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Comparative effectiveness of pediatric integrative medicine as an adjunct to usual care for pediatric inpatients of a North American tertiary care centre: A study protocol for a pragmatic cluster controlled trial

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ABSTRACT

Background: Some pediatric tertiary care centres in North America supplement conventional care with complementary therapies, together known as pediatric integrative medicine (PIM). Evidence to support the safety and efficacy of PIM is emerging, but the cost-effectiveness of an inpatient PIM service has yet to be assessed.

Methods/Design: This study is a pragmatic cluster controlled clinical trial. Usual care will be compared to usual care augmented with PIM in three pediatric divisions; oncology, general medicine, and cardiology at one large urban tertiary care Canadian Children's Hospital. The primary outcome of the feasibility study is enrolment; the primary outcome of the main study is cost-effectiveness. Other secondary outcomes include the prevalence and severity of key symptoms (i.e. pain, nausea/vomiting and anxiety), efficacy of PIM interventions, patient safety, and parent satisfaction.

Discussion: This trial will be the first to evaluate the comparative effectiveness, both clinical and cost, of a PIM inpatient service. The evidence from this study will be useful to families, clinicians and decision makers, and will describe the clinical and economic value of PIM services for pediatric patients admitted to hospital.

1. Introduction

When complementary therapies, for which there is evidence of safety and effectiveness, are combined with conventional medicine, it is known as “integrative medicine” [1]. Use and acceptance of integrative therapies among patients is high, especially in those with chronic conditions, and account for nearly US$34 billion in

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private and out-of-pocket expenses annually in the US [2]. As children and their parents seek non-pharmacological approaches to managing their health, interventions perceived as being effective and safe are increasingly being sought, despite the relative paucity of high quality published medical literature supporting such therapies. Additionally, the cost-effectiveness of integrative medicine programs has not been systematically studied in pediatrics. Dozens of North American pediatric hospitals have begun to offer pediatric integrative medicine (PIM) services, and are providing PIM therapies to inpatients [3,4]. PIM may be helpful in treating highly prevalent symptoms for hospitalized children, such as pain, nausea/vomiting, and anxiety (PNVA), for which pharmacotherapy is available, but not always effective.

Pediatric inpatients commonly experience PNVA during their stay in hospital [5–7]. Poorly managed PNVA can decrease compliance with conventional care, prolong recovery time, and increase costs to the health care system [8–10]. Pain is common in hospitalized children, and despite efforts to improve pain management, under-recognition and under treatment of pain persist [11,12]. Nausea and vomiting are also commonly experienced, and occur in up to 80% of post-operative and up to 90% of oncology patients [9,13–15]. Though improvements in chemotherapy and anti-emetics have been achieved, nausea and vomiting still are known predictors of increased length of stay (LOS) in hospital, and severe nausea and vomiting can lead to a postponement or discontinuation of chemotherapy [9,16]. Anxiety is not only associated with pain and nausea/vomiting, but also with hospitalization experiences and procedures. Untreated anxiety negatively affects physical and psychological health [17–20].

Pharmacotherapy to manage PNVA has varying levels of effectiveness and can be associated with adverse effects, which may be minor (e.g., sedation) or serious (e.g., respiratory depression) [21]. Children and their parents/caregivers may wish to explore non-pharmacological options to augment care. Various complementary therapies have demonstrated safety and efficacy for pain [22–29], nausea and vomiting [25,30], and anxiety [31,32], but robust pediatric data are lacking.

2. Objectives

This study investigates if PIM therapies (such as acupuncture, massage or reiki), in addition to usual inpatient pediatric care, are feasible and cost-effective for a large tertiary care centre, and effective and safe for patients. The effects on outcomes such as patient symptoms, safety, satisfaction, length of stay and costs will be measured and we will identify which of these key outcomes are most affected, for which children, and why. Through mixed methods research (qualitative, quantitative, and health economics), we will also develop a thorough understanding of why parents choose PIM services and health care providers' experience of the PIM service. Our study is intended to provide the rigorous evidence that health care decision-makers need to determine if and when integrative medicine should be offered to children while they are in hospital, and will help address an important gap in public health policy and practice.

