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Enhanced, EHR-facilitated Cancer Symptom Control (E2C2) Pragmatic Clinical Trial

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IRB Minimal Risk Protocol Template

General Study Information

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Study Title: Enhanced, EHR-facilitated Cancer Symptom Control (E2C2) trial

Protocol version number: April 15, 2021 Version 16

Research Question and Aims

Hypothesis: Collaborative case management for control of moderate or worse sleep disturbance, pain, anxiety, depression, fatigue (SPADE symptoms), and physical dysfunction among cancer survivors and patients with cancer will improve quality of life, symptom severity, and adherence to cancer treatment, and will also reduce need for acute care.

Aims:

Specific Aim 1. Conduct a cluster randomized pragmatic trial with a stepped wedge design to test the hypothesis that a symptom control-focused E2C2 intervention will significantly reduce SPADE symptom and physical dysfunction scores, reduce unplanned hospitalizations and emergency department visits, improve adherence to cancer therapies, and improve self-reported quality of life.

Specific Aim 2. Evaluate the hypothesis that use of a multifaceted, evidence-based implementation strategy to support adoption and use of the E2C2 system will result in improvements in implementation and clinical outcomes.

Specific Aim 3. Conduct a mixed methods evaluation to detect, understand and reduce disparities in the adoption and implementation of the E2C2 intervention among elderly and rural-dwelling patients with cancer.

Background:

Cancer and its treatment are often associated with severe, disabling symptoms that have been causally linked to diminished survival, increased healthcare utilization, degraded quality of life (QoL), unemployment, and non-adherence to recommended cancer treatments. The prevalence of inadequate symptom control has been reported to be as high as 90%¹ despite the availability of definitive care guidelines and accurate and efficient assessment tools, and is especially stark among the elderly and rurally-situated patients. This disjuncture is needless as most symptoms can be substantially mitigated.^{2,3}

Reports suggest that two key factors have impeded efforts to achieve better symptom control through heightened clinical awareness. First, the expectation that symptom screening and score reporting alone would lead to better management has been repeatedly refuted. Meta-analyses and high quality trials have failed to show that solely providing clinicians with patient reported outcome (PRO) scores improves outcomes.⁴⁻⁷ Second, symptoms are challenging to manage, even for experts with dedicated time. Success often requires diligent monitoring; multi-modal care plans spanning behavioral, pharmacological, and rehabilitative domains; as well as ongoing adjustment. These demands are particularly salient for the most prevalent and destructive symptoms of the “SPADE” pentad; Sleep disturbance, Pain, Anxiety, Depression, and Energy deficit. Although guidelines exist for each symptom class, their enactment by disease-focused clinicians, who may lack both the training and time necessary to coordinate treatments, has proven unfeasible.

Collaborative care (CC) approaches that include a multidisciplinary team-based patient care strategy with symptom-specific goals, support for self-management training sustained patient follow-up, and decision support for medication changes, have considerable potential to improve the management of symptoms in patients with cancer^{8,9} and the potential to reduce healthcare disparities among vulnerable patient subgroups. A robust evidentiary basis supports the effectiveness of CC approaches in mitigating anxiety and depression; meta-analyses and systematic reviews report positive effect sizes ranging from 0.34 to 0.61 in primary care settings,¹⁰⁻¹⁵ and among patients with co-morbid medical



conditions.^{16,17} Additionally, more recent CC iterations have been shown to significantly improve pain in diverse populations, including patients with cancer.^{18,19} It should be noted that virtually all positive trials of PRO-based symptom monitoring and treatment in cancer populations have incorporated key CC components.²⁰⁻²¹

CC approaches have proven difficult to implement at scale, yet recent information technology advances permit their core components to be simulated through integrated systems embedded in current generation electronic health records (EHRs). Specifically, EHR internal logic and patient interface capabilities can provide automated, “stepped care” decision support that integrates patient and clinical data to match the aggressiveness of management with a symptom’s intensity and impact. Patients with mild to moderate symptoms may achieve relief through self-management education or simple, first-line interventions. Embedded EHR decision support rules can systematically identify these patients and automatically push the appropriate educational materials to them, or assist in the initiation of prescriptive therapies. Some patients, by virtue of the number, intensity, and functional impact of their symptoms, will require dedicated specialist attention. This narrowing of the focus of CC providers to intensely symptomatic patients who fail first-line treatments can permit the optimal deployment of limited resources.

We propose to comprehensively evaluate the implementation and effectiveness of a guideline-informed Enhanced, EHR-facilitated Cancer Symptom Control (E2C2) system that uses two empirically supported levels of stepped care for improving control of SPADE symptoms, low-touch automated CC for mild to moderate symptoms and conventional CC for more intense symptoms. We will conduct a Hybrid II stepped wedge cluster randomized pragmatic clinical trial at the population-level among patients with solid tumors across all phases of cancer care in community settings and clinics within an academic medical center. Malignant hematology (liquid tumor) patients will also be included in community practices. Successful completion of this trial will provide evidence regarding the impact of the E2C2 intervention on the management of SPADE symptoms.

The E2C2 intervention utilizes critical insights from the current evidence base to overcome barriers that have limited previous attempts at the development of scalable, pragmatic approaches to symptom management. Three recent findings are particularly relevant. First, we now know that simply providing symptom patient reported outcome (PRO) data to overloaded, disease-focused clinicians limitedly improves clinical outcomes, as robustly attested by systematic reviews.^{4,22,23 24-26} Second, applying the Collaborative Care Model (CCM) which entrusts mid-level providers with measurement-based symptom management not only mitigates symptoms, as robustly reported in systematic reviews,^{13,27-29} but also results in improved function³⁰ and quality of life (QoL), and reduced health care utilization.³¹ Third, up to 40% of patients experiencing mild or moderate cancer symptoms achieve relief with self-management approaches.³²⁻³⁸ The proposed E2C2 trial leverages these findings, particularly those from the investigators’ successful and completed INCPAD and COPE trials which effectively generalized the CCM to patients with cancer.^{39,40} The proposed E2C2 intervention’s emphasis on the CCM is further supported by the fact that other investigators’ successful PRO monitoring efforts in cancer populations were grounded in the model’s basic tenets – measurement-based care delivered by dedicated non-MD providers. For example, patients in Basch et al’s trial,⁴¹⁻⁴³ received a mean of 13 nurse phone calls during a median 4 months on study, while patients in studies reported by Mooney et al^{20,44} and Cleeland et al²¹ received similar symptom-directed attention from dedicated nurse practitioners.

The E2C2 intervention recognizes historic challenges the CCM’s broad implementation posed by its human resource requirements and proposes to overcome them through three validated strategies that capitalize on increased EHR penetrance and capabilities:

1. EHR-embedded algorithms will deliver validated self-management education for specific symptoms. This will enable nurse symptom care managers (SCMs) to focus their collaborative care efforts on high-needs patients.
2. EHR clinical decision support tools, proven effective in other contexts in improving the frequency of evidence-based care,^{45,46} will be utilized to strengthen the benefits of providing oncological clinicians with PRO score-linked care plans. The Symptom Monitoring II (SyMon II) trial presented oncological clinicians with scores for five PRO domains with guidance in score interpretation and symptom management. While anxiety significantly improved, demonstrating that the strategy can be effective, the other domains did not.^{47,48} The E2C2 intervention will enhance the SyMon II approach by including validated decision support tools to enable clinicians to efficiently manage patients’ symptoms.
3. E2C2 will allocate nursing FTE to designate and train SCMs in efficient EHR-based CC. Cultivation of dedicated niche practitioners to achieve economies of scale has proven effective in both primary and specialty care.⁴⁹ We believe that this strategy will prove broadly scalable and require limited, if any, incremental FTE because: 1) Experienced



SCMs are highly efficient; in INCPAD, a single SCM managed 18 community practices;³⁹ 2) Proactive symptom management can reduce unscheduled office visits;⁵⁰ 3) US oncology practices, on average, employ 6.9 nurses making the dedication of >0.5 FTE for CC practical (this average has steadily increased through practice consolidation into larger hospital- and health system-owned group and multi-specialty practices),⁵¹⁻⁵³ and 4) Prior CCM iterations have used inefficient modes of SCM-care team communication, e.g. repeated phone calls, fax, email, rather than time-saving, seamless intra-EHR order entry by the SCM.

