Effect of Complementary and Alternative Medicine on Pain Among Inpatients

Principal Investigator
Jeffery A. Dusek, PhD
Director of Research
Penny George Institute for Health and Healing
Abbott Northwestern Hospital

Study Team Members
Pamela Jo Johnson, PhD, MPH
Jon Christianson, PhD
Jill Johnson, PhD, MPH
Michael Finch, PhD

Study Sponsor
National Center for Complementary and Alternative Medicine (NCCAM)
NCCAM Grant Number: AT006518-01
9000 Rockville Pike, Bethesda, Maryland 20892

Mail Route 33540
800 E. 28th Street
Minneapolis, MN 55407-3709

1. Background, Rationale, and Purpose

Our *long-term objective* is to develop a comprehensive understanding of the cost effectiveness of offering Complementary and Alternative (CAM) therapies to hospital inpatients and the impact of CAM therapies on a broad array of patient outcomes. As part of this long-term effort, the ***goal of the proposed research*** is to study a model for the delivery of CAM therapies and to evaluate the effectiveness of CAM therapies for pain management among inpatients in a large acute care hospital.

While current pain management guidelines emphasize pharmaceutical interventions, these interventions increase the incidence of adverse events, potential for addiction, and adverse impact on recovery if used excessively.[1,2] Nowhere is this more evident than in the post-operative period where roughly 80% of patients report moderate to severe pain after surgery even after receiving pharmaceutical interventions.[3] In a 2009 New England Journal of Medicine article, Dr. Jean Woodcock (former head of FDA) writes that despite promising non-pharmacologic approaches to managing pain, pain is still most often treated with analgesics even though risk and safety issues are associated with their use.[4] The issues with traditional pain approaches are "undertreatment" and "overtreatment" with the former leading to residual pain and the latter resulting in the potential for adverse events. An integrated approach, utilizing both CAM and traditional pain management strategies, could address residual pain and result in a wider therapeutic margin for providers.

A. Previous research: CAM for pain management

Several systematic reviews report the efficacy of (non-pharmacologic) CAM approaches to pain management in hospitalized, surgical patients.[5-7] As shown in Table 1, 10 studies demonstrate short-term effects of CAM on pre- and post-therapy patient-reported pain scores,[8-17] whereas one study found no short-term change in pain.[18] Four studies have examined long-term effects of CAM on pain reduction several hours after CAM therapy.[12,13,16,19]

Table 1: Studies of efficacy of CAM for pain management in hospitalized patients.

Author (year)	Type of Study	IM Therapy	Control	Short	Short term % Pain Reduction	Long Term (Hours)	Long Term % Pain Reduction	Time points	Patient Type (n=)
Mitchinson (2007)[8]	RCT	Massage	Routine care or individual attention	X	19%*				Surgical: thoracic, abdominal (n=605)
Albert (2009)[18]	RCT	Massage	Usual care	X	0%#				Surgical: cardiac (n=252)
Cutshall (2010)[9]	RCT	Massage	Standard care/20 min. quiet time	X	72%*				Surgical: cardiac (n=53)
Grealish (2000)[10]	NRT	Massage	Complete quiet activity in bed	X	39%				Oncology (n=87)
Smith (2002)[11]	NRT	Massage	Nurse interaction	X	23%				Oncology (n=41)
Weinrich (1990)[12]	RCT	Massage	10 min visitation	X	30%*	X	1 hr: 27.7%*, 2 hr: 43.2%*	1,2 hrs	Male Oncology (n=28)
Wang (2000)[13]	RCT	AQ	Placebo AQ	X	31%*	X	0.5 hr: 40.7%*, 1hr: 48.2%*, 2 hr: 54.6%*, 6 hr: 63.4%*	0.5, 1, 2, 6 hrs	Surgical: spine (n=132)
Mehling (2007)[19]	RCT	Massage + AQ	Usual care			X	32.4%*	~3 hrs	Surgical: cancer (n=138)
Wang (2004)[14]	PP	AQ	No control	X	50%				Surgical (n=17)
Currin (2008)[15]	PP	Massage	No control	X	43%				Oncology (n=251)
Jane (2009)[16]	PP	Massage	No control	X	43%	X	0.5 hr: 48.1%*, 1 hr: 42.6%*, 1.5 hr: 44.4%*, 2 hr: 40.7%*	0.5, 1, 1.5, 2 hrs	Oncology: metastatic bone pain (n=36)
Adams (2010)[17]	PP	Massage	No control	X	55%				Surgical/Medical and OB (n=53)

Legend: RCT= randomized controlled trial, NRT= non-randomized trial, PP= Pre-post study, RO= Retrospective Observational study. AQ= acupuncture. # =Not significantly different than control. * =Significantly different than control group.

Although the efficacy of non-pharmacologic CAM therapies to reduce pain has been demonstrated, there is limited understanding of the effectiveness of CAM therapies in applied settings. While randomized controlled trials are the gold standard for clinical efficacy research, careful observational studies are required to understand the effectiveness of interventions without artificial constraints.[20-22] Observational studies provide an opportunity to assess which CAM therapies are acceptable to patients and clinical care providers as actually implemented in conventional treatment settings[23,24] and in large collaborative non-research settings.[25,26]

Despite the need for effectiveness studies to inform the practical employment of CAM therapies for pain management, there are only two published studies which assessed the effectiveness of CAM on inpatient pain management.[27,28] Cassileth and Vickers[27] conducted a retrospective observational study to investigate whether massage therapy affected self-reported pain scores in hospitalized cancer patients. Patients were referred by a medical professional for the massage intervention. Before and again after the massage, patients provided a written pain score. The initial massage visit yielded a 40% decrease in immediate pain. Within 2 to 5 hours after completion of the massage, pain was re-assessed in a sub-sample of patients. While pain rebounded above the post-intervention level, it remained below the pre-intervention pain level.

Our research team recently published the second study, which examined the effectiveness of CAM on inpatient pain management.[28] Similar to the previous study,[27] patients were referred by medical personnel for treatment and patients provided a self-reported pain score prior to and immediately after the CAM therapy. Extending the work of Cassileth and Vickers, however, our research included a broader array of CAM therapies, including mind/body, acupuncture, massage or combinations of these therapies. Further, we examined data from multiple clinical populations (cardiac, orthopedics, spine, rehabilitation, medical and surgical, and women's health). We found that the initial CAM visit yielded an average immediate pain reduction of 56% and that 33% of these patients reported complete pain relief after receiving the CAM therapy.

