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TITLE: Improving Symptom Control, QOL, and Quality of Care for Women with Breast Cancer: Developing a Research Program on Neurological Effects via Doctoral Education

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14. ABSTRACT

The purpose of this traineeship was to develop the academic, clinical, and research skills of an expert advanced practice nurse within the context of a mentor's (Tim A. Ahles, PhD) funded program of research of the (central nervous system[CNS]) Cognitive Effects of Chemotherapy. The scope of the program was to support the trainee's doctoral education with an ultimate career goal of becoming a Clinical Breast Cancer Research Scientist through a mentored research experience. Ms. Bakitas expanded an established research program on CNS effects by developing a parallel focus on the peripheral nervous system effects of chemotherapy, (Chemotherapy-Induced Peripheral Neuropathy [CIPN]), on quality of life. The major achievements at this final report, are the successful accomplishment of the planned training activities/tasks through the completion of the doctoral degree through successful defense of the dissertation, abstract presentations, acquiring an ACS doctoral scholarship, and receiving the Anthony DiGuida Research Prize for the dissertation. The significance of these achievements is that this funding has supported the training of a clinical nurse expert in a foundation for conduct of clinical breast cancer research.

15. SUBJECT TERMS
cancer control, outcomes research, quality of life, symptom management, neurological effects, doctoral education

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1. Bakitas, MA. (2005) Self-Determination Analysis of the concept and implications for research in palliative care. *Canadian Journal of Nursing Research*. 37 (2): 22-49.

2. **Bakitas, MA,** Lyons, K.D., Dixon, J, Ahles, T. (2006) Palliative Care Program Effectiveness Research: Developing rigor in sampling design, conduct and reporting. *Journal of Pain and Symptom Management*, 31(3): 270-284.

F. Poster Presentation from the Era of Hope Meeting (June 2005)

G. Poster Presentation from the Oncology Nursing Society Meeting (May 2005)

Introduction

This was the final year of a training grant to support a clinical nurse expert in an interdisciplinary, mentored, clinical and academic research experience in the understudied area of neurological effects of breast cancer treatment through a doctoral training program. A no cost extension was granted thus extending the grant period to 14 May 06 (Months 25-36). Hence this final report summarizes the final accomplishments of through the extension period (Months 25-36). A revised Statement of Work was submitted (4/20/05) and approved by Ms. Kimbark and it is included as Appendix A. There have been no changes to the revised Statement of Work and all work that was proposed is now completed.

The purpose of this traineeship was to develop the academic and research skills of the trainee within the context of a doctoral nursing program and the mentor's funded program of research on (central nervous system) Cognitive Effects of Chemotherapy. The traineeship supported Dr. Bakitas in her career goal to develop a program of research relevant to Clinical Breast Cancer Research. Dr. Bakitas expanded the Center for Psycho-oncology Program's focus on Central Nervous System/Cognitive Effects of Chemotherapy, by developing an independent, but related focus on the peripheral nervous system effects of chemotherapy (Chemotherapy-Induced Peripheral Neuropathy [CIPN]) on quality of life. Dr. Bakitas has completed the objectives stated in the Statement of work, successfully completed and defended doctoral dissertation and was awarded a doctor of nursing science degree from Yale University on 5/22/06. She received the YSN Anthony DiGuida/Delta Mu Prize that recognizes scholarship through a meritorious dissertation.

The traineeship was based at two campuses: the Dartmouth Medical School/Norris Cotton Cancer Center, Lebanon, NH and Yale University, New Haven, CT. The trainee's research mentor, Tim Ahles, PhD, Director of Psycho-oncology Research, Norris Cotton Cancer Center supervised the trainee's clinical research skill development at Dartmouth. Professor Ruth McCorkle, PhD and dissertation chair, Tish Knobf, RN, PhD supervised the academic and research components at Yale University.

Body

This section is organized according to the Tasks listed in the revised Statement of Work (Appendix A). Achievements are reviewed and summarized for each of the original three tasks.

Task 1. Develop research skills and abilities, including measurement, data analysis, and conceptual model development in breast cancer research through mentorship and doctoral education. (Months 1-18)

The trainee successfully completed all of the proposed tasks according to the timeline. This was summarized in the accepted 03-04 and 04-05 reports. Tasks 1.a and 1.b were ongoing throughout the grant period. Tasks l.f was completed in Dec. 04 when the trainee successfully defended her proposal and passed the Qualifying Exam. Task 1.g, study initiation occurred as of 1 April 05 with scientific review and IRB approval of the study. Recruitment encompassed April 05-September 05. Task 1. h Dissertation advisement commenced in Summer 04 until successful defense of the dissertation, achieved March 27, 2006.

Task 2. Collect pilot data on chemotherapy-induced peripheral neurological (CIPN) effects in conjunction with serial neuropsychological and quality of life measures in women enrolled in a longitudinal study of cognitive effects of breast cancer treatment (Months 1-24; extension Months 25-36).

The trainee proposed a series of steps to understand the foundational theoretical, instrumental, and clinical skills necessary to perform appropriate assessment of chemotherapy-induced peripheral neuropathy (CIPN). A major finding from the initial literature review (Task 3a) and consultation with neurological experts demonstrated a lack of consensus or gold standard in neurological assessment or self-reported CIPN. The multidisciplinary expert panel/project team composed of Dartmouth consultants (Cohen/Fadul/Smith) considered proposing a pilot study to validate a neuropathy tool modified for use in CIPN (the "reduced" Total Neuropathy Score (TNS) (Cavaletti et al., 2003; Chaudhry, Chaudhry, Crawford, Simmons-O'Brien, & Griffin, 2003). However, further study revealed basic flaws in the ability of this new tool to elicit a patient-based understanding of symptoms and quality of life information. Therefore, the trainee focused the dissertation on a mixed methods study to understand chemotherapy-induced neuropathy. Qualitative interview was the dominant method and the focus of the dissertation, however, quantitative data (using the FACT-Taxane and the EORTC-CIPN 20) was collected on the dissertation sample for future analysis and comparison.

In addition to the data collected for the dissertation, per Task 2.c, the FACT-Taxane was also added to the serial measures collected in two of the mentor's breast cancer studies: (Ahles) A Prospective, Longitudinal Study of the Cognitive Effects of Chemotherapy, and (Ahles/Saykin): Neural Mechanisms of Chemotherapy-Induced Cognitive Disorder. Recruitment is complete on the former study; the following Taxane survey data is now available from breast cancer patients 30 (baseline), 36 (post-treatment), 50 (12 months), and 65 (24 months). Analyses are planned this summer.

Selected analyses of the FACT-Taxane data from the 27 participants (one subject participated in the interview but did not complete the questionnaires). Appendix C Selected Tables and Figures summarize the sample and some dissertation analyses. Findings revealed inconsistencies between what participants reported in the FACT-Taxane, a comparison tool, the EORTC-CIPN20 and the qualitative data. Specifically less neurotoxicity is described in the questionnaires than is reported in interview data. As predicted, discrepancies are likely due to the inability of the tools to adequately describe the CIPN symptom experience. Manuscripts describing the qualitative and quantitative data and comparisons are planned during a proposed post-doctoral fellowship.

Task 3. Identify gaps in knowledge, research hypotheses, and feasible methods to study and develop interventions as a basis for a doctoral dissertation and future program of research (Months 6-24; extension Months 25-36).

The trainee has been extremely productive in this area. In July 05 the trainee participated in an intensive workshop to develop skills in the qualitative software for the dissertation analyses using Atlas.ti. Data analysis was conducted with review of dissertation committee at Yale and expert consultant group at DHMC, including mentor Tim Ahles, PhD. Preliminary findings were shared at a number of forums to assure credibility and trustworthiness of the data. The written and oral defense of the dissertation

occurred in March 06 and the trainee achieved the Doctor of Nursing Science degree from Yale University on May 22, 2006.

Abstracts related to the dissertation topic were submitted for professional meetings and reproductions of the 6/05 Era of Hope Meeting poster and the 5/06 Oncology Nursing Society Annual meeting poster are included as Appendices F and G respectively. An abstract describing selected dissertation results relative to patient appraisal of CIPN was accepted for a podium presentation at the 4/06 Eastern Nursing Research Society.

Additionally two manuscripts were prepared on topics related to patient decision-making and the research methods issue of recruitment to palliative care studies and both were accepted and have been published (See Appendix E for reprints).

Key Research Accomplishments

- Completed and successfully defended doctoral dissertation: Understanding Chemotherapy- Induced Peripheral Neuropathy: The Patient's Perspective on Symptoms and the Impact on Everyday Life".
- Dissertation selected for the Yale School of Nursing Anthony DiGuida/Delta Mu Research Prize.
- Continued consultant role on funded research project on CIPN

Reportable Outcomes

The trainee has continued to participate as a consultant on a Neuropathic Pain funded research grant, and has contributed to national organizations CIPN-related science via serving as a contributor on Neurological Effects portion of the 05-07 ONS research agenda and as a reviewer of an on-line evidence-based guideline for patients on CIPN. Poster abstracts, describing the foundational work of the dissertation related to measurement issue of CIPN, were accepted for presentation at international, national, and regional scientific meetings. A podium presentation and two published manuscripts were developed. The trainee received an American Cancer Society Doctoral Scholarship and Anthony DiGuida/ Delta Mu Research Prize. Study findings and implications for future research are summarized in the abstract (appendix B).

Conclusions

Through this training grant Dr.Bakitas developed and successfully defended a doctoral dissertation on an understudied area of breast cancer treatment, namely chemotherapy-induced peripheral neuropathy. This study examined the patient's symptom experience of CIPN and its impact on quality of life. This research will contribute to an understanding of this dose-limiting effect that can significantly interfere with cancer treatment and quality of life. Furthermore, through this mentored, research training program, the trainee has made significant progress in developing a future career in clinical breast cancer research. The candidate has applied for a post-doctoral fellowship to develop publications and extend her training towards submission of an independent research proposal related to the symptom experiences of women with breast cancer.

References See Appendix D.

Appendices

A. Revised Statement of Work

B. Dissertation Abstract

C. Selected Tables and Figures of Dissertation Study Findings

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F. Poster Presentation from the Era of Hope Meeting (June 2005)

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Appendix A

Revised Statement of Work (4/20/05 to completion 5/06)

This statement of work provides an overview of a two year project in which the candidate will spend half of her week on the Yale Campus and half on the Dartmouth Campus. **A no-cost extension has been granted revising the statement of work to cover an additional year through 5/06).**

Task 1. Develop research skills and abilities, including measurement, data analysis, and conceptual model development in breast cancer research through mentorship and doctoral education. (Months 1-18)

a. Weekly meeting with Dr. Ahles for mentored research supervision (Months 1-24)
b. Participate in 15 hrs/wk supervised Research Activities with doctoral faculty (Month 1-18)
c. Complete Year 1-Spring term (Months 1-5) and Year 2 –Fall and Spring (Months 9-17) required doctoral coursework (Yale)
d. Take Research Methods (CECS), Neurology, or Pharmacology Cognates (DMS) (Months 1-5, 9-12, 13-17)
e. Complete Preliminary Exam (at completion of 1st year of coursework) Month 6
f. Complete Qualifying Exam (at completion of 2nd year of coursework) Month 18
g. Dissertation underway (Month 21-completion)
h. Dissertation advisement (Month 21-completion)

Task 2. Collect pilot data on peripheral neurological (PN) effects in conjunction with serial neuropsychological and quality of life measures in women enrolled in a longitudinal study of cognitive effects of breast cancer treatment. (Months 1-18)

a. Precepted Clinical Neurological Examination Skills (Cohen/Fadul) (Months 1-3)
b. Precepted Neuropsychological Assessment Training (Ahles)
c. Revised: Incorporate FACT-TAXANE (neuropathy assessment) into Cognitive Studies (Months 10-26) and review preliminary data (Months 28-36)
d. Review literature on neuropathy assessment (Cohen/Fadul/Smith) (Month 12-18)
e. Evaluate CIPN measurement methods for use in dissertation proposal (Month 12-24)
f. Submit Abstracts (Month 18) on measurement methods and develop manuscript for publication (Month 18-27).
g. Develop PN Data Management Procedures (Month 5)
h. Attend weekly meetings of Psychooncology Center for Research and Breast Cancer Tumor Board to identify breast cancer patients on study (Months 6-18)
i. (Revised and incorporated this task into 2.c above) Perform neuropathy assessment on breast cancer patients enrolled in Longitudinal Cognitive Effects (Months 6-18)

Task 3. Identify gaps in knowledge, research hypotheses, and feasible methods to study and develop interventions as a basis for a doctoral dissertation and future program of research (Months 6-24 **and extension Months 25-36)**

a. Perform Review of Literature on Neurological Effects (Months 6-9)
b. Perform Secondary analysis of existing data and summarize preliminary data (months 6-9)
c. Develop draft of a model of neurological effects of breast cancer treatment (Month 10)

d. Call expert panel meeting (Month 10 & 17)
e. Incorporate expert panel comments into model (Month 11-12)
f. Generate list of problems/hypotheses and methods to study, determine feasibility of conducting studies of above, determine funding sources, develop patient educational materials on CNS/PNS effects (Months 12-18)
g. Develop dissertation defense based on above to prepare for qualifying exam (Months 12-18)
h. Perform on-going and final analysis of data from dissertation: (Months 25-36).

Dissertation defense: (proposed for Month 36).

Appendix B. Abstract

UNDERSTANDING CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY: THE PATIENT'S PERSPECTIVE ON SYMPTOMS AND THE IMPACT ON EVERYDAY LIFE-MARIE BAKITAS, DNSc, ARNP

Significance/Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common, but understudied dose-limiting toxicity of chemotherapy with few options for prevention or management. CIPN has been identified as a research priority within the 2005-09 Oncology Nursing Society Research Agenda. To date, CIPN has been assessed and reported primarily through neurophysiologic tests, toxicity grading, and self-report surveys assessing symptom severity. Empirical reports identify a wide spectrum of symptoms however data are lacking to explicate the specific symptom experience and its effect on the person's function and everyday life.

Specific Aims: The specific aims of this study were to: 1). Describe the symptom experience of CIPN from the patient's perspective; 2). Explore and describe the patient's experience of living with CIPN.

Methods/Analysis: A naturalistic paradigm guided the development of this exploratory, qualitative-dominant, descriptive, mixed methods study. Subjects completed in-depth interviews and 2 self-report questionnaires (EORTC-CIPN20 and FACT-Taxane). Verbatim transcribed interviews were coded and analyzed using Atlas.ti software. A progressive process of classifying, comparing, grouping, and refining data resulted in symptom descriptions (manifest content) and an over-arching metaphor and themes (latent content). Constant comparative analysis resulted in conceptual redundancy (saturation) after 28 interviews. Descriptive statistics were computed for CIPN self-report questionnaires.

Results: The sample consisted of 28 participants with a mean age of 59 years (±9.6), the majority of whom were female (71%), married (82%), and had a diagnosis of breast cancer (50%). Median time since diagnosis was 34 months (range 3-198 months). Content analysis yielded a rich, thick description of CIPN symptoms and effects on functional ability. The CIPN symptom experience was described by an over-arching metaphor, *Background Noise in Everyday life with Cancer*, with four major themes: a) Becoming Aware; b) Learning New Lyrics; c) Functional, Emotional, and Social/Role Cacophony; and d) Learning to Live with It: Keeping CIPN in the Background. Self-report data demonstrated more severe lower extremity symptoms than upper extremity symptoms.

Conclusions: The findings of this study demonstrate significant and previously undocumented physical limitations, emotional distress, and social role impairments that were often invisible to clinicians and were not assessed by measures commonly used in clinical trials. When CIPN was mild, well-managed, or chronic, participants coped or "learned to live with it"--placing CIPN in the background of their everyday life. Personal factors, treatment goals, and symptom intensity could influence patients' appraisal of the symptom experience and there was not always a direct relationship between the intensity of the symptom experience and the level of symptom distress.

Implications for Practice and Research: The study findings demonstrate the need to expand and improve CIPN assessment and symptom descriptions. Measures and assessments need to be broadened to include physical, emotional, and social role functional effects. Additional research is also needed to explore all of the factors that affect patients' appraisals of the symptom experience and the coping strategies that enable them to cope with chronic, invisible treatment side effects.

Appendix C. Selected Tables and Figures of Dissertation Results

Table 2. Description of the Sample N=28

Age (years)	59 ± 9.6 **[**range 46-81**]**
Time Since Cancer Diagnosis (months)	34 (median)/56 (mean) [range 3-198]
KPS (mean)	80%
Characteristic	**N (%)**
Female	20 (71)
Marital Status	
Married	24 (85)
Widowed	1 (4)
Not married*	3 (11)
Race/Ethnicity	
Non-Hispanic White	28 (100)
Employment Status	
Full Time	5 (18)
Part Time	6 (22)
Homemaker	2 (7)
Retired	9 (32)
Unemployed due to illness	4 (14)
Other	2 (7)
Education	
High school graduate	6 (21)
Trade school	2 (7)
Some college	7 (25)
College graduate	8 (29)
Graduate/Professional degree	5 (18)
Type of Cancer	
Breast	14 (50)
Hematologic malignancy	6 (21)
Ovary	3 (11)
Colon	3 (11)
Other (prostate & oral)	2 (7)
Disease Stage /Treatment Status (at the time of interview)	
Early stage/receiving adjuvant chemotherapy	3 (11)
Late stage/receiving 1st line chemotherapy	4 (14)
Recurrent or metastatic disease/ receiving 2nd or > line chemotherapy	16 (57)
No evidence of disease/ not receiving chemotherapy	5 (18)

*includes separated, divorced
**includes Graduate Equivalency Degree (GED)
KPS=Karnofsky Performance Score

Table 3

Clinician-Rated Karnofsky Performance Score (N=28)

Description	**KPS**	**# (%)**
Minor restrictions in strenuous physical activity	**90%**	**12 (42)**
Active, but tires easily	**80%**	**9 (32)**
Both greater restriction & less time spent in play activity	**70%**	**4 (14)**
Up & around, but minimal active play; keeps busy with quieter activities	**60 %**	**1 (4)**
Gets dressed, but lies around much of the day, no active play, able to participant in all quiet play & activities	**50%**	**1 (4)**
Mostly in bed; participants in quiet activities	**40%**	**1 (4)**

Note. (mean =80%)

Table 4.

