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NIH Collaboratory Ethics and Regulatory Core: UG3 Consultation Call
Implementation of the American College of Physicians Guideline for Low Back Pain (IMPACt-LBP)
October 14, 2021; 4:00-5:00 pm ET (via Zoom)

Attendees:

- Core and Coordinating Center: Joe Ali (Johns Hopkins University), Judith Carrithers (Advarra), Andrew Garland (Johns Hopkins University), David Magnus (Stanford University), Stephanie Morain (Johns Hopkins University), Pearl O'Rourke (retired), Tammy Reece (Duke University), Damon Seils (Duke University), Jeremy Sugarman (Johns Hopkins University), Kevin Weinfurt (Duke University), Dave Wendler (NIH)
- Demonstration Project team: Christine Goertz (Duke University), Adam Goode (Duke University), Jon Lurie (Dartmouth University), Kelley Ryan (Duke University)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	OWNER
Brief review of Demonstration Project	Meeting attendees received the Research Strategy and Resource Sharing Plan for IMPACt-LBP's Coordinating Center and Data Coordinating Center with the meeting agenda. Core members, IMPACt-LBP team members, and staff of the NIH Collaboratory Coordinating Center introduced themselves. The IMPACt-LBP team members present included Christine Goertz, Adam Goode, Jon Lurie, and Kelley Ryan. **Project overview**: Principal investigator Jon Lurie gave a brief overview of the project. IMPACt-LBP is studying implementation of the primary spine provider (PSP) model of multidisciplinary collaborative care for low back pain in primary care. **Healthcare system partners**: Dartmouth-Hitchcock Medical Center, Duke University Health System, University of Iowa **NIH Institute Providing Oversight**: National Center for Complementary and Integrative Health (NCCIH). Additional support from National Institute of Arthritis and Musculoskeletal and Skin Diseases and National Institute of Child Health and Human Development. **Study design**: The project will be a pragmatic, multisite, 2-arm cluster randomized trial that will evaluate the effect of first-contact patient referral to PSPs (physical		

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	therapists and doctors of chiropractic). The study aims to determine if initial contact with these PSPs will improve outcomes for patients with a primary complaint of low back pain, compared with usual medical care. **Outcomes**: The co-primary outcomes will be patient-reported changes in PROMIS Pain Interference and PROMIS Physical Function from baseline to 3 months. Secondary outcomes include opioid prescriptions; PROMIS measures of pain intensity, catastrophizing, sleep, and depression; health-related quality of life and satisfaction; and procedures, prescriptions, and hospital and emergency department visits at baseline and 3, 6, and 12 months. Additional data collection will be done through 24 months on a subset of patients enrolling during the first 18 months of recruitment. Core members had no questions about the project overview.		
Status of IRB approval	Jeremy Sugarman asked about the status of IRB approval in the project's UG3 planning phase. Jon Lurie responded that the UG3 phase does not include human subjects research and, thus, does not require IRB approval. The project team will likely want to conduct focus groups toward the end of the year to interrogate the detailed trial protocol and patient flow plan. IRB approval will be needed at the individual institutions where these focus groups are to be conducted. The team plans to submit the protocol for the UH3 implementation phase for IRB approval in December and plans to request a waiver of documentation of consent. Pearl O'Rourke asked whether all patients who call their primary care clinic with a complaint of low back pain will be informed about the study, invited to participate, and undergo randomization. Jon Lurie clarified that randomization will occur at the clinic level. All patients who call their clinic to schedule an appointment for evaluation of low back pain will be informed that the clinic is participating in a study, and the patients will have an opportunity to opt out of data collection at several time points. Pearl O'Rourke asked whether participants will be informed that they may be contacted later about opportunities to participate in the focus groups described in Aim 3d of the Research Strategy. Jon Lurie confirmed that this is correct.		

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	The study will use Copernicus as the central IRB.		
Risk (Does the project meet regulatory criteria for being considered minimal risk?); and consent (planned processes for relevant subjects)	David Magnus asked about the study team's plan to seek a waiver of consent or a waiver of documentation of consent. Jon Lurie responded that the study team is considering either as a possibility. The study team initially considered whether the project could be considered a quality improvement initiative—specifically whether the planned data collection would be considered part of routine care—because the sites gather some data on the patient outcome measures as part of routine care. However, because some of the questionnaires to be used in the study go beyond the data collected as part of routine care, the activity is properly considered as research for which consent is needed. Nevertheless, the team considers the research to be minimal risk and think it desirable to use an oral consent process. Accordingly, the study team will seek a waiver of documentation of consent. David Magnus recommended that the study team be more precise in their language when describing that the study presents "minimal risk" (rather than "low risk," which was used in the grant application and is not an applicable regulatory standard). Pearl O'Rourke asked whether patients in clinics assigned to the usual care arm will be allowed to seek care from PSP practitioners. Jon Lurie responded that some patients in the usual care clinics may have seen a PSP before contacting the clinic. Because of the pragmatic nature of the trial, the study team does not want to try to require patients to adhere strictly to the provisions of their study arm. When patients in usual care clinics hear about the study, they may decide to seek care from PSPs, but the study team does not expect this to be a common enough occurrence to jeopardize the study. Joe Ali asked whether the disclosure script used for obtaining oral consent will contain language about the patient's clinic being assigned to a particular study arm. Jon Lurie responded that patients will be informed that their clinic is providing care in a certain way and that the researchers will collect data to measure the outcomes of that care. The disclosure script will not disclose the randomization assignment per se. (In correspondence after the meeting, Jeremy Sugarman asked the study team whether patients will be given this information if they ask. Kelley Ryan responded that patients requesting additional details will be provided with them.)		

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	David Magnus asked about the consent strategy, since it has implications for the type of waiver the study team should seek. Jon Lurie clarified that the study team will need to conduct some kind of oral consent process because they will gather patient data that may not otherwise be collected in routine care. The study team has considered whether to seek an alteration of consent to streamline the process. An important factor in this decision will be the length of the disclosure conversation, because this conversation will also serve as the scheduling call for the patient's clinic appointment. Jeremy Sugarman asked who will conduct the scheduling and consent conversation. Jon Lurie responded that a staff member dedicated to the project will be granted privileges to access the clinic's scheduling system and will conduct both the research disclosure and appointment scheduling. Jeremy Sugarman agreed that the study team should be able to make a satisfactory argument for a waiver of documentation of consent. Dave Wendler recommended that the study team write out and time the disclosure script. He agreed it is possible that the study will likely be eligible for a waiver of documentation of consent. However, if the disclosure script is so long that it would prevent the study team from answering the research question by excessively interrupting or burdening the clinic workflow, the study team could consider shortening the script and requesting approval for an alteration of consent. Jeremy Sugarman asked whether any members of the Core had further questions or concerns about whether the project meets the regulatory criteria to be considered minimal risk. None were voiced.		
Privacy (including HIPAA)	Jeremy Sugarman asked if the study team will collect both patient-reported outcomes and data from the electronic health record. He asked whether there were any concerns about privacy when using those data. Jon Lurie confirmed that both data sources are planned and responded that the study team has not identified any privacy concerns. Judith Carrithers noted that the disclosure will require a HIPAA privacy statement and that the study will require an alteration of the requirements of written HIPAA authorization.		

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Monitoring and oversight	Jeremy Sugarman asked about the plan for monitoring and oversight of the study. Jon Lurie responded that NCCIH will have its own DSMB monitor the trial. Jeremy Sugarman also noted that the study team will receive a certificate of confidentiality as a condition of the grant award and will need to be aware of the requirements associated with it, especially with regard to populating the EHR with research data. He recommended the following article: • Sugarman J, Carrithers J. Certificates of confidentiality and unexpected complications for pragmatic clinical trials. *Learn Health Syst*. 2020 Jul 14;5(2):e10238. doi: 10.1002/lrh2.10238. PMID: 33889738; PMCID: PMC8051346.	Share the article by Sugarman and Carrithers with the study team. (Completed)	**Tammy**
Issues beyond this project (regulatory and ethics concerns raised by the project, if any)	Jeremy Sugarman asked whether the PSPs will be "engaged in research." Principal investigator Christine Goertz responded that they would be aware of the research activity and that they will be asked to write a follow-up letter to the patient's primary care provider to inform them that the patient has begun a course of care. This practice is a standard of care for these practitioners. Judith Carrithers and Pearl O'Rourke noted that, if this practice is a standard of care, it may be possible to describe the practitioners as not being "engaged in research," even if the practice is not implemented in every case in real-world routine care.		
Other matters	Pearl O'Rourke asked about the percentages of PSPs treating patients enrolled in the study who will be doctors of chiropractic or physical therapists. Jon Lurie responded that this will be an interesting outcome of the study, because it will depend on patients' preferences. Christine Goertz noted that the study team hopes to include a qualitative component in the study to explore patients' choice of PSP. Joe Ali asked whether the study team will use a standard description of the PSPs when patients are informed about the study and whether a particular type of practitioner could refer a patient to another type of practitioner. Christine Goertz responded that the script will include a description of the practitioners. It is theoretically possible that one practitioner will refer a patient to another type of practitioner, but the study team does not believe this is likely.		

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	Pearl O'Rourke and Joe Ali asked how the study team will deal with receiving information in the study that may not have been collected in routine clinical care and that could trigger some follow-up, such as outcomes that may indicate risk related to depression, anxiety, or suicidal ideation. Jon Lurie responded that the PHQ-9 measure is used in the clinics as part of routine care and that the study team will be alert for these indicators of risk.		
Adjourn	Jeremy Sugarman noted that the minutes of the meeting will be published on the NIH Collaboratory website at https://rethinkingclinicaltrials.org/demonstration-project-ethics-and-regulatory-documentation/. Tammy Reece noted that IMPACt-LBP will be included in the Core's biannual meetings.	Send the Core's biannual meeting invitations to the study team.	**Tammy**

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3. RESEARCH STRATEGIES

3.1 Significance

Low back pain (LBP) is the leading musculoskeletal pain condition and a key source of medical costs and disability.[1-6] An estimated 20% of U.S. adults have LBP, with 50-80% reporting a lifetime significant episode and 23% having disabling pain.[7] LBP impacts over 31 million Americans at any given time[8], has increased threefold in prevalence in a 10-year period[5], and results in $100-$200 billion per year in total healthcare costs.[9] Our companion applications – "Implementation of the American College of Physician guideline for low back pain using a Multidisciplinary Conservative Care (MC2) model at the initial point of patient contact: A cluster randomized trial(IMPACt-LBP)-CCC in response to PAR-18-662 and "Implementation of the American College of Physician guideline for low back pain using a Multidisciplinary Conservative Care (MC^2) model at the initial point of patient contact: A cluster randomized trial(IMPACt-LBP)-DCC" in response to PAR-18-663 - make an important contribution towards addressing this public health crisis by offering a novel, guideline-congruent, non-pharmacological approach to LBP management. The underlying scientific rational for the proposed study, designed to evaluate a multidisciplinary conservative care (MC^2) model for LBP (MC^{2}LBP), is that novel, nonpharmacological approaches have the potential to impact care delivery for LBP in several important ways. First, by providing a mechanism for often challenging patients to receive conservative, evidence-based, patient-centered care that is consistent with existing guideline recommendations. Second, it is likely based on available data that overall per-capita costs for LBP care would decrease if, in those cases when it is appropriate, primary or specialty care was replaced with less expensive options.[3,10] Third, LBP patients can be time consuming and challenging particularly to extremely busy primary care physicians with minimal formal training in pain management.[11] While there are compelling reasons to consider implementation of conservative care models, it is critical that such models be rigorously tested within the context of large, multi-site randomized pragmatic clinical trials to evaluate effectiveness, cost, safety and scalability. Three leading academic Health Care Systems (HCS)- Duke University Health System (DU), University of Iowa (UI) Health Care and Dartmouth-Hitchcock Medical Center (DH) have partnered to take on this important task.

The current standard of care for LBP can lead to more harm than benefit. LBP is one of the most common reasons for ambulatory care visits to US physicians.[12] In 2018, 62% of US adults who reported seeing a healthcare provider for spine pain within the past year said that they had seen a medical doctor.[13] Over half of LBP visits are made to primary care physicians (PCPs).[14] Unfortunately, it is becoming increasingly better understood that the usual medical care for LBP, which most commonly includes prescribed medications and invasive therapies such as non-steroidal anti-inflammatory drugs, opioids, spinal fusions and epidural injections are often ineffective or of questionable benefit; further, many of these standard treatments result in the risk of significant harm to patients.[15-21] The ongoing opioid epidemic is a clear indication of the significance of this problem. Over 60% of opioid related deaths are linked to chronic pain[22] and consistent opioid use is found in a majority (61%) of those with chronic LBP.[23] In 2012, a prescription for opioids was received by 20% of patients who visited a medical doctor for acute or chronic pain[24] and almost half of all opioid prescriptions are written by PCPs.[25] PCPs are aware of this problem, reporting that they "have concerns about opioid pain medication misuse, find managing patients with chronic pain stressful, express concern about patient addiction, and report insufficient training in prescribing opioids".[11]

In response to the concerns outlined above, several high profile public and private organizations have developed guidelines for the treatment of non-cancer pain, including LBP. These include the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain (2017),[26] The Joint Commission new and revised pain assessment and management standards for its accredited hospitals (2017),[27] and the ACP Guideline on LBP (2017).[28] All have found the strength of the evidence sufficient to support the recommendation of publicly available non-pharmacological therapies as preferred treatments for patients suffering from pain. However, the ACP Guideline goes one step further in recommending that frontline treatment be shifted from prescription medication to nonpharmacologic therapies, stating **"for patients with LBP, clinicians and patients should initially select nonpharmacologic treatments"**. Specific ACP treatment recommendations include superficial heat, massage, acupuncture, spinal manipulation, exercise, and progressive relaxation.

Multidisciplinary Conservative Care Model for Low Back Pain (MC^{2}LBP): MC^{2}LBP builds on existing guidelines and borrows from work previously published by Goertz and others describing new models of care for patients with spine-related disorders, including LBP.[29-32] These models include conservative care clinicians such as doctors of chiropractic (DC) and physical therapists (PT) as part of multidisciplinary care teams. Both

DCs and PTs have specific expertise in the diagnosis and treatment of LBP and focus on many of the nonpharmacological approaches for management of LBP outlined in the guidelines mentioned above. Consistent with the ACP Guideline on LBP, MC^{2}LBP engages DCs and PTs to serve as first contact clinicians for LBP patients entering one of the three participating AHCs within the context of a multi-disciplinary team approach to care. **The proposed MC^{2}LBP Model focuses on DCs and PTs as first contact clinicians** because evidence of use, efficacy and effectiveness for these interventions exists**: First, the use of DC and PT services in the U.S. is common.** A recent Gallup survey found that in 2015 more than 50% of U.S. adults sought care from a DC; 14% had done so within the previous year.[33] Data from the most recent Medical Expenditure Panel Survey indicates over 60 million PT visits occur annually.[34] The low referral rates for LBP from primary care to PT and DC support our innovative intervention approach. While the majority of insurers cover DC and PT services, a recent commentary by Goertz and George[35], published in JAMA Network Open, reported copays and deductibles for such coverage are significantly higher than for prescription medications, including opioids. **Spinal manipulation (SM), a treatment delivered by both DCs and PTs, has strong biological plausibility in the treatment of LBP.** SM involves the application of a load (force) to specific body tissues with therapeutic intent. This load, which has traditionally been delivered by hand, can vary in its velocity, amplitude, duration, and frequency, as well as anatomic location, choice of levers, and direction of force".[36] Available evidence suggests SM provides therapeutic benefit through several pathways that include stretching or breaking fibrous adhesions formed in and around spinal joints,[37] disrupting motion restricting and/or painful adhesions,[38] and reducing paraspinal muscle tone.[39,40] **Findings from well-conducted systematic reviews are sufficiently strong to result in the recommendation of SM**[41-43] **and exercise**[44-46] **in national guidelines targeted at LBP,**[47,48] **including the ACP Guideline for LBP.**[49,50] Further evidence in support of DC care was strengthened with the recent publication of data from a pragmatic clinical trial conducted by members of the proposed project team (See ACT under Preliminary Studies).[51] PT delivered spinal manipulation has also been shown to be effective for decreasing pain and improving physical function with acute LBP.[43,52] Exercise is a common intervention employed by both PTs and DCs that has proven effects for reducing LBP intensity,[44-46] increasing physical function across a lifespan[44-46,53] and decreasing re-occurrence of LBP events.[54] Further, research has shown that physical therapy and chiropractic care, including such care at the initial point of contact, is associated with decreased use of opioids in the short and long term.[55-57] **Patient satisfaction with DC and PT care is high when compared to usual medical care.** Studies consistently show that patients receiving chiropractic care are more satisfied than patients receiving medical care alone.[51,58-61] Patient satisfaction with PT care is also very high.[62] Further, the alliance between the PT and the patient has demonstrated positive effects on treatment outcomes for LBP.[63,64] **In addition, DC and PT care is safe.** DCs and PTs are licensed as direct access clinicians in all 50 states.[36,65] Serious adverse events are rare[66-68], with only minimal side effects such as mild muscle stiffness or soreness commonly reported.[69-76] Such care is considerably safer than taking NSAIDS over time.[77] DCs and PTs are well trained to perform a history and evidence-based examination to arrive at a diagnosis and then autonomously manage that patients care or make an appropriate referral for co-management or specialty care. Evidence supports that both PTs and DCs effectively screen and differentially diagnose musculoskeletal disorders from other systemic conditions like cancer.[78,79]

There is a critical need to implement and evaluate the MC^{2}LBP model at a health systems level. First, there is little data to support the premise that either the guidelines described above or physician training based on those guidelines will lead to meaningful change in clinical practice for LBP without concurrent health systems change. In a Gallup Survey conducted one-year after the ACP Guideline for LBP was released, 21% of patients with LBP reported a PCP referral to a DC. In contrast, this same survey identified that more than 28% received a recommendation to take opioids and 28% received a recommendation to take benzodiazepines, medications which have limited effectiveness for the management of either acute or chronic LBP.[80] Further, despite increases in LBP encounters within primary care, referrals to PT have remained stable while opioid prescriptions for LBP have increased.[6,81] Second, a recent study by Heyward and colleagues found that the majority of private and public coverage of nonpharmacological treatments for LBP is suboptimal, health plan executives are not aware of the evidence base supporting these options, and payment policies targeted toward coordination of pharmacological and nonpharmacological care were "virtually non-existent".[82] Third, in the rush to identify strategies to combat the public health crisis created by the burden of LBP and the risks associated with many commonly used treatments, health systems run the risk of exacerbating the crisis by implementing models of care that have not yet been rigorously tested. Much of the evidence currently used to support policy change is based on observational data that is prone to bias. It is critical that such models,

including MC^{2}LBP, be implemented in real world clinical settings in a manner that is scalable and then rigorously evaluated using pragmatic study designs and randomized at the clinic level.