3. Methods

3.1. Design

Complementary therapies are often administered as complex interventions, comprised of a number of separate elements that may interact with each other. A study design suitable for evaluating complex interventions is the pragmatic clinical trial (PCT) [33–35]. As such, we are conducting a 2-arm, cluster controlled, mixed methods pragmatic trial. Each consenting participating Division is assigned to receive PIM services or not in an ABA design, where A is usual care and B is usual care augmented by PIM therapies.

Our design has been informed by two of the largest inpatient integrative medicine programs in the United States. We have chosen target symptoms and complementary therapies based on the successful and long-standing model built by our collaborator, Dr. Tim Culbert, Medical Director, PIM Service, Children's Hospitals and Clinics of Minnesota. We have chosen cost-effectiveness as our primary outcome based on compelling preliminary data from the adult inpatient setting, suggesting that for every $1 spent on integrative therapies, $1.80 is saved (personal communication, Dr. Jeff Dusek, Research Director, Institute of Health and Healing, Abbott Northwestern Hospital).

3.2. Setting

This trial is being conducted at the Stollery Children's Hospital, in Edmonton, Alberta, Canada. We approached many clinical divisions regarding their interest and readiness to participate in our trial. We subsequently partnered with three admitting Divisions: pediatric oncology, general pediatrics and pediatric cardiology.

3.3. Participants: eligibility, screening, and enrolment

Inclusion criteria for study enrolment are: (i) admission to a participating Division; (ii) caregiver communication in English; (iii) caregiver is available to participate; (iv) caregiver consent/child assent. Patients are eligible if they arrive in the ward as a new admission during the study, or if they are currently admitted when the study begins collecting data from their Division. Two additional inclusion criteria are applied at the time of data analysis: (v) length of stay in the participating Division is between 2 and 30 days and (vi) age on admission is less than 16 years. If, at admission, patients are expected to be discharged within 2 days or to stay longer than 30, they will not be approached by the research team.

Length of stay is measured from admission to transfer to ICU, discharge, or death. In the event of a transfer to ICU, data collection is to be paused for that case, and resumed when the patient is transferred back to the admitting Division.

3.4. Blinding and bias

Due to the nature of the intervention, and ethical considerations around parental consent for PIM therapies to be delivered, it is impossible to blind participants, providers or data collection researchers to the intervention. However, we are taking extra precautions to minimize bias with the following:

1) Careful documentation of participant characteristics in order to control for differences between groups, including previous complementary therapy use, as well as beliefs/expectations regarding complementary therapies.
2) Use of an active control group with similar baseline demographics and disease states, being treated in the same Division as the intervention group.
3) Use of cost-effectiveness as an outcome. A conservative assumption is that the patient and provider may be biased towards complementary therapies, leading to their increased use, symptomatic improvement, and satisfaction with care. This will be balanced by measurement of cost-effectiveness, rather than satisfaction or effectiveness alone, as increased use generates increased PIM service related costs.
4) Use of an ABA design. It is possible that the study may bias providers and patients to have a heightened awareness of

patient PNVA. Measuring the control group again, after the intervention will allow us to ensure that no changes in usual care resulted from having symptom awareness augmented with PIM services.

5) Analyzing groups under an intention-to-treat analysis will reduce bias due to systematic differences between individuals who received the intervention and those who did not.

3.5. Control and intervention groups

3.5.1. Control

The control group will receive usual care, including pharmacotherapy, and will be followed as per usual hospital standards in each Division. No complementary therapies under study will be available for inpatients at our hospital during this time. Nursing staff currently make clinical assessments of PNVA during each shift as part of usual care, however, standardized outcome measures are only used for pain in our hospital. Literature supports that PNVA are underreported and under treated [12,36–38]. As such, our research nurse will record PNVA using validated outcome measures daily, on week days only, for all participants.

