PROTOCOL TITLE:

Non-opioid pramipexole suppresses immune NLRP3 reactivity for pain.

PRINCIPAL INVESTIGATOR:

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2.

DATE:

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REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
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Is this a clinical trial under ICH-GCP E6? ☐ Yes X☐ No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☐ Yes ☐ No

ICH-GCP E6 can be accessed by copying and pasting this URL into your browser: http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf

FUNDING:

Indicate if the protocol is funded. If so, provide sponsor and SPO Click ERA record number. This protocol is not funded. It is part of the CTSC RFA for "Linking Clinical Trials to Drug Discovery and Repurposing Award".

Table of Contents

1. Objectives

1.1. The ***long-term goal*** of this proposal is to identify non-opioid drugs that harness endogenous anti-inflammatory mechanisms resulting in the suppression of proinflammatory cytokines such as IL-1β, providing a novel approach to treat chronic pain in people while lacking potential for addictive side effects.

Specific Aim I: pramipexole blocks the activation of NLRP3 and consequent production and release of the proinflammatory cytokines IL-1β, IL-6 and TNF-α, and increases production of the anti-inflammatory cytokine interleukin-10 (IL-10).

> The goal of Aim I (Phase I) experiments is to examine the specific anti-inflammatory mechanisms of pramipexole on PAMP, DAMP and opioid stimulated immune cells, THP-1 cells will be used.

Specific Aim II: pramipexole treatment will provide therapeutic benefit to patients experiencing suboptimal pain relief from current standard therapy with concurrent reduction of TLR4-NLRP3-cytokine expression in peripheral blood mononuclear cells.

> The goal of Aim II (Phase II) will be to determine the therapeutic benefit of pramipexole for pain, which is a repurposing of this FDA-approved drug with a good safety profile.

1.2. Our ***overarching hypothesis*** is that pramipexole will control clinical pain by suppressing the activation of the TLR4-NLRP3-IL-1β pathway and prevent IL-1β release from peripheral immune cells. These findings have provided the current impetus to examine pain therapeutic drugs targeting immune-related factors either upstream or downstream of IL-1β signaling.

2. Background

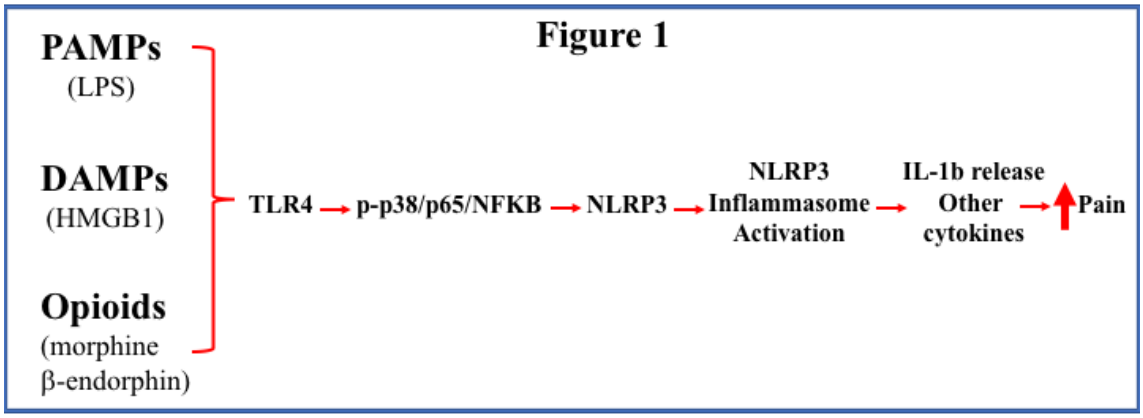
2.1.