Summary of Significance: LBP is a significant public health problem that is not treated optimally. Strategies that bring patients closer to guideline-congruent conservative care for LBP, such as the MC^{2}LBP model, are likely to result in significant improvements in patient outcomes and cost savings. However, such models must be implemented in real world clinical settings in a manner that is scalable, and then rigorously evaluated using pragmatic study designs. The proposed project brings together an outstanding multi-disciplinary team to accomplish these goals, with the potential for widespread impact on both individuals and HCS.

3.2 Innovation

The proposed IMPACt-LBP project proposes a new strategy for LBP management within academic HCS. The MC^{2}LBP model is a highly novel approach to providing guideline-congruent care for LBP, a condition that is in desperate need of innovation. 1) While numerous clinical trials have studied the impact of either DC or PT compared to usual medical care for LBP, access to these clinicians is invariably downstream in the patient care trajectory, often as a treatment of last resort. IMPACt-LBP will be the first study to rigorously evaluate the comparative effectiveness of usual medical care alone vs directing patients with a primary complaint of LBP to conservative care clinicians at the first point of contact within an academic HCS. 2) The fact that we will do so by leveraging novel collaborations within the context of a multi-site pragmatic cluster-randomized clinical trial design within three leading academic HCS further contributes to our innovative approach. During the MC^{2}LBP model implementation phase of this project, we will examine informal information exchange and formal contractual relations among primary care clinics, PTs and DCs in order to identify characteristics needed to support building local, but non-co-located multidisciplinary teams, ultimately leading to an innovative collaboration of healthcare providers focusing on a common complaint that is difficult to treat using current health care delivery strategies. We will also be altering clinical practice within teaching environments, providing a pathway that we believe will be scalable to other academic HCS and has the potential to reach the next generation of primary care clinicians. 3) We will be utilizing a novel combination of the PCORNet Common Data Model and EPIC Electronic Health Records (EHR), along with currently used mechanisms for claims processing and performance measurement in community-based PT/DC clinics as data collection, data management and transfer strategies. We will also be evaluating three different approaches for collecting Patient Reported Outcomes (PRO) data and developing a workable solution that is likely to have impact beyond addressing study aims. 4) Co-led by a medical physician, a DC and a doctoral level trained PT, IMPACt-LBP brings together an outstanding multi-disciplinary study team. In addition to their diverse clinical backgrounds, these investigators bring their collective expertise in the conduct of pragmatic clinical trials, the study of chiropractic and PT care in integrated care settings, and firsthand knowledge of academic HCS from clinical, research and administrative perspectives. 5) Finally, our large sample size will allow us to conduct important secondary analysis. For example, we plan to follow some patients for the entire data collection period of the study, allowing us to collect information on outcomes and healthcare utilization for two or more years in the subset of patients recruited within the first 18 months of study implementation. In addition, we will address an important concern regarding the safety of care initiated by both DCs and PTs by comparing time to diagnosis of LBP "red flags", such as cancer or infections, between participants in the MC^{2}LBP model group vs those receiving usual care alone.

3.3 Approach

Overview: Study efforts begin with a one-year planning phase involving completion of 23 milestones in 2 categories of phased activities that are summarized briefly below. Immediately upon approval of our transition request, we will implement MC^{2}LBP within participating primary care clinics (Aim 1), followed by rigorous evaluation of the comparative effectiveness (Aim 2) and resource use and cost (Aim 3) of MC^{2}LBP vs. usual medical care alone for patients suffering from LBP. The study will include an estimated 1,800 patients age 18 years and older who contact one of 22 participating primary care clinics affiliated with DU, the UI and DH to make an appointment for a primary complaint of LBP of any duration. Clinics cluster-randomized to provide MC^{2}LBP will provide patient information regarding the ACP guideline at the initial point of contact by the scheduling center and assist patients in making an informed decision regarding whether or not to make an appointment for multidisciplinary conservative care with a PT or DC. Control clinics will provide usual medical care alone. For Aim 2, primary outcomes are functional status and pain interference measured using PROMIS, captured through patient self-report at baseline, 3, 6 and 12 months following baseline. Secondary outcomes include opioid use and patient satisfaction with symptoms and treatment. For Aim 3, medical resource use will include prescription medications, visits to MDs, DCs, PTs and other healthcare professionals, as well as

musculoskeletal-related injections, procedures, surgeries, emergency department visits, and hospitalizations. Important exploratory analyses will: 1) evaluate long-term outcomes and healthcare utilization by following patients enrolled in the study during the first 18 months of data collection for up to 24 months; and 2) compare time to diagnosis of LBP "red flags" (ie: Vertebral fractures, Inflammatory disorders (eg, axial spondyloarthritis), malignancy, Infections, Intra-abdominal abnormalities) between participants in the MC²LBP model group vs those receiving usual care alone. Data will be collected via the EHR from each site using the clinical data research network (CDRN) common data model (CDM). All study related data will be coordinated and analyzed by the MC²LBP DCC at Duke University. This project will also include a process evaluation of patient, clinician and clinic administrator perceptions of non-specific treatment factors and the effectiveness of MC²LBP across the 3 sites to assess adoption, implementation challenges, and program acceptability to inform model development and dissemination of study findings (Aim 4). We will also develop a robust dissemination and implementation plan so we are prepared in the event that study findings demonstrate that the MC²LBP model is safe and effective. Both groups will have full access to usual medical care as needed throughout the study.

CCC and DCC Collaboration. Ongoing communication and a close working relationship will be key to ensuring consistent and effective project management across the CCC and DCC. While each will be responsible for their respective reporting requirements, all PIs and respective PLs will meet together weekly to review trial status and progress. The following issues will be reviewed: the status of the timelines, milestones, and metrics; changes in scope of work; financial status; key issues or problems; protocol adherence; recruitment; participant withdrawals; and development and implementation of protocol amendments. Plans will be discussed for the mitigation of existing or anticipated issues. DCC and CCC PIs will also collaborate with the Steering Committee and the NCCIH as described in more detail in the CCC application. The close coordination of CCC and DCC teams will ensure success in meeting project milestones and timelines.

Pragmatic Study Design: Pragmatic clinical trials arose out of concerns that many traditional (i.e. explanatory) RCTs did not adequately inform practice because they were often performed with relatively small samples at sites with highly selected investigators and participants, thereby overestimating potential benefits and underestimating potential harms.[74] As initially discussed by Schwartz and Lellouch, pragmatic trials can more directly inform a clinical or policy decision providing evidence for adoption of an intervention into real-world clinical practice.[73;75;76] Furthermore, pragmatic trials frequently involve complex interventions consisting of several interacting components and involving the skills and experience of healthcare

Figure 1. PRECIS diagram illustrating the pragmatic aspects of this cluster randomized study.

professionals to deliver them.[74] In their update of primary care research priorities in LBP in 2013, Costa et al. found that "organizing more effective primary care for LBP, implementing best practices, and translating research to practice" were viewed with substantially greater importance compared with their prior assessments.[78] Thus, while traditional clinical trials of truly novel interventions still have the potential to be "game-changers", [74] the complex and highly heterogeneous nature of LBP and its treatment, as well as the failure of many traditional approaches to reducing the prevalence and impact of LBP, suggest that more pragmatic approaches, especially those focused on the delivery of LBP care may offer greater value. The MC²LBP model is the type of complex intervention and the question of whether MC²LBP improves outcomes for patients with LBP is the type of policy relevant question that is ideally suited for a pragmatic RCT approach. (**See Figure 1 for PRECIS diagram**).

   Participating Sites. Site selection for the proposed project took into consideration a number of important factors. First, all three HCS utilize sophisticated patient data capture mechanisms through the patient EHR, thus facilitating the conduct of our proposed pragmatic, "low touch" clinical trial. Both Duke and UI HCS belong to PCORNet CDRNs, and utilize the same CDM. The CDM facilitates the capture of health care resource utilization and clinical outcomes data collection for the duration of a study, making research more efficient, less burdensome and costly for both study sites and participants. While DH does not belong to a CDRN, they host a
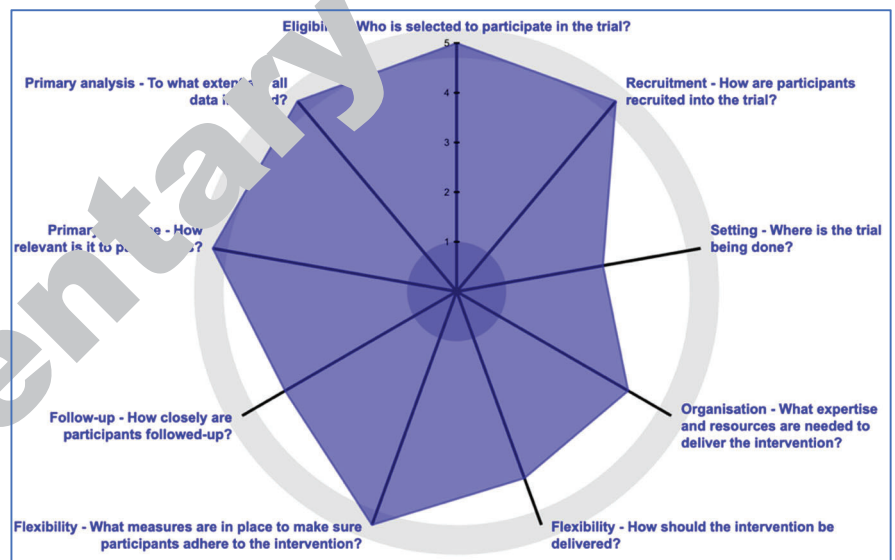
robust Analytics Institute, housed within the NCATs-funded Clinical and Translational Science Institute (Dartmouth SYNERGY) including a specific data extraction team from the EHR informatics group. This team has consistently demonstrated the ability to work on federally funded projects that have harmonized the collection and abstraction of EHR data including utilization measures, prescriptions, admissions and cost. Second, the geographic distribution, variation in populations served, size differences and differing insurer contracts between the three participating academic HCS allow us to better understand issues of scalability and implementation challenges and opportunities across health systems, contributing to the generalizability of our study results. For example, the distribution of women, African-Americans and Latino-Hispanic seeking care for LBP across these combined academic HCS is consistent with population based studies on LBP.[5,83,84] Details of the distribution of LBP, sex, race and ethnicity across these three HCS is located in section 2 Study Population. Details of the three academic HCS are provided in the Facilities document and summarized briefly below:

Duke University: Achieving the robust evidence base for evaluating the effectiveness of the MC²LBP strategy requires an experienced and well-organized DCC with strong existing ties to the CCC)and expertise in trial design, electronic health record (EHR) data, data management, statistical analysis, and the ability to disseminate findings to the broad clinical community. The Duke Clinical Research Institute (DCRI) is uniquely positioned to serve these critical functions. The DCRI is the world's largest academic research organization and ensures close integration of clinical, biostatistics, informatics, and project management expertise. With over 1,000 faculty and staff, the DCRI is capable of conducting any clinical research project, from the smallest pilot study to truly global megatrials. Our experience stretches from Phase I to Phase IV

Table 1 Description of team members, role and expertise		
Team Member / Department	**Role**	**Relevant Area of Expertise**
Clinical Coordinating Center Leadership Team		
Christine Goertz, DC, PhD / University of Iowa and Department of Orthopaedic Surgery at Duke University	PI	Chiropractic, Health Services, LBP, Collaboratory's, PCORNet, Pragmatic Clinical Trials in HCS
Adam P. Goode, DPT, PhD / Duke Clinical Research Institute, Department of Orthopaedic Surgery at Duke University	PI	Physical Therapy, Health Services, LBP, Epidemiology
Jon Lurie, MD, MS / Dartmouth-Hitchcock College	PI	Primary Care, Conservative LBP Care, Pragmatic Clinical Trials
Lesley Curtis, PhD /Duke Population Health	Co-I	Clinical/Comparative Effectiveness, Health Care Delivery, Pragmatic Clinical Trials, and Common Data Models (CDM)
Stacie Salsbury, PhD, RN / Palmer Chiropractic College	Co-I	Qualitative Research Methods
Clinical Study Teams by Health Care System (within CCC)		
Duke University		
Rowena Dolor, MD, MHS / Primary Care Research Consortium	Co-I	Primary Care, Cluster Randomized Trials, Pragmatic Clinical Trials in HCS
Steven George, PT, PhD / DCRI	Co-I	LBP, pragmatic clinical trials
Keith Marsolo, PhD / Population Health	Co-I	Informatics
University of Iowa Team		
Barcey Levy, MD, PhD / Department of Family Medicine	Co-I	Practicing Family Physician, Practice based research networks, Pragmatic Clinical Trials
Patricia Winokur, MD / Department of Internal Medicine	Co-I	Internal medicine, clinical trials
Britt Marcussen, MD /Department of Orthopedics and Rehabilitation	Co-I	Family medicine, sports medicine
Dartmouth-Hitchcock Medical Center Team		
James Stahl, MD / Department of General Internal Medicine	Co-I	Primary care, outcomes research
Sarah Lord, PhD / Psychiatry and Biomedical Data Sciences	Co-I	Implementation research
Shoshanna Hort, MD / Clinical Informatics Leadership Group	Co-I	Primary care, informatics
Data Coordinating Center Leadership Team		
Hrishikesh Chakraborty, PhD / DCRI	PI	Cluster Randomized Trial Design and Analysis. Pragmatic Clinical Trials in HCS
Adrian Hernandez, MD/ DCRI / Population Health	Co-I	Outcomes Research, Multicenter and National Research Coordination, CDM
Elizabeth Chrischilles, PhD / University of Iowa Department of Epidemiology	Co-I	Comparative effectiveness research, Pragmatic Clinical Trials in HCS
Shelby Reed, PhD, RPh / Population Health	Co-I	Economic methods and analysis. Pragmatic Clinical Trials

clinical trials, cluster randomized trials, pragmatic trials, medical device trials, registry, outcomes, and economic studies, many of which have had major impact on patient care. DU is the home of the NIH HCS Collaboratory Coordinating Center with extensive experience in coordinating large multi-site health systems studies. Directly relevant to this proposed project, the NIH HCS Collaboratory program serves as the Resource Coordinating Center for a new group of large-scale embedded pragmatic clinical trials (ePCTs) on pain management and reducing opioid prescribing - Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM) . IMPACt-LBP will benefit from harmonization processes and lessons learned in the execution of PRISM and other Collaboratory efforts through Drs. Adrian Hernandez and Lesley Curtis, as well as their their 7+ years' experience in successfully facilitating embedded ePCTs and overcoming challenges of

