

Research paper

## The Integrative Migraine Pain Alleviation through Chiropractic Therapy (IMPACT) trial: Study rationale, design and intervention validation

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### ABSTRACT

**Introduction:** Approximately 15% of the US population experiences migraine, with women afflicted three times as often as men. While medications are often used as first-line treatments, up to 50% of people with migraine pursue complementary and integrative medicine. One promising non-pharmacological approach for migraine is chiropractic care, due to the co-occurrence of migraine disease and musculoskeletal tension and pain. To date, no large-scale trials have evaluated the impact of a comprehensive model of chiropractic care on migraine.

**Methods:** The Integrative Migraine Pain Alleviation through Chiropractic Therapy (IMPACT) study is a two-arm pilot pragmatic randomized clinical trial evaluating a multimodal chiropractic care intervention plus enhanced usual care (UC) vs. enhanced UC alone for adult women with episodic migraine. A total of 60 women aged 20–55 who meet criteria for episodic migraine will be randomly assigned to an evidence-informed, musculoskeletal focused multimodal chiropractic care (10 sessions over 14 weeks) plus enhanced UC vs. enhanced UC alone. Enhanced UC includes conventional care, migraine education materials, and biweekly check-in phone calls. Study specific aims include: 1) Determine safety and feasibility of the study design; 2) Provide preliminary data on the effectiveness of chiropractic care on migraine frequency, severity, duration and medication use; and 3) Provide preliminary estimates of the effects of chiropractic care on disability, health-related quality of life, and psychosocial well-being.

**Discussion:** Findings will be used to inform the design of a full-scale trial evaluating chiropractic care for women with episodic migraines.

### 1. Introduction

Migraine, a chronic intermittent headache disorder, now ranks globally in the top five for years lived with disability [1]. Approximately 15% of the general US population experiences migraine, with women afflicted approximately three times as often as men [2]. Due to the high disability burden associated with migraine, sufferers often seek treatments which may reduce both the frequency and severity of attacks. While pharmacological medications are often used as first-line treatments for migraine, it is estimated that as many as 50% of individuals

with migraine or severe headache may use complementary and integrative medicine treatment options to reduce the frequency and severity of their migraine episodes [3,4].

One potentially promising integrative medicine treatment option may be chiropractic care. Approximately 15% of individuals with migraine report having used chiropractic care in the past 12 months [3] suggesting that some individuals already view chiropractic care as a potential treatment option. A handful of small clinical trials evaluating spinal manipulation, one component of chiropractic care, suggests potential benefits on migraine frequency and pain intensity [5]. However,

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to date, no rigorous randomized trials have evaluated the impact of a more comprehensive model of chiropractic care that includes multimodal therapeutic approaches (e.g. education, manual therapies, movement/exercise based approaches, ergonomic modifications and lifestyle modifications) on migraine expression.

In this paper, we describe the rationale and design for a pragmatic pilot randomized clinical trial (RCT) evaluating chiropractic care plus enhanced usual care vs. enhanced usual care alone for adult women with episodic migraine. Our enhanced usual care group includes conventional (pharmaceutical and patient education focused) care as well as educational materials on migraine and biweekly check-in phone call. We also report findings of a validity evaluation process for our chiropractic intervention based on the Delphi method [6]. Results of this study will inform the design of a full-scale comparative effectiveness study evaluating chiropractic care for women with episodic migraines, and also provide opportunities for further exploration of adding evidence-based, multimodal chiropractic to usual migraine care.

## 2. Background and rationale

### 2.1. Burden of migraine

Migraine has a substantial disability burden. Among women between the ages of 15 and 49, migraine contributed to an estimated 20.3 million years lived with disability in 2016 alone [1]. In addition to migraine's impact on years lived with disability, migraine is associated with higher direct and indirect cost burdens due to higher work loss, longer periods of work loss, and higher levels of healthcare utilization among individuals with migraine compared to those without migraine.

### 2.2. Co-morbidity of migraine and cervical/musculoskeletal tension/pain

Although migraine symptoms vary by patient, over 75% of migraine patients report associated neck pain, and many note musculoskeletal symptoms, such as neck stiffness, muscle tension, or problems with jaw function [4–6]. However, it is unknown whether the link between migraine and neck pain reflects the causal effect of one condition on the other or shared underlying pathophysiology. Emerging models of migraine pathophysiology postulate that triggering of the trigemino-cervical complex may cause neck pain [7,8]. It may be that a central sensitization process leading to a migraine episode is triggered by noxious stimuli from neck structures in some persons. Pain stimuli originating in the neck may also activate the nucleus caudalis, facilitating or initiating a migraine cascade effect [9,10]. Thus, there exists a potential reciprocal relationship between migraine and musculoskeletal symptoms in individuals who experience migraine through sensitization and other neurological triggering mechanisms, even if a causal relationship does not exist when migraines first manifest.

Regardless of causality, the high prevalence of migraine-related cervical and musculoskeletal tension and pain was a motivation for exploring the use of a musculoskeletal focused intervention for reducing migraine frequency, severity, and disability. As part of the study, we also asked participants to report on neck pain levels to begin to explore the associations between neck pain, chiropractic care, and migraine-related outcomes.

### 2.3. Non-pharmacological approaches for the treatment of migraine

Approximately half of US adults with migraines report using complementary and integrative health (CIH) therapies, including chiropractic. Many patients view CIH therapies as more helpful than conventional headache treatment [11]. However, evidence regarding the safety and effectiveness of such therapies remains limited [11]. A recent systematic review and meta-analysis evaluated the impact of spinal manipulation, a central component to chiropractic care, on people with migraine. The study identified 6 RCTs (pooled  $n = 677$ ; range of

$n = 42$ –218). Intervention duration ranged from 2 to 6 months, and outcomes included measures of migraine days (primary outcome), migraine pain/intensity and migraine disability. In meta-analyses limited to studies of episodic migraine (5 of 6 studies), spinal manipulation showed small effects in reducing migraine days (Hedges'  $g = -0.35$ , 95% CI:  $-0.53, -0.16$ ,  $p < 0.001$ ) and migraine pain intensity (Hedges'  $g = -0.28$ , 95% CI:  $-0.46, -0.09$ ,  $p = 0.004$ ). The conclusions of this study highlighted limitations related to study size and methodological rigor. The study also emphasized the absence of any trials evaluating widely used multimodal chiropractic interventions that integrate soft-tissue manipulation, exercise, and life-style advice, as well as spinal manipulation [5].