Clinician-Rated Motor and Sensory CTCAE Grade of Sample (N=28)

Toxicity Grade Definition	**Toxicity Grade***	**Motor Grade** # (%)	**Sensory Grade** # (%)
Asymptomatic, except by exam	**1**	24 (86)	10 (36)
Symptomatic weakness or sensory alteration/paresthesias (including tingling) interfering w/ function but not interfering w/ ADL	**2**	2 (7)	16 (57)
Weakness/sensory alteration or paresthesias interfering w/ ADL; (bracing or assistance to walk (e.g. cane or walker indicated)	**3**	2 (7)	2 (7)
Life-threatening; disabling (e.g. paralysis)	**4**	0	0
Total		28 (100)	28 (100)

CTCAE=Common Terminology Criteria for Adverse Events (version 3.0)

Table 5

Neurotoxic Drugs Administered to Sample

Neurotoxic Drugs	**N (%)***
Multiple Agents	12 (43)
Taxanes	
Paclitaxel	12 (43)
Docetaxel	7 (25)
Switched	4 (14)
Platinums	
Cisplatin	1 (4)
Carboplatin	5 (18)
Oxaliplatin	3 (11)
Vincas	
Vincristine	2 (7)
Vinblastine	0
Vinorelbine	5 (18)
Thalidomide	2 (7)
Bortezomib	4 (14)
Other	2 (7)

*N (%) equals more that 28(100%) as participants received more than 1 drug and categories are not mutually exclusive

Table 6

The CIPN Experience: Metaphor and Themes

CIPN: Background Noise in Everyday Life with Cancer

- Theme 1: Becoming aware
- Theme 2: Learning New Lyrics
- Theme 3: Functional, Emotional, and Social (Role) Cacophony
  - Sub-theme: Physical Functional Effects
  - Sub-theme: Emotional Effects
  - Sub-theme: Social (Role) Effects
- Theme 4: Learning to Live with It: Keeping CIPN in the Background
  - Sub-theme: Facing the Music
  - Sub-theme: Adjusting the Volume
  - Sub-theme: Tuning it Out

Table 7

Remedies Participants Used to Minimize or Control CIPN

- Self-Care (non-drug remedies):
    - Got help from friends/family
    - Sought information from the Internet, written resources
    - Elevated feet
    - Found ways to do activities/job sitting down
    - Tried to feet warm with blankets or wraps
    - Walking or exercise
    - Massage, rubbing,
    - Went to physical therapy,
    - Got orthotics for shoes
    - TENS unit, acupuncture
    - Used a wheelchair, cane, or other walking aid
- Medications:
    - Gabapentin (Neurontin)
    - Glutamine
    - Opioids: morphine, methadone, oxycodone (Percocet, Oxycontin)
    - Vitamins: B, B6, B12, E
    - Steroids
- Requested change/or clinician decided to change neurotoxic chemotherapy

Table 8

EORTC CIPN20 Item & Subscale Scores*

Item	Description	Mean	Median	Standard Deviation
Q1.1.n	Tingling fingers/hands	51.9	66.7	31.1
Q1.2.n	Tingling toes/feet	40.7	33.3	33.8
Q1.3.n	Numbness fingers/hands	61.7	66.7	33
Q1.4.n	Numbness toes/feet	44.4	33.3	39.2
Q1.5.n	Shooting/burning pain fingers/hands	82.7	100	29.8
Q1.6.n	Shooting/burning pain toes/feet	66.7	66.7	34.6
Q1.7.n	Cramps hands	77.8	100	30.7
Q1.8.n	Cramps feet	71.6	66.7	28.8
Q1.9.n	Problem stand/walk due to diff feeling feet	61.7	66.7	37.8
Q1.10.n	Difficulty distinguishing hot/cold water	85.9	100	25.3
Q1.11.n	Problem holding pen/writing difficult	80.2	100	28.1
Q1.12.n	Diff w/ small objects (buttoning)	64.1	66.7	35.2
Q1.13.n	Diff open jar due to weak hands	62.8	66.7	30.3
Q1.14.n	Diff walk-feet dropped down	79.2	100	27.5
Q1.15.n	Diff climb stairs/rising chair leg weakness	64.1	66.7	29.7
Q1.16.n	Dizzy w/ changing position	75.6	66.7	27.6
Q1.17.n	Blurred vision	84.6	100	19.4
Q1.18.n	Difficulty hearing	89.3	100	24.9
Q1.19.n	If drive; diff w/ pedals	90.3	100	18.3
Q1.20.n	If male; erection**	76.2	100	37.1

EORTC CIPN20 Item & Subscale Scores*

EORTC-CIPN20 Subscales		Mean	Median	Standard Deviation	Cronbach alpha
sensory	9 items	64.4	66.7	21.7	0.83
motor	8 items	73.5	75	17.3	0.74
autonomic	2 items**	80.1	83.3	16.3	0.13
	3 items****	78.8	83.3	16.1	0.15

Note. *All scores have been transformed to a 0-100 scale and oriented such that 0=severe symptoms/poor quality of life and 100= absence of symptoms/best quality of life
**item 20 (male only item) was answered by only 7 of 8 male participants; subscale calculated *without* Q 20
***subscale calculated with Q. 20

Table 9

FACT Taxane Item Scores*

Items	Description	Mean	Median	Standard Deviation
QOL28 NTX1	Numbness/tingling/ hands	54.6	75	31.8
QOL29 NTX2	Numbness/tingling/feet	34.3	25	31.1
QOL30 NTX3	Discomfort hands	63.9	75	33.5
QOL31 NTX4	Discomfort feet	33.3	25	35.4
QOL32 NTX5	Joint pain/muscle cramps	67.6	75	31.6
QOL33 HI12	Feel weak all over	69.4	75	28
QOL34 NTX6	Trouble hearing	82.4	100	29.3
QOL35 NTX7	Ringing/buzzing in ears	85.2	100	28
QOL36 NTX8	Trouble buttoning buttons	75	75	26.9
QOL37 NTX9	Trouble feeling small objects	77.8	100	30.5
QOL38 An6	Trouble walking	63.9	75	34.2
QOL39 Tax1	Feel bloated	84.3	100	27
QOL40 Tax2	Hands are swollen	88.5	100	22.6
QOL41 Tax3	Legs/feet are swollen	80.6	100	28
QOL42 Tax4	Pain in fingertips	87.5	100	22.6
QOL43 Tax5	Bothered how hands/nails look	86.1	100	22.3

Note. All scores have been transformed to a 0-100 scale and oriented such that 0=severe symptoms/poor quality of life and 100= absence of symptoms/best quality of life.

Table 10
FACT-Taxane Sub scale and Composite scores*

Subscale/Composite Scale Abbreviation	Subscale/Composite Scale Description	Mean	Median	Standard Deviation	Cronbach Alpha
PWB	Physical Well-Being	69.8	67.9	18.7	0.82
SFWB	Social/Family Well-Being	86.5	91.7	14.4	0.62
EWB	Emotional Well-Being	74.9	83.3	18.7	0.87
FWB	Functional Well-Being	70.2	78.6	22.5	0.88
TWB	Total Well-Being	75.8	75	15	0.91
TAXANE	Taxane Subscale	70.8	68.3	13.5	0.78
TAXANE TOI	Taxane Trial Outcome Index	70.4	70	14.3	0.89
NTX	NTX Subscale	64.3	61.4	16.7	0.75
NTX TOI	NTX Trial Outcome Index	67.5	68	15.8	0.89
TAX.TOTAL	FACT-Taxane Total Score	74	72.2	12.8	0.91

Note. **TWB**=PWB+SFWB+EWB+FWB
Taxane Subscale = NTX 1, 2, 3, 4, 5, 6, 7, 8, 9, HI 12, An6, Tax 1-5
TAXANE TOI=PWB+FWB+TAXANE
NTX Subscale =NTX 1, 2, 3, 4, 5, 6, 7, 8, 9, HI 12, An6
NTX TOI=PWB+FWB+NTX
FACT TAXANE Total Score=PWB+SFWB+EWB+FWB+TAXANE
*All scores have been transformed to a 0-100 scale and oriented such that 0=severe symptoms/poor quality of life and 100= absence of symptoms/best quality of life.

Figure 1 Codes Grouped by Preliminary Categories

Interference w/ activity&/orQOL <is> Root

Interference w/ activity&/orQOL <is> Root
Driving Problems <is part of> interference w/ activity&/orQOL
Fatigue Issue: ? relationship w/ CIPN <is cause of> interference w/ activity&/orQOL
Role Effects <describes a type of> interference w/ activity&/orQOL
Sleep disturbance <is cause of> interference w/ activity&/orQOL
Walking Problems <describes a type of> interference w/ activity&/orQOL
"I CAN'T tell where my feet are" <is> Root
Footwear Issues <is> Root
Emotional Rx:: Mood effects <is> Root

Sx Description <is> Root

Cramping; muscle cramps <is> Root
?coasting <describes a type of> Sx Description
cold intolerance <describes a type of> Sx Description
Facial symptoms <describes a type of> Sx Description
Location::LE <is associated with> Sx Description
Location::UE <is associated with> Sx Description
nail effects <describes a type of> Sx Description
PPE::Doxil Effects <is> Root
Sx Desc: Balance Issues <is part of> Sx Description
Sx Desc:: Burning <is part of> Sx Description
Sx Desc:: Hard to Describe <is part of> Sx Description
Sx Desc:: Improving <is part of> Sx Description
Sx Desc:: Numbness & Negative Sx <is part of> Sx Description
Sx Desc:: Pattern <is part of> Sx Description
Sx Desc::Graphic <is part of> Sx Description
Sx Desc::Painful <is part of> Sx Description
Sx Desc::Progression <is part of> Sx Description
Sx Description-other; paresthesias <is part of> Sx Description
Unusual symptoms <describes a type of> Sx Description
weakness:: motor <describes a type of> Sx Description
Concurrent Sx <is> Root
What is this? NOT CIPN <is> Root
Sx: NOT CIPN-related <is> Root
The Story of Recognizing Neuropathy <is> Root
CIPN was a surprize <is> Root
CIPN:: Prolonged Course <is> Root

Treatments Recommended or Used for CIPN <is> Root

Find something to help/Tx CIPN <is associated with> Treatments Recommended or Used for CIPN
Tx:: Gabapentin/Neurontin <is part of> Treatments Recommended or Used for CIPN
Tx:: Heat or warmth <is part of> Treatments Recommended or Used for CIPN
Tx:: Massage <is part of> Treatments Recommended or Used for CIPN
TX:: NSAID <is part of> Treatments Recommended or Used for CIPN
Tx:: Opioids <is part of> Treatments Recommended or Used for CIPN
TX:: vitamins <is part of> Treatments Recommended or Used for CIPN
Tx::Exercise <is part of> Treatments Recommended or Used for CIPN
Tx::For CIPN NOS <is part of> Treatments Recommended or Used for CIPN
Tx::glutamine <is part of> Treatments Recommended or Used for CIPN
Tx::Self-Care::Home Remedy <describes a type of> Treatments Recommended or Used for CIPN
Using the Internet to Find Tx <is associated with> Treatments Recommended or Used for CIPN
Find something to help/Tx CIPN <is> Root

Figure 1 (con't)

Learn to live w/ it: CIPN <is> Root

Other people are worse off than me <is> Root
Positive Self Talk-I can overcome this! <is> Root
CIPN as only effect <is> Root
CIPN is a REMINDER of Cancer <is> Root
CIPN is invisible <is> Root

Clinician-Related Codes <is> Root

Clinician asks about/assesses <is associated with> Clinician-Related Codes
Referral to Specialist <is associated with> Clinician-Related Codes
Tx Decision <is associated with> Clinician-Related Codes

Assessing Interview Guide <is> Root

Interview Guide::Autonomic <is> Root

Figure 5 Participants Description of CIPN Sensory Symptoms

Symptom	Participant Language
Numbness	"can't tell if it hurts"; "no longer ticklish", "absence of feeling", "couldn't feel the temperature of water", "like I have no circulation"; "numb, like if you lay on your hand and it falls asleep, only it stays there and it doesn't get better"; "I know there's a foot and a leg out there—but it's just a complete absence of feeling down my leg."
Tingling	"like a vibration", "a rattle-y feeling"; "it's tingling-burning type of feeling and more painful the more I stand"; "It's like pins and needles, if you've had you feet fall asleep it's like that feeling; only it has a burning feeling with it so it's a little more intense than that type of feeling".
Prickly	"It feels prickly I notice it more when I'm in bed. During the course of the day I don't think about very much. It's not painful just different. I didn't have it before"; "like pins and needles"; "the tiniest piece of sand feels like I was stepping on a needle or a thorn"; "It feels like you're walking on pins or broken glass or something. It really hurts"
Dullness	"It feels like I'm walking on a bed of rocks all the time; it's a gravel-y feeling";
Painful	"hurting", "almost like hurting, but not really", "a constant ache", "it's a "6", "7", "8"; "sometimes a 10"; "never less than a 4", "I couldn't get to sleep because it was so painful. And then if got to sleep finally, I would wake up and it would be very painful"; "the neuropathy centered in my feet and I felt stabbing pain, burning pain, and to a lesser degree cramping pain in my feet and up my ankle"; "I had pain-- all I can describe it is a needle being stuck in any toe at any given time, but it didn't last that long"; "It's a C fiber not an A fiber type of pain. It's a small nerve that gives you that yukky pain rather than a sharp pain"; "It was extremely painful. If on a scale of 1-10 and I consider 10 labor pain, I say a 10".
Burning	"burning and stabbing and to a lesser degree cramping", "the most intense sensation was burning, intense burning in my feet". "It was like a thermometer rising, when the mercury goes up I could feel it. And I was like Oh NO!!"; "flashing and the burning and the numbness and for 3 days it is a nightmare"; "my feet felt like they were on fire-even when it was cold outside; I couldn't wear shoes"
Thermal Sensitivity (cold and heat)	"couldn't touch (hands/feet) anything cold; "couldn't warm up (toes/feet)"; "when it's real cold and it bothers me; It brings up the sensitivity more, the same thing with the heat"; "the toes will tingle if I walk across the kitchen floor barefooted and the floor's cold"; "cold weather makes weakness and numbness worse"
Stabbing, shooting, electrical, lancinating	"like electricity shooting up", "like a knife in my foot" "it would start in the middle of the foot and go POW!! A big tingle, in the middle of your foot and then it would go-POW!!-spread out and it would only last for a second--- it would be like a lightening bolt hit it"; "I couldn't stand to walk on that cold floor--it would be like Zing! the electricity would come shooting up" "(my nerves/synapses) were just

	popping, You know with a car engine-you've got so many valves (Makes a popping noise) That is exactly what was going on"; "envision a lightening bolt coming down from the top of your leg and landing at the bottom of your feet. The intensity of the pain is enough to make you sit and sweat! it's like "WOW!!"
Throbbing	"a strong pulsating only in my feet and it was to the point where I felt it was uncomfortable to wear shoes"
Hypersensitive	"I couldn't stand even a light sheet on my feet", "I could feel the stitches on my socks"; "the tips of my toes were kind of tingly and then the whole toe was tingly, and now it's gone to the arch of the foot. It ISN'T numb…it gives the impression that it's numb but actually, it's hypersensitive"; "I can feel everything; any little speck of anything on the floor it would get on my foot and feel like a needle going thru my foot"; "If somebody touches it quick I'll jump. It feels like very painful, but it isn't really a painful feeling"; "between my toes, my toes get swollen--it feels like there is a sock or stocking that was pulling up between my toes"
Itchy	"it feels like tingling itching feeling going up to my legs into my ankle area."; "It was distracting, painful itchy and felt like I was being tortured in the most awful way"; "I have the feeling that I need to rub 'em…I get the anti-itch cream…it felt like I needed to do something. It wasn't really an itch, but I thought maybe the anti-itch cream would help. I'm not sure it did".
Feeling thick or pressure	"feels tight, like there was "fluid or swelling" in hands or feet even when it was not visible", "like there was "padding" or "leather" on the bottom of feet"; "There was a lot of pressure. I guess there was some swelling but it felt like there was more swelling than there was"
Feeling unsteady	"throws balance off", "felt like I was weaving even when standing still" "wobbly" , "had to use a cane or walker", or "had to hold onto the wall or railing", "unsteady on feet", "insecure on feet", "walk different", "falling a lot", "like walking on pegs"
Muscle cramps	"It makes your muscles tighten up, My legs constantly ache. Especially in the evening, I get a cramping in my leg and that will wake me up; like 'Charlie horses in my calves'"
Feeling of vibration or twitching	"it was rattley feeling, a vibration all the way to my tip of toes, my whole leg and all the way to my thigh-- I just felt it I didn't notice anything, it felt like it was not on the surface, it was deeper"; "It was like holding on to one of those vibrators. And it would shoot through the body and that was about it. Nothing that would stop your daily functions".