3.5.2. Intervention

The intervention group will receive usual care augmented by consultation with the PIM service and selected PIM therapies. Patients are eligible if they are symptomatic for PNVA or other distressing symptom; they are referred to the PIM service by the research nurse. Upon referral to the PIM service, patients is assessed by a clinical nurse who is specifically trained for this trial and who has in-depth knowledge of the complementary therapies offered (acupuncture, reiki and massage therapy). The clinical nurse will discuss these three complementary therapies and a decision will be made by consensus among the patient, the family and the research nurse, in consultation with one of our Hospital's pediatric integrative medicine specialists (SV, HJ) as needed. This decision will be based on the child's needs and preferences, and in light of best evidence and therapeutic indications/contraindications, for one or more complementary therapies. The complementary therapy providers have been credentialed by our Children's Hospital based on their training and expertise. Dose, duration, and frequency of PIM therapies are individualized in accordance with real world practice and offered Monday to Friday, usually in the afternoons/early evening based on the availabilities of the patients, caregivers, and therapists.

In accordance with the pragmatic nature of this trial, children will be permitted to choose more than one PIM therapy during the course of their hospital stay, although they will be encouraged to use them in sequence rather than in parallel; timing depends on the child's condition and the complementary therapy providers' clinical judgement and availability. Each patient will be followed until their symptoms resolve; re-consultation with the PIM service for a new or recurring target symptom is permissible and will be offered on an as-needed basis. If patients are transferred into the pediatric intensive care unit, the PIM service is discontinued, but may be resumed, if appropriate, once the patient is transferred back to the participating pediatric Division. A diagram of patient flow through the study is presented in Fig. 1.

3.6. Primary outcome

The primary outcome of the feasibility study is enrolment. The primary outcome of the main study is cost-effectiveness.

3.7. Secondary outcomes

The tools and timelines for all secondary outcomes are detailed in Table 1.

3.7.1. PNVA symptoms

Comparative effectiveness will be assessed by changes in PNVA scores in the intervention and control groups. Patient pain will be measured in pre-verbal children using the Faces, Legs, Activity, Cry, Consolability [39] (FLACC) tool and for verbal children with the Faces Pain Scale-Revised [40] (FPS-R). Nausea and anxiety scores will be collected from verbal children only using Baxter Retching Faces [41] (BARF) and Pediatrics Anxiety Faces Scale [42] (PAFS), respectively. Vomiting will be measured by incidence of vomiting each day.

A research nurse will measure symptoms each morning (Monday to Friday). For patients in the intervention arm, their symptoms will by measured again, both immediately prior to and immediately post PIM therapy intervention. These two additional symptom severity measurements will be assessed on a numerical rating scale (NRS) out of ten.

3.7.2. Safety

Incidence of patient and parent reported adverse events (AEs) pertaining to usual care and specifically to complementary therapy use will be presented. Parent reported AEs will be measured with the BC Children's Hospital patient safety questionnaire [43]. We will also apply the Canadian Pediatric Trigger Tool (CPTT) [44] retrospectively to identify and assign potential AEs to all cases.

3.7.3. Parent satisfaction and anxiety

Parent satisfaction will be assessed quantitatively at discharge using our Hospital's standardized satisfaction survey, verbatim. We did not alter this tool nor verify its validation. Satisfaction will be compared between the two study arms. Changes from baseline to follow up in parental state and trait anxiety will be reported and compared. Parent anxiety will be measured using the State-Trait anxiety Inventory [45].

3.7.4. Economic analysis

Patient length of stay in hospital, resource utilization and costs will be compared between study arms. The hospital cost will be calculated using patient level itemized procedure and cost estimates from the hospital costing database. PIM related costs will be added to the costs based on the individual utilization of the services, the actual fees for those services, and health care utilization and costs after hospital episode will be estimated based on parent follow up survey 30 days after discharge. All costs will be shown in 2015 Canadian dollar values.

3.7.5. Baseline and other trial data

Patient and caregiver demographic information will be collected at baseline along with data regarding history of complementary therapy use. Pediatric Quality of Life Inventory version 4.0 (PedsQL 4.0) questionnaire [46] (child and parent proxy version for nonverbal children) will be collected at admission. Medication intake and PIM service therapy consultations and utilization will be measured daily (M-F). Other symptoms that may trigger a PIM consult will be captured using the Measure Yourself Medical Outcome Profile (MYMOP) [47]. A chart review for diagnoses, treatments and discharge data will be done at discharge. Follow up data on patient symptom prevalence, and outpatient complementary therapy and other health care utilization will be assessed by telephone at follow up, 30 days after discharge.

