer Care Innovation, The University of Texas MD Anderson Cancer Center, Houston TX
2. Department of Plastic and Reconstructive Surgery, The University of Texas MD Anderson Cancer Center, Houston TX
3. Baker Institute for Public Policy, Rice University, Houston, TX
4. Division of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston TX
5. Patient Experience Clinical Programs, The University of Texas MD Anderson Cancer Center, Houston TX
6. Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston TX
7. Office of the Chief, Data and Technology Office, The University of Texas MD Anderson Cancer Center, Houston TX
8. Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, Houston TX
9. Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston TX

Corresponding author:

Anaeze C. Offodile II MD MPH

University of Texas MD Anderson Cancer Center, Houston TX

1400 Pressler Street, Unit #1488

Houston, TX 77030

Email: acoffodile@mdanderson.org

Introduction: Remote patient monitoring (RPM) has emerged as a potential avenue for optimizing the management of symptoms in patients undergoing chemotherapy. However, RPM is a complex, multi-level intervention with technology, workflow, contextual and patient experience components. The purpose of this pilot study is to determine the feasibility of protocol implementation with respect to decentralized recruitment, patient retention, adherence to reporting recommendations, RPM platform usability and patient experience in ambulatory cancer patients at high risk for chemotherapy-related symptoms.

Methods and Analysis: This protocol describes a single-arm decentralized feasibility pilot study of technology-enhanced outpatient symptom management system in patients with gastrointestinal and thoracic cancer receiving chemotherapy and cancer care at a single site (MD Anderson Cancer Center, Houston Texas). An anticipated total of 25 patients will be recruited prior to the initiation of chemotherapy and provided a set of validated questionnaires at enrollment and after our one-month feasibility pilot trial period. Our intervention entails the self-reporting of symptoms and vital signs via a HIPAA-compliant, secure tablet interface that also enables a) the provision of self-care materials to patients, b) generation of threshold alerts to a dedicated call-center, and c) video-conferencing. Vital sign information (heart rate, blood pressure, pulse, oxygen saturation, weight, and temperature) will be captured via Bluetooth-enabled biometric monitoring devices which are integrated with the tablet interface. Protocolized triage and management of symptoms will occur in response to the alerts. Feasibility and acceptability metrics will characterize our recruitment process, protocol adherence, patient retention, and usability of the RPM platform. We will also document the perceived effectiveness of our intervention by patients.

Ethics and Dissemination: This study has been granted approval by the institutional review board of MD Anderson Cancer Center. We anticipate dissemination of our pilot and subsequent effectiveness trial results via presentations at national conferences and peer-reviewed publications in the relevant medical journals. Our results will also be made available to cancer survivors, their caregivers and hospital administration.

Trial Registration: NCI-2021-07464; pre-results; 2-14-2022

Strengths and Limitations of This Study

- The present pilot study will allow researchers to delineate the feasibility of recruitment, acceptability, and implementation of a remote patient monitoring platform for the active surveillance of and early intervention for chemotherapy-related symptoms.
- The study is limited to patients with gastrointestinal and thoracic cancers, so the results may not be generalizable to other solid organ or hematogenous cancers.
- The study is limited to patients at a single, high volume institution, which may limit the generalizability of the outcomes with regard to smaller hospitals and care systems.
- The study has been designed to include a diverse patient population, with respect to age, gender and race, which should allow the feasibility results to be generalized to a broad demographic of patients within gastrointestinal and thoracic cancers.

INTRODUCTION

The motivation for applying telemedicine and digital health tools in oncology has been evident for several years.[1] However, their potential to transform clinical care is now beginning to be realized, partly due to the unparalleled scope of the SARS-CoV2 pandemic and need to maintain continuity of care within the context of quarantine and self-isolation.[2] Technologies now in use include remote patient monitoring (RPM), apps, wearables, and chatbots among others.[3] RPM characterizes the real-time acquisition and transmission of health-related data using home-based, sensor-enabled digital monitoring devices and mobile applications to assess vital signs, symptoms and other health-related outcomes.[3] RPM has been successfully leveraged for the outpatient management of several chronic conditions including diabetes, heart failure, chronic wounds and chronic obstructive pulmonary disease.[4–7] RPM implementation in these clinical settings have been associated with reduced emergency room (ER) utilization, improved quality-of-life, reduced healthcare spending and better symptom control. [8–11]

Although overall mortality from cancer is declining,[12] patients with cancer still face debilitating physical and psychosocial treatment side-effects including fatigue, myalgias, pain, shortness of breath, sleep disturbance and depression.[13,14] Unfortunately, clinicians often fail to recognize the incidence and severity of chemotherapy-induced symptoms, even in instances that mandate the reporting of treatment toxicities.[15–17] Poor symptom management is associated with increased healthcare spending, and worse quality of life, clinical outcomes, and overall survival.[9,18–20] This has led to considerable interest in leveraging symptom self-reporting during ambulatory cancer care. Pioneering work by Basch et al. identified statistically significant reductions in ER utilization, chemotherapy disruptions, and gains in quality-adjusted survival.[21] A recent phase III randomized controlled trial by Absolom et al. identified improved physical well-being (6 and 12 weeks) and self-efficacy (18 weeks) among patients with breast, colorectal, or gynecological cancers that were exposed to electronic self-reporting of symptoms during cancer treatment.[22] Of note, there were no associated improvements in treatment delays, dose reductions, chemotherapy drug changes, or hospital admissions in the treatment

group.[22]

However, despite evidence of RPM effectiveness, systematic approaches for symptom assessment, patient-provider communication, and early intervention are still lacking.[23] This is largely because the full integration of ePROs with a health system's medical record and clinical informatics platform has not been widespread.[24] As a result, clinicians do not have "real time" access to patient generated- health data (e.g. vitals signs and ePROs) and the prevailing care model for treatment-toxicities is largely patient-initiated and reactive i.e. unable to proactively monitor and mitigate symptom burden before they escalate.[25] RPM-enabled *digital touch points* can reassure patients that their treatment team is connected to them and informed about all aspects of their disease course. Furthermore, the American Society of Oncology (ASCO) has strongly advocated for the increased integration of standardized personal health information (e.g. demographics, health status, treatment status, side effects, and symptoms) in real time into routine inpatient and outpatient patient care.[26,27] Unfortunately, the evidence for RPM efficacy in oncology is limited and most studies have excluded the caregivers' experiences and involvement, which is not a realistic representation of the utility of remote monitoring in the oncology population.[28,29]

We posit that the implementation of a RPM platform that facilitates electronic patient-reported outcomes (ePRO) capture and protocolized, point-in-time vital sign measurements has the potential to enhance real-time clinical decision-making, improve health related quality-of-life, lower symptom burden, mitigate treatment delays, and engender greater patient engagement. Additionally, moving from an episodic care model to a more continuous care model has the potential of improving patient experience. At MD Anderson Cancer Center (MDACC), we have developed a technology and operational infrastructure for remotely monitoring chemotherapy symptoms in-between clinic visits. It entails the active surveillance of patient-reported biometrics (heart rate, blood pressure, temperature, oxygen saturation, and weights) and adverse events (PRO-CTCAE) by advanced care practitioners (i.e., nurse practitioners), guided by backend threshold alerts for both vitals and ePROs. Automated self-care advice for patients and caregivers is also delivered across the platform. In this work,

we articulate our framework for the development and pilot-testing of an RPM platform, for the active surveillance of treatment-related symptoms, in patients with gastrointestinal and thoracic cancers who are receiving neoadjuvant or adjuvant chemotherapy in the ambulatory setting.[30] Lastly, the evolving COVID-19 pandemic has also catalyzed greater awareness and implementation of decentralized clinical trials in the life sciences sector.[31] This paradigm shift is in response to pandemic-related regulatory waivers for trial conduct, a need to preserve the availability of personnel protective equipment for hospital staff, and an acknowledgment of the high cost structure and limited patient access in traditional "brick and mortar" trial infrastructure.[31–33] We will also use the proposed pilot study to develop and implement a decentralized or virtual workflow for patient recruitment, education about the RPM platform, enrollment, symptom monitoring, and study completion (Figure 1).[34]

AIMS

Primary aims **-** The primary aim of this external pilot study is to investigate the feasibility of protocol implementation (i.e., recruitment process, evaluation of eligibility criteria, assessment of usability of technology platform) prior to a non-blinded, randomized controlled trial of the effectiveness of technology-enhanced (i.e. RPM with ePRO capture) outpatient management of treatment-related symptoms. Our *a priori* specified feasibility objectives are as follows:

1) Patient eligibility and recruitment – Defined as an approach-to-consent rate of > 60% among eligible patients (i.e., enrollment rate). 2 patients per month, on average, should be consented into the program.

2) Adherence – Defined as > 70% adherence with PRO-CTCAE surveys $\geq$ 4 days per week and > 80% adherence to biometrics reporting $\geq$ 4 days per week.

3) Implementation outcomes – The feasibility, acceptability, and appropriateness of our intervention will be assessed via the following validated 4-item psychometric tools: FIM ("Feasibility of Intervention Measure"), AIM ("Acceptability of Intervention Measure"), and IAM ("Intervention Appropriateness Measure").[35] Each item is scored on a 5-point Likert scale (completely disagree to completely agree) and our pilot will be considered

successful if the calculated mean scores for each of the implementation measures is > 3.[35]

4) Feasibility outcomes – We will monitor the generation of an alert (red or yellow) after an abnormal vital sign or self-reporting of a severe symptom burden. We will also record the number of adverse events related to the use of the biometric devices i.e., blood pressure cuff, weight scale, thermometer etc. Lastly, we will track the clinical action that is associated with an alert generation e.g., phone consultation, video visit, care escalation to the emergency room.

Secondary aims – Following completion of the one-month pilot reporting period, participants will also be invited to share their experiences with our RPM platform through the use of questionnaires.

1) Perceived effectiveness – Participating patients will be asked to respond to the following two questions: "I found the remote monitoring system helped me manage my symptoms" and "I found that this remote monitoring system helped me better communicate with my care team".[17] Responses will be graded according to a Likert scale (1-5) based on these responses: "strongly disagree", "disagree", "neither agree nor disagree", "agree", "strongly agree".