We recognize important inadequacies of these two retrospective studies that limit both our knowledge of how CAM therapies are implemented in hospitals and the effect of various CAM therapies on pain management. These include incomplete information about: (1) which patients are referred for CAM pain management; (2) which patients benefit most from receiving CAM therapies; (3) whether there are differential effects of pain reduction for specific CAM interventions; (4) the dose of CAM therapies required for short-term pain reduction; and 5) the duration of pain relief for these CAM interventions. **The proposed research is aimed at addressing these important limitations.**

B. Implications for knowledge and clinical practice changes: Improved integration of CAM therapy and usual care to improve pain management

The percent of hospitals providing CAM to inpatients nearly doubled from 2004 to 2007 (8% to 15%), with continued rapid growth expected.[29,30] While CAM therapies can be used to address many symptoms, the most common in the inpatient setting is residual pain experienced after treatment with usual care (e.g., opioids and other analgesics).

Answers to the above questions will inform the clinical practice of both CAM providers and physicians. Specifically, we will examine the differential effect on pain of different CAM therapies, which patients respond to which therapies, and evidence of the dose and duration of pain relief. In addition, our results will provide hospitals with a clear model of how CAM can be delivered in acute care settings. **Taken together, this information will address many of the traditional barriers in hospitals to the integration of usual care and CAM therapy for pain management.**

2. Investigator Qualifications

Jeff Dusek, PhD, is the lead investigator. Dr. Dusek currently serves as the Research Director of the Penny George Institute for Health and Healing and as Research Director of the Integrative Health Research Center for Allina's Center for Healthcare Innovation (CHI). For over a decade, Dr. Dusek has demonstrated a record of successful and productive projects of high relevance for the field of CAM. His role in this study will include oversight of data collection and management as well as assisting with data analyses and dissemination.

Pamela Jo Johnson, MPH, PhD, Co-Investigator, is a Research Investigator, Senior Research Consultant for the Healthcare Equity Research program at Allina Health, Adjunct Assistant Professor of Epidemiology & Community Health in the University of Minnesota School of Public Health with graduate faculty appointments in Health Services Research and in Population Studies and Assistant Professor in the Center for Spirituality & Healing, University of Minnesota. Her research interests are focused on healthcare disparities, complementary and alternative medicine/integrative healthcare, and women's health. Dr. Johnson has extensive experience with

health services research, medical statistics, analytic techniques for complex survey data, and methods for non-experimental, observational studies. Dr. Johnson will assist with data analyses and dissemination for this study.

Dr. Jon Christianson, a health economist, is the James A. Hamilton Chair in Health Policy and Management at the University of Minnesota. He is an expert in the use of quantitative and qualitative data to evaluate large-scale organizational redesign efforts and has written extensively on the implementation of evidence-based treatment processes in healthcare organizations. Dr. Christianson has a well-established relationship with Allina, as he is currently Co-Investigator of a large randomized trial examining care coordination in clinics conducted by the Center for Healthcare Innovation. Dr. Christianson will assist with data collection, data analyses, and dissemination for this study.

Michael Finch, PhD, is a methodologist and currently an independent research consultant and an Adjunct Associate Professor at the University of Minnesota with appointments in the Division of Health Services Research and the Carlson School of Management's Department of Finance. Dr. Finch recently co-authored a book with Dr. Christianson exploring the experience of different hospitals across the United States in use of CAM. He also has an established relationship with Allina's George Institute and recently co-authored the paper on CAM and pain change with Dr. Dusek. For this study, Dr. Finch will assist with data analyses.

Jill Johnson, PhD, MPH, is a Senior Scientific Advisor at the Penny George Institute for Health and Healing and the Integrative Health Research Center for Allina's Center for Healthcare Innovation (CHI). Dr. Johnson is an epidemiologist with an extensive and broad background analyzing, interpreting, and publishing basic, epidemiologic, and clinical studies. Dr. Johnson will assist Dr. Dusek with oversight of data collection and management and will contribute to data analysis and dissemination.

3. Study Hypothesis and Objectives/Specific Aims

Our proposed research is an **observational study of a model for the delivery of CAM therapies and an evaluation of the effectiveness of CAM therapies for pain management** in an acute care inpatient hospital. Specifically, we plan to study the use of CAM therapies as a complement to usual pain control regimens in an acute care setting where CAM modalities are in routine use. Additionally, we would like to explore the interaction between pain and anxiety. To accomplish this, we will address the following *specific aims*:

Aim 1a: Quantitatively describe a model for delivering CAM therapies to understand selection of patients and CAM therapies for pain management. We will use a series of binomial and multinomial logit models to describe the process by which patients are referred, triaged, assessed, and finally treated with CAM for pain management. Controlling for patient demographics, clinical group characteristics, and time from admission, these models will allow us to predict: 1a) which patients are referred for CAM, 1b) of those referred, which patients are seen by a CAM provider, 1c) of those seen by a CAM provider, which patients are in pain, and 1d) of those patients in pain, which CAM therapy is provided to address their pain.

Aim 1b: Qualitatively describe the referral and data collection processes. Through interviews of administrators, physicians, nurses, IM practitioners, and research assistants dedicated to this study, we will qualitatively describe the process by which patients are referred, triaged, assessed, and finally treated with CAM for pain management to:

1) More thoroughly understand the effectiveness and acceptance of our data collection methodology, and
2) Understand the influence of physicians, nurses, and administrators' own attitudes and beliefs towards integrative care, their personal experience with integrative care, and the experience of their patients on making referrals for integrative care.

Aim 2a: Examine the effects of selected CAM therapies on immediate change in pain. We will examine the effectiveness of Mind Body (MB), Massage (MA), and Acupuncture (AQ) therapies alone, or in combination, on self-reported pain measured just before and immediately after service delivery. Analyses will include an assessment of the effects of type(s) of CAM therapy and CAM therapy dose (i.e., minutes of service) on self-reported immediate pain change accounting for differences in demographic (including street address), clinical, and CAM visit characteristics among patients. Differential effects of CAM on immediate pain change will also be examined for selected subgroups (e.g., clinical group, initial pain status). Specifically, we will: 2a) estimate the effect of CAM type(s) on amount of immediate pain change, and 2b) estimate the effect of CAM dose (in minutes) on amount of immediate pain change.

Aim 2b: Comparison of the effects of CAM therapies vs other pain management strategies (i.e., pain medications) on self-reported pain. Analyses will include a comparison of the immediate pain score changes in the patients receiving CAM vs patients who do not receive CAM. Since the cost effectiveness of CAM interventions for symptom relief is important for the Allina Health system, this aim will also compare the cost effectiveness of pain management interventions across these two groups.

Aim 3: Examine the effects of selected CAM therapies on duration of pain change. We will examine the effectiveness of MB, MA, AQ alone, or in combination, on repeated measures of self-reported pain and anxiety over several hours after therapy to assess the distribution and decay of the pain change effect. Assessment of the effects of type(s) of CAM therapy and CAM therapy dose on duration of pain change will be explored using techniques for repeated measures and accounting for differences in patient characteristics as above. Growth curve models will be used to estimate the shape of the pain change curve overall and for selected subgroups. We will: 3a) estimate the duration of pain change and the shape of the pain curve by CAM therapy type(s), and 3b) estimate the duration of pain change and the shape of the pain curve by CAM therapy dose.

