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TITLE: Advance Care Planning: Experience of Women with Breast Cancer

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CONTRACTING ORGANIZATION: Michigan State University
East Lansing, MI 48824-1046

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13. ABSTRACT (Maximum 200 Words) Advance care planning (ACP) enables women with breast cancer to proactively document their end-of-life preferences. The purpose of this study is to describe the prevalence and predictors of ACP during and following chemotherapy treatment among women with breast cancer enrolled in a cognitive behavioral trial for symptom management. Interim analyses of 110 women with breast cancer were conducted. Predictors entered in the logistic regression were demographic (education, marital status, number in household, and age), health (quality of life, stage and recurrence of cancer, co-morbidities, hospital admissions, and symptom interference), and emotional (depression and optimism). Forty-one women (37%) reported having ACP. The predictors reliably distinguished between women with an ACP and those without (57% and 76% prediction success respectively). Age was the most reliable predictor of ACP. All predictors accounted for 32% of the variance in ACP. ACP prevalence among women with breast cancer is greater than previously reported. As age increased women with breast cancer were more likely to have ACP; however, none of the health factors were found to be significant predictors of ACP. This suggests that greater communication may need to occur about ACP in relation to health status.				
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INTRODUCTION:

Breast cancer is the second leading cause of cancer deaths in women. Documented shortcomings in end-of-life care include deficiencies in provider/patient communication, excess reliance on aggressive treatment, and disparity between the way people die and the way they want to die. Advance care planning (ACP) enables women with breast cancer to proactively document their end-of-life preferences, which may lower deficiencies in end-of-life care. The purpose of this study is to describe the prevalence and predictors of ACP during and following chemotherapy treatment among women with breast cancer enrolled in a cognitive behavioral trial for symptom management.

BODY:

The following research and training accomplishments correspond to the approved Statement of Work outline.

Statement of Work: Development, refinement, and finalizing Task I # 1. Brochures and recruitment materials; Task I #2. Interview instruments; and Task I # 3. Advance care planning intervention.

Recruitment materials included brochures and invitation letters sent to potential participants. Recruitment materials were revised to be at the 5th-grade reading level. Instruments considered for the interview were required to be reliable and valid for women with breast cancer. After review of several ACP approaches, the decision was made to base the intervention script on the *Five Wishes* and *Next Steps* literature. This literature was developed by Aging with Dignity, with support from the Robert Wood Johnson Foundation.

The refinement and revision process for the recruitment, interview, and intervention materials included review for content appropriateness by my mentors, Charles W. Given, Barbara Given, Janet Osuch; members of the Wayne State University End-of-Life Interdisciplinary Project (WSU-EOLIP); and women with breast cancer. Further refinement and revision was possible during the pilot test of the interview and intervention scripts. During this pilot test, both scripts were found to take under an hour and be easy to understand.

Statement of Work Task I #4. Obtain institutional review board approval: Department of Defense(DoD), Michigan State University (MSU), and other participating sites. (See Appendix A for Institutional Review Board (IRB) approval letters.)

- DoD HSRRB approval was obtained on September 20.
- Saint Mary's Health Care IRB approval was obtained June 28, 2004.
- St. Joseph Mercy, Oakland, IRB approval was obtained July 12, 2004.
- Northern Indian Cancer Research Consortium IRB approval was obtained October 12, 2004.
- William Beaumont Hospital IRC approval was obtained December 6, 2004.
- Indiana University-Purdue University, Indianapolis, IRB approval was obtained January 12, 2005.
- Michigan State University UCRIHS renewal approval was received October 5, 2004.

Statement of Work Task I #5 and Task II #8. Research participation:
gain experience/skills in multi-site randomized control trials.

Until August 1, 2004, I participated as Interviewer Coordinator for the multi-site, randomized control trials (RCTs) *Family Home Care for Cancer - A Community-Based Model*, Dr. Barbara Given, PI (R01 CA030724), and *Automated Telephone Monitoring for Symptom Management*, Dr. Charles Given, PI (R01 CA079280). These two studies focus on providing symptom management interventions for individuals with solid tumors, including women with breast cancer.

As Interviewer Coordinator, I assisted with developing the interview manual, the concept grid, and the measures manuals. The interviewer manual is comprised of the interviewer job description and interview procedures, which include how to contact patients, and how to schedule, conduct, and complete the interviews. It also includes a section on how to deal with a specified list of special circumstances, for example a suicidal or emotionally distressed patient, should they arise.

To determine the measures to be used in the studies, I conducted statistical analysis of a prior RCT to determine response rate to various items. Items that had response rates above 20% were retained for the current studies. For scales, reliability and validity analyses were conducted. Scales demonstrating adequate reliability (alphas above 0.80) were retained for use in the current studies.

I assisted with selecting and training interviewers. The training included presenting an overview of the studies and the role of the interviewer in the studies, as well as a review of the interviewer manual and the policies and procedures, such as how to engage ethnic minorities in health research. Interviewers were trained to use the in-house email and the web tracking system developed specifically for these RCT studies. The website has study announcements; important shared documents, such as letters, forms, and hand outs; and the participant enrollment/tracking information. Interviewers use the web tracking system to receive their assignments, document each participant, interview completion or attrition event, and results. The interviewers were also trained on the use of SNAP, a questionnaire software package, used to enter interview data.

During training, interviewers were required to complete a minimum of three full-length mock interviews. All interviewers were recorded, and interviewers were asked to listen to the tape of the mock interview, complete a self-evaluation, and then submit the tape and self-evaluation. I then listened to the tape, completed an evaluation, and met with the interviewer to review their self-evaluation in conjunction with my evaluation of their performance. If their mock interviews were deemed to be acceptable, they were given participant assignments. Interviewers taped at minimum the first 10 interviews, completed self-evaluations, and submitted the tape and self-evaluations in for my evaluation. Once acceptable competence was reached, two interviews were randomly selected per month for the interviewers to complete and submit with a self-evaluation.

An additional responsibility of my position was ongoing communication with providers if a symptom reached a critical threshold: 5 for pain or 7 for other symptoms. If an urgent symptom was noted by the interviewer, he or she emailed me, the Interviewer Coordinator. I then notified the provider by telephone of the urgent symptom(s).

During my four months as Interviewer Coordinator, I coordinated, jointly with my mentor Charles W Given, bi-monthly interviewer

meetings, including developing interviewer agendas. Meetings items included skill development, interviewing issues, policies, and procedures. I also participated in regular bi-monthly multidisciplinary team meetings, which included reviewing accrual of participants.

Activities to date relating to the accrual of women and minorities have included review of *Family Home Care for Cancer - A Community-Based Model* grant application to identify specified activities to be implemented if minority accrual and retention is not reflective of the population; review of the literature regarding minority accrual and retention; review of the participant web tracking system; and requesting the data to be used to determine if differential women and minority accrual and retention is occurring as part of the ongoing RCTs.

Statement of Work Task I #6 and Task II #9. Preparation and submission of four manuscripts from Family Care Research Program (FCRP) data sets. (See appendix B.)

Currently one manuscript from the FCRP data set has been accepted:

Doorenbos, A. Z., Verbitsky, N., Given, B., & Given, C. W. (in press). An analytic strategy for modeling multiple item responses: A breast cancer symptom example. *Nursing Research*.

Two manuscripts are to be revised for resubmission:

Doorenbos, A. Z., Given, B., Given, C. W., Wyatt, G., Gift, A., Rahbar, M., & Jeon, S. Impact of end-of-life care for caregivers of family members with cancer. Submitted to *Research in Nursing and Health*.

Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. Physical functioning: Effect of symptom-based limitations, depressive symptomatology, age, site and stage of cancer over time. Submitted to *Nursing Research*.

The final manuscript is currently in draft form and is expected to be submitted this summer for consideration in the *Journal of Pain and Symptom Management*.

Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. Symptom experience at end-of-life among individuals with cancer.

Statement of Work Task I # 7 and Task II # 7. Coursework.

(A) Michigan State University, EPI 827: *The Nature and Practice of Scientific Integrity*. Spring semester 2004.

The Nature and Practice of Scientific Integrity stressed the responsible conduct of research as a component of the process of inquiry. Some of the active discussion in the course covered the responsible conduct of research; the future of science, including the NIH Director's Panel on Clinical Research; examples of misconduct, including historical and institutional lapses, conflict of interest, and ethical challenges. Increasing my knowledge base regarding the responsible conduct of research was an essential first step in my training.

(B) National Institutes of Health, *Summer Institute on Randomized Clinical Trials with Behavioral Interventions*. Summer.2004.