The value of evaluating a multimodal model of chiropractic care for migraine is further supported by two related areas of research. First, studies show that combining spinal manipulation with neck strengthening exercises is more beneficial to patients with chronic neck pain than the use of spinal manipulation or exercise alone [12,13]. Second, multiple individual therapies commonly included in multimodal chiropractic care including soft tissue massage, exercise, and mind-body training techniques (e.g. mindfulness and breath awareness) independently show promise in reducing migraine frequency and associated symptoms [14–18]. All of these treatment approaches are included in standard chiropractic education and are within the scope of practice for chiropractors.

## 3. Materials and methods

### 3.1. Study design, specific aims and hypotheses

The IMPACT study is a two-arm pilot pragmatic RCT evaluating a multimodal chiropractic care intervention plus enhanced usual care (UC) vs. enhanced UC alone for adult women with episodic migraine. A total of 60 women aged 20–55 who meet criteria for episodic migraine (between 4 and 13 episodes during the four week run-in period) as defined by the International Classification of Headache Disorders (ICHD) criteria [19] will be randomly assigned to a well-defined program of chiropractic care (10 session over 14 weeks) plus enhanced UC vs. enhanced UC alone. Our enhanced UC will include conventional care as well as providing participants with education materials and biweekly check-in phone calls (see Section 4.2). The overall design of the study is described in Fig. 1. The study will be conducted at the Osher Clinical Center (OCC), Brigham and Women's Hospital (BWH) in collaboration with the Division of Headache Medicine in the BWH Department of Neurology. It is registered in [ClinicalTrials.gov](https://clinicaltrials.gov).

The study has three specific aims and associated hypotheses.

**Specific Aim 1:** Determine the safety and feasibility of a RCT of chiropractic care in adult women with migraine. A total of 60 women aged 20–55 meeting criteria for episodic migraine (between 4 and 13 episodes per month) as defined by the International Classification of Headache Disorders (ICHD) criteria [19] will be randomly assigned to a defined program of multimodal chiropractic care (10 sessions over 14 weeks) plus enhanced UC vs. enhanced UC alone.

**Hypothesis 1a.** Chiropractic care is a safe intervention for women with migraines, and there will be few and only minor adverse events reported that are related to the clinical delivery of chiropractic care or during home practice of prescribed exercise.

**Hypothesis 1b.** Recruitment, retention, and protocol adherence of women into a RCT evaluating chiropractic care is feasible. Specifically, we will demonstrate that 60 patients can be successfully recruited within 12 months, and that more than 85% will complete baseline and outcomes assessments, and attend 75% of proposed treatments.

**Specific Aim 2:** To provide preliminary data on the effectiveness of

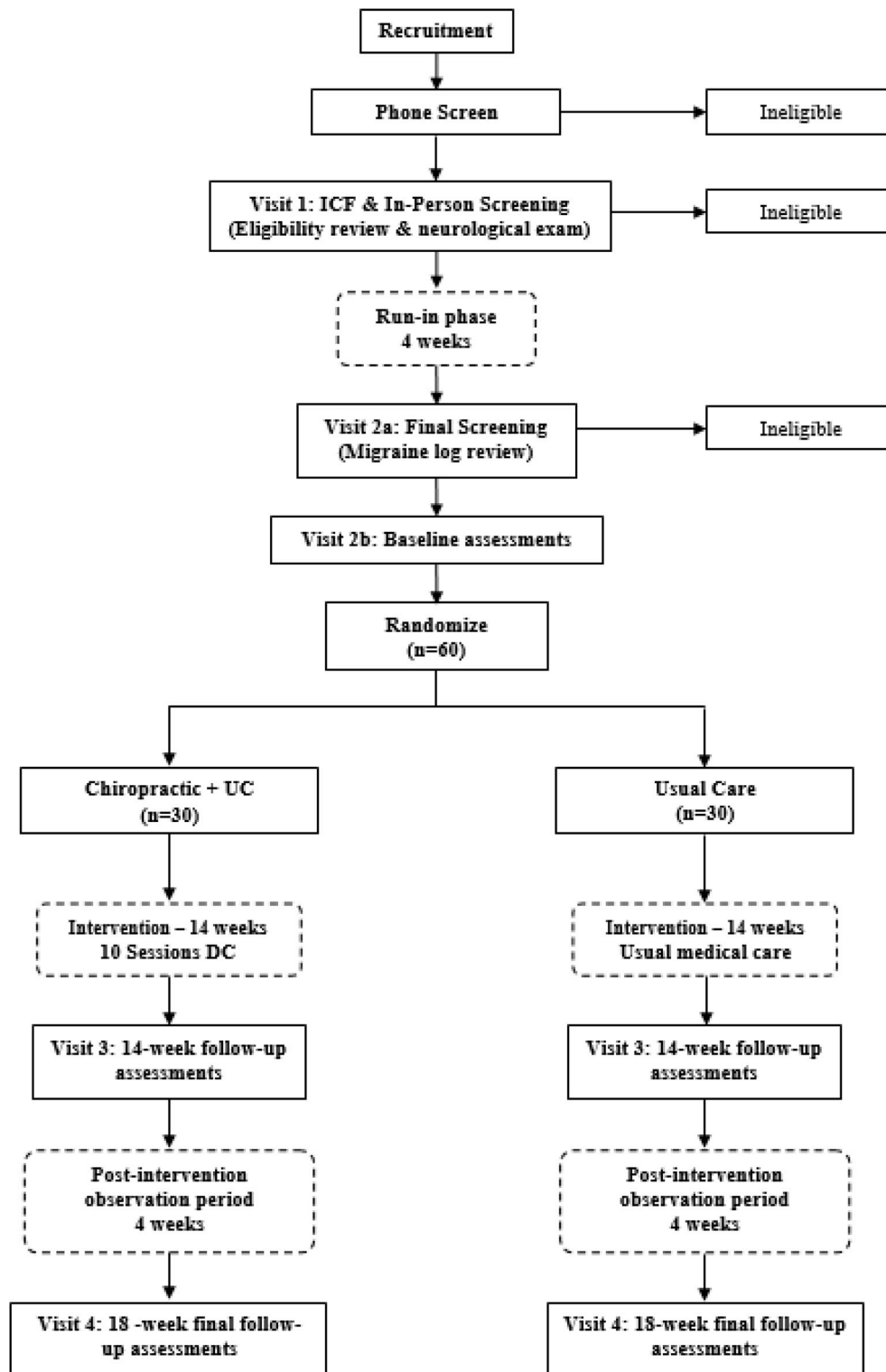


Fig. 1. Study design and patient flow.

chiropractic care on migraine frequency, severity, duration, and medication use in adult women with migraine. Patient-completed migraine logs will be used to record the number of migraines per month, severity of each migraine (1–10), duration (<4 h, 4–12 h, 13–24 h), and medicines taken to treat their migraines.

