Requesting Organization:
The Johns Hopkins University School of Medicine

A. COVER PAGE:

Project Title: Reducing Discontinuation Rate of Adjuvant Endocrine Therapy through Symptom Monitoring and Management

Grant ID Number: 36009705

Abstract

Five to 10 years of adjuvant endocrine therapy (ET) for early stage hormone receptor-positive (HR+) breast cancer is associated with significant reductions in recurrence and death. Despite these proven benefits, up to 40% of patients are non-adherent (take it irregularly) or discontinue ET early. Patients who discontinue adjuvant ET early often do so soon after initiation, with published 12-month discontinuation rates of approximately 20%. Side effects are often cited as the reason for early discontinuation. Data indicate that symptoms present at the time of initiation of adjuvant ET or that emerge soon thereafter are associated with early discontinuation. Ongoing symptom monitoring through collection of electronic patient reported outcomes (ePRO) offers the opportunity for early identification of symptoms and appropriate intervention. We aim to implement serial ePRO collection for patients initiating adjuvant ET for early stage HR+ breast cancer at Johns Hopkins clinical sites. Severe or worsening scores on ePRO measures assessing common symptoms during adjuvant ET will trigger an alert to the clinical team. We will develop evidence-based pathways to guide management of these symptoms. The overall goal of this project is to evaluate whether implementation of symptom assessment through collection of ePRO early during the course of adjuvant ET along with timely management of symptoms according to standardized clinical pathways will reduce the early discontinuation rate of adjuvant ET compared to the historical discontinuation rate.

Requesting Organization:
The Johns Hopkins University School of Medicine

B. TABLE OF CONTENTS:

Requesting Organization:
The Johns Hopkins University School of Medicine

Requesting Organization:
The Johns Hopkins University School of Medicine

C: REVIEWER COMMENTS: Not applicable

D: MAIN SECTION OF THE PROPOSAL:
1. Overall Goal and Objectives:
Introduction: Multiple trials have demonstrated that treating early stage hormone receptor positive (HR+) breast cancer with adjuvant endocrine therapy (ET) reduces risks of loco-regional and distant recurrence, new contralateral breast cancer and death.[1] Historically, adjuvant ET has been administered for 5 years, although evolving research demonstrates benefits of longer therapy.[1-4] Current guidelines recommend a course of 5-10 years of adjuvant ET.[5-7]

Despite the established benefits of adjuvant ET, up to 40% of patients are non-adherent (take it irregularly) or discontinue therapy early.[8-11] We and others have demonstrated that many patients who discontinue ET early do so soon after initiation of treatment (median time to discontinuation 6.1 months).[11,12] Indeed, approximately 20% of patients discontinue adjuvant ET within the first 12 months of treatment.[8-19] Outcomes are inferior among patients who are non-adherent or who discontinue adjuvant ET early, evidenced by higher risks of recurrence and death.[8,20,21] Once metastatic, breast cancer is incurable, therefore, interventions to improve adherence and to reduce early discontinuation are urgently needed.[22]

We and others have identified factors predictive of ET non-adherence and early discontinuation, some of which are potentially modifiable**.** Interventions targeting these potentially modifiable factors may reduce early discontinuation and, ultimately improve breast cancer outcomes. Many patients who discontinue adjuvant ET early cite side effects as their primary reason for stopping.[14] Evidence indicates that both the presence of baseline and treatment-emergent symptoms predict premature ET discontinuation.[10,11,13,15,18,19,23-25]

Symptoms experienced during adjuvant ET are likely under-appreciated and under-treated by clinicians.[24,26] This gap in care may be eliminated by remote symptom monitoring through electronic patient reported outcomes (ePRO). The use of ePRO offers the opportunity for ongoing symptom assessment that can allow for rapid intervention to manage symptoms with the aim of reduced early discontinuation and, ultimately, improved breast cancer survival.
Overall Goal: The overall goal of this project is to evaluate whether implementation of symptom assessment by collecting ePRO early during adjuvant ET along with timely symptom management according to standardized pathways reduces the 12-month adjuvant ET discontinuation rate. We hypothesize that identifying and managing symptoms present at the initiation of adjuvant ET or which emerge soon thereafter will reduce early ET discontinuation.
Key Objectives:
Objective 1: To evaluate the feasibility of symptom monitoring by collecting ePRO data via a mobile app during the first 6 months of adjuvant ET in patients with early stage HR+ breast cancer*.* We will consider baseline collection of ePRO data feasible if at least 65% of patients complete the baseline ePRO survey. We will consider collection of ePRO data during ongoing adjuvant ET feasible if at least 65% of patients complete ≥1 follow-up ePRO survey during the first 6 months of adjuvant ET (at 1, 3, and/or 6 months after treatment initiation).
Objective 2: To implement clinical pathways guiding timely management of common symptoms identified through ePRO collected via mobile app during the first 6 months of adjuvant ET. We will develop and implement evidence-based pathways guiding management of

common symptoms during adjuvant ET and link these pathways to alerts sent to clinicians regarding severe or worsening symptoms based on ePRO survey scores. We will summarize and report the compliance rate with pathway interventions within 4 weeks of receipt of alerts.

Objective 3: To evaluate the 12-month adjuvant ET discontinuation rate in early stage HR+ breast cancer patients enrolled in ePRO symptom monitoring. We will consider our intervention successful if ≤ 15% of enrolled patients discontinue ET within the first 12 months.

Through these objectives, we will implement two new clinical tools for our HR+ breast cancer patients initiating ET: 1) ePRO surveys for symptom assessment, and 2) standardized clinical pathways to manage baseline and emerging symptoms early during ET. This intervention will address the current need for better symptom assessment and management. We hypothesize that better symptom assessment and management through ePRO and the use of pathways will minimize ET discontinuation. The implementation of these clinical tools aligns with the focus of this RFP by utilizing pathways to improve the quality of breast cancer care and with our institutional goal for high quality breast cancer care.

2. Current Assessment of Need in Target Area:

Adjuvant ET improves outcomes for HR+ breast cancer.[1] However, despite the established benefits, up to 40% of patients do not complete the recommended 5-10 years of ET.[5-11] We and others have identified factors associated with non-adherence and early discontinuation. Some are not modifiable, such as age, race, marital status, comorbidities, socioeconomic status, co-payment, concomitant medications, and receipt of prior taxane.[8,10,17,18,27,28] However, as we and others have demonstrated, some factors associated with non-adherence and early discontinuation are potentially modifiable and interventions targeting these factors to enhance adherence, reduce early discontinuation and, ultimately, to improve breast cancer outcomes, are urgently needed.

Modifiable Factors Associated with Poor Adherence and Early Discontinuation: Many patients who discontinue adjuvant ET cite side effects as their primary reason for stopping.[14] We and others have demonstrated that both the presence of baseline and treatment-emergent symptoms, in particular, pain at baseline, and the emergence of musculoskeletal symptoms, are predictive of early ET discontinuation.[10,11,13,15,18,19,23-25] We have also demonstrated that high overall symptom burden prior to initiation of adjuvant ET or an increase in overall symptom burden early during ET is associated with early discontinuation.[13] Psychological factors, such as baseline poor sleep and trouble concentrating, distress early during ET, and worsening of anxiety or depression early during ET also predict premature ET discontinuation.[11,13,14,19]

Evidence-based interventions can improve many symptoms during adjuvant ET.[29] For example, guidelines outline the management of depression and anxiety in cancer patients and survivors[30] and data demonstrate that exercise improves arthralgias during ET[31] and that both pharmacologic and non-pharmacologic interventions can reduce hot flashes.[32] Weight gain in breast cancer survivors is also of concern. Although the impact of weight on ET adherence and discontinuation is uncertain, these factors are associated with increased symptoms [33-36] and may therefore contribute to non-adherence and early discontinuation.

Incorporating the Patient Voice in Symptom Assessment: The association between symptoms and ET adherence and discontinuation suggests that early identification of symptoms during adjuvant ET followed by rapid symptom management may lead to improved treatment delivery.

