Study Title: ***Implementing systematic distress screening in breast cancer***

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STUDY PROTOCOL: *Distress Screening in Breast Cancer_V2*

TITLE: *Implementing systematic distress screening in breast cancer*

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TABLE OF CONTENTS

1.0 BACKGROUND AND HYPOTHESES

There are currently over 3 million breast cancer survivors in the United States, representing approximately 41% of all female cancer survivors.[1] The majority of breast cancer patients will survive their disease and enter into a prolonged survivorship phase of care.[2] Breast cancer patients are at heightened risk for a multitude of physical and psychosocial effects of disease and treatment, including psychological distress (defined as psychiatric morbidity or prevalence of psychiatric disorders, particularly anxiety and depression).[3] Distress is associated with substantial morbidity in breast cancer patients.[4-5] A recent systematic review concluded that patients who experience breast cancer have higher rates of psychological distress than the general population.[6-7] Negative effects of distress in breast cancer patients include decreased health-related quality of life,[8-9], decreased cellular immunity,[10] poorer medication adherence,[11] increased hospitalizations and health care utilization,[12-13] maladaptive coping,[14] increased symptom burden,[15-16] delayed return to work,[17] and poorer overall survival.[18-20] Meta-analyses of psychosocial and medical interventions for breast cancer patients, such as counseling, pharmacotherapy, health education, exercise, and coping skills training, concluded that these techniques can improve psychosocial functioning, health-related quality of life, symptom burden, and emotional well-being.[21-22]

Unfortunately, it has been shown that identification of distress in breast cancer patients is sub-optimal, leading to increased burden of disease as well as increased strain on our health care system.[4] Cancer patients report that clinicians do not understand their psychosocial needs, and fail to recognize, treat, or offer referral for treatment of distress.[4] In addition, several studies have shown that oncologists substantially underestimate patient psychosocial needs.[4] Prominent oncology organizations such as the American Psychological Oncology Society, Association of Oncology Social Work, and the Oncology Nursing Society now endorse large-scale distress screening programs for cancer patients[23-25, 26]

However, the effectiveness of systematic distress screening on improved identification of distress, referral for services, and outcomes for breast cancer patients in non-academic settings has not been established.[27-29] Distress screening programs are not without costs, and the benefits may be limited.[30] Small randomized trials of distress screening have shown modest benefits for cancer patients, typically in improved initiation of referrals;[31-33] however, observational trials have found only partial, if any, benefit. The impact of distress screening on referral completion, patient-reported outcomes, and utilization of health care services in larger, community-based studies is rarely measured.[33-35] This raises serious questions about the effectiveness of large scale distress screening programs in non-academic settings, as evidenced in recent literature calling for the need for continued research in this area.[36,29] Our translational research proposal addresses the gap between efficacy and effectiveness of distress screening..

In addition to the issue of effectiveness, barriers and facilitators to implementation have largely been unaddressed, as well as other critical implementation outcomes such as fidelity, acceptability, or stakeholder-perceived achievements (e.g., successes and failure). To date, a small number of studies show that oncology clinicians and care managers express mixed opinions regarding distress screening programs, with many reporting concerns regarding the acceptability, usefulness, practicality, and sustainability of such programs, and implementation of pilot distress screening programs has not been uniformly successful.[29] Only about half of American College of Surgeons (ACoS) accredited cancer programs report feeling confident that they can implement a distress screening program in their organization.[37] There are significant barriers to successful implementation of distress screening programs, including the acceptability of the program to patients and clinicians and fidelity to the screening program components. Additionally, effective linkages and/or referral pathways to risk-stratified treatment programs are necessary (e.g., documented clinical workflow for referral of patients endorsing severe versus mild distress).[30,26,38] Failure to explicitly address these issues may lead to wasteful, unsuccessful programs.[39] Given this context, and the fact that many evidence-based interventions that are shown to have efficacy in controlled trials will fail to translate into meaningful effectiveness in