The rate of US opioid-related overdose deaths from 2013 - 2016 increased by an astonishing 88% per year, while overdose deaths due to other drugs remained virtually unchanged [1, 2]. These increasing opioid-related death rates are linked to increases in prescription opioid misuse (medical and non-medical) as well as illicit opioid use (heroin) [3, 4]. Despite medical prescription opioid misuse generally declining during recent years [5, 6], the number of individuals who misuse prescription and illicit opioids continues to increase [7, 8]. These data reveal an emerging opioid misuse epidemic (medical, non-medical, and illicit) [5, 9-13]. Recent data reveal the discrete geographical regions where states have been hardest hit by this growing epidemic [3]. Indeed, data analyzed from just 2014 alone reflect New Mexico had undergone the greatest opioid-related overdose death rate relative to other Mountain states, the Pacific and the Western south-central state regions [14]. These statistics reflect an unprecedented public health crisis of prescription opioid and heroin abuse both regionally and nationally. While the underlying causes related to this public health crisis are largely speculative, one possible contributing factor is the dramatic escalation of prescription opioid treatment for chronic pain over the past decade [15].

The escalation of opioid treatment is particularly disconcerting because preclinical studies convincingly support that not only do opioids exert negative consequences for

pain [16-19], but also that chronic pain can be targeted by non-opioid drugs that lack direct actions on neurons thereby reducing addiction liability [20, 21]. In point of fact, a large number of reports using animal models reveal that trafficking immune cells to the central nervous system (CNS) and immune-like glial cells within the CNS (e.g. astrocytes and microglia) are necessary for the development and maintenance of acute-to-chronic pain problems [22-24]. Notably, experimental chronic pain that is induced by a variety of manipulations modeling different etiologies of clinical pain is mediated by peripheral immune cell and CNS-derived proinflammatory cytokines that act to exacerbate pain signals. The most widely studied immune and glial cell factor is the proinflammatory cytokine, interleukin-IL-1β (IL-1β). This cytokine, considered a "gatekeeper of inflammation and neuroexcitatory events", is necessary and sufficient for mediating the transmission of pathological chronic pain. Evidence from preclinical and clinical studies shows that blocking immune and/or glial IL-1β production and/or its action suppresses chronic pain [21].

The discovery that cytokines like IL-1β as well as others including tumor necrosis factor-alpha (TNF-α) were critical for mediating pathological chronic pain was significant because these immune-derived signaling molecules have been known for decades to play essential roles in mounting an innate immune response (e.g. myeloid-derived cells such as macrophage but not T or B cells) including leukocyte migration to tissue damaged sites and fever. Indeed, IL-1β was originally identified as a pyrogenic factor stimulated by pathogen invasion such as bacteria; gram negative bacterial cell wall particles such as lipopolysaccharide (LPS). LPS is a widely-used immune activator to experimentally mimic pathogen invasion and induces macrophage release of IL-1β and TNF-α [25]. LPS mimics pathogen invasion via receptor recognition of pathogen associated molecular pattern (**PAMPs**). LPS delivered spinally in experimental mice develop pain that is now thought to occur via IL-1β release [26]. In other words, the pain system is capable of harnessing ancient molecular pathways of the innate immune system for the purpose of facilitating host survival and wound healing (triggering the disuse of the injured tissue). The cytokine release from immune and glial cells is triggered upon factors released from stress/damaged cells, now characterized as danger-associated molecular patterns (**DAMPs**) that bind discrete immune receptors (discussed below). Recognition of DAMPs allow cells to distinguish between non-injured vs. injured self [27]. Therefore, when conditions become pathological, adverse sterile neuroimmune stimulation drives acute-to-chronic pain states via DAMP stimulation. **Figure 1** is a schematic that represents the factors that stimulate and are induced within the classic immune pathway that ultimately lead to the release of proinflammatory



cytokines like IL-1β.