The E2C2 trial takes advantage of our growing recognition of the interrelatedness of symptoms, as its targeting of commonly co-occurring symptoms will enhance our understanding of symptom clusters. Emerging research demonstrates the substantial co-occurrence of cancer-related symptoms and, consequently, the impracticality and, indeed, artificiality of evaluating and treating symptoms in isolation⁵⁴⁻⁶¹ rather than in clusters such as the SPADE grouping (Sleep disturbance, Pain, Anxiety, Depression, and Energy deficit/fatigue), which represents a prevalent and potentially treatable group of overlapping symptoms.^{54,56,57,59,62-67} Cross-sectional analyses will provide insights into the co-occurrence rates of these 5 symptoms as well as their individual and additive effects on functional status and quality of life. Longitudinal analyses will determine the responsiveness of individual symptoms and overall symptom burden to treatment as well as patient- and disease-specific mediators and moderators of improvement.

The E2C2 trial is clinically and methodologically significant because it will comprehensively evaluate the use of ubiquitous and inexpensive EHR functionalities – automated assessment, decision support, and implementation – to enhance symptom control. While these capabilities are increasingly EHR agonistic, our utilization of Epic may be particularly beneficial as it is used across 250 U.S. healthcare organizations and as 65% of the US population has an Epic record, and 69 million Americans have Epic My Chart accounts.⁶⁸ The Epic internal logic, assessment, audit and feedback, and alert functionalities used in the E2C2 intervention are straightforward to configure, requiring only 1 to 2 weeks of builder time, thereby limiting the human resource requirements for E2C2 intervention implementation. As noted above, these capabilities are increasingly EHR agonistic and while build specifics will differ in Cerner, Meditech, and other EHRs, the fundamental principles will remain constant.⁶⁹ Our detailed Resource Sharing Plan emphasizes the development of manuals that outline build specifics that will be pertinent to both Epic and non-Epic using organizations. This strategy has the potential to radically accelerate the uptake and broad implementation of E2C2 capabilities with limited resource investment.

Study Design and Methods

Methods:

Overall Study Design: The Enhanced, EHR-facilitated Cancer Symptom Control (E2C2) is a pragmatic, cluster-randomized clinical trial that will rigorously assess the impact of the intervention in controlling SPADE symptoms among patients with cancer spanning the cure-directed, survivorship, and palliative phases of disease management, while also exploring factors relevant to its implementation. The E2C2 trial is population based; all patients receiving care for solid tumors at the MC Cancer Center Rochester (MCR) will be included in the study sample irrespective of cancer type or stage. A similar sample will be included from community clinics within the Mayo Clinic Health System in Minnesota and Wisconsin, with the addition of malignant hematology patients at those community sites. Patients will be assigned the ePRO “Basic Symptom and Function Screen” (BSFS) questionnaire via their EHR approximately 4 days prior to their oncology appointment (in-clinic or virtual visit) as the standard of care process. The EHR algorithm will be set to assign questionnaires no more than every 2 weeks. The patient will have the ability to complete the BSFS via their portal but will be prompted to complete it via welcome tablet at check in if they do not. Additionally, if patients do not respond to questionnaires via portal or welcome tablet, they will be given an opportunity to complete it via Interactive Voice Response, otherwise known as IVR. When a patient fails to complete their assigned BSFS questionnaire, they will receive an automated phone call and will be prompted to answer the questions via touchpad. While Mayo Clinic is using an external vendor (IPT), all data is maintained on Mayo Clinic servers. We are not releasing data to IPT at any point in time. The ePRO (questionnaire) Health platform resides on our server and is not going outside of the firewall. Data going to the platform is transient in nature and is purged once the results are sent back into Epic. SPAD approval has been granted and there are Business Associate Agreements (BAA) and Information Security Agreements (ISA) in place, which covers how PHI can be used and stored. The trial’s stepped wedge design (SWD) will randomize the order of E2C2



implementation among 15 clusters. Clusters will be defined at the level of the cancer care team, and will be randomized to one of five different tranches to receive the implementation at staggered 8 month intervals. Between 2 to 20 oncologists/hematologists and mid-level providers will comprise each of the 15 clusters. Clusters will be randomized to initiate the E2C2 intervention at each of the steps. This design will allow data to be sequentially collected from all clusters for a minimum of 3 months during pre-E2C2 usual care, and a minimum of 12 months during the implementation phase. This stepped wedge design will allow us to compare outcomes at each clinic both across intervention groups and with historical controls at the same clinic, providing a rigorous assessment of the impact of E2C2 on controlling SPADE symptoms among patients with cancer while also exploring factors relevant to its implementation across all sites.

The primary outcome will be SPADE symptom and physical function numerical rating scale (NRS) scores collected in association with medical oncology clinic appointments. Secondary outcomes will include PROMIS-CAT measures for anxiety, depression, pain, and physical function, assessed up to every four months depending on visit frequency. Additional secondary outcomes will include health care utilization, adherence to cancer treatment, and survival. Variation in ePRO response rates and outcomes will be assessed for all participants, but special emphasis will also be given to disparities in outcomes among elderly and rurally-based patients.

Process measures will capture stakeholders' use of the EHR graphic and decision support tools, and will be abstracted from the EHR. All analyses will be performed using methods appropriate for cluster randomized stepped wedge trials. In parallel with conduct of the E2C2 trial, mixed methods will be used to comprehensively assess system usability, multi-stakeholder experience, and barriers and facilitators for stakeholders' use of the system. Qualitative interviews will also be conducted to understand possible reasons for disparities in the adoption and implementation of the E2C2 intervention among elderly and rural-dwelling patients with cancer.

Cancer Patient Enrollment: This is a population based study, where all eligible patients seen by clinicians at the Medical Oncology Clinic in Rochester and hematology/oncology in the Midwest Mayo Clinic Health Systems (MCHS) will be enrolled. This inclusive enrollment approach substantially increases the generalizability and external validity of our real-world pragmatic trial. Rochester campus will act as primary research site and there will be no study team responsibilities at any of the MCHS sites.

Among the roughly 2.5K patients with new cancer diagnoses annually treated by the MC practices, 50% are rurally situated, 50% are elderly, and 18% are covered by Medicaid, comparable to the upper Midwest.⁷⁰ The population's ethnic and racial characteristics are also representative of the upper Midwest, excepting higher inclusion of Native Americans, ~3.8%. The anticipated distribution of cancer types and stages in the study population parallels those described in the American Cancer Society 2018 Facts and Figures,⁷¹ excepting higher proportions of patients with melanoma, neuroendocrine tumors, and sarcomas, which reflect MCR emphases.