I was selected to participate at the NIH summer institute on randomized control trials (RCT) with behavioral interventions. This is a semester course taught in the span of two weeks in July at the Arlie conference center by leading experts in RCT using behavioral interventions. Benefits of this experience went far beyond active participation in the dyadic lectures offered, as this institute provided networking opportunities with other early-career researchers in the field of cancer research, as well as consultation with leaders in RCT methodology.

(C) Michigan State University, EPI 823: *Cancer Epidemiology*
Currently being taken.

This course focuses on cancer surveillance and biology. It reviews research methods in cancer epidemiology and provides the opportunity to further develop my skills in critically reading and evaluating published cancer epidemiology literature, as well as gaining up-to-date knowledge of important issues in the field of cancer.

Statement of Work Task I #8. Seminar Attendance and Participation.

(A) Behavioral Cooperative Oncology Group (BCOG)

The BCOG Fall meeting, *Decomposition of Interventions*, was held in Indianapolis, Indiana. Interactive discussion of cutting-edge behavioral research was facilitated by Sara Czaja, PhD, of the University of Miami School of Medicine and Richard Schulz, PhD, of the University of Pittsburgh Center for Social and Urban Research. BCOG senior scientists Dr. C. Given, Dr. B. Given, Dr. L. Northouse, and Dr. B. Cimprich each presented their progress, deconstructing their successful behavioral interventions, and all attendees were included in the interactive discussion.

Our presentation, *Advance Care Planning: Experience of Women with Breast Cancer* provided the opportunity for interaction with BCOG faculty researchers, focusing specifically on the ongoing DoD sponsored research. BCOG is unique in that it specifically plans for and facilitates interactive discussion by asking pre- and post- doctoral fellows to bring forth questions and concerns regarding their research. Discussion included the most efficacious "teachable moment" in the breast cancer treatment trajectory for discussing ACP, and the best location to access women with breast cancer and offer ACP intervention. Being given the floor, within an intellectually nurturing environment, to present our specific concerns for discussions with senior cancer researchers was invaluable. This additional mentoring further enhanced my ability to conduct research founded on a multidisciplinary platform that contributes to, and focuses on, individuals with cancer.

(B) College of Nursing End-of-Life seminar

The presentation of *Prevalence and Predictors of Advance Care Planning among Women with Breast Cancer* was an hour-long, interactive discussion with doctoral students and an MSU College of Nursing (CON) faculty member. Access to this interactive environment in which to discuss our interim results assisted us in moving ideas forward, specifically in determining other potential recruitment areas.

(C) Department of Epidemiology

I have regularly attended the Department of Epidemiology sponsored biweekly seminar series during the academic year. Speakers have included Michigan State University faculty members, Michigan Department of Community Health public health professionals, and invited guests from across the US.

(D) Michigan State University Graduate School

The MSU Graduate School offered six workshops during the academic year. The topics of the workshops were (1) the graduate experience, (2) ethical challenges, (3) responsibility for integrity, (4) responsibility to the institution, (5) responsibility to the subject, and (6) responsibility for objectivity.

Statement of Work Task I #9. Conference Attendance and Participation.

(A) Michigan Cancer Consortium (September, 2004)

The Michigan Cancer Consortium (MCC) is a statewide, broad-based partnership of public and private organizations. The MCC annual meeting is a forum for collaboration to reduce the burden of cancer among residents of Michigan. We developed a poster presentation of our work examining the impact of end-of-life care on caregivers of family members with cancer.

B) National Congress on the State of the Science in Nursing Research (October, 2004)

The purpose of this conference is to create a national forum for communicating emerging scientific discoveries related to nursing practice, to disseminate research findings that can influence practice, education, research and health care policies, and to influence the nursing research agenda of the future. This conference included our presentation of the paper *The impact of a cognitive behavioral intervention on symptom-based limitations and physical function*.

(C) The Gerontological Society of America 67th Annual Scientific Meeting (November, 2004)

The Gerontology meeting provides interaction with an interdisciplinary group, many of whom have end-of-life interests. Membership in the cancer interest group facilitated interactions with an interdisciplinary group of researchers interested in cancer and oncology. As the burden of cancer is increasing in the elderly, and elderly cancer patients are more likely to experience mortality and morbidity, the ability to network with researchers with an expertise in gero-oncology enhances my ability to conduct research with this growing segment of the population. This conference included a podium presentation of our paper *Impact of End-of-Life Care for Caregivers of Family Members over 65 with Cancer*.

(D) NIH State-of-the-Science conference on improving end-of-life care (December, 2004)

This three-day conference raised key questions regarding what defines the transition to end of life: those outcome variables that are important indicators of the quality of the end-of-life experience for both dying persons and their families. Discussions and presentations also addressed health care system factors associated with end-of-life

outcomes, and interventions found to impact end-of-life outcomes. The conference concluded with discussion about the future research directions for improving end-of-life care.

(E) 8th National Conference on Cancer Nursing Research (February, 2005)

The attendees of this conference are the top cancer nursing researchers in the country. The purpose of this conference is to provide a forum for scholarly exchange related to the foundation and advancement of cancer nursing science and practice. As it is a specifically focused conference, interactions are highly relevant to the exchange of ideas concerning emerging cancer nursing research issues, methods, and findings. Our abstract, *An Analytic Strategy for Measuring and Modeling Cancer Symptoms: A Breast Cancer Symptom Example*, was given as a podium presentation, and was one of the highest rated abstracts of the conference.

Statement of Work Task II #1. Recruit women with breast cancer from ongoing RCTs.

This task relates to Research Aim 3, to test the effectiveness of ACP information intervention in increasing ACP implementation, in the presence of varying levels of stressors and exposure to behavioral intervention or attention self-management intervention. During an interview for either *Family Home Care for Cancer - A Community-Based Model* (R01 CA-79280) or *Automated Telephone Monitoring for Symptom Management* (R01 CA-30724), women with breast cancer are asked if they would like more information about ACP. To date, four women with breast cancer from the RCTs have responded affirmatively to desiring more information regarding ACP.

Statement of Work Task II #2. Data collection, entry, and cleaning;

Task II #3. Deliver advance care planning intervention; and Task II #4. Quality assurance: enrollment, interview, and intervention data.

Currently, all four women with breast cancer who responded affirmatively to desiring more information regarding ACP, completed the ACP intervention portion of this study. Two of the four women have completed the final interview; one woman dropped out due to being too ill; the other is scheduled to complete the final interview in two weeks.

Intervention and follow-up interview data was entered into SNAP and transferred to SPSS. Ongoing quality assurance activities have included the taping of selected interview and intervention interactions, listening to the tapes and completing a self-evaluation. My mentor has listened to the tapes and provided further constructive feedback for how to improve the delivery of the ACP intervention and collect data during the interviews.

Statement of Work Task II #5. Preliminary data analysis by specific aim.

An interim analysis of 110 women with breast cancer focused on the first aim of *Advance Care Planning: Experience of Women with Breast Cancer*: to describe the prevalence and predictors of having ACP during and following chemotherapy treatment among women with breast cancer participating in either *Family Home Care for Cancer - A Community-Based Model* (R01 CA-79280) or *Automated Telephone Monitoring for Symptom Management* (R01 CA-30724). The dependent variable for the analysis was ACP documentation (yes/no). Predictors entered in the logistic

regression were demographic (education, marital status, number in household, and age), health (quality of life, stage and recurrence of cancer, co-morbidities, hospital admissions, and symptom interference), and emotional (depression and optimism). (See Appendix C for a table reporting the demographic characteristics of the women.)

Forty-one women (37%) reported having ACP. The model was moderately successful in reliably distinguished between women with ACP (57% prediction success). The model had good success in predicting women who did not have ACP (76% prediction success). Increasing age ($p = .002$) and increasing optimism ($p = .005$) were significant predictors of ACP status. All predictors accounted for a good portion (32%) of the variance in ACP status.

To assess change in ACP status during chemotherapy treatment, the prevalence of ACP at the baseline interview was compared to the week 10 interview. At baseline, 37% of women reported having ACP. Although by the week 10 interview 42% of women with breast cancer had completed ACP, the change was not significant.

Statement of Work Task II #6. Modification of recruitment and retention strategies. (See appendix D.)

To be recruited from the ongoing RCTs for the ACP intervention, a woman with breast cancer must not have already completed ACP documents, and must answer yes to desiring information about ACP. This recruitment from the ongoing RCTs is only in relation to answering Research Aim 3 of the ACP study: to test the effectiveness of an ACP intervention.