implementation in health care systems. Also at DU, the Primary Care Research Consortium (PCRC) has successfully completed an NIH funded cluster randomized clinical trial on osteoarthritis. This study utilized 10 Duke PCP clinics enrolling n=537 patients. **University of Iowa:** External research funding at the University of Iowa totaled $541M in FY2016. The University Hospitals and Clinics are the only Comprehensive Academic Medical Center in the state of Iowa. UI Health Care maintains 770 inpatient beds and cares for over 31,000 acutely ill children and adults and provides nearly 997,000 clinic visits each year. **Dartmouth-Hitchcock:** DH is New Hampshire's only academic HCS including a 396-bed (licensed) hospital with the only Level 1 trauma center. DH is a nonprofit academic health system serving communities in northern New England. DH provides access to more than 1,000 primary care doctors and specialists in almost every area of medicine at DH; four affiliate hospitals; 24 ambulatory clinics across New Hampshire and Vermont. Annually, across the DH system, there are more than 1.3 million outpatient visits, nearly 22,000 surgeries, and 27,000 patients discharged.
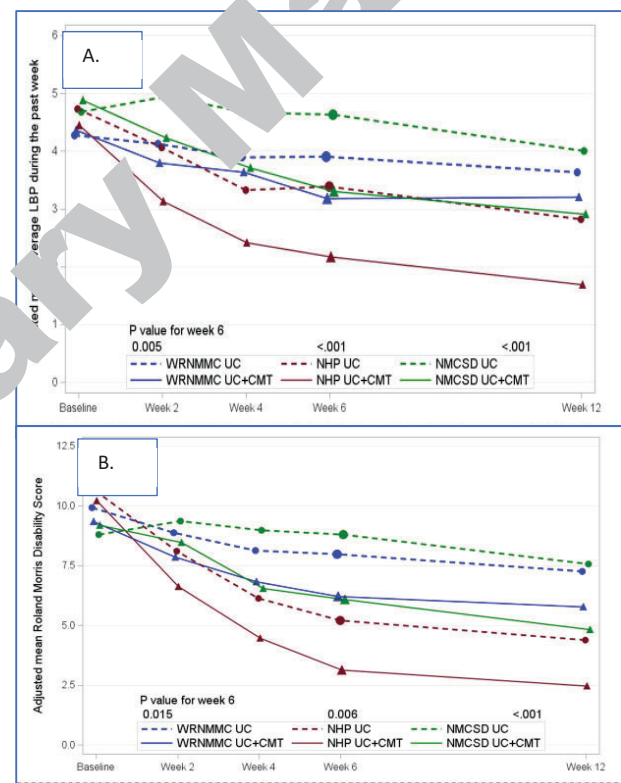
Summary of investigative team and areas of specialty are critical to the success of the proposed project. The truly outstanding investigators (**See Table 1**) assembled for the proposed project collectively for both the DCC and the CCC by PIs Goertz (CCC), Goode (CCC), Lurie (CCC) and Chakraborty (DCC) is a major strength of this proposal. Our study teams are comprised of researchers and clinicians with synergistic expertise in primary care, physical therapy, chiropractic, LBP clinical care and research, biostatistics, informatics, the CDRN common data model , clinical data registries, UG3/UH3 Projects and ePCTs, PBRNs, mixed methods,

and academic HCS settings. Space does not allow us to more fully describe the study team here but more information can be found in our biosketches, the Clinical Trial Table in Section 5.1.1, Facilities, section 3.5 Study Team, Letters of Support and the Budget Justifications.

Preliminary Work and Results (see Clinical Trials Experience section 5 for more preliminary studies)

Assessment of Chiropractic Treatment (ACT) I, a pragmatic, prospective, multisite, parallel group comparative effectiveness study enrolled 750 participants across 3 US military healthcare systems.[85] Study results published in JAMA Network Open in May 2018, have been viewed more than 80,000 times.[86] (**See Figure 2 for ACT I results**) **Relevance to the proposed project:** Lessons learned from ACT I informed the proposed project in several key ways. 1) Study outcomes showed that patients with a range of LBP diagnoses experience clinically meaningful improvements in pain and function following chiropractic care; 2) It is feasible to implement a standardized study protocol for a pragmatic clinical trial that includes key aspects of the MC²LBP model across multiple health system sites by making small changes to accommodate local processes; 3) We were able to successfully capture PROs using electronic data capture in a population that is difficult to follow; 4) Two of the three health systems required referral to chiropractic by a medical physician prior to enrollment in the study. At the third site, San Diego, a Coreman referred patients directly to DC when they presented to the medical clinic with LBP. Direct referral to a DC did not result in more adverse

Figure 2. A. Findings from the ACT I study demonstrating a significant decrease in low back pain over the 12 week period among those getting usual medical care plus chiropractic care. B. Findings from the ACT I study demonstrating a significant decrease in Roland-Morris measured disability over the 12 week period among those getting usual medical care plus chiropractic care.

events and these participants actually reported greater improvement with fewer chiropractic visits when compared to the other sites.

COCOA Studies: Members of our interdisciplinary team (Goertz and Salsbury) randomized 131 adults aged 65 or older with chronic LBP to 3 treatment groups: 1) conventional medical care; 2) co-occurring medical care and chiropractic care; or 3) collaborative medical and chiropractic care in which doctors shared health records and developed joint treatment plans.[79 80] **Relevance to the proposed project:** The results of this project demonstrated that it is possible for DCs and medical physicians to deliver co-managed care to LBP patients through community-based clinics and that outcomes are not impacted if the clinicians are not co-located or affiliated within the same HCS.[30,31,86] Further, prior to conducting our pilot trial, we completed 3

preliminary studies that informed the proposed project in meaningful ways. The first was a health services study[87] characterizing the prevalence of co-concurrent care for LBP by medical doctors and DCs in this population. The second study identified patient preferences for LBP co-management;[85] and the third identified co-management practice patterns and attitudes of DCs toward integrative medicine.[86] These findings informed the 1) COCOA trial, which found that chiropractic participants perceived greater improvements in LBP, overall health, and quality of life at 12-weeks than patients assigned to medical care alone and 2) original development of the MC^{2}LBP model concept, including the interprofessional education program proposed for IMPACt-LBP.

Pragmatic Clinical Trial Experience: Drs. Goertz and George are PIs on funded UH3 awards through the NIH-DoD-VA Pain Management Collaboratory (PMC). VERDICT (Veterans Response to Dosage in Chiropractic Therapy) , led by Goertz, is a pragmatic, rigorous, randomized controlled trial to be conducted at 4 Veterans Health Administration hospitals across the country to determine the effectiveness of different doses of chiroprcirc are in 766 Veterans with chronic LBP. Outcomes of interest include LBP-related disability and relative resource Dr. George has led successful cluster randomized trials[87-89] and is in now leading the AIM-Back PMC study, a pragmatic, rigorous, cluster randomized controlled trial conducted in 16 clinics in the VA hospitals across the country. The primary outcomes are pain interference and physical function. **Relevance to the proposed project:** These studies, funded under the same mechanism as IMPACt-LBP and using similar outcomes measures, will inform the proposed project based on lessons learned from the successful transition from UG3 to UH3 mechanism. Further, VERDICT resulted in the development of a decision aid for chiropractic management of LBP[90] that will be used as provider education in IMPACt-LBP.

Collaborative Care for Veterans with Spine Pain and Mental Health Conditions (COCOV; R34AT008427): The ultimate goal of COCOV (Goertz, Salsbury) was to assess the feasibility, acceptability, safety, tolerability and target outcomes for a future randomized controlled trial. Study activities included a pilot study that enrolled 40 Veterans with LBP, successfully completed in November, 2018 that served as the pilot study for the VERDICT trial described above. **Relevance to the proposed project:** An integrative care pathway development process provided key information that will inform our efforts in the current proposed project as it relates to integration of the MC^{2}LBP model into existing primary care models. Lessons learned relate to operational definitions, standardized treatment algorithms (clinical evaluation, imaging, documentation), clinical outcomes, case management, referral/collaboration, and specific communication and referral steps for DC care.[91]

Musculoskeletal Physical Therapy in Primary Care: Dr. Goode completed a one-year pilot and feasibility study called the IMPaC Study, funded by the Duke Clinical and Translational Science Institute. (**see letter of support Ebony Boulware, MD, MPH – PI of Duke CTSA**) IMPaC studied the effect of using PTs as the initial contact for patients with MSK pain entering a Duke primary care clinic. Active patients received a letter notifying them of a change in the current practice model that included an offer to participate in a clinical trial randomizing them to PT versus a PCP for their MSK pain. The study flow consisted of working with the Duke centralized scheduling center or the clinic front desk to identify patients with a chief complaint of MSK pain. In this protocol driven[92], single-site, one-year pilot study patients were randomized with equal allocation to one of two study arms (PT or PCP) and stratified by the pain location (i.e., back, knee, other) to determine differences by body sites. We demonstrated

Table 2. Summary of Outcomes with Chronic Low Back Pain by study arm		
Measure	**PT Arm**	**PCP Arm**
Total Charges (n=53)	Median $2,121 (IQR=$826, $4,156)	Median $2,836 (IQR=$861, $12,525)
ED Visits (n=53)	n=0 (0.0%)	n=2 (11.0%)
New Opioid Prescription (n=53)	n=1 (6.3%)	n=1 (5.6%)
Pain Intensity (0-100) (n=39)	Mean Change= -7.40	Mean Change= 0.79
Global Health Rating (0-100) n=(39)	Mean Change= 15.88	Mean Change= 6.91
Physical Function (PROMIS-HAQ) (n=39)	Mean Change= 2.14	Mean Change= 1.05
Patient Satisfaction (PSQ-18) (n=39)	Mean Change= -0.68	Mean Change= 0.09
ED=emergency department; pain intensity=lower scores better; global health rating=higher scores indicate better health; PROMIS HAQ=health assessment questionnaire; PSQ-18 = patient satisfaction questionnaire -18 items		

feasibility by enrolling n=146 participants of which 97% (n=141) had complete outcomes of total costs, opioid prescriptions and emergency department (ED) visits and n=102 (70%) completed 3-month follow-up outcome measures. Among the 36% (n=53) with a chief complaint of LBP (**See Table 2**), those patients that were randomized to the PT arm had lower costs, fewer ED visits, decreased pain, improved global health, physical function and general satisfaction. **Relevance to the proposed project:** In this pilot study we were able to overcome many of the challenges associated with changing the traditional model of initial PCP care for MSK complaints. First, we identified that many PCPs welcomed PTs as the initial contact for patients with MSK pain as they felt that PTs had the training and examination expertise. Second, we learned that the scheduling staff

were more than willing to provide this simple change to the traditional model. Third, we conducted a qualitative assessment of patients enrolled in the study (n=17 patients with LBP, n=8 PCP arm and n=9 PT arm). A majority of patients with LBP (76%) reported confidence in PTs as initial point of care for MSK pain.

Summary and Plans to Address Published and Preliminary Study Weaknesses: The studies described in Preliminary Studies, as well as other foundational work conducted by members of our study team and others, have found that incorporating PTs or DCs within the patient treatment experience can result in significant improvements in pain and function, as well as decreases in opioid prescriptions, emergency department visits and healthcare costs. However, an important step must now be accomplished, namely to bring the findings outlined above together under the synergistic umbrella of the MC^{2}LBP model, placing these providers at the forefront of the patient care experience, and determining if MC^{2}LBP can be translated into meaningful, scalable, academic HCS change. While there are many strengths in the literature comparing direct access, without physician referral, to a PT or DC to usual PCP care, there are also notable gaps and weaknesses. First, previous studies used observational designs with claims or registry data[10,93-98], which are prone to confounding and measurement bias. Our proposed study will overcome these weaknesses with a cluster- randomized design across three large academic HCS. Second, previous studies have focused on a single discipline (i.e., either PT[93,94,97,98] or DC[96]) rather than looking at either PT or DC as a component with an overall multi-disciplinary co-management model such as that proposed in this application. Third, previous studies of PT and DC often involved referral from primary care to conservative care, which may lead to increased cost and delays in evidence-based nonpharmacological care.

UG3 Planning Phase Approach. Our previous work has taught us how critical appropriate planning activities are to the successful completion of pragmatic clinical trials in real world HCS. Fortunately, the UG3/UH3 mechanism allows a one-year planning phase to obtain required regulatory approvals, establish feasibility, refine protocols, finalize a budget, and develop tools to facilitate data collection and transfer involving multiple HCS. The UG3 planning phase for the proposed project will be used to accomplish the following Specific Aims: 1) finalize the infrastructure required to implement MC^{2}LBP in 3 academic health systems and 2) complete a study protocol developed to test this model using a pragmatic, rigorous, multi-site, cluster randomized controlled trial design. These efforts will involve completion of 23 milestones that involve the following activities – a) Finalizing the study organizational and committee structure, b) obtaining regulatory compliance and other required approvals, c) planning for Implementation of MC^{2}LBP, e) pragmatic clinical trial infrastructure development and f) transition from project phase UG3 to UH3. **Proposed evidence of Milestone completion and methods for how these benchmarks will be achieved are summarized in Section 5.1.2 Milestone Plan, while a detailed timeline can be found in Section 2.7 Study Timeline**.

Potential Problems, Alternative Strategies and Benchmarks for UG3 Success. As reflected by our comprehensive list of milestones (section 5.1.2 Milestone (MS) Plan) and study timeline (section 2.7 Study Timeline), we recognize that this is a highly ambitious project. Thus, much of our work during the UG3 planning year will be focused on identifying and overcoming barriers to both the implementation of the MC^{2}LBP model and the execution of a rigorous pragmatic clinical trial designed to evaluate MC^{2}LBP. Issues we expect to address include the following: health care provider adaptation to change, workflow, and expanding the use of EHR. Implementation of MC^{2}LBP will require clinicians to rethink their current treatment strategy for LBP. Primary care clinicians and the HCS in which they practice will need to embrace the ACP Guideline for LBP using a model that places them further along in the patient care trajectory than they may be used to currently (CCC MS-6). DCs and PTs will need to incorporate evidence-based diagnostic and treatment strategies (CCC MS-3,6). HCSs will need to change patient data collection and scheduling protocols as well as patient triage procedures that currently do not include referral to community-based DCs or first-line access to PT (CCC MS-6,10, 12 and DCC MS-7). Based on results from our previous work and independent rapidly evolving changes in health policy at both the national and state level, we believe that achieving the changes we have outlined in our research strategy is possible for a number of reasons. 1) The burden placed on society by the high prevalence of LBP and the opioid crisis are clear mandates for change. 2) Our outstanding multi-disciplinary team is highly committed to the successful completion of all study aims and well-positioned within participating academic HCS to effect required changes. ACT I, COCOA, COCOV and IMPaC (see Preliminary Studies) all successfully implemented varying levels of clinician and academic HCS changes that are directly relevant to the proposed work, collectively providing a feasible roadmap. 3) Our work has shown that PCPs are open to alternative strategies such as the MC^{2}LBP model, provided that they include patient co-management.[30,31,99-102] Additionally, there are significant challenges associated with conducting this "low touch" pragmatic trial, which involves multiple data sources and is highly dependent on both new and existing informatics infrastructure. We are confident that these challenges can be overcome during the UG3 planning phase given that all three

academic HCS use EPIC, have access to CTSA infrastructure, and already utilize tablet-based or other electronic means of PRO data collection that include questionnaires that are the same or similar to our proposed primary outcomes as part of routine care (DCC MS-7). We have a feasible plan in place for collecting data from small chiropractic practices (CCC MS-9). Finally, Our experience with milestone driven pragmatic clinical trials, including those using the UG3/UH3 mechanism, has prepared us to be successful in the transition to the demonstration project in the UH3 phase of this award (CCC MS-22). In addition to the anticipated challenges outlined above, we also recognize that unexpected challenges may arise during the UG3 planning phase, challenges which we are fully prepared to address given our previous experience with model development and the conduct of pragmatic clinical trials.

UH3 Demonstration Phase – Scientific Approach. Specific Aims for the UH3 phase include the following: 1) Operationalize the integration of new organizational policies and procedures required to facilitate implementation of MC^2LBP at PCP clinics; 2) Determine the comparative effectiveness of MC^2LBP vs usual care alone; 3) Estimate and compare medical resource use and costs of implementing MC^2LBP; and 4) Evaluate patient, provider, system and policy level barriers and facilitators to implementing MC^2LBP using a mixed method, process evaluation approach.

UH3 SA1 - Clinical Implementation of the MC^2 Model. During the first 6 months of the UH3 phase of the proposed project, study investigators will work to implement MC^2LBP within academic HCS and community-based MC^2LBP clinics. Deliverables for successful execution of this aim include the initiation of qualitative interviews, engaging in stakeholder educational activities, aligning EHR PRO data collection with UH3 SA2 and integrating changes required to include MC^2LBP within clinic policies and procedures.