The symptoms experienced by patients receiving adjuvant ET are likely under-appreciated by clinicians due to both incomplete assessment during clinic visits and the emergence of symptoms between visits.[24,26] The current model for symptom assessment at the time of intermittent clinic visits relies on the clinician eliciting each patient's retrospective report of symptoms since the prior visit, a process subject to under-ascertainment and recall bias. Due to its retrospective timing, the current model limits the clinician's ability to intervene quickly to manage symptoms.[37,38] Data also suggest that clinicians do not address all symptoms elicited during adjuvant ET.[24] *Incomplete symptom assessment and inadequate symptom management represent a gap in care which may contribute to early discontinuation of adjuvant ET.*

Symptom monitoring by collecting patient reported outcomes (PRO) offers an opportunity for clinicians to better assess their patients' symptoms in real-time during treatment.[39] PRO are assessments from patients about their health status without interpretation by a clinician and are typically collected by completion of questionnaires.[40] The symptom burden captured by PRO during adjuvant ET exceeds that reported by clinicians.[26] PRO enhance the clinician's ability to detect unrecognized problems during therapy and the clinician's awareness of patient pain. Evolving research indicates that data collected through PRO may lead to changes in management.[41,42]

We have previously demonstrated the feasibility of serial collection of PRO during adjuvant ET within the context of a clinical trial with >75% of patients completing PRO measures 6 months after ET initiation.[11] The incorporation of PRO measures into routine clinical oncology care (outside of the context of clinical trials) has been a recent focus.[39] Incorporation of PRO into routine care during adjuvant ET may lead to improved symptom detection and the opportunity for rapid intervention to address symptoms, thus potentially minimizing early ET discontinuation.[26,43] To the best of our knowledge, the impact of PRO assessments during routine oncology care on the ET discontinuation rate has not been well characterized,[41,42] and its implementation has the potential to lead to improved breast cancer-related outcomes.

Oncology Care Pathways: In order for PRO data collected during adjuvant ET to promote symptom management and lead to a reduced early discontinuation rate, clinicians must not only identify symptoms by interpreting PRO data, but also must offer effective interventions to reduce the symptoms in a timely manner. The incorporation of PRO into routine clinical care may be burdensome for clinicians if the data are difficult to interpret and if the appropriate steps to take in response to the data are not clear. Our institution has spearheaded efforts to clarify how to best present PRO data to clinicians, highlighting current results and trends over time, and drawing attention to clinically important symptoms such as those that are severe or worsening.[44,45] We also have experience using expert consensus to develop management recommendations to guide clinicians responding to symptoms identified from PRO data.[46]

The use of oncology care pathways has recently expanded. Pathways offer treatment protocols with the goal of limiting variability in care, promoting value and providing effective and safe interventions. The American Society of Clinical Oncology (ASCO) recently outlined recommendations for optimal development and incorporation of pathways into oncology clinical care and recommended that pathways be developed to address the entire spectrum of cancer care including survivorship.[47] The symptom burden experienced by patients receiving adjuvant ET, the array of options for managing these symptoms and the data obtained by serial

PRO for symptom assessment during adjuvant ET create an ideal scenario for the incorporation of clinical pathways. Linking PRO scores with evidence-based pathways that outline appropriate interventions stratified according symptom severity has the potential to expand the clinical utility of PRO assessments in the care of patients receiving adjuvant ET.

Electronic Patient Reported Outcomes: The recent widespread availability of web access and smart devices facilitates the collection of ePRO. Moreover, the increasing use of electronic health records (EHR) offers the chance to link ePRO data with the medical record, notifying clinicians of symptoms in real-time.[39,48,49] Alerts can be used to flag severe or worsening symptoms with links to care recommendations based on pre-established pathways.[48]

Published data indicate that collecting ePRO is feasible in several settings such as ambulatory gynecologic cancer patients receiving routine care[48] and chemotherapy patients participating in clinical trials,[50] but, to the best of our knowledge, ePRO data collection has not been systemically evaluated in patients receiving routine adjuvant ET. Notably, a landmark randomized trial recently evaluated collection of ePRO during chemotherapy for advanced cancer and demonstrated improved delivery of chemotherapy, improved health-related quality of life, fewer emergency room visits and improved survival in participants randomized to the ePRO arm. Rapid clinical response to symptoms is a likely explanation for the improvement in outcomes among patients randomized to the ePRO arm in this trial[51,52] and supports our hypothesis that improved symptom management based on better identification of symptoms through ePRO may improve adjuvant ET delivery and breast cancer outcomes.

A New Conceptual Model of Care: We propose to evaluate a new conceptual model of care for patients receiving adjuvant ET that utilizes ePRO and standardized pathways to guide symptom management, with the ultimate intent of improving treatment delivery (Figure 1). This innovative concept builds upon the published data demonstrating that ePRO collection improves clinical outcomes, including treatment delivery, in patients receiving chemotherapy.[51,52] Given the significant improvement in breast cancer-related outcomes with adjuvant ET and the detrimental effects of poor adherence and early

Figure 1: Conceptual Model Depicting Proposed New Approach to Symptom Assessment and Management During Adjuvant Endocrine Therapy

Ongoing symptom assessment through ePRO

Endocrine therapy initiation

Baseline symptoms

Treatment-emergent symptoms

Symptom assessment during routine intermittent clinic visits

Improved symptom management through better identification of symptoms and use of management pathways

Improved adherence

Reduced treatment discontinuation

discontinuation, interventions to minimize reasons underlying poor adherence and early discontinuation, such as incomplete symptom identification and management, are needed. Current rates of treatment delivery ("what is") are inadequate; efforts are needed to reduce early discontinuation rates ("what should be"). We hypothesize that incorporation of this new care model which addresses the current gap in symptom assessment and management will reduce premature discontinuation of adjuvant ET.
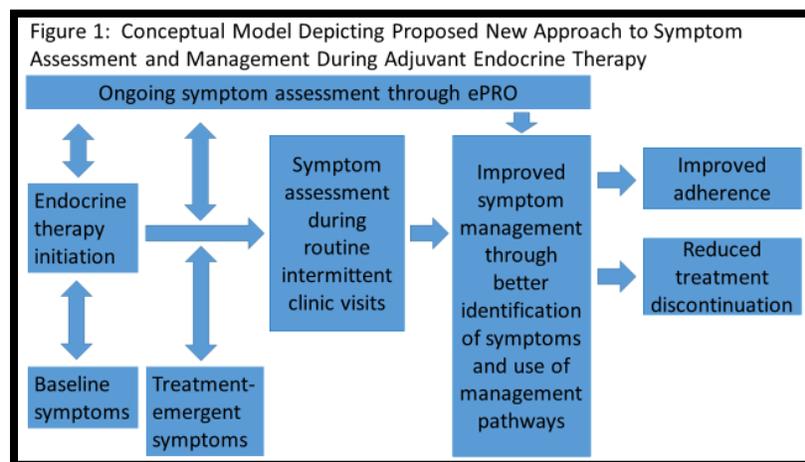
While many institutions are incorporating ePRO into routine oncology care,[39,48] we are not aware of any applications of ePRO linked to clinical pathways for symptom management with the aim of reducing early discontinuation of ET. We anticipate that this novel approach will lead to improved symptom assessment and management in breast cancer patients receiving adjuvant ET and, as was demonstrated in chemotherapy patients,[51] that it will result in enhanced treatment delivery as measured by a reduced early ET discontinuation rate.

Quantitative Baseline Data Summary: In addition to our published data cited above, we enrolled 329 patients initiating adjuvant ET in an IRB-approved prospective clinic-based cohort. We are using the Patient Viewpoint web-based interface[53,54] to collect longitudinal ePRO assessing common symptoms and adherence during adjuvant ET in this study population. Median follow-up to date is 24 months. To date, completion rates of each ePRO measure at 3 and 6 months after initiation of adjuvant ET in this cohort are approximately 85% and 75% respectively. Scores indicating severe symptoms in absolute terms and/or worsening of scores exceeding pre-defined thresholds trigger alerts to clinicians caring for the study participants. Clinical interventions in response to the alerts are not standardized in this cohort, however, Patient Viewpoint provides suggested clinician responses that we developed from expert consensus[46] which can serve as a foundation for the development of the clinical pathways for the proposed intervention.