Currently, the number of women with breast cancer recruited from *Family Home Care for Cancer - A Community-Based Model* (R01 CA-79280) or *Automated Telephone Monitoring for Symptom Management* (R01 CA-30724) falls significantly short of the 5- to 6-per-month proposed. Thus, modification of recruitment strategies was put into place.

Recruitment from outside the ongoing trials modifies the population base on which Aim 3, "test the effectiveness of an advance care planning intervention" will be tested. The population will now include women with breast cancer recruited not only from the ongoing trials but also from support groups or other mailing lists of women with breast cancer. This allows for greater generalizability of Aim 3 study findings to women with breast cancer; however, it looses the richness of the additional data derived from the ongoing RCTs.

Since these added participants will not have completed the ongoing trial interviews which form baseline data for this study, they will undergo an added interview to provide equivalent data. Because of these differences in procedures, separate consent forms must be used for the two groups. Hence, a revision to the protocol was written which includes revisions to recruitment, informed consent procedure, and procedures, with the addition of a baseline interview for women recruited from support groups.

The modification to procedure was approved by DoD HSRRB on March 1, 2005. In the month since opening recruitment to women with breast cancer from support groups, eleven women have returned consent forms and have been enrolled in the ACP intervention portion of this study. Thus, the current recruitment of 15 women with breast cancer (4 from RCTs and 11 from support groups) represent only 15% of the 100 women proposed in the grant application. At this rate, the target recruitment level will not be reached within the coming year. Future recruitment efforts will continue to reach additional women from support groups with more focus applied to drive the intake rate to a viable level.

KEY RESEARCH ACCOMPLISHMENTS:

- Paper to be revised for *Research in Nursing and Health*: Doorenbos, A. Z., Given, B., Given, C. W., Wyatt, G., Gift, A., Rahbar, M., & Jeon, S. Impact of end-of-life care for caregivers of family members with cancer.
- Paper to be revised for *Nursing Research*: Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. Physical functioning: Effect of symptom-based limitations, depressive symptomatology, age, site and stage of cancer over time.

REPORTABLE OUTCOMES:

- National Institute of Health Fellowship. Summer Institute on Randomized Clinical Trials Involving Behavioral Interventions
- Paper accepted in *Nursing Research*. Doorenbos, A. Z., Verbitsky, N., Given, B., & Given, C. W. An analytic strategy for modeling multiple item responses: A breast cancer symptom example.
- Poster presentation. Doorenbos, A. Z., Given, B., Given, C. W., Wyatt, G., Gift, A., Rahbar, M., & Jeon, S. (September, 2004). *Impact of end-of-life care for caregivers of family members with cancer*. Michigan Cancer Consortium, Lansing, MI.
- Postdoctoral presentation. Doorenbos, A. Z., Given, C. W., & Given, B. (October, 2004). *Advance care planning: Experience of women with breast cancer*. Annual Fall Conference of the Behavioral Cooperative Oncology Group, Indianapolis, IN.
- Paper presentation. Doorenbos, A. Z., Given, B., Given, C. W., Jeon, S., & Rahbar, M. (October, 2004). *The impact of a cognitive behavioral intervention on symptom-based limitations and physical function: Results of a randomized clinical trial*. 2004 National State-of-the-Science Conference, Washington, DC.
- End-of-Life Seminar presentation. Doorenbos, A. Z., Given, C. W., & Given, B. (November, 2004). *Prevalence and predictors of advance care planning among women with breast cancer*. Michigan State University College of Nursing, East Lansing, MI.
- Paper presentation. Doorenbos, A. Z., Given, B., Given, C. W., Wyatt, G., Gift, A., Rahbar, M., & Jeon, S. (November, 2004). *Impact of end-of-life care for caregivers of family members over 65 with cancer*. Gerontological Society of America 57th Annual Scientific Meeting, Washington, DC.
- Paper presentation. Doorenbos, A. Z., Given, B., Given, C. W., & Verbitsky, N. (February, 2005). *An analytic strategy for measuring and modeling cancer symptoms*. 8th National Conference on Cancer Nursing Research, Fort Lauderdale, FL.

CONCLUSIONS:

The results from the interim analysis show that ACP prevalence among women with breast cancer undergoing a cognitive behavioral trial for symptom management is greater than previously reported. As age increased women with breast cancer were more likely to have ACP; however, none of the health factors were found to be significant predictors of ACP completion, suggesting that greater communication may need to occur about ACP in relation to health status.

Appendix A: IRB approval letters

**MICHIGAN STATE
UNIVERSITY**

October 5, 2004

TO: Charles GIVEN
B427 W. Fee
MSU

RE: **IRB # 03-762 CATEGORY: 2-7 EXPEDITED**

RENEWAL APPROVAL DATE: October 5, 2004

EXPIRATION DATE: October 4, 2005

TITLE: **ADVANCE CARE PLANNING: EXPERIENCE OF WOMEN WITH BREAST CANCER**

The University Committee on Research Involving Human Subjects' (UCRIHS) review of this project is complete and I am pleased to advise that the rights and welfare of the human subjects appear to be adequately protected and methods to obtain informed consent are appropriate. Therefore, the **UCRIHS APPROVED THIS PROJECT'S RENEWAL.**

Revision to include a change in the study cover letter, brochure and follow letter.

RENEWALS: UCRIHS approval is valid until the expiration date listed above. Projects continuing beyond this date must be renewed with the renewal form. A maximum of four such expedited renewals are possible. Investigators wishing to continue a project beyond that time need to submit a 5-year renewal application for complete review.

REVISIONS: UCRIHS must review any changes in procedures involving human subjects, prior to initiation of the change. If this is done at the time of renewal, please include a revision form with the renewal. To revise an approved protocol at any other time during the year, send your written request with an attached revision cover sheet to the UCRIHS Chair, requesting revised approval and referencing the project's IRB# and title. Include in your request a description of the change and any revised instruments, consent forms or advertisements that are applicable.



PROBLEMS/CHANGES: Should either of the following arise during the course of the work, notify UCRIHS promptly: 1) problems (unexpected side effects, complaints, etc.) involving human subjects or 2) changes in the research environment or new information indicating greater risk to the human subjects than existed when the protocol was previously reviewed and approved.

OFFICE OF

**RESEARCH
ETHICS AND
STANDARDS**

University Committee on
Research Involving
Human Subjects

Michigan State University
202 Olds Hall
East Lansing, MI
48824

517/355-2180

FAX: 517/432-4503

Web: www.msu.edu/user/ucrihs

E-Mail: ucrihs@msu.edu

If we can be of further assistance, please contact us at 517 355-2180 or via email:
UCRIHS@msu.edu.

Sincerely,

A handwritten signature in black ink, appearing to read 'Peter Vasilenko', is placed above the printed name.

Peter Vasilenko, Ph.D.
UCRIHS Chair

PV: jm

cc: Ardith Doorenbos
B418 west Fee Hall
MSU



William Beaumont Hospital
Royal Oak

Human Investigation Committee
Phillip J. Bendick, Ph.D.
Chairman

December 6, 2004

Veronica Decker RN,MS,CNS
William Beaumont Hospital
Cancer Clinical Trials Office
Royal Oak, MI 48067

HIC # 2003-204 (Amendment received: 11/16/2004)

**Protocol Title: FAMILY HOME CARE FOR CANCER - A COMMUNITY BASED
MODEL & AUTOMATED TELEPHONE MONITORING FOR SYMPTOM
MANAGEMENT**

I have reviewed the protocol amendment to add Jeane Archer, PhD, APN as an investigator of this study and to include a substudy "ADVANCE CARE PLANNING: EXPERIENCE OF WOMEN WITH BREAST CANCER". I believe the amendment involves no more than minimal risk to human subjects as detailed in Docket #87N-0032 of the Federal Register (6/18/91).

The amendment request has been extended **FULL APPROVAL** under the Expedited Review policy (21 CFR 56.110) of the Human Investigation Committee.

All amendments to the protocol, except those necessary to eliminate apparent immediate hazards to human subjects, may not be initiated without review and approval by the Human Investigation Committee. Note: any deviation from protocol must be reported immediately.

Sincerely,

A handwritten signature in black ink that reads "Phillip J. Bendick, Ph.D." with a stylized flourish at the end.

Phillip J. Bendick, Ph.D.
Chairman
Human Investigation Committee
/vkj

June 15, 2004

Albert Brady, MD
Director of Oncology Services
44405 Woodward Avenue
Pontiac, MI 48341

RE: **Advance Care Planning: Experience of Women with Breast Cancer.**
SJMO 04-06-04 Brady

Dear Dr. Brady:

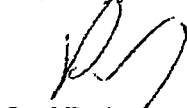
The St. Joseph Mercy Oakland Institutional Review Board/Research Committee reviewed your request for the protocol cited above at the June 14th, 2004 meeting. The committee voted to approve the above protocol for a period of one year. The committee also voted to approve the SJMO version of the informed consent, and SJMO standard HIPAA form. Dr. Brady was not present for the vote. This will be given the St. Joseph Mercy Oakland IRB #04-06-04 Brady.