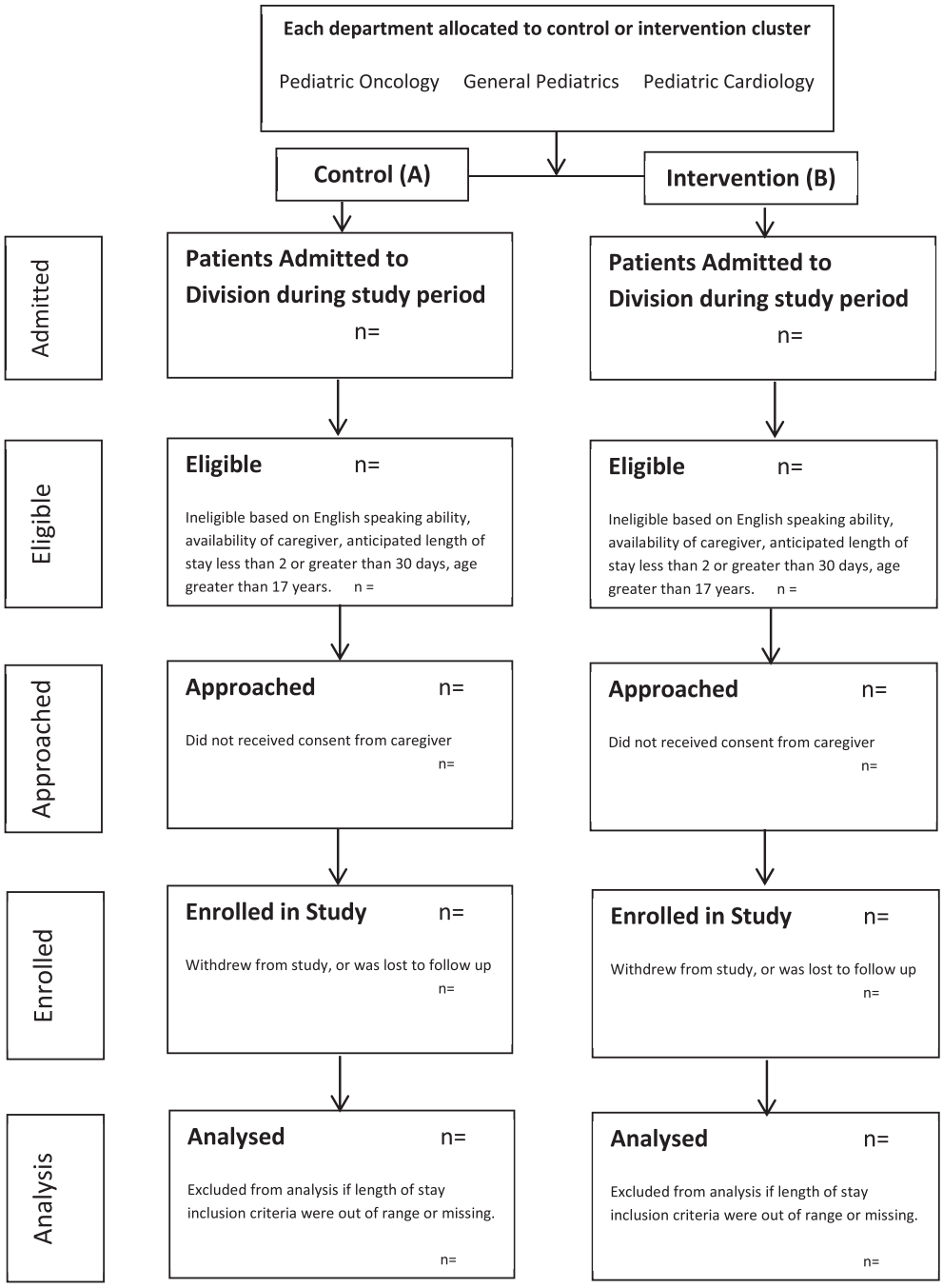

Fig. 1. CONSORT Patient flow chart showing patient flow through each of the control (A) and intervention (B) trial arms. Data are collected in an ABA sequence.