Mean baseline scores for depression, anxiety, sleep disturbance, physical function, sexual function, endocrine symptoms, pain impact and fatigue in our study population are within the normal range. Not surprisingly, endocrine symptoms increased during the first 6 months of ET. Over 50% of our study population is overweight/obese. Only 75% of the study population had good adherence 6 months after ET initiation. Preliminary analysis demonstrates that, compared to participants with good adherence at 6 months, those with moderate or poor adherence at 6 months had more baseline endocrine symptoms and anxiety and greater increase in fatigue at 6 months (unpublished data). Analysis is ongoing to evaluate early ET discontinuation rates in this population and their association with ePRO and weight. Our preliminary results will be presented at the 2017 San Antonio Breast Cancer Symposium.

3. Target Audience:

The target audience for this intervention is patients with HR+ stage 0-III breast cancer initiating adjuvant ET at our institution. The Breast Cancer Program at the Kimmel Cancer Center at Johns Hopkins University has 3 medical oncology clinics located in Baltimore City, Baltimore County, and in Washington DC. Together, more than 1,200 new patients are treated by our 9 breast cancer medical oncologists annually. Most have HR+ early breast cancer and are candidates for adjuvant ET and therefore for the proposed intervention. Our work can also be expanded to the Johns Hopkins Clinical Research Network (JHCRN) consisting of 5 regional community and academic sites where many more breast cancer patients are seen.

The proposed intervention will be offered as a component of standard clinical care for patients initiating adjuvant ET at our institution. Every patient seen at our sites will be offered access to our breast cancer app, which will include personalized educational material including links to symptom management webinars and videos), wayfinding and appointment schedule information. ePRO collection through the app will be available to patients initiating adjuvant ET. When a clinician prescribes adjuvant ET to a patient in the EHR, a link will connect them to a

registration website with an invitation to enroll the patient in the ePRO intervention. Our research staff routinely screens patient charts prior to clinic visits and will flag patients expected to initiate adjuvant ET to remind clinicians to enroll them. Patients will be encouraged to complete the ePRO surveys as a means of communicating with their clinical team above and beyond existing communication avenues. Given that this intervention will be a component of standard clinical care, no recruitment efforts other than confirming access to and ability to use a smart device are planned. We will educate our clinical team about the ePRO intervention and encourage them to enroll their patients when they prescribe adjuvant ET. Data indicate that 77% of US adults had a smart phone as of 2016 with the proportion increasing steadily over time,[55] so we do not anticipate inability to access the app to be a significant barrier to participation. We will encourage patient engagement by sending electronic reminders to complete the ePRO assessments. We anticipate that each ePRO survey will take no more than 15 minutes to complete. Unless individual clinical circumstances dictate otherwise, patients will continue follow up with their clinicians every few months according to standard breast cancer guidelines,[56] thus the level of additional commitment required for patients participating in this intervention beyond routine clinical follow-up care will be minimal.

If successful, our intervention will directly impact our target audience by improving symptom identification and management and will reduce early discontinuation of adjuvant ET. In the future, this model could be replicated in patients receiving adjuvant ET at other institutions and could potentially be modified for use in patients receiving other oral cancer therapies. This proposed intervention is scalable and could potentially be available globally and incorporated into guidelines such as the NCCN Clinical Practice Guidelines for Breast Cancer.

4. Project Design and Methods:

In collaboration with emocha Mobile Health, the Johns Hopkins Breast Cancer Program is developing a mobile app called "Thrive". The goal of the app is to provide individualized educational materials, wayfinding navigation, treatment path communication and schedule tracking for all of our breast cancer patients. Funds for the app have been secured, a design prototype is available, focus groups have been completed and the design phase has been completed with development of low- and high-fidelity mock-ups. The app is under development and pilot testing is expected in November 2017. If awarded, these Pfizer/NCCN funds will be used to incorporate ePRO surveys into the app for patients initiating adjuvant ET, to develop and incorporate clinical pathways for symptom management based on ePRO scores into the app, to link ePRO data to the EHR and to evaluate the impact of ePRO collection during adjuvant ET on symptom management and ET discontinuation.

We have already received guidance from our IRB indicating that a research consent will not be required for this intervention. Prior to initiating the baseline ePRO survey, patients will be informed that their ePRO data will be monitored by their clinical teams and that it will be tabulated for the purpose of quality improvement. If a patient initiates the baseline ePRO survey, it will be assumed that he/she agrees with this stipulation. During the first 3 months of the funding period, we will submit an IRB application requesting a consent waiver to summarize our results and to review medical records for breast cancer patients prescribed adjuvant ET during the enrolment period for this project.

Our goal is to evaluate whether implementation of symptom assessment through ePRO collection early adjuvant ET along with timely symptom management according to standardized clinical pathways reduces the 12-month discontinuation rate of adjuvant ET. All HR+ breast cancer patients initiating adjuvant ET at our institution during an 8 month enrolment period will be eligible to participate. Based on the proportion of breast cancer cases diagnosed with locoregional disease (94%)[57] and on the proportion of breast cancer cases that are HR+ (approximately 75%),[58] we estimate >550 patients will be seen at our institution over an 8 month period who will have early stage HR+ breast cancer and therefore be candidates for adjuvant ET and for participation in our ePRO intervention. A maximum of 500 patients will be enrolled in this intervention and followed for 12 months. We will monitor the proportion of potentially eligible patients who enroll via chart review of all patients who initiate adjuvant ET. Basic clinical and demographic factors will be compared between eligible patients who do and do not enroll to ensure our enrolled patients are representative of our overall population. If necessary, we will expand enrolment to include patients seen at two centers within the JHCRN with whom we have a strong track record of collaboration with interventions including ePRO measures (unpublished data, presented at SABCS 2016 by Santa-Maria C et al).

Patients will complete ePRO surveys via the app at baseline and 1, 3, and 6 months after initiation of adjuvant ET. Each survey will be available for completion over approximately 2 weeks. We will measure the proportion of patients who complete the surveys to assess the feasibility of this intervention and as a measure of target audience engagement. Patients will receive electronic reminders to complete the surveys to facilitate engagement.

We will monitor symptoms which are common during adjuvant ET (based on our experience in our clinic-based cohort and on our literature review) and those for which established interventions are available for symptom management. We intend to use validated brief measures, primarily PROMIS and PRO-CTCAE tools, to create an ePRO survey with approximately 25 symptom questions at each time point). Based on emocha's extensive experience with public health interventions such as tuberculosis, hepatitis C and opioid addiction medication adherence with supplemental surveys, we anticipate a high proportion of patients will be willing to complete at least a symptom survey of this length via an app on their smart device.[59-61] Patients will also be given the option to complete each survey via the web if preferable. We have selected PROMIS and PRO-CTCAE measures based on brevity, reliability and validity in the outpatient cancer population, ease of score interpretation and demonstrated responsiveness to change in the outpatient cancer population.[62,63] Symptoms we plan to monitor include: anxiety, depression, joint pain, vaginal dryness, hot flashes, fatigue and sleep disturbance.

We will assess ET discontinuation by patient self-report of ET medication type and start/stop dates through the app at 1, 3, 6 and 12 months after treatment initiation and will confirm these data as needed through medical record review and/or clinician query. Adherence at 1, 3, 6 and 12 months will be assessed through the app using the 3-question Voils Measure of Nonadherence Part 1.[64] Patients will also self-report weight via the app. We plan to build the new app pages for the ePRO symptom survey, medication self-report, adherence questionnaire and weight self-report during the first 3 months of the funding period. ePRO symptom scores will be linked with the EHR and the clinical team will be able to review current scores and

trends over time prior to or at clinic visits. Once our ePRO survey tools are drafted by our project team, we will conduct focus groups and individual interviews with clinicians and breast cancer patients to obtain feedback and will modify the surveys as needed.

For each symptom measure, we will define a score threshold beyond which the symptom will be considered severe and a threshold for change compared to baseline beyond which the symptom will be considered to be worsening. These thresholds will be selected during the first 3 months of the funding period by considering score interpretation, responsiveness to change and the expected score distribution for each measure. In addition, we will engage stakeholders in the selection of these thresholds through focus groups and individual interviews with patients and clinicians. We will build triggers for electronic alerts to the clinical team into the app in case of any score which surpasses these pre-defined thresholds. Patients will be notified that their responses to submitted ePRO surveys have been received and, in case of score(s) which trigger alerts, that their clinical team will be contacting them regarding symptom management. The frequency of alerts will be reviewed over time and thresholds to define severe or worsening symptoms will be re-evaluated and modified as necessary.