Transparency and Institutional Review. E2C2 will be sequentially implemented across the Rochester medical oncology practices, as per the stepped wedge random allocation. Neither current regulations, nor the peer-reviewed literature explicitly defines when a formal patient consent process is required for pragmatic clinical trials, particularly when testing the implementation of proven effective interventions at scale. This type of research, sometimes referred to as "standard of care" research in which the primary research objective is to implement and evaluate a strategy that better satisfies the existing clinical standard of care, has been debated in recent high profile cases.¹³⁸⁻¹⁴⁰ Opinions from ethicists vary but all emphasize the vital importance of IRB engagement and assiduous efforts to foster disclosure and transparency across all relevant stakeholders.¹⁴¹⁻¹⁴³ We believe, and in consultation with our local Research Ethics Consult Service have confirmed, that this study meets the criteria for being standard of care research in which the marginal incremental risks of the proposed interventions do not foreseeably introduce even incremental net risk to individuals in the participating practices being studied. The MC Cancer Center Patient and Family Advisory Council contributed to the current E2C2 "Transparency Promotion and Patient Preference Protection Plan." All patients who have previously opted out of having their records used in medical research (~3% of the Mayo Clinic patients) will have their data redacted from any final analysis files.

Transparency is both a vital human subject protection concern and an implementation tool with the potential to enhance patient engagement. The E2C2 intervention will include a simply produced 2 minute video that will describe



key aspects of the intervention and will visually communicate patients' anticipated experience with it. It will emphasize the intervention as an improvement in care delivery and not as a research project. This video will be available on the patient facing website (cancersymptoms.mayoclinic.org). A welcome packet will be sent to all patients with upcoming appointments at the time of E2C2 rollout. This packet will include a welcome letter that gives information about how to view the video and other IRB and Office of Patient Experienced approved material on the external website (cancersymptoms.mayoclinic.org). Patients will also have the opportunity to receive educational materials in the form of "toolkits," which is discussed in the "[Dispensing of self-management education modules](#)" section.

Provider and staff data collection

In parallel to the E2C2 study, we will enroll clinical stakeholders at multiple levels to participate in surveys, interviews, and focus groups designed to explore factors relevant to the experience of implementing the intervention. Measures and methods for this process are as follows:

System Stakeholder Context Survey and Interviews: Approximately 20 system-level stakeholders within medical oncology or related practice (e.g. administrators, practice leadership, information technology) will be recruited via an email invitation during the Pre-E2C2 stage to participate in a brief survey and semi-structured interview. We will use a 12-item Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) to assess system-level context prior to implementation (see survey drafts). Interviews will comprise 15-30 minute elaborations of the same constructs, with prompts informed by the Consolidated Framework of Implementation Research. The aim of this data collection is to understand the factors that may impact implementation of the intervention, including stakeholder perceptions of how it will impact their work. Interviews will be completed in person or by phone, and they will be recorded with permission. Participants will complete oral consent before the interview. After the interview, the study team member who completed the interview will write field notes summarizing the participant's impressions of E2C2, readiness to implement E2C2, etc. He or she will also forward items requiring immediate action to the appropriate study team member or resource.

Care Team Implementation Survey: The perspectives of care team members will be elicited during implementation using the Care Team Implementation Survey. At baseline, the Care Team Implementation Survey consists of questions from two widely used implementation questionnaires: 1) the 12-item IAM-AIM-FIM survey, and 2) a 23-item instrument based on Normalization Process Theory (i.e., The NoMAD questionnaire). The NOMAD questions will assess, among other things, care team members' perceptions of intervention leadership, integrated workflow, training adequacy, and organizational understanding, as well as perceptions of the value of the intervention and its impact on working relationships. Just prior to initiation of the intervention (baseline), all care team members (e.g. physicians, nurses) within a given cluster will be invited to complete the surveys. Participants will be recruited at cluster engagement "kick-off" meetings and provided with a paper copy of the survey for completion. Care team members who are not recruited in-person will be sent an email link to complete the surveys online. Version 2 of the Care Team Implementation Survey will be repeated at 2-4 months after initiation of the intervention and 12 months later throughout the funding period, via email link or paper copy. Version 2 includes the same IAM-AIM-FIM and NoMAD questions, along with a set of questions that assess the care team members' current use of various components of E2C2. All surveys will be preceded with consenting information describing the study, risks, benefits, and alternatives, including the option to not participate.

Care Team Implementation Focus Groups: To supplement implementation survey data, members of care teams will also be invited by email to participate in focus groups. Up to two focus groups will be held with each cluster. A trained focus group facilitator will moderate the groups using a semi-structured interview guide informed by survey constructs (e.g., acceptability, integration of E2C2 into workflow), as well as the preliminary results of the cluster's survey data. Focus groups will function like reflective team meetings and will be recorded with permission and transcribed for analysis. Participants will complete oral consent prior to the focus group.

System Stakeholder Implementation Interviews: To further contextualize and explain interesting findings from the survey data and to explore the insights of key stakeholders that do not correspond to individual care team clusters (e.g. system-level implementation work), we will invite up to 35 stakeholders (MD, administration, IT, NP) (including all RN symptom



care managers to participate in approximately 30-minute qualitative interviews. Stakeholders will be identified by members of the study team and the engagement workgroup, and potential participants will be recruited by email. Interviews will take place in person or by phone, based on participant preference, and they will be timed to follow analysis of surveys conducted at 2-4 months after initiation of the intervention and 12 months later. They will be conducted by a member of the study team using a semi-structured interview guide developed using NPT constructs and existing literature on implementation of EHR and symptom management innovations. Interviews will be audio recorded with permission and transcribed for analysis. Field notes will also be completed after each interview. Participants will complete oral consent prior to the interview.

System Stakeholder Sustainability Assessment: Approximately 40 system-level stakeholders within medical oncology or related practice (e.g. administrators, practice leadership, information technology), including those who participated in the context assessment or stakeholder interviews, will be asked to complete the short form version of the Clinical Sustainability Assessment Tool (CSAT). The CSAT short form is a 21-item assessment of clinical and organizational stakeholder perspectives on how sustainable a practice is over time (e.g., whether the practice has champions, whether it is easy to use, and whether it has sufficient resources). Surveys will be distributed by paper or using an email link after 12 months of intervention go-live.

Implementation Documents: Implementation documents, including executive team meeting minutes, project correspondence and materials, periodic study reflections, and study logs maintained by study team members will also be collected for textual analysis of how the intervention unfolded in practice.

Provider and staff data analysis

System Stakeholder Context Survey and Interviews: AIM-IAM-FIM surveys will be collected and entered into a secure REDCap database, and scores will be compiled for the overall group of participants. Interview data will be analyzed using methods of content analysis to identify impressions related to AIM-IAM-FIM and CFIR constructs. Analysis will be completed during the pre-E2C2 study period, and findings will be summarized in an analytic memo to facilitate further reflection on context-related findings at the completion of the study.

Care Team Implementation Surveys: The implementation survey will be collected and entered into a secure REDCap database. Analysis will be completed after each wave of data collection. Scores will be compiled for the 4 NPT construct levels within NOMAD and overall and within the 3 domains of Acceptability, Appropriateness, and Feasibility for IAM-AIM-FIM and as a composite readiness for implementation score. Team/cluster and tranche level scores will be determined for all outcomes at each scheduled time point. Differences will be explored between groups and across time.