different settings,[40] it is imperative to conduct rigorous research on effectiveness and implementation of distress screening for breast cancer patients in non-academic settings. We propose to use approaches and tools from the field of dissemination and implementation science (D&I) to provide a robust framework and study design. The rapidly growing field of D&I emphasizes the need for researchers to engage in ongoing evaluation beyond measurement of efficacy from randomized controlled trials, including rigorous assessment of effectiveness (versus efficacy-only studies), as well as study of implementation factors including acceptability and feasibility, context (e.g., processes, systems), and culture (e.g., norms and values).[41] Post-implementation evaluation is integral to the success of translational research.[42] It provides critical insights into the barriers, facilitators, and outcomes associated with the program and lays the groundwork for successful dissemination, scale-up, and spread of effective programs.[41]

2.0 OBJECTIVES AND PURPOSE

This study is a pragmatic cluster-randomized control trial (RCT) to determine the effectiveness of a guideline-recommended distress screening program for breast cancer patients in improving a) identification of distressed patients, b) initiation/completion of referrals to behavioral health, and c) patient-reported and utilization outcomes as compared to usual care within Kaiser Permanente Southern California (KPSC), which is a large integrated health care system serving over 4 million members. We will use a hybrid effectiveness-implementation study design. We will implement and evaluate the effectiveness of the distress screening recommendations (the intervention) from the joint task force of the American Psychosocial Oncology Society, Association of Oncology Social Work, and Oncology Nursing Society, which includes recommendations for the timing of distress screening (e.g., initial visit, timed intervals) designated screening responsibility, distress screening instruments, and referral thresholds. We will use strategies from implementation science to potentially enhance uptake and adoption of the screening intervention.

To achieve our objectives, we propose the following specific aims:

Aim 1: Evaluate the effectiveness of a guideline-recommended distress screening program for breast cancer patients in improving identification of distressed patients, initiation and completion of referrals to behavioral health, and patient-reported and utilization outcomes as compared to usual care within KPSC, using a pragmatic cluster randomized control trial design.

Aim 2: Identify patient-, clinician-, and system-level barriers and facilitators to implementation of the program, and assess stakeholder-perceived acceptability, fidelity, and achievements of the program.

Note that we are not developing or evaluating a new type of distress screening instrument, or developing/evaluating a new psychosocial intervention/treatment.

3.0 STUDY DESIGN

We will use an effectiveness-implementation hybrid study design that allows for simultaneous study of the clinical effectiveness and implementation of distress screening to address the need for evidence in both areas. Hybrid designs have *a priori* focus on assessing outcomes relevant to both effectiveness of an intervention and implementation-related outcomes.[42] We will employ a sequential mixed methods study design that integrates qualitative and quantitative methods, as is appropriate to address the proposed research questions. Our highly pragmatic approach is guided by the Pragmatic-Explanatory Continuum Indicator Summary-2 with adaptive workflow design. We will use the Consolidated Framework for Implementation Research (CFIR) to guide collection and analysis of implementation outcomes.