Using the guidelines for symptom management in response to ePRO scores that our institution previously developed via expert consensus as a foundation,[46] along with standard clinical guidelines for symptom management in breast cancer survivors such as the NCCN Clinical Practice Guidelines in Oncology for Survivorship[65] and relevant ASCO clinical guidelines,[30,66,67] we will develop evidence-based clinical pathways guiding the management of severe or worsening symptoms identified through the ePRO surveys. These pathways will be drafted by our project team and evaluated in focus groups and/or individual interviews with other members of our breast cancer clinical team and breast cancer patients. Pathways will be re-assessed on an ongoing basis to ensure they reflect up-to-date care. Pathways will be linked to the symptom alerts clinicians receive in response to concerning ePRO scores. We will measure timely clinician compliance with interventions in the clinical pathways byreviewing medical records during the 4 weeks after each symptom alert is triggered to assess for clinician documentation of recommending at least 1 intervention in the pathway to address the relevant symptom.

At the end of the funding period, we expect to have an app available for ongoing use in our ET patients with a symptom assessment tool and management pathways that will allow our clinical teams to personalize care and reduce ET discontinuation. Should this project prove successful in reducing ET discontinuation, we will continue collecting ePRO during adjuvant ET using our app as a standard component of care at our institution. In addition, our app with its embedded ePRO measures, could be adjusted for use by other breast cancer programs or, with modification, to programs using other oral cancer therapies. If successful at reducing ET discontinuation, access to ePRO for symptom monitoring could potentially be offered by NCCN to its member institutions as a strategy to expand availability of this clinical tool. In addition, our institution could consider expansion of availability of our app to other programs.

5. Evaluation Design:

We will assess whether we have addressed the gap in clinical care (incomplete symptom assessment and symptom management during adjuvant ET) by evaluating our first two

objectives. The feasibility of symptom monitoring by collecting ePRO data via mobile app early during adjuvant ET (objective 1) will be assessed in two parts. First, we will evaluate if at least 65% of the patients enrolled in the ePRO intervention complete the baseline ePRO survey. Second, we will evaluate if at least 65% of the patients enrolled in the ePRO intervention complete at least one follow-up ePRO survey during the first 6 months of adjuvant ET (1, 3 and/or 6 months after treatment initiation). The target 65% completion rate for the ePRO surveys was selected based on published PRO completion rates in clinical trial populations of approximately 70-80%[11,50] with the expectation that completion rates may be lower when PRO measures are administered during routine clinical care. Although the main purpose of this proposal is to implement ePRO and symptom management, it is important to define expectations and the probability of success, therefore, we will continuously evaluate our design and progress. As a run-in step, if fewer than 25 of the first 50 enrolled patients complete the baseline ePRO survey, we will engage stakeholders and modify our intervention as needed to increase the completion rate of the baseline ePRO survey. Enrolment may also be expanded to additional sites within the JHCRN within the first few months if appropriate. Should we make any modifications in our strategy, we will report ePRO survey completion rates both prior to and after modification(s) in addition to summarizing overall survey completion rates. For the purposes of this objective, we will consider an ePRO survey to be "complete" if at least 1 question is answered. Bayesian continuous monitoring will be conducted to evaluate the feasibility of ePRO collection in our population. The Bayesian analysis will be started when a minimum of 100 patients have been enrolled, or approximately 2 months from the beginning of the study. On a monthly basis, the posterior probabilities of completing the baseline ePRO assessment and completing at least one follow-up ePRO assessment will be computed. We will conclude that the ePRO collection is infeasible if at any of the monitoring analyses, there is >50% chance to believe that the criteria are not met for either of the two probabilities. Table 1 gives the study operating characteristics based on the proposed Bayesian monitoring plan.

Scenario	Baseline Rate[A]	Follow-up Rate[B]	Expected Duration (Months)	Expected Sample Size	Success Rate[C]
I*	65%	65%	4.6	223	3.9%
II	70%	70%	14.6	415	59.0%
III	72%	72%	18.0	461	80.0%

Table 1: Study operating characteristics.
- Non-informative priors for Bayesian analysis
- Monthly enrolment rate assumed to be 55 patients
*: Scenario that corresponds to the null hypothesis
A: True baseline ePRO survey completion rate
B: True completion rate of at least 1 follow-up ePRO survey
C: Probability of concluding that the study is feasible for ePRO assessment

Implementation of pathways to guide the timely management of common symptoms identified through ePRO surveys (objective 2) will be evaluated by summarizing and reporting the clinician compliance rate with pathway recommendations and its confidence interval. We will consider clinicians to be compliant if they recommend any pathway-driven intervention within 4 weeks of the date that completion of an ePRO survey triggers a symptom alert. Clinician compliance with pathways will be assessed by chart review and, if necessary, by clinician query. Since the expected frequency of symptom alerts is not known, we will not set a

target compliance rate *a priori*, thus reporting of this objective will be descriptive and may inform the design of potential future studies evaluating clinician pathway compliance.

The overall aim of our intervention is to reduce ET discontinuation. We will consider our ePRO intervention successful if the 12-month ET discontinuation rate (objective 3) is ≤ 15%. This target was selected based on the historic published 12-month discontinuation rate of approximately 20%,[8-19] with the expectation that our intervention will halve discontinuation to 10%. With a sample size of 500, there will be >80% power to reject the null hypothesis at a two-sided type 1 error rate of 5%. In addition to reporting the 12-month discontinuation rate among all enrolled patients (intent to treat analysis), we will report the 12-month discontinuation rate with 95% confidence intervals separately among those who do and do not complete the baseline ePRO survey and among those who do and do not complete at least one follow-up ePRO survey. We will also report the 12-month discontinuation rate among all patients initiating adjuvant ET at our institution during our enrolment period regardless of enrolment in the ePRO intervention. Patients who are off ET for ≥6 consecutive weeks will be considered to have discontinued therapy. Whenever possible, ET discontinuation status will be based upon patient self-report via the app, however, we will obtain this information by chart review and clinician query if necessary. We will also describe ET adherence at each time point. We will evaluate whether the discontinuation rate is related to our intervention by correlating adherence and discontinuation with ePRO completion and symptom severity. We will explore relationships between weight and adherence, discontinuation and symptoms.

Appropriate statistical approaches including multiple imputation and sensitivity analysis will be used to handle missing data. Our results will be disseminated by submitting abstracts to major oncology meetings and by submitting manuscripts to leading oncology journals. If successful, we hope that this intervention will be disseminated to other programs and that symptom monitoring via ePRO during adjuvant ET will be incorporated into guidelines.

6. Detailed Workplan and Deliverables Schedule:

During the first 3 months of funding (January 1, 2018-March 31, 2018), we plan to submit an IRB application requesting a consent waiver, to develop and implement the clinical pathways, to incorporate the ePRO surveys into the app with links to the EHR, to define the symptom thresholds to trigger alerts and to develop the alert mechanism with links to the pathways. We plan to enroll patients during the next 8 months of funding (April 1, 2018-November 30, 2018). Data collection will be ongoing during the 8 months of enrolment and for ~12 months afterward. Treatment discontinuation will be assessed at the end of the 12-month follow-up period for each patient. Throughout the enrolment and follow-up period, we will conduct ongoing assessment of enrolment, ePRO completion rates, symptoms and pathway compliance. The first objective will be analyzed and reported in two parts: 1) the completion rate of the baseline ePRO survey will be reported approximately January 2019 and 2) the completion rates of the follow-up ePRO surveys will be reported after the conclusion of the funding period in approximately January 2020.   The second objective (clinician pathway compliance) will be analyzed and reported by approximately August 2019. The third objective (12-month ET discontinuation rate) will be analyzed in December 2019 and reported after the conclusion of the funding period in approximately January 2020. Data will be finalized, submitted for publication and disseminated after the completion of the funding period.