Please be aware that you should report to the committee concerning this project when you are completed with it, or when it is due for renewal next year (June 14th, 2005). You must also submit a summary of the study progress for protocol by June 14th, 2005, or at the conclusion of the study if the study is concluded prior to the renewal date.

Should you wish to make any further changes in your protocol, the Institutional Review Board/Research Committee must approve the changes before they are implemented. In the case of revisions, the changes between the new and the old protocol should be submitted in detail and the pertinent areas of the changes highlighted to facilitate review by the Research Office and Chair of the IRB/RC. Should you develop abstracts, posters, or manuscripts involving the hospital, or using of the hospital's name in any way related to this work, please be aware that IRB/RC policy is that such submissions must be conveyed to the Research Office for review at least one week prior to submission.

We wish you continued success with your projects.

Sincerely,



Paul D. Stein, MD
Chairperson, Institutional Review Board/Research Committee

A MEMBER OF  TRINITY HEALTH

OUR MISSION: We serve together in Trinity Health in the spirit of the Gospel to heal the body, mind and spirit, to improve the health of our communities and to steward the resources entrusted to us.



NORTHERN INDIANA CANCER RESEARCH CONSORTIUM

Indiana's First Community Clinical Oncology Program

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Institutional Review Board

October 13, 2004

Robin Zon, MD
Michiana Hematology Oncology
100 Navarre Place ~ Ste 5550
South Bend, IN 46601

Dear Dr. Zon:

At the meeting on October 12, 2004 the Northern Indiana Cancer Research Consortium (NICRC) IRB conducted a full board review of the protocol, "Advanced Care Planning: Experience of Women with Breast Cancer IUCRO 0091

As Chair, it is my pleasure to inform you that your research protocol (dated 03/05/04) and consent form have been approved by the Board for an initial one year period beginning October 12, 2004 and expiring October 11, 2005. The NICRC is in compliance with federal regulations for the protection of human subjects and has been assigned assurance number T-4913.

Please be advised that an annual progress report will be required. In addition, the IRB must be notified of significant complications in subjects enrolled in the study. Any death from any cause while a subject is receiving protocol treatment and any death following protocol treatment that is felt to be treatment-related must be reported by phone within 24 hours. Adverse reactions that are judged to be definitely, probably or possibly related to protocol treatment must be reported in writing within 10 days.

Thank you for your interest in conducting research in our community. If you are in need of additional information, please contact me at 239-5297.

Sincerely,

Bettye Green, RN
Chair, Institutional Review Board

cc: Mary Jean Wasielewski, RN, Oncology Research Coordinator
IRB File

MEMBERS

Elkhart General Hospital • LaPorte Hospital • Memorial Hospital of South Bend • Saint Joseph Regional Medical Center

AFFILIATIONS

*Cancer & Leukemia Group B • Hoosier Oncology Group • Gynecology Oncology Group • National Surgical Adjuvant Breast & Bowel Project
Phase II Consortium, University of Chicago • Radiation Therapy Oncology Group • Pharmaceutical Studies*

INTERDEPARTMENTAL COMMUNICATION
Research Compliance Administration
Indiana University - Purdue University Indianapolis

DATE: January 12, 2005

TO: Victoria L. Champion
Environments for Health
NU 340G
IUPUI

FROM: Melissa Margol *MM*
Research Compliance Administration

SUBJECT: Final Approval

Study Number: 0411-03B

Study Title: Advance Care Planning: Experience of Cancer Patients and Advance Care Planning: Experience of Women with Breast Cancer

Sponsor: Department of Defense

The study listed above has received final approval from the Institutional Review Board (IRB-01). **IMPORTANT NOTICE:** The Institutional Review Board (IRB) requires that the consent statement given to subjects have the IRB approval stamp on the last page.

Please note that although this study has been granted final approval by the IRB, special requirements apply if the principal investigator becomes aware that an individual enrolled on the study either is a prisoner or has become a prisoner during the course of his/her study participation (and the study has not been previously granted approval for the enrollment of prisoners as a subject population). In such cases, all research interactions and interventions with the prisoner-participant must cease and if it is wished to have the prisoner-participant continue to participate in the research, Research Compliance Administration (RCA) must be notified immediately. In most cases, the IRB will be required to re-review the protocol at a convened meeting before any further research interaction or intervention may continue with the prisoner-participant. Refer to the IUPUI/Clarian Standard Operating Procedure (SOP) on *Involving Prisoners in Research* for further information.

As the principal investigator of this study, you assume the responsibilities as outlined in the SOP on *Responsibilities of Principal Investigators*, some of which include (but are not limited to):

1. **CONTINUING REVIEW** - A status report must be filed with the Board. The Research Compliance Administration (RCA) staff will generate these reports for your completion. Additionally, you must contact RCA to request that this report be generated for your completion within 90 days after termination or completion of the investigation or the investigator's part of the investigation. This study is approved from January 7, 2005 to November 5, 2005.
2. **STUDY AMENDMENTS** - Investigators are required to report on these forms ANY changes to the research study including protocol design, dosages, timing or type of test performed, population of the study, and informed consent statement. An amendment form can be obtained on our website. See link <http://www.iupui.edu/~resgrad/spon/amendment-irb.htm>.
3. **ADVERSE EVENTS** - If this is a medical study, all side effects or adverse reactions which are serious and unexpected and associated with the study intervention must be reported immediately to the Board as they occur. See link <http://www.iupui.edu/~resgrad/spon/adverse-report-notice.htm> for adverse reaction reporting requirements and to obtain an Adverse Reaction Reporting Form. If the study involves gene therapy, all serious adverse events must be reported to both the IRB and the Institutional Biosafety Committee (IBC).
4. **UPDATED INVESTIGATIONAL BROCHURES, PROGRESS REPORTS and FINAL REPORTS** - If this is an investigational drug or device study, updated clinical investigational brochures must be submitted as they occur. See link <http://www.iupui.edu/~resgrad/spon/cibrequire.htm> for requirements. Three copies of progress or final reports must be provided to the Board with the investigator's written assessment of the report, briefly summarizing any changes and their significance to the study.
5. **ADVERTISEMENTS** - If you will be advertising to recruit study participants for a drug or device study regulated under FDA requirements, i.e., investigational drugs or devices will be used, and the advertisement was not submitted to the Board at the time your study was reviewed, a copy of the information contained in the advertisement and the mode of its communication must be submitted to the reviewing board as an amendment to the study. These advertisements must be reviewed and approved by the Board PRIOR to their use.
6. **LEAVING THE UNIVERSITY** - If the principal investigator leaves the Institution, the Board must be notified as to the disposition of EACH study.

PLEASE REFER TO THE ASSIGNED STUDY NUMBER AND THE EXACT TITLE IN ANY FUTURE CORRESPONDENCE WITH OUR OFFICE. In addition, SOPs exist which cover a variety of topics that may be relevant to the conduct of your research. See link <http://www.iupui.edu/~respoly/human-sop/human-sop-index.htm>. All documentation related to this study must be neatly typed and must also be maintained in your files for audit purposes for at least three years after termination of the research; however, please note that research studies subject to HIPAA may have different requirements regarding file storage after termination. If you have any questions, please call RCA at 274-8289.

Enclosures: ☒ Documentation of Review and Approval
☒ Informed Consent Statement
☒ Authorization form

☐ Advertisement
☐ Waiver of authorization for recruitment
☐ Other



June 28, 2004

Ardith Z. Doorenbos, PhD, RN
Michigan State University
B418 West Fee Hall
East Lansing, MI 48824

RE: New study: "Advance Care Planning Experience of Women with Breast Cancer"

Dear Ms. Doorenbos:

On June 28, 2004, Saint Mary's IRB met and reviewed the aforementioned study and its associated consent document. We found your study protocol and its associated documents to be in order. We made one request: include a Saint Mary's HIPAA authorization document to accompany the consent document. You agreed to do so.

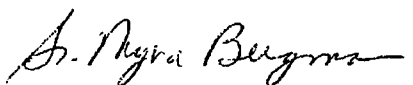
Therefore, Saint Mary's IRB approves the study and the consent documents for a period of one year, beginning June 28, 2004, and concluding June 28, 2005. Should there be any changes in the study protocol and or consent document during that period of time, these will need to be submitted for approval before implementation.