Pragmatic Trial for UH3 Specific Aim 2 and Specific Aim 3: Overview (See Figure 3). This 4-year demonstration project will use a cluster-randomized (at the level of the clinic) pragmatic clinical trial design within three academic HCS. Outcomes data collection will take place using a combination of passive electronic health record data augmented with patient collection through email and phone (centralized at Duke). This study will test the *overall hypothesis* that implementation of MC^2LBP will improve physical function and reduce pain interference as compared to usual care alone. Below are brief summaries of our plans, with more detailed information available elsewhere within this application. **Informed Consent:** In accordance with the 2012 Ottawa
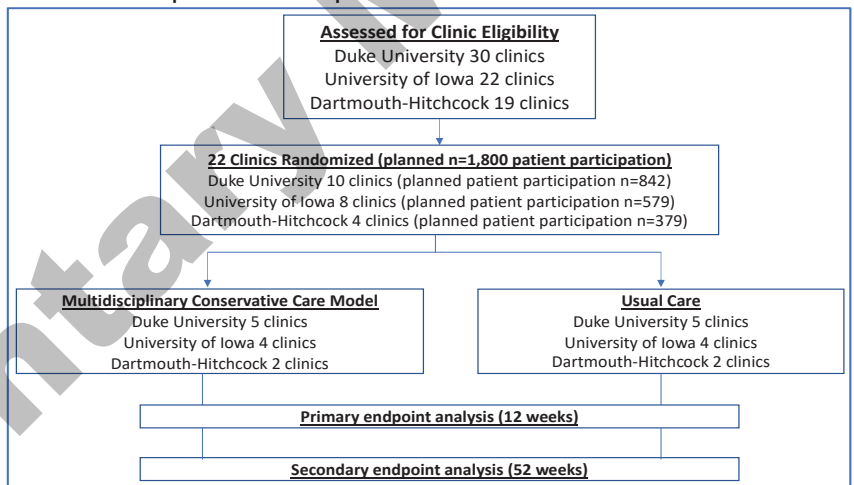

Figure 3. Consort diagram illustrating the clinic selection, patient enrollment, academic health care systems, primary and secondary endpoint analysis

Statement on Ethical Design and Conduct of CRTs and Consistent with the practice of the NIH HCS Collaboratory demonstration projects incorporating randomized cluster designs, we will seek a waiver of the requirement for individual level consent to participate in the study from all participating IRBs. For additional rationale and information on informed consent, see Section 3.3.1, Protection of Human Subjects. **Randomization:** Primary care clinics across the three academic HCS will be allocated 1:1 to each arm of the study. Clinic sites will be rolled out using a staggered two block randomization (one block of 10 matched pairs and one block of 12 matched pairs). **Study Population**. **Clinics:** In this pragmatic cluster-randomized clinical trial, the unit of randomization is participating primary care clinics (Primary Care, General Internal Medicine or Family Medicine affiliated with our 3 academic HCS. Although a final determination will be made on the number of clinical care sites following consultation with the DCC during our UG3 phase, it is anticipated that a minimum of 22 clinics will be involved, 11 that implement MC^2LBP and 11 that serve as usual care clinics. **Patients:** We anticipate that a total of 1800 patients who contact a participating clinic with a primary complaint of LBP will be included in our study. Based upon our assessment of the landscape of LBP patients within these academic HCS, recruiting this number of patients is feasible. **Implement access to multidisciplinary conservative care**: Patients seeking care at MC^2LBP model clinics will be given the option of seeing either a DC or a PT as their first

contact clinician for an initial trial of care. PT/DC care will be presented to patients within the context of making an informed choice. Any patient can decline the MC²LBP model approach and all will have access to the same
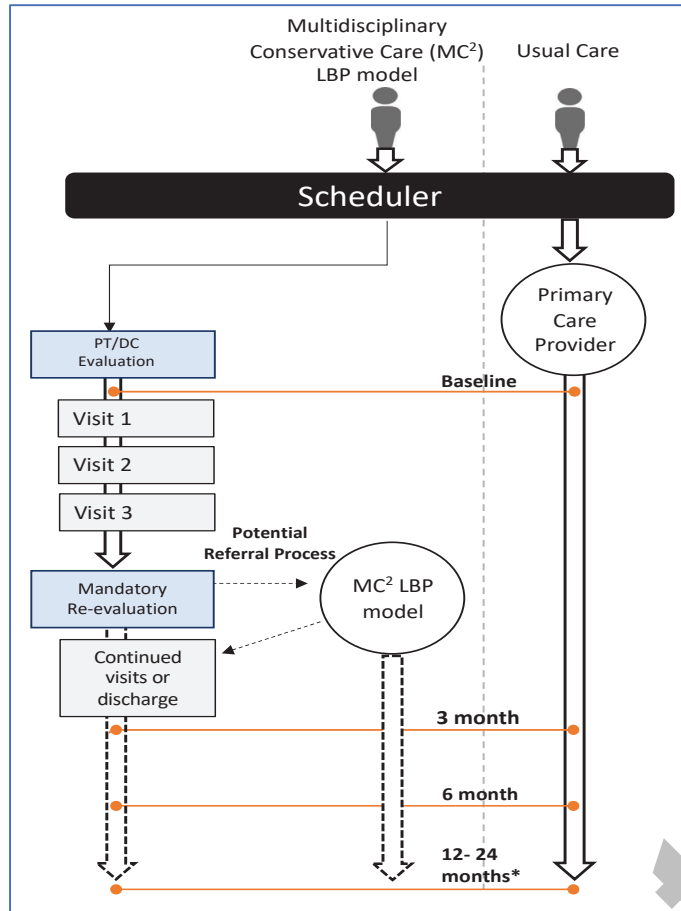
Figure 4. Comparison of the multidisciplinary conservative care model and usual care from baseline to follow-up. * Some participants may have extended follow-up past 12-months

usual medical care available to all LBP patients at all times during the study timeframe. Consistent with our preliminary data we will work with the scheduling centers at our three academic HCS to implement access to MC²LBP. Patients in the MC²LBP group who agree to conservative care will receive an evaluation by either a PT or DC, including a treatment plan to address LBP that includes up to three visits for conservative care. Patients may choose to discontinue conservative care at any time during the three visits. Following the third visit, patients will have a mandatory re-evaluation by the PT or DC. At this time, or any time prior, the patient may be referred to a PCP for additional evaluation. In turn, the PCP may refer back to the PT or DC for continued treatment. This bi-directional communication will ensure multidisciplinary approach for the best patient care. Patients may be discharged from care at any point, based upon the recommendation of the conservative care provider or the desires of the patient. (**See Figure 4.**)

Training: As outlined in milestone CCC MS6-MI, the training goal for patients is to make them more informed consumers regarding conservative treatments for LBP. They will be introduced to the ACP guideline for LBP, understand the training and qualifications of DCs and PTs, know what treatment approaches to expect when being treated by a DC or PT, be made aware of insurer payment policies/potential out-of-pocket expenses and Choosing Wisely lists for both PT and DC. One-page fact sheets will be created for patients based upon previous work conducted by study investigators and new findings from qualitative work conducted during the UG3 phase of this project. The goal of training PCPs will be to ensure that they are aware of guideline-congruent care for LBP, and how to best co-manage LBP patients with a PT or DC. PCP training will involve Grand Rounds, section meetings, and lunch-and-learn sessions based upon successful strategies used previously by study investigators. CE credits will be made available when possible. The goal of training DC/PTs is to ensure that they are aware of patient-centered, evidence-based conservative care strategies and can operate effectively as part of a multi-disciplinary healthcare delivery team. They will be trained on the MC²LBP model, an evidence-based diagnostic classification system for diagnosing LBP, existing clinical care pathways for LBP, profession-specific Choosing Wisely campaigns, communicating with PCPs and co-management strategies based on previous work conducted by study investigators.

While the specific treatments received by individual patients may vary and each patient is likely to receive a variety of different interventions, the comparison of interest remains the differences in outcomes and associated health care utilization between two models of care, one that involves MC²LBP at the initial point of care. Thus, the variability of treatments received after the patient's first visit does not confound the pragmatic question of interest, which is the difference between the two structurally different models of care. The result of this comparison of care models will thus be highly generalizable and if MC²LBP is found to improve outcomes, it will be easily disseminated across a wide range of academic HCS. **Therapeutic approaches**: Treatments delivered by either DCs or PTs will include the following evidence-based approaches - spinal manipulation/mobilization, myofascial therapies, education, superficial heat, self-care, motor control exercise, therapeutic exercise, and lifestyle management specifically targeted toward patients suffering from LBP (See detailed intervention description in section 4.2.a Narrative Study Description). These interventions have

demonstrated efficacy, effectiveness and are supported by numerous national guidelines. [28,42,47,48,103,104] The MC[2]LBP model does not preclude the use of additional treatments by these or other clinicians, such as psychological interventions, that are delivered as part of a multidisciplinary care approach.

UH3 SA 2 Primary Outcomes: IMPACt-LBP primary outcomes are patient reported change in PROMIS Pain Interference and Physical Function, assessed by a primary endpoint change from baseline to 3-months. **PROMIS Pain Interference Instrument (Short Form 4a):** The PROMIS Pain Interference instrument measures the self-reported consequences of pain across aspects of life including social, cognitive, emotional, physical and recreational activities; this instrument refers to the past seven days. This validated scale has five response options, with scores ranging from one to five.[105] It has been shown to be a valid and reliable instrument[105] that is responsive to change in low back pain status (i.e., 3.5 to 5.5 points).[106] **PROMIS Physical Function (Short Form 4a) from** baseline to 3-month follow-up. This is a valid and reliable measure of self-reported physical function that uses 4 items of the 29-item PROMIS short form. It performs well in multiple race-ethnicity and age groups.[107,108] It has excellent reliability, minimal ceiling/floor effects, limited item bias and is sensitive to change among patients with low back pain[109] and spinal disorders.[110] These measures were chosen to be consistent with recommendations from the NIH Task Force on Research Standards for Chronic Back Pain.[111] **Secondary Measures.** Secondary endpoints will be collected at baseline, 3, 6, and 12 months (with additional data collection at 18 and 24 months for the subset of patients enrolled in the study during the first 18 months of recruitment) and will include opioid prescriptions, PROMIS measures of pain intensity, catastrophizing, sleep, and depression, health related quality of life and satisfaction, and information about procedures, prescriptions, and hospital/emergency room visits. We will also compare time to diagnosis of LBP "red flags" (ie: Vertebral fractures, Inflammatory disorders (eg, axial spondyloarthritis), malignancy, Infections, Intra-abdominal abnormalities) between participants in the MC[2]LBP and usual care groups. A complete list of secondary endpoints, as well as a description of important exploratory analysis focused on extended follow-up and safety is available in Section 4.4 Statistical Design and Power.

All statistical analysis and data management will occur within the Data Coordinating Center.

Analytical Plan Aim II. Sample Size Estimation. The primary endpoint is the change in PROMIS Physical Function from baseline to 3-month follow-up between MC[2]LBP and usual care arms. Because randomization will occur at the clinic level and enrolled patients may be correlated within clinics, analyses must account for the intra-cluster correlation (ICC). The ICCs for this estimation was assumed at 0.02 to account for clinic clustering and effect sizes and standard deviations based on data from the Goode et al. [53 53 53 53 53 54] pilot study.[53] The type-I error is 2.5% to account for two primary outcomes and power is conservatively assumed to be 90% to guard against deviations from assumptions with an assumed attrition rate of 20% during the first three months of the trial. A study population of 1,800 participants in 22 clinics will detect a 0.4 effect size for a difference in mean changes in the PROMIS Pain Interference. This level of effect size corresponds clinically relevant changes i.e., 3.5 to 5.5 points[106] in the PROMIS Pain Interference and within the changes found in the Goode et al[53] pilot study and those found in the studies by Goertz et al.[51,85] The mean change in the PROMIS Pain Interference are more conservative than those of the PROMIS Physical Function. **Primary outcome endpoint**: We will compare the change from baseline to 3-month follow-up between usual care and MC[2]LBP arms using a linear mixed-effects models (LMM) with random effects to account for clustering. This primary analysis will be conducted according to the intent-to-treat principle with participants analyzed and endpoints attributed according to the treatment arm to which the participants were randomized, regardless of subsequent crossover or post-randomization treatment. To account for possible cross-overs, we will conduct as-treated analyses with participants analyzed according to the treatment actually received. **For subgroup analyses, we will examine whether the therapeutic effect is similar for all participants, or whether it varies according to sex or race as important biological variables, and acuity of LBP (acute vs chronic).**

Specific Aim III Approach: Estimate and compare medical resource use and costs of implementing MC[2]LBP vs usual care for patients suffering from LBP Medical resource use will include prescription medications, visits to MDs, DCs, PTs and other types of healthcare professionals, as well as musculoskeletal-related injections, procedures, imaging, surgeries, emergency department admissions, and hospitalizations. Institutional cost accounting data used to estimate mean direct medical costs per patient will be compared between clinical sites implementing MC[2]LBP versus usual care. We also will compute within-trial quality-adjusted life-years to estimate the incremental cost effectiveness of MC[2]LBP versus usual care. Medical

resource use data will be collected via EHR from each site using the clinical data research network common data model and local data collection at DH. These data will be supplemented with cost accounting to value medical resource use. If necessary, additional PROs will be collected using one of several centralized data capture methods that will be evaluated during the UG3 planning phase. The primary endpoint for these analyses is from baseline to 12-months.

Specific Aim IV Approach: Evaluate at the patient, provider, system and policy level barriers and facilitators to MC^{2}LBP **using a mixed method, process evaluation approach.** We will adopt an 'effectiveness-implementation hybrid design' to our mixed methods process evaluation of MC^{2}LBP. Briefly, we will conduct qualitative data analysis using NVIVO software (QSR International Pty Ltd., Victoria, Australia). Coding will use both inductive and deductive approaches, building on the facets of the DC/PT model as an initial codebook. Qualitative data will be compared across individuals, treatment groups, and study sites to understand the range, variability, and areas of consensus and divergence on the benefits and feasibility of the study interventions for managing LBP and to understand patient perceptions of the usefulness, safety, acceptability, and effectiveness of MC^{2}LBP.

Overall Study Timeline: We estimate that our total study timeline will extend for five years, with a start-up phase of one year (UG3), followed by a four year implementation and clinical trial execution phase (UH3). At the end of the UG3 Phase, we will have evidence of completion for 23 planned primary Milestones. Key efforts will focus on a) finalizing study organizational and committee structures, b) obtaining regulatory compliance and other required approvals, c) planning for Implementation of the MC^{2}LBP model, e) pragmatic clinical trial infrastructure development and f) transition from project phase UG3 to UH3. At the end of the 4-year UH3 Phase, we will have evidence of completion for an additional 20 Milestones. For more information on Timeline and Milestones, see Section 2.7 Study Timeline and 5.1.2 Milestone Plan.

Dissemination and Implementation Plan. The entire IMPACt-LBP study group is fully committed to the public dissemination of the study results and public access to the trial data. Moreover, because the findings of the IMPACt-LBP trial may have immediate and direct impacts on participant outcomes, rapid dissemination of these results is critical. Accordingly, we will distribute study results and data using a variety of mechanisms. A detailed dissemination and implementation plan can be found in section 4.7 Dissemination Plan and section 10 Resource Sharing Plan.

Limitations and Alternative Plans. We are well aware that successful implementation of the MC^{2}LBP model will be a challenge. Our outstanding team of investigators is strongly committed to the successful completion of all study aims, bringing a combination of clinical and research experience, combined with strong administration support. As demonstrated by our strong letters of support from academic HCS administrators, the study aligns with key strategic goals across the participating academic HCS and there is strong enthusiasm and support among key health system leaders. This support is critical, as implementation of the MC^{2}LBP model will require system level adaption. Recruitment and retention remains a primary challenge to all RCTs. It can be difficult to estimate the number of eligible subjects from a site prior to the actual implementation of a protocol. We have minimized the exclusion criteria for this pragmatic trial in order to maximize generalizability but it is anticipated that this will also have a positive impact on participation. Our experience and success with past pragmatic RCTs conducted within HCS has shown that keeping the respondent questionnaire burden low is important to enrolling and retaining participants, as is flexibility in terms of the method of data collection. We have incorporated these lessons into the design of this trial. Overall as a project team, we have collectively enrolled and followed thousands of patients across numerous clinical trials that involved similar patient populations, pragmatic designs, and the need to alter clinical care pathways. These previous experiences give us substantial confidence in our ability to meet our recruitment and retention goals. We have learned that ongoing monitoring of participation and follow-up trends is critical to successful trial management. Our data management system will allow for both regular and *ad hoc* trial management reports. These reports will be used to make adjustments during the trial, including reallocating resources for site-based recruitment issues and/or adding new sites in a timely manner if needed. Investigators will review participation and retention at the weekly videoconferences, and adjust our recruitment strategies accordingly if needed. For additional information on limitations and alternative plans, see CCC section Other Attachments-Project Management Plan and section 4.2.a. Narrative Study Description.

10.   RESOURCE SHARING PLAN(S)

10.1   Data Sharing Plan

In a policy issued on February 26, 2003 and revised on June 27, 2005, the NIH reaffirmed its support for the concept of "data sharing," that is, making data from a research study available to other interested researchers. The policy states: "We believe that data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health. The NIH expects and supports the timely release and sharing of final research data from NIH-supported studies for use by other researchers."

In addition to the NIH policies, we have also reviewed the NIH Collaboratory Living Textbook of Pragmatic Clinical Trials, specifically sections related to data sharing and embedded research. Recognize that data will be obtained via two methods (electronic medical record and patient reported outcomes) that standard approaches for data sharing are complex. In year 1, we will collaborate with the NCCIH to finalize the below Data Sharing Plan and each HSC has provided institutional support and agrees to abide by the Resources and Data sharing Plan.

Assuming a standard data sharing approach and that no restrictions are imposed by institutional policies, the local IRBs, as well as local, state, and federal laws and regulations (including the HIPAA Privacy Rule), we are prepared to follow the February 2003 policy, revised on June 27, 2005, for the data generated from this application. We have approached Data Sharing Plans in three main ways, although under HIPAA regulations and the NIH grant directives, there are a number of degrees of flexibility. Three options include: 1) a Limited Data Set with Data Use Agreement (LDS/DUA) and IRB approval, 2) de-identified use of the datasets, and 3) fully identified data sets with subject authorization and IRB approval. Each approach has advantages and disadvantages. For the clinical data, our proposed data sharing plan for this application includes options 1 or 2 on a case-specific basis.