Requesting Organization:
The Johns Hopkins University School of Medicine

Project Title: Reducing Discontinuation Rate of Adjuvant Endocrine Therapy through Symptom Monitoring and Management

Table of Deliverables

Objective 1: To evaluate the feasibility of symptom monitoring by collecting ePRO data via a mobile app during the first 6 months of adjuvant ET in patients with early stage HR+ breast cancer			
Activity	**Deliverable**	**Responsible Person(s)**	**Target Completion Date**
Finalize list of symptoms to monitor by collecting ePRO data via mobile app	List of symptoms to monitor	Karen Smith, MD MPH Vered Stearns, MD Claire Snyder, PhD Elissa Bantug, MHS	January 31, 2018
Finalize list of questionnaires to use to monitor selected symptoms	List of symptom questionnaires	Karen Smith, MD MPH Vered Stearns, MD Claire Snyder, PhD Elissa Bantug, MHS	January 31, 2018
Establish thresholds to define severe and worsening symptoms based on scores on selected questionnaires	List of cut-off scores beyond which symptoms will be considered severe and degree of change in scores compared to baseline beyond which follow-up scores will be considered representative of worsening symptoms	Karen Smith, MD MPH Vered Stearns, MD Claire Snyder, PhD Elissa Bantug, MHS	January 31, 2018
Incorporate ePRO measures into app	Draft text to be incorporated into app • Introduction • Questions and answer options for selected symptom questionnaires (to be administered at baseline and 1,3, and 6 months after initiation of ET)	Karen Smith, MD MPH Vered Stearns, MD Claire Snyder, PhD Elissa Bantug, MHS	January 31, 2018

	- Questions and answer options for Voils Measure of Nonadherence (to be administered at baseline and 1,3, 6 and 12 months after initiation of ET) - Wording for self-report questions regarding endocrine therapy regimen and start/stop dates (to be administered at baseline and 1,3, 6 and 12 months after initiation of ET) - Wording for self-report questions regarding weight (to be administered at baseline and 1,3, 6 and 12 months after initiation of ET) - Wording for notification patients will receive regarding receipt of their answers and expected contact from clinical team (if scores are concerning)		
	Mock-up and implement app pages for ePRO measures	emocha Mobile Health	March 31, 2018
	Develop mechanisms to trigger each ePRO survey at appropriate time points, for each survey to stay open for completion over approximately 2 weeks and for electronic reminders to be sent to patients regarding each survey	emocha Mobile Health	March 31, 2018

Requesting Organization:
The Johns Hopkins University School of Medicine

Develop process for enrolling patients in ePRO intervention	Create HIPAA-compliant link between EHR and emocha website allowing clinicians prescribing adjuvant ET through the EHR to enroll patients in ePRO intervention on emocha website	emocha Mobile Health	March 31, 2018
Develop ePRO score reports and link between ePRO scores and EHR	Mock-up of score report (including current scores and trends over time)	Karen Smith, MD MPH Vered Stearns, MD Claire Snyder, PhD Elissa Bantug, MHS	January 31, 2018
	Create link between ePRO scores (current and trending over time) and EHR	emocha Mobile Health	March 31, 2018
Develop mechanism for alerts to clinical team for severe or worsening symptoms based on ePRO scores	Draft text of alert to be sent electronically to clinical team for severe or worsening symptoms; identify clinical team members to receive alerts	Karen Smith, MD MPH Vered Stearns, MD Claire Snyder, PhD Elissa Bantug, MHS	January 31, 2018
	Implement automated electronic alerts to send to clinical team in case of concerning scores on ePRO measures which exceed pre-defined thresholds	emocha Mobile Health	March 31, 2018
Enroll patients with HR+ early breast cancer initiating adjuvant ET in ePRO intervention	Not applicable	Johns Hopkins breast cancer clinical team	Enrolment will be ongoing from April 1, 2018 through November 30, 2018
Evaluate enrolment in ePRO intervention	# of patients initiating adjuvant ET, # of patients initiating adjuvant ET whose clinicians go to emocha enrolment website, # of patients initiating adjuvant ET who are enrolled in ePRO intervention, proportion of patients	emocha Mobile Health Karen Smith, MD MPH Vered Stearns, MD Chenguang Wang, PhD	Enrolment will be evaluated on an ongoing basis from April 1, 2018 through November 30, 2018

	enrolled after clinician goes to enrolment website (to be summarized monthly)		
Evaluate completion rate of baseline ePRO survey	# of patients who complete baseline survey, proportion of enrolled patients who complete baseline survey, (to be summarized monthly, strategy to be reassessed if <25 of first 50 enrolled patients do not comlete baseline ePRO survey, Bayesian continuous monitoring to be implemented once enrolment surpasses predefined target)	emocha Mobile Health Karen Smith, MD MPH Vered Stearns, MD Chenguang Wang, PhD	Baseline surveys may be completed within approximately 2 weeks of enrolment (i.e. baseline surveys will be able to be completed April 1, 2018 through approximately December 15, 2018) We anticipate reporting this endpoint approximately January 2019.
Evaluate completion rate of follow-up ePRO surveys	# of enrolled patients who complete each follow-up ePRO survey, proportions of enrolled patients who complete ePRO surveys at 1, 3, 6 and 12 months after initiation of adjuvant ET	emocha Mobile Health Karen Smith, MD MPH Vered Stearns, MD Chenguang Wang, PhD	Follow-up surveys will be able to be completed from 1 month after enrolment until 12 months after enrolment (plus approximately 2 weeks). (i.e. follow-up surveys will be able to be completed approximately May 1,

			2018 through December 15, 2019)
			We anticipate reporting this endpoint approximately January 2020.
Follow patients enrolled in ePRO intervention	Patients will receive electronic reminders asking them to complete ePRO surveys at baseline and at 1, 3, 6 and 12 months after initiation of adjuvant ET. Symptoms will be assessed by ePRO at all time points except the 12 month time point. Adherence, ET regimen and weight will be assessed at all time points.	Not applicable	Patients will be followed for ~12 months (+ 2 weeks) after enrolment (i.e. follow-up will be ongoing until approximately December 15, 2019)
Describe ePRO data over time	Summary of data collected from ePRO surveys at each time point (to be summarized monthly)	emocha Mobile Health Karen Smith, MD MPH Vered Stearns, MD Chenguang Wang, PhD	Ongoing throughout follow-up period
Obtain stakeholder feedback regarding ePRO intervention through focus groups and individual interviews with breast cancer patients and breast cancer clinical team	Written summaries from focus groups and individual interviews addressing any of the following issues (or other issues related to the ePRO intervention as the need arises): • Selected symptoms for monitoring • Questionnaires chosen to monitor symptoms • Process of enrolment into ePRO intervention	Elissa Bantug, MHS	Ongoing as needed throughout funding period; schedule to be determined

	• App interface • Thresholds to define severe and worsening symptoms • ePRO score reports		
Modify ePRO intervention based on feedback from stakeholders as needed	To be determined	Karen Smith, MD MPH Vered Stearns, MD Claire Snyder, PhD Elissa Bantug, MHS emocha Mobile Health	Ongoing throughout funding period as needed; schedule to be determined
Objective 2: To implement clinical pathways guiding timely management of common symptoms identified through ePRO collected via mobile app during the first 6 months of adjuvant ET			
Finalize selection of symptoms for which evidence-based management pathways will be created	List of symptoms for which pathways will be created	Karen Smith, MD MPH Vered Stearns, MD Claire Snyder, PhD Elissa Bantug, MHS	January 31, 2018
Draft management pathways for selected symptoms	Draft of pathways for selected symptoms	Karen Smith, MD MPH Vered Stearns, MD Claire Snyder, PhD Elissa Bantug, MHS	January 31, 2018
Obtain stakeholder feedback regarding symptom pathways	Written summaries from focus groups and individual interviews with clinicians and breast cancer patients	Elissa Bantug, MHS	Ongoing throughout funding period as needed; schedule to be determined
Link pathways to symptom alerts	Develop electronic links that connect symptom alert message(s) sent to clinical team with appropriate pathway(s) guiding management for relevant symptom(s)	emocha Mobile Health	March 31, 2018
Implement symptom management pathways	Not applicable	emocha Mobile Health	Links to pathways will be sent to clinicians receiving symptom