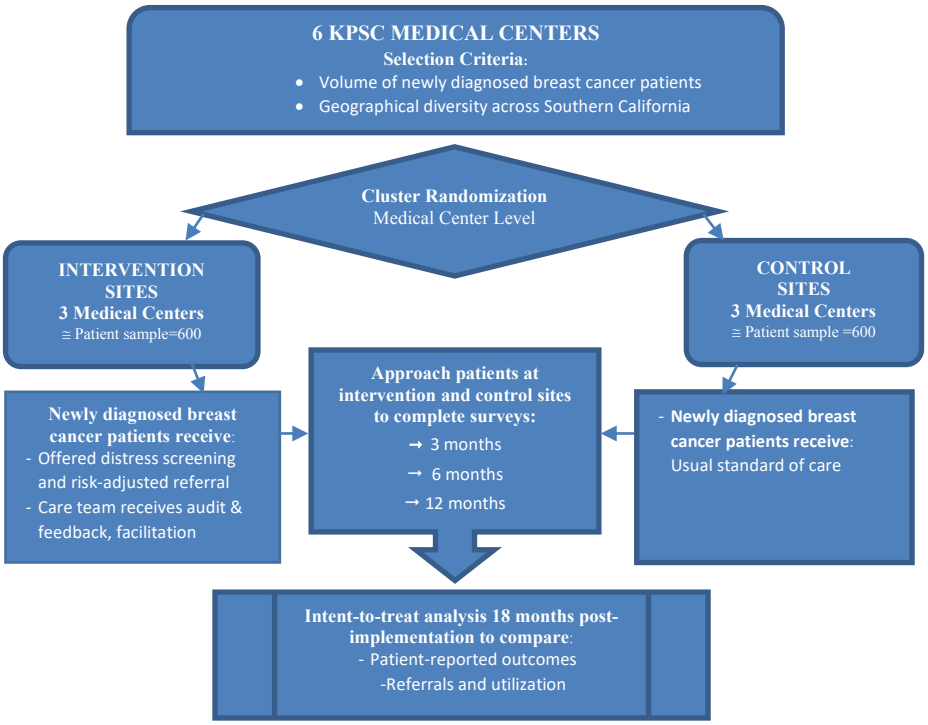
We will use cluster randomization at the medical center level. There will be 6 KPSC medical centers participating in total: 3 intervention sites and 3 control sites.

The screening program will be implemented at the 3 intervention sites, offering the program to all newly diagnosed breast cancer patients within the intervention site over a 12-month period with no exclusions. Under the intervention condition, distress screening using the Patient Health Questionnaire (PHQ), available in the electronic record, will be offered to patients in clinic (paper-based surveys or completed online with the assistance of the LVN, MA, RN or other member of the clinical team administering the screening). Patients are free to refuse distress screening.

Control condition patients will receive the current standard of care (ad hoc distress screening at the clinician's discretion) and basic education about the study. Control sites will not be prohibited from using the PHQ. We anticipate a total sample of 1,200 newly diagnosed patients, 600 in each arm.

Intervention sites will receive audit and feedback of performance data and implementation facilitation throughout the 12-month intervention period (implementation strategies).

Figure 1: Pragmatic cluster randomized control trial



We will collect data from the electronic medical record on screening, initiation and completion of referrals to behavioral health, and utilization outcomes. We will also collect patient-reported outcomes survey data (Aim 1) for patients in both the intervention and control sites (at -3 months, -6 months, -12 months), and will conduct qualitative interviews (n=30) with medical oncologists, breast cancer care coordinators/navigators, social workers, oncology nurses (RNs, LVNs or MAs), clinical leadership and/or patients regarding implementation outcomes (Aim 2).

4.0 STUDY METHODS

4.1 Implementation strategies: All sites will have access to the PHQ-9 questionnaire in the electronic health record, information about the study, and basic education on distress screening. Sites randomized to intervention will additionally receive electronic audit and feedback of their site performance (percent of eligible patients offered screening and anonymized comparison to the other sites) and implementation facilitation (a research RN checking in with the sites to troubleshoot, train, and re-configure workflow as needed).

4.2 Identification of participants for screening: We will identify potential participants at all 6 sites with a new diagnosis of breast cancer using pathology data and appointment/referral data from the KPSC electronic record. We validated our pathology identification algorithm using cancer registry data for recent breast cancer cases diagnosed between 2014 and 2016. Diagnosis is confirmed via chart review and appointment data as needed. All eligible patients will be tracked for screening, referral, utilization, and other outcomes. Eligible patients at intervention sites will be flagged for screening. As this is a highly pragmatic trial, no patients will be individually contacted for recruitment and enrollment as the intervention is applied at the system level; eligible patients will be offered the distress screening program at intervention sites as part of usual clinical care.

4.2.1 Secondary chart review to identify potentially benign patients in cohort: In April 2018, we determined that several patients who had scheduled initial consultation visits with medical oncology and were identified by our data algorithm as newly diagnosed breast cancer patients were later determined (through downstream pathology reporting) to not have breast cancer; these are patients who are ultimately determined to have benign hyperplasia. To mitigate this identification issue, we instituted a secondary chart review process to capture these patients and determine them ineligible for the study based on their "benign" status.