Figure 6. Functional Effects of CIPN by Location

Location	Functional Problems
fingers/hands/arms	• DRESSING: Buttoning buttons (needed help from spouse to dress or just didn't wear clothes with buttons any longer), zipping zipper,fastening bra; "couldn't put on earrings" • COOKING: opening jars, " "I have to wear gloves to get things out of the refrigerator" "I can't crack eggs". • SEWING: threading a needle, unable to knit for very long or at all, • HOUSEHOLD: working with tools (for home or car repairs), holding the phone for a long time, picking up pills, coins, or small objects • WORK: typing, working with tools (for home or car repairs), holding the phone for a long time, holding a pen and "scrawling" handwriting, "loss of fine motor skills", "loss of strength", "dropping things • LEISURE: turning book pages, picking up a ball, , "couldn't use remote/controller for video game", "loss of fine motor skills", "loss of strength", "dropping things"
toes/feet/legs	• DRESSING: FOOTWEAR ISSUES: Preferred to go barefoot so they could feel the ground or because any type of shoes were confining, painful and made their feet feel numb or "tight"; could not tolerate going without sox and shoes; could not wear their usual shoes and switched to wearing loose shoes, sandals, slippers; more secure in shoes with a heel or wedge; (oxaliplatin) could not go barefoot due to cold hypersensitivity • MOBILITY: pain, burning, numbness, "legs were weak"; problems with balance or concerns about falling; problems with walking, hiking, running, biking, and standing for prolonged periods; "I trip", "feel clumsy", "walk like I'm drunk", "walk like a little old lady/man", "I have to concentrate to walk straight", "have trouble with stairs", "I trip on the rug", "I'm clumsy", "I shuffle when I walk • DRIVING: trouble feeling the gas, brake, clutch pedals of their car; switched to driving an automatic rather than standard shift car; lack of feeling in feet made them feel unsafe • WORK: "it complicates my everyday activities", "I do less-work half days", "changed my responsibilities at work so I don't have to stand","I had to allow myself a longer time to do anything"; (see also MOBILITY, DRIVING) • LEISURE: can't do yardwork/gardening, leisure activities and hobbies; (see also effects on MOBILITY & DRIVING)

Figure 7 Sample by FACT NTX Score

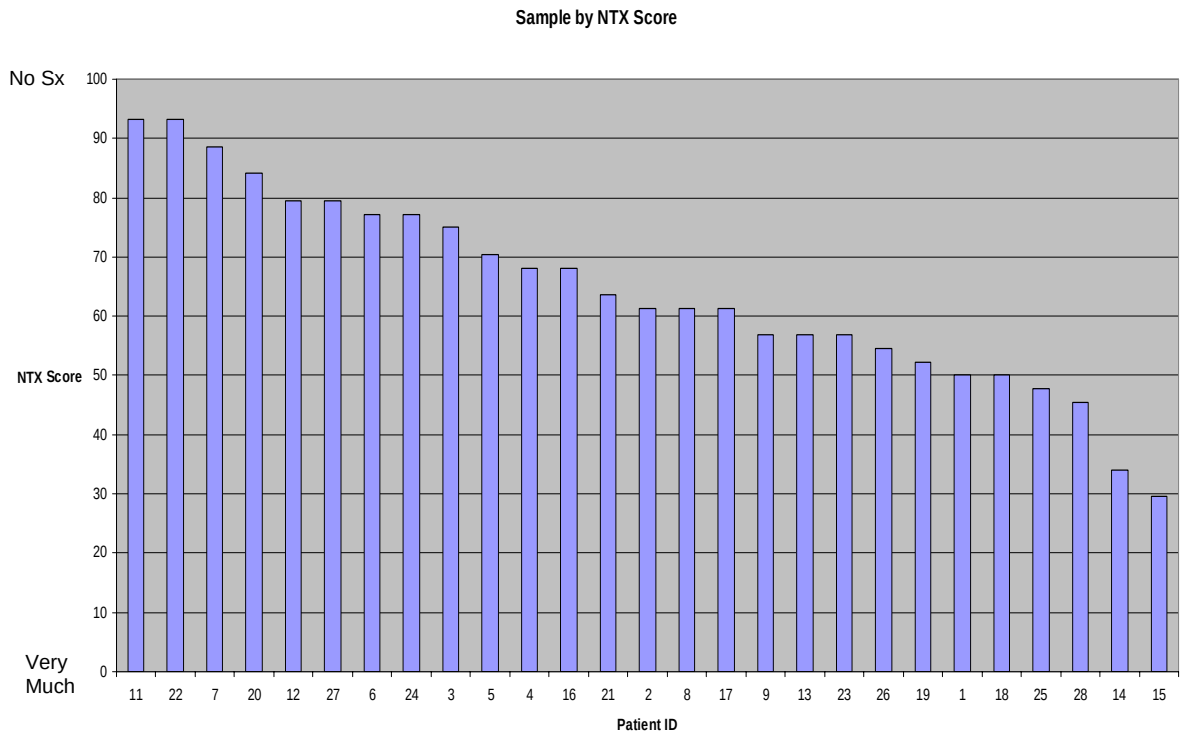
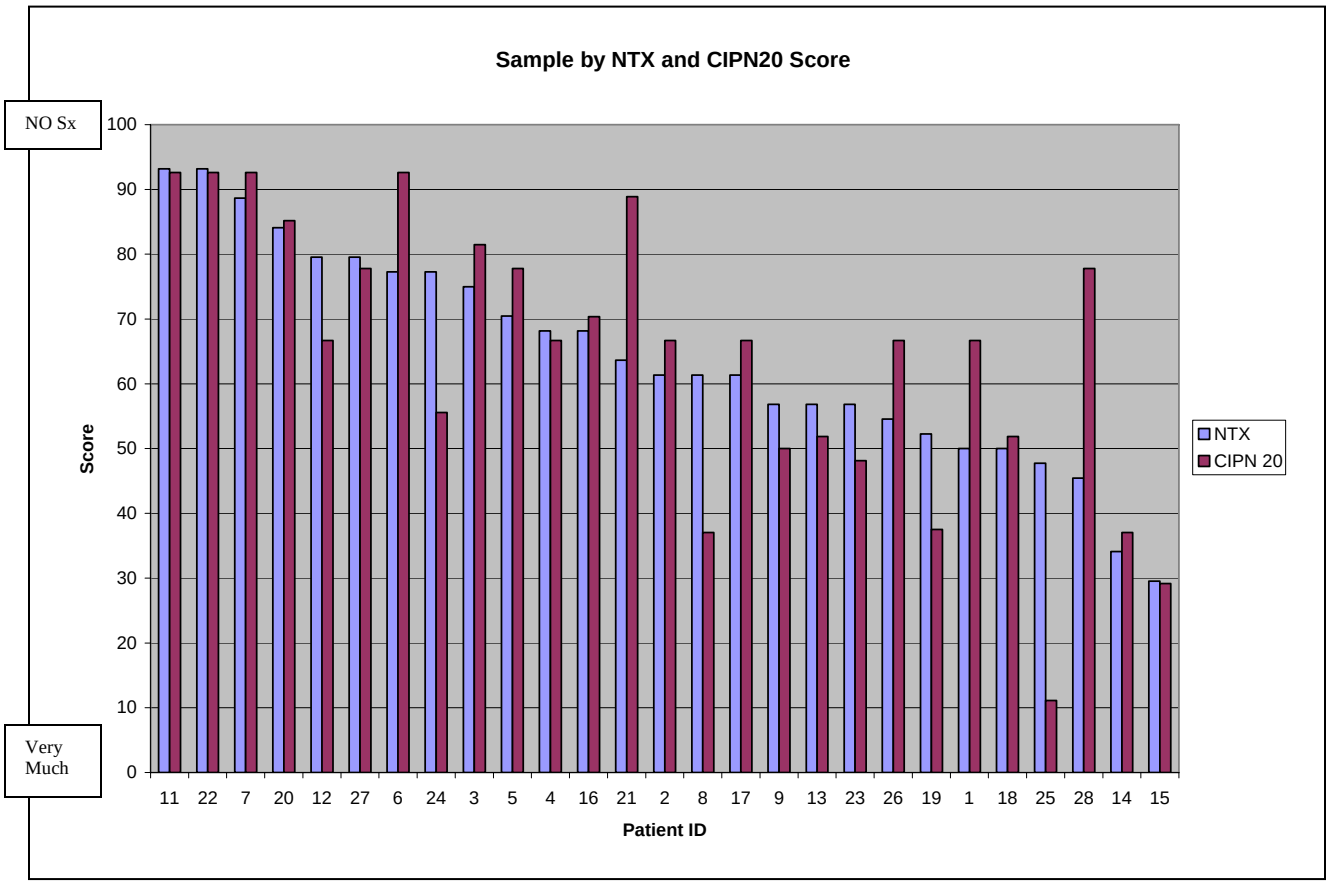


Figure 8 Sample by both FACT NTX and EORTC CIPN 20 Scores



Appendix D
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Résumé

L'autodétermination : analyse du concept et implications sur la recherche dans le domaine des soins palliatifs

Marie A. Bakitas

Cet article analyse l'évolution, la définition, l'emploi courant et l'application du concept d'autodétermination dans le cadre de la recherche et de la pratique en soins palliatifs. L'analyse présentée vise à servir de base au développement du programme de recherche sur les soins palliatifs. L'auteure examine une littérature choisie portant sur les soins de santé aux adultes atteints d'une maladie chronique ou mortelle, notamment sur l'aspect historique, bioéthique, clinique, médical et infirmier. À partir d'une synthèse de la documentation, celle-ci propose une définition conceptuelle tout en identifiant des moyens d'intégrer le concept d'autodétermination dans la recherche portant sur les interventions palliatives.

Mots clés : autodétermination, soins palliatifs

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Self-Determination: Analysis of the Concept and Implications for Research in Palliative Care

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This paper analyzes the evolution and the definition, current use, and application of the concept of self-determination in palliative care research and practice. Undertaken as a foundation for the development of a palliative care research program, the analysis considers selected historical, bioethical, legal, clinical, and relevant medical and nursing health-care literature on adults with chronic and terminal illness. Based on a synthesis of the literature, a conceptual definition is proposed and ways of integrating the concept of self-determination into palliative care intervention research are identified.

Keywords: self-determination, autonomy, concept analysis, integrative review, palliative care, Rodgers method

Introduction

The goal of palliative care is to improve the quality of living and dying of patients with life-limiting illness (World Health Organization, 1990). A tenet of palliative care philosophy is the determining, acknowledging, respecting, and honouring of patients' values and wishes as they approach the close of life (von Gunten, Ferris, Portenoy, & Glajchen, 2001). The concept of self-determination is embodied in this philosophy. Experts in palliative care see the enhancement or support of self-determination as one way of improving the quality of a patient's final days (American Geriatrics Society Ethics Committee, 1998; American Nurses Association [ANA], 2001; Ferris et al., 2002; National Hospice Organization, 1997). How can key aspects of self-determination best be integrated into palliative care practice and research? A concept with such a high degree of abstractness is not easily translated into everyday clinical practice. The task is further complicated if one attempts to identify, describe, measure, or design interventions that exemplify an amorphous concept to improve the care of persons with serious illness. A first step is to return to the literature in order to examine the evolution and current use of the concept (Rodgers, 2000). Self-determination has evolved from its societal origins as the right of a people to be free, independent, and protected

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from oppression, to its application in health care through laws and bioethical principles. In 1991 the *Patient Self-Determination Act (PSDA)*, a milestone in the evolution of palliative care in the United States, decreed that health professionals have an obligation to recognize patient choice in health-care decision-making (*Omnibus Budget Reconciliation Act [OBRA] of 1990*, 1990). Since then, many attempts have been made to formally integrate principles of self-determination into palliative care practices, quality improvement activities, and research.

This paper analyzes the evolution and the definition, current use, and application of the concept of self-determination in palliative care research and practice. Undertaken as a foundation for the development of a palliative care research program, the analysis considers selected historical, bioethical, legal, clinical, and relevant medical and nursing health-care literature on adults with chronic and terminal illness. Based on a synthesis of the literature, a conceptual definition is proposed and suggestions for integrating the concept of self-determination into palliative care intervention research are identified.

Sample and Setting

A literature search was conducted to examaine the concept of self-determination in palliative care using Rodgers's (2000) evolutionary method. The purpose of the search was to identify literature on the origin, definitions, attributes, antecedents, consequences, and exemplars of the concept. Computer searches for the years 1985 through 2003 using MEDLINE, the Cumulative Index to Nursing and Allied Health (CINAHL), and PsycINFO were conducted using the search terms self-determination, *Patient Self-Determination Act*, autonomy, advance care planning, and advance directives, which were then joined with the terms palliative care and terminal care. The original 516 cited titles and abstracts were then reviewed for relevance using the following criteria: historical background, focus on a cancer or palliative adult population, and use of the concept prior to and following the passage of the *PSDA*. Articles and reference lists were then reviewed for relevance. Pertinent articles from the reference lists were also examined.

One study (SUPPORT Principal Investigators, 1995) generated more than a hundred articles (some identified through the initial search and the remainder in reference lists). Only two of the most representative and relevant articles reporting study results (Covinsky et al., 2000; SUPPORT Principal Investigators, 1995) and three analyzing the meaning of the findings (Lynn et al., 2000; SUPPORT Principal Investigators, 1997; Teno, 1998) were included in the analysis.

A preponderance of the literature cited the *PSDA,* a US law; however, several international studies exploring the related concept of "family determination" were identified. This literature was retained and analyzed to assist in concept clarification.

Also reviewed were two Institute of Medicine reports on improving end-of-life care and palliative care in cancer (Field & Cassel, 1997; Foley & Gelband, 2001), literature on background ethics (e.g., *Code of Ethics for Nurses*) (ANA, 2001), historical and legal materials (including electronic sources), the National Hospice Organization's (1997) *A Pathway for Patients and Families Facing Terminal Illness,* a chapter from a major palliative care text, and a study of the "concept analysis" of self-determination in a population of long-term psychiatric patients (Valimaki & Leino-Kilpi, 1998). A total of 65 references met the criteria for inclusion.

Concept Analysis Results

The results of the literature analysis are organized as follows: historical context, definitions and attributes, antecedents, consequences, and exemplars.

Historical Context

Self-determination has origins in societal, ethical, legal, and, more recently, health-care, contexts. Regardless of context, a pattern of protecting and promoting self-determined choice is seen most vividly in response to oppression of an individual or group. Historically, a period of oppression often resulted in the adoption of rules or laws protecting the rights of the oppressed group. An early example of self-determination in a societal context is the 1620 voyage of Separatist Puritans to North America aboard the *Mayflower* seeking freedom from religious oppression (Pilgrim.net, 2002). This concept essentially gave birth to the United States and is pervasive in common law, in the *Declaration of Independence* and the *US Constitution* (THOMAS Web-based historical documents, 2002).

The concept of self-determination in health care grew out of the need for individual (patients') rights. Before the advent of medical discoveries related to the prevention or treatment of fatal diseases and conditions, patients with illnesses such as cancer experienced deterioration and death. The role of doctors and nurses was to provide comfort in the progression towards "natural death." As more and more means of fighting disease or prolonging life became available (e.g., antibiotics, vaccines, chemotherapy, cardiopulmonary resuscitation), patients could no longer passively await death with a caring doctor or nurse standing by to offer comfort (Robinson & Mylott, 2001). Physicians employed the new tools

to postpone or prevent death. Death was the enemy, to be defeated at all costs.

Thus evolved the practice of medical care in which every possible therapy was used simply because it existed. This phase of health care was marked by a paternalistic approach whereby the physician determined which therapies would be applied (Gadow, 1989) based on anecdote, experience, and availability — there being a dearth of scientific evidence. Rarely were patients' treatment preferences considered (Gadow). Nurses and patients played a passive role. Nurses followed doctors' orders and provided care that was consistent with a "death-defeating" approach, while patients accepted the care and treatments provided without question. Patient self-determination or choice was in the background, if present at all.

A legal precedent in self-determination was set by a 1914 ruling by New York Supreme Court Justice Cordoza: "Every human being of adult years and sound mind has a right to determine what shall be done with his own body and cannot be subjected to medical treatment without his consent" (*Schloendorff v. Society of New York Hospital,* 1914). Throughout the 1960s and 1970s more obvious applications of the concept of self-determination emerged in biomedical ethics (Beauchamp & Childress, 2001) and health-care legislation (Bradley & Rizzo, 1999; Meisel, 1998), in response to violations against vulnerable populations such as prisoners and the seriously ill. In research, self-determination was clearly transgressed in the use of unwilling, uninformed subjects (e.g., Nazi prisoner experimentation and the Tuskegee syphilis study) (Bradley & Rizzo; Department of Health, Education and Welfare, 1979). In the early years, scientific inquiry with human subjects placed a higher value on the knowledge to be gained than on the lives of subjects, resulting in many human rights violations (Katz, 1992).

In response to these events, efforts to protect basic human rights and autonomy and self-determination in health research were widely supported (Bradley & Rizzo, 1999). The 1979 Belmont Report set out ethical principles and guidelines for the protection of human research subjects (Department of Health, Education and Welfare, 1979). It defined autonomous decision-making (informed consent) and outlined protections for persons at risk for diminished autonomy (e.g., subjects of biomedical research) based on ethical principles such as the bioethical principle of respect for autonomy embodied in the value of self-determination and its related clinical ethical practices of truth-telling, information disclosure, and informed consent (Fan, 1997). Protection for health-care consumers came somewhat later.

In clinical practice, paternalism and indiscriminate use of life-saving technologies in health care was viewed by some as oppression (Gadow,

1989; Robinson & Mylott, 2001; Salem, 1999). As a result, basic human rights in medical care began to dominate public and health-care discourse. Concerns about the inappropriate use of life-sustaining treatments and the absence of patient self-determination in medical decision-making culminated in the US Supreme Court case *Cruzan v. Director, Missouri Department of Health and Human Services* (cited in Bradley & Rizzo, 1999). The decision in this case of a 25-year-old woman left in a permanent vegetative state after a car accident affirmed the importance of formally documenting one's treatment wishes in advance of a medical crisis. In 1989, months after the Cruzan decision, a bill was proposed (and ultimately passed under the federal Medicare/Medicaid-related *OBRA of 1990*) according responsibilities to institutional health-care providers with respect to advance directives (*OBRA of 1990,* 1990). These provisions grew out of an earlier (1989) version of the *PSDA*.

The central patient right addressed by this legislation was that of autonomy. The Act accorded patients the right to access information pertaining to decision-making about their care, to accept or refuse treatment, and to issue advance directives. As interpreted by Meisel (1998), "the *PSDA* does not apply solely to information about advance directives but rather applies to a patient's medical decision-making rights in general" (p. 52). Medical decision-making was later defined as inclusive of "consent to treatment, informed consent, and end-of-life decision-making" (p. 52). Appendix 1 summarizes key aspects of the *PSDA*.