One of the IRB members, Dr. Thomas Gribbin, declared conflict of interest, due to his involvement with the Home Care Cancer studies of Dr. Charles and Dr. Barbara Given. Therefore, he was excused from the room and voting procedures. His vote is recorded as "abstaining" on our records.

A progress report is due to the IRB no later than May 1, 2005.

We appreciate your cooperation with our procedures and wish you success with this study.

Sincerely,


Sister Myra Bergman, IRB Chair

cc. Charles Given, Ph.D.
Barbara Given, Ph.D.

Appendix B: Manuscript

Doorenbos, A. Z., Verbitsky, N., Given, B., & Given, C. W. (in press).
An analytic strategy for modeling multiple item responses: A
breast cancer symptom example. *Nursing Research*.

TITLE

An analytic strategy for modeling multiple item responses:
A breast cancer symptom example

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Family Home Care for Cancer: A Community-Based Model
PI Barbara Given

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RUNNING HEAD

Three-level HLM model

Acknowledgment: The authors wish to thank Professor Stephen W. Raudenbush, PhD, School of Education, University of Michigan, for his review of and comments on this manuscript.

Abstract

Background: Item Response Theory (IRT) is increasingly applied in health research to combine information from multiple item responses. IRT posits that a person's susceptibility to a symptom is driven by the interaction of the symptom's and a person's characteristics. This paper describes the statistical background of incorporating IRT into a multilevel framework and extends this approach to longitudinal health outcomes, where the self-report method is used to construct a multi-item scale.

Approach: A secondary analysis of data from two descriptive longitudinal studies is performed. The data include 21 symptoms reported across time by 350 women with breast cancer. A three-level hierarchical linear model (HLM) was used for the analysis. Level 1 models the item responses, consisting of symptom presence or absence. Level 2 models the trajectory of each individual, representing change over time of the IRT created latent variable, symptom experience. Level 3 explains that trajectory using person-specific characteristics such as age and location of care. The purpose of the analysis is to examine if older and younger women with breast cancer differ in their symptom experience trajectory after controlling for location of care.

Results: Fatigue and pain were the most prevalent symptoms. The symptom experience of women with breast cancer was found to improve over time. Neither age nor location of care were significantly associated with the symptom experience trajectory.

Discussion: Embedding IRT into an HLM framework produces several benefits. The example provided demonstrates benefits through the creation of a latent symptom experience variable that can be used either as an outcome or covariate in another model, examining the latent symptom experience trajectory and its relationship with covariates at the individual level, and managing symptom item non-response.

Keywords: Item response theory, hierarchical linear model, cancer symptoms, women with breast cancer

An analytic strategy for modeling multiple item responses:

A breast cancer symptom example

In studying symptoms of disease, exposure to risk, behavior, beliefs, and attitudes, nursing researchers frequently have to combine a number of item responses. In such studies, participants may be repeatedly assessed over time and/or nested within social settings, such as hospitals, nursing homes, or communities. With social settings in particular, a wide variability of gathered data results from a multitude of sources which are sometimes unknown. Missing item-level data are often unavoidable as well. Some examples of questions that arise in such cases, requiring robust analytical methodologies are: How does the symptom experience of women with breast cancer change over the course of the chemotherapy treatment? Does age affect engagement in risky behaviors that contribute to AIDS/HIV? Do individual beliefs and cultural attitudes influence the acceptance of differing end-of-life care paradigms?

Item Response Theory

Item Response Theory (IRT) was developed in the 1980s in educational research to address some of the issues of measurement practices in scoring tests (McDonald, 1999; van der Linden & Hambleton, 1997). The IRT models postulate that characteristics of a test item, such as its difficulty, interact with an individual's ability or trait, to determine the probability of a correct response to that item (Lord, 1980; Cheong & Raudenbush, 2000). The most simple IRT model, the Rasch model, has only one parameter per item, namely difficulty. The Rasch model makes the assumption that each item is equally discriminating. When this assumption is true, the resulting scale has a clear interpretation: that difficult items will be answered correctly less frequently than easy items. Besides an item-difficulty scale, the IRT can also provide estimates

of latent abilities that can be studied as either explanatory or outcome variables in other models. Of particular significance to this class of analysis, IRT reduces the skewness that commonly arises in composite measures, such as the sum or proportion. This framework has recently been applied to health outcomes (Hays, Morales, & Reise, 2000; Fortinsky, Garcia, Sheehan, Madigan, & Tullai-McGuinness, 2003).

Hierarchical Linear Models

Statistical models that account for nesting of data (e.g., hierarchical linear models [HLM]) have been growing in popularity (Raudenbush & Bryk, 2002). There has been an increase in the use of HLM in nursing research, especially in research examining patient and organizational outcomes (Cho, 2003; Cho, Ketefian, Barkauskas, & Smith, 2003; Whitman, Davidson, Sereika, & Rudy, 2001). In the past, when confronted with data on individuals nested in organizations, a researcher had to decide whether to perform the analysis at the individual level, thus ignoring the nested structure of the data, or whether to aggregate the variables to the higher level, thus ignoring individual variation within the organizations. In using an HLM analysis, the researcher no longer has to decide at which level to perform the analysis. This avoids problems of misestimating standard errors and of incorrect statistical inference.

There are several benefits of incorporating the IRT into an HLM framework for nursing researchers: (a) It includes the ability to examine multiple dimensions of abilities, traits, or symptoms; (b) it can separate the variation between social settings, such as hospitals, nursing homes, or communities, from the variation between individuals who are nested within these settings; (c) it provides a way to examine the measurement error in the assessment of social settings where individuals are used as informants about their social setting; (d) it allows the researcher to examine the relationship between explanatory variables at various levels (e.g.,

individual or setting) and the ability or trait, (e) it provides a framework for incorporating repeated observations of item responses in order to examine changes in the latent ability over time, and (f) the combined framework also provides a way to manage item non-response (Raudenbush & Bryk, 2002). These items exemplify the benefits of embedding an IRT model into an HLM framework as a tool for studying symptoms and other self-reported health behavior. A more detailed theoretical discussion regarding incorporating the IRT into an HLM framework can be found in Raudenbush, Johnson, and Sampson (2003) and Johnson and Raudenbush (in press).

The purpose of this article is, having described the statistical background of incorporating IRT into an HLM framework, to illustrate this methodology using an example of the symptom experience for women with breast cancer. This demonstrates the methodology by extending the approach to longitudinal data with health outcomes, where the self-report method is used to construct a multi-item scale. The aim of the analysis is to examine if older and younger women differ in their symptom experience trajectory after controlling for location of care.

An Example: Three-level HLM model incorporating a symptom IRT

An important aspect of symptom research is how symptom experience varies over time according to the characteristics of the individual and setting. For example, the symptom experience may change differently over time for each woman with breast cancer. Age may influence the relationship, as older women may tend to report fewer symptoms and thus have better symptom experience, than younger women at diagnosis and start of chemotherapy. However, younger women may tend to return to the pre-diagnosis symptom experience faster than older women. Additionally, medical care can affect the symptom experience trajectory.

Women receiving care at urban hospitals may have a greater accessibility to medical treatments and thus experience fewer symptoms overall than those at rural hospitals. Incorporating IRT into an HLM framework allows us to examine these and other similar questions.

This example describes a longitudinal Rasch model, which incorporates repeated measures on 21 symptoms at four time points over a one-year period. Following HLM terminology, we have symptoms at level 1 nested in repeated measures at level 2 that are, in turn, nested in individuals at level 3. To keep the model simple, only three covariates are included in the model: two individual characteristics (age and location of care), and time since diagnosis. In this analysis, the Rasch model orders the responses to a set of items (symptom presence or absence) according to a symptom's characteristic of prevalence in lieu of the traditional "item difficulty." The analog to the typical IRT latent ability is then a latent symptom experience.

Data and Participants

This example involves a secondary analysis of data from two descriptive longitudinal studies conducted from 1990 to 1998. The first study recruited 242 women from urban hospitals; the second study recruited 108 women from rural hospitals. These 350 women were newly diagnosed with breast cancer and undergoing chemotherapy. The participants were followed for one year, and completed telephone interviews on four occasions. At each interview, the presence of 21 symptoms was recorded along with other characteristics.

Inclusion criteria for the primary studies required that women with breast cancer be at least 21 years of age; cognitively intact; and able to speak, read, and write English. Women under the care of a psychologist or psychiatrist, or with a diagnosed emotional or psychological disorder, were excluded. Nurse recruiters approached women who met the inclusion criteria, explained the studies, and obtained written consent. At mutually convenient times, the

participants were interviewed by telephone; they also completed self-administered questionnaires. The ages of the participants ranged from 28 to 98, with a mean of 67.72 years (SD = 11.36).