4.3 Timing of distress screening: Eligible patients at intervention sites will be asked to complete the PHQ-9 at their initial visit with the medical oncologist, and encouraged to repeat the screening at follow-up visits with the oncologist.

4.4 Method of screening: We are using PHQ, a recommended distress screening instrument (the PHQ is available in multiple languages). This instrument has been shown to be a valid, reliable tool with high sensitivity and specificity for measuring distress in the cancer population. The instrument is also credible and acceptable to KPSC clinicians and the PHQ are already built into the KPSC electronic health record. The screening will be offered as part of usual care at the intervention sites. Patients are free to refuse distress screening.

4.5 Adaptive workflow design and responsibility of screening program: We have developed an adaptive approach to the screening workflow, where the screening process can be completed differently at intervention sites depending on local context and resources. While the timing of the screening (e.g., initial visit, follow-up visit), instrument, scoring, and referral algorithm remains the same across all intervention sites, the type of staff overseeing the screening, screening mode (e.g., on paper, entered into computer), and place of screening during the visit (e.g., while in waiting room, while in exam room) can vary. As recommended in the guidelines, we have identified specific staff embedded in the oncology breast care teams to be the main points of contact for the screening program. These staff include: Oncology Department Administrators (DAs) and Assistant Department Administrators (ADAs), as well as oncology RNs, LVNs, MAs, and social workers where appropriate. Accountability and oversight of screening at each site can

vary per local context. We have provided ongoing training and support to the clinical care teams identified at each intervention site (implementation facilitation).

4.6 Scoring of screening instrument: We have incorporated a validated KPSC scoring algorithm for the PHQ screening, based on the PHQ scoring instructions, to ensure correct scoring and appropriate referral. Results will group a patient into one of 3 categories: 1) Low score: referral to Health Education (e.g., stress reduction classes, mind/body classes and sleep improvement classes, etc.); 2) Moderate score: referral to Depression Care Management (a program of KPSC Complete Care, see 4.6.1) or local oncology social worker to discuss referrals and individual options; 3) High score: immediate referral to Behavioral Health/psychiatry. In the event of endorsement of suicidal ideation (regardless of overall score), an in-person or telephone consultation with a behavioral health provider will be initiated; escort to behavioral health and/or the emergency department will be decided by the behavioral health provider and medical oncologist. A detailed protocol and training will be provided to all intervention sites.

4.6.1 Complete Care Depression Program. The Depression program is an integrated, regionally supported program based in primary care and using a population based approach to: 1) identify and treat depression based on evidence and best practices; 2) offer screening and assessment models (i.e. integrated into current care processes); and 3) advance treatment care models (both core and customizable components). The goal of the program is to improve the care of adult patients with co-morbid conditions by the appropriate screening, assessment, and treatment of depression as an extension of Primary Care/Care Management in conjunction with Behavioral Health. Depression Care Specialists provide treatment, including medication initiation and management, education, problem solving treatment and behavioral activation. Under a program redesign, new workflows were developed, which typically begin with the administration of the PHQ.

4.7 Referral pathways: Per guideline recommendations, we will leverage referral pathways to behavioral health services which may include the oncology social worker (if such a resource is available at the site), depression care managers, and psychiatry/behavioral health. This approach leverages existing resources from the KPSC Complete Care Depression Program.

4.8 Identification of participants for patient-reported outcome surveys. All eligible patients who speak English or Spanish will be invited to participate in a survey of patient-reported outcomes. We will confirm if the potential participant has an active email address via our membership databases. Those who do will be initially contacted via email; those who do not will be initially contacted via postal mail (see contact workflow descriptions, below). Those who agree to participate will be asked to complete these two brief surveys at 3 time points (3-, 6- and 12-months). We will alert the oncology teams at all participating medical centers, as well as KPSC Member Services, in advance so that they are aware of the survey administration schedule and prepared to address any patient questions about the surveys and/or the study.