For De-identification of the datasets, we apply HIPAA definitions by adding back variables to the dataset that express all dates as number of days since a milestone event, enrollment, and a variable storing just the year. For example, the milestone event would be "Day 0" in this case. We propose use of a de-identified dataset because the de-identification only has to be done once, and the de-identified data stored for sharing. A de-identified data set is not subject to HIPAA's minimum necessary standards, so all of the data in the de-identified dataset can be included and shared. A limited data set is subject to HIPAA's minimum necessary standards, so the dataset for each sharing request would have to be custom created to include just the subset of data needed. Sharing of de-identified data also provides easier book-keeping. For example, no Data Use Agreement (DUA) is required. De-identified datasets can even, conceptually, be posted to a web site for downloading. The de-identified dataset can include a 'link' field to connect back to the original, identified, data. This field cannot be derived from any data in the original dataset (basically it's a table-look-up field). Under recent guidance from OHRP, a de-identified dataset can be declared to be "not human subjects" and thus not subject to the recipient's IRB review.

10.1.1 Preparing Data to be Shared

In collaboration with the NCCIH, we will finalize our data sharing plan, however protection of the identities of the participants is a top priority and the shared data set must be free of identifiers that could lead to the identification of individuals. The central database maintained by the DCRI will not have direct identifiers, such as name, contact information, or social security number, but will have dates. We thus will de-identify the data (i.e., strip all personal health information (PHI) in compliance with the HIPAA privacy rule). This makes the data free of identifiers that would permit linkages to the research participants and free of content that would create unacceptable risk of subject identification. All DCRI personnel are required to maintain yearly HIPAA training.

Under the HIPAA Privacy Rule, PHI will be stripped from the database. Specifically, de-identification of a dataset includes removal of the following PHI variables:

- Names;
- Geographic information (including city, state, and zip code);
- Elements of dates such as those for birth, hospital admission and discharge, and death;
- Telephone numbers and fax numbers;
- Electronic mail addresses;

- Social Security Number;

- Medical record and prescription numbers;

- Health plan beneficiary numbers;

- Account numbers;

- Certificate or license numbers;

- Any vehicle identifier or serial number, including license plate number;

- Any device identifier or serial number;

- Web Universal Resource Locator (URL);

- Internet Protocol (IP) address number;

- Any biometric identifiers, including finger or voice prints;

- Full face photographic images or any comparable images.

Based on our experience, other data often not listed as PHI are indirect identifiers and could lead to what the NIH data sharing workbook calls "deductive disclosure" of participants' identities. This is more likely in small, geographically limited or specialized populations. However, it is also recognized that clinical study data lacking time variables, demographic information, and information regarding risk factors are often not very useful. Therefore, de-identification of other data must come with tools to rebuild and or retain the aforementioned information. For example, the time information can be retained by picking a reference date, the same for all subjects (e.g., date of enrollment), and calculating all dates as the number of days since that date. For information about geographical location that would jeopardize identity because a very small number of patients reside within a particular geographical vicinity, different aggregation algorithms can be employed as appropriate. For example, if there are too few subjects at a site, then the site may be combined with another site. Similarly, racial/ethnic groups can be collapsed when there are few individuals in certain groups or cells. We will also consider de-identifying on a variable or field level such as comment fields, optional fields, other specify fields, site number, investigator, and site name. For comments and "specify" fields, we will first recommend not collecting them during the study unless absolutely necessary. We will then only report the coded data and not the specifics. Inevitably, some data sharing situations will arise for which no predefined solution exists. In these cases, we will work with network leadership to define an acceptable reporting solution and evaluate the data to ensure that the risk of re-identification is very small. We will also ensure that the common consent form discloses that de-identified data will be shared.

10.1.2 Process for Providing Data

We recognize that interested parties will want access to the data. Only de-identified data or limited datasets for proposed use, with appropriate documentation, will be provided via secure transfer methods to the requestor following institutional approval and data use agreements as appropriate. In collaboration with theNCCIH, we will develop a process to facilitate providing other investigators with access to de-identified study data in the format that is most helpful to them. Data formats include e.g., SAS transport files or CSV files.

All SAS programs developed at the DCRI for data provision purposes are written and documented according to institutional SOPs and final specification plans. The study data provided, whether it is in SAS data sets or already programmed tables and listings will be made available to the user under an agreement containing the following stipulations.

1. The data will be used for research purposes and not to identify individual subjects.

2. The data must be secured using appropriate computer technology with user access controlled.

3. The authors of any manuscript resulting from this data must acknowledge the source of the data upon which their manuscript is based.

4. Any analyses for the purpose of presentations, abstracts, and/or publications must be coordinated through the Data Dissemination Committee, so that there can be some coordination of analyses to ensure that redundant analyses are not being performed independently.

5. All coauthors must be given a chance for review and approval of a draft manuscript prior to submission for publication.

10.1.4 Dissemination of Study Results

We will support and promote data sharing after study completion. A major objective of the DCRI will be to disseminate to the medical community new information learned through studies conducted. The timing of release and the definition of the data set to be made available is a complex issue related to issues of study participant confidentiality and issues concerning data availability.

A Data Dissemination Committee will be created and will consist of the CCC PIs (Goode, Goertz, and Lurie) and the DCC PI (Chakraborty). The Data Dissemination Committee provides review and general oversight of the publications and public presentations that report scientific findings of the study. The Data Dissemination Committee will ensure that the study results are presented by individuals who have working knowledge of the study design, implementation, data synthesis/analysis, and interpretation. The Data Dissemination Committee will ensure that any confidential or proprietary information is protected, and that all appropriate statistical analyses have been included. The Data Dissemination Committee, in collaboration with the NCCIH, will develop a Publications Policy that outlines the governing structure of the Data Dissemination Committee.

All manuscripts, abstracts, presentations at scientific meetings (in format of slides or posters), and other published works derived from work supported by these funds, must submit to the Publication Committeee before submission to a scientific journal, conference, organization, or other publishing body, or before being posted in a public domain.

All publications must conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors [ICMJE]) with regards to authorship, disclosure, scientific integrity, and other requirements. All public presentations shall be consistent with usual academic standards. All publications must include a statement acknowledging the study award number.

10.1.5 NIH Public Access Policy Compliance

All authors will follow the National Institutes of Health (NIH) Public Access Policy and must ensure that all published manuscripts are submitted to PubMed Central, as required.

As part of the NIH policy, authors will adhere to copyright and citation requirements:

    a) **Copyright compliance** - All authors will ensure that agreements with publishers permit the submission of the author's manuscript to NIH.

    b) **Citing PubMed Central ID Numbers** - When a manuscript is submitted to the NIH, the publication will receive an NIH Manuscript Submission (NIHMS) ID number. Once a manuscript is available in PubMed Central, it will be assigned a PubMed Central ID number. Effective May 25, 2008, authors will cite PubMed Central ID or (NIHMS) ID numbers for any articles cited in progress reports, new applications, and renewals.

10.2   Sharing Model organisms

NA

10.3   Genomic Data Sharing

NA

3.0   RESEARCH STRATEGY

3.1   SIGNIFICANCE

Low back pain (LBP) is the leading musculoskeletal pain condition and a key source of medical costs and disability.[1-6] An estimated 20% of U.S. adults have LBP, with 50-80% reporting a lifetime significant episode and 23% having disabling pain.[7] Over half of LBP visits are made to primary care physicians (PCPs).[8] Unfortunately, it is becoming increasingly better understood that the usual medical care for LBP, which most commonly includes prescribed medications and invasive therapies such as non-steroidal anti-inflammatory drugs, opioids, spinal fusions and epidural injections are often ineffective or of questionable benefit; further, many of these standard treatments result in the risk of significant harm to patients.[9-15] The ongoing opioid epidemic is a clear indication of the significance of this problem. Over 60% of opioid related deaths are linked to chronic pain[16] and consistent opioid use is found in a majority (61%) of those with chronic LBP.[17] In response to the concerns outlined above, several high profile public and private organizations have developed guidelines for the treatment of non-cancer pain, including LBP. These include the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain (2017),[18] The Joint Commission new and revised pain assessment and management standards for its accredited hospitals (2017),[19] and the ACP Guideline on LBP (2017).[20] All have found the strength of the evidence sufficient to support the recommendation of publicly available non-pharmacological therapies as preferred treatments for patients suffering from pain. The ACP guideline on LBP (2017)[20] recommends that frontline treatment be shifted from prescription medication to non-pharmacologic therapies such as superficial heat, massage, acupuncture, spinal manipulation, exercise, and progressive relaxation. Our companion applications – "Implementation of the American College of Physicians guideline for low back pain using a Multidisciplinary Conservative Care (MC2) model at the initial point of patient contact: A cluster randomized trial (IMPACt-LBP)-CCC in response to PAR-18-662 and "Implementation of the American College of Physician guideline for low back pain using a Multidisciplinary Conservative Care (MC2) model at the initial point of patient contact: A cluster randomized trial (IMPACt-LBP)-DCC" in response to PAR-18-663 – will implement and evaluate a novel, guideline-congruent, non-pharmacological approach to LBP management based upon ACP recommendations.

Multidisciplinary Conservative Care Model for Low Back Pain (MC²LBP): MC²LBP borrows from work previously published by Goertz and others describing new models of care for patients with spine-related disorders, including LBP.[21-24] These models include clinicians such as doctors of chiropractic (DC) and physical therapists (PT) as part of multidisciplinary care teams. MC²LBP engages DCs and PTs to serve as first contact clinicians for LBP patients entering one of the three participating academic healthcare systems. The proposed MC²LBP model focuses on DCs and PTs as first contact clinicians because evidence of use, efficacy, and effectiveness for these interventions exists. Patient satisfaction with DC and PT care is high when compared to usual medical care. Studies consistently show that patients receiving chiropractic care are more satisfied than patients receiving medical care alone.[25-29] DCs and PTs are licensed as direct access clinicians in all 50 states.[30,31] Direct access to DC/PT is demonstrated to be safe for LBP. Serious adverse events are rare, with only minimal side effects such as mild muscle stiffness or soreness commonly reported.[32-39]

There is a critical need to implement and evaluate the MC²LBP Model at a health systems level. There is little data to support the premise that either the guidelines described above or physician training based on those guidelines will lead to meaningful change in clinical practice for LBP without concurrent health systems change.[40-42] In a Gallup Survey conducted one-year after the ACP Guideline for LBP was released, 21% of patients with LBP reported a PCP referral to a doctor of chiropractic. In contrast, this same survey identified that more than 28% received a recommendation to take opioids and 28% received a recommendation to take benzodiazepines, medications which have limited effectiveness for the management of either acute or chronic LBP.[43] Further, despite increases in LBP encounters within primary care, referrals to physical therapy have remained stable while opioid prescriptions for LBP have increased.[6,44] A recent study by Heyward and colleagues found that the majority of private and public coverage of non-pharmacological treatments for LBP is suboptimal, health plan executives are not aware of the evidence base supporting these options, and payment policies targeted toward coordination of pharmacological and non-pharmacological care were "virtually non-existent".[45] In the rush to identify strategies to combat the public health crisis created by the burden of LBP and the risks associated with many commonly used treatments, health systems run the risk of exacerbating the crisis by implementing models of care that have not yet been rigorously tested. Much of the evidence currently used to support policy change is based on observational data that is prone to bias. It is critical that such

models, including MC²LBP, be implemented in real world clinical settings in a manner that is scalable and rigorously evaluated using pragmatic study designs and randomized at the clinic level.

A pragmatic, multi-center trial is warranted to assess the implementation of the MC²LBP model in real world clinical settings. The IMPACt-LBP randomized trial will compare the effectiveness of MC²LBP versus usual care in patients with LBP. The IMPACt-LBP trial will test if the MC²LBP model leads to improvements in patient physical function and reduced pain interference (via the PROMIS Pain Interference Instrument) compared with usual care alone. The results from this study have the potential to inform future implementation and policy efforts to improve the quality of pain management for patients suffering from LBP while simultaneously reducing opioid prescriptions, health care costs, and utilization of services.

Achieving the robust evidence base for evaluating the effectiveness of the MC²LBP strategy requires an experienced and well-organized Data Coordinating Center (DCC) with strong existing ties to the Clinical Coordinating Center (CCC) and expertise in trial design, electronic health record (EHR) data, data management, statistical analysis, and the dissemination of findings to the broad clinical community. Importantly, the Duke Clinical Research Institute (DCRI) is uniquely positioned to serve these critical functions as the IMPACt-LBP DCC. The DCRI is the world's largest academic research organization. DCRI ensures close integration of clinical, biostatistics, informatics, and project management expertise. With over 1,000 faculty and staff, the DCRI is capable of conducting any clinical research project, from the smallest pilot study to truly global megatrials. Our experience stretches from Phase I to Phase IV clinical trials, cluster randomized trials, pragmatic trials, medical device trials, registry, outcomes, and economic studies, many of which have had major impact on patient care.

3.2 INNOVATION

Pragmatic cluster randomized trials. A pragmatic cluster randomized trial (CRT) design is the most appropriate approach for evaluating the MC²LBP model. Pragmatic trials often include complex interventions consisting of several interacting components and involving the skills and experience of healthcare professionals to deliver them appropriately. Chiropractic and physical therapy interventions represent this type of complex intervention, and the question of what happens when health systems adopt new models of care that focus on these interventions is the type of policy relevant question best suited for a pragmatic CRT approach.

Pragmatic risk-based monitoring strategies. The DCC views on data surveillance, quality, and monitoring practices extend beyond typical activities aimed primarily to contain costs associated with monitors traveling to study sites. Instead, we implement a holistic data-driven management approach. Through this process, the DCC ensures that each clinical trial adheres to the following five guiding principles: 1) the correct participants are enrolled, 2) acceptable treatment adherence is met, 3) complete efficacy data are ascertained, 4) complete safety data are ascertained, and 5) good clinical practices are followed. The DCC will identify potential trial and data risks prior to enrollment and develop plans to monitor and mitigate/prevent these risks. Specifically, the DCC will identify potential risks, and enter risks into a risk register that categorizes the risk, identifies an owner, and ranks the probability, impact, and priority of the risk. Mitigation actions will be identified and assigned to the risk owner. These risks will then be evaluated quarterly throughout the trial and appropriate mitigation actions implemented.

Leverage network of experts experienced in embedded pragmatic clinical trials (ePCTs). DCRI is the home of the NIH Health Care Systems (HCS) Research Collaboratory Coordinating Center with extensive experience in coordinating large multi-site health systems studies. The NIH HCS Research Collaboratory program also serves as the Resource Coordinating Center for a new group of large-scale ePCTs on pain management and reducing opioid prescribing. The Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM) Resource Center, now integrated with the NIH HCS Research Collaboratory, provides technical support and pragmatic trial expertise for its pain management trials. The DCC for this trial will maintain connections with the NIH HCS Research Collaboratory/PRISM Resource Center through Dr. Hernandez, benefiting from the program's 7+ years' experience in successfully facilitating ePCTs and overcoming challenges of implementation in health care systems. Through connections with the NIH HCS Research Collaboratory/PRISM Resource Center, we will be able to learn from the experiences of other ePCTs. Building on these existing program linkages for knowledge sharing will bring considerable additional value and mutually benefit all the projects. Our relationships with these established programs will dramatically expand IMPACt-LBP's reach, avoid redundant creation of materials that already exist, benefit from a vast number of lessons learned and provide multiple channels to disseminate knowledge created.

3.3   APPROACH

3.3.1   Organization, DCC Leadership, Project Team, and Coordination

The Duke Clinical Research Institute (DCRI). The IMPACt-LBP DCC will be housed at the DCRI at Duke University, the world's largest academic research organization. DCRI's experience stretches from Phase I to Phase IV clinical trials, cluster randomized trials, pragmatic trials, medical device trials, registry, outcomes, and economic studies. DCRI has a 45-year history of collecting structured electronic data for generating the knowledge needed to take better care of participants. Beyond their clinical interests, our faculty's focus on research methodology has contributed to the best practices in Data and Safety Monitoring Boards (DSMBs), clinical events committees, registry-based trials, "single-source" trials using EHR data, and large distributed research networks. Our operations teams were early proponents of master contracts, protocol templates, shared institutional review boards (IRBs), manuals of operations, risk-based monitoring plans, standardized case report forms, EHR-based data collection, machine learning, and the integration of registries and clinical trials, and have made many academic contributions to professional societies and publications. This application builds on DCRI's long history of clinical trial expertise and multidisciplinary infrastructure, and our prior successes with randomized clinical trials (RCTs). Select examples of previous/current experience coordinating randomized clinical trials relevant to this proposal are summarized in **Table 1**.