**Hypothesis 2a.** The frequency, severity, and duration of migraines will decrease from baseline through follow-up for those in the chiropractic plus enhanced UC group compared to the enhanced UC control

group.

**Hypothesis 2b.** The frequency of use of migraine medication will decrease from baseline through follow-up in the chiropractic plus enhanced UC group compared to the enhanced UC control group.

Specific Aim 3: To provide preliminary estimates of the effects of chiropractic care on disability, health-related quality of life, and psychosocial well-being. Headache Related Disability will be measured using the validated HIT-6 and the Migraine Disability Assessment

(MIDAS) questionnaire. Quality of life will be assessed using the Migraine Specific Quality of Life Questionnaire (MSQ). We will also assess neck pain, anxiety, and depression in our sample.

**Hypothesis 3a.** Patients in the chiropractic care plus enhanced UC group will demonstrate reduced migraine-related disability, improved quality of life, reduced neck pain, and reduced depression and anxiety, compared to the enhanced UC control group.

An additional secondary aim of this study was to evaluate the validity of the chiropractic intervention protocol being tested in this trial using an expert chiropractic panel approach (see sections 4.1.a, and 4.1. b below).

3.2. Ethical oversight

The study has been approved by Partners HealthCare institutional review board (IRB).

3.3. Pragmatic design features included in the IMPACT trial

It has been argued that placebo-controlled explanatory trial designs widely used to evaluate pharmacological interventions are not appropriate in non-pharmacological trials due to challenges associated with distinguishing specific vs. non-specific effects, controlling for multiple specific effects, characterizing dosage, and participant blinding, among other reasons [20,21]. Employing elements of pragmatic designs has been suggested as a way to overcome these challenges [20–24]. Using the framework of the revised Pragmatic Explanatory.

Continuum Indicator Summary (PRECIS-2) [25], the IMPACT trial is best described as a pragmatic trial with elements of explanatory trials that enhance the degree of internal validity (see Fig. 2). Elements that are pragmatic include: the multimodal and clinically adaptable chiropractic protocol; use of an enhanced usual care comparison intervention that only modestly attempts to control for attention and expectation; the inclusion of outcomes that are patient centered (e.g., Migraine Disability Assessment (MIDAS), Headache Related Disability (HIT-6)); and the use

of an intent-to-treat paradigm for primary analyses. Elements of our study design that are more explanatory include: our relatively narrow participant eligibility; staff efforts to encourage intervention and overall protocol compliance; relatively intensive and frequent follow-up assessments; and inclusion of planned per-protocol secondary analyses. Additionally, while the chiropractic protocol was designed to allow flexibility based on patients’ presentations and preferences (e.g. opt out of any component of care) and clinicians’ judgement, treatments will be delivered by carefully selected chiropractors. In summary, the IMPACT trial attempts to strike a balance between pragmatic and explanatory elements. Pragmatic elements enhance broader generalizability and translatability to community-based programs. Explanatory elements minimize bias and help with the interpretation of results.

3.4. Study population and eligibility criteria

The IMPACT trial will recruit women, ages 20-55 years, with a confirmed diagnosis of episodic migraine with or without aura (International Classification of Headache Disorders-II). Migraine frequency will be required to be between 4 and 13 days per month with a history of migraines dating for at least one year. Participants must be willing to complete all study procedures, be randomized to either exposure group, and be fluent in English.

Participants will be excluded from the trial if they have any major systemic illness or unstable medical condition (e.g. Parkinson’s disease, cancer) or psychiatric condition requiring immediate treatment or that could lead to difficulty complying with the protocol; history of stroke, carotid artery dissection, or vertebral artery dissection; head or neck trauma within the past year; current alcohol or substance abuse (self-reported); or diagnosis of medication overuse headache (International Classification of Headache Disorders-II) [19]. Participants will be excluded by the study neurologist if they show high risk for adverse events from cervical spine manipulation including signs of myelopathy or carotid bruits. Participants will also be excluded if they begin use of new prophylactic medication for migraine headaches within the last 3 months, are currently taking prophylactic migraine medications other



Fig. 2. PRECIS-2 wheel highlighting relatively pragmatic and explanatory features of the trial design.

than propranolol and topiramate, currently or recently (past 6 months) received Botox treatment for migraine, or currently or recently received chiropractic care (past 3 months) for any condition. Finally, participants will be excluded for failure to complete baseline diary recordings of migraine activity and medication use during run-in phase.

### 3.5. Recruitment, patient screening, and informed consent

Participants will be recruited from four sources. Our primary source of recruitment will be through Partners HealthCare neurology, primary care, and women's health programs. A study team member (CB) informed clinicians about the goals and eligibility criteria of the study at seminars and faculty meetings, and study brochures and flyers will be placed in clinic waiting areas. Registered Partners patients were also contacted using the "Research Opportunities Direct to You" program through Partners HealthCare. The trial will also be listed on Rally, a searchable database of ongoing studies within the Partners HealthCare system, which also sends out a weekly email to subscribers announcing ongoing trials. Finally, the study recruitment material will be posted in newspapers and online postings. All recruitment procedures will follow IRB and HIPAA guidelines.

Eligible and interested patients will be directed to call the study coordinator, who will describe the study in detail and complete a phone screen to assess initial eligibility. Those interested and eligible will be scheduled for an in-person visit at the OCC to confirm initial eligibility and to provide informed consent. A copy of the informed consent form will be sent to potential participants to review ahead of time.

In-person initial eligibility screening and informed consent procedures will be performed by a board-certified neurologist and headache specialist (CB). Patient's medical and medication history will be reviewed, and a full neurological exam will be conducted to confirm the subject's migraine diagnosis, and to rule out candidates at high risk for adverse events from cervical spine manipulation (e.g., signs of myelopathy or carotid bruits). Study procedures and risks will be described to patients before they sign the ICF.