Care Team Implementation Focus Groups and System Stakeholder Implementation Interviews: Preliminary qualitative analysis of focus group and interview transcripts, as well as field notes, will follow completion of each wave of qualitative data collection (e.g., the months following completion of focus groups/interviews in each tranche). Additional analysis (including between tranches and overall across the study) will be completed at the end of the study. The analyses will employ a theoretically driven thematic approach. The study team will begin by reading the textual data, discussing manifest and latent content, and developing a list of concepts represented in the data. These concepts will be reviewed in light of NPT and other relevant implementation constructs, but not constrained by them. A coding framework will be developed using these concepts and applied to the text data. Coded data will be entered into NVivo 11.4 (QSR International Pty Ltd.)—a qualitative analysis software package—to facilitate data organization and queries and maintain an audit trail of the analysis. Members of the study team will meet to discuss the data and narrative memos will be used to describe themes or major findings in the data, along with variation in experience. Individual



survey results, implementation metrics, and individual- or site-level characteristics of interview participants will be used as appropriate to aid in interpretation. Furthermore, a side-by-side comparison of qualitative and quantitative findings, along with study team discussion, will further explore how the different data findings converge or diverge in order to enrich understanding of E2C2 implementation. This type of data and methods triangulation, along with the inclusion of study team members from different disciplines, will reduce interpretive bias.

System Stakeholder Sustainability Assessment: The CSAT will be scored through calculation of an overall average and averages per each of the subscales included in the instrument. Responses will be reported at the study level rather than by tranche or cluster.

Implementation Document Analysis: Analysis of documents—collected during the course of study implementation—will take place at the end of the study and will use methods of content analysis. Documents will be reviewed for occurrences of information that describe theoretical constructs including those from CFIR. Those will be coded in NVivo using a predetermined, theory-informed coding framework. New codes will be added if they arise during analysis.

Patient enrollment, data collection and analysis

Quantitative data collection and analysis. In order to understand variation in the use of the E2C2 symptom management strategies, we will first use data from the EHR to identify if the intervention is similarly accessed/adopted and if symptom management and utilization patterns are similar across age groups and by patients in rural and urban areas. We will calculate ePRO response rates (dividing the number of ePROs returned/the number sent) during the pre-E2C2 usual care period and then again during the intervention period, comparing rates by age, urban/rural residence, and age/rural residence. To analyze response rate data, we will use both simple unadjusted descriptive statistics as well as generalized regression models. We will calculate simple proportions of response rates for the total population and by age and urban/rural status. We will then create regression models to determine predictors of being a high responder. Additional explanatory variables will include patient demographics (e.g., employment status, insurance status, gender), cancer type and stage and cluster. Response rates at each time point will be calculated for analyses, and models will include a random intercept to account for repeated measures over patients. We will then aggregate data and examine trends over time to determine if, over time, response rates have increased significantly. Similarly, we will calculate responses to PROMIS CAT scores (individually and composite scores) during the pre-E2C2 usual care period and then again during the intervention period, comparing rates by age, urban/rural residence, and age/rural residence. For the PROMIS CAT scores, we will use a similar analytic approach as with the response rate analysis.

Qualitative data collection and analysis. Quantitative data will inform subsequent qualitative interviews aimed at examining patient barriers and facilitators to optimal symptom management, understanding experiences with symptom management strategies included in E2C2 (e.g., patient education; collaborative care), and identifying feasible and patient-centric solutions for refining and improving E2C2 in order to reduce disparities in outcomes for the elderly and rural residents. We will recruit patients for interviews that will help us understand barriers and facilitators for ePRO reporting and to solicit potential refinements that could improve ePRO reporting success. We will use a random sample of patients for interviews. Starting with the clusters randomized to the first tranche, we will randomly select up to 100 patients stratified by age (<65, 65-75, >75), sex, and by urban/rural residence. We will aim to complete up to 20 patient interviews per tranche, with balance on key characteristics such as PRO responders/non-responders, cancer type, cancer stage, and experience with E2C2. Additional random samples will be drawn as needed to meet interview goals. As the interviews continue, we may move to more purposive sampling to capture the broadest set of qualitative experiences. These procedures will be repeated for tranches 2-5.

We will quantitatively evaluate the intervention's effectiveness among elderly and rural patients (using secondary EHR data methods described in Aim 1), and then qualitatively compare experiences among those with little change in SPADE symptoms to those with significant improvements. During this part of the evaluation we will also solicit feedback and suggestions on how to refine the intervention to improve symptom management analyses. All patients who participate



in the interviews will be consented. We will collect written HIPAA authorization for patients as part of this consenting process. If the subject is agreeable, documentation of HIPAA authorization will involve the use of Electronic Informed Consent (otherwise referred to as Docu-Sign) for HIPAA authorization forms. This is an institutionally approved process for documenting consent/HIPAA authorization using an on-line process. The subject may print or electronically save the consent form, or may contact the study team to provide a copy of the consent. If the subject prefers not to use Electronic Informed Consent, the study team will utilize a paper form for enrollment of these subjects, either via mail or in-person.

After participants are randomly selected, the study coordinator will send a letter describing the study, along with a HIPAA form and reply envelope and a copy of the HIPAA form for the patient’s records. Patients will be directed to return the HIPAA form if they are interested in participating or call the study staff with any questions. The study coordinator will follow up with a phone call. Those who are interested in participating will be read the oral consent script and scheduled for an interview date and time. Prior to a scheduled interview, a variety of techniques will be utilized to remind participants of their upcoming interview. Depending on participant preference, they will be able to choose the method in which they are reminded: by telephone, by text message to a mobile device, by mail (letter), or by e-mail. Participants will also be given the option of having a calendar invitation sent to them to remind them of their upcoming interview. E-mail address will be collected for participants who opt to have an e-mail reminder and/or calendar invitation sent to them. For participants who elect to have their reminder sent by text message, we will collect phone carrier information (this data is needed for determining the appropriate SMS gateway domain).

Interviews will be conducted over the telephone or Zoom and are expected to last 30-45 minutes. If the patient prefers to use video conferencing, such as Zoom, the interview will be scheduled using a MC Health account, which is approved for PHI. They will be audio recorded with permission and transcribed for analysis and the video conference interview recorded. Upon completion of the interview, participants will be sent a hand-written thank you note. Participants will receive \$40 in remuneration for their time. The interview schedule will follow an iterative process of data collection and analysis, a standard technique in qualitative methodology designed to ensure the identification and testing of analytic categories until thematic saturation has been achieved. Methods of data analysis will be similar to those used for clinical stakeholders, although the study team will also include methods of framework analysis. Initial analysis steps are comparable to those for clinical stakeholder data, but the coding framework will be applied in order to generate a matrix of results,^{197,198} allowing for within- and across-case analysis. This approach will facilitate systematic but flexible analysis of variation in experiences by characteristics such as rural/urban and elderly/non-elderly.

See the below timeline for a summary of when clinical stakeholder and patient implementation data will be collected:

	Pre E2C2, funding outset	Baseline**	2-4 Months after Intervention Initiation	6 Months after Intervention Initiation	12 Months after last assessment
System-level practice stakeholder context assessment IAM-AIM-FIM surveys and interviews	X				
Care Team Implementation Survey		X	X		X
Cluster implementation work focus groups *			X		X
System implementation work key stakeholder interviews *			X		X



System Stakeholder Sustainability Assessment					X
Interviews to assess patient disparities in implementation and outcomes*				X	

*Interviews and focus groups will commence following survey assessment.

**For survey administration, baseline refers to the period prior to implementation and just after the tool has been introduced to the care team.

Clusters

Disease-focused clinical teams, e.g., breast, colorectal, etc. will comprise the clusters. All clusters will include both medical oncologists and mid-level providers.

Allocation. There will be 5 tranches in our design, with 3 clusters randomized to initiate the intervention for each tranche. Pre-E2C2 baseline assessment will occur for all clusters starting 6 months prior to the first tranche. Each tranche will occur 8 months apart; data collected prior to the intervention will provide a within-site control group for each site. The allocation is illustrated in **Figure 1**. To ensure balanced cluster characteristics we will stratify randomization based on cluster size and site.