			alerts throughout the period during which patients complete baseline and 1,3, and 6 month surveys (i.e. from approximately April 1, 2018-June 15, 2019)
Manage symptomatic patients according to pathways	Not applicable	Johns Hopkins breast cancer clinical team	Ongoing while patients complete baseline and 1,3, and 6 month surveys and for 4 weeks afterwards (i.e. from approximately April 1, 2018-July 15, 2019).
Describe pathway triggers	# of instances each pathway is triggered by severe or worsening ePRO scores (to be summarized monthly)	emocha Mobile Health Chenguang Wang, PhD	Ongoing while patients complete baseline and 1,3, and 6 month surveys (i.e. from approximately April 1, 2018-June 15, 2019)
Evaluate clinician compliance with pathways	Proportion of cases in which chart review (or clinician query) confirms that any pathway-driven intervention was recommended within 4 weeks of each instance in which a severe or worsening symptom triggers an alert linked to a symptom pathway	Karen Smith, MD MPH Vered Stearns, MD Chenguang Wang, PhD emocha Mobile Health	Pathway compliance to be evaluated during period in which patients complete baseline and 1,3, and 6 month surveys and for 4 weeks afterwards (i.e. from

			Approximately April 1, 2018-July 15, 2019). We anticipate reporting this endpoint approximately August 2019.
Describe clinical steps taken in response to alerts due to severe or worsening ePRO scores	Chart review summarizing clinical steps taken in response to alerts	Karen Smith MD MPH	Clinical steps taken in response to alerts will be described at the same time as pathway compliance is assessed.
Objective 3: To evaluate the 12-month adjuvant ET discontinuation rate in early stage HR+ breast cancer patients enrolled in ePRO symptom monitoring			
Describe ET use over time	# of patients who initiate ET (according to type of endocrine therapy), proportion of patients who discontinue ET at each time point after baseline, 12-month ET discontinuation rate Note: patients who switch from one type of ET to another will not be considered to have discontinued ET. Note: patients who are off ET for ≥ 6 consecutive weeks will be considered to have discontinued ET	Karen Smith, MD MPH Vered Stearns, MD Chenguang Wang, PhD emocha Mobile Health	We anticipate summarizing and analyzing this data at the end of the funding period (December 2019). We anticipate reporting our findings after the conclusion of the funding period (approximately January 2020).

Additional Activities (not linked to specific objectives)			
Submit IRB application requesting a consent waiver to review medical records for breast cancer patients prescribed adjuvant ET during the funding period and to summarize results from ePRO collection in this population	Letter indicating IRB approval	Karen Smith, MD MPH Vered Stearns, MD	March 31, 2018
Describe weight over time	Summary of patient-reported weight at each time point	emocha Mobile Health Chenguang Wang, PhD	To be summarized by end of funding period with plan to report approximately January 2020.
Describe adherence to ET over time	Scores on Voils Measure of Nonadherence	Chenguang Wang, PhD emocha Mobile Health	To be summarized by end of funding period with plan to report approximately January 2020.
Explore relationships between ET discontinuation, adherence, symptoms, weight, pathway compliance and clinical/demographic factors over time	Exploratory statistical analysis	emocha Mobile Health Chenguang Wang, PhD Karen Smith, MD MPH Vered Stearns, MD Claire Snyder, PhD Elissa Bantug, MHS	We plan to analyze and report this data at the conclusion of the funding period (approximately January 2020).
Disseminate findings	Submit findings for presentation/publication and disseminate on social media	Karen Smith, MD MPH Vered Stearns, MD Elissa Bantug, MHS	After completion of funding period (early 2020)

Requesting Organization:
The Johns Hopkins University School of Medicine

E. REFERENCES:

1.	Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, McGale P, Pan HC, Taylor C, Wang YC, Dowsett M, Ingle J, Peto R: Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 378:771-84, 2011

2.	Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, Abraham M, Medeiros Alencar VH, Badran A, Bonfill X, Bradbury J, Clarke M, Collins R, Davis SR, Delmestri A, Forbes JF, Haddad P, Hou MF, Inbar M, Khaled H, Kielanowska J, Kwan WH, Mathew BS, Mittra I, Muller B, Nicolucci A, Peralta O, Pernas F, Petruzelka L, Pienkowski T, Radhika R, Rajan B, Rubach MT, Tort S, Urrutia G, Valentini M, Wang Y, Peto R, Adjuvant Tamoxifen: Longer Against Shorter Collaborative G: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 381:805-16, 2013

3.	Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Therasse P, Palmer MJ, Pater JL: A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 349:1793-802, 2003

4.	Goss PE, Ingle JN, Pritchard KI, Robert NJ, Muss H, Gralow J, Gelmon K, Whelan T, Strasser-Weippl K, Rubin S, Sturtz K, Wolff AC, Winer E, Hudis C, Stopeck A, Beck JT, Kaur JS, Whelan K, Tu D, Parulekar WR: Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. N Engl J Med 375:209-19, 2016

5.	Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Rowden D, Solky AJ, Stearns V, Winer EP, Griggs JJ: Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol 32:2255-69, 2014

6.	Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz MP, Goldstein LJ, Isakoff SJ, Lyons J, Marcom PK, Mayer IA, McCormick B, Moran MS, O'Regan RM, Patel SA, Pierce LJ, Reed EC, Salerno KE, Schwartzberg LS, Sitapati A, Smith KL, Smith ML, Soliman H, Somlo G, Telli M, Ward JH, Shead DA, Kumar R: NCCN Guidelines Insights: Breast Cancer, Version 1.2017. J Natl Compr Canc Netw 15:433-451, 2017

7.	Morigi C: Highlights from the 15th St Gallen International Breast Cancer Conference 15-18 March, 2017, Vienna: tailored treatments for patients with early breast cancer. Ecancermedicalscience 11:732, 2017

8.	Hershman DL, Kushi LH, Shao T, Buono D, Kershenbaum A, Tsai WY, Fehrenbacher L, Gomez SL, Miles S, Neugut AI: Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 28:4120-8, 2010

9.	Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW: Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. Breast Cancer Res Treat 134:459-78, 2012

10.	Henry NL, Azzouz F, Desta Z, Li L, Nguyen AT, Lemler S, Hayden J, Tarpinian K, Yakim E, Flockhart DA, Stearns V, Hayes DF, Storniolo AM: Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. J Clin Oncol 30:936-42, 2012

11.	Kadakia KC, Snyder CF, Kidwell KM, Seewald NJ, Flockhart DA, Skaar TC, Desta Z, Rae JM, Otte JL, Carpenter JS, Storniolo AM, Hayes DF, Stearns V, Henry NL: Patient-Reported Outcomes and

Early Discontinuation in Aromatase Inhibitor-Treated Postmenopausal Women With Early Stage Breast Cancer. Oncologist 21:539-46, 2016

12.   Henry NL, Giles JT, Ang D, Mohan M, Dadabhoy D, Robarge J, Hayden J, Lemler S, Shahverdi K, Powers P, Li L, Flockhart D, Stearns V, Hayes DF, Storniolo AM, Clauw DJ: Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. Breast Cancer Res Treat 111:365-72, 2008

13.   Kidwell KM, Harte SE, Hayes DF, Storniolo AM, Carpenter J, Flockhart DA, Stearns V, Clauw DJ, Williams DA, Henry NL: Patient-reported symptoms and discontinuation of adjuvant aromatase inhibitor therapy. Cancer 120:2403-11, 2014

14.   Hershman DL, Kushi LH, Hillyer GC, Coromilas E, Buono D, Lamerato L, Bovbjerg DH, Mandelblatt JS, Tsai WY, Zhong X, Jacobson JS, Wright JD, Neugut AI: Psychosocial factors related to non-persistence with adjuvant endocrine therapy among women with breast cancer: the Breast Cancer Quality of Care Study (BQUAL). Breast Cancer Res Treat 157:133-43, 2016