Initially eligible subjects who sign the ICF will then participate in a four-week 'run-in' period to confirm eligibility with respect to migraine frequency (4–13 per month) and compliance in completing daily logs. The printed and manually completed log prompts for data on frequency, severity, and duration of migraines, use of migraine-related medications, level of relief achieved, characteristics of the migraine attacks, days of menstruation, and adverse symptoms. For eligible patients, these data will also be used as the 4-week baseline information on migraine frequency, severity, and duration and medication use.

Following the run-in phase, participants will return to the OCC for a final screening, during which migraine logs will be reviewed. Eligible participants will then complete a battery of additional baseline outcome assessments (section 5) and undergo randomization.

### 3.6. Randomization, blinding and concealment

Subjects will be randomized 1:1 to either the intervention (chiropractic plus enhanced UC) or control group (enhanced UC alone). Randomization will be stratified by use of prophylactic migraine medication (two tiers: non-prophylactic and prophylactic) and then stratified by migraine frequency during the run-in phase (two tiers: 4–7 or 8–13). Treatment assignments will be generated electronically by a permuted blocks method with randomly varying block size. The randomization database will be created by the study biostatistician. Study staff will be responsible for implementing randomization within REDCap, informing participants of their assignment, and entering newly randomized participant's name, study ID, assignment, and date randomized into a randomization log.

## 4. Study interventions

### 4.1. Chiropractic intervention

In North America, licensed practitioners hold a Doctor of Chiropractic (DC) degree. Services are typically accessed without the need for referral. Chiropractic training and care are focused on diagnosis and non-pharmacological/non-surgical management, or co-management, of spinal and other neuromusculoskeletal conditions. With a special emphasis on spine-related care, DCs function as primary spine-care practitioners [26,27]. Manual therapies, commonly including spinal manipulation, are typically employed. In addition, chiropractors are licensed to and regularly provide a variety of integrated therapeutic modalities including soft-tissue manipulation, lifestyle recommendations, fitness coaching and nutritional advice. Chiropractic care is commonly used for treatment of a number of painful disorders, including headache [11,28–30]. As optimal chiropractic treatment strategies for the treatment of episodic migraines have not been defined, and protocols employed in trials to date primarily focused on spinal manipulation [5], a secondary goal of this study was to develop an expert-validated chiropractic treatment protocol for women with episodic migraine. Specifically, we aimed to develop a manualized, multimodal integrative care approach that: 1) utilized the diverse set of therapeutic modalities afforded by the scope of chiropractic practice; 2) targeted migraine-related musculoskeletal symptoms and sequelae; 3) and was flexible enough to accommodate variability in presentation and preferences of patients, while still following a defined overall strategic method and clinical decision-making process.

#### 4.1.1. Delphi validation process

The process of protocol validation followed the Delphi method. The Delphi method is a structured systematic, iterative and interactive consensus building method which relies on a panel of experts [31,32]. Our Delphi protocol included four phases. Phase I involved the drafting of an initial chiropractic care treatment protocol led by a senior chiropractic clinician (MK), with input from other members of the study team. General sections of the protocol included overall evaluation, categorization, consent, and a multi-modal treatment approach covering the scope of chiropractic care. Phase II involved the recruitment and engagement of a national panel of chiropractic experts. Chiropractic experts were recruited using the following criteria with the goals of assembling a diverse and representative panel: ten or more years of clinical practice experience; a mix of chiropractic clinicians, educators and researchers; experience in the practice of chiropractic in various clinical settings (e.g. private practice, hospital-based, military facilities); representation of the most popular treatment technique approaches (e.g., manual, instrumented, rehabilitation); and knowledge of insurance reimbursement for chiropractic services. We asked the expert chiropractic panel to anonymously review the first draft of the protocol, and complete a questionnaire quantifying the level of agreement to 12 statements related to how the clinical protocol reflected a typical chiropractic approach for migraines, the capacity of the average chiropractor to understand and perform the protocol without extensive additional training, the sufficiency of the clinical approach to comprehensively address the most likely clinical scenarios; and the ease of delivery, safety, efficacy, and appropriateness of the clinical protocol for the selected cohort.

The questionnaire included both a 7-point visual analog scale for each statement, as well as prompts for open-ended narrative comments. Phase III involved synthesis of survey quantitative and qualitative input from experts by our study team, and dissemination of these synthesized blinded data to all panel members. Panel members were then convened for a teleconference with the study team during which overall findings were discussed, with priority focused on questionnaire items with the lowest levels of consensus. The study team facilitators (MK, PW) aimed to clarify areas of misunderstanding, and solicit suggestions for



improving areas with high levels of disagreement. Phase IV involved integrating expert panel suggestions into a revised protocol manual, and redistributing the protocol to panel member along with a second endorsement questionnaire.

4.1.2. Delphi validation process results

The expert panel, including the facilitator (MK), was composed of 12 doctors of chiropractic, with an average of 29.1 years of clinical experience. Six of the 12 had research experience.

Table 1 lists the items included in the validation questionnaire, and expert panel scores before and after integration of suggested modifications. Overall levels of agreement were moderately high at baseline, with an average of 4.84 (standard deviation (SD) = 1.39) (7 highest agreement) and a median of the averages of 4.83. Generally, average mean agreement increased (5.83), SD decreased in follow-up (1.12), and the median increased (6.00). Of note, questions related to evidence-informed care and safety received higher and more uniform endorsements, while questions related to scope of practice were scored lower and more variably.

4.1.3. Final chiropractic protocol

An outline of the final protocol is summarized in Table 2.

All chiropractic treatment visits will take place at the OCC. Participants will be treated by one of two OCC chiropractors: MK or an experienced DC trained by MK. MK designed procedures for diagnostic processes and treatment delivery. Chiropractors also will have the option to prescribe home exercises for participants to practice in between visits for the purposes of reinforcing or enhancing the effectiveness of

care provided in-office and/or to build self-efficacy leading to a greater ability to self-manage symptoms. Handouts with instructions about the exercises will be provided. Average frequency of home exercise practice will be recorded during follow-up evaluation visits. Chiropractors will track the date and time of each participant’s appointment to monitor subject compliance. Clinical details of the treatment will be systematically recorded in the subject’s medical record.