Measures

Symptoms were assessed using the self-report Physical Symptom Experience tool (Given et al., 1993). Participants responded regarding the presence of 21 symptoms commonly experienced by individuals with cancer, indicating whether they experienced the symptom (1) or not (0).

Time was coded in days since diagnosis. Demographic information included age and location of care. Location of care was coded rural = 1 if a rural hospital and rural = 0 if an urban hospital. To render the intercept of the regression line meaningful, age was grand-mean centered.

Analysis

Level-1 Model

The level-1 model is a standard one-parameter item response or Rasch model, with random effects. In applying the Rasch model, item difficulty was operationalized as symptom prevalence. Let $Y_{ijk} = 1$ if the symptom i was present at time j for person k and 0 otherwise. The probability of a symptom being present, $Pr(Y_{ijk} = 1)$, is denoted by μ_{ijk} . At this level, there are 20 dummy variables, D_{mijk} , representing 20 of the 21 symptoms measured. So the level-1 equation is

$$\log\left(\frac{\mu_{ijk}}{1 - \mu_{ijk}}\right) = \pi_{0jk} + \sum_{m=1}^{20} \pi_{mjk} D_{mijk} \quad (1)$$

π_{mjk} is interpreted as the prevalence of the symptom m at time j for person k , compared with the reference symptom (i.e., the symptom for which a dummy variable was not included in the

model). This model creates an interval scale for the symptoms, where large values of π_{mjk} indicate more prevalent symptoms, while low values indicate less frequent symptoms. By IRT convention, the prevalence for the reference symptom (fatigue) is fixed at zero. This generates the IRT ordering of symptoms by prevalence.

The IRT latent variable describing aggregated symptoms is symptom experience, or π_{0jk} , which indicates the overall symptom experience at time j for person k . π_{0jk} becomes an outcome at level 2, where the symptom experience trajectory is examined. Larger values of π_{0jk} indicate a higher relative prevalence of symptoms, while smaller values indicate a lower relative prevalence of symptoms.

Level-2 Model

The level-2 model accounts for variation in symptom experience over time for each woman with breast cancer. Equation 2 models parameters from the level-1 model, π_{0jk} and π_{mjk} . To conform to the Rasch methodology, we fixed the prevalence of each symptom (π_{mjk}) across time (level 2) and individuals (level 3) in the model. This constraint reflects the belief that given a symptom experience, random samples of women with breast cancer will experience a symptom with the same prevalence. Otherwise, the symptom may be regarded as biased against a subset of women with breast cancer. At level 2, the symptom experience (π_{0jk}) is described as a function of time.

$$\begin{aligned}\pi_{0jk} &= \beta_{00k} + \beta_{01k} * time_{jk} + u_{0jk} \\ \pi_{mjk} &= \beta_{m0k}, \text{ for } m = 1, \dots, 20\end{aligned}\tag{2}$$

β_{00k} and β_{01k} represent the initial symptom experience, and the linear daily rate of change in symptom experience for individual k , respectively. The random effects, u_{0jk} , are the deviations at

time j of individual k 's symptom experience from the predicted. β_{m0k} represents the prevalence of the symptom m , compared with the reference symptom for individual k .

Level-3 Model

At level 3, the symptom experience trajectory is explained using person-specific characteristics, such as age and location of care.

$$\begin{aligned}\beta_{00k} &= \gamma_{000} + \gamma_{001} * (age_k - 67.72) + \gamma_{002} * rural_k + v_{00k} \\ \beta_{01k} &= \gamma_{010} + \gamma_{011} * (age_k - 67.72) + \gamma_{012} * rural_k + v_{01k} \\ \beta_{m0k} &= \gamma_{m00}, \text{ for } m = 1, \dots, 20\end{aligned}\tag{3}$$

In this equation, γ_{000} is the average initial symptom experience for women with breast cancer who are receiving care in urban hospitals; γ_{001} is the expected difference in the initial symptom experience between two women who differ by one year in age; γ_{002} is the expected difference in the average initial symptom experience between the rural and urban locations of care; γ_{010} is the expected average daily rate of change in symptom experience for women receiving care at the urban hospitals; γ_{011} is the difference in the expected daily rate of change in symptom experience between two women who differ by one year in age; γ_{012} is the difference in the expected daily rate of change in symptom experience between the rural and urban studies; and γ_{m00} is the prevalence of the symptom m compared with the reference symptom.

By combining the level-1, -2, and -3 models, the hierarchical generalized linear model can be estimated. The combined model tests how the log-odds of experiencing a symptom vary with time and person-specific characteristics, such as age and location of care. This three-level hierarchical model can be viewed as an item-response model embedded within a hierarchical structure, in which repeated measures are nested within women with breast cancer.

Missing data was addressed by using complete case analyses (Little & Rubin, 2002), i.e. if at least one symptom was recorded as present or absent during an interview, then this interview information was used in the analysis. The number of symptoms recorded (present or absent) during interviews ranged from 10 to 21. Some women had fewer than four interviews, resulting in 1,184 interviews (rather than $350 * 4 = 1,400$) included at level 2. Since every woman had at least one interview, and all women had both age and location of care recorded, 350 individuals were included in the analysis at level 3.

We present two models, an unconditional and a conditional, estimated using HLM 6.20 (Raudenbush, Bryk, Cheong, & Congdon, 2004). The unconditional model has no covariates at level 2 or level 3, which yields a readily interpretable ordering of symptoms as well as the unadjusted symptom experience estimates for each person at each occasion that they recorded at least one symptom's presence or absence. We examined the symptom experience over time by testing linear and quadratic trajectories at level 2. To test the associations between individual variables and symptom experience, these variables were incorporated into the multivariate model at level 3. In the final model, level 1 remains the same as in the unconditional model (see equation 1), but now, entered into the model are the time-level variable (days since diagnosis) at level 2, and the individual-level variable (age and location of care) at level 3, as shown in equations 2 and 3 above.

Model Results

Unconditional Model

Fatigue, the most common symptom in the raw data, was used as the reference symptom (Table 1). The results of the unconditional model yield a readily interpretable ordering of

symptoms. Figure 1 shows the symptoms organized by their prevalence (γ_{m00}); the more prevalent symptoms appear at the top (high values), while less prevalent appear at the bottom (low values). Symptoms appearing close together in Figure 1 have similar symptom prevalence. Construct validity for this scale was confirmed by the fact that pain and fatigue occurred with greatest frequency, which has been well established in the cancer literature (Given, Given, Azzouz, Kozachik, & Stommel, 2001; Mock, 2003; Patrick et al., 2003). The lowest-frequency symptom during chemotherapy treatment for breast cancer was dehydration (Table 1).

This model produced an unadjusted symptom experience estimate for each individual and each occasion when the presence of at least one symptom was recorded (Figure 2a). These symptom experience estimates are approximately normally distributed and may be used as either a covariate or an outcome in other models.

Conditional Model

Since our focus was to determine the trajectory of symptom experience as well as its association with important individual variables, partial output for level 2 and 3 is reported in Table 2. Both the linear and quadratic trajectories were tested; however, the quadratic term did not significantly improve the model fit. Therefore, a linear trajectory was used in the final model. Time was significantly, negatively associated with symptom experience ($\hat{\gamma} = -.002$, $p < .001$). So, as women with breast cancer moved through the year, on average their symptom experience improved. Since we hypothesized that the symptom experience trajectory may differ according to women's age and location of care, age and rural were used to explain initial symptom experience and change in symptom experience. Neither age nor location of care was found to be statistically significantly associated with change of symptom experience over time

($p = .085$ and $p = .819$, respectively), nor were they found to be statistically significantly associated with symptom experience ($p = .173$ and $p = .150$, respectively) (Table 2).

Discussion

The benefits of using IRT are illustrated by the results of the unconditional model. First, IRT created a meaningful metric that reflects the varying prevalence of symptoms in women with breast cancer (Figure 1), while reducing the skewness that commonly arises in composite measures of symptoms (Figures 2a and 2b). Second, the analysis provided estimates of the latent symptom experience for each person at each occasion when the presence or absence of at least one symptom was recorded. These symptom experience estimates can be used as explanatory or outcome variables in other models.

Several of the numerous benefits of embedding IRT into an HLM framework were illustrated in the example above. First, this methodology provided a framework for incorporating repeated observations on the presence of symptoms in order to examine changes in the latent variable symptom experience over time. The results on the conditional model showed that the symptom experience of women with breast cancer improved over time. Second, this methodology allowed us to examine the relationship between individual variables and the latent symptom experience. Contrary to our hypothesis, controlling for the location of care, no statistically significant association of age with the symptom experience trajectory was found.