2) Usability – The validated symptom usability scale (SUS) will be provided to patients to assess usability of the RPM platform.[36] The scale is a reliable tool that consists of 10-questions regarding the usability of an electronic or technology system. Responses are on a 5-point Likert scale (1-5) and our RPM platform will be considered usable if the mean score is greater than 68, concordant with published work.

METHODS AND ANALYSIS

Setting, Patient Population and Eligibility Criteria

This will be a single-arm, single-institution pilot study in the gastrointestinal and thoracic medical oncology clinic at MD Anderson Cancer Center. We will approach adult English-fluent adults (≥18 years) with gastrointestinal (stomach, liver, gallbladder, bile duct, pancreas, small bowel, appendix, colon, rectum, and anal) and thoracic (esophageal and lung) cancers who are scheduled to initiate or continue outpatient chemotherapy at The University of Texas MD Anderson Cancer Center in Houston, Texas. There will be no restrictions or

exclusions applied based on underlying tumor histology. Patients on combination chemotherapy and immunotherapy or combination chemotherapy and biologics will also be eligible for inclusion. We plan to recruit a diverse sample of patients (n = 25), reflecting at least three patients of age > 65 years, at least three patients from racial/ethnic minority groups and a balanced gender distribution.[17] Patients will be invited by their oncologist providers to participate in the study based on the following published clinical criteria: 1) baseline co-morbidities that increase risk of chemotherapy adverse events, 2) provider-identified social barriers to care, 3) inability to tolerate oral intake or ailment sufficient, 4) high tumor burden, 5) high levels of psychosocial distress or multiple symptomatic complaints, 6) recent emergency room visits or hospitalizations, defined as within the preceding six months, 7) recent dose reduction with initial antineoplastic treatment, and 8) combined modality therapy e.g. chemoradiation.[37]

Exclusions

Patients receiving investigational new drug treatments (i.e. not yet FDA approved) or concurrently enrolled in a phase 1 clinical trials will be excluded due to the associated structured reporting and regulatory requirements. Patients with a requirement for inpatient infusion (i.e. CAR-T cell therapy), living in institutional settings (i.e. prison), with a history of dementia, physical disability or neurological deficits that prohibit their ability to report symptom burden will also be excluded. These disabilities include but are not limited to severe visual, hearing or cognitive impairments which prevent a patient from using the tablets and biometric devices, and an inability to stand that would prevent them from using the weight scale. Patients may participate if they do not have a caregiver or if their caregiver declines participation. Caregivers will participate only with consent of the patient.

RPM Intervention

Eligible patients will be provided with an orientation on the Vivify platform for RPM program (VivifyHealth, Plano, TX) that outlines program goals, proper use of the equipment, and technical instructions for self-reporting. The process for identifying of eligible patients, patient and caregiver education, study consent,

and RPM training materials will be implemented in a contactless fashion via electronic medical record-enabled Zoom videoconferencing (Figure 1). The "teach-back" method will be used to ensure patient understanding.[38] The Vivify platform is HIPAA-compliant, FDA-registered as a Class 1 Medical Device Data System that is commercially available and allows for transmission of biometric data to MDACC's patient call center (*askMDAnderson*), staffed by a dedicated team of oncology trained nurses and advanced care practitioners (i.e. nurse practitioners and physician assistants). These clinicians have received additional training in the assessment and management of advanced cancer symptoms as well as the Vivify platform used in this study.

The Vivify platform includes a set of wireless, Bluetooth-connected biometric devices that are provided to patients, including a scale, blood pressure cuff, pulse oximeter, thermometer, and tablet computer loaded with the Vivify mobile application and a measure of frequency and severity of twelve treatment-related symptoms (i.e., appetite loss, nausea, vomiting, cough, constipation, hot flashes, diarrhea, dyspnea, pain, neuropathy, fatigue, and dysuria).[19,39,40] Furthermore, if necessary, an internet hot-spot also will be provided. Consistent with our decentralized study design, these devices will be delivered directly to patients by mail from Vivify.[34] Vivify will also be responsible for troubleshooting technical problems. The Vivify RPM biometric devices and tablet are comparable to commercially available devices that can be purchased by consumers. At the time of study completion, the kits will be picked up from the patient's home by Vivify. Patients will be asked to take one reading per day (Monday through Friday) with each device, and to complete one symptom assessment per day (Monday through Friday) via the tablet. Weight assessments will be performed weekly. Study staff will monitor completion of daily device usage and ePRO completion via the Vivify dashboard and will contact patients to address potential technical issues if 3 or more days of data are missing. In our previous studies, this "digital navigation" approach has resulted in early resolution of technical problems and improved data collection.[41]

As part of the informed consent and study onboarding process, patients will be asked to follow instructions for proactively seeking medical care that have been provided as part of patient education and by

their health care team, and not to rely on any feedback received as a result of data submitted through the Vivify platform.

The Vivify platform supports the creation of algorithms to detect vital signs or symptom PROs that exceed predetermined threshold values. Biometric or PRO data that exceed pre-specified threshold values will generated an alert email to the *askMDAnderson* staff (Table 1).[19] Our self-reporting system for symptom burden will be adapted from the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) pertaining to the following common symptoms encountered during chemotherapy: constipation, diarrhea, fatigue, dry mouth, decreased appetite, difficulty swallowing, nausea, pain, vomiting. These symptoms are graded on a 0 (non-present) to 4 (very severe) and the corresponding alert will be triggered by absolute values of greater than or equal to 2 (Table 1).

The alerts, based on biometric and/or ePRO data, will also be transmitted in near real-time a secure, HIPAA-compliant Web dashboard that is accessible to *askMDAnderson* staff. Upon receipt of an alert email, the *askMDAnderson* staff will review the data via the Vivify dashboard and will provide follow-up and referral as clinically appropriate, using National Comprehensive Cancer Network (NCCN) symptom management guidelines as a point of reference for non-pharmacologic recommendations.[42,43] The Vivify platform is fully integrated with MDACC's electronic medical record (EMR) (Epic, Madison, WI), allowing the primary clinical team to also have access to the patient-reported data. Lastly, the end-user license agreement (EULA) associated with the Vivify device and study consent documents will reinforce that patients should not substitute the RPM program with the need to notify their care team if they are experiencing concerning symptoms. Following the initiation of a severe symptom alert, this message will appear on the Vivify platform: "*The Chemo Remote Monitoring Program hours are 8 a.m. to 8 p.m., Monday through Friday. If you are concerned, need assistance after hours, or feel that the symptoms are worsening, please contact your primary oncologist office or go to your local emergency room. In case of an emergency, call 911".*

Table 1: Threshold values for alerts on RPM platform

Biometric variable	**Medium trigger**	**High trigger**
BP Systolic (hypertension) Systolic (hypotension) Diastolic (hypertension) Diastolic (hypotension)	155- 179 90-99 101-109 None	>=180 <=89 >110 None
Oxy sat	<94%	<90%
HR Bradycardia Tachycardia	 None None	 <55 >110
Finger stick	<70, >120	<55, > 150
Temp	>100.5,	>102
Weight	None	Loss of 10 lbs
PRO Measure for Symptom burden	**Medium trigger**	**High trigger**
PRO-CTCAE value	2	>3 or increase by more than 2 points from prior value

PRO: Patient-reported outcome, BP: Blood pressure; HR: Heart rate; CTCAE: Common Terminology Criteria for Adverse Events

Data Collection

Using a combination of data abstraction from the electronic medical record by the study team and patient feedback via surveys, we hope to collect the following information:

1) Patient demographics - age, race, sex, presence of caregiver, and marital status

2) Clinical information – cancer histology, stage, location, chemotherapy regimen, line of chemotherapy, Eastern Cooperative Oncology Group (ECOG) status

3) Implementation and feasibility measures as outlined above i.e., consent rate, AIM, FIM, IAM, perceived effectiveness rating, and SUS score.

All data points will be collated and stored on a REDCap (Research Electronic Data CAPture) database. REDCap is a secure web application that is widely used in health services research. It is able to support the administration of surveys, data export from external sources such as an EMR, and provides a user-friendly interface for data entry.[44]

Data analysis plan

Descriptive statistics (e.g., means, medians, numbers, percentages, ranges, and standard deviations) for demographic and clinical characteristics of participants will be reported. Response rates (i.e., completion of required assessments), most frequent symptoms, proportion of actioned alerts will also be described. Graphical methods (e.g., boxplots and histograms) will also be employed to examine the distributions of outcome measures. By design, the present pilot study is not intended or powered to determine the efficacy of RPM in the outpatient management of treatment-related symptoms. This important scientific question will be addressed with our planned RCT. Our anticipated sample size of 25 will allow us to be relatively precise in our conclusions with respect to continuous implementation outcomes (FIM, AIM, IAM) and also facilitate preliminary estimates for our larger trial. All data analysis will be carried out with SAS statistical software (SAS Institute Inc, Cary, NC, USA).

Patient and public involvement

The research team has engaged with the Patient and Family Advisory Council (PFAC) during the conceptualization and design phase of our pilot. Specifically, they provided timely guidance on the patient-centeredness of our research methods and the ways in which our anticipated pilot study results were meaningful. PFAC members also provided information on the acceptability and feasibility of our schedule for patient self-reporting of PROs and biometric data i.e., daily Monday through Friday. PFAC is a unique program comprised of patients, survivors, and caregivers, it serves as the patients' "voice" for institutional committees, operational projects, and department-level initiatives. The PFAC will be retained in an advisory capacity for the duration of both the pilot and subsequent RCT. PFAC members were not directly involved in study conduct or

patient recruitment. Given our implementation focus, we do not intend to distribute pilot study results to participants. The study leadership team (Drs Offodile and Peterson) plan to meet with the PFAC two to three times a year to review and iterate study plans and seek feedback with respect long-term sustainability and implementation of RPM at MDACC.

Experience design

We utilized a human-centered design thinking approach to anticipate the needs of our patients and created end-to-end experiential touchpoints that would enable a seamless experience on the program.