Chiropractic evaluation will include a thorough headache history, assessment for risk factors that may contraindicate any treatment component, and a clinical examination. The clinical history will also specifically screen for habit and ergonomic factors that may contribute to musculoskeletal strains, neck pain/strain, and headaches. The physical examination will assess cervico-thoracic spine posture, ranges of motion, the presence of myofascial trigger points, cervical and temporomandibular joint movement restrictions, tenderness, and hypersensitivity, muscle hypertonicity, and general muscular imbalances.

Patients will receive a course of 10 treatments over a 14 week period in addition to migraine education literature (see below). The first treatment and assessment visit will last 40 min; all other visits will be 20 min. The treatment plan will not be rigidly standardized, but rather, personalized to the patient’s clinical needs following the protocol specifically developed for this study based on standard clinical practices employed at the OCC. Rather than limit treatment to a single component of chiropractic care (e.g., spinal manipulative therapy), interventions will be inclusive of patient specific needs and followed the scope of chiropractic practice in the Commonwealth of Massachusetts and taught in Council on Chiropractic Education accredited United States chiropractic institutions. These interventions include: posture correction and

Table 1

Summary scores for chiropractors’ responses to 12 questions regarding the IMPACT clinical protocol. Responses were solicited at baseline and follow-up through the Delphi method.

Survey Question	Time	Survey Responders (1–11)											Median	Mean	SD <sup>a</sup>
		1	2	3	4	5	6	7	8	9	10	11			
1.The protocol is reflective of an evidence-based chiropractic approach for managing episodic migraine headaches.	Baseline	4	6	7	7	6	6	6	7	7	6	5	6	6.09	0.94
	Follow-up	6	6	7	7	5	6	7	6	7	7	7	6	6.45	0.69
2.The protocol is reflective of the average chiropractor’s ability and training.	Baseline	6	6	6	7	6	5	4	7	7	4	5	6	5.73	1.10
	Follow-up	5	3	6	7	3	6	5	6	7	6	7	6	5.55	1.44
3.The protocol accurately represents a chiropractor’s typical approach to migraine headache management.	Baseline	4	4	6	4	5	6	4	6	2	4	3	4	4.36	1.29
	Follow-up	4	3	6	5	3	6	5	6	7	6	4	5	5.00	1.34
4.There are additional chiropractic treatment approaches that should be included in the treatment protocol.	Baseline	1	4	2	6	7	5	1	6	6	2	6	5	4.18	2.27
	Follow-up	6	1	6	7	4	6	7	7	7	7	6	6	5.82	1.83
5.The protocol includes treatments that are not usual and customary to the average chiropractor’s practice.	Baseline	4	2	2	1	2	2	4	5	6	5	3	2	3.27	1.62
	Follow-up	6	2	6	7	3	6	3	6	7	6	6	6	5.27	1.74
6. There are additional exercises that should be included in the treatment protocol.	Baseline	1	4	2	2	4	5	1	1	4	2	2	2	2.55	1.44
	Follow-up	6	4	6	7	4	5	7	6	7	7	6	6	5.91	1.14
7. There are additional self-care approaches that should be included in the treatment protocol.	Baseline	2	6	2	6	6	5	1	1	4	4	5	4	3.82	1.99
	Follow-up	6	4	6	7	4	6	7	6	7	7	6	6	6.00	1.10
8.The protocol is manageable in a standard practice with respect to billing, time constraints, and support staff.	Baseline	4	6	6	4	6	6	6	5	2	4	7	6	5.09	1.45
	Follow-up	5	6	5	6	6	6	6	5	7	5	6	6	5.73	0.65
9.The treatment protocol will be effective in reducing migraine frequency, severity, or duration.	Baseline	4	5	6	6	6	6	5	7	4	6	6	6	5.55	0.93
	Follow-up	4	4	6	6	6	6	6	7	7	7	6	6	5.91	1.04
10.The frequency and duration of care is sufficient to measure a treatment response.	Baseline	4	2	6	7	6	6	7	3	2	6	7	6	5.09	1.97
	Follow-up	6	3	6	7	6	7	6	3	7	7	6	6	5.82	1.47
11.The treatment protocol appears safe.	Baseline	7	6	6	7	7	7	7	7	7	6	6	7	6.64	0.50
	Follow-up	7	6	6	7	6	7	6	7	7	7	7	7	6.64	0.50
12.The selection criteria represent a cohort that is likely to respond to the treatment protocol.	Baseline	4	6	7	4	6	6	6	7	4	6	7	6	5.73	1.19
	Follow-up	5	5	6	6	6	6	6	6	7	6	6	6	5.91	0.54

<sup>a</sup> SD: standard deviation.

**Table 2**  
Chiropractic clinical protocol.

Condition	Manipulation or Mobilization	Passive therapies	Active therapies	Education/home exercise and advice	Treatment frequency
Myofascial Pain Syndrome	Joint manipulation or mobilization if indicated and as tolerated	- Manual or Instrumented soft-tissue relaxation techniques - Muscle stretching	- Compress - stretch techniques as tolerated - Postural correction exercise(s)	- Education about condition & treatment - Ergonomic advice - Self-administered techniques →Mindfulness/meditation →Home exercise	- 10 Tx delivered over 14 weeks - Alter care and reduce frequency or discharge depending on response
Postural or mechanical spinal disorders	<u>Joint manipulation or mobilization as tolerated</u>	- Manual or Instrumented soft-tissue relaxation techniques when indicated	- Postural correction exercise(s)	- Education about condition & treatment - Ergonomic advice - Self-administered techniques →Mindfulness/meditation →Home exercise	- 10 Tx delivered over 14 weeks - Alter care and reduce frequency or discharge depending on response
TMD <sup>a</sup> dysfunction	Joint manipulation or mobilization if indicated and as tolerated	- Manual or Instrumented soft-tissue relaxation techniques when indicated	- Compress - stretch techniques - Postural correction exercise(s) when indicated	- Education about condition & treatment - Ergonomic advice - Self-administered techniques →Mindfulness/meditation →Home exercise	- 10 Tx delivered over 14 weeks - Alter care and reduce frequency or discharge depending on response

<sup>a</sup> TMD: Temporomandibular; Underlined italics indicates primary treatment approach within each diagnostic category; Standard lettering indicates treatment that may be employed depending on co-occurring clinical findings or recognized need; TMD dysfunction may be caused by joint, postural, and/or myofascial components leaving no default primary treatment approach; Participants may also exhibit a combination of diagnostic categories (e.g., postural/mechanical and myofascial pain syndrome). When this occurs, the treatment approach addresses the identified condition(s) considered most important at any given timepoint within the treatment period.

spinal stabilization exercises; soft tissue release techniques; spinal manipulation (i.e. chiropractic adjustment) and joint mobilization; breathing and relaxation techniques; stretches and self-care; ergonomic modifications.