Table 1. Selected Examples of Relevant CCC/DCC Trial Experience	
Project & Sponsor	Description/Activities
Implementing Genomics in Practice (IGNITE) Network (NHGRI)	Network Coordinating Center for large genomic medicine. Conducting four multi-site genomic pragmatic randomized control trials for genetic testing to understand and address renal disease disparities, depression, acute pain, and chronic pain incorporating Pharmacogenetics.
Heart Failure Network (HFN) (NHLBI)	DCC to accelerate research in the diagnosis and management of heart failure and to improve patient outcomes through evaluation of novel therapies in multiple clinical trials across 9 regional clinical centers.
STICH/STICHES (NHLBI)	Coordinated CCC and DCC of a randomized clinical trial (STICH) that compared optimal medical therapy (MED) with CABG and/or surgical ventricular reconstruction for patients with congestive heart failure and coronary artery disease. The DCRI also coordinated the CCC and DCC for STICHES (the STICH Extension Study), which followed surviving subjects randomized in the STICH trial for an additional 5 years to acquire critically important longer-term (10-year average) information on patients with heart failure and LVSD treated with MED with and without CABG.
CABANA (NHLBI)	DCC of a global randomized study, conducted across 122 sites, 4 continents and 10 countries, comparing catheter ablation therapy against current drug therapy in the treatment of patients with atrial fibrillation (AF).
ISCHEMIA (NYU Langone Health, NHLBI)	DCC of an international, multicenter, comparative effectiveness study to determine the best way to manage stable ischemic heart disease in patients with moderate or severe ischemia, with or without stress imaging.
TRANSFORM HF (NHBLI)	Coordinate CCC and DCC of a prospective, unblinded, 2-arm, phase III clinical trial of 6,000 hospitalized heart failure patients comparing torsemide versus furosemide as treatment for heart failure.

DCC Investigators. The DCC team will be led by Dr. Hrishikesh Chakraborty with Drs. Adrian Hernandez, Shelby Reed, Elizabeth Chrischilles and experienced project management, data management, bioinformatics, and statistical reporting team members. The DCC team has unparalleled experience in the coordination and analysis of clinical trials and pragmatic CRTs (see biosketches and budget justification for individual experience of the proposed project team).

Hrishikesh Chakraborty, DrPH, DCC PI, is the Director of Pragmatic Clinical Trial Biostatistics at DCRI and the Co-Director of the Duke Center for AIDS Research (CFAR) Quantitative Core. He is currently the joint Principal Investigator (PI) for the Implementing Genomics in Practice (IGNITE) Pragmatic Clinical Trails Coordinating Center (CC) at Duke University, which coordinates four pragmatic trials to evaluate and implement genomic medicine interventions in health systems where he is conducting one trial on acute pain and another one in chronic pain. He has served as PI for three DCCs including a large surgical quality control study across 8 hospitals, a multi-site international oral cleft prevention treatment trial, and a multi-site multi-country behavioral health intervention for babies requiring resuscitation at birth. He was the Director of Epidemiology and Biostatistics at Health Sciences South Carolina, a statewide research collaborative, which combined the databases of five major South Carolina hospital systems into one large statewide clinical data warehouse used for research. In addition, he was co-PI on a DCC for a national registry of Genetically Triggered Thoracic Aortic Aneurysms and Other Cardiovascular Conditions, and has served as senior statistician for two DCC projects. He has over 25 years' expertise in collaborative trial management, study

design including CRTs,[46-53] sample size calculation, data management, data quality control, data analysis, report writing, and publication of results. Dr. Chakraborty will manage the DCC, DCC-CCC coordination, submission of annual National Institutes of Health (NIH) progress reports, and all communication with the NIH. He will oversee trial design, development, and execution, monitoring of data collection, data management and quality, operational monitoring, analysis of trial data, and DCC team meetings.

Adrian Hernandez, MD, MHS, DCC Co-Investigator, is Vice Dean for Clinical Research for the Duke University School of Medicine and has direct responsibility for advancing the clinical research mission of the School of Medicine. He works with leaders in single and multi-site based human research, patient care delivery, information technology, and health data science within School of Medicine departments, and centers and institutes including the DCRI, Clinical and Translational Science Institute, and Margolis Center for Health Policy, in order to achieve the vision of advancing health and executing a coordinated strategy in clinical research to evolve the model of care and improve outcomes. Dr. Hernandez oversees the Institutional Review Board (IRB) for Duke Health, the Duke Office of Clinical Research, the Office of Regulatory Affairs & Quality, and the Research Integrity Office. A Professor of Medicine in the Division of Cardiology, Dr. Hernandez previously served as Director of Health Services and Outcomes Research and was a Faculty Associate Director of the DCRI. He has extensive experience in clinical research ranging from clinical trials to outcomes and health services research. He is the Coordinating Center PI for multiple networks and clinical trials such as the National Heart, Lung, and Blood Institute's Heart Failure Clinical Research Network, PCORI's National Patient-Centered Clinical Research Network (PCORnet) and the NIH's HCS Research Collaboratory. Dr. Hernandez will work closely with the team to provide input into the clinical, technical, and governance aspects of the DCC. He will facilitate engagement with the NIH HCS Research Collaboratory in support of the trial to incorporate lessons learned and best practices from the NIH HCS Research Collaboratory.

Shelby Reed, PhD, DCC Co-Investigator, is a Professor in the Department of Population Health Sciences and the Department of Medicine in the School of Medicine at Duke University. Dr. Reed has 20 years of experience leading multidisciplinary health outcomes research studies and has extensive expertise in designing and conducting trial-based and model-based cost-effectiveness analyses of diagnostics, drugs, and patient-centered interventions. She served on the ISPOR Task Forces for Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials in 2005 and 2015. Dr. Reed is the Director of the Center for Informing Health Decisions at the DCRI and the Co-founder and Director of the Preference Evaluation Research Group. She will oversee the planning, implementation, and analysis of the economics aim (Aim 3c).

Elizabeth Chrischilles, PhD, DCC Co-Investigator, is a Professor and Department Chair of Epidemiology specializing in pharmacoepidemiology and comparative effectiveness of medical products and care management interventions. In her role as an Associate Director in the UI Institute for Clinical and Translational Science (ICTS), she oversees and contributes to the data science portfolio of ICTS. In Biomedical Informatics she is responsible for ICTS leadership in national networks and for expanding rural networks, especially using people-centered tools such as the Iowa Personal Health Record (PHR). In addition, she directs the UI Department of Epidemiology Health Effectiveness Research Center which is the home for the PCORnet Greater Plains Collaborative Iowa Research Core as well as several prospective observational studies and intervention trials. These activities provide a rich environment and resources for pharmacoepidemiology and comparative effectiveness research, particularly using electronic healthcare data and prospective EHR-derived registries. Dr. Chrischilles will serve as a voting member on the Executive Committee, Chair the Informatics Committee, and participate in other committee meetings.

DCC Project Team. The DCC operations team will be comprised of a Project Leader (PL) (Mary Mills), site enrollment and data monitoring team, data transfer and management team, data analysis and economic analysis team, and dissemination team (**Figure 1**). Briefly, the PL will function as the DCC PIs' operations partner, providing cross-functional coordination for all DCC project activities. The enrollment and data monitoring team will coordinate with the CCC to help provide site monitoring, coordinate with sites, and coordinate with data management personnel in providing central data surveillance. The harmonized data transfer and management team will be responsible for data coordination, data management, data transfer, and creating analysis dataset for reporting. They will work with the informaticist at each of the HCS to identify common data elements, data extraction tools, quality control methods, patient-reported outcomes (PRO) collection tools, and finalize the protocol for data coordination. The data analysis and economic analysis team will be comprised of the lead statistician, a Data and Safety Monitoring Board (DSMB) statistician, and a statistical programmer. This team will support the trial by preparing a very detailed statistical analysis plan

(SAP) during the planning phase, providing review and comments on the protocol, programming the randomization scheme, ensuring the development and approval of the DSMB Charter, preparing DSMB reports, and assisting with the final report and manuscripts. The statistics/programming team and data management team will collaborate to prepare several reports to ensure data quality and efficient trial operations including enrollment reports, protocol deviation reports, data quality reports, and administrative reports. The dissemination team will work with the National Center for Complementary and Integrative Health (NCCIH) and sites to develop and execute a publication and dissemination plan and track the progress of manuscripts and presentations. The publication and dissemination plans will include several avenues for the dissemination of results, tools, and data including publications, presentations, websites, and open access databases.
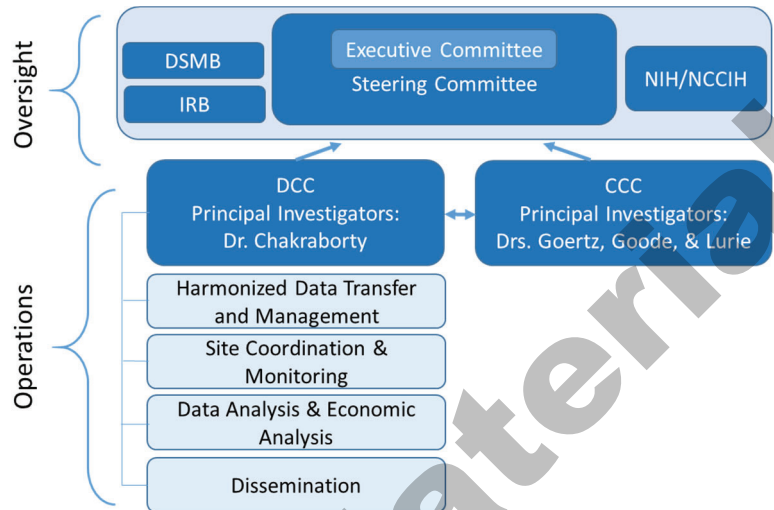

Figure 1. IMPACt-LBP DCC team structure and coordination.

DCC Operations Team Coordination. The DCC operations team (described above) will meet on a regular basis to ensure cross-functional coordination for all DCC project activities. Dr. Chakraborty will chair the DCC team meetings, which will be held weekly in the first year, then bi-weekly afterwards. Dr. Chakraborty and the DSMB statistician will work closely with the DSMB to schedule meetings and prepare DSMB materials. The PL will work with Dr. Chakraborty and the operations teams on a daily basis, particularly during the initial year of the project to discuss project needs, timelines, and issues. The data management and statistics/programming teams will also have joint and independent meetings periodically throughout the trial and at important milestones to ensure data quality.

CCC and DCC Collaboration. Ongoing communication and a close working relationship will be key to ensuring consistent and effective project management across the CCC and DCC for the IMPACt-LBP trial. While the CCC and DCC will each be responsible for their respective reporting requirements, the DCC and CCC PIs and respective PLs will meet weekly to review trial status and progress. The following issues will be reviewed: the status of the timelines, milestones, and metrics; changes in scope of work; financial status; key issues or problems; protocol adherence; recruitment; participant withdrawals; and development and implementation of protocol amendments. Plans will be discussed for the mitigation of existing or anticipated issues. DCC and CCC PIs will also collaborate with the Steering Committee and the NCCIH as described in more detail in the CCC application. The close coordination of CCC and DCC teams will ensure success in meeting project milestones and timelines.

3.3.2 Aim 1: To design the IMPACt-LBP trial.

Design. The IMPACt-LBP trial is a pragmatic, cluster-randomized trial that will compare the effectiveness of MC^2LBP to usual care in 1,800 adult participants aged 18 years or older with a primary complaint of LBP of any duration who contact one of 22 participating primary care clinics. The study will assess whether MC^2LBP will lead to improvements in patient physical function and reduced pain interference as compared to usual care alone. Clinics cluster-randomized to provide MC^2LBP will provide patient information regarding ACP guidelines and assist patients in making an appointment for multidisciplinary conservative care at the initial point of contact by the scheduling center. Control clinics will provide usual medical care alone. Detailed inclusion and exclusion criteria are summarized in the CCC Research Strategy.

Description of the Intervention. Patients seeking care at MC^2LBP model clinics will be given the option of seeing either a DC or a PT as their first contact clinician for an initial trial of care. Patients in the MC^2LBP group who agree to conservative care will receive an evaluation by either a PT or DC, including a treatment plan to address LBP that includes up to three visits for conservative care. Patients may choose to discontinue conservative care at any time during the three visits. Following the third visit, patients will have a mandatory re-evaluation by the PT or DC. At this time, or any time prior, the patient may be referred to a PCP for additional evaluation. In turn, the PCP may refer back to the PT or DC for continued treatment. This bi-directional communication will ensure multidisciplinary approach for the best patient care. Patients may be discharged from care at any point, based upon the recommendation of the conservative care provider or the desires of the

patient. It is important to note that while the specific treatments received by individual patients may vary and each patient is likely to receive a variety of different interventions, the comparison of interest remains the differences in outcomes and associated health care utilization between the two models of care, one that involves multidisciplinary conservative care at the initial point of care. Thus, the variability of treatments received after the patient's first visit does not directly confound the pragmatic question of interest which is the difference between the two structurally different models of care within the academic HCS. The treatments provided by MC^{2}LBP have demonstrated effectiveness. These include the following: the application of a load (force) in the form of spinal manipulation to specific body tissues with therapeutic intent;[31] myofascial therapies designed to stimulate sensory tissue, reduce pain, increase blood flow, relax muscle tone, and break fibrous adhesions between neighboring body tissues;[54,55] therapeutic exercise which can improve symptoms, prevent injury, encourage a team-based active treatment approach, and enhances self-efficacy;[56] proprioceptive neuromuscular facilitation that focuses on producing controlled movement to reduce abnormal muscle or joint strain;[57] neural mobilization to improve nerve mobility and reduce tension on spinal nerves impaired by adhesions, inflammation, or vascular compromise;[58] and nutritional/lifestyle and self-care strategies to reduce stress and/or change unhealthy behaviors, such as smoking.[161] The use of these interventions are supported by numerous national guidelines.[20,59,60,61,62,63]

Primary Endpoints: The co-primary outcomes will be patient reported change in PROMIS Pain Interference and Physical Function from baseline to 3-months. The PROMIS Pain Interference instrument will be used to measure the self-reported consequences of pain across aspects of life including social, cognitive, emotional, physical and recreational activities; this instrument refers to the past seven days. This validated scale has five response options, with scores ranging from one to five.[64] It has been shown to be a valid and reliable instrument[64] that is responsive to change in low back pain status (i.e., 3.5 to 5.5 points).[65] Our second co-primary endpoint is the change in PROMIS Physical Function (Short Form 4a) from baseline to 3-month follow-up. This is a valid and reliable measure of self-reported physical function that uses 4 items of the 29-item PROMIS short form. It performs well in multiple race-ethnicity and age groups.[66,67] It has excellent reliability, minimal ceiling/floor effects, limited item bias and is sensitive to change among patients with LBP[68] and spinal disorders.[69] These measures were chosen to be consistent with recommendations from the NIH Task Force on Research Standards for Chronic Back Pain.[70]

Secondary Endpoints: Secondary endpoints will be collected at baseline, 3, 6, and 12 months and will include opioid prescriptions, PROMIS measures of pain intensity, catastrophizing, sleep, and depression, health related quality of life and satisfaction, and information about procedures, prescriptions, and hospital/emergency room visits. A complete list of secondary endpoints is available in the Statistical Design and Power document. The analysis section below (Aim 3) describes statistical analyses for primary and secondary endpoints.

Sample Size. Sample size and power estimates for the co-primary endpoints were based on results obtained from the Goode et al.[71] pilot study. A study population of 1,800 participants in 22 clinics (11 randomized to each arm) will detect a 0.4 effect size for a difference in mean changes in the PROMIS Pain Interference between treatment groups with greater than 90% power, assuming a 2.5% level of significance, and a conservative 20% dropout rate during the first three months of the trial. Because randomization will occur at the clinic level and enrolled patients may be correlated within clinics, analyses must account for the intra-cluster correlation (ICC). An ICC between 0.01-0.05 will be able detect a difference of differences with minimum effect sizes ranging from 0.3-0.5. Sample size and power calculations for the primary and main secondary endpoints are presented in the Statistical Design and Power document.

Randomization. Because CRTs like IMPACt-LBP implement interventions at the cluster level, randomization necessarily also happens at the cluster level. With a limited number of clusters randomized, simple randomization may not be effective in reducing bias and differences between control and intervention groups.[72] Thus, in order to more effectively minimize variation between groups, we propose a covariate-constrained randomization scheme (CCR). [72,7370,71] To conduct CCR, a set of baseline variables that may be associated with study outcome or may be potential confounders is selected. Simulation is then used to generate all possible randomizations of the clusters into control and intervention arms. The balance between arms according to cluster-level covariates of interest for each possible randomization is calculated, a cut-point is established for the maximum allowable difference between study groups, and a single randomization scheme is randomly selected from the set of optimal randomizations that meet the maximum allowable difference criterion. Baseline covariates will be examined during the UG3 planning phase and will include average pain scores, clinic location (main medical center/community clinic), number of participating primary care providers,

and average level of opioid exposure of LBP patients at the clinic. During the UG3 planning phase we will further examine potential covariates and limit the number to 1 or 2.

Our proposed randomization scheme allows us to accommodate the potential for clinic drop-out. In our 2-block design, if a clinic that is randomized to the first block discontinues participation or a clinic has a lower than expected number of patients with LBP this block design may allow for additional clinics to be added to the second block of clinics. This block design may also allow us to use information obtained from the clinics within the first block of randomized clinics to inform and improve our enrollment process for the second block of clinics.