15.   Kadakia KC, Kidwell KM, Seewald NJ, Snyder CF, Storniolo AM, Otte JL, Flockhart DA, Hayes DF, Stearns V, Henry NL: Prospective assessment of patient-reported outcomes and estradiol and drug concentrations in patients experiencing toxicity from adjuvant aromatase inhibitors. Breast Cancer Res Treat, 2017

16.   Rae JM, Sikora MJ, Henry NL, Li L, Kim S, Oesterreich S, Skaar TC, Nguyen AT, Desta Z, Storniolo AM, Flockhart DA, Hayes DF, Stearns V, investigators C: Cytochrome P450 2D6 activity predicts discontinuation of tamoxifen therapy in breast cancer patients. Pharmacogenomics J 9:258-64, 2009

17.   Kimmick G, Anderson R, Camacho F, Bhosle M, Hwang W, Balkrishnan R: Adjuvant hormonal therapy use among insured, low-income women with breast cancer. J Clin Oncol 27:3445-51, 2009

18.   He W, Fang F, Varnum C, Eriksson M, Hall P, Czene K: Predictors of Discontinuation of Adjuvant Hormone Therapy in Patients With Breast Cancer. J Clin Oncol 33:2262-9, 2015

19.   Kemp A, Preen DB, Saunders C, Boyle F, Bulsara M, Malacova E, Roughead EE: Early discontinuation of endocrine therapy for breast cancer: who is at risk in clinical practice? Springerplus 3:282, 2014

20.   Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, Kwan M, Gomez SL, Neugut AI: Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 126:529-37, 2011

21.   Chirgwin JH, Giobbie-Hurder A, Coates AS, Price KN, Ejlertsen B, Debled M, Gelber RD, Goldhirsch A, Smith I, Rabaglio M, Forbes JF, Neven P, Lang I, Colleoni M, Thurlimann B: Treatment Adherence and Its Impact on Disease-Free Survival in the Breast International Group 1-98 Trial of Tamoxifen and Letrozole, Alone and in Sequence. J Clin Oncol 34:2452-9, 2016

22.   Hershman DL: Sticking to It: Improving Outcomes by Increasing Adherence. J Clin Oncol 34:2440-2, 2016

23.   Kimmick G, Edmond SN, Bosworth HB, Peppercorn J, Marcom PK, Blackwell K, Keefe FJ, Shelby RA: Medication taking behaviors among breast cancer patients on adjuvant endocrine therapy. Breast 24:630-6, 2015

24.   Chim K, Xie SX, Stricker CT, Li QS, Gross R, Farrar JT, DeMichele A, Mao JJ: Joint pain severity predicts premature discontinuation of aromatase inhibitors in breast cancer survivors. BMC Cancer 13:401, 2013

25.   Hadji P, Jackisch C, Bolten W, Blettner M, Hindenburg HJ, Klein P, Konig K, Kreienberg R, Rief W, Wallwiener D, Zaun S, Harbeck N: COMPliance and Arthralgia in Clinical Therapy: the COMPACT trial, assessing the incidence of arthralgia, and compliance within the first year of adjuvant anastrozole therapy. Ann Oncol 25:372-7, 2014

Requesting Organization:
The Johns Hopkins University School of Medicine

26.   Oberguggenberger A, Hubalek M, Sztankay M, Meraner V, Beer B, Oberacher H, Giesinger J, Kemmler G, Egle D, Gamper EM, Sperner-Unterweger B, Holzner B: Is the toxicity of adjuvant aromatase inhibitor therapy underestimated? Complementary information from patient-reported outcomes (PROs). Breast Cancer Res Treat 128:553-61, 2011

27.   Hershman DL, Tsui J, Meyer J, Glied S, Hillyer GC, Wright JD, Neugut AI: The change from brand-name to generic aromatase inhibitors and hormone therapy adherence for early-stage breast cancer. J Natl Cancer Inst 106, 2014

28.   Neugut AI, Zhong X, Wright JD, Accordino M, Yang J, Hershman DL: Nonadherence to Medications for Chronic Conditions and Nonadherence to Adjuvant Hormonal Therapy in Women With Breast Cancer. JAMA Oncol 2:1326-1332, 2016

29.   Cella D, Fallowfield LJ: Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy. Breast Cancer Res Treat 107:167-80, 2008

30.   Andersen BL, DeRubeis RJ, Berman BS, Gruman J, Champion VL, Massie MJ, Holland JC, Partridge AH, Bak K, Somerfield MR, Rowland JH, American Society of Clinical O: Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol 32:1605-19, 2014

31.   Irwin ML, Cartmel B, Gross CP, Ercolano E, Li F, Yao X, Fiellin M, Capozza S, Rothbard M, Zhou Y, Harrigan M, Sanft T, Schmitz K, Neogi T, Hershman D, Ligibel J: Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. J Clin Oncol 33:1104-11, 2015

32.   Hickey M, Saunders C, Partridge A, Santoro N, Joffe H, Stearns V: Practical clinical guidelines for assessing and managing menopausal symptoms after breast cancer. Ann Oncol 19:1669-80, 2008

33.   Imayama I, Alfano CM, Neuhouser ML, George SM, Wilder Smith A, Baumgartner RN, Baumgartner KB, Bernstein L, Wang CY, Duggan C, Ballard-Barbash R, McTiernan A: Weight, inflammation, cancer-related symptoms and health related quality of life among breast cancer survivors. Breast Cancer Res Treat 140:159-76, 2013

34.   Caan BJ, Emond JA, Su HI, Patterson RE, Flatt SW, Gold EB, Newman VA, Rock CL, Thomson CA, Pierce JP: Effect of postdiagnosis weight change on hot flash status among early-stage breast cancer survivors. J Clin Oncol 30:1492-7, 2012

35.   Forsythe LP, Alfano CM, George SM, McTiernan A, Baumgartner KB, Bernstein L, Ballard-Barbash R: Pain in long-term breast cancer survivors: the role of body mass index, physical activity, and sedentary behavior. Breast Cancer Res Treat 137:617-30, 2013

36.   Su HI, Sammel MD, Springer E, Freeman EW, DeMichele A, Mao JJ: Weight gain is associated with increased risk of hot flashes in breast cancer survivors on aromatase inhibitors. Breast Cancer Res Treat 124:205-11, 2010

37.   McPhail S, Haines T: Response shift, recall bias and their effect on measuring change in health-related quality of life amongst older hospital patients. Health Qual Life Outcomes 8:65, 2010

38.   Coolbrandt A, Van den Heede K, Vanhove E, De Bom A, Milisen K, Wildiers H: Immediate versus delayed self-reporting of symptoms and side effects during chemotherapy: does timing matter? Eur J Oncol Nurs 15:130-6, 2011

39.   Basch E: Patient-Reported Outcomes - Harnessing Patients' Voices to Improve Clinical Care. N Engl J Med 376:105-108, 2017

40.   Snyder CF, Jensen RE, Segal JB, Wu AW: Patient-reported outcomes (PROs): putting the patient perspective in patient-centered outcomes research. Med Care 51:S73-9, 2013

Requesting Organization:
The Johns Hopkins University School of Medicine

41.   Chen J, Ou L, Hollis SJ: A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. BMC Health Serv Res 13:211, 2013

42.   Kotronoulas G, Kearney N, Maguire R, Harrow A, Di Domenico D, Croy S, MacGillivray S: What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol 32:1480-501, 2014

43.   Basch E, Iasonos A, McDonough T, Barz A, Culkin A, Kris MG, Scher HI, Schrag D: Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. Lancet Oncol 7:903-9, 2006

44.   Snyder CF, Smith KC, Bantug ET, Tolbert EE, Blackford AL, Brundage MD, Board PRODPSA: What do these scores mean? Presenting patient-reported outcomes data to patients and clinicians to improve interpretability. Cancer 123:1848-1859, 2017

45.   Bantug ET, Coles T, Smith KC, Snyder CF, Rouette J, Brundage MD, Board PRODPSA: Graphical displays of patient-reported outcomes (PRO) for use in clinical practice: What makes a pro picture worth a thousand words? Patient Educ Couns 99:483-90, 2016

46.   Hughes EF, Wu AW, Carducci MA, Snyder CF: What can I do? Recommendations for responding to issues identified by patient-reported outcomes assessments used in clinical practice. J Support Oncol 10:143-8, 2012