Interventions

The E2C2 intervention will include patient- and clinician-directed elements that are designed to increase the frequency with which patients receive individualized, preference-concordant, and guideline-based care for their symptoms and to increase rates of symptom control (**Figure 2**).

Automated Symptom Monitoring: Following the transition from pre-E2C2 usual care to the E2C2 intervention, the ePROs used to assess SPADE symptoms, physical function, social participation, distress, and QoL will not change, however, assessment frequency will increase, particularly for symptomatic patients. After initiating E2C2, the Symptom Control Bundle will be activated and patients and clinicians will be able to access graphic displays for SPADE score tracking, and patients will be able to enter ePRO data via a telephonic symptom assessment in addition to the web, smart phone, and tablet modes.

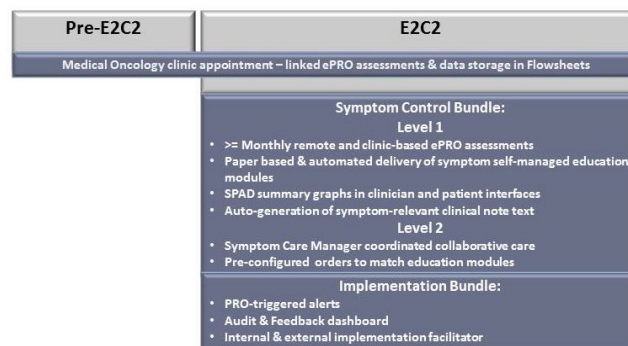


Figure 2. E2C2 Interventions

Presentation of symptom data to patients and clinicians. For PRO data to be useful in clinical practice, patients and clinicians need to understand what the scores mean. In order to facilitate intuitive ePRO interpretation, the E2C2 intervention will include a dedicated view in the clinician-facing Synopsis section of the Epic EHR and in the patient-facing My Chart interface. The views will be identical for both patients and clinicians to support communication and will be specified per the findings of Snyder et al. to optimize accurate interpretation.⁷² Data collected regarding symptom intensity and context will also be presented to clinicians in brief auto-generated text that will populate their clinical



notes with a patient's longitudinal SPADE scores and a hyperlink to the graphic Synopsis view. Presenting data to clinicians in graphic form for decision support has been shown to have a small to moderate effect size in improving patient outcomes.^{73,74}

EHR Triage and Decision Support Algorithms. EHR algorithms are foundational to the E2C2 intervention. Algorithms populated by automatically abstracted PRO and clinical data from the EHR will determine which symptom-directed services are offered to patients at multiple points in the intervention. Algorithms will be built into Epic using specification capabilities integral to the foundation system and available in all Epic iterations after 2014.

Triage to Level 1 or 2. Patients' responses to the BSFS questionnaire will initially assign symptomatic patients to one of 2 incremental Levels of stepped care (**Figure 2**). Patients will be triaged to Level 1 (moderate symptoms) unless they meet Level 2 (severe symptoms) criteria based on SPADE symptom or physical dysfunction intensity; non-response to treatment; patient preference for SCM contact; or clinician referral. Patients may move between the "no symptom" state and Levels 1 and 2, as depicted in **Figure 2**, depending on treatment response, and symptom onset and/or worsening.

Dispensing of self-management education modules. A second algorithm, irrespective of Level assignment, will determine which self-management education modules (also referred to as "Symptom Toolkits") will be automatically dispensed to symptomatic patients either via their web portal, where they will be directed to the E2C2 patient facing website (cancersymptoms.mayoclinic.org) or in print. Each printed symptom toolkit will contain an assortment of patient education and IRB approved materials in paper and digital form. Patients' preferences for mode of delivery will be electronically captured in their EHRs. Criteria that will determine whether and which materials are dispensed include symptom number and type, and request for reissue.

Order pre-configuration for first-line symptom management. A third algorithm for patients triaged to Level 2 will identify first-line, guideline-supported prescriptive interventions *matched to those listed in the self-management modules* and will automatically present these to the clinicians as pre-configured orders.

Automated provision with guideline concordant, self-management education and resource information (all levels). All patients, irrespective of Level status, will receive validated educational modules on SPADE symptom and physical dysfunction self-management in the form of a paper booklet. Subsequently, patients will receive Portal-based links to videos and additional written content modules matched to the symptoms that they endorse at a moderate or greater level, with the content of these educational materials. The educational materials are based upon cognitive-behavioral principles, and were developed and refined through 5 previous studies conducted by Given et al. Each symptom module was developed using evidence-based guidelines written at the 8th grade level.⁷⁵⁻⁷⁸ Each module is presented in an identical format (frequently asked questions): what the symptom is, how people describe the symptom, the causes of the symptom including medications, and a set of strategies presented in bullet points for managing the symptom. For each symptom, there are indications as to when and for what reasons to contact the oncology team, and other resources for management are listed. All module information is based on NCCN guidelines, Mayo Clinic expert opinion, and the Oncology Nursing Society PEP guides.⁷⁹⁻⁸¹ The content of the symptom modules will be cross-referenced annually against current guidelines.

Nurse Symptom Care Manager (SCM)-facilitated Collaborative Care (Level 2). The SCM will provide symptom-specific medication management, specialist referrals, and reinforced self-management. Level 2 is designed to optimally align treatment with each patient's specific symptoms, preferences, and response to therapy; thus, the frequency and content of nurse calls will vary with our "treat to target" approach. Similar to our INCPAD and COPE trials,^{39,40} we will systematically document in detail the frequency, duration, and content of all SCM calls. All self-management strategies discussed will be documented on a structured checklist for each call. Additionally, the time spent on the call reinforcing self-management and discussing medication management will be documented. This will allow us to secondarily examine the independent effect of the intensity and content of nurse contacts as mediators of outcomes. Phone calls between the patients and SCM will be recorded for fidelity monitoring and quality assurance purposes. Patients will give verbal consent to, and will have the ability to opt out of, having the recording used. Due to the set up of the call system and processes set in place by Legal, when a patient opts out of having their recording used for fidelity purposes it (the recording) because the responsibility of the Medical Oncology department. The study team will maintain records of the



patients who do not wish to have their recording used so that they are not included in the fidelity monitoring and quality assurance.

The SCM will contact patients in response to ePRO *symptom-triggered* alerts and trend reports. Patients will be able to view a short video (SCM Intro Video) explaining the role of the SCM when they are completing their BSFS questionnaire and indicating whether they'd like the assistance of a nurse Symptom Care Manager. In efforts to create awareness of the SCM role, patients will have the opportunity to receive a printed "face sheet" with photos of the SCMs and details on their role and how to request intervention materials. The E2C2 Face Sheet will be handed out by clinical Oncology staff. The SCM will monitor trend reports weekly, respond to automated monitoring clinical alerts and patient calls daily, configure orders for the oncology care team via the Epic EHR, and serve as the "triangulating" linchpin between patient and the oncology care team (including the supervising oncologist). The Symptom Care Managers will assess patients' needs for resistance band and pedometer (up to 2 pedometers per patient) interventions/therapies and will request these for the patient via Clinical Research Coordinator who will mail the items with the IRB approved cover letter and patient education materials. For E2C2, the SCM will have weekly case management sessions with the Palliative Care Service physician to review new Level 2 patients and patients not responding to therapy. In addition, the Clinical Research Coordinator will send a portal message to 2 groups of patients: a group who requested contacted from a Symptom Care Manager (SCM) and a group without SCM contact. This message will include a link to patient education material and to Mayo Clinic Connect.