ETHICS AND DISSEMINATION

All study documents (i.e., protocol, consent, educational materials) have been approved by the MDACC Institutional Review Board. Patients will be informed that their participation is completely voluntary and that there will receive no compensation. They will also be assured that they will receive standard-of-care and shall be exposed to no negative consequences as a result of either their participation or refusal. All patients will be able to opt out of the study at any time and for any reason. We anticipate dissemination of our pilot and subsequent effectiveness trial results via presentations at national conferences and peer-reviewed publications in the relevant medical journals. No patient identifying information will be used in the publication of findings.

PROTECTION AGAINST RISKS TO PATIENT SAFETY

The present pilot study is of minimal risk to patients. We will use validated survey questionnaires, the content of which are not sensitive in nature. It is possible that our remote monitoring devices may incite anxiety, annoyance or distress in patients. However, we believe that the possibility of such adverse events is minimal. To reduce this risk of distress, during the onboarding and consent process, patients will be instructed to a) not substitute routine medical care with the device readings and b) contact their primary oncology care team if at any point they feel concern or worry. Furthermore, all patients will receive standard chemotherapy education, which includes explicit guidance as to when to seek urgent medical care. The Vivify devices are FDA approved, HIPAA-compliant, commercially available, and meet the highest standards of protecting patient privacy. All data

transmission will leverage standard encryption and security protocols. Vivify will not participate in the study design, patient recruitment, data interpretation, analysis, or dissemination of results. Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

All information extracted from the medical record will be entered onto coded data sheets which will be maintained on stored in approved locations. Each patient will be assigned a unique study identification number by MDACC research staff which will be programmed into the Vivify tablet and devices. Electronic data will be strictly stored only on password-protected Institutional computers, accessible only to the PI and collaborators. Only the PI and the collaborators will be participating in the collection and analysis of data. No patient identifying information will be used in presentation or publication of this material. Upon study termination, all data, questionnaires, and remaining identifiers will be banked indefinitely in REDCap according to institutional policy for future use only in IRB-approved research settings. Lastly, all study personnel will undergo the requisite human subjects research training which includes procedures for maintaining patient confidentiality.

TRIAL STATUS: Pilot study is now open and recruiting patients.

REFERENCES

1. Sirintrapun SJ, Lopez AM. Telemedicine in Cancer Care. *Am Soc Clin Oncol Educ B*. 2018; 38: 540-545

2. Hollander JE, Carr BG. Virtually Perfect? Telemedicine for Covid-19. *N Engl J Med*. 2020; 382(18): 1679-81

3. Andreu-Perez J, Leff DR, Ip HMD, Yang GZ. From Wearable Sensors to Smart Implants-Toward Pervasive and Personalized Healthcare. *IEEE Trans Biomed Eng*. 2015; 62(12): 2750-62

4. Barnett TE, Chumbler NR, Vogel WB, Beyth RJ, Qin H, Kobb R. The effectiveness of a care coordination home telehealth program for veterans with diabetes mellitus: A 2-year follow-up. *Am J Manag Care*. 2006; 12(8): 467-74

5. Louis AA, Turner T, Gretton M, Baksh A, Cleland JGF. A systematic review of telemonitoring for the management of heart failure. *Eur J Heart Fail*. 2003; 5(5): 583-90

6. Rasmussen LM, Phanareth K, Nolte H, Backer V. Internet-based monitoring of asthma: A long-term, randomized clinical study of 300 asthmatic subjects. *J Allergy Clin Immunol*. 2005; 115(6): 1137-42

7. Bartoli L, Zanaboni P, Masella C, Ursini N. Systematic review of telemedicine services for patients affected by chronic obstructive pulmonary disease (COPD). *Telemed e-Health*. 2009; 15(9): 877 - 83

8. Cleland JGF, Louis AA, Rigby AS, Janssens U, Balk AHMM. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: The Trans-European Network-Home-Care Management System (TEN-HMS) study. *J Am Coll Cardiol*. 2005; 45(10): 1654-64

9. Noel HC, Vogel DC, Erdos JJ, Cornwall D, Levin F. Home telehealth reduces healthcare costs. *Telemed e-Health*. 2004; 10(2): 170-83

10. Santamaria N, Carville K, Ellis I, Prentice J. The Effectiveness of Digital Imaging and Remote Expert Wound Consultation on Healing Rates in Chronic Lower Leg Ulcers in the Kimberley Region of Western Australia. *Prim Intent Aust J Wound Manag*. 2004; 12(2): 62-70

11. Bartoli G, Cipolletti R, Di Antonio G, et al. A convergent approach to (R)-Tiagabine by a regio- and stereocontrolled hydroiodination of alkynes. *Org Biomol Chem*. 2010; 8: 3509-17

12. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021; 71(1): 7-33

13. Rhondali W, Yennurajalingam S, Chisholm G, et al. Predictors of response to palliative care intervention for chronic nausea in advanced cancer outpatients. *Support Care Cancer*. 2013; 21(9): 2427-35

14. Tookman AJ, Jones CL, DeWitte M, Lodge PJ. Fatigue in patients with advanced cancer: A pilot study of an intervention with infliximab. *Support Care Cancer*. 2008; 16(10): 1131-40

15. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. *J Clin Oncol*. 2004; 22(17): 3485-90

16. Di Maio M, Gallo C, Leighl NB, et al. Symptomatic toxicities experienced during anticancer treatment: Agreement between patient and physician reporting in three randomized trials. *J Clin Oncol*. 2015; 33(8): 910-5

17. Wright AA, Raman N, Staples P, et al. The HOPE Pilot Study: Harnessing Patient-Reported Outcomes and Biometric Data to Enhance Cancer Care. *JCO Clin Cancer Informatics*. 2018; 2:1-12

18. Kirkova J, Walsh D, Rybicki L, et al. Symptom severity and distress in advanced cancer. *Palliat Med*. 2010; 24(3): 330-9

19. Basch E, Deal A, Kris M, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: a Randomized Controlled Trial. *J Clin Oncol*. 2016;34(6):557-565.

20. Basch EM. Overall survival results of a randomized trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA*. 2017; 318(2): 197-198.

21. Judson TJ, Bennett A V., Rogak LJ, et al. Feasibility of long-term patient self-reporting of toxicities from home via the Internet during routine chemotherapy. *J Clin Oncol*. 2013; 31(20): 2580-5

22. Absolom K, Warrington L, Hudson E, et al. Phase III Randomized Controlled Trial of eRAPID: eHealth Intervention During Chemotherapy. *J Clin Oncol*. 2021; 39(7): 734-747

23. Maguire R, Fox PA, McCann L, et al. The eSMART study protocol: A randomised controlled trial to evaluate electronic symptom management using the advanced symptom management system (ASyMS) remote technology for patients with cancer. *BMJ Open*. 2017 Jun 6; 7(5): e015016

24. Basch E, Bennett A, Pietanza MC. Use of patient-reported outcomes to improve the predictive accuracy of clinician-reported adverse events. *J Natl Cancer Inst*. 2011; 103(24): 1808-10

25. Richards HS, Blazeby JM, Portal A, et al. A real-time electronic symptom monitoring system for patients after discharge following surgery: A pilot study in cancer-related surgery. *BMC Cancer*. 2020; 20(1): 543. doi:10.1186/s12885-020-07027-5

26. Meropol NJ, Kris MG, Winer EP. The American Society of Clinical Oncology's blueprint for transforming clinical and translational cancer research. *J Clin Oncol*. 2012; 30(7): 690-1

27. American Society of Clinical Oncology. *ASCO's Blueprint for Transforming Clinical and Translational Cancer Research*. Available at: https://www.asco.org/sites/new-www.asco.org/files/content-files/research-and-progress/documents/2011-blueprint-accelerating-progress-against-cancer.pdf. Accessed August 2nd, 2021.

28. Peterson SK, Shinn EH, Basen-engquist K, et al. Identifying early dehydration risk with home-based sensors during radiation treatment: A feasibility study on patients with head and neck cancer. *J Natl Cancer Inst - Monogr*. 2013; (47): 162-68

29. Kamdar M, Centi AJ, Agboola S, et al. A randomized controlled trial of a novel artificial intelligence-based

smartphone application to optimize the management of cancer-related pain. *J Clin Oncol*. Published online 2019. doi:10.1200/jco.2019.37.15_suppl.11514

30. Moore CG, Carter RE, Nietert PJ, Stewart PW. Recommendations for planning pilot studies in clinical and translational research. *Clin Transl Sci*. 2011; 4(5): 332-37

31. Offodile AC, Aloia T. Oncology Clinical Transformation in Response to the COVID-19 Pandemic. *JAMA Heal Forum*. Published online 2020. doi:10.1001/jamahealthforum.2020.1126

32. Kadakia KT, Asaad M, Adlakha E, Overman MJ, Checka CM, Offodile AC. Virtual Clinical Trials in Oncology—Overview, Challenges, Policy Considerations, and Future Directions. *JCO Clin Cancer Informatics*. 2021; 5: 421-425

33. Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. *J Natl Cancer Inst*. 2019; 111(3): 245-55

34. Kadakia KT, Halperin DM, Offodile AC. Operationalizing Virtual Trials in Oncology—From Aspiration to Action. *JCO Clin Cancer Informatics*. 2021; 5:953-957

35. Weiner BJ, Lewis CC, Stanick C, et al. Psychometric assessment of three newly developed implementation outcome measures. *Implement Sci*. 2017; 12(1): 108doi:10.1186/s13012-017-0635-3

36. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. *Int J Hum Comput Interact*. Published online 2008. doi:10.1080/10447310802205776

37. Daly B, Kuperman G, Zervoudakis A, et al. InSight Care Pilot Program: Redefining Seeing a Patient. *JCO Oncol Pract*. 2020; 16(10): e1050-1059

38. White M, Garbez R, Carroll M, Brinker E, Howie-Esquivel J. Is “teach-back” Associated with knowledge

retention and hospital readmission in hospitalized heart failure patients? *J Cardiovasc Nurs*. 2013; 28(2): 137-46

39. Daly B, Gorenshteyn D, Nicholas KJ, et al. Building a Clinically Relevant Risk Model: Predicting Risk of a Potentially Preventable Acute Care Visit for Patients Starting Antineoplastic Treatment. *JCO Clin Cancer Informatics*. 2020; 4: 275-289

40. Daly B, Nicholas K, Gorenshteyn D, et al. Misery Loves Company: Presenting Symptom Clusters to Urgent Care by Patients Receiving Antineoplastic Therapy. *J Oncol Pract*. 2018; 14(8): e484 - e495

41. Offodile AC, Seitz AJ, Peterson SK. Digital Health Navigation: An Enabling Infrastructure for Optimizing and Integrating Virtual Care Into Oncology Practice. *JCO Clin Cancer Informatics*. 2021; 5: 1151-54

42. Vidall C, Dielenseger P, Farrell C, et al. Evidence-based management of chemotherapy-induced nausea and vomiting: A position statement from a European cancer nursing forum. *Ecancermedicalscience*. Published online 2011. doi:10.3332/ecancer.2011.211

43. NCCN. National Comprehensive Cancer Network (NCCN) Guidelines for Supportive Care. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#supportive. Accessed April 1, 2021.

44. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42 (2): 377-81

FIGURE 1: Process map of workflow for decentralized remote patient monitoring pilot study

ACKNOWLEDGMENTS: The authors are very grateful to all the clinicians and advance practice providers in the gastrointestinal and thoracic medical oncology clinics who have been critical to this pilot study (patient recruitment, providing feedback on protocol elements, assisting with patient education). We also thank members of the PFAC at MDACC for their dedicated support to this program.

CONTRIBUTORSHIP STATEMENT: ACO, DD, SJ, MO and SP developed the initial pilot study concept. ACO, SD, SJ, JF, DD, MO, SP assisted with the study design. CM and ED contributed to drafting the protocol. SS provided oversight of the analytical plan. All authors made critical revisions to the manuscript. ACO is the principal Investigator and assumes final responsibility for all aspects of trial design, the protocol, and the trial conduct. All authors have read and approved this manuscript

FUNDING STATEMENT: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT: The authors declare that they have no competing interests.

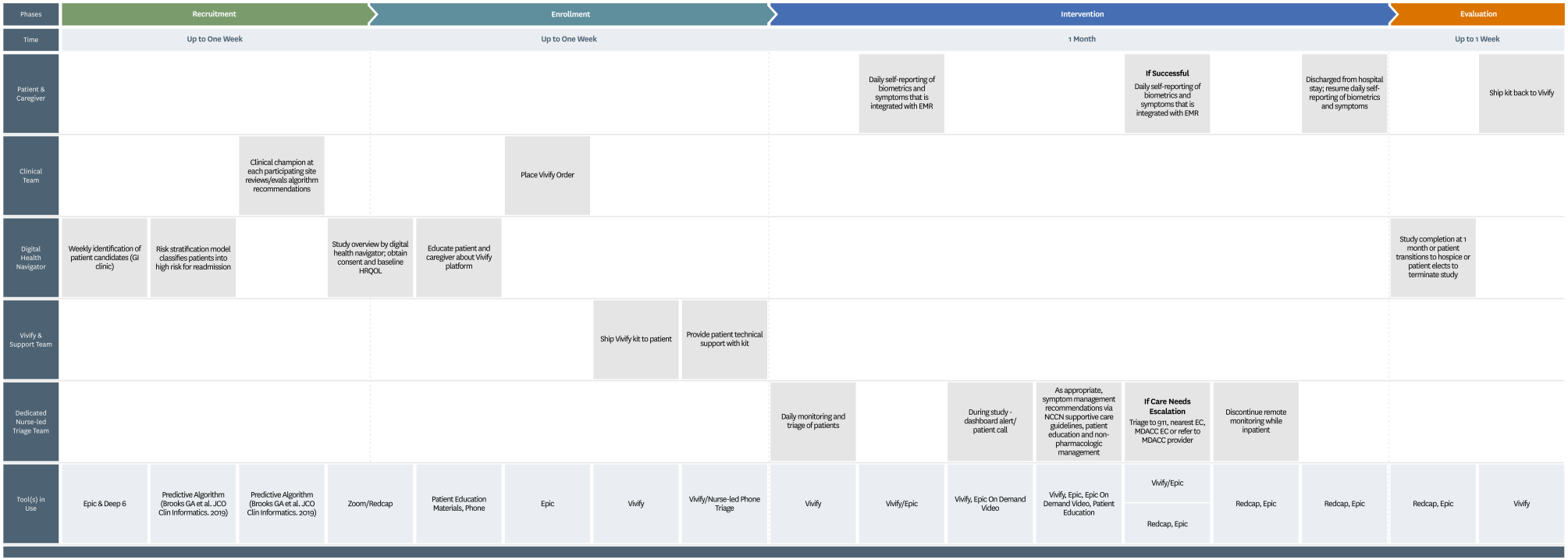
WORD COUNT: 3380

REMOTE PATIENT MONITORING PROGRAM

SERVICE DELIVERY PROCESS DIAGRAM

Last updated: 02.02.2022

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Location (page)	Section/item	ItemNo	Description
	Administrative information		
1	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
3	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
		2b	All items from the World Health Organization Trial Registration Data Set
3	Protocol version	3	Date and version identifier
22	Funding	4	Sources and types of financial, material, and other support
1	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
2		5b	Name and contact information for the trial sponsor
NA		5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
NA		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
5	**Introduction**		
5	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
6-8		6b	Explanation for choice of comparators

7-8	Objectives	7	Specific objectives or hypotheses
8	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
	Methods: Participants, interventions, and outcomes		
8	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
8-9	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
9-11	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
10		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
10		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
10-11		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
7-8	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Fig 1	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

7, 13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
NA	**Methods: Assignment of interventions (for controlled trials)**		
	Allocation:		
NA	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
NA	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
NA	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
NA	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
NA		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
12	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
12, 13		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
13	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

13	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
13		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
NA		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
NA	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
NA		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
14	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
NA	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
3,14	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
NA	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
7	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
NA		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

13,15	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
22	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
NA	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
3, 14	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
NA		31b	Authorship eligibility guidelines and any intended use of professional writers
NA		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
	Appendices		
Appendix 1	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
NA	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Active Surveillance of Chemotherapy-Related Symptom Burden in Ambulatory Cancer Patients via the Implementation of Electronic Patient Reported Outcomes and Sensor-enabled Vital Signs Capture – Protocol for a Decentralized Feasibility Pilot Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057693.R2
Article Type:	Protocol
Date Submitted by the Author:	01-Mar-2022
Complete List of Authors:	Offodile, Anaeze ; The University of Texas MD Anderson Cancer Center, Institute for Cancer Care Innovation; The University of Texas MD Anderson Cancer Center, Department of Plastic and Reconstructive Surgery DiBrito, Sandra; The University of Texas MD Anderson Cancer Center, Division of Surgical Oncology Finder, Janice; The University of Texas MD Anderson Cancer Center, Patient Experience Clinical Programs Shete, Sanjay; The University of Texas MD Anderson Cancer Center, Department of Biostatistics Jain, Sanchita; The University of Texas MD Anderson Cancer Center, Office of the Chief Delgado, Domenica; The University of Texas MD Anderson Cancer Center, Office of the Chief Miller, Christopher; The University of Texas MD Anderson Cancer Center, Department of Behavioral Science Davidson, Elenita; The University of Texas MD Anderson Cancer Center, Department of Behavioral Science Overman, MJ; The University of Texas MD Anderson Cancer Center, Department of Gastrointestinal Medical Oncology Peterson, Susan; The University of Texas MD Anderson Cancer Center, Department of Behavioral Science
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Patient-centred medicine, Health informatics, Health services research
Keywords:	CHEMOTHERAPY, Adult oncology < ONCOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

Active Surveillance of Chemotherapy-Related Symptom Burden in Ambulatory Cancer Patients via the Implementation of Electronic Patient Reported Outcomes and Sensor-enabled Vital Signs Capture – Protocol for a Decentralized Feasibility Pilot Study

Anaeze C. Offodile II MD MPH[1,2,3] Sandra R. DiBrito MD PhD,[4] Janice P Finder MSN,[5] Sanjay Shete PhD MPhil,[6] Sanchita Jain MBA,[7] Domenica Delgado MBA,[7] Christopher Miller,[8] Elenita Davidson,[8] Michael J. Overman MD,[9] Susan Peterson PhD MPH[8]

Affiliations:

1. Institute for Cancer Care Innovation, The University of Texas MD Anderson Cancer Center, Houston TX
2. Department of Plastic and Reconstructive Surgery, The University of Texas MD Anderson Cancer Center, Houston TX
3. Baker Institute for Public Policy, Rice University, Houston, TX
4. Division of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston TX
5. Patient Experience Clinical Programs, The University of Texas MD Anderson Cancer Center, Houston TX
6. Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston TX
7. Office of the Chief, Data and Technology Office, The University of Texas MD Anderson Cancer Center, Houston TX
8. Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, Houston TX
9. Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston TX

Corresponding author:

Anaeze C. Offodile II MD MPH

University of Texas MD Anderson Cancer Center, Houston TX

1400 Pressler Street, Unit #1488

Houston, TX 77030

Email: acoffodile@mdanderson.org

Introduction: Remote patient monitoring (RPM) has emerged as a potential avenue for optimizing the management of symptoms in patients undergoing chemotherapy. However, RPM is a complex, multi-level intervention with technology, workflow, contextual and patient experience components. The purpose of this pilot study is to determine the feasibility of protocol implementation with respect to decentralized recruitment, patient retention, adherence to reporting recommendations, RPM platform usability and patient experience in ambulatory cancer patients at high risk for chemotherapy-related symptoms.

Methods and Analysis: This protocol describes a single-arm decentralized feasibility pilot study of technology-enhanced outpatient symptom management system in patients with gastrointestinal and thoracic cancer receiving chemotherapy and cancer care at a single site (MD Anderson Cancer Center, Houston Texas). An anticipated total of 25 patients will be recruited prior to the initiation of chemotherapy and provided a set of validated questionnaires at enrollment and after our one-month feasibility pilot trial period. Our intervention entails the self-reporting of symptoms and vital signs via a HIPAA-compliant, secure tablet interface that also enables a) the provision of self-care materials to patients, b) generation of threshold alerts to a dedicated call-center, and c) video-conferencing. Vital sign information (heart rate, blood pressure, pulse, oxygen saturation, weight, and temperature) will be captured via Bluetooth-enabled biometric monitoring devices which are integrated with the tablet interface. Protocolized triage and management of symptoms will occur in response to the alerts. Feasibility and acceptability metrics will characterize our recruitment process, protocol adherence, patient retention, and usability of the RPM platform. We will also document the perceived effectiveness of our intervention by patients.