In nursing, self-determination is grounded in the *Ethical Code for Nurses* of the American Nurses Association (ANA). In Canada both the *Code of Ethics for Registered Nurses* and the *Joint Statement on Advance Directives* uphold the "client's right to self-determination" (Canadian Nurses Association, 1994, 2002). In the United States the ANA originally generated its code in 1950 and revised it in 1960, 1968, 1976, 1985, and 2001 (Daly, 2002). The 1985 version was heavily influenced by aspects of self-determination and concepts directly applicable to end-of-life nursing care (Scanlon, 1996). Specifically, it encouraged nurses to assess patients' ability to make decisions about end-of-life care; defend patients' care wishes and promote their freedom to make end-of-life decisions; prevent and/or relieve suffering associated with dying; evaluate the benefits and drawbacks of treatment to the patient; and support decisions on the withdrawal or withholding of treatments (including cardiopulmonary resuscitation, artificial nutrition, and hydration) (Scanlon). These interpretations and ANA position statements in the 1990s were an attempt to protect the vulnerable population of dying patients with regard to issues that could greatly affect the quality of their living/dying (e.g., assisted suicide, withholding of food and fluids, provision of adequate pain relief).

An additional historical trend in self-determination comes from social sciences research. Deci and Ryan (1985) propose a theory of intrinsic motivation and self-determination to explain human behaviour. According to this theory, human beings can be proactive and engaged or passive and alienated largely as a function of the social conditions under which they develop and survive. Autonomy, in addition to competence and relatedness, is postulated as an innate psychological need: when satisfied, it yields self-motivation and mental health; when unsatisfied, motivation and well-being are decreased. This theory has been applied to research in education, work, sport, religion, psychotherapy, and health care. In health care, self-determination theory has been applied to alcohol treatment, weight loss in morbidly obese patients, smoking cessation, glucose control, and medication adherence (Ryan & Deci, 2000; Williams, Rodin, Ryan, Grolnick, & Deci, 1998). No studies of self-determination theory in palliative or end-of-life care were found.

Definition and Attributes of Self-Determination

Self-determination is defined as "free choice of one's own acts or states without external compulsion; determination by the people of a territorial unit of their own form of government, future political status, without coercion or outside influence" (Merriam-Webster OnLine, 2003). It generally refers to the rights of both a people and an individual and is broadly thought to include the principles of liberty, privacy, individual choice, free will, and being one's own person (Beauchamp & Childress, 2001). Synonyms and related terms include autonomy, independence, choice, decision-making, empowerment, and freedom. The terms autonomy and self-determination are often used as surrogates (ANA, 2001). Autonomy comes from the Greek *autos,* or self, and *nomos*, rule or governance, whereas self-determination is the process of exercising one's right to autonomy.

As concepts become more abstract, "their reality basis and their empiric indicators become less concrete and less directly measurable" (Chinn & Kramer, 1999, p. 55). Self-determination is relatively abstract as a concept, its definition broad and context-dependent. In Western bioethical principles, it is a "subjective conception of the good and promotes the value of individual independence" (Fan, 1997, p. 309). As a right of persons and patients, it is defined as a process related to expression of the ethical principle of respect for autonomy (Beauchamp & Childress, 2001). It is also defined as the opposite of paternalism (Gadow, 1989; Sutherland, Llewellyn-Thomas, Lockwood, Tritchler, & Till, 1989). In law, self-determination has a very specific definition. The *OBRA* regulations state that patients are entitled to be aware of and use advance directives when they enter a facility that accepts Medicare funding

(Meisel, 1998; *OBRA of 1990,* 1990). Additional aspects of the law are summarized in Appendix 1.

Nordgren and Fridlund (2001) interviewed 17 Swedish hospitalized medical and surgical patients in order to define self-determination from the patient's perspective. Responses to the question "How do you perceive that your right of self-determination finds expression in the context of care?" produced the themes of trust in the health-care team, acceptance of the care that is provided, and feelings of powerlessness. The patients did not feel empowered to participate in decision-making and lacked the information on treatment strategies necessary to do so. Hence, instead of supporting the attribute of self-determination, they identified characteristics of its absence.

Proponents of assisted suicide use the term "ultimate self-determination," defined as the patient's right to choose the time and place of death (Baginski, 1992; Folker et al., 1996; Swarte & Heintz, 1999). While assisted suicide is prohibited by law in most US states, some also question its ethical soundness and its consistency with the principles of self-determination, as it conflicts with the fundamental ethical principles of professional autonomy and non-maleficence (Burt, 2002; Low & Pang, 1999; Muller-Busch, 2001; Salem, 1999). Salem argues that instead of supporting autonomy, assisted suicide (which requires physician sanction and prescription of a lethal combination of medications) is actually an impediment to self-determination, its parameters returning "ultimate authority over this 'private and deeply personal' decision to medicine and society" (p. 30).

Four characteristics of self-determination were identified in the literature: personal (self-) appraisal, decision-making process, activities, and goals or outcomes (see Table 1). *Personal appraisal* requires the mental capacity, functional "strength," freedom, power, and information to evaluate one's values and preferences related to health-care decision-making. Koenig (1997) describes seven attributes of individual self-determination in Western culture (see Table 2). These can be summarized as the need for information, desire for control, freedom, openness, personal health beliefs about the future, religion, and family. They are quite specific and suggest that patients possess a relatively high level of sophistication, particularly with regard to Western cultural beliefs. Koenig challenges the notion that these attributes apply to patients of different cultural backgrounds and different value structures related to individual autonomy. Similarly, Fan (1997) proposes that an East Asian definition of autonomy requires family-determination, "an objective conception of good [that] upholds the value of harmonious dependence" (p. 309). Valimaki and Leino-Kilpi (1998) conducted a "concept analysis" of self-determination based on content analysis of qualitative interviews with 72 long-term

Table 1 *Attributes of Self-Determination in Various Sources*

Attribute	Ethical	Legal	Health Care
Personal appraisal • possessing physical and emotional strength • possessing power • possessing knowledge • possessing mental capacity • not controlled by others	ANA (1991); Department of Health, Education and Welfare (1979); Gadow (1989); Scanlon (1996); Sutherland et al. (1989)	Bradley & Rizzo (1999); Low & Pang (1999); Meisel (1998); Salem (1999)	Koenig (1997); Nordgren & Fridlund (2001); Valimaki & Leino-Kilpi (1998)
Decision-making process • advance care planning for when capacity is diminished • refuse or accept care or treatment • rights of others not violated • continuity of providers	ANA (2001); Baginski (1992); Beauchamp & Childress (2001); Bradley & Rizzo (1999); Department of Health, Education and Welfare (1979); Fan (1997); Gadow (1989); Hern et al. (1998); Katz (1992); Koch et al. (1999); Koenig (1997); Quill (2002); Ruhnke et al. (2000); Scanlon (1996); Swarte & Heintz (1999)	Bradley & Rizzo (1999); Cerminara (1998); Engel et al. (1997); Haynor (1996); Meisel (1998); *OBRA of 1990* (1990); Ott (1999); Salem (1999)	Nordgren & Fridlund (2001); Valimaki & Leino-Kilpi (1998)

Activities • completing values history • provider- or patient-initiated discussions; family conferences • making a living will or appointing a proxy (durable power of attorney for health care) • completing "do not resuscitate" order • choosing "comfort measures" • completing unfinished business (relationships, finances, funeral)	American Geriatrics Society Ethics Committee (1998); ANA (2001); Candib (2002); Cantor (1998); Cerminara (1998); Engel et al. (1997); Havens (2000); Haynor (1996); Johnston et al. (1995); Miller (1991); Murphy et al. (2000); Ott (1999); Ruhnke et al. (2000); Scanlon (1996)	Bradley & Rizzo (1999); Cerminara (1998); Engel et al. (1997); Haynor (1996); Meisel (1998); *OBRA of 1990* (1990); Ott (1999); Salem (1999)	Havens (2000); Haynor (1996); Robinson & Mylott (2001); SUPPORT Principal Investigators (1997)
Goal/outcome • self-determined life closure • peaceful death	ANA (2001)		National Hospice Organization (1997)

Table 2 *Attributes of a Self-Determined Patient: The Western Perspective*
• a clear understanding of the illness, prognosis, and treatment options, which is shared with the members of the health-care team • a temporal orientation to the future and a desire to maintain control into that future • the perception of freedom of choice • a willingness to openly discuss the prospect of death and dying • a balance between fatalism and belief in human agency that favours the latter • a religious orientation that minimizes the likelihood of divine intervention (or other "miracles") • an assumption that the individual, rather than the family or any other social group, is the appropriate decision-maker
Source: Koenig (1997).

psychiatric patients; the patients' personal appraisal focused on the importance of freedom of choice, access to power, and having the active support of others in pursuing their goals.

The characteristic of *decision-making process* is central in the *PDSA*. It is clearly specified as well in the ANA's (2001) *Ethical Code for Nurses*, which also speaks to the role of nurses in enhancing the patient's right to self-determination in terms of accepting, declining, or terminating treatment without "deceit, undue influence, duress, coercion, or penalty" (Provision 1, Section 1.4, "The right to self-determination"). Nurses are obliged to provide support throughout the decision-making process. The *Ethical Code for Nurses* speaks specifically to the patient's right to elicit the support and advice of family members, partners, and nurses and other health professionals (Valimaki and Leino-Kilpi, 1998). More recent sources identify the role of the patient-appointed proxy in decision-making when the patient no longer possesses the ability to make decisions (Sullivan, 2002). The proxy, whether informal (family) or formal (health professional), must possess sufficient knowledge of the patient's values and preferences to determine what care the patient would choose or refuse (Meisel, 1998). The standard is one of "substituted judgement" (recreating the patient's choice), in contrast to "best interest" (doing what the proxy's believes to be in the patient's best interest) (Sullivan).

The third attribute, *activities*, refers to the many manifestations of self-determination, most notably the issuing of advance directives (Cantor, 1998; Cerminara, 1998; Engel et al., 1997; Havens, 2000; Ott, 1999;

SUPPORT Principal Investigators, 1997) but also issuing "do not resuscitate" orders, requesting "comfort care," and attending to unfinished business (National Hospice Organization, 1997; Robinson & Mylott, 2001). Fear of over-treatment and desire for control are characteristic of persons who engage in these activities (Eisemann & Richter, 1999), an important legal aspect of which is the fact that self-determination supersedes the patient's ability to state treatment preferences and allows for the appointment of a proxy (durable power of attorney for health care).

Lastly, *goals or outcomes* refers to the wishes that a patient hopes to fulfil as a result of self-determination, primarily with regard to dying on his or her own terms (Fan, 1997; Nordgren & Fridlund, 2001; Silveira, DiPiero, Gerrity, & Feudtner, 2000; Tulsky, Fischer, Rose, & Arnold, 1998). The goal of hospice care, as identified by an expert panel of the National Hospice Organization, is "self-determined life closure": "Anticipating death, mentally competent patients will have full autonomy to make decisions about how the remainder of their life is spent within the allowances of law" (National Hospice Organization, 1997, p. 5).

In summary, self-determination is defined in the palliative care literature as an ethical principle, a right, a law, a care process, and an outcome of expert palliative care (ANA, 2001; Beauchamp & Childress, 2001; Koenig, 1997; Meisel, 1998; National Hospice Organization, 1997; *OBRA of 1990,* 1990). Its attributes include personal appraisal of individual rights, power, freedom of choice, decision-making process, activities, and outcomes. Following passage of the *PDSA*, activities of self-determination became more formalized through the use of a living will and/or the appointment of a health-care proxy (Bradley & Rizzo, 1999; Eisemann & Richter, 1999; Havens, 2000; Meisel; Rodgers, 2000; SUPPORT Principal Investigators, 1995). Palliative care professionals have contributed "self-determined life closure" as an outcome of palliative care. These attributes suggest the following revised definition of self-determination in palliative care: a process of decision-making that includes personal appraisal, the support and advice of others (family, health-care professionals), and activities that result in successful life closure and peaceful death.

Contextual Basis of Self-Determination

According to Rodgers (2000), clarification of a concept involves exploration of the contextual aspects (temporal [antecedents and consequences], socio-cultural, and disciplinary contexts, and exemplars) to gain an understanding of the situations in which the concept is apparent.

Table 3 gives a temporal perspective of self-determination.

Table 3 *Temporal Context of Self-Determination*

Antecedents	Attributes	Consequences
• healthy person with awareness of mortality • "becoming ill": diagnosed with serious illness; worsening of chronic illness; admission to hospital, ICU, nursing home • reasonable functional status • mental capacity (or DPOA-HC appointment) • cultural/religious orientation • age — frequently older • relationship with health-care provider — primary care, palliative care (assessment or provider-initiated discussion) • information about condition/prognosis • family discussions • education about *PDSA*	**Personal appraisal** • possessing physical and emotional strength • possessing power • possessing knowledge • possessing mental capacity • not controlled by others **Decision-making process** • advance care planning for when capacity is diminished • refuse or accept care or treatment • rights of others not violated • continuity of providers **Activities** • completing values history • provider- or patient-initiated discussions; family conferences • making living will or appointing a proxy (durable power of attorney for health care) • completing "do not resuscitate" orders • choosing "comfort measures" • completing unfinished business (relationships, finances, funeral) **Goal/outcome** • self-determined life closure • peaceful death	• discussions with family, physicians, social workers, lawyers • completion of AD • peaceful death • dying and death not consistent with patient's wishes • less aggressive care at time of death than desired • family- or physician-determined circumstances around death **Organizational consequences** • increased ethics consultations and moral dilemmas • increased AD documentation compliance • increased patient requests for information • increased patient and professional education about AD • increased workload and role redundancy (MD, MSW, RN, APRN) • increased family conferences

Antecedents

The literature suggests various antecedents to the concept of self-determination. The first and most obvious one is becoming ill. This could occur in conjunction with the diagnosis or awareness of a life-threatening or terminal illness, a sudden worsening of a chronic illness, or admission to hospital or transfer to an intensive care unit (SUPPORT Principal Investigators, 1995). The latter was the context of the *PDSA* (Bradley & Rizzo, 1999; Haynor, 1996; *OBRA of 1990,* 1990). However, the expression of self-determined choices and values is not necessarily associated with illness. In fact, healthy people are often encouraged to complete advance directives (Havens, 2000; Johnston, Pfeifer, & McNutt, 1995; Silveira et al., 2000). This trend was evident following publication of results showing that patients' expressed wishes (as stated in advance directives in hospital medical charts) had not been incorporated into the plan of care at the time of death (Covinsky et al., 2000; Lynn et al., 2000; SUPPORT Principal Investigators, 1997).

Mental competency or capacity is an antecedent to self-determination in many contexts (Valimaki & Leino-Kilpi, 1998), but appointment of a proxy could ensure durability of preferences in the case of incapacity. Other antecedents are functional status, age (Johnston et al., 1995), and cultural or religious orientation (Koenig, 1997; Ruhnke et al., 2000). There are conflicting views between patients and providers regarding age and functional or health status. Patients generally say they prefer to have discussions with physicians when they are young and healthy, during preventative medical visits (Havens, 2000; Johnston et al., 1995; Silveira et al., 2000), whereas physicians tend to state that they initiate such conversations with older, sick, hospitalized patients (Hesse, 1995; Johnston et al.; Tulsky et al., 1998). One review cites the lack of physician payment for discussions about advance care planning as a barrier to its increased frequency in an office setting (Cerminara, 1998).

Other antecedents include the need for relevant information about a condition and about available therapies (Tulsky et al., 1998), family discussions and appointment of a proxy (Hesse, 1995; Tulsky et al.), knowledge about end-of-life legal issues (refusal/withdrawal of treatment, assisted suicide, euthanasia, double effect) (Silveira et al., 2000), and factors related to physicians and the health-care system. Physician factors include assessment of patients' knowledge about their prognosis in order to clear up misconceptions (Silveira et al.), patients' values (Tulsky et al.), patients' desired level of participation in decision-making (Barry & Henderson, 1996; Havens, 2000; Sutherland et al., 1989), and physicians' personal beliefs about futility or, based on prior conversations, about the patient's wishes (Haynor, 1996; Hesse). The main antecedent to self-

determination in the health-care system is passage of the *PDSA* (Bradley & Rizzo, 1999; Haynor; Meisel, 1998; *OBRA of 1990,* 1990). Although one intervention study found that knowledge about advance directives increased compliance (Murphy, Sweeney, & Chiriboga, 2000), this did not translate into self-determined choices (in the form of advance directives) regarding end-of-life care (Covinsky et al., 2000; SUPPORT Principal Investigators, 1995, 1997). Contact with clinicians experienced in palliative care has been identified as an antecedent to "self-determined life closure" and peaceful death (Ferris et al., 2002; Field & Cassel, 1997; Foley & Gelband, 2001; National Hospice Organization, 1997).

Consequences

The consequences of self-determination, for patients (including healthy individuals), organizations, and health-care providers, are evident. Those found in studies with healthy individuals include discussions with physicians and family member about treatment preferences in the event of terminal illness, and, for some, use of a living will and/or durable power of attorney for health care (Eisemann & Richter, 1999; Havens, 2000; Johnston et al., 1995; Murphy et al., 2000; Ruhnke et al., 2000). Despite attempts to educate patients in the use of advance directives, understanding and use of advance directives did not always increase (Havens; Hesse, 1995; Nordgren & Fridlund, 2001; Ott, 1999; Sutherland et al., 1989).

For ill patients, self-determination does not necessarily result in a death experience that is consistent with their values and preferences (Covinsky et al., 2000; Hesse, 1995; SUPPORT Principal Investigators, 1997). Various strategies consistent with a patient's wish for limited life-sustaining treatment and for comfort care may be integrated — for example, advance directives, actions regarding life closure, use of comfort measures, "do not resuscitate" or "no code" orders, referral to hospice or palliative care, and symptom management, including pain relief — but this cannot be attributed directly to the presence of an advance directive. Some patients receive *less* aggressive care than they have expressed a desire for (Covinsky et al.; Hesse; Ott, 1999; SUPPORT Principal Investigators, 1995, 1997).