3.7.6. Qualitative outcomes

We will report results of decision-making and parent satisfaction that stem from one-on-one telephone interviews. Results will be compared between parents of patients who are offered and utilized PIM, and those who are only offered conventional care. Results from one-on-one, semi-structured interviews with health care providers and with CAM providers will be presented to explain their experiences with providing care to patients.

3.8. Assessment timeline

Data will be collected at baseline (t_0), daily during admission ($t_{2\text{-}30}$), at discharge (t_{31}) and by telephone at follow up (t_{32}) which is 30 days post-discharge. An overview of timelines and outcome measures is shown in Table 1.

3.9. Sample size calculation and recruitment

Since this study is one of the first of its kind, data for sample size calculations and for minimally important differences in patient symptoms and length of stay are sparse. The feasibility assessment will inform future sample size calculations in this study population. We hope to enroll 50 children in each arm (control and intervention) of pediatric oncology and cardiology, and 100 in each arm of general pediatric inpatients.

In order to reach saturation of qualitative data, we will conduct

Table 1
PIM trial outcome measures, data instruments and timelines.

Data collection instrument	Baseline and day 1 (t_0)		Daily during admission ($t_{2\text{-}30}$)		Discharge (t_{31})		Telephone follow up (t_{32})	
Study group	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Screening/Consent	X	X						
Baseline Demographics	X	X						
Daily Assessment	X	X	X	X				
Medication	X	X	X	X	X	X		
Pain (FPS_R)	X	X	X	X				
Nausea (BARF)	X	X	X	X				
Anxiety (PAFS)	X	X	X	X				
Anxiety (NRS)	X	X	X	X				
General Symptom (NRS)	X	X	X	X				
NRS Pre-post CAM		X		X				
MYMOP		X		X				
CAM Therapy Intake, Interruption and Follow Up		X		X				
PIM Referral, consult and AE		X		X				
Parent STAI	X	X	X	X			X	X
Parent Peds QL	X	X	X	X			X	X
Patient Peds QL	X	X	X	X			X	X
Chart Review					X	X		
Patient Safety					X	X		
Parent Satisfaction					X	X		
Follow Up Questionnaire							X	X

approximately 10 one-on-one semi-structured interviews in each division with parents who choose PIM and with parents offered only usual care, for a total of approximately 60 interviews. Approximately 10 interviews will be conducted with health care providers and 10 interviews with CAM providers in the third year of the project.

3.10. Data management

Raw data forms will be secured and stored in the Women and Children's Health Research Institute (WHCRI) offices at the University of Alberta. Study data are entered and managed using REDCap (Research Electronic Data Capture) hosted at the University of Alberta [48]. These data will be accessible only to the authors listed on this protocol.

3.11. Quantitative data analysis

Since there is such variety between each admitting Division, each will be analyzed separately. The quantitative effectiveness outcomes will be pursued under an intention-to-treat and a per protocol analysis.

Baseline data on all enrolled patients will be summarized using descriptive statistics and will be compared in three ways: those enrolled and those who refused to participate, usual care pre and post intervention (comparing the two 'A' arms of the ABA design) and, treatment and control groups (A vs B). Feasibility will be analyzed to compare all eligible patients with those who were enrolled and those with complete measurements collected.

Comparison tests of two independent means or proportions will be performed on the symptom scores, safety outcomes, quality of life and parental satisfaction outcomes. The comparisons will be made with independent t-tests, analysis of variance or with the non-parametric equivalents as appropriate. χ^2 analysis, with Fisher's exact test as necessary, or logistic regression will be performed on dichotomous outcomes, such as parental satisfaction and patient safety, allowing us to control for confounders identified *a priori*.

The analysis of the cost data will be done using different regression methods estimating the difference in total costs between the two study arms. Decision analysis modeling will be used to estimate the Incremental Cost-Effectiveness Ratio (ICER) with 95% confidence interval, and probabilistic sensitivity analysis and treatment acceptability curve analysis will be used to support decision making.