47.   Zon RT, Frame JN, Neuss MN, Page RD, Wollins DS, Stranne S, Bosserman LD: American Society of Clinical Oncology Policy Statement on Clinical Pathways in Oncology. J Oncol Pract 12:261-6, 2016

48.   Wagner LI, Schink J, Bass M, Patel S, Diaz MV, Rothrock N, Pearman T, Gershon R, Penedo FJ, Rosen S, Cella D: Bringing PROMIS to practice: brief and precise symptom screening in ambulatory cancer care. Cancer 121:927-34, 2015

49.   Snyder C, Wu AW: Users' Guide to Integrating Patient-Reported Outcomes in Electronic Health Records, 2017

50.   Judson TJ, Bennett AV, Rogak LJ, Sit L, Barz A, Kris MG, Hudis CA, Scher HI, Sabattini P, Schrag D, Basch E: Feasibility of long-term patient self-reporting of toxicities from home via the Internet during routine chemotherapy. J Clin Oncol 31:2580-5, 2013

51.   Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, Rogak L, Bennett AV, Dueck AC, Atkinson TM, Chou JF, Dulko D, Sit L, Barz A, Novotny P, Fruscione M, Sloan JA, Schrag D: Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol 34:557-65, 2016

52.   Basch E, Deal AM, Dueck AC, Scher HI, Kris MG, Hudis C, Schrag D: Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA, 2017

53.   Snyder CF, Blackford AL, Wolff AC, Carducci MA, Herman JM, Wu AW, PatientViewpoint Scientific Advisory B: Feasibility and value of PatientViewpoint: a web system for patient-reported outcomes assessment in clinical practice. Psychooncology 22:895-901, 2013

54.   Wu AW, White SM, Blackford AL, Wolff AC, Carducci MA, Herman JM, Snyder CF, PatientViewpoint Scientific Advisory B: Improving an electronic system for measuring PROs in routine oncology practice. J Cancer Surviv 10:573-82, 2016

55.   Pew Research Center Mobile Fact Sheet. http://www.pewinternet.org/fact-sheet/mobile/. Accessed September 18, 2017.,

56.   Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, Cannady RS, Pratt-Chapman ML, Edge SB, Jacobs LA, Hurria A, Marks LB, LaMonte SJ, Warner E, Lyman GH, Ganz

Requesting Organization:
The Johns Hopkins University School of Medicine

PA: American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol 34:611-35, 2016

57.   Siegel RL, Miller KD, Jemal A: Cancer Statistics, 2017. CA Cancer J Clin 67:7-30, 2017

58.   Li CI, Daling JR, Malone KE: Incidence of invasive breast cancer by hormone receptor status from 1992 to 1998. J Clin Oncol 21:28-34, 2003

59.   Seiguer S, Rios K, Townsend K: Video DOT Implementation in Maryland: Outcomes And Opportunities.
https://phpa.health.maryland.gov/OIDPCS/CTBCP/CTBCPDocuments/2017%20Annual%20Update/VideoDOT%20(1).pdf. Accessed September 19, 2017.,

60.   Holzman S, Shah M: Feasibility, Acceptability, and Cost of Video Directly Observed Therapy in Maryland. Presented at the National Tuberculosis Controllers Association Annual Conference, Atlanta, GA., April 19-21, 2017,

61.   Rubinstein R, Saddiqui S, Wiltz-Beckham D, Fields K: Costs Saved Using Video Directly Observed Therapy on Tuberculosis Patients. . Presented at the National Association of County and City Health Officials Annual Conference, Pittsburgh, PA. , July 11-13, 2017,

62.   Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, Atkinson TM, Bennett AV, Denicoff AM, O'Mara AM, Li Y, Clauser SB, Bryant DM, Bearden JD, 3rd, Gillis TA, Harness JK, Siegel RD, Paul DB, Cleeland CS, Schrag D, Sloan JA, Abernethy AP, Bruner DW, Minasian LM, Basch E, National Cancer Institute PROCSG: Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol 1:1051-9, 2015

63.   Cook KF, Jensen SE, Schalet BD, Beaumont JL, Amtmann D, Czajkowski S, Dewalt DA, Fries JF, Pilkonis PA, Reeve BB, Stone AA, Weinfurt KP, Cella D: PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across a range of chronic conditions. J Clin Epidemiol 73:89-102, 2016

64.   Voils CI, Maciejewski ML, Hoyle RH, Reeve BB, Gallagher P, Bryson CL, Yancy WS, Jr.: Initial validation of a self-report measure of the extent of and reasons for medication nonadherence. Med Care 50:1013-9, 2012

65.   Denlinger CS, Ligibel JA, Are M, Baker KS, Broderick G, Demark-Wahnefried W, Friedman DL, Goldman M, Jones LW, King A, Ku GH, Kvale E, Langbaum TS, McCabe MS, Melisko M, Montoya JG, Mooney K, Morgan MA, Moslehi JJ, O'Connor T, Overholser L, Paskett ED, Peppercorn J, Rodriguez MA, Ruddy KJ, Sanft T, Silverman P, Smith S, Syrjala KL, Urba SG, Wakabayashi MT, Zee P, McMillian NR, Freedman-Cass DA: NCCN Guidelines Insights: Survivorship, Version 1.2016. J Natl Compr Canc Netw 14:715-24, 2016

66.   Paice JA, Portenoy R, Lacchetti C, Campbell T, Cheville A, Citron M, Constine LS, Cooper A, Glare P, Keefe F, Koyyalagunta L, Levy M, Miaskowski C, Otis-Green S, Sloan P, Bruera E: Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 34:3325-45, 2016

67.   Bower JE, Bak K, Berger A, Breitbart W, Escalante CP, Ganz PA, Schnipper HH, Lacchetti C, Ligibel JA, Lyman GH, Ogaily MS, Pirl WF, Jacobsen PB, American Society of Clinical O: Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. J Clin Oncol 32:1840-50, 2014

68.   Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz M, Goldstein LJ, Hudis CA, Isakoff SJ, Marcom PK, Mayer IA, McCormick B, Moran M, Patel SA, Pierce LJ, Reed EC, Salerno KE, Schwartzberg LS, Smith KL, Smith ML, Soliman H, Somlo G, Telli M, Ward JH, Shead DA, Kumar R: NCCN Guidelines Insights Breast Cancer, Version 1.2016. J Natl Compr Canc Netw 13:1475-85, 2015

Requesting Organization:
The Johns Hopkins University School of Medicine

69.   Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz M, Goldstein LJ, Hudis CA, Isakoff SJ, Marcom PK, Mayer IA, McCormick B, Moran M, Patel SA, Pierce LJ, Reed EC, Salerno KE, Schwartzberg LS, Smith KL, Smith ML, Soliman H, Somlo G, Telli M, Ward JH, Shead DA, Kumar R: Breast Cancer Version 2.2015. J Natl Compr Canc Netw 13:448-75, 2015

70.   Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz M, Goldstein LJ, Hudis CA, Isakoff SJ, Marcom PK, Mayer IA, McCormick B, Moran M, Patel SA, Pierce LJ, Reed EC, Salerno KE, Schwartzberg LS, Smith KL, Smith ML, Soliman H, Somlo G, Telli M, Ward JH, Shead DA, Kumar R: Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 14:324-54, 2016

71.   Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Solky AJ, Stearns V, Winer EP, Griggs JJ: Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression. J Clin Oncol 34:1689-701, 2016

72.   Krop I, Ismaila N, Andre F, Bast RC, Barlow W, Collyar DE, Hammond ME, Kuderer NM, Liu MC, Mennel RG, Van Poznak C, Wolff AC, Stearns V: Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. J Clin Oncol 35:2838-2847, 2017

73.   Venook AP, Arcila ME, Benson AB, 3rd, Berry DA, Camidge DR, Carlson RW, Choueiri TK, Guild V, Kalemkerian GP, Kurzrock R, Lovly CM, McKee AE, Morgan RJ, Olszanski AJ, Redman MW, Stearns V, McClure J, Birkeland ML: NCCN Working Group report: designing clinical trials in the era of multiple biomarkers and targeted therapies. J Natl Compr Canc Netw 12:1629-49, 2014