Fidelity to the clinical intervention protocol will be evaluated through a review of medical records. A subset of participant records will be randomly reviewed using a fidelity checklist. The checklist will include elements to ensure clinicians are 1) accurately documenting intervention visit details using EMR templates specifically designed for the study 2) consistently inquiring for and recording adverse event data, 3) including appropriate education, self-management advice, active and passive therapies in the treatment plan, 4) documenting clinical findings consistent with the major diagnostic category, 5) documenting informed consent process, 6) documenting all treatments that were rendered, and 7) excluding interventions that are not protocol-approved.

#### 4.2. Control group

Subjects randomized to the enhanced usual care control group will continue using their usual medical care as prescribed by their physician. Usual medical care for migraine follows guidelines published by the American Headache Society. These guidelines summarize the evidence for the use of pharmacological treatments for migraine and mention that biobehavioral therapies may be an option for some patients. As part of our study, we will ask all participants in the enhanced usual care group to avoid any new treatments for the migraine headache, including both pharmacological and non-pharmacological therapies [33]. Subjects in the control group will also receive migraine education literature as a part of their usual care. Information about medication use is collected at baseline and other therapy use is collected at 14- and 18-week follow-ups. Since the chiropractic care group is provided with increased attention in the form of 10 chiropractic sessions, we also decided to provide the control subjects with increased attention in the

form of biweekly calls from the study research assistants. Subjects in the control group will be asked not to seek chiropractic treatment during the study. All subjects will be asked not to initiate new pharmacological therapies or chiropractic care for their migraines during the study unless prescribed by their physician.

Upon completion of the 18-week final follow-up, subjects randomized to the control group will be offered 10 sessions of chiropractic treatment at the OCC both as a courtesy, and also to enhance recruitment and retention.

## 5. Outcomes

### 5.1. Overview of outcomes

As a pilot study, our primary outcomes center on the assessment of protocol safety, feasibility of participant recruitment, retention, and adherence to all aspects of the protocol. Secondary aims include the evaluation of migraine frequency, severity, duration, and medication use as well as migraine-related disability, health-related quality of life, and psychosocial well-being. All outcomes will be assessed at baseline, post-treatment (14 weeks), and four weeks post-treatment to evaluate the longer-term stability of outcomes. Although this pilot study is not designed or powered to evaluate efficacy, migraine frequency was chosen *a priori* as the clinical outcome of primary interest. Collectively, feasibility and clinical outcomes, in combination with qualitative interview data conducted at baseline and 14 weeks (subset of patients in chiropractic group only), will be obtained to inform the design of a future fully powered trial.

### 5.2. Migraine logs

For 4 weeks prior to randomization, during the interventions, and for 4 weeks post-interventions, participants will be provided daily migraine

logs to record the number of migraine days/month, severity of each migraine (1–10), duration (<4 h, 4–12 h, 13–24 h), migraine symptoms, medicines taken to treat their migraines, and other related health information (e.g. menstrual cycle, exercise, and other symptoms). Migraine logs will be completed daily and submitted to the study RA monthly via mail or email during the study. The study RA will remind subjects to complete and mail the logs during monthly check-in calls.

### 5.3. Additional patient reported outcome measures

At randomization as well as at the 14- and 18-week follow-up time points, participants will also complete these additional questionnaires.

**Headache Related Disability:** HIT-6 is a 6-item assessment that evaluates the impact headaches have on a patient's life and is highly valid and reliable in patients with headaches [34–36].

**Migraine Disability Assessment (MIDAS)** is a 5-item questionnaire; it is the most frequently used disability instrument in migraine research and is highly reliable and valid [37,38].

**Migraine Specific Quality of Life Questionnaire, version 2.1 (MSQv2.1)** is a 14-item questionnaire that measures how migraines affect a patient's daily life and is a highly reliable and valid instrument [39,40].

**Numeric Rating Pain Scale (NRS)** will be used to measure neck pain. The NRS is a single item tool that can be used to measure current pain and usual, best, and worst pain in the past week.

**Depression** will be measured using the 9-item Patient Health Questionnaire (PHQ-9) [41].

**Anxiety** will be measured with Generalized Anxiety Disorder 7-item (GAD-7) scale [42].

**Patient-Reported Outcomes Measurement Information System (PROMIS-29)** is a system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being [43].

**Godin Leisure-Time Exercise Questionnaire** will be used to measure the amount and intensity of general exercise during the study period. This validated instrument consists of 4 items measuring the frequency of light, moderate, and vigorous-intensity leisure-time physical activity [44].

**EXPECT Questionnaire (short form)** [Baseline & 14-week follow-up only for chiropractic group only] is a recently developed and validated questionnaire used to assess individuals' expectations of treatments for chronic pain [45].

### 5.4. Sociodemographic and co-interventions

At baseline, we will assess a range of sociodemographic and health characteristics including age, education, marital status, height and weight, and reproductive phase. At baseline, 14-weeks, and 18-weeks, we will collect information about other interventions used by participants, including frequency of medical appointments related to their migraines or chiropractic care outside of the study visits.

### 5.5. Qualitative interviews

Qualitative research in an increasingly appreciated tool for elucidating practical barriers and facilitators of participant engagement in pilot clinical trials, and for understanding the effectiveness of new therapies by providing insight into aspects of subjects' experiences that may not be adequately captured by surveys and quantitative outcome measures [46–48]. We will conduct standard semi-structured open-ended interviews lasting approximately 30 min at baseline and 14 week follow-up with 50% of subjects randomized to the chiropractic group. Specifically, we are interested in participants' reasons for joining and remaining in the trial, experiences of migraines prior to the study, expectations for chiropractic treatment (baseline), and experience with and perceived effects of chiropractic treatment (14-week follow-up). Each interview will be audio recorded, then transcribed verbatim. The qualitative data will be analyzed using the constant comparative method

of analysis for generating grounded theory [49,50]. Results of this qualitative analysis are reported separately.