An unexpected finding of the analysis is patient reliance on or desire for more family or physician involvement in end-of-life decision-making, which is apparent in more recent studies and studies with patients from non-Western cultures (Candib, 2002; Covinsky et al., 2000; Fan, 1997; Hern, Koenig, Moore, & Marshall, 1998; Murphy et al., 2000; Ott, 1999; Quill, 2002; Ruhnke et al., 2000; Sutherland et al., 1989).

One study (Haynor, 1996) and one review (Ott, 1999) summarize organizational consequences following passage of the *PDSA*. Haynor describes an increase in the complexity and volume of ethics committee

cases, in professional moral dilemmas, in compliance with advance directives, in patient requests for information, and in patient and professional education. Professional consequences were increased workload (for social workers and advanced practice nurses) and role redundancy in clarification of patient preferences (for physicians, nurses, social workers, and admitting clerks). Professionals also reported increased responsibilities related to patient and family discussions, family conferences, and clarification of the term "no heroics" (Haynor). Ott describes inconsistent consequences related to utilization rates and discussion of advance directives with providers and family proxies, effectiveness of interventions to increase the use of advance directives, patients' understanding of and ability to complete advance directives, choices and application of treatment in the event of an advance directive, and cost issues.

Exemplars

Two published palliative care cases, those of an anesthesiologist with pancreatic cancer (Whedon, 2001) and a patient with breast cancer (Groopman, 2002), are presented as exemplars of self-determination.

In the first case the patient makes choices from diagnosis to death. He chooses symptom-relief methods that are consistent with his own beliefs and preferences:

> Fred was admitted for uncontrolled pain for the third time in a week. He signed himself out against medical advice the day before. From the outset Fred was plagued by abdominal pain, nausea, fatigue, and weight loss. He declined a recommended celiac plexus block for pain management, nausea strategies, and nutritional advice. Rather than continuous analgesics by oral, subcutaneous, or transdermal routes for chronic pain, he chose intermittent intravenous injections via peripheral intravenous catheters inserted for his weekly chemotherapy. (In locations carefully selected so they would not interfere with his golf swing.) He chose smoking pot over other antiemetic regimens. He chose a diet of calorie and protein rich gourmet meals accompanied by an appropriate bottle of wine from his cellar. He altered his treatment schedules and traditional oncology appointment times to undergo Reiki treatments through which he found comfort and strength. He accepted Hospice home care only to alleviate the financial consequences of the treatment and symptom management. He did his utmost to maintain the same lifestyle post-diagnosis as he had pre-diagnosis. As it became clear that he was dying a long-standing relationship with the palliative care team allowed for frank discussions. Reconciliation, family gathering, communication, and planning for his death marked his final days. In a quote from his wife's letter after his death she said, "he respected your knowledge and experience regarding the pain meds he needed. Let me assure you how much of a coup this was for you. And to your credit, you were able to back off when necessary and let him do things his way." (Whedon, 2001, p. 32)

In the second case a physician describes a conversation with a patient newly diagnosed with advanced-stage breast cancer in which he solicits (and documents) her choices in the event of progression of the disease:

> "We talked about the best-case scenario. But we also have to acknowledge that there is a worst-case scenario."
>
> I had found that this part of the discussion was best completed rapidly, as if removing an adhesive bandage.
>
> "The worst-case scenario is that ultimately the cancer becomes resistant to all the treatments we have, and even experimental therapies are no use. Most people say that if they reach a point in the illness when their brain is impaired, and there is no likelihood of improving their quality of life, then nothing should be done to keep them artificially alive, through machines like respirators. It's essential, Maxine, that I know what you want done if we reach that point."
>
> "I — I don't think I would want that," she said, haltingly.
>
> "You mean that you would want only comfort measures to alleviate pain, and nothing done to prolong your life, like a respirator or cardiac resuscitation?"
>
> "Yes, I think so," Maxine whispered.
>
> I nodded. This was her "end-of-life directive." I would put it in writing in her medical chart.
>
> "We have a plan of therapy and an understanding. Now let's look on the positive side," I said, trying to spark some of the determination she would need in order to endure the months of chemotherapy ahead. "You are young, your organ function is excellent — despite the deposits of tumor, your liver is still working well, and your blood counts are fine — so there is every reason to think that you will tolerate the drugs and we will make real progress." (Groopman, 2002, p. 62)

Both cases contain attributes (personal appraisal, decision-making process, activities, and outcomes) that help to clarify self-determination as it exists in expert palliative care situations. In both cases the health-care providers demonstrate respect for autonomy. They share information that will be of value to the patients in making self-determined choices consistent with their values and preferences throughout the dying process. Family is an integral part of the decision-making process. Both cases show evidence of preparation for future dependence, while the patient still has mental capacity, including documentation of wishes and provider continuity throughout the illness trajectory. Opportunities for other means of ensuring "self-determined life closure" are evident, given the preparation for the possibility of a future marked by continued deterioration and death. Both patients experience the desired consequences of a peaceful death.

Discussion

This literature review demonstrates that the concept of self-determination, a relatively abstract, complex idea, has been actualized in many different ways in various health-care settings. As described by Rodgers (2000), concepts are dynamic, constantly changing and evolving contextually and over time. This is certainly true for the concept of self-determination. Societal, legal, ethical, cultural, and palliative care practice and research influences have contributed to the evolution of definitions and attributes. Historically, in periods of oppression of vulnerable groups the focus of self-determination was freedom and self-governance. Bioethical, legal (specifically, the *PDSA*), and palliative care practice and research attempted to guarantee self-determined choice to vulnerable groups, such as hospital patients, through the documentation of treatment preferences and appointment of a proxy to ensure that the patient's plan of care was respected. Self-determination was often conceptualized as the completion of an advance directive, an attempt to reduce the entire process of decision-making on end-of-life care to a single act.

However, it became apparent that completion of a simple form could not ensure that complex patient choices, which are often situation-dependent, will be effectively captured and consistently applied within complex health-care systems. This view, which has been expressed by many health-care researchers, is summarized by Teno (1998) in a comment by Mencken: "For every human problem, there is a solution, which is simple, neat, and wrong" (p. 1170). Clarification of self-determination as a complex process is an important step in concept development.

Many studies focus on self-determination as a basic human right without considering the fact that an individual's personal appraisal of self-determination is shaped by a host of multidimensional individual factors (e.g., ethnicity, age, health status). The ethicist Renée Fox (1990) describes this lack of cultural perspective: "There is a sense in which bioethics has taken its American (Western) societal and cultural attributes for granted, ignoring them in ways that imply that its conception of ethics, its value systems, and its mode of reasoning transcend social and cultural particularities" (p. 207). Several recent studies eliciting the views of patients, especially those from non-Western cultures, on self-determination add to our understanding of self-determination in health-care decision-making. Despite the fundamental nature of self-determination, some patients do not feel empowered to make choices (Nordgren & Fridlund, 2001; Valimaki & Leino-Kilpi, 1998), while others prefer to turn decision-making functions over to family members or health-care providers because of underlying cultural beliefs (Baker, 2002; Candib, 2002;

Fan, 1997; Hern et al., 1998; Koch, Braun, & Pietsch, 1999; Koenig, 1997; Quill, 2002; Ruhnke et al., 2000; Shapiro & Bowles, 2002) or in times of serious illness (Barry & Henderson, 1996; Covinsky et al., 2000; Haynor, 1996; Prendergast, 2001; Tulsky et al., 1998).

Patients' views concerning their own level of involvement and that of others in the decisions about their care highlight the need for partnerships among patients, family members, and providers prior to serious illness. This approach is evident in the World Health Organization's (1990) definition of palliative care, which focuses on holistic care from the perspective of the patient and family. It places the patient's values and preferences at the foundation of care over the entire illness continuum, beginning with diagnosis (and emphasizing the importance of self-determination as a process).

Although health professionals have expressed a firm belief in self-determination, often affirming patients' rights in their professional codes and position statements (American Geriatrics Society Ethics Committee, 1998; ANA, 2001; Cain & Hammes, 1994; Cerminara, 1998; Department of Health, Education and Welfare, 1979; Engel et al., 1997; Ferris et al., 2002; Haynor, 1996; Scanlon, 1996; World Health Organization, 1990), they are still uncomfortable with advance care planning and lack the ability to manage it skilfully (Baker, 2002; Jezewski, Meeker, & Schrader, 2003; Prendergast, 2001; Shapiro & Bowles, 2002). Interventions to improve communication (Johnston et al., 1995; Murphy et al., 2000; Tulsky et al., 1998), increase the use of advance directives (Havens, 2000), and increase patient access to information (Barry & Henderson, 1996; Bradley & Rizzo, 1999; Eisemann & Richter, 1999; Silveira et al., 2000) often fall short of actualizing self-determined choices in end-of-life care (Covinsky et al., 2000; SUPPORT Principal Investigators, 1995, 1997). Improved provider understanding of individual patient factors to be assessed, including their desired level of involvement, fears, misconceptions, cultural beliefs, and values, might be more effective in matching providers' desires with patient outcomes.

The health-care system appears unprepared to consistently accommodate individual choices regarding end-of-life care. This is graphically illustrated in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT), which found that thousands of patients in leading academic medical centres suffered needless pain and discomfort in an effort to prolong life rather than to provide comfort (SUPPORT Principal Investigators, 1995). The SUPPORT intervention, conducted by advanced practice nurses trained in communications and armed with state-of-the-art prognosis predictions, failed to achieve the desired outcomes. A vast literature has been generated in

attempting to identify the reasons for this failure (Bookbinder, Rutledge, Donaldson, & Pravikoff, 2001; Rutledge, Bookbinder, Donaldson, & Pravikoff, 2001; Rutledge & Donaldson, 2001; Rutledge, Donaldson, & Pravikoff, 2001). Canada has no corollary legislation to the *PDSA* and its focus is broader, with professional, institutional, and regional efforts being made to improve patient and family involvement in decision-making (Bowman & Richard, 2004; Canadian Nurses Association, 1994, 2002; Davidson & Degner, 1998; Singer et al., 2001; Singer, Martin, & Kelner, 1999).

Clarification of the concept of self-determination in the palliative care setting is hampered by three additional research issues. First, because of the many gaps in the scientific evidence on quality-of-life outcomes, it is difficult for health-care providers to determine what a patient can expect from different palliative therapies (Field & Cassel, 1997; Foley & Gelband, 2001), a key factor in patient self-determination. Second, the manner in which health-care providers communicate information to patients can influence the way in which patients receive and use that information (Johnston et al., 1995; SUPPORT Principal Investigators, 1997; Tulsky et al., 1998); patients can make self-determined choices reflecting their personal values and wishes only if they have access to the relevant information. Finally, informed patients and families who wish to take an active role in their health-care decisions — the essence of self-determination — cannot be accommodated without widespread changes to health-care systems.

Limitations of the Study

The choice of Rodgers's (2000) concept-analysis method seemed appropriate to the goal of identifying the evolution and current status of self-determination as a foundation for developing a program of palliative care research. However, this method has several limitations. Selection procedures for abstract ideas such as concept evolution, attributes, antecedents, consequences, and exemplars may exclude literature that examines conceptual meaning in other ways. As a literature-based form of inquiry, this method does not reflect the perspectives of patients, clinicians, or researchers, which could be captured through in-depth qualitative interviews. Further, instead of describing self-determination definitively, it provides a conceptual understanding based on a finite literature at a particular point in time (Rodgers). Interactive or participative methods, such as dimensional analysis, or critical methods may also be appropriate for a dynamic concept with this degree of abstractness (Rodgers & Knafl, 2000).

Conclusion

The concept of self-determination requires clarification. It is an abstract, complex concept that is likely to change over time and within the multiple contexts in which it is actualized. Following passage of the *PDSA*, the lack of a clear definition of self-determination and its process hindered efforts to develop interventions to enhance it and hence to improve end-of-life care. This is illustrated in the negative results of the multimillion-dollar SUPPORT intervention, which failed to yield improved outcomes for thousands of seriously ill patients in five well-respected academic medical centres (SUPPORT Principal Investigators, 1995).

The implications of this concept analysis for palliative care research are summarized in Appendix 2. Future palliative care interventions should consider the complexity and evolutionary nature of self-determination. Research interventions and other strategies should consider the essential attributes of personal appraisal, decision-making process, activities, and outcomes. Such a comprehensive view takes into account the variety of patient (especially socio-cultural), provider, and health-system factors that might support or facilitate self-determination.

Fostering the broader idea of advance care planning rather than simply completing advance directives (Cantor, 1998), reimbursement of self-determination activities, especially in managed care environments (Cerminara, 1998), provider training in communication skills, and determining the influence of different cultural perspectives on views of self-determination are some of the areas of research suggested by the results of this analysis.

Future concept analysis could compare the actualization of self-determination research and policy in different countries. For instance, US research has been dominated by the *PDSA*, whereas Canada has favoured a non-legislative approach to self-determination, resulting in the development of policy and research focused on patient autonomy in decision-making (Bowman & Richard, 2004; Davidson & Degner, 1998; Singer et al., 2001). Comparison of the outcomes of these different approaches may serve to inform the development of best practices and palliative care research directions concerning self-determination.

The concept of self-determination has evolved from the notion of group self-governance to that of individual self-determination in health-care matters by means of advance directives. Another transition seems to be imminent: from the notion of self-determination as the completion of a form to that of a dynamic process of communicating health-care values and preferences among individuals, their families, and health-care providers (Agency for Healthcare Research and Quality, 2003; Brooks,

Hardy, Moseley, Myrick, & Jones, 2003; Lynn et al., 2000; Teno, 1998). The next step calls for health-care systems and health-care providers that are prepared to care for patients who exhibit all shades of self-determined decision-making.

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Appendix 1 ***General Provisions of the*** **PSDA**

- applicability: applies to hospitals, "skilled nursing facilities," home-care agencies, hospices, and "prepaid" health-care organizations
- provision of written policies: describing patients' right to make decisions concerning medical care, right to accept or refuse treatment, and right to issue advance directives
- provision of written information to adult patients at time of admission to medical facility
- documentation: must be provided in medical record on whether advance directive has been issued
- non-discrimination: health-care providers are forbidden to discriminate on the basis of whether a patient has issued an advance directive
- compliance with state law
- provider education about advance directives: staff and the community at large must be provided with education in advance directives
- conscientious objection: health-care providers need not implement the law if they object as "a matter of conscience"
- written description of state law: states must develop laws concerning advance directives (including medical decision-making — e.g., consent to treatment, informed consent, and end-of-life decision-making) that are distributed to patients by providers
- public education campaign: the Department of Health and Human Services is required to "develop and implement a national campaign to inform the public of the option to execute advance directives and of a patient's right to participate and direct health care decisions"

Source: Adapted from Meisel (1998).

Appendix 2 *Concept Analysis of Self-Determination: Implications for Palliative Care Research*
• Consider the complexity and dynamic nature of self-determination in the development of palliative care interventions. • Consider the nature of self-determination as a cultural, social, ethical, and legal construction. • Recognize the importance of family; persons from non-Western cultures are more likely to view family and others as key participants in decision-making. • Intervention research should consider opportunities for system change, as many health-care systems do not feature a patient-centred approach that encourages and supports individual choice in end-of-life decisions. • A focus solely on increasing self-determination through the use of advance directives does not address the complexity of the process of communicating patients' values and preferences within complex health-care systems. • Increasing the evidence base for palliative care practice (e.g., symptom control, communication skills) can serve to improve the quality of patient and family decision-making. • Creative strategies and interventions are needed, to honour the wishes of those patients who tend to interact passively with clinicians and the health-care system.

Special Article

Palliative Care Program Effectiveness Research: Developing Rigor in Sampling Design, Conduct, and Reporting

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Abstract
Research on palliative care presents some unique sampling challenges. The purpose of this paper is to articulate the sampling challenges that palliative care researchers face during phases of study design, conduct, and the reporting of results. Challenges include identifying a target population, avoiding selection bias in the face of clinician and patient denial of serious illness, developing eligibility criteria for a seriously ill population, minimizing high patient refusals due to illness, and accurate reporting of all screened and eligible participants. These challenges are explored within the context of a randomized clinical trial testing a palliative care intervention. Suggestions for improving scientific rigor in sampling design include 1) defining a target population that is consistent with research goals; 2) identifying eligibility criteria that are objective and understandable to clinicians to yield the desired sample; and 3) reporting results about the target population, sample eligibility/exclusions, and participation using standardized criteria. J Pain Symptom Manage 2006;31:270–284. © *2006 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Palliative care, sample, research methods, sampling issues, program effectiveness, randomized clinical trial

Introduction

Since the mid-1990s, in response to discouraging results from research on the state of end-of-life care, increasing numbers of palliative care programs (PCP) and services have been developing nationwide to improve the quality of care of patients with serious illness.[1–5] According to American Hospital Association (AHA) surveys, 951 hospitals (20% of those reporting) had a PCP in 2002, an increase from 580 since 2000, the first year that these data were collected.[6] However, as a relatively new model of care, few PCPs have undergone rigorous testing for clinical efficacy or effectiveness.[7–10] A number of reviews have summarized clinical trials (mostly conducted in Europe) to determine the effectiveness of PCPs.[11–13] However, many U.S. PCP development investigations have been designed as demonstration projects and to date have

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focused primarily on determining the feasibility of incorporating palliative care into existing infrastructures of health care.[9,10,14,15]

PCP effectiveness research is vital for ongoing program development to 1) demonstrate program feasibility; 2) determine efficacy and effectiveness (including cost effectiveness) for improving care; and 3) determine moderators of effectiveness, i.e., which subgroups of patients benefit most from various care models. However, PCP research is difficult to perform due to a myriad of methodological challenges.