3. Study Procedures

Aim 1a The George Institute receives referrals from physicians, nurses and allied health professionals on a daily basis. A patient, family or friend may also request a referral, but a nurse or physician must approve and submit the referral through the hospital's electronic health record (EHR). Acupuncture referrals require a specific physician order and patients are required to sign a consent form to receive acupuncture.

The George Institute maintains 50-60 ongoing patients and obtains 25-35 new referrals daily. An average daily staffing of 10-13 practitioners provide CAM services to 60-65 patients each weekday. Each weekday morning the providers meet as a group to triage cases. During the triage meeting, providers review current patient load and new referrals are assigned to an appropriate CAM provider, who serves as the care coordinator for the duration of the hospital stay or until a patient is discharged from the CAM service. Whether a specific patient is seen by the provider depends on the number of referrals the CAM provider is assigned, the number of hours the provider works, and the availability of the patient when the provider arrives at the patient's room. After the triage meeting, providers review the priority in which their assigned patients will be seen. Priority depends on the urgency of the request, patient condition, the proximity of patients and patient availability.

Prior to providing a CAM therapy to the patient, practitioners complete an assessment which involves: (1) reviewing the patient's record; (2) communicating with the patient's traditional care provider; and (3) completing a formal face-to-face assessment with the patient.

The target population for Aim 1 (describing CAM referral and service delivery decision making) is all Abbott Northwestern Hospital inpatients during the data collection period. Subsets of those patients will be selected for analysis for the sub-aims based on their referral status for CAM and whether they received services from a CAM provider. Because the data used to examine Aim 1 are collected for clinical purposes and available in the EHR for all patients admitted to the hospital, referred for CAM, and seen by a CAM provider, the sample for this portion of the study will be accessed through electronic health record extraction based on dates of admission and discharge within the study time period.

Aim 1b We will conduct an interview-based qualitative study among Abbott Northwestern employees/consultants in the same clinical service lines used for the other aims of the study: Cardiovascular, Mother Baby, Neuroscience & Spine, Orthopedics, and Oncology.

Research Director, Dr. Jeff Dusek, will initially propose the study to potential participants via an email letter. In the case of low response rates, a second contact may be made via hard copy letter or telephone call. A 'Common Questions' document and a consent information document will accompany the email letter and the hard copy letter (when applicable) and will provide additional details on the study. If a potential participant is interested in learning more about the study and/or scheduling an interview, they are asked to contact study staff.

In each of these service lines, we will interview the following: physicians and nurses who have the opportunity to refer patients for integrative medicine services; hospitalists who have the opportunity to refer patients for integrative medicine services; and administrators of the aforementioned service lines. In addition, we will interview Integrative Medicine practitioners who provide integrative services and research assistants (RAs) from the Integrative Health Research Center who are collecting the quantitative data for Aim 3.

One 30-45 minute visit will be required of each participant and it will take place at a scheduled appointment time convenient to the participant. For physicians and administrators, research staff will consent and conduct interviews in the physician/administrator's office. For nurses and IM practitioners, participants will be asked to come to the Integrative Health Research Center (IHRC) for consenting and interviews. IHRC has two private rooms available for patient consent and study procedures. For RAs, research staff will consent and conduct interviews in a private conference room located outside of the IHRC.

Aims 2a, and 2b In deciding which CAM therapy to provide to a patient, practitioners discuss the proposed treatment options with the patient prior to delivery of the therapy. Practitioners use their clinical judgment to provide whichever CAM therapies, within their scope of practice, they deem necessary and therapeutic to reduce pain in a given patient. CAM visits average 25 minutes in duration and are provided in patients' rooms at no expense to patients. Before beginning a treatment, CAM providers ask patients to rate, on a scale of 0 to 10, their current level of pain. After the treatment, CAM providers again ask patients to rate their pain on a scale of 0 to 10. Providers then discuss treatment and/or discharge goals and, before leaving a patient's room, set expectations for follow up treatment visits.

Aim 3 Aim 3 requires the collection of repeated follow up measures for the same group of patients as Aim 2a and 2b, but will require active consent. Once a patient is identified by the CAM provider as part of the target population for Aims 2 and 3, and a pre pain score of >0 is obtained, they will call and refer a patient to a research assistant (RA). The RA will then check the patient's EHR to see whether or not the patient has consented to release his/her EHR information for research purposes. The RA will also check other eligibility requirements at that time. Once a patient has been identified as eligible, the RA will enter the patient's room and go through a verbal consent process with the patient for collection of additional pain and anxiety scores in six scheduled visits over five hours. Within those scheduled time windows for visits, if a patient is awake and available, the RA will collect the pain and anxiety scores. If a patient is not available, the RA will record the reason scores were not collected (out of room, sleeping, with physician, etc.)

4. Participants

Aim 1a The target population for Aim 1 (describing CAM referral and service delivery decision making) is all Abbott Northwestern Hospital inpatients during the data collection period.

A. Inclusion Criteria

- Admission to Abbott Northwestern Hospital
- Consent to release of electronic health record for research purposes
- 18 years of age or older Length of stay greater than 24 hours

B. Exclusion Criteria

- None

Aim 1b The study population for Aim 1b is comprised of the following individuals:

- 24 physicians: two high and two low CAM referring physicians from Cardiovascular, Mother Baby, Neuroscience & Spine, Orthopedics, and Oncology Clinical Service Lines and the Hospitalist service.
- 20 nurses: two high and two low CAM referring nurses from Cardiovascular, Mother Baby, Neuroscience & Spine, Orthopedics, and Oncology Clinical Service Lines.
- 7 administrators of the Cardiovascular, Mother Baby, Neuroscience & Spine, Orthopedics, and Oncology Clinical Service Lines and the Hospitalist service.
- Integrative medicine practitioners who provide services to Cardiovascular, Mother Baby, Neuroscience & Spine, Orthopedics, and Oncology Clinical Service Lines inpatients.
- Research Assistants from the Integrative Health Research Center who enroll patients and collect data.

All Integrative Medicine practitioners and Integrative Health Research Center research assistants will be identified from the AKN or staff rosters provided by department management.