Ethics and Dissemination: This study has been granted approval by the institutional review board of MD Anderson Cancer Center. We anticipate dissemination of our pilot and subsequent effectiveness trial results via presentations at national conferences and peer-reviewed publications in the relevant medical journals. Our results will also be made available to cancer survivors, their caregivers and hospital administration.

Trial Registration: NCI-2021-07464; pre-results; 2-14-2022

Strengths and Limitations of This Study

- The present pilot study will allow researchers to delineate the feasibility of recruitment, acceptability, and implementation of a remote patient monitoring platform for the active surveillance of and early intervention for chemotherapy-related symptoms.
- The study is limited to patients with gastrointestinal and thoracic cancers, so the results may not be generalizable to other solid organ or hematogenous cancers.
- The study is limited to patients at a single, high volume institution, which may limit the generalizability of the outcomes with regard to smaller hospitals and care systems.
- The study has been designed to include a diverse patient population, with respect to age, gender and race, which should allow the feasibility results to be generalized to a broad demographic of patients within gastrointestinal and thoracic cancers.

INTRODUCTION

The motivation for applying telemedicine and digital health tools in oncology has been evident for several years.[1] However, their potential to transform clinical care is now beginning to be realized, partly due to the unparalleled scope of the SARS-CoV2 pandemic and need to maintain continuity of care within the context of quarantine and self-isolation.[2] Technologies now in use include remote patient monitoring (RPM), apps, wearables, and chatbots among others.[3] RPM characterizes the real-time acquisition and transmission of health-related data using home-based, sensor-enabled digital monitoring devices and mobile applications to assess vital signs, symptoms and other health-related outcomes.[3] RPM has been successfully leveraged for the outpatient management of several chronic conditions including diabetes, heart failure, chronic wounds and chronic obstructive pulmonary disease.[4–7] RPM implementation in these clinical settings have been associated with reduced emergency room (ER) utilization, improved quality-of-life, reduced healthcare spending and better symptom control. [8–11]

Although overall mortality from cancer is declining,[12] patients with cancer still face debilitating physical and psychosocial treatment side-effects including fatigue, myalgias, pain, shortness of breath, sleep disturbance and depression.[13,14] Unfortunately, clinicians often fail to recognize the incidence and severity of chemotherapy-induced symptoms, even in instances that mandate the reporting of treatment toxicities.[15–17] Poor symptom management is associated with increased healthcare spending, and worse quality of life, clinical outcomes, and overall survival.[9,18–20] This has led to considerable interest in leveraging symptom self-reporting during ambulatory cancer care. Pioneering work by Basch et al. identified statistically significant reductions in ER utilization, chemotherapy disruptions, and gains in quality-adjusted survival.[21] A recent phase III randomized controlled trial by Absolom et al. identified improved physical well-being (6 and 12 weeks) and self-efficacy (18 weeks) among patients with breast, colorectal, or gynecological cancers that were exposed to electronic self-reporting of symptoms during cancer treatment.[22] Of note, there were no associated improvements in treatment delays, dose reductions, chemotherapy drug changes, or hospital admissions in the treatment

group.[22]

However, despite evidence of RPM effectiveness, systematic approaches for symptom assessment, patient-provider communication, and early intervention are still lacking.[23] This is largely because the full integration of ePROs with a health system's medical record and clinical informatics platform has not been widespread.[24] As a result, clinicians do not have "real time" access to patient generated- health data (e.g. vitals signs and ePROs) and the prevailing care model for treatment-toxicities is largely patient-initiated and reactive i.e. unable to proactively monitor and mitigate symptom burden before they escalate.[25] RPM-enabled *digital touch points* can reassure patients that their treatment team is connected to them and informed about all aspects of their disease course. Furthermore, the American Society of Oncology (ASCO) has strongly advocated for the increased integration of standardized personal health information (e.g. demographics, health status, treatment status, side effects, and symptoms) in real time into routine inpatient and outpatient patient care.[26,27] Unfortunately, the evidence for RPM efficacy in oncology is limited and most studies have excluded the caregivers' experiences and involvement, which is not a realistic representation of the utility of remote monitoring in the oncology population.[28,29]

We posit that the implementation of a RPM platform that facilitates electronic patient-reported outcomes (ePRO) capture and protocolized, point-in-time vital sign measurements has the potential to enhance real-time clinical decision-making, improve health related quality-of-life, lower symptom burden, mitigate treatment delays, and engender greater patient engagement. Additionally, moving from an episodic care model to a more continuous care model has the potential of improving patient experience. At MD Anderson Cancer Center (MDACC), we have developed a technology and operational infrastructure for remotely monitoring chemotherapy symptoms in-between clinic visits. It entails the active surveillance of patient-reported biometrics (heart rate, blood pressure, temperature, oxygen saturation, and weights) and adverse events (PRO-CTCAE) by advanced care practitioners (i.e., nurse practitioners), guided by backend threshold alerts for both vitals and ePROs. Automated self-care advice for patients and caregivers is also delivered across the platform. In this work,

we articulate our framework for the development and pilot-testing of an RPM platform, for the active surveillance of treatment-related symptoms, in patients with gastrointestinal and thoracic cancers who are receiving neoadjuvant or adjuvant chemotherapy in the ambulatory setting.[30] Lastly, the evolving COVID-19 pandemic has also catalyzed greater awareness and implementation of decentralized clinical trials in the life sciences sector.[31] This paradigm shift is in response to pandemic-related regulatory waivers for trial conduct, a need to preserve the availability of personnel protective equipment for hospital staff, and an acknowledgment of the high cost structure and limited patient access in traditional "brick and mortar" trial infrastructure.[31–33] We will also use the proposed pilot study to develop and implement a decentralized or virtual workflow for patient recruitment, education about the RPM platform, enrollment, symptom monitoring, and study completion (Figure 1).[34]

AIMS

Primary aims **-** The primary aim of this external pilot study is to investigate the feasibility of protocol implementation (i.e., recruitment process, evaluation of eligibility criteria, assessment of usability of technology platform) prior to a non-blinded, randomized controlled trial of the effectiveness of technology-enhanced (i.e. RPM with ePRO capture) outpatient management of treatment-related symptoms. Our *a priori* specified feasibility objectives are as follows:

1) Patient eligibility and recruitment – Defined as an approach-to-consent rate of > 60% among eligible patients (i.e., enrollment rate). 2 patients per month, on average, should be consented into the program.

2) Adherence – Defined as > 70% adherence with PRO-CTCAE surveys $\geq$ 4 days per week and > 80% adherence to biometrics reporting $\geq$ 4 days per week.

3) Implementation outcomes – The feasibility, acceptability, and appropriateness of our intervention will be assessed via the following validated 4-item psychometric tools: FIM ("Feasibility of Intervention Measure"), AIM ("Acceptability of Intervention Measure"), and IAM ("Intervention Appropriateness Measure").[35] Each item is scored on a 5-point Likert scale (completely disagree to completely agree) and our pilot will be considered

successful if the calculated mean scores for each of the implementation measures is > 3.[35]

4) Feasibility outcomes – We will monitor the generation of an alert (red or yellow) after an abnormal vital sign or self-reporting of a severe symptom burden. We will also record the number of adverse events related to the use of the biometric devices i.e., blood pressure cuff, weight scale, thermometer etc. Lastly, we will track the clinical action that is associated with an alert generation e.g., phone consultation, video visit, care escalation to the emergency room.

Secondary aims – Following completion of the one-month pilot reporting period, participants will also be invited to share their experiences with our RPM platform through the use of questionnaires.

1) Perceived effectiveness – Participating patients will be asked to respond to the following two questions: "I found the remote monitoring system helped me manage my symptoms" and "I found that this remote monitoring system helped me better communicate with my care team".[17] Responses will be graded according to a Likert scale (1-5) based on these responses: "strongly disagree", "disagree", "neither agree nor disagree", "agree", "strongly agree".

2) Usability – The validated symptom usability scale (SUS) will be provided to patients to assess usability of the RPM platform.[36] The scale is a reliable tool that consists of 10-questions regarding the usability of an electronic or technology system. Responses are on a 5-point Likert scale (1-5) and our RPM platform will be considered usable if the mean score is greater than 68, concordant with published work.

METHODS AND ANALYSIS

Setting, Patient Population and Eligibility Criteria

This will be a single-arm, single-institution pilot study in the gastrointestinal and thoracic medical oncology clinic at MD Anderson Cancer Center. Patient enrollment began on July 1st 2021 and is anticipated to conclude by March 25th, 2022. We will approach English-fluent adults (≥18 years) with gastrointestinal (stomach, liver, gallbladder, bile duct, pancreas, small bowel, appendix, colon, rectum, and anal) and thoracic (esophageal and lung) cancers who are scheduled to initiate or continue outpatient chemotherapy at The University of Texas

MD Anderson Cancer Center in Houston, Texas. There will be no restrictions or exclusions applied based on underlying tumor histology. Patients on combination chemotherapy and immunotherapy or combination chemotherapy and biologics will also be eligible for inclusion. We plan to recruit a diverse sample of patients (n = 25), reflecting at least three patients of age > 65 years, at least three patients from racial/ethnic minority groups and a balanced gender distribution.[17] Patients will be invited by their oncologist providers to participate in the study based on the following published clinical criteria: 1) baseline co-morbidities that increase risk of chemotherapy adverse events, 2) provider-identified social barriers to care, 3) inability to tolerate oral intake or ailment sufficient, 4) high tumor burden, 5) high levels of psychosocial distress or multiple symptomatic complaints, 6) recent emergency room visits or hospitalizations, defined as within the preceding six months, 7) recent dose reduction with initial antineoplastic treatment, and 8) combined modality therapy e.g. chemoradiation.[37]

Exclusions

Patients receiving investigational new drug treatments (i.e. not yet FDA approved) or concurrently enrolled in a phase 1 clinical trials will be excluded due to the associated structured reporting and regulatory requirements. Patients with a requirement for inpatient infusion (i.e. CAR-T cell therapy), living in institutional settings (i.e. prison), with a history of dementia, physical disability or neurological deficits that prohibit their ability to report symptom burden will also be excluded. These disabilities include but are not limited to severe visual, hearing or cognitive impairments which prevent a patient from using the tablets and biometric devices, and an inability to stand that would prevent them from using the weight scale. Patients may participate if they do not have a caregiver or if their caregiver declines participation. Caregivers will participate only with consent of the patient.