Recruiting an adequate, representative, and unbiased sample is one of the most common and difficult methodological challenges cited in PCP effectiveness research.[7,8,11,13,16–18] Palliative care researchers often identify challenges with recruitment of appropriate types and numbers of patients, at times preventing study completion.[8,13,19–21] In completed studies with adequate recruitment, highly selective or overly broad eligibility criteria leave doubt as to whom results may be applied.[8,9,22] Researchers must make tradeoffs between strengthening study internal validity (using selective homogeneous samples) and external validity (using broad, representative samples to increase generalizability).

Given these tradeoffs, researchers must be clear and explicit regarding the process of sample selection and the characteristics of participants so that readers can judge the applicability of results to practice. For example, studies conducted in tertiary, academic medical centers, tend to have participants who are younger, sicker, and atypical in their responses to treatment; an awareness of such selection biases is an important sample consideration when evaluating study results.[23] The Consolidated Standards of Reporting Trials (CONSORT) and Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) are guidelines to improve the transparency of reporting the results of randomized and nonrandomized studies (discussed later); they provide specific recommendations for reporting sample design and participant information.[24–26]

In preparation for recruitment to a randomized clinical trial (RCT) of a novel PCP, our team embarked on an analysis of sampling issues in published palliative care clinical trials. Sampling challenges are not unique to palliative care research, however, palliative care research does have unique sampling challenges. The purpose of this paper is to identify, describe, and analyze the unique sampling issues of PCP effectiveness research that occur during study design, conduct, and the reporting of results. We use a broad definition of sampling issues because we consider all issues of study design that relate to identifying, recruiting, and describing study participants. Our palliative care RCT in progress will illustrate some of these challenges and our efforts to minimize their impact.

Overview of Case Example

Three of the authors are currently conducting an RCT, referred to as "ENABLE," to test the efficacy of a psychoeducational intervention for persons with advanced cancer and their families. The acronym "ENABLE" stands for "Educate, Nurture, Advise Before Life Ends." The intervention focuses on early intervention, prevention of complications of progressive illness, and improving quality of life and quality of care. Participants who are randomized to the program (intervention group) have weekly telephone sessions with advanced practice nurses who specialize in palliative care. The nurses guide participants (and a family member) through a self-paced educational manual, teach problem-solving skills, and coordinate care by making sure that participants are aware of and have access to palliative care and community resources. Participants in the intervention group are also invited to attend monthly shared medical appointments where they can discuss nonurgent health concerns with a palliative care nurse practitioner and physician and other persons living with advanced cancer. Participants in both the intervention and standard care groups have access to a palliative care consultation service. We hypothesize that participants in the intervention group will have better symptom management, higher quality of life, and will report care that better reflects their values and preferences as compared to participants randomized to the standard care group. Fig. 1 summarizes recruitment and other aspects of the sample

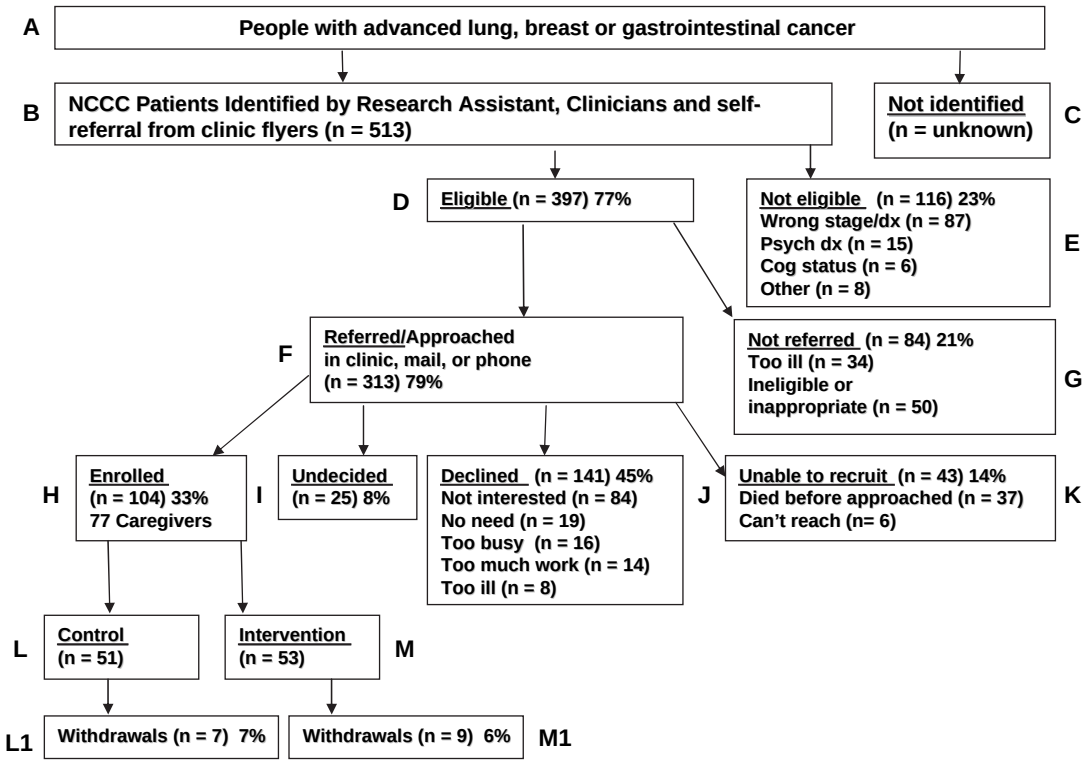

Fig. 1. Flow diagram describing the sample of Project ENABLE (11/03–1/05) in progress.

that will be described throughout the remainder of this paper.

Sampling Challenges During Study Design

Conceptual Issues

During study design, researchers must identify the target population, i.e., the entire group of people to whom the researcher wishes to generalize the study results.[27] By most definitions, persons appropriate for a palliative care intervention or program are a very heterogeneous group.[28] For example, the AHA defines palliative care population within their program definition as

> "An organized program providing specialized medical care, drugs, or therapies for the management of acute or chronic pain and/or the control of symptoms administered by specially trained physicians and other clinicians; also provides supportive care services, such as counseling on advanced directives, spiritual care, and social services to *patients with advanced disease and their families.*"[29 p. 21] (italics added).

Similarly, the World Health Organization definition states: "Palliative care is an approach that improves the quality of life of *patients and their families facing the problem associated with life-threatening illness….*"[30] (italics added).

Given this broad target population it is apparent how researchers, clinicians, administrators, patients, and families might have different perspectives on who would comprise the sample of a palliative care effectiveness study.

Rigorous sampling designs are aimed at selecting a representative sample from the target population. The target population is operationalized by the identification of eligibility criteria that determine who will be invited to

participate in the study.[27] Determining who is considered "eligible" for the study is defined by the inclusion criteria; exclusion criteria determine who will not be included. As will be described, researchers must consider scientific, pragmatic, ethical, and safety issues when developing each inclusion and exclusion criterion or sample boundary.[31]

Although researchers will attempt to clearly state criteria that will yield the desired sample, "unstated" forces can sometimes create unintended exclusions. For example, particular settings or clinicians may be overlooked or choose not to participate; clinicians may be biased in patients to refer for studies, while certain patients may choose not to participate.[31] The extent to which researchers analyze how such forces have influenced their sample is unknown; but it is seldom reported explicitly.[32] Such analysis is an important aspect of the sampling design to determine selection criteria that will yield a representative sample. Ongoing attention to the intentional and unintentional forces that can bias a sample should continue while the study is underway, and later be described when study results are reported.

As in all health care research, palliative care researchers must consider many participant characteristics (e.g., age, gender, ethnicity, diagnosis, etc.) when determining eligibility criteria. However, there are some criteria that may be particularly problematic in palliative care research. These include criteria related to selecting from those referred to palliative care services, prognosis, disease stage, performance status (PS), mental status, and presence of a family member or caregiver. These characteristics are discussed below relative to how they might affect the selection of a sample for a palliative care study.

Referral to Palliative Care. A number of palliative care studies have included only those persons referred to a newly developed or existing PCP or service.[9,33] This approach raises a number of important issues. First, the researcher must clearly articulate who is "eligible" to be referred to the palliative care service in a particular setting. Clinicians may have a bias about which patients are "appropriate" for a PCP. Similar to both patients' and clinicians' views regarding referral to hospice services, referral to a PCP may be viewed as "giving up."[34] Physicians' and nurses' reluctance to identify or label patients as "hospice-appropriate" is apparent in clinical care by late and low hospice referral rates.[35] Similarly, clinicians' desire to "protect" their patients from exposure to the truth of incurability of illness may delay referral for a variety of reasons including waiting until all "disease-oriented" treatment has been exhausted.[36,37]

Because of known clinician referral bias, a sample that results primarily from persons receiving palliative care services raises several questions: To what extent does this sample represent the population of all of the persons in the agency or region who could have been eligible for the PCP? Are important groups from the agency or region not referred to the palliative care intervention/program? What are the characteristics of nonreferred patients and their clinicians? If nonreferred patients are substantially different from referred patients, how effectively can the study results be generalized to future patients (who may include individuals of the type not currently being referred)? Researchers must uncover whether systematic biases existed between those who were referred to a palliative care service versus those who were not, as such bias limits the generalizability of the findings.

Prognosis. Because PCPs address the needs of patients with "life-limiting" illness, eligibility criteria for many studies include some judgment about prognosis. There is general agreement that "palliative care" can be appropriate for patients along a continuum including those who are newly diagnosed with life-threatening illness (e.g., metastatic or Stage IV lung cancer), those who are eligible for hospice care (e.g., cancer or noncancer diagnosis that meets specific parameters predictive of survival for 6 months or less), and those who are actively dying.[30] Prognostic models have varying degrees of sophistication from clinician "intuition" to multivariate statistical models (in which several factors are combined to yield an estimate).[38,39] Studies of health care providers' determinations of prognosis (e.g., clinical hunches based primarily on prior experience and disease estimates) demonstrate inaccuracies, specifically overestimation of length of life.[40,41] Overestimation can result

in "late referral" in which patients may be more ill and die sooner than the duration of the intervention. If prognosis is used as inclusion criteria, but not carefully defined, researchers run the risk of introducing two types of bias into the sample: (1) inconsistent (i.e., unreliable) identification and (2) unintentional exclusions via late referral.[42–44]

Prognostic models for many diseases are improving,[45] however, prognosis may be more predictable in some types of cancer than for other conditions, such as congestive heart failure.[34,46] An evaluation of prognostic factors in 24 studies representing 6,424 cancer patients with a median survival of 3 months or less using multivariate analyses yielded the following predictors: poor PS and the presence of cognitive failure, weight loss, dysphagia, anorexia, and dyspnea.[44] In contrast, physician clinical estimation (the criterion often used in palliative care eligibility criteria)[44] was not a statistically significant predictor of survival in multivariate analyses. Use of objective clinical indicators (such as those mentioned above) in conjunction with clinician estimation may result in a more accurate estimate of patient eligibility based on prognosis.[17,47] Developing objective prognostic inclusion criteria is likely to increase homogeneity of participant prognosis—a strategy that can minimize bias due to selection-maturation interaction.[48]

Disease Type and Stage. Disease type and stage are inclusion criterion often used to achieve sample homogeneity. A study may focus on a particular disease (e.g., cancer, one type of cancer, or another serious illness like congestive heart failure) as a characteristic for eligibility to minimize extraneous variables from different biological responses.[48] However, even within a single disease, disease stage can cause significant variability in symptoms and other outcomes of interest addressed by PCP studies. To identify a homogeneous population of persons with advanced stage cancer, even use of the most advanced stage IV designation, may still be inadequate to achieve symptomatic and prognostic homogeneity. Depending on whether women with stage IV breast cancer have bone (nonvisceral) metastases or visceral metastases, prognosis and palliative care needs will vary widely. Women with visceral metastases will likely have a much shorter prognosis and experience qualitatively different pain (e.g., visceral pain) in contrast to women with primarily bony disease.[49]

Due to different illness and symptom patterns even within the same disease, the sample may be very heterogeneous. However, there are many characteristics of interest in PCP research that are shared and more relevant across participants with various advanced diseases. It may be more logical to group participants according to these characteristics rather than divide patients along traditional disease categories.[48,50] Unlike drug studies that require subjects to be homogeneous "biologically" (e.g., by disease type or stage), other categories of selection may be more important in answering questions in a palliative care population.[8,48,50]

Because of this, palliative care investigators often select participants using a method described by Jessop and Stein[50] called "non-categorical sampling." Noncategorical sampling is an approach that identifies participants based on common disease features (e.g., symptoms such as dyspnea) or consequences (e.g., loss of independence) rather than by a specific biological disease (breast cancer or acquired immunodeficiency syndrome).[50] Noncategorical sampling emphasizes the "illness experience" as more important than the specific diagnosis per se.[50–52] Therefore, in a palliative care study, eligibility criteria may define homogeneity or "typicality" by including participants who share a common symptom or prognosis, rather than a common disease.[8,48,53] Defining criteria to achieve "typicality" in palliative care may require researcher creativity as well as tolerance for subjectivity in how criteria are applied.

Performance Status. PS is a commonly used eligibility criterion in cancer clinical trials. Eligibility for a palliative care study based on PS may be appropriate if the intervention is only intended to benefit persons of a certain functional level (e.g., if the intervention must be delivered outside of the home, then persons who are homebound will not be able to participate) or if study procedures require a certain level of performance (e.g., if participants must independently complete self-report questionnaires). In some studies, PS measures are used for eligibility as in some conditions they

may also relate to prognosis (discussed earlier).

A variety of measures of activities of daily living (ADLs) (e.g., Katz ADL scale) are available to assist in determining functional status depending on the purpose of this eligibility criterion.[54] The Karnofsky Index of Performance Status (KPS) is a clinician-rated measure that describes patients' functional level given their "mobility status" at 10% increments on a 10% (moribund) to 100% (normal functioning) scale. The KPS is reported to be an acceptably reliable, valid, and simple global measure of functional status in cancer clinical trials.[55] Typical measures of PS may be problematic in two ways: first, because palliative care patients may have overall poorer function, a large number of otherwise appropriate participants may be excluded; second, distinguishing between broad categories of function along a continuum of fully functional to bedridden may not have the specificity needed to differentiate among palliative care patients with overall "poorer function."

An alternative PS measure for palliative care studies is the Palliative Performance Status (PPS) scale, which was based on the KPS and also uses a 0–100% scale.[56] The scale measures three broad areas of function: intake, mobility, and level of consciousness. The PPS definitions of each of the categories describe the functional abilities of patients who represent a range of function more consistent with an "illness" trajectory. The PPS determines the level of function using other palliative patients as a standard versus "normal functioning" healthy patients. It has been found in a number of palliative care studies to have high interrater reliability, construct validity (as compared to the KPS), and good correlations with prognosis.[56] Eligibility criteria related to PS in a PCP effectiveness study may be more appropriately based on a tool designed for this population.

Mental Status. Mental status is often an important eligibility criterion in clinical trials.[31] Reduced mental status can interfere with the subjects' ability to understand the study and therefore provide valid consent. Beyond consent, study procedures may require a certain level of cognition to fully participate. For example, if the intervention requires participating in an educational program, learning new information, complex decision making, and/or completing of self-report questionnaires,[31] then a certain minimal level of cognitive function will need to be defined. Having a defined level of mental status may be a routine criterion for many studies; however, for studies of PCP effectiveness it can be a major source of sample bias. Patients with serious illness who are otherwise appropriate for a PCP are likely to have intermittent or progressive impairments of mental status especially as disease progresses.[17]

The Mini-Mental State Exam (MMSE)[57] has been used in some palliative care studies to define a minimum level of cognitive function to be eligible for study entry.[20] Beyond its use to define patients who can consent and participate in study procedures, a "normal" MMSE score has been found to identify a sample of patients with a better prognosis, because cognitive failure has been associated with an overall poorer prognosis.[17] If a minimum prognosis is required for the intervention to be evaluated, then the addition of a mental status measure as one marker of prognosis may be justified. However, it is important to consider whether results from the studies of PCPs enrolling only patients with "normal" mental status will generalize to a "typical" population of persons with advanced disease who may be intermittently sedated or experience delirium. This is especially true to the extent that the normal mental status is necessary due to processes specific to the study, such as study consent or completion of questionnaires, as opposed to being considered necessary to benefit from the palliative care intervention.

Presence of Family or Caregiver. Palliative care definitions explicitly include family as the unit of care.[58,59] Therefore, participation of family/caregivers is an important consideration in sample selection and eligibility criterion for PCP effectiveness studies. Because most palliative care patients can be predicted to become debilitated and dependent, requiring some sort of nonprofessional caregiver for a period of time prior to death, addressing inclusion of a family member or caregiver within sample design may be necessary. In one study, 75% of the sample of cancer

patients were able to meet the eligibility criteria of having a family caregiver in the home.[20] Specific issues in including family/caregiver within the sample include the following: How is "family" defined? Must the participating family member be a blood relative? Must the family member and participant live in the same household? Is the family member identified and selected by the researcher or the participant? Does the family member have to be the same category (e.g., spouse) for each member of the sample? What is the role of the family member regarding study procedures? Will many patients be excluded if presence of a family member is an inclusion criterion? How will decisions about the use of this criterion affect study generalizability?