## 6. Safety monitoring

### 6.1. Risks of chiropractic treatment

The risks of adverse events, and especially serious adverse events associated with chiropractic care are generally believed to be very low, but these conclusions are based on limited data of varying quality. A 2009 systematic review of chiropractic publications (primarily case reports and observational studies) concluded that most AEs reported are benign and transitory, however, there are reports of complications that are rare and life threatening, such as arterial dissection and epidural hematomas [51]. One recent trial prospectively evaluated the occurrence of AEs in 70 people with migraine (83% women, avg age 40y+/-) randomly exposed to real and placebo (low velocity, low amplitude sham maneuver) chiropractic spinal manipulation therapy (CSMT) [52]. A total of 73/355 CSMT sessions versus 29/348 placebo sessions resulted in a reported AE. The most common attributable AEs were local tenderness and tiredness on the day of treatment, which were moderately higher in the real CSMT group. No severe or serious AEs were observed.

One rare yet serious potential AE reportedly associated with chiropractic manipulation is cervical arterial dissection (CD) which may lead to stroke in some individuals. Published reports on the association of chiropractic care and risk of CD and stroke due to CD vary greatly and are debated [53–59]. A recent scientific statement from the American Heart Association/American Stroke Association published in 2014 summarized the existing literature on the association between cervical arterial dissections (CD) and cervical manipulative therapy (CMT). Of the six case-control studies cited in their literature review, two studies were deemed to be small and of very poor quality [57,58]. The remaining four studies in the review examined the association between chiropractic care and risk of stroke associated with CD. Among younger individuals, those who received chiropractic care had a 3.1–6.6-fold increase in risk of experiencing a stroke associated with CD (particularly vertebral artery) compared to those who did not received chiropractic care. However, there are limitations and potential biases inherent in the available data including the observational nature of all studies and potential for recall or interview bias. Additionally, due to the very low incidence of CD in the general population (~2.6–2.9 per 100,000 population), most studies have small sample sizes and wide confidence intervals [60,61]. The AHA/AHA scientific statement explicitly states that it is not clear whether this association is a causal association or if the association is “due to lack of recognition of preexisting CD in these patients.” The authors conclude: “although the incidence of CMT-associated CD in patients who have previously received CMT is not well established, and probably low, practitioners should strongly consider the possibility of CD as a presenting symptom, and patients should be informed of the statistical association between CD and CMT prior to undergoing manipulation of the cervical spine.” [62] Further questioning a causal association between CMT-associated CD are data from studies demonstrating equivalent associations with CD following primary care practitioner visits [63–66]. The long-theorized causal mechanism of carotid and/or vertebral artery overstretching, which leads to CD, thrombus formation, and stroke is now far less plausible after biomechanical studies demonstrated CMT causes significantly less arterial strain than normal range of motion [67,68].

All patients in our study will be informed of the potential risk of CD during the informed consent process, using language that is included in the text box below. This same language will be used by the chiropractic clinician when discussing the risks associated with some types of



## cervical manipulation.

### Language used in informed consent regarding chiropractic risk

#### Common side effects

Neck or upper back soreness or stiffness that occurs within one day of treatment and self-resolving.

Tiredness/fatigue (short duration, self-resolving).

Headache occurring within one day of treatment (short duration, self-resolving).

Exam procedures may cause neck or upper back stiffness or soreness usually resolving within a few minutes and rarely lasting 1–2 days.

Radiating discomfort from the neck or upper back (short duration, self-resolving).

#### Rare side effects

Light-headedness or dizziness within 1 day following treatment and self-resolving.

Nausea/vomiting (short-duration, self-resolving).

Blurred or impaired vision (short-duration, self-resolving).

Ringing in ears (short-duration, self-resolving).

Arm or leg weakness (short-duration, self-resolving).

Confusion or disorientation (short-duration, self-resolving).

Injury to a blood vessel in the neck (cervical or vertebral artery dissection) that could lead to a stroke.

## 6.2. Adverse events monitoring and classification

We will utilize a multi-pronged approach to monitor safety and track adverse events throughout the study with formal oversight from our institutional IRB and a Data Safety and Monitoring Committee. An adverse event (AE) is defined as any untoward medical occurrence in a participant including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. AEs will be graded as Mild, Moderate or Severe; Expected or Unexpected; and Unrelated, Unlikely related, Possibly related, Probably related, or Definitely related to an intervention in the research protocol.

Adverse events will be proactively tracked in both treatment groups in several ways. We will track events in both groups to account for any adverse events due to usual care (for example, use of migraine medications) and to be able to determine whether the chiropractic care group experienced more adverse events than the enhanced usual care group. During the consenting process, participants will be instructed to track any symptoms of concern on their daily migraine logs, and to directly report any serious symptoms to study staff. Patients in both groups will also be queried about adverse events during monthly calls through both open-ended questions about change in symptoms and directed queries about presence of adverse symptoms listed in the informed consent form (lightheadedness, nausea/vomiting, tiredness/fatigue, increased migraine intensity or frequency, blurred/impaired vision, ringing in ears, arm or leg weakness, confusion or disorientation, neck or back stiffness). If patients report any adverse symptoms, study staff will gather information about relatedness to intervention, severity, and whether medical care was sought. All adverse events will be reported to the study principal investigator, neurologist (CB) and senior chiropractor (MK). If an event is deemed unexpected and possibly related to any study intervention, it will be reported to the IRB. All adverse events will be recorded in a log and submitted for Continuing Review to the IRB. Finally, for those randomized to receive chiropractic care, patients will be queried by clinicians about responses to prior treatments.

## 7. Analysis plan

### 7.1. Evaluation of feasibility

For Aim 1, we will compare the frequency of all treatment-emergent adverse events and severe treatment-emergent adverse events between the treatment groups by negative binomial regression. If serious adverse events are common, we will use the same analysis. If they are rare, we will compare time to first treatment-emergent serious adverse event by log-rank test. We will compare the proportion of participants experiencing a given type of adverse event as classified by MedDRA system

organ class and preferred term by Fisher's exact test. We will compare the closest degree of relatedness to the intervention experienced by each participant by Cochran-Armitage trend test. Using the total number of participants determined eligible as our denominator, we will calculate the frequency of completion of baseline assessments. Using the number of patients randomized to a given treatment group as our denominator, we will calculate the treatment specific frequency of completion of outcome assessments and compare them by Fisher's exact test. For each randomized participant, we will calculate the proportion of attended treatments. We will then calculate the mean and median proportion of attended treatments for our study population.