Informed Consent. We will seek a waiver of the requirement for individual level consent to participate in the study from all participating IRBs. PRO data collection will be implemented into existing patient flow processes as routine collection at primary care clinics, additional data elements will be collected through the EHR as part of the regular practice, consenting of patients is not practical since study staff will not have face-to-face contact with patients, and the risks involved with non-pharmacological approaches provided by DCs and PTs are low when compared to other commonly used conventional medical approaches. Both clinics and patients will have the ability to opt out of participation or being seen at a MC^{2}LBP clinic. The ability of patients to forego MC^{2}LBP evaluation and care is part of the safeguards that we believe will justify a waiver of consent for this study and the frequency of that non-adherence is part of the pragmatic assessment of the real-world effectiveness of the MC^{2}LBP model. In the event that this waiver is not granted, we will utilize informed consent processes that have worked successfully in our previous clinical trials and seek approval for individual patient consent. For more information on informed consent, see CCC Section 3.1.

Project Management Plan & Feasibility Assessment. The DCC will coordinate with the CCC to create a project management plan that will include a feasibility assessment, plans for managing and monitoring trial conduct, and strategies for the completion of project milestones on-time and on-budget. The feasibility assessment will be conducted in the first year to identify region-, institution-, or investigator-specific challenges that may impact overall trial completion, quality, and outcomes early in the trial process. The DCC will conduct the feasibility assessments for all sites, develop a site-specific feasibility report, and work closely with the CCC, Steering Committee, and NCCIH to identify solutions to anticipated obstacles, improve trial conduct, and increase chances of trial success.

Central Institutional Review Board (cIRB). The IMPACt-LBP trial will use the SMART IRB Master Common Reciprocal Institutional Review Board Authorization Agreement (SMART IRB Agreement), the cIRB Letter of Indemnification (CIRB LOI), and the IRB Reliance Exchange (IREx) to support single IRB review in compliance with the NIH policy on the Use of a single IRB (sIRB) for multi-site research. The cIRB will be coordinated by the IMPACt-LBP CCC and the plan for the cIRB is included with this proposal as an attachment in the Single IRB Plan section of the submission.

3.3.3 Aim 2: To implement advanced data collection, data management, monitoring, and trial management techniques.

Data Sources and Data Collection. The IMPACt-LBP trial will collect a variety of different data types from different sources as summarized in **Figure 2**. We will be utilizing a novel combination of the PCORNet Common Data Model (CDM) and EPIC Electronic Health Records (EHR) along with currently used
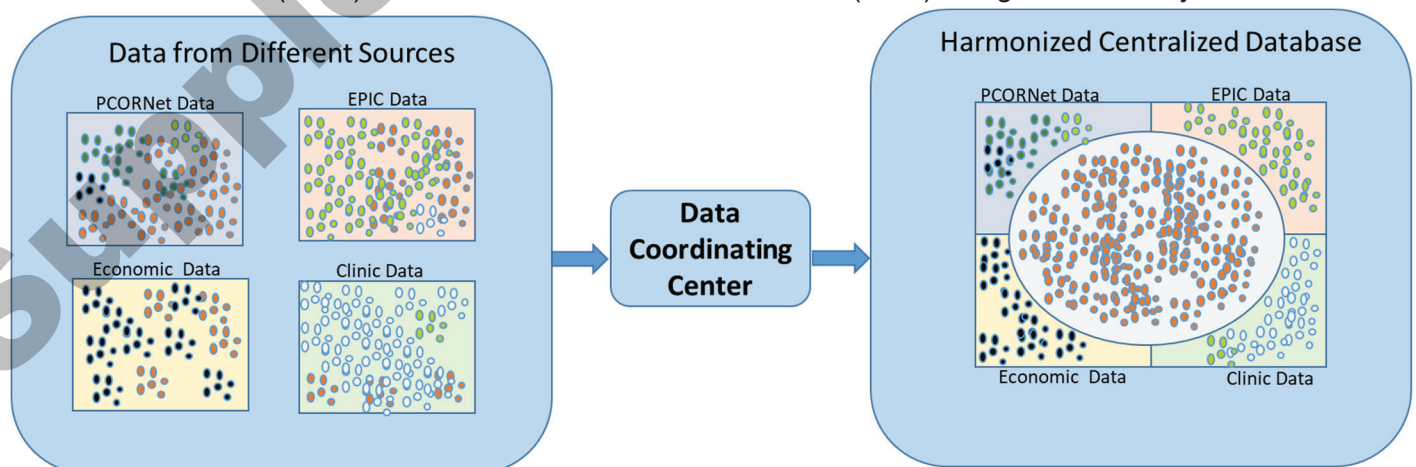

Figure 2. IMPACt-LBP Data Processing Workflow and Harmonized Centralized Database for analysis.

mechanisms for claims processing and performance measurement in community-based PT/DC clinics as data collection, data management, and transfer strategies. The CDM includes at least 10 data domains, e.g., patient demographics, vitals, diagnoses, procedures, prescribing data for inpatient and outpatient clinical data. The data are harmonized across participating member institutions, are updated monthly, and routinely undergo extensive data quality checks. Since some of our MC^{2}LBP providers will not be co-located within academic HCS, during the UG3 planning phase we will examine feasibility and finalize mechanisms of data collection. One option for EHR data collection is the use of Quality Value Health, LLC (QVH). QVH programmers are experienced in acquiring data from EHR and claims processing software in private medical offices, chiropractic offices and institutional facilities. The data can be uploaded into a QVH Enterprise SQL Server database for secure storage, query and manipulation of participant data. Study data transfers are encrypted and placed into a QVH's SFTP server. QVH provides a login credential in a secured/encrypted email to only approved email address. At Duke, the PROMIS patient reported outcomes measures required for this study are already located within the EHR (EPIC). At both University of Iowa and Dartmouth, similar models exist, in which patients complete routine patient forms including PROMIS measures through a patient portal prior to the clinic appointment and via tablets during clinic visits. Duke informatics will work with Dartmouth and University of Iowa to assist in operationalizing and standardizing a joint model of PRO collection and assist with developing data abstraction methods follow-up time points. We will consider three strategies for collecting PRO data from community-based MC^{2}LBP clinics during the UG3 planning phase: 1) PRO data can be collected and managed from QVH's ACE Patient Portal using web based data collection strategies that have been used previously by study principals; 2) PRO data will be collected and managed using web-based data collection strategies that have been used previously by study investigators; or 3) we will utilize PRO data collection methods used successfully in the IMPaC pilot study.

Risk-Based Monitoring, Trial Management, & Quality Control. As described previously in the Innovation section above, the DCC will implement a risk-based data-driven trial management approach to ensure the highest data quality and most efficient, timely trial management. The DCC will identify potential trial and data risks prior to enrollment, and enter risks into a risk register that categorizes the risk, identifies an owner, and ranks the probability, impact, and priority of the risk. These risks are then evaluated quarterly throughout the trial and mitigation actions implemented. This risk-based approach to monitoring combined with periodic reports that monitor enrollment and data quality will allow the DCC team to quickly detect and respond to emerging problems and optimizing the use of in-person clinical site visits.

In addition, we will develop and maintain comprehensive quality assurance (QA) and quality control (QC) programs documented in a data-monitoring plan. QA components include certification of research clinical center staff on processes and assessments, administrative, regulatory and facility compliance checks, site staff training, and early evaluation of compliance with study procedures. The statistics/programming team will create periodic data quality reports to identify data errors, protocol deviations, standardization failures, missing data, or other inconsistencies. Clinical sites will be given regular feedback to discuss issues identified by QA and QC assessments and study status reports. At study completion, we will review site close-out procedures with all clinical sites. Together with trial management and site monitoring, the QA/QC implementation will ensure efficient, high quality data collection and trial operations. Finally, DCRI has extensive Standard Operating Procedures (SOPs) that ensure and document that best practices are followed to ensure highest quality data management, data completeness and accuracy, and deliverables.

Recruitment/Retention Monitoring and Contingency Plan. The validity and generalizability of clinical trials depend on the recruitment of a diverse representative population in adequate numbers for statistical power, and retaining participants in the trial long enough to obtain adequate follow-up. Accordingly, the DCC will work closely with the CCC to develop a recruitment and retention plan for the trial including retention methods described in the Innovation Section above. As part of this plan, the DCC will establish enrollment targets for each site. The DCC will then monitor the recruitment and retention of participants throughout the trial with weekly, monthly, and on-demand operations reports to review enrollment and monitor participant demographics according to racial, ethnic, and gender categories. If enrollment falls below targets, the DCC will work with clinical sites to overcome recruitment and retention challenges. If these efforts are not sufficient, the DCC will work with the CCC, Steering Committee, and NCCIH to identify and activate additional sites.

3.3.4 Aim 3: To provide robust statistical analyses and safety monitoring.

General Analytic Considerations. A detailed SAP will be developed by the DCC statistical team and contained in a separate document. Study population details including the number randomized in each treatment arm, in each stratum, and lost to follow-up will be described. Baseline participant characteristics will be summarized as means, standard deviations, medians, and 25th, 75th percentiles for continuous variables, and as counts and percentages for categorical variables. Differences in baseline characteristics between the randomized arms will be compared using a Wilcoxon rank-sum test for continuous variables and a chi-square test or the Fisher's exact test for categorical variables, as appropriate. Model assumptions will be examined prior to analysis and transformations implemented, if necessary, to more adequately meet the assumptions.

Aim 3a: To provide robust statistical analyses for CCC primary hypothesis that implementation of MC^{2}LBP will improve physical function and reduce pain interference as compared to usual care.

To test the primary hypothesis that initial patient contact with DC/PT will improve patient physical function and decrease pain interference at 3 months, we will compare the change in PROMIS Pain Interference and PROMIS Physical Function, individually, from baseline to 3-month follow-up between usual care and intervention arms using a linear mixed-effects models (LMM) with random effects to account for clustering. This model will include the baseline PROMIS Pain Interference or PROMIS Physical Function to control for baseline differences. We will select the appropriate covariance matrix (e.g., compound symmetry, autoregressive, unstructured, etc.) based on the data. This primary analysis will be conducted according to the principle of intention-to-treat with participants analyzed and endpoints attributed according to the treatment arm to which the participants were randomized, regardless of subsequent crossover or post-randomization medical care. Refer to the Statistical Design and Power document for details about additional analyses.

Aim 3b: To provide robust statistical analyses for CCC secondary endpoints.

For continuous secondary measures at 3, 6, and 12 months (i.e., PROMIS sleep, depression, pain intensity and catastrophizing, health relate quality of life (EQ-5D-5L), opioid prescriptions and patient satisfaction (PHQ-18) we will compare the change from baseline to 3 months, change from baseline to 6 months, and change from baseline to 12 months using the LMMs described above (with random effects, the appropriate covariance structure, and baseline endpoint measure as a covariate). Harmonized NIH Pain Management PRISM Initiative definitions will be used to identify prescribed opioid medications.[74] Opioid exposure (naive and tolerant) will be captured through EHR and the common data model at baseline (and in 12 months prior to baseline). We will compare total opioid dosage (morphine equivalents) in the 12 months after enrollment. In order to be able to compare opioid doses across classes, we will use a standard formula to calculate morphine equivalents from the CDC Morphine Equivalent Factors. Within 12 months after enrollment, we will determine: morphine equivalent dose, and duration of prescription opioid use. We will also compare differences in the time trend of these continuous secondary endpoints between treatment arms with a repeated measures mixed-effects models as described above. For secondary measures that are counts (health utilization measures and medication) in the 12 month follow-up period (i.e., number of imaging and diagnostic referrals, number of provider referrals, number of injection procedures, number of surgical procedures, number of medication prescriptions, number of hospital admissions, and number of emergency department visits), we will compare differences in the endpoints among treatment arms using general linear mixed models (GLMM) that account for clustering and the distribution of count data.

Aim 3c: To provide robust statistical analyses of medical resource use and costs, health utilities, and cost effectiveness.

Medical Resource Use and Costs. Three main outcome metrics will be used in the economic evaluation in Aim 3. These are described in detail in CCC section 4.3 Protocol Synopsis. Medical Resource Use EHR data will be used to determine medical resource use for patients enrolled across the three participating institutions. Medical resource use will include visits to MDs, DCs, PTs and other types of healthcare professionals, as well as musculoskeletal-related injections, procedures, surgeries, emergency department admissions, and hospitalizations. Specific CPT, DRG and ICD-10 codes will be used to identify medical resources associated with managing LBP. For Direct Medical Costs, if cost accounting or paid claims can be provided by all participating institutions, patient-level cost data will be used for analysis. If the Dartmouth or University of Iowa health systems cannot provide patient-level cost data, resource-specific unit costs will be derived using cost accounting data from Duke to assign costs to medical services received by patients for whom institutional cost data are not available. To estimate costs associated with prescribed outpatient drugs, unit costs will be estimated using the Federal Supply Schedule.[75]

Analysis of Medical Resource Use and Costs. To describe medical resource use and total costs in the MC^{2}LBP model as compared to usual care, we will use multilevel generalized linear models to make comparisons between treatment arms accounting for clustering at the clinic and institutional levels. For cost comparisons, models will be specified with gamma error distributions and log links. For comparisons of medical resource use negative binomial error distributions and log links will be specified. In addition to a variable representing study arm assignment, baseline covariates will be included to account for medical resource use and costs associated with age, gender, and common comorbid conditions. All analyses of medical resource use and costs will apply intention-to-treat analysis principles.

Health Utilities. To describe differences in health-related quality of life experienced by patients randomized to the MC^{2}LBP model versus usual care in a cost-effectiveness analysis, the preference-weighted 5-level EQ-5D (EQ-5D-5L) will be administered at baseline, 3, 6, and 12 months. The EQ-5D-5L uses 5 levels (no problems, slight problems, moderate problems, severe problems and extreme problems) to measure health status across 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The 5-level instrument has been shown to be superior to the historical 3-level version in regard to ceiling effects and being more sensitive to changes in health status.[76,77] The 3,125 possible health states represented by the EQ-5D-5L have corresponding US preference weights wherein a weight of 1 represents perfect health, a weight of 0 represents death, and negative weights represents states considered worse than death.[78]

Analysis of Health Utilities. We also will apply repeated-measures multilevel generalized linear models to describe EQ-5D-5L health utility weights measured at baseline, 3, 6 and 12 months between study groups as measured by fixed-effect group*time interaction terms. A random intercept term will be used to control for differences in baseline health status across participants. We also will describe changes on the PROMIS Pain Interference score at 3 months and their association with changes in EQ-5D-5L health utility weights. For that analysis, we will use a similar repeated-measures mixed model and pain score*time interaction terms.

Cost-Effectiveness Analysis. We will use an incremental net health benefits (iNHB) approach[79] to evaluate within-trial cost-effectiveness in which iNHB= ΔQALY*λ – ΔCost, where λ represents maximum willingness to pay per QALY, and ΔQALY and ΔCost represent differences in mean QALYs and costs, respectively, for the DC/PT versus usual care groups. This approach avoids a number of statistical and interpretational issues that arise with negative incremental cost-effectiveness ratios that occur when an intervention is less costly or less effective than usual care (i.e. negative numerator or denominator in the ICER calculation).[80] Non-parametric bootstrapping will be used to generate 95% confidence intervals for NHBs. The net benefits approach can also be used to estimate NHBs at the patient-level to facilitate regression modeling to identify factors associated with greater or lesser value with alternative medical providers initially managing LBP.[81] Cost-effectiveness acceptability curves will be used to report findings across a range of willingness-to-pay per QALY thresholds. Sensitivity analyses will be employed to evaluate the effects of applying alternative sources for unit costs and alternative approaches to adjust for baseline patient-level NHBs.[82]

Exploratory Analyses. Exploratory analyses will include subgroup analyses, covariate-adjusted analyses, and as-treated analyses. First, if the data provide evidence of an overall difference in the primary outcomes between treatment groups, we will further examine whether the therapeutic effect is similar for all participants, or whether it varies according to race (African American vs White), sex and low back pain acuity (acute versus chronic). All subgroup analyses will use linear mixed models or general linear mixed models as described above to test for interactions between treatment and subgroup variables. Effect estimates for subgroups will be carefully (conservatively) interpreted in conjunction with the formal interaction tests. Second, we will repeat analyses for all secondary endpoints with adjustment for several covariates known to influence function outcomes including, at minimum those covariates easily obtained from the EHR such as age, sex and race. Finally, to account for possible cross-overs, we will conduct as-treated analyses with participants analyzed according to the treatment actually received.

As an exploratory safety analysis, we will determine if there is a delay in diagnosis of conditions that require immediate medical attention in patients receiving care from a PT or DC by examining the length of time between study enrollment and LBP diagnosis. Details are provided in the Statistical Design and Power document.

We will assess whether MC^{2}LBP leads to long term improvement compared to usual care using the PROMIS Pain Interference and Physical Function at 18 and 24 months. Similarly, we will determine if MC^{2}LBP leads to lower healthcare utilization by comparing prescription medications, visits to providers, musculoskeletal-related injections, procedures, surgeries, and emergency department visits and hospital admissions for any cause and

for LBP in patients randomized to MC^{2}LBP vs. usual care at 18 and 24 months. We will only follow patients who are enrolled within the first 18 months of the data collection phase in this exploratory analysis.