RPM Intervention

Eligible patients will be provided with an orientation on the Vivify platform for RPM program (VivifyHealth, Plano, TX) that outlines program goals, proper use of the equipment, and technical instructions for

self-reporting. The process for identifying of eligible patients, patient and caregiver education, study consent, and RPM training materials will be implemented in a contactless fashion via electronic medical record-enabled Zoom videoconferencing (Figure 1). The "teach-back" method will be used to ensure patient understanding.[38] The Vivify platform is HIPAA-compliant, FDA-registered as a Class 1 Medical Device Data System that is commercially available and allows for transmission of biometric data to MDACC's patient call center (*askMDAnderson*), staffed by a dedicated team of oncology trained nurses and advanced care practitioners (i.e. nurse practitioners and physician assistants). These clinicians have received additional training in the assessment and management of advanced cancer symptoms as well as the Vivify platform used in this study.

The Vivify platform includes a set of wireless, Bluetooth-connected biometric devices that are provided to patients, including a scale, blood pressure cuff, pulse oximeter, thermometer, and tablet computer loaded with the Vivify mobile application and a measure of frequency and severity of twelve treatment-related symptoms (i.e., appetite loss, nausea, vomiting, cough, constipation, hot flashes, diarrhea, dyspnea, pain, neuropathy, fatigue, and dysuria).[19,39,40] Furthermore, if necessary, an internet hot-spot also will be provided. Consistent with our decentralized study design, these devices will be delivered directly to patients by mail from Vivify.[34] Vivify will also be responsible for troubleshooting technical problems. The Vivify RPM biometric devices and tablet are comparable to commercially available devices that can be purchased by consumers. At the time of study completion, the kits will be picked up from the patient's home by Vivify. Patients will be asked to take one reading per day (Monday through Friday) with each device, and to complete one symptom assessment per day (Monday through Friday) via the tablet. Weight assessments will be performed weekly. Study staff will monitor completion of daily device usage and ePRO completion via the Vivify dashboard and will contact patients to address potential technical issues if 3 or more days of data are missing. In our previous studies, this "digital navigation" approach has resulted in early resolution of technical problems and improved data collection.[41]

As part of the informed consent (supplemental file) and study onboarding process, patients will be

asked to follow instructions for proactively seeking medical care that have been provided as part of patient education and by their health care team, and not to rely on any feedback received as a result of data submitted through the Vivify platform.

The Vivify platform supports the creation of algorithms to detect vital signs or symptom PROs that exceed predetermined threshold values. Biometric or PRO data that exceed pre-specified threshold values will generated an alert email to the *askMDAnderson* staff (Table 1).[19] Our self-reporting system for symptom burden will be adapted from the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) pertaining to the following common symptoms encountered during chemotherapy: constipation, diarrhea, fatigue, dry mouth, decreased appetite, difficulty swallowing, nausea, pain, vomiting. These symptoms are graded on a 0 (non-present) to 4 (very severe) and the corresponding alert will be triggered by absolute values of greater than or equal to 2 (Table 1).

The alerts, based on biometric and/or ePRO data, will also be transmitted in near real-time a secure, HIPAA-compliant Web dashboard that is accessible to *askMDAnderson* staff. Upon receipt of an alert email, the *askMDAnderson* staff will review the data via the Vivify dashboard and will provide follow-up and referral as clinically appropriate, using National Comprehensive Cancer Network (NCCN) symptom management guidelines as a point of reference for non-pharmacologic recommendations.[42,43] The Vivify platform is fully integrated with MDACC's electronic medical record (EMR) (Epic, Madison, WI), allowing the primary clinical team to also have access to the patient-reported data. Lastly, the end-user license agreement (EULA) associated with the Vivify device and study consent documents will reinforce that patients should not substitute the RPM program with the need to notify their care team if they are experiencing concerning symptoms. Following the initiation of a severe symptom alert, this message will appear on the Vivify platform: "*The Chemo Remote Monitoring Program hours are 8 a.m. to 8 p.m., Monday through Friday. If you are concerned, need assistance after hours, or feel that the symptoms are worsening, please contact your primary oncologist office or go to your local emergency room. In case of an emergency, call 911".*

Table 1: Threshold values for alerts on RPM platform

Biometric variable	**Medium trigger**	**High trigger**
BP Systolic (hypertension)	155- 179	>=180
Systolic (hypotension)	90-99	<=89
Diastolic (hypertension)	101-109	>110
Diastolic (hypotension)	None	None
Oxy sat	<94%	<90%
HR		
Bradycardia	None	<55
Tachycardia	None	>110
Finger stick	<70, >120	<55, > 150
Temp	>100.5,	>102
Weight	None	Loss of 10 pounds
PRO Measure for Symptom burden	**Medium trigger**	**High trigger**
PRO-CTCAE value	2	>3 or increase by more than 2 points from prior value

PRO: Patient-reported outcome, BP: Blood pressure; HR: Heart rate; CTCAE: Common Terminology Criteria for Adverse Events

Data Collection

Using a combination of data abstraction from the electronic medical record by the study team and patient feedback via surveys, we hope to collect the following information:

1) Patient demographics - age, race, sex, presence of caregiver, and marital status

2) Clinical information – cancer histology, stage, location, chemotherapy regimen, line of chemotherapy, Eastern Cooperative Oncology Group (ECOG) status

3) Implementation and feasibility measures as outlined above i.e., consent rate, AIM, FIM, IAM, perceived effectiveness rating, and SUS score.

All data points will be collated and stored on a REDCap (Research Electronic Data CAPture) database. REDCap is a secure web application that is widely used in health services research. It is able to support the administration of surveys, data export from external sources such as an EMR, and provides a user-friendly interface for data entry.[44]

Data analysis plan

Descriptive statistics (e.g., means, medians, numbers, percentages, ranges, and standard deviations) for demographic and clinical characteristics of participants will be reported. Response rates (i.e., completion of required assessments), most frequent symptoms, proportion of actioned alerts will also be described. Graphical methods (e.g., boxplots and histograms) will also be employed to examine the distributions of outcome measures. By design, the present pilot study is not intended or powered to determine the efficacy of RPM in the outpatient management of treatment-related symptoms. This important scientific question will be addressed with our planned RCT. Our anticipated sample size of 25 will allow us to be relatively precise in our conclusions with respect to continuous implementation outcomes (FIM, AIM, IAM) and facilitate preliminary estimates for our larger trial. All data analysis will be carried out with SAS statistical software (SAS Institute Inc, Cary, NC, USA).

Patient and public involvement

The research team has engaged with the Patient and Family Advisory Council (PFAC) during the conceptualization and design phase of our pilot. Specifically, they provided timely guidance on the patient-centeredness of our research methods and the ways in which our anticipated pilot study results were meaningful. PFAC members also provided information on the acceptability and feasibility of our schedule for patient self-reporting of PROs and biometric data i.e., daily Monday through Friday. PFAC is a unique program comprised of patients, survivors, and caregivers, it serves as the patients' "voice" for institutional committees, operational projects, and department-level initiatives. The PFAC will be retained in an advisory capacity for the

duration of both the pilot and subsequent RCT. PFAC members were not directly involved in study conduct or patient recruitment. Given our implementation focus, we do not intend to distribute pilot study results to participants. The study leadership team (Drs Offodile and Peterson) plan to meet with the PFAC two to three times a year to review and iterate study plans and seek feedback with respect long-term sustainability and implementation of RPM at MDACC.

Experience design

We utilized a human-centered design thinking approach to anticipate the needs of our patients and created end-to-end experiential touchpoints that would enable a seamless experience on the program.

ETHICS AND DISSEMINATION

All study documents (i.e., protocol, consent, educational materials) have been approved by the MDACC Institutional Review Board. Patients will be informed that their participation is completely voluntary and that there will receive no compensation. They will also be assured that they will receive standard-of-care and shall be exposed to no negative consequences as a result of either their participation or refusal. All patients will be able to opt out of the study at any time and for any reason. We anticipate dissemination of our pilot and subsequent effectiveness trial results via presentations at national conferences and peer-reviewed publications in the relevant medical journals. No patient identifying information will be used in the publication of findings.

PROTECTION AGAINST RISKS TO PATIENT SAFETY

The present pilot study is of minimal risk to patients. We will use validated survey questionnaires, the content of which are not sensitive in nature. It is possible that our remote monitoring devices may incite anxiety, annoyance or distress in patients. However, we believe that the possibility of such adverse events is minimal. To reduce this risk of distress, during the onboarding and consent process, patients will be instructed to a) not substitute routine medical care with the device readings and b) contact their primary oncology care team if at any point they feel concern or worry. Furthermore, all patients will receive standard chemotherapy education, which includes explicit guidance as to when to seek urgent medical care. The Vivify devices are FDA approved,

HIPAA-compliant, commercially available, and meet the highest standards of protecting patient privacy. All data transmission will leverage standard encryption and security protocols. Vivify will not participate in the study design, patient recruitment, data interpretation, analysis, or dissemination of results. Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

All information extracted from the medical record will be entered onto coded data sheets which will be maintained on stored in approved locations. Each patient will be assigned a unique study identification number by MDACC research staff which will be programmed into the Vivify tablet and devices. Electronic data will be strictly stored only on password-protected Institutional computers, accessible only to the PI and collaborators. Only the PI and the collaborators will be participating in the collection and analysis of data. No patient identifying information will be used in presentation or publication of this material. Upon study termination, all data, questionnaires, and remaining identifiers will be banked indefinitely in REDCap according to institutional policy for future use only in IRB-approved research settings. Lastly, all study personnel will undergo the requisite human subjects research training which includes procedures for maintaining patient confidentiality.