4.9 Survey administration and tracking: We will use RedCap software for all recruitment and survey tracking, as well as for on-line consenting and administration of the surveys whenever possible (e.g., for all patients with a viable email address), as well as for tracking postal mail and phone recruitment contact attempts.

4.10 Outcomes:

Primary. Our primary outcome is percent of eligible patients screened and referred (based on PHQ score) at intervention versus control sites.

Secondary. Our secondary outcomes include: completion of recommended referrals, utilization of outpatient medical oncology visits, primary care visits, behavioral health visits, urgent care visits, and emergency department visits; we will also examine patient-reported outcomes using the Functional Assessment of Cancer Therapy-Breast survey, and the Breast Cancer Prevention Trial (BCPT) Symptom Checklist.

Please note: We received a waiver of written informed consent for the electronic health record data collection aspect of the study to identify newly diagnosed breast cancer patients at intervention and control sites during the screening intervention period (12 months) on September 22, 2016; we received a waiver of written informed consent for the survey portion of the study on May 8, 2017.

5.0 DATA SOURCES

We will obtain and compare data from the sources described below for patients from both the intervention and the control condition.

5.1 Distress screening: We will use a recommended distress screening instrument (PHQ), which is part of the electronic health record.

5.2 Referral: We will access referral data using Tapestry, a database linked to the KPSC electronic medical record that records all referral activities, including those to behavioral health services. We will collect referral data retrospectively at completion of the 12 month screening intervention. We will collect and compare the number of referrals to relevant behavioral health services, including: depression care management, psychiatry, psychology, social work, and health education. We will also obtain information on referral initiation and completion (e.g., patient visit with referred provider).

5.3 Utilization of health care services: To compare patient utilization of health services between intervention and control sites, we will capture utilization of health services from our electronic medical record using Current Procedural Terminology (CPT) and International Classification of Disease (ICD) codes as appropriate. We will collect utilization data retrospectively at 18 months after the initiation of the distress screening program in the intervention centers. This will provide utilization data for a maximum of 18 months. We will capture number of emergency department visits, hospitalizations, urgent care visits, primary care and oncology visits, and behavioral health visits, including interactions with psychology, psychiatry, and social workers (in-person, email, and telephone contact).

5.4 Covariates and breast cancer treatment data: We will collect covariate information from the electronic health record and data from the KPSC tumor registry. Covariates from the registry will include date of diagnosis, age at diagnosis, stage of disease, estrogen receptor/progesterone receptor/human epidermal growth factor receptor 2 status, treatment types and dates including use of Herceptin and aromatase inhibitors, laterality, tumor size and histology, sequence number, and treating medical center. Covariates from the electronic record will include age, date of birth, gender, race/ethnicity, and geocoded census tract education and income.

5.5 Surveys. We will invite all newly diagnosed breast cancer patients at the intervention and control sites to complete two short patient-reported outcome surveys, the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) and the Breast Cancer Prevention Trial Symptom Checklist (BCPT). Those who agree to participate will be asked to complete these two brief surveys at 3 time points (3-, 6- and 12-months).

6.0 DRUG/DEVICE INFORMATION

This section is not applicable. We are not testing any drug or device in this proposed study. We are not proposing to develop or evaluate a new type of distress screening instrument or program, or to develop or evaluate a new psychosocial intervention or treatment.

7.0 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria: All patients with a visit to medical oncology for a new diagnosis of breast cancer at a study site are eligible for inclusion, with no exclusions due to gender, age, stage of disease, sequence of disease, comorbidity, spoken or written language, or other demographic or cancer characteristic.

7.2 Exclusion Criteria: Non-breast cancer patients.

8.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

We are conducting a pragmatic cluster-randomized trial with randomization at the medical center level. There are 6 KPSC medical centers participating in total. SAS was used to generate the site randomization scheme.

9.0 STUDY AGENT ADMINISTRATION/TOXICITY PLAN

This section is not applicable.