Multiplicity. Adjusting for the effects of the repeated significance testing for the multiplicity of secondary endpoints and exploratory analyses would require that very small significance levels be used for every comparison. Therefore, rather than adjusting for multiple comparisons, statistical results (e.g., p values) will only be presented for the co-primary endpoint analyses. We will be conservative in the interpretation of secondary analyses and report only point estimates and 95% confidence intervals. We have also pre-specified the primary and secondary outcome variables to avoid over-interpretation of strictly exploratory comparisons.

Missing Data. Several efforts will be made to reduce the amount of missing data for all endpoints. Despite these efforts, missing data for primary and secondary endpoints are possible. For primary and secondary analyses that examine the change from baseline (to 3-, 6-, or 12-months), missing data in either baseline or the follow-up time point will lead to missing endpoint data for the patient. For these analyses, multiple imputation will be used. Multiple imputation will also be used for secondary endpoints that are counts in the 12 month follow-up period (i.e., number of imaging and diagnostic referrals, number of provider referrals, number of injection procedures, number of surgical procedures, number of medication prescriptions, number of hospital admissions, and number of ER visits). To ensure that the missing at random assumption for multiple imputation is valid, we will compare these results to those obtained without imputation. Missing data are easily handled in repeated measures LMM and GLMM and so no imputation will be needed.

Aim 3d: To provide robust statistical analyses of patient, provider, system, and policy level barriers and facilitators to MC^{2}LBP.

Originally developed through the Department of Veterans Affairs Quality Enhancement Research Initiative (VA QUERI), hybrid designs blend elements of clinical effectiveness and implementation studies to support rigorous, policy-applicable evaluation of pragmatic clinical trials and promote rapid translation of key findings into real world settings.[83] While our primary focus of this trial is evaluation of the clinical impacts of the **MC^{2}LBP** model (patient-level outcomes), the process evaluation emphasizes the implementation strategy (provider, clinical unit, and system levels) to discern barriers and facilitators of model uptake and sustainability (hybrid design approach 1). Hybrid 1 designs are recommended for minimal risk clinical interventions with preliminary evidence of effectiveness in similar populations or settings, and are especially useful for trials conducted within clinical trial or practice-based research networks, as is the focus of the IMPACt-LBP trial. We will use mixed methods approaches to conduct a multi-stakeholder evaluation of factors influencing the delivery of the clinical intervention. In each year, administrative and/or clinical personnel will complete standardized instruments to describe the organizational context of each setting (e.g., patient characteristics, patient visit numbers overall and lbp related, provider types and numbers, significant changes to clinic function, readiness to change, adoption rates, etc.) as a means of describing the unique and varying clinical environments and to determine whether and to what extent systems-level initiatives may have influenced the study model. Early in GY2, we will conduct site visits to complete stakeholder interviews and focus groups to establish perceived barriers and facilitators to model implementation with the goal of tailoring organizational policies and procedures to facilitate **MC^{2}LBP** across the 3 academic HCS. Summative process evaluations in GY4/GY5 will again evaluate barriers and facilitators of **MC^{2}LBP**, determine how these diverse clinical units addressed challenges to implementation, and assess the robustness with which the guideline-based LBP care was integrated into existing care delivery systems. Throughout this evaluation, we will seek to determine patient, provider, clinic and system phenotypes of model best fit, or the circumstances under which MC2 works most efficiently and effectively for LBP patients. Individual interviews will be digitally audio-recorded, last about 15-45 minutes in duration, professionally transcribed, and assessed for data quality before data analysis. Focus group sessions will last 60 minutes and will be constituted with stakeholders of similar backgrounds (patients, providers, etc.). We will conduct qualitative data analysis using NVIVO software (QSR International Pty Ltd., Victoria, Australia). Coding will use both inductive and deductive approaches, building on the facets of the **MC^{2}LBP** model as an initial codebook. Qualitative data will be compared across individuals, treatment groups, and study sites to understand the range, variability, and areas of consensus and divergence on the benefits and feasibility of the study interventions for managing LBP and to understand patient perceptions of the usefulness, safety, acceptability, and effectiveness of DCs/PTs as first line providers for LBP care.

Aim 3e: To provide robust statistical analyses and reports for the IMPACt-LBP DSMB.

The IMPACt-LBP trial will have a DSMB appointed by NCCIH and that will monitor efficacy, participant safety, and the performance of the study. The DSMB will be responsible for providing recommendations regarding trial's conduct and guidance to NCCIH leadership to ensure the safety and well-being of participating

participants. A separate DSMB charter will outline the operating guidelines for the committee, the protocol for evaluation of data, and data tables to be provided. The charter will be created prior to study enrollment and agreed upon during the initial meeting of the DSMB. It is anticipated that the DSMB will have one planning meeting and then meet to review key safety endpoints every 6 months. An examination of key safety and effectiveness endpoint data will be performed every 6 months during the course of the trial. The results of the safety analyses and status reports will be carefully and confidentially reviewed by the DSMB. No interim efficacy analyses are currently planned, but may be performed upon request by the DSMB. The IMPACt-LBP trial leadership will recommend that the DSMB has access to the actual study assignments of randomized participants following the 2009 FDA Guidance for DSMBs.[84] Please see Data and Safety Monitoring Plan for more details.

3.3.5 Aim 4: To facilitate publication and dissemination of data and study findings.

Effective and powerful communication of trial results and knowledge is crucial to achieving DCRI's mission of improving the practice of medicine. Our faculty focus strongly on disseminating research results and tools, publishing more than 1,000 articles per year in peer-reviewed journals for a total of more than 10,000 since its inception. Their effects on patient care and the state of medicine are felt around the world. The entire IMPACt-LBP study group is fully committed to the public dissemination of the study results and public access to the trial data. Moreover, because the findings of the IMPACt-LBP trial may have immediate and direct impacts on participant outcomes, rapid dissemination of these results is critical. Accordingly, we will distribute study results and data in several ways. IMPACt-LBP investigators and Executive Committee members are leaders in a variety of professional organizations that can serve as vehicles for study result dissemination. Accordingly, the IMPACt-LBP team will disseminate the findings of this project initially through annual meetings of these and other organizations. The primary and secondary results of the IMPACt-LBP trial will also be communicated to the medical community through publications in high-impact, peer-reviewed journals and by the reporting of results on clinicaltrials.gov. We will also make the results available on the DCRI's website and share results and trial learning/experience on the key stakeholders at IMPACt-LBP sites.

In addition, the DCC will ensure that the project datasets will be widely shared with the scientific community for research, while carefully observing standards of participant privacy, confidentiality, and management of health information. De-identified IMPACt-LBP data will be prepared in accordance with requirements for NCCIH data repository datasets. In addition, we will provide requested unrestricted data to parties who sign a data sharing agreement, which stipulates that data must be: 1) used solely for research purposes, 2) properly acknowledged in resulting publications, 3) kept confidential and inaccessible to third parties, and 4) destroyed or returned after analyses are completed. Additionally, users must agree not to use data to identify individual participants. Letters of agreement will be executed so that research materials can be provided to not-for-profit institutions. The IMPACt-LBP study team agrees that all resource sharing agreements comply with the Bayh-Dole Act of 1980 and the Technology Transfer Commercialization Act of 2000.

We will also work to disseminate lessons learned from the design and implementation of the study. These lessons will be made available with the NIH HCS Research Collaboratory online Living Textbook of Pragmatic Clinical Trials. The Living Textbook website is the Collaboratory's online collection of expert consensus regarding special considerations, standard approaches, and best practices in the design, conduct, and reporting of pragmatic clinical trials. Through the Living Textbook, the DCC will be able to harmonize its lessons learned with those of the Collaboratory pragmatic trials and reach a large existing audience interested in the conduct of embedded pragmatic trials.

3.3.6 Milestones, Challenges, & Mitigation Strategies

The IMPACt-LBP trial will be driven and managed according to a well-established timeline and milestone plan, presented in detail in the Study Timeline section 2.7 and Milestones Plan section 5. Potential challenges may involve retention of participants. As described in Aim 2 above, we will implement several strategies to increase retention of participants and reduce loss to follow-up. We will monitor data quality and missingness on a monthly basis and provide detailed feedback reports to sites to obtain the required data elements. In addition to efforts to reduce missing data, we use several statistical analysis strategies to handle missing data when they do occur. Lastly, we have implemented a trial management approach that identifies all possible risks at the outset to quickly and efficiently respond to and mitigate any obstacles and challenges that arise during the trial. These strategies together will ensure an efficient and effective trial with high quality data and results at database lock.

10. RESOURCE SHARING PLAN(S)

10.1 Data Sharing Plan

In a policy issued on February 26, 2003 and revised on June 27, 2005, the NIH reaffirmed its support for the concept of "data sharing," that is, making data from a research study available to other interested researchers. The policy states: "We believe that data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health. The NIH expects and supports the timely release and sharing of final research data from NIH-supported studies for use by other researchers."

In addition to the NIH policies, we have also reviewed the NIH Collaboratory Living Textbook of Pragmatic Clinical Trials, specifically sections related to data sharing and embedded research. Recognize that data will be obtained via two methods (electronic medical record and patient reported outcomes) that standard approaches for data sharing are complex. In year 1, we will collaborate with the NCCIH to finalize the below Data Sharing Plan and each HSC has provided institutional support and agrees to abide by the Resources and Data sharing Plan.

Assuming a standard data sharing approach and that no restrictions are imposed by institutional policies, the local IRBs, as well as local, state, and federal laws and regulations (including the HIPAA Privacy Rule), we are prepared to follow the February 2003 policy, revised on June 27, 2005, for the data generated from this application. We have approached Data Sharing Plans in three main ways, although under HIPAA regulations and the NIH grant directives, there are a number of degrees of flexibility. Three options include: 1) a Limited Data Set with Data Use Agreement (LDS/DUA) and IRB approval, 2) de-identified use of the datasets, and 3) fully identified data sets with subject authorization and IRB approval. Each approach has advantages and disadvantages. For the clinical data, our proposed data sharing plan for this application includes options 1 or 2 on a case-specific basis.

For De-identification of the datasets, we apply HIPAA definitions by adding back variables to the dataset that express all dates as number of days since a milestone event, enrollment, and a variable storing just the year. For example, the milestone event would be "Day 0" in this case. We propose use of a de-identified dataset because the de-identification only has to be done once, and the de-identified data stored for sharing. A de-identified data set is not subject to HIPAA's minimum necessary standards, so all of the data in the de-identified dataset can be included and shared. A limited data set is subject to HIPAA's minimum necessary standards, so the dataset for each sharing request would have to be custom created to include just the subset of data needed. Sharing of de-identified data also provides easier book-keeping. For example, no Data Use Agreement (DUA) is required. De-identified datasets can even, conceptually, be posted to a web site for downloading. The de-identified dataset can include a 'link' field to connect back to the original, identified, data. This field cannot be derived from any data in the original dataset (basically it's a table-look-up field). Under recent guidance from OHRP, a de-identified dataset can be declared to be "not human subjects" and thus not subject to the recipient's IRB review.

10.1.1 Preparing Data to be Shared

In collaboration with the NCCIH, we will finalize our data sharing plan, however protection of the identities of the participants is a top priority and the shared data set must be free of identifiers that could lead to the identification of individuals. The central database maintained by the DCRI will not have direct identifiers, such as name, contact information, or social security number, but will have dates. We thus will de-identify the data (i.e., strip all personal health information (PHI) in compliance with the HIPAA privacy rule). This makes the data free of identifiers that would permit linkages to the research participants and free of content that would create unacceptable risk of subject identification. All DCRI personnel are required to maintain yearly HIPAA training.

Under the HIPAA Privacy Rule, PHI will be stripped from the database. Specifically, de-identification of a dataset includes removal of the following PHI variables:

- Names;
- Geographic information (including city, state, and zip code);
- Elements of dates such as those for birth, hospital admission and discharge, and death;
- Telephone numbers and fax numbers;
- Electronic mail addresses;

- Social Security Number;

- Medical record and prescription numbers;

- Health plan beneficiary numbers;

- Account numbers;

- Certificate or license numbers;

- Any vehicle identifier or serial number, including license plate number;

- Any device identifier or serial number;

- Web Universal Resource Locator (URL);

- Internet Protocol (IP) address number;

- Any biometric identifiers, including finger or voice prints;

- Full face photographic images or any comparable images.

Based on our experience, other data often not listed as PHI are indirect identifiers and could lead to what the NIH data sharing workbook calls "deductive disclosure" of participants' identities. This is more likely in small, geographically limited or specialized populations. However, it is also recognized that clinical study data lacking time variables, demographic information, and information regarding risk factors are often not very useful. Therefore, de-identification of other data must come with tools to rebuild and or retain the aforementioned information. For example, the time information can be retained by picking a reference date, the same for all subjects (e.g., date of enrollment), and calculating all dates as the number of days since that date. For information about geographical location that would jeopardize identity because a very small number of patients reside within a particular geographical vicinity, different aggregation algorithms can be employed as appropriate. For example, if there are too few subjects at a site, then the site may be combined with another site. Similarly, racial/ethnic groups can be collapsed when there are few individuals in certain groups or cells. We will also consider de-identifying on a variable or field level such as comment fields, optional fields, other specify fields, site number, investigator, and site name. For comments and "specify" fields, we will first recommend not collecting them during the study unless absolutely necessary. We will then only report the coded data and not the specifics. Inevitably, some data sharing situations will arise for which no predefined solution exists. In these cases, we will work with network leadership to define an acceptable reporting solution and evaluate the data to ensure that the risk of re-identification is very small. We will also ensure that the common consent form discloses that de-identified data will be shared.

10.1.2 Process for Providing Data

We recognize that interested parties will want access to the data. Only de-identified data or limited datasets for proposed use, with appropriate documentation, will be provided via secure transfer methods to the requestor following institutional approval and data use agreements as appropriate. In collaboration with theNCCIH, we will develop a process to facilitate providing other investigators with access to de-identified study data in the format that is most helpful to them. Data formats include e.g., SAS transport files or CSV files.

All SAS programs developed at the DCRI for data provision purposes are written and documented according to institutional SOPs and final specification plans. The study data provided, whether it is in SAS data sets or already programmed tables and listings will be made available to the user under an agreement containing the following stipulations.

1. The data will be used for research purposes and not to identify individual subjects.

2. The data must be secured using appropriate computer technology with user access controlled.

3. The authors of any manuscript resulting from this data must acknowledge the source of the data upon which their manuscript is based.

4. Any analyses for the purpose of presentations, abstracts, and/or publications must be coordinated through the Data Dissemination Committee, so that there can be some coordination of analyses to ensure that redundant analyses are not being performed independently.

5. All coauthors must be given a chance for review and approval of a draft manuscript prior to submission for publication.

10.1.4 Dissemination of Study Results

We will support and promote data sharing after study completion. A major objective of the DCRI will be to disseminate to the medical community new information learned through studies conducted. The timing of release and the definition of the data set to be made available is a complex issue related to issues of study participant confidentiality and issues concerning data availability.

A Data Dissemination Committee will be created and will consist of the CCC PIs (Goode, Goertz, and Lurie) and the DCC PI (Chakraborty). The Data Dissemination Committee provides review and general oversight of the publications and public presentations that report scientific findings of the study. The Data Dissemination Committee will ensure that the study results are presented by individuals who have working knowledge of the study design, implementation, data synthesis/analysis, and interpretation. The Data Dissemination Committee will ensure that any confidential or proprietary information is protected, and that all appropriate statistical analyses have been included. The Data Dissemination Committee, in collaboration with the NCCIH, will develop a Publications Policy that outlines the governing structure of the Data Dissemination Committee.

All manuscripts, abstracts, presentations at scientific meetings (in format of slides or posters), and other published works derived from work supported by these funds, must submit to the Publication Committeee before submission to a scientific journal, conference, organization, or other publishing body, or before being posted in a public domain.

All publications must conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors [ICMJE]) with regards to authorship, disclosure, scientific integrity, and other requirements. All public presentations shall be consistent with usual academic standards. All publications must include a statement acknowledging the study award number.

10.1.5 NIH Public Access Policy Compliance

All authors will follow the National Institutes of Health (NIH) Public Access Policy and must ensure that all published manuscripts are submitted to PubMed Central, as required.

As part of the NIH policy, authors will adhere to copyright and citation requirements:

a) **Copyright compliance** - All authors will ensure that agreements with publishers permit the submission of the author's manuscript to NIH.
b) **Citing PubMed Central ID Numbers** - When a manuscript is submitted to the NIH, the publication will receive an NIH Manuscript Submission (NIHMS) ID number. Once a manuscript is available in PubMed Central, it will be assigned a PubMed Central ID number. Effective May 25, 2008, authors will cite PubMed Central ID or (NIHMS) ID numbers for any articles cited in progress reports, new applications, and renewals.

10.2 Sharing Model organisms

NA

10.3 Genomic Data Sharing

NA