TRIAL STATUS: Pilot study is now open and recruiting patients.

REFERENCES

1. Sirintrapun SJ, Lopez AM. Telemedicine in Cancer Care. *Am Soc Clin Oncol Educ B*. 2018; 38: 540-545

2. Hollander JE, Carr BG. Virtually Perfect? Telemedicine for Covid-19. *N Engl J Med*. 2020; 382(18): 1679-81

3. Andreu-Perez J, Leff DR, Ip HMD, Yang GZ. From Wearable Sensors to Smart Implants-Toward Pervasive and Personalized Healthcare. *IEEE Trans Biomed Eng*. 2015; 62(12): 2750-62

4. Barnett TE, Chumbler NR, Vogel WB, Beyth RJ, Qin H, Kobb R. The effectiveness of a care coordination home telehealth program for veterans with diabetes mellitus: A 2-year follow-up. *Am J Manag Care*. 2006; 12(8): 467-74

5. Louis AA, Turner T, Gretton M, Baksh A, Cleland JGF. A systematic review of telemonitoring for the management of heart failure. *Eur J Heart Fail*. 2003; 5(5): 583-90

6. Rasmussen LM, Phanareth K, Nolte H, Backer V. Internet-based monitoring of asthma: A long-term, randomized clinical study of 300 asthmatic subjects. *J Allergy Clin Immunol*. 2005; 115(6): 1137-42

7. Bartoli L, Zanaboni P, Masella C, Ursini N. Systematic review of telemedicine services for patients affected by chronic obstructive pulmonary disease (COPD). *Telemed e-Health*. 2009; 15(9): 877 - 83

8. Cleland JGF, Louis AA, Rigby AS, Janssens U, Balk AHMM. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: The Trans-European Network-Home-Care Management System (TEN-HMS) study. *J Am Coll Cardiol*. 2005; 45(10): 1654-64

9. Noel HC, Vogel DC, Erdos JJ, Cornwall D, Levin F. Home telehealth reduces healthcare costs. *Telemed e-Health*. 2004; 10(2): 170-83

10. Santamaria N, Carville K, Ellis I, Prentice J. The Effectiveness of Digital Imaging and Remote Expert Wound Consultation on Healing Rates in Chronic Lower Leg Ulcers in the Kimberley Region of Western Australia. *Prim Intent Aust J Wound Manag*. 2004; 12(2): 62-70

11. Bartoli G, Cipolletti R, Di Antonio G, et al. A convergent approach to (R)-Tiagabine by a regio- and stereocontrolled hydroiodination of alkynes. *Org Biomol Chem*. 2010; 8: 3509-17

12. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021; 71(1): 7-33

13. Rhondali W, Yennurajalingam S, Chisholm G, et al. Predictors of response to palliative care intervention for chronic nausea in advanced cancer outpatients. *Support Care Cancer*. 2013; 21(9): 2427-35

14. Tookman AJ, Jones CL, DeWitte M, Lodge PJ. Fatigue in patients with advanced cancer: A pilot study of an intervention with infliximab. *Support Care Cancer*. 2008; 16(10): 1131-40

15. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. *J Clin Oncol*. 2004; 22(17): 3485-90

16. Di Maio M, Gallo C, Leighl NB, et al. Symptomatic toxicities experienced during anticancer treatment: Agreement between patient and physician reporting in three randomized trials. *J Clin Oncol*. 2015; 33(8): 910-5

17. Wright AA, Raman N, Staples P, et al. The HOPE Pilot Study: Harnessing Patient-Reported Outcomes and Biometric Data to Enhance Cancer Care. *JCO Clin Cancer Informatics*. 2018; 2:1-12

18. Kirkova J, Walsh D, Rybicki L, et al. Symptom severity and distress in advanced cancer. *Palliat Med*. 2010; 24(3): 330-9

19. Basch E, Deal A, Kris M, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: a Randomized Controlled Trial. *J Clin Oncol*. 2016;34(6):557-565.

20. Basch EM. Overall survival results of a randomized trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA*. 2017; 318(2): 197-198.

21. Judson TJ, Bennett A V., Rogak LJ, et al. Feasibility of long-term patient self-reporting of toxicities from home via the Internet during routine chemotherapy. *J Clin Oncol*. 2013; 31(20): 2580-5

22. Absolom K, Warrington L, Hudson E, et al. Phase III Randomized Controlled Trial of eRAPID: eHealth Intervention During Chemotherapy. *J Clin Oncol*. 2021; 39(7): 734-747

23. Maguire R, Fox PA, McCann L, et al. The eSMART study protocol: A randomised controlled trial to evaluate electronic symptom management using the advanced symptom management system (ASyMS) remote technology for patients with cancer. *BMJ Open*. 2017 Jun 6; 7(5): e015016

24. Basch E, Bennett A, Pietanza MC. Use of patient-reported outcomes to improve the predictive accuracy of clinician-reported adverse events. *J Natl Cancer Inst*. 2011; 103(24): 1808-10

25. Richards HS, Blazeby JM, Portal A, et al. A real-time electronic symptom monitoring system for patients after discharge following surgery: A pilot study in cancer-related surgery. *BMC Cancer*. 2020; 20(1): 543. doi:10.1186/s12885-020-07027-5

26. Meropol NJ, Kris MG, Winer EP. The American Society of Clinical Oncology's blueprint for transforming clinical and translational cancer research. *J Clin Oncol*. 2012; 30(7): 690-1

27. American Society of Clinical Oncology. *ASCO's Blueprint for Transforming Clinical and Translational Cancer Research*. Available at: https://www.asco.org/sites/new-www.asco.org/files/content-files/research-and-progress/documents/2011-blueprint-accelerating-progress-against-cancer.pdf. Accessed August 2nd, 2021.

28. Peterson SK, Shinn EH, Basen-engquist K, et al. Identifying early dehydration risk with home-based sensors during radiation treatment: A feasibility study on patients with head and neck cancer. *J Natl Cancer Inst - Monogr*. 2013; (47): 162-68

29. Kamdar M, Centi AJ, Agboola S, et al. A randomized controlled trial of a novel artificial intelligence-based

smartphone application to optimize the management of cancer-related pain. *J Clin Oncol*. Published online 2019. doi:10.1200/jco.2019.37.15_suppl.11514

30. Moore CG, Carter RE, Nietert PJ, Stewart PW. Recommendations for planning pilot studies in clinical and translational research. *Clin Transl Sci*. 2011; 4(5): 332-37

31. Offodile AC, Aloia T. Oncology Clinical Transformation in Response to the COVID-19 Pandemic. *JAMA Heal Forum*. Published online 2020. doi:10.1001/jamahealthforum.2020.1126

32. Kadakia KT, Asaad M, Adlakha E, Overman MJ, Checka CM, Offodile AC. Virtual Clinical Trials in Oncology—Overview, Challenges, Policy Considerations, and Future Directions. *JCO Clin Cancer Informatics*. 2021; 5: 421-425

33. Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. *J Natl Cancer Inst*. 2019; 111(3): 245-55

34. Kadakia KT, Halperin DM, Offodile AC. Operationalizing Virtual Trials in Oncology—From Aspiration to Action. *JCO Clin Cancer Informatics*. 2021; 5:953-957

35. Weiner BJ, Lewis CC, Stanick C, et al. Psychometric assessment of three newly developed implementation outcome measures. *Implement Sci*. 2017; 12(1): 108doi:10.1186/s13012-017-0635-3

36. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. *Int J Hum Comput Interact*. Published online 2008. doi:10.1080/10447310802205776

37. Daly B, Kuperman G, Zervoudakis A, et al. InSight Care Pilot Program: Redefining Seeing a Patient. *JCO Oncol Pract*. 2020; 16(10): e1050-1059

38. White M, Garbez R, Carroll M, Brinker E, Howie-Esquivel J. Is “teach-back” Associated with knowledge

retention and hospital readmission in hospitalized heart failure patients? *J Cardiovasc Nurs*. 2013; 28(2): 137-46

39. Daly B, Gorenshteyn D, Nicholas KJ, et al. Building a Clinically Relevant Risk Model: Predicting Risk of a Potentially Preventable Acute Care Visit for Patients Starting Antineoplastic Treatment. *JCO Clin Cancer Informatics*. 2020; 4: 275-289

40. Daly B, Nicholas K, Gorenshteyn D, et al. Misery Loves Company: Presenting Symptom Clusters to Urgent Care by Patients Receiving Antineoplastic Therapy. *J Oncol Pract*. 2018; 14(8): e484 - e495

41. Offodile AC, Seitz AJ, Peterson SK. Digital Health Navigation: An Enabling Infrastructure for Optimizing and Integrating Virtual Care Into Oncology Practice. *JCO Clin Cancer Informatics*. 2021; 5: 1151-54

42. Vidall C, Dielenseger P, Farrell C, et al. Evidence-based management of chemotherapy-induced nausea and vomiting: A position statement from a European cancer nursing forum. *Ecancermedicalscience*. Published online 2011. doi:10.3332/ecancer.2011.211

43. NCCN. National Comprehensive Cancer Network (NCCN) Guidelines for Supportive Care. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#supportive. Accessed April 1, 2021.

44. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42 (2): 377-81

FIGURE 1: Process map of workflow for decentralized remote patient monitoring pilot study

ACKNOWLEDGMENTS: The authors are very grateful to all the clinicians and advance practice providers in the gastrointestinal and thoracic medical oncology clinics who have been critical to this pilot study (patient recruitment, providing feedback on protocol elements, assisting with patient education). We also thank members of the PFAC at MDACC for their dedicated support to this program.

CONTRIBUTORSHIP STATEMENT: ACO, DD, SJ, MO and SP developed the initial pilot study concept. ACO, SD, SJ, JF, DD, MO, SP assisted with the study design. CM and ED contributed to drafting the protocol. SS provided oversight of the analytical plan. All authors made critical revisions to the manuscript. ACO is the principal Investigator and assumes final responsibility for all aspects of trial design, the protocol, and the trial conduct. All authors have read and approved this manuscript

FUNDING STATEMENT: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT: The authors declare that they have no competing interests.