To identify prospective physician and nurse participants based on referrals, data will be obtained from the Electronic Data Warehouse (EDW). Using the 'Orders' file from EMR, three order codes will be retrieved: 207179-Acupuncture Evaluation and Treatment, 207180-IP Consult to Integrative Medicine, and 207853-

Nursing Consult to Integrative Medicine. Authorized provider and order writer names will be extracted from the file, and the physicians and nurses will be categorized according to specialty/location: hospitalist (MDs only) or clinical service line (Oncology, Cardiovascular, Mother Baby, Orthopedics and Neuroscience & Spine). Specialty/location designation will be determined by physician and hospitalist rosters obtained from the Medical Staff department and nursing rosters obtained from the Nursing department at Abbott Northwestern. Within each of the clinical service line/hospitalist and nurse groups, frequencies will be obtained to determine high, moderate, and low authorized providers for physicians and nurses. Within the high and low distribution groups, people will be randomly selected by a computer program for participation in the study. Random selection of participants will occur until two interviews are completed from both the high and the low referring groups. Dependent on accrual rates, a convenience sampling approach may be adopted.

To minimize the effects of employment length on referral rate, we will only count referrals from nurses and physicians who have continuously worked at Abbott Northwestern Hospital and had referral privileges for the previous year. Physician and nurse staff rosters will be used to identify years/dates of employment.

A. Inclusion Criteria:

- Abbott Northwestern Hospital administrator of one of the following Clinical Service Lines: Cardiovascular, Mother Baby, Neuroscience & Spine, Orthopedics and Oncology.
- Abbott Northwestern Hospital hospitalist, physician or physician with consulting privileges for one of the following Clinical Service Lines: Cardiovascular, Mother Baby, Neuroscience & Spine, Orthopedics, and Oncology.
- Abbott Northwestern Hospital nurse for one of the following Clinical Service Lines: Cardiovascular, Mother Baby, Neuroscience & Spine, Orthopedics, and Oncology.
- Abbott Northwestern Hospital Integrative Medicine practitioner who currently delivers services to patients or who delivered services to patients during a portion of quantitative data collection.
- Research Assistant at the Integrative Health Research Center, Penny George Institute for Health and Healing, Abbott Northwestern Hospital who enrolls patients and collects data on study AT006518-01 Phase II Abbott Northwestern Hospital Pain Study.
  And:
- For physician and nurse participants: Must have made at least one patient referral for integrative medicine services.

B. Exclusion Criteria:

- None

Aims 2a and 2b The target sample for Aim 2 is all Abbott Northwestern Hospital inpatients within the data collection period including both patients who did and did not receive CAM services.

A. Inclusion Criteria

- Admission to Abbott Northwestern Hospital
- Consent to release of electronic health record for research purposes
- 18 years of age or older
- Length of stay greater than 24 hours

B. Exclusion Criteria

- None

AIM 3 The target sample for Aim 3 is all Abbott Northwestern Hospital inpatients within the data collection period who received CAM services. It is anticipated that we will need to consent 7,000 participants in order to obtain enough data on approximately 3,575 participants.

A. Inclusion Criteria

- Admitted to Abbott Northwestern Hospital
- Length of stay greater than 24 hours
- Consent to release of electronic health record for research purposes
- 18 years of age or older
- Received CAM therapy in current hospitalization

- Pain level of 1 or greater at the pre-treatment assessment by practitioner
- English-speaking
- Integrative medicine therapy ended between 9:00 am and 4:00 pm

B. Exclusion Criteria

- Refuses consent
- Unable to provide consent due to competency concerns
- Has declined study participation 3 times during current hospitalization
- Has hard declined during current hospitalization
- Has been approached 6 times during current hospitalization
- Has been approached to consent earlier that day

5. Consent Process

Aims 1a, 2a, and 2b Since all the data required for Aims 1 and 2 are in the EHR, we will follow Allina Health system-wide policies for EHR data use for research. Under this policy, all patients are asked for permission to use their electronic health data for research purposes. Traditionally, the IRB approves a waiver of consent for these data. This means that data from any patient who has indicated they are unwilling to share their medical record data for research purposes (historically 4%) will be excluded from the sample. For patients who have provided general research consent, we will extract data from the EHR which includes such data as patient demographics (including street address), clinical diagnosis, age, pre-therapy and immediate post-therapy pain and anxiety scores as well as cost data (i.e., billing records).

Aim 1b The informed consent process will take place at the beginning of the scheduled interview appointment time. Staff will verbally consent the study participants for collection of interview data and separately for the recording of responses.

Research staff conducting the informed consent process will introduce the study as an investigation to describe the referral, triage, assessment, and therapy decision process for the delivery of CAM in a large hospital. Consent will be obtained for participants in a private area – either the administrator or physician's office, the Integrative Health Research Center participant rooms, or a private conference room. The consent information sheet will be reviewed with participants by the research staff, and participants will be encouraged to ask questions throughout the process. Staff will stress that this is a voluntary study and that a participant is able to withdraw from the study at any time and their employment/consulting privileges at Abbott Northwestern/Allina Health will not be affected. Only individuals able to consent of their own volition will be recruited.

Aim 3 If a patient has consented to release his/her EHR information for research purposes and meet all other eligibility criteria, they will be approached by a RA from the study. The RA will go through a verbal consent process with the patient and offer a study information sheet. The consent process will take place within the privacy of the patient's hospital room and time will be provided for the patient to ask any questions they may have. Only individuals able to consent of their own volitions will be enrolled in Aim 3. RAs will stress that this is a voluntary study and that a participant is able to withdraw from the study at any time without affecting the care they receive.

6. Data Quality and Safety Review Plan and Monitoring

A. Confidentiality

- Protection of Subject Privacy / Data – When information collected during the visit becomes part of the EHR, these data will become subject to all the privacy, confidentiality, and protection offered by Allina's EHR system, which is bound and protected by HIPAA. Although stored in an internal database separate from the EHR, the repeated pain scores (Aim 3) and interviews (Aim 1b) will be under the same level of protection. All Allina EHR data are strictly protected by password-only access, secure data archival practices, and data encryption. EHR data will only be extracted for patients who have a signed HIPAA data release form in the medical record indicating they have explicitly authorized use of their EHR data for purposes of research. Patient data that resides in the EHR will be accessed only by physicians and clinic staff and project investigators will not require access to data on an individually identifiable basis. Data security will be monitored through monthly scheduled audits, ensuring only staff from the research team are able to get to and use study data.

The majority of data used for this study is part of standard clinical practice data collection, and thus part of the patient's EHR. All EHR data will be subject to the same stringent access and security as currently applied to the EHR according to HIPAA standards. Additional measures, primarily follow-up pain scores for sub-study in Aim 3 will not become part of the patient's EHR, but will be stored in a secure database using an internal Allina application that is linked to the EHR via each patient's unique medical record number and hospital stay number. Data from these two sources (internal database and EHR) will be extracted and linked together for analyses. Data to be analyzed by the investigators of this project will have been stripped of personal identifiers and all results will be presented in aggregate.

Disruption of patients participating in the sub-study for Aim 3 will be minimized by not waking patients or interrupting care by medical providers. Additionally patients have the option of refusing any single measurement or dropping out of the study entirely.