All descriptive and inferential statistics will be two-tailed and reported with 95% confidence intervals and p-values at $\alpha = 0.05$ level of significance.

3.12. Qualitative data analysis

Analysis of all one-on-one interviews will follow a constant comparison technique that will lead to theory or model development.

4. Discussion

To our knowledge, this landmark study is the first comparative effectiveness trial to assess the impact of PIM as adjunctive care for pediatric inpatients. We have chosen common symptoms that negatively affect the health of the majority of pediatric inpatients. This study will help describe the complex decision-making associated with use of complementary PIM therapies and will rigourously assess the impact of hospital-based complementary treatments on patient symptoms, safety, quality of life, and parent and health care provider satisfaction. Most importantly, this study will provide valuable evidence to health care administrators and policy makers on the cost-effectiveness of providing pediatric integrative medicine services to inpatients in a North American tertiary care centre.

4.1. Strengths

A key strength of this study lies in the pragmatic design of the trial, which will enable us to draw conclusions while accommodating the diversity of the three Divisions studied. Because we are striving to describe the effects of complementary therapies under typical conditions, rather than ideal conditions, the pragmatic design is a suitable method that can inform decision makers on additional options for care [49]. Close monitoring of baseline

patient characteristics as well as daily pharmacologic and non-pharmacologic treatments allows for careful control of patient health outcome predictors, maximizing the accuracy of the treatment effect measures. Lastly, the external validity and generalizability to other children's hospitals is high. We have verified that the patient demographics, illness, types of treatment, and patient outcomes of children seen at our hospital compare to others in North America [50,51]. Furthermore, they reflect national averages for reasons for admission and length of stay when compared with Canadian Institute for Health Information database (personal communication, Donna Scheurman, Clinical Information Coordinator, Stollery Children's Hospital).

4.2. Limitations

Measurement bias in symptom scores may occur in our study because patients and researchers are not blinded to the intervention. This may exaggerate symptom improvements when receiving PIM therapies, and likewise underreport improvements in the control groups. Reporting cost-effectiveness as our primary outcome mitigates this bias.

Because it is impossible to blind participants to their allocation group, there is potential for response bias in symptom scores. It is possible that if patients know there are additional therapies being offered, they may be more inclined to report more severe symptoms. Nonetheless, even if a patient's knowledge of their treatment in a pragmatic trial was a part of their therapy, this too would be the case in clinical practice [52].

Trial status

Participant recruitment commenced in January 2013, and as of March 2016, was ongoing. Data collection was approximately 70% complete at the time of manuscript submission. This protocol is version 2 and was prepared in accordance with the SPIRIT 2013 checklist.

Ethics

Approval and renewal

Ethics approval was granted by the Health Research Ethics Board – HREB Biomedical Panel at the University of Alberta (study ID: Pro00010904). Initial approval was granted on February 22, 2011 and will be renewed yearly by HREB-Biomedical Panel.

Consent and assent

Trained research nurses introduce the trial to participants and caregivers. They provide study information sheets, detailing the benefits and potential harms of participating. Separate information and consent forms are prepared for the conventional care arm, the PIM intervention arm, and one-on-one interviews. Informed and written consent is obtained from primary caregivers and assent from participants is also obtained from participants who are old enough to communicate.

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Competing interests

The authors declare no competing interests.

Authors' contributions

SV is the grant holder. She conceived of the study and its methods, and will oversee its conduct. She is the guarantor of the work. MS drafted the manuscript and is conducting the primary statistical analysis. HJ contributed to the study protocol and lead the intervention phase of the trial, including all clinical documents, credentialing and supervision of CAM providers, and providing clinical support. DH contributed to the study design and initial implementation, and as well has provided expertise in patient safety analysis. MM lead the qualitative inquiry and AO lead the economic study. BW, MS and PG contributed to the study design and implementation. All authors contributed to revision of the protocol and approved the final manuscript.

Trial registration

Clinicaltrials.gov registration number NCT0202883.

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