WORD COUNT: 3383

REMOTE PATIENT MONITORING PROGRAM

SERVICE DELIVERY PROCESS DIAGRAM

Last updated: 02.02.2022

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Phases	Recruitment			Enrollment			Intervention							Evaluation	
Time	Up to One Week			Up to One Week			1 Month							Up to 1 Week	
Patient & Caregiver							Daily self-reporting of biometrics and symptoms that is integrated with EMR		**If Successful** Daily self-reporting of biometrics and symptoms that is integrated with EMR		Discharged from hospital stay; resume daily self-reporting of biometrics and symptoms				Ship kit back to Vivify
Clinical Team			Clinical champion at each participating site confirms high-risk designation			Place Vivify Order									
Digital Health Navigator	Weekly identification of patient candidates (GI clinic)	Risk stratification process classifies patients as high risk for acute care visit		Study overview by digital health navigator; obtain consent and baseline HRQOL	Educate patient and caregiver about Vivify platform									Study completion at 1 month or patient transitions to hospice or patient elects to terminate study	
Vivify & Support Team						Ship Vivify kit to patient	Provide patient technical support with kit								
Dedicated Nurse-led Triage Team							Daily monitoring and triage of patients		During study - dashboard alert/ patient call	As appropriate, symptom management recommendations via NCCN supportive care guidelines, patient education and non-pharmacologic management	**If Care Needs Escalation** Triage to 911, nearest EC, MDACC EC or refer to MDACC provider	Discontinue remote monitoring while inpatient			
Tool(s) in Use	Epic & Deep 6	Daly et al. JCO Oncology Practice. 2020;16(10): e1050-59	Daly et al. JCO Oncology Practice. 2020;16(10): e1050-59	Zoom/Redcap	Patient Education Materials, Phone	Epic	Vivify	Vivify/Nurse-led Phone Triage	Vivify	Vivify/Epic	Vivify, Epic On Demand Video	Vivify, Epic, Epic On Demand Video, Patient Education	Vivify/Epic Redcap, Epic	Redcap, Epic	Redcap, Epic	Vivify

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

There is no place like home- A Pragmatic Effectiveness Trial of Technology-enhanced Outpatient Symptom Management to Reduce Acute Care Visits due to Chemotherapy-related Adverse Events

2020-0702

Subtitle: There is no place like home

Study Chair: Anaeze C. Offodile II, MD

_____ _____

Participant's Name Medical Record Number

This is an informed consent and authorization form for a research study. It includes a summary about the study. A more detailed description of procedures and risks is provided after the summary.

STUDY SUMMARY

The goal of this research study is to learn if telemedicine and remote patient monitoring (RPM) can help cancer patients have better outcomes (such as fewer avoidable Emergency Room [ER] visits and hospitalizations, better quality of life, fewer symptoms, and fewer treatment delays) than those who receive usual care.

This study will be performed while you are receiving chemotherapy, and is being done to track how you respond to chemotherapy using these 2 different methods. The chemotherapy you receive will not be affected by your participation in this study.

This is an investigational study.

Taking part in this study may help improve your outcomes during and after chemotherapy. There may be no benefits to you on this study. Future patients may benefit from what is learned.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment. It is possible that wearing or being monitored

by the sensing devices (described later) may cause you to become upset, annoyed or distressed.

You can read a full list of potential side effects below in the Possible Risks section of this consent.

Your participation in the study will be over the course of 2 cycles of chemotherapy (up to 6 months).

There will be no cost to you for taking part in this study.

You may choose not to take part in this study.

1. STUDY DETAILS

Up to 600 patients receiving chemotherapy at MD Anderson will be enrolled in this study.

If you agree to take part in this study, you will be randomly assigned (like flipping a coin) to 1 of 2 groups:

- If you are in Group 1, you will receive the standard of care.
- If you are in Group 2, you will receive remote monitoring in addition to the standard of care.

You will have an equal chance of being in either group.

All patients in this study will complete questionnaires at the beginning of the study and at the end of each chemotherapy cycle. The questionnaires will be about your quality of life and your engagement in your own health care. The questionnaires should take between 15-20 minutes to complete. The questionnaires may be done over phone or email.

If you are in Group 2, you will receive the following RPM devices from Vivify to use at home:

- A blood pressure device to check your blood pressure and heart rate
- A weight scale to measure your weight
- A pulse oximeter to measure blood oxygen saturation
- A thermometer to measure body temperature
- A tablet computer to type in answers to questions about your chemotherapy symptoms. You will answer these questions every day while you are on study.

You will receive training about how to use these devices. You will be asked to use the devices each day during your chemotherapy treatment. It should take about 10-15 minutes to complete the tasks above each day. The study staff will call you after you initially receive the devices to make sure that they are working and will respond to any calls that you may have if you encounter device problems. After each chemotherapy

cycle, you will also be asked questions about how easy the devices were to use, and whether you encountered any problems using them.

The devices will electronically send encrypted (scrambled) information collected from you to a cloud-based platform that is managed by VivifyHealth, a private company that has contracted with MD Anderson to provide remote monitoring devices and services for patients.

MD Anderson staff in the patient call center will view this information using a secure, password-protected website. If the information indicates that you may be experiencing a medical problem, the staff will attempt to contact you by phone or text message.

After completion of your planned treatment cycles, all devices will be returned to the study staff or to VivifyHealth using pre-paid mail.

No matter which group you are assigned to, you will still receive the standard of care, which involves education for you and/or your primary caregiver about chemotherapy. In-person and video follow-up visits with the treating oncology team will be scheduled with you.

During the study, researchers may call to collect additional information about any ER visits or hospitalizations that you may have had. These calls should take about 5-10 minutes each time.

Information about your cancer diagnosis and treatment from your medical record will also be collected and stored in an electronic password-protected research database, which will be accessible only by the study staff. This information will help the study staff understand how the remote monitoring group participants are different, if at all, from those in the standard of care group. Any information that could be used to identify you will not be used. Only information about the group will be used in any publications. You will be asked to provide permission to access medical records if you have an ER visit or are hospitalized outside of MD Anderson.

If you have a caregiver, you will be asked if the study staff can contact him/her to take part in this study. Caregivers will be asked to complete the questionnaires about quality of life and caregiver burden at the beginning of the study and at the end of each chemotherapy cycle. If you have a caregiver who takes part in the study and who completes the questionnaire, the caregiver's questionnaire responses will be linked with your data for analysis.

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. You should discuss these with the study staff. The known side effects are listed in this form, but they will vary from person to person.

The **questionnaires** may contain questions that are sensitive in nature. You may refuse to answer any question that makes you uncomfortable. If you have concerns after completing any questionnaire, you are encouraged to contact the study staff.

Using the **study devices** (for example, the blood pressure device) should not take the place of your normal medical care, because the measurements may not always be accurate. If you become concerned about a device reading or a symptom you may be having, it is important that you contact your regular doctor as you typically would.

If any device is stolen or damaged, you will not have to pay for it. However, you must report the loss to the study staff right away. Please note that once you return the devices, any of your information that is stored on them will be deleted.

Using the **internet** for certain purposes outside of this study may put you at risk for identify theft. You should be careful in providing personal information on other websites.

Although every effort will be made to keep study data safe, there is a chance that your **personal health information** could be lost or stolen. All study data will be stored in password-protected computers and/or locked file cabinets. There will be no personal identifying information connected to your questionnaire answers. There are no plans to destroy the study data.

This study may involve unpredictable risks to the participants.

3. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-6477 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

Additional Information

4. You may ask the study chair (Dr. Anaeze Offodile, at 713-563-6785) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.

7. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study, including the results of all of your standard tests performed as part of this research, and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

Future Research

Data

Your personal information is being collected as part of this study. These data may be used by researchers at MD Anderson and/or shared with other researchers and/or institutions for use in future research.

Before being used or shared for future research, every effort will be made to remove your identifying information from any data. If all identifying information is removed, you will not be asked for additional permission before future research is performed.

In some cases, all of your identifying information may not be removed before your data are used for future research. If future research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

If this research is not performed at MD Anderson, MD Anderson will not have oversight of any data.

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:
   - Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
   - The IRB and officials of MD Anderson

- VivifyHealth
- Study monitors and auditors who verify the accuracy of the information
- Individuals who put all the study information together in report form

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.

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

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

LEGALLY AUTHORIZED REPRESENTATIVE (LAR)

The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

_____ _____
SIGNATURE OF LAR DATE

_____
PRINTED NAME and RELATIONSHIP TO PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol 2020-0702.

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

_____
PRINTED NAME OF WITNESS TO THE VERBAL CONSENT

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____
PERSON OBTAINING CONSENT DATE

_____
PRINTED NAME OF PERSON OBTAINING CONSENT

TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into_____and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

_____ _____ _____
NAME OF TRANSLATOR SIGNATURE OF TRANSLATOR DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION (OTHER THAN TRANSLATOR, PARENT/GUARDIAN, OR STUDY CHAIR) DATE

_____
PRINTED NAME OF WITNESS TO THE VERBAL TRANSLATION

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Location (page)	Section/item	ItemNo	Description
	Administrative information		
1	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
3	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
		2b	All items from the World Health Organization Trial Registration Data Set
3	Protocol version	3	Date and version identifier
22	Funding	4	Sources and types of financial, material, and other support
1	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
2		5b	Name and contact information for the trial sponsor
NA		5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
NA		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
5	**Introduction**		
5	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
6-8		6b	Explanation for choice of comparators

7-8	Objectives	7	Specific objectives or hypotheses
8	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
	Methods: Participants, interventions, and outcomes		
8	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
8-9	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
9-11	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
10		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
10		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
10-11		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
7-8	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Fig 1	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

7, 13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
NA	**Methods: Assignment of interventions (for controlled trials)**		
	Allocation:		
NA	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
NA	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
NA	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
NA	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
NA		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
	Methods: Data collection, management, and analysis		
12	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
12, 13		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
13	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

13	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
13		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
NA		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
	Methods: Monitoring		
NA	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
NA		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
14	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
NA	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
	Ethics and dissemination		
3,14	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
NA	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
7	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
NA		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

13,15	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
22	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
NA	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
3, 14	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
NA		31b	Authorship eligibility guidelines and any intended use of professional writers
NA		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
	Appendices		
Appendix 1	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
NA	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.