Patients under the age of 18 will not be included in the study so there are no issues related to participation and protection of minors.

B. Confidentiality During AE Reporting

AE reports and annual summaries will not include subject-identifiable material. Each will include the identification code only.

C. Adverse Event Information

Definition – An adverse event (AE) is any untoward medical occurrence in a subject temporally associated with participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.) or any combination of these.

A Serious Adverse Event (SAE) is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- Important medical event based upon appropriate medical judgment

Classification of AE Severity – The investigators will monitor participants, and document and report any undesirable experiences and/or events that occur during the course of the study. Severity will be determined by the PI using the following categories:

Mild: Does not adversely impact (in any way) the subject's course of wellness or illness.
Moderate: Impacts the subject's course of illness but is not life-threatening or incapacitating.
Severe: Fatal, life threatening, permanently disabling; severely incapacitating; requires/prolongs hospitalization.

AE Attribution Scale – AEs will be categorized according to the likelihood that they are related to the study intervention.

Not related: The event is clearly related to factors such as the subject's clinical state, not with therapeutic interventions associated with the study protocol.
Remote: The event was most likely related to factors such as the subject's clinical state, not with therapeutic interventions associated with the study protocol.
Possible: The event follows a reasonable temporal sequence from initiating the intervention, but is possibly related to factors such as the subject's clinical state.
Probable: The event follows a reasonable temporal sequence from initiating the intervention and cannot be reasonably explained by factors such as the subject's clinical state.
Highly Probable: The event follows a reasonable temporal sequence from initiating the intervention and cannot be reasonably explained by factors such as the subject's clinical state. In addition, the

event occurs immediately following intervention or as a direct result of intervention-initiated procedures.

Expected Risks – Due to the nature of this project, adverse events are expected to be minimal. Providing pain scores is extremely low risk for adverse events. There is potential risk for invasion of privacy, including use of personal information or the improper disclosure of information. Patients participating in the sub-study for Aim 3 with repeated follow-up pain measures may experience some disruption of their schedule. The risk and inconveniences are addressed in the protocol and consent form. Staff will be trained to keep all written and electronic data secure and confidential.

SAE Reporting – SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the IRB and NCCAM in accordance with requirements.

Safety Review Plan – Study progress and safety will be reviewed yearly. AEs will be provided to the Independent Monitors yearly. An annual report will be compiled and will include a list and summary of AEs. In addition, the annual report will address (1) whether adverse event rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; and (3) whether all participants met entry criteria. The annual report will be signed by the Independent Monitors and will be forwarded to the IRB and NCCAM. The IRB and other applicable recipients will review progress of this study on an annual basis.

D. Monitoring

Per NIH requirements, Dr. Dusek will submit the Data and Safety Monitor's annual report to NCCAM.

Data Quality and Management and Subject Accrual

Description of Plan – Data security will be monitored through monthly audits, ensuring only staff from the research team are able to get to and use study data.

Data integrity for Aim 3 relates primarily to the repeated measures collected by the RAs as well as study consent materials. After training, RAs will be shadowed by the PI, Co-Investigator, or Research Coordinator for a select number of patients to ensure that RAs are appropriately following the protocol for eligibility screening, study consent, and data collection. Repeated measures data quality monitoring will be examined by a senior research staff member to examine differences in the data collection protocol by RA. Any differences identified will be addressed through re-training, and more intense supervision of RAs.

Frequency of Data Review for this Study – Dr. Mary Jo Kreitzer and Dr. Patricia Herman will be the independent health care professionals serving as the Data and Safety Monitors. Dr. Kreitzer is the Director of Center for Spirituality and Healing at the University of Minnesota and Dr. Herman is a Research Scientist in the Health Outcomes and PharmacoEconomics Center at the University of Arizona. As shown in the table below, Drs. Kreitzer and Herman will monitor the quality of the collected data, summaries of study progress to ensure that the consent process documentation is properly obtained and stored on a quarterly basis. The monitors will also review subject accrual, enrollment and adverse events on a quarterly basis. The monitors will issue a report annually to the PI and the IRB, which will be forwarded to NCCAM.

Data type	Frequency of review	Reviewer
Subject accrual (adherence to protocol regarding demographics, inclusion/exclusion)	Quarterly	Principal Investigator, Independent Monitors

Adverse event rates (injuries)	Quarterly	Principal Investigator, Independent Monitors
Report	Yearly	Independent Monitors

7. Quantitative Statistical Analysis – Aims 1a, 2a, 2b, and 3

A. Data sources

Two sources of data will yield the information required to generate measures for analysis: **EHR data** generated by providers and **ancillary database records** generated by research assistants. Abbott Northwestern Hospital's electronic health record, an Epic product (Excellian®), contains patient demographic information, clinical information, CAM referral information, CAM provider triage outcomes, and CAM service delivery information (including detailed therapy information about each visit), and pre- and post-therapy pain and anxiety scores. ANW has had a fully-implemented EHR in place since July 2005.

In addition to data extracted from the EHR, research assistants will obtain verbal consent from patients who meet all eligibility criteria as noted above. If subjects consent, then the research assistants will collect six additional pain scores. The first pain score will be obtained from consented patients about 30 minutes after the immediate post-therapy pain score. The second pain score will be obtained 30 minutes after that, and then every hour after that up to five hours post-therapy. Anxiety scores will be collected similarly. The five hour follow-up time period was selected based on a synthesis of previous research.[12,13,16,19] Data for the pre and immediate post-service measures will be directly entered into the EHR. Subsequent pain and anxiety scores and information collected from the patient's EHR will be entered and stored into a password protected custom Microsoft Access research database along with a unique identifier to link to the EHR.

B. Data management & quality control

We will extract and create an analytic data set combining data from the EHR and the ancillary database, which will be imported into STATA (version 11), SPSS (version 18), or SAS (version 9.2) for analysis. In addition to the safeguards implicit in the electronic data collection we employ, we will conduct weekly quality checks to identify obviously erroneous and/or missing data. Validation rules will be imposed to detect invalid or out-of-range entries. Error reports will be generated and a research assistant will be charged with verification of proper values. Both missing and invalid data will be tracked to the original source of the data for verification. In cases where missing or invalid values cannot be corrected, we will use statistical methods to handle missing data (see end of analysis section).

C. Data elements

Dependent variables: For Aim 1a, we have four separate outcome variables: *CAMorder* is a classification of whether or not the patient had a CAM referral order entered into the EHR; *triage* is a three-category variable indicating the result of the triage process (i.e., patient seen; triaged to be seen, but not seen; and patient not seen); *pain* is a dichotomous variable indicating whether the patient was documented to have pain at the visit; and *CAM type*, which is an 8-category variable representing our seven CAM type(s) of interest (MB, MA, AQ, MB/MA, MB/AQ, MA/AQ, MB/MA/AQ) and a residual other.