10.0 ASSESSMENT OF EFFICACY AND SAFETY

This study poses minimal risk to participants, and the screening instrument (PHQ) we will be using is already in regular use within the KPSC region.

11.0 STUDY CALENDAR

	Year 1 Q1-Q2	Year 1 Q3-4	Year 2 Q1-2	Year 2 Q3-4	Year 3 Q1-2	Year 3 Q3-4
IRB approval, initial study planning	X					
Randomization at center level for distress screening	X	X				
Initiate distress screening program at intervention sites		X	X			
Ongoing training and support for intervention sites		X	X	X		
Patient surveys at 3, 6, 12 months after diagnosis			X	X		
Develop interview guides; recruitment and interviews				X	X	
Qualitative coding and analysis					X	X
Implementation survey					X	X
Study wrap-up, stakeholder meetings, manuscript planning						X

12.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

- **Distress screening**:
  - PHQ instrument was completed by the patient either during an oncology-related visit or online within 10 days pre- or post-visit.
  - Score of PHQ (continuous) and categorized to low, medium, high score
- **Utilization**:
  - Number of urgent care visits and associated diagnostic codes
  - Number of emergency department visits and associated diagnostic codes; subsequent discharge or hospitalization
  - Hospitalizations, length of stay, and associated diagnostic codes
  - Primary care visits
  - Medical oncology visits
  - Behavioral health visits
  - Number of referrals to behavioral health services

- **Patient-reported outcomes:**
  - Fact-B Functional Well-Being (Likert scale, 0-28)
  - Fact-B Social/Family Well-Being (Likert scale, 0-28)
  - Fact-B Emotional Well-Being (Likert scale, 0-24)
  - Fact-B Functional Well-Being (Likert scale, 0-28)
  - Breast Cancer Subscale (Likert scale, 0-40)

13.0 DATA COLLECTION AND MONITORING

13.1 Screening. Newly diagnosed breast cancer patients will be offered the PHQ screening tool at the initial consult visit within oncology as part of usual care. Patients will have the right to refuse completing the tool. The PHQ is already built into the electronic medical record with results available in a dedicated PHQ results tables in Clarity (the backend of electronic medical record). Questionnaire data will be entered into the medical record by the screening LVN, MA or RN and we will capture data from the PHQ database. Patients may also be offered screening at subsequent visits.

13.2 Referrals. We will access referral data using Tapestry, a database linked to the KPSC electronic medical record that records all referral activities, including those to behavioral health services.

13.3 Utilization of health care services: To compare patient utilization of health services between intervention and control sites, we will capture utilization of health services from our electronic medical record using Current Procedural Terminology (CPT) and International Classification of Disease (ICD) codes as appropriate.

13.4 Covariate and breast cancer treatment data. We will collect covariate information from the electronic health record and data from the KPSC tumor registry.

13.5 Surveys. We will invite all newly diagnosed breast cancer patients at the intervention and control sites to complete two short patient-reported outcome surveys, the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) and the Breast Cancer Prevention Trial Symptom Checklist (BCPT). Those who agree to participate will be asked to complete these two brief surveys at 3 time points (3-, 6- and 12-months).

13.6 Standardized data collection. Data collection from the electronic record for screening, referral, and utilization data will use standardized approaches to ensure equitable collection of high-quality data.

13.7 Security. All data files will be kept on a secured shared drive with access restricted to project staff using password-protected computers. Initially, research and medical records will be used to build the analytic databases. Each subject will be assigned a unique study identification number and all other identifiers will be removed as early as possible without compromising the conduct of the study. The linkage file between study identification number and medical record number will be stored separately on a password-protected server accessible only to the principal investigator, project manager, research associates, and programmer/analysts. Confidentiality of patient information will be protected by using password-protected computers for all data analysis and management, as well as keeping confidential information printed on hard copies in locked file cabinets within the Department of Research & Evaluation. Only project staff will have access to confidential information; staff have been trained in compliance and working with protected health information.