Moreover, the hierarchical framework provides a way to manage item non-response. Presently, two common approaches for combining symptom information use the sum or the proportion of the symptoms present. When using a summary score, a nursing researcher must make an arbitrary decision regarding how to handle item non-response. Using the sum assumes

that everyone has the same number of symptoms recorded, but not necessarily present; the symptoms that are not recorded are assumed to be not present. The proportion approach assumes that each symptom contributes the same amount of information, which is again problematic, since some symptoms occur more frequently than others. A researcher can use an IRT model without having to decide what to do with missing data, as long as the data are assumed missing at random (MAR), a comparatively mild assumption (Little & Rubin, 2002).

In conclusion, the task of combining information from multiple item responses arises frequently in studies of health outcomes. In many of these studies, the items are measured over time and nested within individuals, and item-level missing data are often unavoidable. This report demonstrates how embedding a Rasch model into HLM can address these research challenges.

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Table 1.

Raw Data Symptom Frequency (All Observations Combined)

Symptoms	Yes	No	Total	% Yes
Fatigue	693	491	1184	58.53
Pain	462	722	1184	39.02
Insomnia	426	758	1184	35.98
Dry Mouth	402	781	1183	33.98
Loss Of Feeling	326	857	1183	27.56
Urinary Frequency	301	882	1183	25.44
Weakness	289	894	1183	24.43
Cough	262	921	1183	22.15
Constipation	225	958	1183	19.02
Nausea	208	975	1183	17.58
Concentration	187	997	1184	15.79
Poor Appetite	182	1000	1182	15.40
Shortness Of Breath	169	1015	1184	14.27
Weight Loss	161	1017	1178	13.67
Coordination Problems	103	1081	1184	8.70
Diarrhea	102	1082	1184	8.61
Mouth Sores	66	1117	1183	5.58
Difficulty Swallowing	57	1124	1181	4.83
Vomiting	46	1138	1184	3.89
Fever	45	1138	1183	3.80
Dehydration	26	1156	1182	2.20

Note: Some of the 350 women had fewer than four interviews and the presence of fewer than 21 symptoms recorded at each interview, resulting in 1,184 interviews and varying totals.

Figure 1. Symptom prevalences (γ_{m00}) according to the unconditional model.

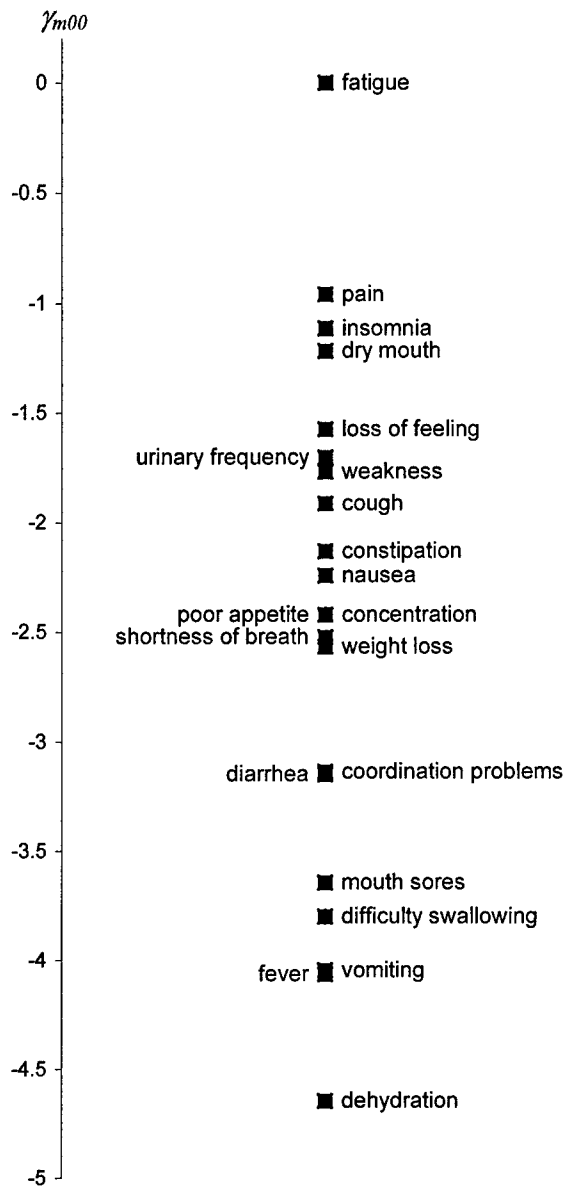
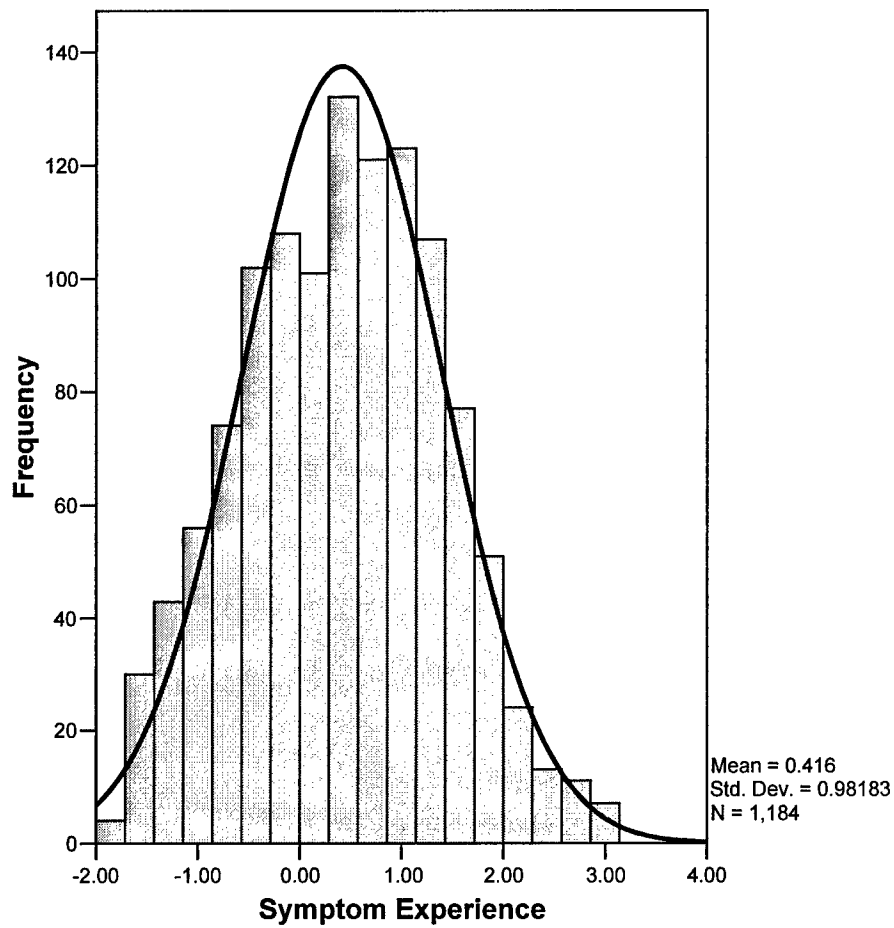


Table 2.