For Aims 2a and 2b, our primary outcome variable is change in self-reported pain. *Pain change* will be modeled as the difference in self-reported pain from just before the CAM treatment and just after the CAM treatment (i.e. postpain-prepain). The pre and post pain scores will be collected by the CAM therapist. Nursing staff collect pain scores before and after all pain management interventions and these scores will be used in analyses comparing CAM and other pain management interventions on change in pain. For Aim 3, *duration of pain relief* is defined as the elapsed time from CAM therapy to sustained increases in self-reported pain. *Pain and anxiety scores* will be collected by the RAs as noted above. The corresponding curves will be modeled as a series of repeated measures up to five hours post therapy.

Independent variables and covariates: The primary independent variable and covariates for each analysis are shown in Table 2 below, where "DV" indicates dependent variable, "IV" indicates primary independent variable and "x" indicates covariate. For aims 2a, 2b and 3, the independent variables are *CAM type*, a set of

indicator variables for CAM therapy type (MB, MA, AQ, MB/MA, MB/AQ, MA/AQ, MB/MA/AQ) and *CAM dose*, which represents the amount of time (in minutes) the CAM therapy was delivered. Relevant covariates include: *demos* is a set of variables for patient demographic characteristics (e.g., sex, age, street address); *MDC* is a set of indicator variables representing aggregated medical diagnosis code groups; *M/S* is an indicator variable distinguishing medical and surgical patients; and *admtime* and *proctime* represent the time from admission and last major procedure, respectively, to CAM service; *referring unit* (refunit) is a set of indicator variables for the nursing unit that initiated the CAM referral; *camtime* is the time of day the CAM therapy was provided; *camprov* is an indicator for which CAM provider delivered the therapy; *camvis* represents the visit number (e.g., 1st, 2nd). *Opioid* and *NonOpioid* are two time-varying variables that represent the dose of either non-opioid or opioid analgesics translated into equivalent units of pain medication.[31]

Table 2. Summary of analytic variables by specific aim

			Specific Aims							
Variable	**Variable Description**	**Source**	**1.a**	**1.b**	**1.c**	**1.d**	**2.a**	**2.b**	**3.a**	**3.b**
camorder	CAM referral order (y/n)	EHR	**DV**							
triage	CAM triage outcome	EHR		**DV**						
pain	Pain as reason for visit (y/n)	EHR			**DV**					
camtype	CAM therapy type provided	EHR				**DV**	**IV**		**IV**	
camdose	Duration of CAM service	EHR						**IV**		**IV**
prepain	Pre-therapy pain score	EHR					**DV**	**DV**	**DV**	**DV**
postpain	Immediate post-therapy pain score	EHR					**DV**	**DV**	**DV**	**DV**
post30	Post pain 30 minutes	RA							**DV**	**DV**
post60	Post pain 1 hr	RA							**DV**	**DV**
post120	Post pain 2 hrs	RA							**DV**	**DV**
post180	Post pain 3 hrs	RA							**DV**	**DV**
post240	Post pain 4 hrs	RA							**DV**	**DV**
post300	Post pain 5 hrs	RA							**DV**	**DV**
DEMOS	Demographics (age, gender, etc.)	EHR	x	x	x	x	x	x	x	x
mdc	Major Diagnostic Category (MDC)	EHR	x	x	x	x	x	x	x	x
ms	Medical/Surgical indicator	EHR	x	x	x	x	x	x	x	x
admtime	Time from admission	EHR	x	x	x	x	x	x	x	x
proctime	Time from major procedure	EHR	x	x	x	x	x	x	x	x
refunit	Referring unit	EHR	x	x	x	x	x	x	x	x
camtime	Time of CAM assessment/service	EHR			x	x	x	x	x	x
camprov	CAM provider	EHR				x	x	x	x	x
camvis	CAM visit number	EHR					x	x	x	x
opioid	Time & dose of opioid analgesics	EHR							x	x
nonopioid	Time & dose of non-opioid analgesics	EHR							x	x

EHR = Electronic Health Record; RA = Research Assistant; DV = Dependent variable; IV = Indepndent variable; x = covariates

D. Analysis and interpretation of results

In this section, we briefly describe the analytic techniques to be used for Aims 1a, 2a, 2b and 3, followed by an overview of our statistical methods for handling missing data and our sample size estimates.

Aim 1a: Quantitatively describe a model for delivering CAM therapies so as to understand the selection of patients, and therapies, for pain management.

We will use a series of binomial and multinomial logit models to describe the process by which patients are referred, triaged, assessed, and finally treated with CAM for pain management. These models will allow us to predict: 1a) which patients are referred for CAM, 1b) of those referred, which patients are seen by a CAM provider, 1c) of those seen by a CAM provider, which patients are in pain, 1d) of those patients in pain, which CAM therapy is provided to address their pain. Below we outline the relevant patient population, dependent and independent variables for each of these questions.

1a.a Logistic regression model to predict who gets a CAM referral order

Population = all inpatients
Outcome = CAM referral order entered in EHR: yes or no
CAM order = demos + referring unit + MDC + M/S + admit time

1a.b Multinomial logistic regression model to predict who is seen by a CAM provider
Population = inpatients with EHR documented CAM order
Outcome = Triage status: 1-patient seen, 2-triaged to be seen but not seen, 3-patient not seen
Triage status = demos + referring unit + MDC + M/S + admit time

1a.c Logistic regression model to predict who is assessed with pain at CAM visit
Population = inpatients triaged for CAM service & assessed by CAM provider
Outcome = Practitioner assessed pain: yes or no
Pain status = demos + referring unit + MDC + M/S + admit time + camtime
(Note: We have added time of day (camtime) to control for the effects of circadian rhythm on pain)

1a.d Multinomial logistic regression model to predict what CAM therapy is provided
Population = inpatients assessed with pain as CAM visit focus
Outcome = CAM type: 1-MB, 2-MA, 3-AQ, 4-MB/MA, 5-MB/AQ, 6-MA/AQ, 7-MB/MA/AQ
CAM type = demos + referring unit + MDC + M/S + admit time + camtime + provider

For Aim 1a, all of our analyses are either binomial or multinomial logit. We will present for each model both the regression coefficients and the odds ratios for each category. We will use z-tests from the logistic regression output to assess the significance of the coefficients. Our discussion of these results will lie primarily with the odds ratios, because of their ease of interpretation. However, one disadvantage of odds ratios is that, because they are non-linear, they only reflect changes at the mean of the distribution. In our interpretation, we will also develop prototypic cases to illuminate effects at different points on the distribution.[32,33] In other words, we will calculate predicted probabilities for "ideal types" of patients, as defined by specific clinical and demographic characteristics.