13.8 Quality monitoring. Weekly quality monitoring checks with the study team to monitor screening and referrals will ocurr. Study information will only be shared among project staff as needed to complete the study objectives using standard Research & Evaluation practices, including password-protected files on restricted-access secured shared drives. Emails will be encrypted if data will be sent between project staff; however, emails will be minimized as weekly quality monitoring checks with the study team to monitor screening and referrals will be conducted in-person whenever possible.

13.9 Recruitment. Recruitment oversight for participant surveys will be conducted by the study team, with data checks via team meetings and RedCap reporting statistics. Emails will be encrypted if data will be sent between project staff; however, emails will be minimized as weekly in-person study team meetings will occur whenever possible to conduct data checks and review updated reporting.

14.0 STATISTICAL CONSIDERATIONS

Aim 1: Evaluate the effectiveness of a guideline-recommended distress screening program for breast cancer patients in improving identification of distressed patients, initiation and completion of referrals to behavioral health, and patient-reported and utilization outcomes as compared to usual care within KPSC, using a pragmatic cluster randomized control trial design.

14. 1 Power and sample size. Of the 14 KPSC medical centers, we have selected 6 centers with the highest average number of new breast cancer cases diagnosed between 2011 and 2014. Based on the average number of cases. We expect a total of at least 1,200 newly diagnosed patients across the 6 sites, and to enroll anywhere from 50 to 300 newly diagnosed breast cancer patients per intervention site, entering all such cases into our cohort with no exclusions. We performed cluster randomization to select the intervention and control sites. While cluster randomization may be less statistically efficient than individual randomization, we believe it makes the study more feasible for several reasons. First, it allows us to truly evaluate the effectiveness of the distress screening program, with the screening offered to all newly diagnosed patients in the intervention centers. This will provide real-world information on uptake and effectiveness. Second, it allows us to avoid contamination between the distress screening intervention and other possible competing interventions, as well as outside information that may be publicly available to patients. Third, it allows us to balance (on average) medical center-level factors that we are otherwise unable to measure reliably. For all outcomes, we expect relatively small standardized effect sizes (measured in terms of z-scores) ranging from 0.2-0.4, because this is an effectiveness study. To achieve 80% power with a significance level of 0.05, our per-center sample size requirement ranges from as few as 20 for large effect size (0.4) and zero intraclass correlation (ICC), to about 400 for small effect size

and large ICC (0.2 and 0.01, respectively). Given that we can expect 50 to 300 newly diagnosed breast cancer patients per center, we should be adequately powered to detect effect sizes as small as 0.2, given ICCs no greater than 0.007. This is a lower bound on our power, since we expect to have as many as 200 more patients at some medical centers, and so our power is most likely greater than reported here.

14.2 Statistical analysis plan: All variables will be described with summary statistics appropriate for measurement type, such as frequency and percent, mean, median, standard deviation, minimum, and maximum. Patterns of missing values will be examined and evaluated for randomness using the method described by Enders. Diagnostic plots and inferential tests for tenability of assumptions will be evaluated for our primary and secondary outcomes, and appropriate remedial methods (e.g., Box-Cox transformations) applied where required. We will analyze referral and utilization outcomes as the total amount of services used during the study period, and use said diagnostic tests to determine the best modeling strategy for examining relationships with relevant demographic and clinical characteristics, exploring potential disparities by race/ethnicity and socioeconomic status. If necessary, we will analyze relationships with referral and utilization outcomes using Poisson or Negative Binomial regression models. We will use an intent-to-treat analysis, including data on all newly diagnosed patients in the intervention and control groups without regard to their screening status, appropriate for a cluster RCT.