Implementation Bundle

Implementation Strategies. The Implementation Bundle will be initiated at the same time as the Symptom Control Bundle as part of the stepped-wedge design.

Practice Facilitation: Practice facilitation, supportive services provided to clinicians by a trained individual to assist with engagement in clinical practice changes, has been shown to be moderately effective in changing clinician behavior.^{82,83} Practice facilitators use a variety of organizational, project management, and quality improvement approaches and methods to support practice change or redesign. We will implement a practice facilitation model wherein "Symptom Sages" will be trained to support adoption and use of the E2C2 EHR clinical decision support tools.⁸⁴ The Symptom Sage practice facilitator role will ensure readiness and sustained support for use of the symptom monitoring and management system. The facilitator will provide hands-on training and support to clinicians to foster understanding of and engagement with the symptom monitoring and management system.

Point-of-Care Computer Reminders: Point-of-care computer reminders/alerts, delivered through a computer system routinely used by clinicians, have been demonstrated to be moderately effective in changing clinician behavior.^{85,86} We will use point-of-care computer reminders/alerts embedded within the EMR as Epic Best Practice Advisories (BPA) which will appear as alerts on the clinician EMR interface. The EMR will record the actions that clinicians take and these data can then be aggregated and presented to the user in graphic form (see audit-and-feedback) and used as a measure of fidelity to the intervention. Clinicians may respond to the best practice advisory by linking to the pre-configured orders or Synopsis SPADE summary view.

Audit and Feedback: Audit and feedback, the collection and summary of clinical performance data over a specified time period provided to clinicians in written, verbal, or electronic form, has been shown to be moderately effective in changing clinician behavior.⁸⁶ Clinical performance data including the frequency with which a clinician; 1) responds to the Best Practice Advisories, 2) accesses the SPADE summary view, 3) issues orders pre-configured in SmartSets, 4) issues orders queued by the SCM, and 4) retains SPADE symptom-related text in clinical notes will be collected through automated Epic EHR tracking. Individual- and group-level quarterly performance data will be provided to clinicians as feedback via Epic's dashboard functionality. Upon initiation of the Symptom Control Bundle, the dashboard will be presented weekly on the landing page of the clinician when they first log into the Epic EHR. Clinicians can also freely access the dashboard via the Epic Navigator. The EMR will record the frequency and duration of dashboard access and whether a clinician drills down more granularly into their performance data. These data will be used to assess the degree to which use of the dashboard may be associated with Implementation Bundle effects.

Resources:

Department of Physical Medicine and Rehabilitation



The Mayo Clinic Department of Physical Medicine and Rehabilitation (PM&R) provides comprehensive and long-term rehabilitation to over 10,000 patients each year. The Department of PM&R occupies approximately 60,000 square feet in Mayo-Clinic Rochester facilities that include group and individual treatment areas, patient kitchens, a patient apartment, fully equipped gyms and treatment areas, and patient computers. The Chronic Disease Rehabilitation Program spans an outpatient clinic, inpatient consultation service, and designated beds on the acute inpatient rehabilitation ward. Drs. Cheville serves regularly as physician consultant in the Chronic Disease Rehabilitation Clinic. The outpatient Chronic Disease Rehabilitation Clinic is housed within the PM&R Department's 45,688 square foot outpatient treatment facility. This facility was renovated in 2009 and includes 20 physician exam rooms, 33 therapy treatment rooms, two therapy gyms (PT and OT), 35 physician offices (including Dr. Cheville's), 41 therapist workstations, eight physician workstations, 24 secretarial stations, and three patient education stations.

Department of Health Sciences Research

The main activities related to this project take place in the Department of Health Sciences Research (HSR).

Division of Biomedical Statistics and Informatics

The Division of Biomedical Statistics and Informatics (BSI) is comprised of over 300 members, including faculty, statisticians, bioinformatics specialists, statistical programmer analysts, and support personnel. BSI provides integrated collaborative research support in biostatistics, bioinformatics, and medical informatics. The Division has provided consultation on design and analysis for the clinical and laboratory research staff at Mayo Clinic since it was introduced in 1932. The Division of BSI includes 31 PhD statisticians and 17 PhD bioinformaticians who are engaged in collaborative research activities with Mayo's investigators. In addition to working with faculty, investigators can request access to the technical expertise provided by 197 MS and BS statisticians and 43 MS bioinformaticians that are respectively part of the technical statistic and bioinformatics core. The BSI team provides their expertise to more than 2,000 ongoing investigation projects, many funded by NIH research grants. The BSI is organized in four sections, described below.

Section of Medical Informatics

The Section of Medical Informatics supports clinical data normalization, natural language processing, information retrieval, machine learning, knowledge management, clinical terminology and formal ontology development and deployment. These services are enriched by a broad program of basic informatics research and embedded informatics cores in partnership with clinical and basic biology researchers; faculty are PI or co-PI on three core resources, and eight R01s. Members of the Section contribute prominently to national and international health informatics and standards communities. The Section comprises two senior faculty, five junior faculty, and five research assistants, and support personnel. This team is enriched by dedicated research IT support including programmer and analyst resources. The team meets weekly for alternating update and methodology seminars.

Division of Medical Oncology The Division of Medical Oncology includes over 45 physicians who see hundreds of patients with cancer weekly. Inpatient and outpatient facilities include state-of-the-art treatment units on Gonda building floors 9 and 10, and on three different units at Rochester Methodist Hospital.

The outpatient clinical area includes 51 examining rooms, an infusion facility with 18 chairs and 13 beds, and a small adjacent laboratory for processing blood, urine, and other samples for pharmacologic studies; multiple large rooms for multidisciplinary group consultation; an appointment office; offices for oncologists, mid-level providers, and nurses; a large waiting room; secretarial space; a patient library; a medical oncology staff library; a seminar room; and a conference room.

Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery



The Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery (CSHCD) is a Mayo Clinic Board designated transformative center that focuses resources and expertise to analyze, evaluate, and implement care delivery models that improve value for patients and leads to better health outcomes. Led by Andrew H. Limper, MD, Associate Dean of Practice Transformation, and a pulmonologist, the center brings together and expands Mayo Clinic's already extensive efforts in health care delivery research; systems engineering; and value, quality and policy analysis. The CSHCD was created in 2011 to accelerate the clinic's efforts to improve care delivery systems. Through the integration and application of scientific disciplines (engineering, health services research, epidemiology, and economics), this group of researchers will create evidence based and sustainable care delivery systems to provide higher value, decrease variability, and increase reliability and quality of care for all patients. The CSHCD serves as both an actual physical (housed in the Harwick Building) and virtual connection for health care practitioners and multidisciplinary researchers to integrate knowledge and investigate solutions needed for the future of health care.

The center works with physicians, medical researchers and experts from other academic disciplines (including systems engineers, health economists, social scientists, and epidemiologists) to design, study, implement and share new models of clinical care. Success requires data analysis, engineering principles and scientific rigor as well as a history of proven results translated into patient-centered care. As a result of the Center's work, patients receive improved health care value and better outcomes. Evidence and approaches for higher value care are shared broadly by Center staff. This center, which is internally and externally funded (over \$20 million), is organized around the following key focus areas which make up the center's five programs:

Offices

Drs. Cheville, Rutten, Griffin, Ridgeway and Storlie all have offices on the second floor of the Harwick Building. Dr. Cheville has an additionally office on the 14th floor of the Mayo Building. Drs. Ruddy, Okuno, and Hubbard have offices on the 10th floor of the Gonda building which adjoins the Mayo building. Dr. Chlan has an office in the Rosa Parks Pavilion. Dr. Leppin has an office on the 3rd floor of the Plummer Building.