Aim 1b: See Section 8 (Qualitative Data Analysis) below

Aim 2a: Examine the effects of selected CAM therapies on immediate change in pain.

We will examine the effects of MB, MA, and AQ therapies alone or in combination on self-reported pain change measured just before and immediately after service delivery. Analyses will include an assessment of the effects of type(s) of CAM therapy and amount of CAM therapy dose (i.e., minutes of service) on self-reported immediate pain change accounting for differences in demographic, clinical, and CAM visit characteristics among patients. Differential effects of CAM on immediate pain change will also be examined for selected subgroups (e.g., clinical community, initial pain status).

2a.a OLS model to estimate effect of CAM therapy type on amount of immediate pain change
Population = inpatients receiving MA, MB, AQ or any combination for pain
Outcome = amount of pain change (prepain - postpain)
Pain change = **CAM type(s)** + visit + demos + clinical

2a.b OLS model to estimate effect of CAM dose (in minutes) on amount of immediate pain change
Population = inpatients receiving MA, MB, AQ or any combination for pain
Outcome = amount of pain change (prepain - postpain)
Pain change = **CAM minutes** + visit + demos + clinical

Where: VISIT is a set of CAM visit characteristics (e.g., CAM provider, visit number [1st, 2nd, 3rd], time of day)
DEMOS is a set of patient demographic characteristics (e.g., age, sex)
CLINICAL is a set of clinical characteristics (e.g., referring unit, MDC, med/surg, admit time)

In addition to modeling results for the stated population, each model will be stratified by selected clinical communities and by initial pain score where sample size permits.

For aims 2a.a and 2a.b we will examine the data for violations of normality of the dependent variable using the Box-Cox procedure to determine the appropriate transformation as needed. For ease of interpretation, all results will be discussed in appropriately retransformed form.[34] We will estimate all standard errors using Stata's robust variance estimation option (Huber/White/sandwich estimator) to correct for violations of the

homoscedasticity assumption. We will also examine the possibility of non-linear relationships between the independent and dependent variables by introducing and testing various polynomial forms.

Interpretation of the effects of our analyses for Aim 2a is straightforward because the OLS estimators are linear. We will examine unstandardized effects (when comparing across populations) and both unstandardized and standardized effects when comparing within equations. This allows us to examine the effect of differing metrics of the independent variables.

Aim 2b: Comparison of the effects of CAM therapies vs other pain management strategies (i.e., pain medications) on self-reported pain.

2b.a OLS model to estimate effect of CAM therapies versus other pain management on amount of immediate pain change.
Population = all Abbott Northwestern Hospital inpatients
Outcome = Amount of pain change (pre-pain – post pain)
Pain change = **CAM type(s)** + demographics + clinical + opioid + nonopioid

Aim 3: Examine the effects of selected CAM therapies on duration of pain change.

We will examine the effectiveness of MB, MA, AQ alone or in combination on repeated measures of self-reported pain status over five hours after therapy to assess the distribution and decay of the pain change effect. Assessment of the effects of type(s) of CAM therapy and CAM therapy dose (in minutes) on duration of pain change will be explored using techniques for repeated measures and accounting for differences in patient characteristics as above. Growth curve modeling techniques are the current method of choice for estimating change over time.[35-38]

We will employ growth curve techniques as they overcome the many problems posed by traditional approaches such as repeated measures ANOVA and MANOVA. They are flexible and accommodate a number of problems typically encountered in repeated measures data collection, such as missing data and unbalanced designs. In addition, they are statistically more efficient than their predecessors and allow for both linear and non-linear estimation.

3.a Bayesian growth curve analysis to estimate the duration of pain change and the shape of the pain curve by CAM therapy type
Population = inpatients receiving MA, MB, AQ or any combination for pain
Outcome = repeated measures of pain change over time
Pain change = **CAM type(s)** + visit + demos + clinical + pain meds

3.b Bayesian growth curve analysis to estimate the duration of pain change and the shape of the pain curve by CAM therapy dose
Population = inpatients receiving MA, MB, AQ or any combination for pain
Outcome = repeated measures of pain change over time
Pain change = **CAM dose** + visit + demos + clinical + pain meds

Where: VISIT is a set of CAM visit characteristics (e.g., CAM provider, visit number [1st, 2nd, 3rd], time of day)
DEMOS is a set of patient demographic characteristics (e.g., age, sex, etc.)
CLINICAL is a set of clinical characteristics (e.g., referring unit, MDC, med/surg, admit time)
PAIN MEDS is two time-varying covariates that represent non-opioid and opioid analgesics

Similar to Aims 2a and 2b, in addition to overall models for Aim 3, we will stratify each by selected clinical communities and by initial pain score as sample size permits.

The interpretation of results for aim 3 will be presented in graphical form. Using the estimated parameters from the growth curve we will draw the curve for each population of interest. This provides a more intuitive view of the results than simply reporting the coefficients and very clearly illustrates both the amount and duration of pain reduction for each analysis. Duration of pain reduction will be defined as the inflection point of the growth curve after smoothing.

E. Treatment of missing data

As noted previously, during the data collection and quality control process, research assistants will attempt to verify any missing data through chart review or follow-up. Missing values will be flagged, documented, and manually corrected in the analytic database. When no additional information can be used to manually correct missing information, a statistical approach will be used.

Analytic datasets will be assessed to understand patterns of missing data (i.e., MCAR, MAR). Even in cases where data are missing completely at random (MCAR), we prefer not to case-wise delete because of the impact on sample size and standard errors. Rather, we will use accepted "hot deck" methods to impute missing data for the independent variables and covariates.[39] Specifically, we will use the *hotdeck* procedure for Stata to impute missing values.[40,41] Following standard practice, we will not impute missing dependent variables.

In the case of missing repeated pain measures for Aim 3, the approach to growth curves that we propose to use accommodates unbalanced designs and thus reasonable amounts of missing data pose no problem to the estimation of effects. As long as each subject has 2 or more repeated pain measures, they can be included in these models without biasing estimates of the models' coefficients.