Having a family member/caregiver as an eligibility criterion is one way in which some palliative care studies have attempted to deal with "data attrition"; i.e., loss of data for a period of the study duration due to subjects' debilitation.[60] Some investigators have attempted to overcome the challenge of data attrition by substituting proxy reports when the patient becomes impaired. A review of several studies that have considered the accuracy of proxy reports of palliative patients concluded that proxies are accurate on specific parameters.[61] Specifically, there was nearly perfect agreement between participant and family member on support from family and friends, physical activity, ADLs, dyspnea, and immobility. In contrast there was poor agreement found for dysphagia, anorexia, pain, confusion, depression, and mood. Hence, family members were most reliable reporters on concrete, observable, physical, and functional aspects of care, and they were less reliable on outcomes that were subjective or "feeling-oriented."[61–63]

The benefits and burdens of requiring family participation as an eligibility criterion must be weighed carefully within the context of study purpose. The benefits of including family members in the sample are increased homogeneity in one sense (patients with family) that could maximize internal validity and reduce data attrition. Burdens of including family members are increased cost and methodological issues involved in operationalizing family inclusion. Hence, the tradeoffs need to be carefully evaluated from a sampling rigor perspective.[64]

Application

The ENABLE psychoeducational intervention was designed with a goal of teaching skills and symptom management strategies to prevent avoidable medical and decisional issues. It is appropriate for persons with advanced cancer who will face an "end-of-life" phase of illness within a year or two. The program was intended to be initiated at or shortly following diagnosis of an advanced cancer and to continue through an interview with a family member at approximately 3 months after the participants' death. The target population was identified as persons with newly diagnosed advanced breast, lung, and gastrointestinal malignancies (Fig. 1; Box A). From the cancer center tumor registry figures we estimated that at least 300 persons yearly would comprise the target population. The accessible/identified population (Fig. 1; Box B) comprises those individuals who are referred to or seek care at the cancer center. Box C in Fig. 1 indicates the unknown number of persons with cancer in our geographic area who do not receive care at the cancer center. This includes individuals who choose to not seek treatment for the signs of their disease as well as some persons who seek treatment outside of the cancer center. Though the number of persons in this category is unknown, given the rural nature and limited cancer resources in the region, it is presumed to be small. The enrollment numbers represent our first 14 months of recruitment (November 03-January 05).

To obtain an adequate representative sample from the target population of "adults with advanced cancer" (represented in Box A), we established the following broad eligibility criteria.

Inclusion Criteria. The inclusion criteria are as follows:

- Age 18 years or older;
- Stage IIIB or IV nonsmall cell lung cancer or extensive small cell lung cancer;
- Stage IV breast cancer with poor prognostic indicators (including clinician estimate of prognosis of 2 years or less; visceral crisis, lung or liver metastases, estrogen receptor negative status, Her 2 neu positive status, and cancer recurrence within 2

years of first treatment or recurrence while on treatment); or
- Unresectable Stage III or IV gastrointestinal cancer.

Exclusion Criteria. Exclusion criteria are as follows:

- Dementia or significant confusion (MMSE score of less than 25) or
- Axis I psychiatric disorder (DSM-IV) (e.g., schizophrenia, bipolar disorder, or active substance use disorder).

We established a minimum age, however, few children have these diagnoses. Furthermore, we believe a palliative care intervention for children or adolescents would require a team of health professionals who specialize in pediatric oncology issues. We placed no restrictions on gender, race, or ethnicity due to the absence of a hypothesis that the intervention would be appropriate only for a particular group. We chose three diagnoses and disease stages that are life-limiting for the vast majority of cancer patients and that would allow recruitment of sufficient participants to meet our accrual goals. This strategy resulted in a sample that would not represent patients with less common cancers (e.g., primary brain tumor). Additionally, there were no exclusions for patients receiving disease-oriented standard or investigational treatment.

Because prognosis of patients with advanced, metastatic, Stage IV breast cancer can be quite variable and prolonged, we added specific prognostic factors to help clinicians identify persons most appropriate for the intervention. All referring breast cancer clinicians were asked to come to a consensus in defining prognostic factors to accurately predict subjects with a 1–2 year prognosis. By developing consensus prospectively, we intended to minimize selection bias that might arise when individual clinicians are asked to estimate prognosis on a particular patient. We chose not to use any formal physical PS as eligibility criterion. The KPS is measured for all patients and will be explored as a potential moderator of efficacy.

The intervention is telephone based. This design was chosen to reduce participant travel burden and to accommodate subjects with a minimal PS. Because participants would be asked to engage in education and problem-solving therapy, we did need to establish a minimum level of mental ability for participants. We chose to use the MMSE as an efficient, objective measure of mental status. We exclude persons with psychiatric disorders because they would likely require more intensive services than our intervention was designed to provide.

Referral to the clinical palliative care consult team (PCT) is available as an aspect of "usual care" for all patients at NCCC. PCT referral was neither an inclusion nor exclusion criterion for our RCT. The intervention provides a comprehensive, coordinated approach with unique aspects that would complement the services provided by the PCT if a patient was also being seen by this service. For example, the intervention program focuses on teaching problem-solving skills to patients who are typically asymptomatic. In contrast, palliative care team referral is rarely initiated in such patients. Recommendation of referral to PCT by the study nurse educator is also appropriate, and conversely some study participants are referred to the study by the palliative care team. Therefore, referral to palliative care is not explicitly mentioned as an eligibility criterion.

Family members and caregivers were invited to participate in the study because we believe that an effective PCP/intervention should incorporate family and/or caregivers as much as possible. However, participants were not excluded from the study if they chose not to identify a family member to participate. Family was broadly defined as "one person who knows you well and is involved in your care." Furthermore, our study design included an evaluation of care by this family member following the participant's death.

In summary, as illustrated in Box C, recruiters identified and screened 513 patients in the first 14 months of this study in progress. Of these, 397 (77%) met our formal inclusion/exclusion criteria (Box D). We tried to specifically avoid selection bias by being as descriptive and clear as possible to minimize the need for interpretive judgments on behalf of the clinicians. However, establishing of eligibility criteria was only the first step in the process. Constant attention to possible

recruitment bias is needed as the study progresses.

Sampling Challenges During Study Conduct

Conceptual Issues

Sampling challenges during the study relate to the mechanics of identifying and recruiting persons who meet the eligibility criteria and then maintaining the sample. Eligibility criteria must be clear, objective, and easily understood by recruiters and referring clinicians. If posters or flyers are used to address the general population, then eligibility criteria must also be translated into lay language so that the members of the target audience will recognize themselves as eligible to participate. This latter aspect calls for creativity in recruiting seriously ill patients, some of whom will be unaware of their "eligibility" as their condition may not have been presented to them by their physician as "serious" or "life-limiting." Even when clinicians inform patients of their advanced illness status, patients may be in denial regarding the seriousness of their illness and unlikely to identify with an advertisement that is looking for "seriously ill, dying, or terminally ill" patients. Few patients recognize or understand the meaning of the term "palliative care"; euphemisms such as "supportive care" or "symptom management" may be chosen for a lay audience.

Denial of advanced illness by clinicians and patients may create barriers to recruitment when it results in a protective "gate-keeping" function that prevents eligible patients from being invited to consider whether they wish to participate in a palliative care research study.[8,11,17,19,47,65,66,67] In a review of methodological difficulties in palliative care, Glimelius[16] proposed that rather than protecting seriously ill patients, well-meaning providers were actually violating patients' rights when they denied eligible patients the right to participate in clinical trials. In the studies of what patients' values at end-of-life, control over treatment decisions and helping others have been identified as key aspects of quality of life.[68,69] Such sentiments may be consistent with a patient wishing to participate in a clinical trial. A recent report found that 50% of "eligible" hospice patients were willing to participate in an interview study of depression and anxiety.[70]

Another aspect of "gate keeping" is physicians' concern about losing control of their patient's care. Some clinicians believe that a study of palliative care means turning their patients over to another care provider. If physicians believe that a palliative care intervention will interfere with their treatment plan or relationship with a patient, then they may be reluctant to refer that patient to the study.

Because the aforementioned issues can interfere with representative and unbiased sampling, researchers must monitor clinician referral patterns throughout the study for trends that may suggest bias. It is similarly important to track if there are systematic reasons for participant refusals. These efforts can inform investigators about the need to modify recruitment strategies before the study progresses too far and a large pool of potential participants is missed.

Another key element is maintaining the sample or minimizing attrition. In an RCT, a major threat to internal study validity is differential withdrawal or attrition between the control and intervention groups. Cognitive decline, physical deterioration, and death are all expected outcomes in palliative care patients. Study design, intervention features, and data collection instruments and schedules must consider the sample disability and deterioration to minimize patient burden and maintain the sample throughout the study period.[18] An extensive discussion of strategies to minimize data attrition and nonrandom missing data (e.g., selecting brief instruments and proxy measures) is beyond the scope of this paper but is discussed in an excellent review by Tang and McCorkle.[71]

Application

Prior to beginning recruitment for the ENABLE project, the research team began assembling a packet of recruitment materials for patients and staff. The team decided to use the term "supportive care," as opposed to "palliative care," on these materials. Team members believed that even in a comprehensive cancer center with a well established and integrated palliative medicine program the label "palliative care" was still ambiguous or foreign to many patients. We hoped that the

terms "supportive care" and "additional supportive services" would be more recognizable; specifically patients (and clinicians) may be able to recognize that they needed "support" more so than "palliation." Participants randomized to the intervention group subsequently received educational materials that explain the concept and definition of palliative care, and many have reported an appreciation of a health care practitioner focusing on their comfort and quality of life needs. However, we have found that self-referral is not the strongest mechanism for study recruitment at our comprehensive cancer center. Perhaps because there are a variety of supportive services advertised and available to patients at this cancer center, participants tend to express interest primarily after their clinician specifically mentions or endorses the study.

Therefore, it is important to enlist clinicians' cooperation in facilitating recruitment. Confidentiality and Institutional Review Board standards require that patients first hear of any research study from the clinicians involved in their care (e.g., their doctor or nurse as opposed to a research assistant). To communicate the eligibility criteria to the staff, we created flyers and pocket cards. We scheduled a meeting with the clinical staff of the lung, breast, and GI disease management programs ("tumor boards") and the PCT to discuss the purpose of the study and give them a chance to ask any questions or raise any concerns. Oncology clinicians requested more information about how referring a patient to this study would be different from referring the patient to PCT. Another meeting with each of the groups was scheduled 9 months after study enrollment had begun; both meetings gave us an opportunity to assess whether clinicians were introducing some systematic bias into the sample. We found that clinicians had a good understanding of the eligibility criteria, and there were very few instances of "gate keeping."

The research assistants (RAs) (recruiters) at our cancer center are members of the disease management team meetings where all newly diagnosed patients are presented for multidisciplinary input on best available treatment options. Hence, the RAs are aware of all newly diagnosed patients and are able to perform an initial screen of patients based on the inclusion and exclusion criteria. From the meeting they are able to generate a list of potentially eligible study participants to present to clinicians. This structure has provided our study team with a sense of how many patients initially appear to be eligible for the study but are subsequently not referred by the providers (Fig. 1; Box G). Each discrepancy between potential eligibility and clinician invitation is evaluated for "gate-keeping" issues. These issues are addressed either one-on-one by a member of the study team or with the entire clinician group if a trend is detected.

Seventy-nine percent ($n = 313$) of the 397 eligible patients were "referred" to the study, i.e., the clinician informed the patient about the study. Clinicians rarely decline to mention the study to an eligible patient but they did often adjust the timing of when the study is presented based upon their judgment of when the patient will be best able to take in this information. For example, the clinician may choose to wait for a second or third appointment after sharing the initial diagnosis when the patient is likely less overwhelmed by the newness of his or her diagnosis and treatment. After the clinician obtained patients' permission to be contacted, patients were contacted by the research assistant at clinic appointments, or via phone or mail invitation.

As of January 2005, 45% of referred patients have declined to participate (Fig. 1, Box J). This includes patients who told their clinician that they did not want to be approached or agreed to be approached but declined after the study was described. For patients who declined to participate, age, diagnosis, and gender are recorded. Reasons given by the patients for declining are recorded and then categorized by the research team. The main reason cited by two-thirds of eligible patients who declined was "not interested." This includes both patients who were not interested in this study as well as patients who were not interested in participating in any research study.

One goal of ENABLE is to intervene before symptoms or problems arise. While clinicians have embraced this approach, some eligible patients have declined with the reason of "not needed." This was particularly true if they were approached about the study before they experienced any symptoms, physical deterioration, or emotional distress. Clinicians

have been instrumental in helping us monitor patients and have mentioned the study on a second occasion to patients who were experiencing a difficult issue that could be addressed within the study interventions. Some subjects have chosen to enter the study some months after they were initially diagnosed and identified as eligible.

Box I lists the patients who have been approached but are "undecided." This includes some patients who are actively considering the study, but it also includes patients who apparently do not wish to participate, but who do not verbalize this refusal. We have informally labeled them as "socially acceptable no." Although these patients do not verbally decline, their lack of follow through behavior with consent and baseline questionnaire completion implies to the team that they wish to decline but do so in a "socially acceptable" way. We have become sensitive to the possibility of pressure that palliative care patients feel to "please" their clinicians by complying with what is being asked. The team, recruiters, and clinicians regularly discuss ways to avoid what might be termed "beneficent coercion" as we attempt to diligently follow-up on all eligible patients.

Sampling Challenges During Reporting of Results

Conceptual Issues

Once the study is completed, clear and accurate reporting of characteristics and number of participants and nonparticipants can help the reader determine the presence of possible sample selection biases and associated threats to internal and external study validity. The CONSORT statement recommends standards for reporting study sample selection and characteristics within the methods and results sections, respectively, for all publications of clinical trials to facilitate evaluation of study quality.[25] The TREND statement provides similar guidelines for nonrandomized trials.[26] These recommendations are not commonly followed in trial reports. However, this level of detail is especially salient in palliative care effectiveness research given the sampling complexities of this population. Clear identification of each level of "non-participation" is crucial in evaluating potential selection bias.[32]

In palliative care studies, flow diagrams can reveal how nonparticipation affected sample size and final sample characteristics. A diagram can systematically demonstrate to the reader the extent to which all cases were identified and whether certain groups were preferentially affected by eligibility criteria. Identification of characteristics of nonparticipants may reveal subtleties of provider and family "gate keeping," and differentiate between patient or data attrition due to deterioration or death.[8,11,66] Accurate and complete reporting of nonparticipation, refusals, and withdrawals can allow for evaluation of selection biases that may result in threats to internal validity.

Rabow et al.[72] adopted a broad eligibility criteria in their a study of an outpatient palliative care consultation service in a 70-physician general medical practice that: diagnoses of cancer, advanced chronic obstructive pulmonary disease (COPD), or advanced CHF, with anticipated life expectancy of 1–5 years and who were not yet ready for hospice care. Two hundred and thirty-one of the 330 referred patients were found to be eligible. However, refusal rates of 58% and 65% of eligible intervention and control patients, respectively, were reported with a primary reason of "being too ill."[72] Unfortunately, no demographic data were provided about nonparticipants, so the extent to which the sample represented the population could not be determined. The investigators concluded that studies with broad eligibility criteria that represented the true nature of the palliative care population encountered in clinical practice should anticipate "high" refusals due to illness demands.[72]

Rinck et al.[8] noted either of the two trends, listed below, related to attrition in their review of palliative cancer care effectiveness research: (1) few refusals and a high attrition rate or (2) many refusals and a low attrition rate. They concluded that narrow selection criteria (which may exclude patients a priori who might later withdraw) or broad criteria (which take "all comers") may have a more significant role in determining refusal and attrition rates than the other factors that are commonly noted (e.g., patient deterioration and death).

A cancer center in the United Kingdom systematically and prospectively recorded,

analyzed, and published its experience with the enrollment of patients to 23 palliative care studies (mostly pharmacologic trials rather than a "program") over a 4-year period.[69] The cancer center had an established department of palliative medicine. Of 1206 patients referred, 648 (56%) were not approached as they did not meet the eligibility criteria for any of the 23 studies. Of 558 invited to participate in the study, 362 (30% of those originally referred) signed consents, and 248 completed all study procedures—only 21% of those originally referred. One hundred and ninety-six eligible patients did not participate—35% of those invited. The top three of 16 reasons given included "preferred to wait before entry," "too unwell/deterioration in condition," and "lives too far away." Although participation in drug treatment trials may affect patient decision making in different ways than choosing to participate in a PCP trial, this comprehensive analysis of the sampling process in palliative care research provides important eligibility, recruitment, refusal, and attrition benchmark data.

Application

Because this is a study in progress, application relates to our proposed approach to this issue. A flow diagram that complies with CONSORT standards was created early in the process of study recruitment. This diagram (Fig. 1) provided us with an explicit data-based process to consider how to access all advanced cancer patients within the region. All possible "selection forces" that might create selection bias were determined by brainstorming and reflecting with a variety of clinicians and patients within and outside of the cancer center. It allows "real time" documentation of the outcome of every patient screened and enrolled in the study. The diagram has been modified over time in response to sample variation. It has allowed us to carefully monitor recruitment and flow of participants through the study process.

We believe our rate of 33% enrollment (Box H) and 45% "declined" rates (Box J) are favorable compared to other benchmarks.[32,69,72] In our center, about 22% of newly diagnosed patients enroll in cancer clinical trials. Nationally, about 10–20% of eligible patients participate in National Cancer Institute or other U.S. cancer center sponsored trials.[32,73] A 30% participation rate of palliative care patients in a U.K. cancer center has been reported.[69] Rates of "refusal," especially in RCTs are quite variable, depending on the study goal and many patient factors.[74]

When the study is completed, we anticipate that this diagram will provide useful benchmarking information and also allow other palliative care researchers and clinicians to evaluate our study findings in relation to the effects of sampling on study outcomes.

Recommendations and Conclusions

As the number of PCPs of various models increases, it is important that there is increased research and rigor in determining effective models of care. Evaluation studies have predominated U.S. PCP research, a sign of the early stage of the development of the field. Experimental designs testing palliative care interventions are few and have had significant methodological issues limit the generalizability of results. Regardless of design, attention to sampling issues is needed during design, conduct, and reporting of results for internal and external validity.[11,17,19,20,47,75]

Suggestions for improving scientific rigor in sampling design include (1) defining a target population that is consistent with research goals; (2) identifying objective eligibility criteria that are understandable to clinicians and that will yield a representative sample; and (3) reporting comprehensive information about the target population, sample eligibility/exclusions, and participation. Ultimately replication of studies of PCP models in a variety of samples will allow programs to determine clinical applicability in a cost-effective manner.