### 7.2. Clinical study endpoints

We will summarize the baseline characteristics of those randomized to the intervention versus those randomized to usual care using means and standard deviations or medians and interquartile ranges for continuous variables and counts and percentages for dichotomous or categorical variables.

Our primary clinical outcome will be change in the number of migraine days recorded in participant diaries from the run-in period to weeks 11 through 14 of the intervention period. Secondary outcomes will include a responder analysis with responders defined as participants who had a  $\geq 50\%$  reduction in days with migraine from the run-in period to weeks 11 through 14 of the intervention period. Other secondary outcomes will include change in the number of migraine days from the run-in period to weeks 15 through 18, the responder rate from baseline to weeks 15 through 18, change in severity and duration of migraine and doses of acute migraine medications used from baseline to weeks 11 through 14 and weeks 15 through 18, and change in scores on the HIT-6, the MIDAS, MSQ, neck pain, and mood (PHQ-9, GAD-7, PROMIS-29) from baseline to 14 and 18 weeks.

For the analysis of Aim 2 and 3, "baseline" refers to the 4-week run-in period prior to the intervention; "initial follow-up" refers to the weeks 11 through 14 of the intervention period; and "final follow-up" refers to the 4-week period after the intervention. Analyses will be conducted using an intention-to-treat sample to estimate effectiveness in preparation for a future definitive trial and using a pre-specified per-protocol sample to estimate optimal efficacy as a guide to the potential benefit of chiropractic. We will report point estimates and 95% confidence intervals.

We will analyze the effect of treatment assignment on number of migraine days in each period using a linear mixed model to account for correlation among repeated measurements. We will include terms for treatment group (two levels) and a three-way interaction between treatment, time period (three levels: baseline, initial follow-up and final follow-up), and an indicator variable for post-randomization time period. Unstructured covariance will be assumed between the repeated measurement periods. This model will allow us to examine mean number of migraine days at each time period when analyzing migraine days as the outcome as well as changes in the mean number of migraine days over time when analyzing change scores. It will also provide estimates of the between- and within-person variance. The primary contrast for testing the effect of treatment will be analysis of change scores at the initial follow-up (11–14 weeks) period. The model will also yield treatment-dependent differences in migraine days at the final follow-up time point (15–18 weeks). Maximum likelihood estimates from the mixed model will be unbiased due to loss to follow-up if observed outcomes are predictive of future, unobserved outcomes, e.g., if improvement leads participants to decline further intervention if not needed or if worsening of dysfunction impedes participation. We will perform sensitivity analyses using perturbed multiple imputation if there is evidence of strong treatment dependence in drop-out rates. An equivalent model and analytic approach will be used to test our secondary outcomes of change in severity and duration of migraine, doses of acute migraine medications used, scores on the HIT-6, the MIDAS, MSQ, neck

pain, and mood assessed at baseline and 14 and 18 weeks. In secondary analyses, we will perform separate analyses of the effect of chiropractic care + enhanced UC group versus enhanced UC control group on all outcomes among those on prophylactic medications and among those not on prophylactic medications.

For Aim 2, we will also calculate the proportion of participants experiencing  $\geq 50\%$  reduction in the number of migraine days between baseline and the follow-up periods. We will compare the proportions of “responders” among the chiropractic care + enhanced UC group and the enhanced UC control group by calculating an odds ratio and 95% confidence interval.

### 7.3. Sample size

As a pilot study, we did not plan to test for efficacy but rather to obtain information on the feasibility of our design. Thus, we did not perform power calculations. We chose a sample size of 60 as we anticipated this would be a sufficient sample size that would enable us to provide adequate numbers of run-in participants to estimate how many remain eligible and adhere to completing daily headache diaries; test recruitment methods and rates; and estimate variability of outcome measures.

## 8. Data management

Study data from paper forms will be double-entered into REDCap (Research Electronic Data Capture) tools hosted at Partners HealthCare. REDCap provides a secure, web-based interface for validated data entry with auditing features for tracking data manipulation and export, as well as export of data to common statistical packages and data importation from external data sources.

## 9. Discussion

Migraine is a significant public health concern and there is strong interest, among both health care providers and patients, for non-pharmacological options for migraine management. The results of this study will provide essential information on the feasibility of a RCT of chiropractic care in adult women with migraine and provide preliminary evidence on the efficacy of chiropractic care on reducing migraine days, severity, and duration. Information obtained in this study on effective recruitment and retention strategies will be used to inform the design and conduct of a larger scale multi-site trial to evaluate the effectiveness of chiropractic care on migraine frequency and related outcomes.

This study has a number of limitations. First, as a pilot study, it has not been designed or powered to test efficacy. Its main purpose is to evaluate feasibility and use preliminary findings to inform the design of a future trial. Second, we limited our sample to women because the burden of disease is higher in women and peaks at the age range we examined. However, limiting the sample to women may reduce the generalizability of the results. Future studies may want to include men and a broader range of ages. Third, the intention of our enhanced usual care group is to use bi-weekly calls to both partially offset the higher attention received by participants in the chiropractic arm, and also to provide support to enhance study engagement and adherence. As such, this design has elements that are both explanatory and pragmatic. Future more explanatory studies may wish to develop comparison interventions that more specifically and fully control for activities in the chiropractic arm (e.g. alternative time- and attention-matched exercises). Alternatively, more fully pragmatic designs might consider eliminating all non-essential contact with the control group. Finally, our evaluation of fidelity of treatment delivery is limited to medical chart review. Future studies may wish to also include direct fidelity monitoring via observation and/or video recording.

This pilot study represents a novel contribution to the field because

prior studies among individuals with migraine have only focused on spinal manipulation and have not evaluated chiropractic care as an integrative approach to migraine treatment [5]. In addition, as part of this pilot study, we developed and report here a chiropractic care protocol for individuals with migraine that was validated by a team of senior chiropractors using the Delphi method. As a next step in a large trial, we will evaluate the fidelity of protocol delivery. Finally, we used the PRECIS-2 framework to articulate the rationale for choosing key study design elements, which includes both pragmatic and explanatory features. This analysis could assist others in the design of other complex, multimodal and non-pharmacological interventions for the treatment of other neuromusculoskeletal pain-related conditions.

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