F. Sample size estimation

Given our 5+ years of providing CAM at Abbott Northwestern Hospital, we have a reasonably good estimate of the number of patients who will receive each of the three CAM therapies to relieve their pain. We anticipate that, based on our current workflow, we will see approximately over 200 patients per month who receive a CAM therapy for pain management. We are planning for a 30 month data collection period, which will yield approximately 6,000 patients in our target population. There will of course be attrition at several steps of the process. The first is a patient's refusal to sign the general research consent for use of medical records for research purposes, which all patients are asked to sign at admission. At Abbott Northwestern Hospital, roughly 96% of all patients sign this consent. Data from individuals who do not provide this consent will neither be approached for study participation (Aim 3), nor will their medical records be used (Aims 1a, 2a, 2b). The second point of attrition will be missed opportunities, which result from the inability of an RA to respond to a therapist's request to recruit and consent a patient. We estimate this, from our experience shadowing therapists as they provide the CAM intervention, to be not more than 20% lost. Our last point of attrition is the patient's refusal to consent to the collection of additional pain scores (Aim 3). We estimate this to be no more than 25% as the additional data collection is both nominal and non-intrusive. Note that the second and third points of attrition do not affect the sample size for Aims 1a, 2a and 2b. **This approach yields an anticipated sample size of approximately 5,900 subjects for Aim 2 and 3,575 for Aim 3.**

We performed a traditional power analysis for our anticipated Aim 3 sample size, a more conservative approach than powering for Aim 2, using the historical number of patients by CAM therapy type. This yields an anticipated sample of 793 patients receiving mind/body, 627 patients receiving acupuncture, and 2,157 patients receiving massage. Using the smallest of these, acupuncture, and assuming a type I error rate (alpha) of 0.05 and a power of 80%, we can estimate average immediate pain reduction within plus/minus 4%. Because of the Bayesian repeated measures techniques that we will employ to analyze the duration of pain data, we are confident that these sample sizes will provide estimates that are at least as precise as the plus/minus 4% obtained for the immediate pain change analysis.

Aim 1a is a purely descriptive analysis, which serves to provide context for Aims 2 and 3. As such, we did not perform a power analysis. However, with an estimated sample size of more than 83,000 patients over 30 months, we feel confident these equations are adequately powered to address substantive differences.

In our research experience, it is sometimes the case that our attrition assumptions are not accurate. We have powered this study for 30 months of data collection, but our timeline allows for up to 36 months of data collection. We did this to assure that at the end of our data collection period, we can reasonably expect to have met our sample size goals.

8. Qualitative Data Analysis – Aim 1b

Our analytical methods will adhere to common practices in the field of qualitative analysis; as such, statistical tests are not applicable.

Investigators and study staff will read the transcripts from all interviews conducted, identifying themes that emerge from the transcripts relating to the research questions. Atlas.ti version 7 software will be used to organize and code transcripts and visually represent relationships between codes and themes as they emerge. This process will occur sequentially, as typed interview transcripts become available, so that we can use insights

from earlier interviews to inform later interviews. Interview questions will be used to establish a basic coding structure, which will be combined with inductive analysis, as described by Patton[42] and drawing from Glaser and Strauss's "grounded theory."[43] The inductive analysis process involves open coding to develop codes, categories, patterns, and themes. These elements are then refined, finally using deductive processes to form analytical hypotheses about the data. Within each of the five types of interviewees, the themes identified in the first few interviews will be tested against evidence gathered in subsequent interviews and against the data gathered in interviews with respondents in the other three respondent categories. Themes will be refined and modified as data accumulate throughout the interviewing process. The evolving coding scheme will be discussed during periodic team meetings.

All transcripts will be verified to assure accuracy by comparing the transcript to the audio file. Should we find significant quality problems in the early transcripts, we will address these problems by working with the transcriptionist or hiring a new transcriptionist.

Intercoder reliability (i.e., consistency in the application of codes to the text) will be measured on a subset of data (15%) by computing the ratio of the total number of disagreements in code applied to the total number of items coded by the two coders. If necessary, discrepancies will be resolved with the assistance of a third investigator, and a second round of intercoder reliability testing will be conducted until we reach a reliability level of .90, before the two primary coders code the remaining transcripts.

9. Anticipated Results and Potential Pitfalls

This research, if positive, will help focus attention on leveraging integrative medicine, which adds CAM as an adjunct to traditional care, as a mechanism to address pain management. In addition, the methodological approaches employed in this research can be transferred to other outcomes, many of which are related to pain, including anxiety, stress and nausea. This research will also enable a long-term focus on the cost effectiveness of an integrative model.

The results of the proposed study will provide critical guidance to both physicians and CAM practitioners on how best to balance the use of pharmaceutical interventions and CAM to manage patients' pain. In addition, managing patients' pain remains one of the highest priorities in hospitals. If we demonstrate CAM is an effective adjunct to traditional pain management, hospitals will have a new tool, and the beginnings of an evidence base to use that tool, in meeting the pain management goals of the Joint Commission[44,45] and ultimately, of patients.

We have carefully considered several challenges in the design of this study. First, since we propose collecting additional pain scores on a large number of patients, it is possible that the attrition rate will exceed our anticipated 25% and require a longer data collection period. While this might be a concern for applicants proposing to implement a new CAM service, our estimates are based on 5+ years of providing CAM at Abbott Northwestern Hospital. Regardless, should it be necessary, we could recruit the required patients in 36 months rather than the 30 months proposed and still meet our enrollment goals.

Second, since we will be studying the effectiveness of CAM therapies on pain management in a non-controlled research setting, patients will receive opioids and other pain analgesics as part of their standard clinical care. The issue is whether the provision of pharmacologic pain interventions will interfere with our ability to examine the effects of CAM therapies on duration of pain change. Anticipating this possibility, we can reliably access the EHR to document the time/day of all pain medications provided during patients' hospital stay. We have included in our analytic plan accepted procedures for comparing differences in type and dose of these opioid and non-opioid analgesic medications.

Third, it is possible that collecting repeated pain scores for up to five hours may not capture the complete pain reduction curve. However, the decision to use a five hour duration was based on 3 factors: (1) we used comparable timepoints as previous studies;[12,13,16,19] (2) five hours is approximately the same duration of typical dosing of narcotic pain medications;[46-48] and (3) there are logistical barriers to longer data collection (e.g., patients sleeping), which would lead to an unacceptable amount of missing data.

Finally, our proposed study will result in data based on the experience of patients in one hospital, which raises the concern of generalizability. While this may be a concern for a hospitals serving one type of patient population (e.g., cancer or pediatrics), our study would take place in a typical tertiary hospital suggesting that its experience will be generalizable to a considerable degree to other tertiary hospitals across the US.

10. Risk/Benefits and Reporting

This study involves no physical or psychological risks. There are minimal risks to the confidentiality and privacy of participants. Risk is limited to the possible breach of confidentiality of the pain and anxiety scores and interview data. The probability and magnitude of risk is small. Risks are minimized by using a limited access, password protected database as well as using the smallest number of identifiers necessary. The Data Safety Monitoring Plan outlines the procedures for identifying and reporting any adverse events. There are no direct benefits to participants. We hope that information learned from this study will help us better understand CAM therapies for pain and anxiety management.

11. Regulatory and Ethical Considerations

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Belmont Report, Good Clinical Practice and applicable regulatory requirements. The study will be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and, applicable laws and the IRB requirements. The study's data will be made available for monitoring, auditing, IRB review, and regulatory inspection by providing direct access to study-related source data.

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