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MEASUREMENT ISSUES IN CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY (CIPN)

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ABSTRACT

Purpose: To evaluate objective and subjective measures of chemotherapy-induced peripheral neuropathy (CIPN) used in cancer clinical trials.

Background/Significance: CIPN is a derangement in structure and function of peripheral nerves caused by chemotherapy. CIPN is an understudied side effect that can cause significant functional and quality of life impairments. Although, other chemotherapy toxicities have been minimized or eliminated (e.g. anemia, neutropenia, nausea/vomiting), CIPN remains a dose-limiting toxicity. However, CIPN presents clinical and research challenges because of its variable presentation, course, pattern of effects, and measurement issues. Clinician judgment, patient tolerance, and "objective" grading systems are used to determine when dose limits are reached.

Methods: Two MEDLINE searches of CIPN were conducted to investigate available CIPN measures and clinical chemotherapy trials reporting CIPN from 1980-October 2004.

Results: The first search yielded a variety of available objective and subjective measures of CIPN used in clinical trials **(Table 1)**. Nerve biopsy **(Fig. 1)** was infrequent illustrating patterns of axonal loss and/or demyelination. Several grading scales exist and rate patients on a combination of subjective and objective findings **(Fig. 2)**. Composite measures represent objective and subjective findings, but the parameters are standardized and a severity score is summed **(Fig. 3)**. Recently, self-report tools have been developed to standardize investigator-developed symptom checklists **(Fig. 4)**.
Within the second search, of 58 citations, 45 articles met criteria (reported CIPN and CIPN measurement; within a chemotherapy clinical trial) and were reviewed **(Fig. 5)**. Toxicity grading systems (e.g. NCI-Common Toxicity Criteria, WHO, ECOG) alone or in combination with other measures were the predominant CIPN assessment method (N=27). Other evaluations in order of most to least frequent included investigator-developed measures, clinical neurological examination , quantitative sensory testing (QST), nerve conduction studies (NCS), objective and quantitative tests, self-report scales, and composite measures (e.g. Total Neuropathy Score (TNS) nerve biopsy.

Conclusions: CIPN measurement lacks consistency across trials and there is no consensus on a "gold standard". Inter-scale and inter-rater reliability and validity varies. Hence, a great deal of the variability of incidence and severity between studies may be due to the measurement used rather than a difference in actual toxicity. Self-report questionnaires identify symptoms, however no tools rate the degree of functional or quality of life as a specifically from CIPN. Therefore it is difficult to evaluate the degree of toxicity and quality of life impairment that results from this common, dose-limiting toxicity.

Implications: Lack of precision in measurement can result in under-recognition and under-treatment of potentially dose-limiting CIPN. Standardized, reliable and valid measures could inform researchers and clinicians regarding true drug toxicity as well as the patient's symptom experience and quality of life effects.

METHODS

Two literature reviews were synthesized:

1) **CIPN Measurement Review**
- MEDLINE, CINAHL search, hand search of references, personal communication with measurement developers

2) Chemotherapy trials that reported CIPN
- MEDLINE, CINAHL search (search terms: chemotherapy, clinical trials, peripheral neuropathy; English language, 1980-2004) yielded 59 citations. Additional sources included reference lists, web sources, and personal communication with investigators.

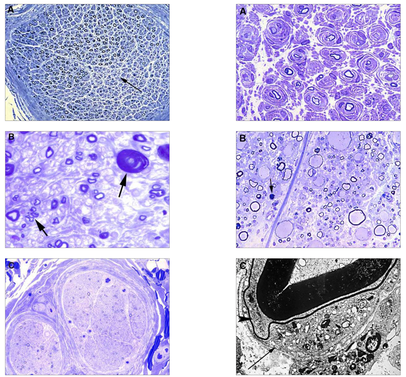
- Research reports met the following criteria:
  - 1) original report of chemotherapy trial or trial to test agents to prevent or reduce CIPN;
  - 2) peripheral neuropathy noted;
  - 3) CIPN measures described.

TABLE 1. CIPN OBJECTIVE & SUBJECTIVE MEASURES

Measure	Validity	Reliability	Sensitivity/ Specificity	Comments
Nerve Biopsy	N/A	N/A	Not for CIPN	To describe mechanisms
Nerve Conduction Studies EMG		Not in CIPN		Costly equipment Patient tolerance MD must do Does not correlate w/ clinical degree of CIPN
Quantitative Sensory Testing (QST) -light touch-pressure -vibration -sensory thresholds -heat/ cold thresholds	inconsistent	Not in CIPN		Costly equipment Technician/clinician can do Does not correlate w/ clinical degree of CIPN
Vibration Perception Threshold				
128 Hz Tuning Fork	*	Inter-rater	*	
CASE IV WR Electronics Minneapolis, MN	*		*	
Vibrameter SOMEDIC Stockholm, SW	*	Test-retest Intra-rater Inter-rater	*	
Vibratron II Physitemps Instruments Inc. Clifton, NJ	*	Test-retest Inter-rater		
Grading Systems WHO ECOG NCIC-CTC NCI-CTC CTCAE	inconsistent	inconsistent	poor	Inexpensive Clinician/Technician can do Poor agreement among scales
Composite Measures				
TNS	*	*		Addresses need to include subjective and objective data
TNSr	*	*		Additional reliability/ validity needed
Self-Report Measures				
FACT-GOG/NTX & TAXANE	Known groups	Alpha (0.84-0.86)	1 study-superior to VPT	Additional psychometrics needed Developed w/ limited patient input
EORTC-CINP20	Not reported	Not reported	Not Reported	In phase III field testing

- denotes data available
- VPT data adapted from (Ruppert & Croarkin, 2003)

FIG. 1 NERVE BIOPSY



Axonal Degeneration and Loss
(Axonal neuropathy)

Demyelination/ Remyelination
(onion bulbs)
Demyelinating Neuropathy

FIG. 2 CIPN MEASURES - GRADING

Scale	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO	None	Paresthesia and/or decreased tendon reflexes	Severe paresthesia and/or mild weakness	Intolerable paresthesia and/or marked motor loss	Paralysis
ECOG	None	Decreased deep tendon reflexes, paresthesia, mild constipation	Absent deep tendon reflexes, severe paresthesia, severe constipation, mild weakness	Disabling sensory loss, severe peripheral neuropathy, severe obstipation, severe weakness, bladder dysfunction	Respiratory dysfunction secondary to weakness, paralytic ileus requiring surgery, paralysis confining patient to bed/wheelchair
NCIC-CTC Neurosensory	None or no change	Mild paresthesia, loss of deep tendon reflexes	Mild or moderate objective sensory loss, moderate paresthesia	Severe objective sensory loss or paresthesia that interfers with function	-
Neuromotor	None or no change	Subjective weakness, no objective findings	Mild objective weakness but no significant impairment of function	Objective weakness with impairment of function	Paralysis
Ajani Sensory	None	Paresthesia, decreased deep tendon reflexes	Mild objective abnormality, absence of deep tendon reflexes, moderate paresthesia, functional disturbance	Severe paresthesia, moderate objective abnormality, severe functional disturbance	Complete sensory loss, loss of function
Motor		Mild or transient muscle weakness	Persistent moderate weakness but ambulatory	Unable to ambulate	Complete paralysis
NCI-CTC – v.2 Neuropathy – cranial	Absent		Present, not interfering with activities of daily living	Present, interfering with activities of daily living	Life-threatening, disabling
Neuropathy – motor	Normal	Subjective weakness, but no objective findings	Objective weakness interfering with sports, but not interfering with activities of daily living	Objective weakness interfering with activities of daily living	Paralysis
Neuropathy – sensory	Normal	Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	Sensory loss or paresthesia interfering with activities of daily living	Permanent sensory loss that interferes with function

Scale	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE – v.3 Neuropathy – cranial CN I – CN XII	Asymptomatic, detected on examthesing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy – motor	Asymptomatic weakness on examthesing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g. cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
Neuropathy – sensory	Asymptomatic; loss of deep tendon reflex or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death

Abbreviations: ADL=activities of daily living; CN=cranial nerve; CTCAE=Common Terminology Criteria for Adverse Events; ECOG=Eastern Cooperative Oncology Group; NCIC-CTC=National Cancer Institute of Canada-Common Toxicity Criteria; NCI-CTC= National Cancer Institute Common Toxicity Criteria; WHO=World Health Organization; Adapted from : Pavlina, et al. Annals of Oncology 9:739-744, 1998

FIG. 3 COMPOSITE MEASURE - TNS

	Score				
Parameter	0	1	2	3	4
Sensory symptoms	None	Limited to fingers or toes	Extend to ankle or wrist	Extend to knee or elbow	Extend to above knee or elbows/functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Require help/assistance
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild weakness (MRC 4)	Moderate weakness (MRC 3)	Severe weakness (MRC 2)	Paralysis (MRC 0 or 1)
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	All reflexes reduced	All reflexes absent
Sural amplitude	Normal/reduced <5%	76-95% of LLN	51-75% LLN	26-50% LLN	0-25% LLN
Peroneal amplitude	Normal/reduced <5%	76-95% of LLN	51-75% LLN	26-50% LLN	0-25% of LLN
*Autonomic symptoms	0	1	2	3	4 or 5
*Vibration sensation (QST vibration),% ULN	Normal to 125	126-150	151-200	201-300	>300

MRC = Medical Research Council; ULN= upper limit of normal; LLN = lower limit of normal; QST=quantitative sensory test
*Italicized items are excluded in "reduced TNS" (rTNS) without adversely affecting reliability
TNSr Score range (0-28)
Adapted from: Cornblath et. al. Neurology 1999;53: 1660-1664; Chaudhry, et al. Neurology 2003;60:337-340; Cavaletti et al. Neurology 2003; 61:1297-1300

FIG. 4 SELF REPORT MEASURES

FACT-Taxane (Version 4)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1 I have a lack of energy	0	1	2	3	4
GP2 I have nausea	0	1	2	3	4
GP3 Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4 I have pain					
GP5 I am bothered by side effects of treatment					
GP6 I feel ill					
GP7 I am forced to spend time in bed					

EORTC QLQ – CINP20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :	Not at All	A Little	Quite a Bit	Very Much
31 Did you have tingling fingers or hands?	1	2	3	4
32 Did you have tingling toes or feet?	1	2	3	4
33 Did you have numbness in your fingers or hands?	1	2	3	4
34 Did you have numbness in your toes or feet?	1	2	3	4
35 Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36 Did you have shooting or burning pain in your toes or feet?	1	2	3	4

FIG. 5 REVIEW OF 45 CIPN CLINICAL TRIALS (1980-2004)

Chemotherapy Trials Reporting CIPN (N=45)
Of original 58 citations, 22 met criteria; 23 additional studies located through reference review

CIPN Incidence: mean 43% (range 10-100%)

Cancers Represented	# pts
"advanced solid tumors"	538
breast	1816
colorectal	793
gastric	56
glioma	18
gyn	979
head and neck	23
testicular	90
lung	860
multiple myeloma	65
sarcoma	34

Neurotoxic Drugs Represented (alone or combined):

Platinums-cisplatin, carboplatin, oxaliplatin

Taxanes-paclitaxel, docetaxel

Vincas-vincristine, vinblastine, etoposide, vinorelbine, vindesine

Other-thalidomide

Fig. 5a Study Review Demographics (N=45)

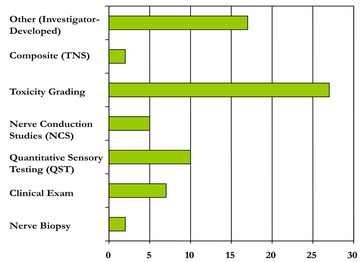


Fig. 5b CIPN Measures

CONCLUSIONS

- CIPN incidence varies due to drug, dose, patient variables, and measurement techniques. **"Dose-limiting toxicity"** criteria are not standardized.
- **Nerve biopsy** is not indicated for routine clinical diagnosis, but may define neurotoxic mechanisms of new agents.
- **Nerve conductions studies (NCS)**, considered the "gold standard" in evaluating polyneuropathy have limited utility in diagnosing CIPN. NCS and patient report lack concurrence.
- **Quantitative Sensory Testing (QST)** methods have limited utility in CIPN evaluation due to varying reliability, validity, sensitivity and specificity. It may be less sensitive than clinical examination.
- **Grading** scales predominate in CIPN clinical trial measurement but lack sensitivity and specificity.
- **Self report measures** show initial reliability & validity.
- **Composite measures (e.g. TNS)** standardize subjective symptom reports and neurological examination providing reliable & valid measurement.
- **Chemotherapy clinical trial reports lack comprehensive description of neuropathy symptoms, and functional status & quality of life effects.**

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Chemotherapy-Induced Peripheral Neuropathy (CIPN): Patient Perspectives on Continuing Neurotoxic Treatment

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BACKGROUND

Chemotherapy-induced peripheral neuropathy (CIPN) is a common, but understudied dose-limiting toxicity of chemotherapy with few options for prevention or management. CIPN has been identified as a research priority within the 2005-09 ONS Research Agenda. Empirical reports identify a wide spectrum of symptoms however data are lacking to explicate the specific symptom experience, functional effects and the factors that influence decisions to continue neurotoxic treatment. Within a larger study an over-aching metaphor and 4 themes were discovered to describe the CIPN symptom experience. One theme, "Learning How to Live with It" describes 3 coping processes and factors that influenced whether participants and clinician's decided to continue neurotoxic chemotherapy in the face of CIPN symptoms.

OVERALL STUDY AIMS

- 1). Describe the CIPN symptom experience from the patient's perspective.
- 2). Explore and describe the patient's experience of living with CIPN.

METHODS

- **Design:** exploratory, qualitative-dominant, descriptive, mixed methods
- **Instruments:** in-depth interviews
- **Data Analysis:** Verbatim transcribed interviews were coded and analyzed using Atlas.ti software to determine manifest content (symptom descriptions) and an over-arching metaphor and themes (latent content).

Table 1: Neurotoxic Drugs Received

	N (%)*
Taxanes	
Paclitaxel	**12 (43)**
Docetaxel	**7 (25)**
Platinums	
Cisplatin	1 (4)
Carboplatin	5 (18)
Oxaliplatin	3 (11)
Vincas	
Vincristine	2 (7)
Vinorelbine	5 (18)
Thalidomide	2 (7)
Bortezomib	4 (14)
Other	2 (7)
More than 1 Ntx drug	**12 (43)**

*#/(%) equals more that 28 (100%) as participants received more than 1 drug

TABLE 2: Description of the Sample N=28

Age (years)	59 ± 9.6 [range 46-81]
Characteristic	N (%)
Female	20 (71)
Married	24 (85)
Non-Hispanic white	28 (100)
Not employed	17 (60)
Some college	20 (71)
Time (mo) Since Cancer Diagnosis	**34 (median)** [range 3-198]
Type of Cancer	
Breast	**14 (50)**
Hematologic Malignancy	6 (21)
Ovary	3 (11)
Colon	3 (11)
Other	2 (7)
Disease/Treatment Status	
Early/adjuvant chemo	3 (11)
Late/1st line chemo	4 (14)
Rec/mets/2nd or >chemo	**16 (57)**
NED/ not receiving chemo	5 (18)
KPS	80% (mean)
90-80%	**21 (76%)**
<= 70 %	7 (24%)

CTCAE Toxicity

Grade	Motor	Sensory
1	**24 (85)**	10 (36)
2	2 (7)	**16 (57)**
3	2 (7)	2 (7)

RESULTS

CIPN: Background Noise in Everyday Life

Becoming Aware
Learning New Lyrics
Functional, Emotional, Social Cacophony

PARTICIPANTS' PERSPECTIVES ON CONTINUING NEUROTOXIC TREATMENT

Learning How to Live With It: Keeping CIPN in the Background

Facing the Music

- Tolerated CIPN to achieve cure or avoid death; used "emotion-focused coping"; relied on clinicians; rationalized, focused on CIPN as time-limited
- Exemplar Quotes:
  - *"I do whatever they tell me…*
  - *"I would have continued taking the chemo, no matter what…"*
  - *"It's the price I had to pay for staying alive";*
  - *"[It] was a desperation move… I had to do something [or] I'd die…I was facing the firing squad!"*

Adjusting the Volume

- When CIPN was severe, painful, or interfered with valued activities, participants used active problem-solving including: Self-care strategies, Medications / Referrals, Dose adjustments
- Exemplar Quotes:
  - *…[after] my last dose…I started getting [CIPN]…I didn't have any coordination or strength in my hands… [they] just didn't feel like my hands…I'm a painter and I write a lot and I couldn't really use my hands…they would numb up and I didn't have any endurance… I would shake them out but that didn't really help… [So] he sent me to (a specialist) [who] prescribed vitamin E and sent me to PT and OT for some strength-building and to get the nerves remembering what they were suppose to do"*
  - *"I just bolt thru things and that is what I did with the treatment the first time…But when you have a metastatic diagnosis you have to just say "oh I can't bolt thru this anymore". If it had been the last time, I'd say "give me as much as you can I can do it!!! I'm fine!!!"Now I have a different attitude. This time she (the doctor) said "we'll reduce the navelbine because of the neuropathy". My first reaction was, "NO, you can't do that … I'll be fine."… But then I thought "okay reduce the navelbine…".I think that's a big difference in how I'm approaching my life at this point…one day at a time…I just try to get through today."*

Tuning it Out

- Coping with mild, long-term or chronic residual CIPN; Strategies included minimizing; denying; ignoring.
- Exemplar Quote:
  - *"I'd think, 'No wonder that hurts. You've got a blister there! It's supposed to be hurting and you should have listened to the hurt'… I've learned to just not listen to it…I don't pay attention to it - even at times when I probably should".*

CONCLUSIONS

- Factors that influenced participants ability to cope with CIPN and decisions to continue neurotoxic treatment included:
  - Aspects of the Symptom Experience (e.g. Duration, Severity, Quality)
  - Functional Effects: Baseline function (age, gender, occupation), Social support
  - Goals of Treatment: Curative or Palliative

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