Partial Output of Estimates for the Conditional Model (Excluding Symptoms' Prevalence)

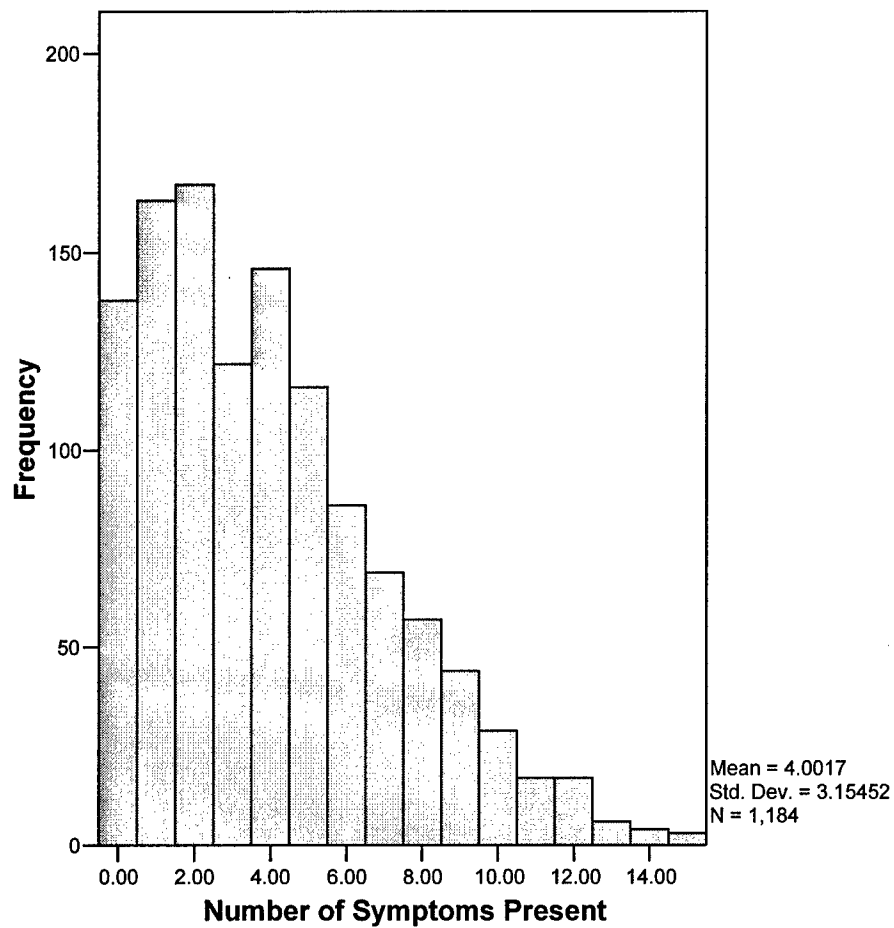
Variable	Coefficient	Standard Error	P value
Intercept, γ_{000}	0.605	0.106	< .001
Age, γ_{001}	-0.010	0.007	.173
Rural, γ_{002}	0.268	0.185	.150
Time, γ_{010}	-0.002	0.0003	< .001
Time*Age, γ_{011}	0.00005	0.00003	.085
Time*Rural, γ_{012}	0.0002	0.0007	.819

Figure 2a. Histogram of symptom experience from the unconditional model, π_{0jk}



Note: Some of the 350 women had fewer than four interviews, resulting in 1,184 total interviews.

Figure 2b. Histogram of total number of symptoms present



Note: Some of the 350 women had fewer than four interviews, resulting in 1,184 total interviews.

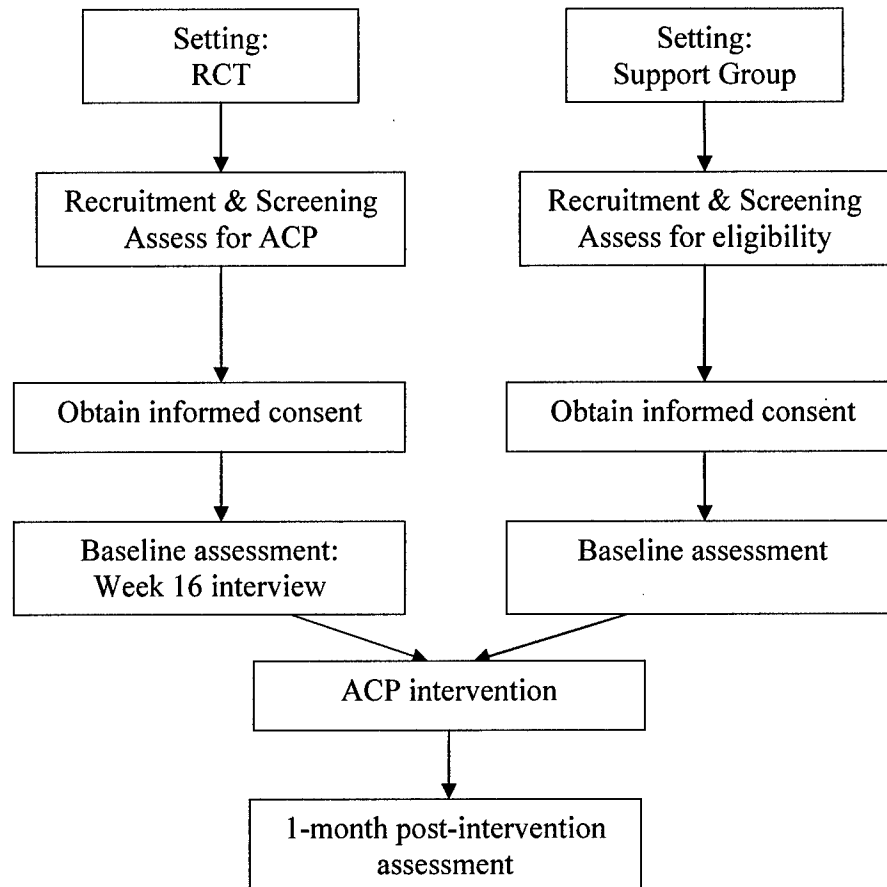
Appendix C: Data analysis Table 1

Table 1. Descriptive statistics of women with breast cancer

Demographic variables	
Age	Range 26-82 Mean 52 + 10
	N (percent)
Race/ethnicity	
White	96 (87%)
African American/Black	10 (9%)
Hispanic	2 (2%)
Native American	2 (2%)
Education	
Some high school	6 (6%)
Completed high school	20 (18%)
Some college	37 (34%)
Completed college	20 (18%)
Completed graduate school	26 (24%)
Marital status	
Never married	16 (15%)
Married	69 (63%)
Divorced/separated	17 (16%)
Widowed	6 (6%)
Living together	2 (2%)
Number in household	Range 1-7 Mean 2.7 + 1.4
Children under 13	25 (25%)
Children between 13-17	22 (22%)
Health variables	
	N (percent)
Stage of cancer	
Stage 1	11 (10%)
Stage 2	50 (48%)
Stage 3	15 (14%)
Stage 4	23 (22%)
Advanced	6 (6%)
Reoccurrence of cancer	
No	72 (65%)
Yes	38 (25%)
Hospital admission in last 3 months	
No	67 (61%)
Yes	43 (39%)
Comorbidities	
No other comorbidities	24 (22%)
1 comorbid condition	21 (19%)
2 comorbid conditions	24 (22%)
3 comorbid conditions	24 (22%)
3+ comorbid conditions	17 (15%)
Symptom interference	Range 0 - 102 Mean 32 + 22
Emotional variables	
Optimism	Range 14 - 29 Mean 24 + 2.9
Depressive symptomatology	Range 1 - 35 Mean 14 + 6.7

Appendix D: Modification of recruitment

Study flow for women with breast cancer recruited from both settings



Description of support-group recruitment process

Women associated with support groups will be recruited by oral announcements and the distribution of written information at support group meetings, written announcements in newsletters, and letters of invitation sent by leaders of the support group to members. Brochures describing the ACP study will also be available for support group members to pass out to their network of women with breast cancer who may be interested in ACP.

Women with breast cancer who indicate interest in receiving information about advance care planning and contact the PI will be mailed a packet containing a cover letter, a brochure (describing the study), and two consent forms (one to sign and return in an enclosed, pre-addressed, stamped envelope, and the other for reference).

Description of the informed consent process for support groups

Women with breast cancer who indicated interest in receiving information about advance care planning and contact the PI will be mailed a packet containing a cover letter, a brochure (describing the study), and two consent forms (one to sign and return in an enclosed, pre-addressed, stamped envelope, and the other for reference).

Opportunities to discuss the study are provided by the inclusion in the information packet of (1) the PI's email address, and (2) a toll free number to contact the PI to discuss the study before making a decision to participate.

If the signed consent form is not returned in two weeks, telephone contact will be attempted by the PI calling every day over two weeks at various times a day. No more than three messages will be left. If the potential participant is reached by telephone, she will be asked about her interest in the study, about mailing back the consent form, and the PI will answer any questions regarding the study.

If the consent form is not returned in four weeks and the participant is not reached by telephone, a reminder letter will be sent by the PI. If a signed consent is not returned after the follow-up letter no further contact will occur.

Baseline interview of support groups

Upon return of a signed consent form, a baseline interview will be scheduled for women with breast cancer recruited from support groups. The interview will be administered over the telephone by the PI, using a computer-assisted telephone interview program. The interview takes approximately 45 minutes to administer and will be broken up into sections for participants who become fatigued during the interview.

Baseline interviews for both groups are similar on most measures. Differences arise in the timing of the demographics, optimism, and comorbidity assessments. These measures are assessed at the RCT baseline interview rather than the week-16 interview. Additional questions for women recruited from support groups include questions to assess diagnosis and treatment, and an additional symptom question regarding lymph edema.