Patient-reported outcomes from our mailed patient surveys (FACT B and BCPT) will be subjected to the same diagnostic testing as the utilization outcomes. To account for having repeated measurements for these patient-reported outcomes (3, 6, and 12 months post-diagnosis), we will use generalized estimating equations or linear mixed effects models, for situations where no or some repeated measures are missing, respectively. We will also analyze patient-reported outcomes using non-parametric regression techniques, such as quantile regression, to assess the sensitivity of our findings to other key modeling assumptions. Additionally, to analyze any improvement in identification of highly distressed patients by the systematic screening program, we will compare patients reporting high levels of distress on the FACT-B with patients receiving referral for high-level distress services (psychiatry, psychology). Statistical analyses will be conducted using SAS, R and/or MPlus. The study team will meet regularly to review adherence to the study protocol, evaluate study progress, and identify and resolve issues. Frequencies tables will be examined and out-of-range checks of all variables will be conducted, and results checked for consistency. Our advocate and advisors will provide insights and suggestions to guide our analyses to ensure we are considering a broad range of views

Aim 2: Identify patient-, clinician-, and system-level barriers and facilitators to implementation of the program, and assess stakeholder-perceived acceptability, fidelity, and achievements of the program

14.3 Study Population and Identification. Using semi-structured interviews with key stakeholders, including medical oncologists, breast cancer care coordinators and/or navigators, licensed clinical social workers, oncology nurses (RNs, LVNs or MAs), oncology operational leaders, and breast cancer patients, we will identify barriers and facilitators to program implementation of large-scale distress screening. Our target sample size is 30. We will identify key informants in collaboration with Joanne Schottinger, MD, our oncology advisor who is a senior leader in KPSC oncology clinical practice as well as an operational leader within KPSC as Assistant Medical Director of the Southern California Permanente Medical Group. We will also use snowball sampling, a purposeful non-probability sampling technique, asking participants to identify other key informants that we may have overlooked. Potential patient participants will be identified in collaboration with our clinical participants, as well as with the KPSC Regional Medical

Advisory Council (RMAC), a member-led council that provides feedback to KPSC clinicians, researchers, and operational leaders on a variety of topics. RMAC has sub-councils for disease specific groups, including oncology. We will target breast cancer patients 1 to 3 years post-diagnosis to gain insights into how distress screening could be integrated most effectively throughout the cancer care continuum.

14.4 Qualitative data management. One-to-one interviews will be conducted in person or over the telephone by the research study team. We estimate that each interview will take between 35 and 45 minutes to complete. We will obtain oral consent from each participant prior to the beginning of each interview. All interviews will be recorded and transcribed. Our analysis will focus on thematic development related to barriers and facilitators to implementation, guided by the domains from the Consolidated Framework for Implementation Research.[43] We will develop a coding structure inductively, using the constant comparative method,[44] and with input from our advocate, co-investigators, and oncology consultant. Codes may include concept and sub-concept codes, relationship codes, and participant perspective and characteristic codes.[45] Consensus on the coding structure will be achieved via iterative testing of structure development by members of the research team, followed by review and resolution of discrepancies and discussion with our advocate and advisors. To help ensure rigor and transparency, all coding development steps will be tracked and reported. All analyses will be performed using appropriate qualitative analytic software (ATLAS.ti, version 7.5.10).

14.5 Qualitative interviews. We will use CFIR to identify relevant domains, including: 1) *Acceptability*, or the perception that the program is satisfactory; 2) *Fidelity*, or the degree to which the program was implemented as prescribed, typically measured by comparing the planned intervention and the actual intervention in terms of adherence to the protocol; and 3) *Adoption*, or "uptake" of the program. We will use Helfrich et al.'s (2009) Organizational Readiness to Change Assessment, a validated survey instrument which operationalizes the CFIR domains for measurement and has been mapped to each construct, to develop questions regarding contextual factors.[46] This information will be critical in aligning the program with provider and system-level needs to facilitate dissemination, scale-up, and spread throughout KPSC, to KP nationally, and other health care settings.

15.0 REGISTRATION GUIDELINE

In this pragmatic cluster randomized trial, randomization is at the medical center level. We will not recruit or consent patients individually; those at intervention sites will be offered the distress screening program as part of usual clinical care, and we have been granted a waiver of written informed consent from the IRB.

16.0 BIOHAZARD COMTAINMENT

This section is not applicable. No biological samples will be collected.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form for patient surveys will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

18.0 REFERENCES

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