(1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

(1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: All patients being followed by Medical Oncology at Mayo Clinic Rochester and Hem Onc in Midwest MCHS.

Subject population (children, adults, groups): Adults 18 years of age or older

Inclusion Criteria: Being seen for a solid or liquid cancer at a Midwest Mayo Clinic MCHS site or for a solid tumor at Mayo Clinic Rochester.

Exclusion Criteria: No Minors (under age 18) will receive the questionnaires but no further exclusions can be made based on the standard of care for questionnaire assignment.



Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. **Drug & Device:** Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)
 2. **Blood:** Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.
 3. **Biological specimens other than blood:** Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.
 4. **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)
 5. **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.
 6. **Digital Record:** Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)
 7. **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)
- NIH has issued a *Certificate of Confidentiality* (COC). When checked, provide the institution and investigator named on the COC and explain why one was requested. _____

Review of medical records, images, specimens – Category 5

For review of existing data:

Date Range:

Check all that apply (data includes medical records, images, specimens).

(5a) Only data that exists before the IRB submission date will be collected.

(5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.

Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.



- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

(5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol.*

Enter one IRB number per line, add more lines as needed

Data Specimens Data & Specimens _____

Data Specimens Data & Specimens _____

Data Specimens Data & Specimens _____

(5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

(6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

All paper-based and digital audio data will be transferred within a locked case or on an encrypted device to secure Mayo servers. Names will be removed from any audio transcripts and survey records will use study IDs to identify participants after linking their data from a master file. Completed paper surveys will be stored in locked cabinets.

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject’s identifier that will be recorded at Mayo Clinic by the study staff.

External refers to the subject’s identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	



Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. Note: Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images	X	
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address	X	
Street address, city, county, precinct, zip code, and their equivalent geocodes	X	
Phone or fax numbers	X	
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	<input type="checkbox"/> None	<input checked="" type="checkbox"/> None

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement:

Stepped wedge cluster randomization trials typically have more statistical power than other cluster randomized designs.⁸⁷ This is because each cluster is able to serve as its own control, accounting directly for the within cluster correlation of outcomes. Because of the complex nature of the design and statistical model, we estimate statistical power using simulation.⁸⁸

A version of the statistical model above was fit to 79 weeks of preliminary baseline data (i.e., with no intervention effect X_{kt}) in order to estimate the parameters (e.g., v_A, Σ_A) needed to simulate longitudinal data for the 15 clusters. Clusters were randomly allocated to the steps in **Figure 1**, and treatment effects due to intervention were generated on a grid of eight values $v_{1B} = 0.00, 0.01, 0.02, 0.03, 0.05, 0.10, 0.15, 0.20$, with the remaining $v_{2B} = v_{3B} = v_{4B} = v_{5B} = 0$ to assume the most conservative case (i.e., only a single symptom is affected by the intervention). The cluster effects were then generated according to $B_k \sim N(v_B, \sqrt{v_{1B}} \Sigma_A)$. This data generation process was used to simulate 100 data sets under

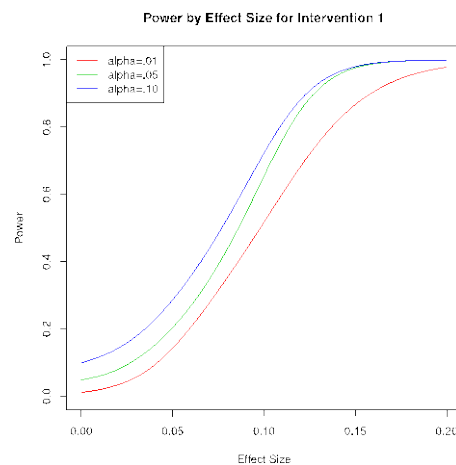


Figure 3. Power simulations for E2C2 Interventions



each of the eight grid values for \mathbf{v}_{1B} . The full model above was then used to estimate \mathbf{v}_B and test the hypothesis that all $\mathbf{v}_{jB} = \mathbf{0}$, via simultaneous credible bounds.⁸² The results are provided in **Figure 3**. As can be seen in the figure, the test keeps very close to the nominal level (i.e., 0.01, 0.05, or 0.10, respectively) when there is no effect. However, the power rises quickly to detect even a small average score difference of even 0.10 with 70% power (at 0.05 LOS) and a difference of 0.20 with nearly 100% power.

Data Analysis Plan:

Specific Aim 1 Analyses. We will summarize patient characteristics (sex, age, insurance status) by intervention status (pre-E2C2, E2C2). All patients will be analyzed on an intention to treat status; this principle will be extended to the cluster status, so that delays in implementation of an intervention will not affect the intervention status of patients.⁹⁰ All methods will account for correlation of outcomes within clusters and across patients. To test the primary hypotheses we will use generalized models to assess the effects of the interventions.⁹⁰ Our main model will be a mixed effects (i.e., multilevel) generalized linear model specified as follows. Let Y_{jkt} be the average of the j^{th} SPADE score among eligible patients in the k^{th} cluster ($k = 1, \dots, 21$), during step time period t ($t = 1, \dots, T$). In this analysis, weekly time periods (i.e., weekly averages) will be used over a period of four years so that $T = 208$. The SPADE score model is then,

$$Y_{jkt} = \mu_{jt} + A_{jk} + B_{jk}X_{kt} + \delta_{jkt}$$

where (i) μ_{jt} is a common mean trend for the j^{th} SPADE score across t , shared among all clusters. The multivariate vector $\boldsymbol{\mu}_t = [\mu_{1t}, \dots, \mu_{5t}]'$ is modeled as a multivariate auto-regressive process of order two, AR(2), to allow for more efficient estimation via smoothing of the trend over time. (ii) $\mathbf{A}_k = [A_{1k}, \dots, A_{5k}]'$ is a vector of random effects (one for each spade score) for cluster k , $\mathbf{A}_k \sim N(\mathbf{v}_A, \boldsymbol{\Sigma}_A)$. (iii) X_{kt} is equal to 0 during the control period for cluster k , and equal to 1 once the intervention begins.

(iv) $\mathbf{B}_k = [B_{1k}, \dots, B_{5k}]'$ is a vector of random effects (one for each spade score) for the effect of the intervention on cluster k , $\mathbf{B}_k \sim N(\mathbf{v}_B, \boldsymbol{\Sigma}_B)$, so that $\mathbf{v}_B = [v_{1B}, \dots, v_{5B}]'$ is the average effect that the intervention had on the five spade scores. (v) Finally, the $\boldsymbol{\delta}_{kt} = [\delta_{1kt}, \dots, \delta_{5kt}]'$ are error terms which are treated as a multivariate AR(1) with Gaussian noise, independently for each cluster. It can be critical to allow for this correlation in time in longitudinal data,⁹¹ which is often ignored in analysis of step-wedge designs. This is primarily due to the complication of fitting the above model which has several random effects (in both time and across cluster). This is further complicated with five responses due to the multivariate nature of the random effects. However, Markov Chain Monte Carlo is very effective at fitting such models⁹² and will be used here. In the event of a large imbalance in any patient characteristics among clusters between baseline and intervention periods, those characteristics will also be included in model (1). We can then test the primary aim of the study by testing the joint hypotheses that $\mathbf{v}_{1B} = \mathbf{v}_{2B} = \mathbf{v}_{3B} = \mathbf{v}_{4B} = \mathbf{v}_{5B} = \mathbf{0}$. For secondary outcomes, we will estimate a model similar to (1) as well. For all models we will report measures of fit such as predictive R^2 values and between-cluster variance estimates.

Finally, as a secondary objective of this aim, to better understand the effectiveness of different components of the E2C2 intervention in reducing symptoms, we will perform a separate set of analyses to assess the impact of specific process measures (D.2.d) on SPADE scores and other clinical outcomes. For each process measure we will first examine the distribution of values (frequency or duration) and, if highly skewed, categorize into 2 or more categories. We will then estimate for each outcome a mixed effects linear model with a random cluster effect, where the outcome is the dependent variable and the main independent variable is the continuous or categorized process measure, adjusting for patient covariates as described above. By testing for an overall process measure effect we can assess which processes contribute most to reducing outcomes; we will also report measures of variance explained to enable relative comparison



of process measure effects.

Specific Aim 2 Analyses. We will summarize patient characteristics (sex, age, insurance status) by intervention status (baseline, intervention). We will also summarize all survey responses by cluster implementation status, including clinician characteristics (age, sex, years of practice). All patients will be analyzed on an intention to treat status; this principle will be extended to the cluster status, so that delays in implementation of an intervention will not affect the intervention status of patients.⁹⁰ All methods will account for correlation of outcomes within clusters and across patients. As a secondary objective of this aim, we will assess the change in clinician survey constructs over time. This analysis will include each clinician with at least two completed surveys at least 6 months apart.

As in Aim 1, we will also assess the effect of process measures on SPADE scores and other clinical outcomes. We will use models appropriate for count data, selecting standard or zero-inflated Poisson or negative binomial models according to Aikake's Information Criteria, or logit models for binary measures. For each outcome we will estimate a) bivariate models including only one survey score; b) a model with all scores; and c) a final model which also includes clinician characteristics.

Aim 3

Endpoints

Primary:

SPADE and physical function NRSs will serve as both the E2C2 primary outcome and a critical component of the E2C2 intervention since NRS scores populate the EHR algorithms that determine whether patients are triaged to Level 1 or 2, and whether patients are offered specific intervention components (education, medications, etc.). Patients will complete NRSs for SPADE symptoms and physical function prior to medical oncology clinic appointments at all stages of the trial, i.e., prior to and after E2C2 initiation. ePROs will be more frequently administered to symptomatic patients outside of their appointment-linked assessments as part of the intervention. *To avoid potential bias from oversampling of symptomatic patients, only SPADE symptom NRSs collected in association with clinic appointments will be included in the primary analysis.*

NRSs. Simple 11-point NRSs have been used for decades in the assessment of diverse latent traits among patients with cancer of all types and stages.⁹³⁻⁹⁵ These single-item assessments have been the most often-used QOL and symptom measures in National Cancer Institute (NCI) cancer control clinical trials,⁹⁶ and they feature prominently in the most reliable and valid symptom assessment tools, both generic and cancer-specific.^{97,98} The NRSs utilized in E2C2 to assess the SPADE symptoms and physical function will be patterned on the extensively validated MD Anderson Symptom Assessment Scale and Edmonton Symptom Assessment Scale with respect to the 24 hour recall period, and verbal anchors identical to the, e.g., "No pain" and "Worst possible pain," respectively.^{99,100} NRSs have been shown to be more responsive than either Likert or verbal rating scales,¹⁰¹ and preferred by patients over visual analogue scales.¹⁰²

Secondary:

PROMIS CATs. Depression, anxiety, pain, and physical function will be assessed with the PROMIS CATs (www.promis.org). In addition to strong endorsement by the NIH,^{103,104} use of CATs is justified because IRT-based instruments have generally better discrimination across the entire trait range than legacy PROs, being less prone to floor and ceiling effects.^{105,106} Moreover, administering IRT-modeled banks with CATs enhances the efficiency and precision of measurement relative to short forms.^{107,108} The PROMIS item banks utilized in E2C2 have been validated, with robust IRT calibration across different clinical populations.¹⁰⁹⁻¹¹¹

Health care utilization. Healthcare utilization for E2C2 will consider health care encounters including hospitalizations, ED visits, clinic outpatient visits, and calls to the oncology care team. EHR entries and administrative billing data will be aggregated to construct a comprehensive data set of all clinical encounters. Data collected for hospitalizations will include admission and discharge diagnoses, length of stay, ICU admission/transfer, and whether an admission was planned for anti-cancer treatment or unplanned, and if the latter, initiated from the ED or an office visit. For ED encounters, we will capture diagnoses and whether an encounter resulted in hospital or ICU admission. Clinic visits will be captured using billing data which will include CPT codes, ICD-10 codes, location, and clinician NPI numbers. We will



be able to ascertain clinician discipline and specialty from the NPI numbers. Calls to the oncology care team are not billed but are reliably captured in the EHR. A recent audit established that 87% of calls to medical oncology practitioners were recorded in the EHR, and that rates of capture did not vary systematically across disciplines. However, call characteristics, e.g., duration, were not reliably recorded. Therefore we will use count data in analyses to model call frequency.

The majority, but not all, of patients' health care utilization will occur at MC facilities. Established patterns suggest that 75% to 80% of patients care will occur at an MC facility and that this frequency will not vary across E2C2 clusters, or phases of the E2C2 intervention, e.g., pre-E2C2, Stage 1. However, we will use imputation methods and sensitivity analyses to assess the impact of mis-ascertainment of utilization data.

Cancer treatment adherence. The literature does not offer a definitive definition of cancer treatment adherence, even for medications, or clarify which of the many candidate measures should be considered.¹¹² We will therefore assess adherence broadly and examine the frequency of missed imaging, medical oncology clinic visits, and chemotherapy appointments. Additionally, we will capture any unplanned hiatuses in cancer treatment or dose reductions. This information is routinely recorded on electronic chemotherapy administration forms from which discrete structured data elements can be abstracted. For oral hormonal regimens we will use the accepted definition of at least 80% of recommended doses to create a binary variable.¹¹³ Dr. Ruddy (E2C2 Co-I) has contributed seminal to the literature on adherence to breast cancer adjuvant therapies.^{114,115} We will apply this criterion to oral chemotherapy and immunotherapy as well.

Vital status. Vital status will be verified through death certificates, the Mayo Clinic EMR, next-of-kin reports, the Mayo Clinic Tumor Registry and the Social Security Death Index website.

Reporting mode and rates. Patient reported outcomes will be collected via several modes for the E2C2 trial. These include remote modes; the patient portal and interactive voice response, and point of care modes; tablets and provider entry via Epic Care. Data regarding patients' mode of PRO reporting are automatically stored by the Epic EHR. We will perform descriptive statistics to characterize how reporting modes differ across subgroups defined by demographic, clinical, cancer-related, and symptom characteristics. Additionally, we will create uni- and multi-variate mixed models to estimate associations of reporting frequency and mode with patient characteristics.

Receptivity to receipt of symptom support. The E2C2 intervention provides low and high touch support for moderate and severe symptoms, respectively. Patients who endorse moderate symptoms (4-6/10) are offered the option to receive symptom self-management education materials for specific symptoms; Sleep disturbance, Pain, Anxiety, Depression, Fatigue, and Deficits in physical function. Similarly, patients who endorse severe symptoms (7-10/10) are offered the opportunity to discuss the same symptoms with a nurse symptom care manager. We will calculate descriptive statistics to characterize patients' preferences with regard to receipt of symptom support in subgroups defined by symptom type and intensity, as well as the stability of their preferences for symptom support. Additionally, we will estimate associations between patients' demographic and clinical characteristics and their interest in receiving support by constructing multivariate mixed models.

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