However, even more intriguing is the mounting evidence that repeated opioid exposure/treatment results in significant negative consequences for pain [16, 20, 28, 29]. Preclinical studies of the past few years show opioid drugs activate the same innate immune proinflammatory pathways necessary for the production and release of IL-1β in both peripheral immune and glial cells [29-32] (see **Figure 1**). The action of opioids on immune and glial cells was discovered to occur through the non-classical opioid receptor, toll-like receptor 4 (TLR4) [32-35]. TLR4 activation triggers the active formation of the intracellular NOD-like receptor protein 3 (NLRP3) inflammasome, a protein complex necessary for the ultimate production of IL-1β [36, 37]. Thus, the activation of TLR4 on immune cells and glia by opioids may underlie the reported observation that chronic opioids paradoxically induce pain (e.g. opioid induced hyperalgesia) [38, 39]. It therefore follows that neuropathic pain is exacerbated and prolonged by opioid repeated/chronic treatment [16, 28, 29]. In addition, recycling of opioid receptor upon activation by opiate drugs (e.g. morphine) is profoundly distorted in neurons such that the intracellular opiate-receptor interaction is substantially prolonged [40]. Taken together, these reports suggest non-opioid compounds may provide substantially better therapeutic benefit than opiate drugs. Therefore, the ***long-term goal*** of this proposal is to identify non-opioid drugs that harness endogenous anti-inflammatory mechanisms resulting in the suppression of proinflammatory cytokines such as IL-1β, providing a novel approach to treat chronic pain in people while lacking potential for addictive side effects.

Pramipexole: FDA approved drugs that demonstrate an excellent safety profile in humans while also demonstrating the above-noted anti-inflammatory profile could be explored **as repurposed drugs for non-opioid pain therapeutics**. One such compound that satisfies this profile is pramipexole, which is now documented to reduce inflammation in several preclinical animal models of peripheral inflammatory pain [41]. While this study did not examine rodent pain behaviors, the classic hallmarks of hindpaw edema and neutrophil accumulation were assessed, with pramipexole significantly blunting these inflammatory processes. In a separate study examining brain inflammatory cytokines in mice following low-dose LPS inflammation, IL-1 mRNA levels were blunted following treatment with pramipexole [42]. Pramipexole is well-documented as a preferred dopamine-2/3 (D2/D3) receptor agonist that is FDA approved for alleviating movement disorders in Parkinson Disease and for treating restless leg syndrome, with modest therapeutic outcomes [43-48]. Therefore, based on the documented safety profile of pramipexole, we propose to explore whether it exerts anti-inflammatory (anti- IL-1beta actions) resulting in therapeutic pain suppression in people.

2.2. Preliminary data.

All experiments in this phase will be performed at the Center for Molecular Discovery (Dr. Sklar, co-I and Director of this core) using the human monocytic leukemia cell line, THP-1. This cell line is routinely used in the core facility to examine drug effects on the TLR4-NLP3-IL-1β pathway by quantifying dose-dependent effects on IL-1β protein release. Upon stimulation by LPS, these cells can provide a reliable indication of specific TLR4-NLRP3 activation as measured by the production of the adaptor protein apoptosis-associated speck-like protein (ASC) and IL-1β release [49]. Additionally, THP-1 cells activate upon adenosine triphosphate (ATP), which signal to cells as a DAMP [28, 49].

It is important to note that following TLR4 activation by PAMPs, DAMPs or opioids, subsequent phosphorylation of protein kinases p-p38 and p65 and nuclear factor kB (NFkB), generates NLRP3 inflammasome complex formation required for IL-1β transcription and production [50].

Figure 2 demonstrates the feasibility of utilizing THP-1 (human myeloid cells) upon stimulation as a cellular screen to examine the suppression of cellular activation, as measured by a reduction in IL-1β following drug application. Other reports show that following LPS stimulation, Alprostadil, also known as prostaglandin E1 (PGE1), reduces NF-KB activity and spinal proinflammatory cytokine IL-1β and TNFα production [51, 52]. In the current pilot data provided Dr. Sklar (co-Investigator), THP-1 stimulated cells with LPS reveal an Alprostadil dose-dependent reduction in IL-1β. Conversely, examination of Resveratrol, a drug that is characterized to act at the integrin αVβ receptor to induce phagocytosis [53], generates a distinctly different profile of IL-1β release from THP-1 cells. While Resveratrol is characterized to induce the anti-inflammatory related nuclear receptor, peroxisome proliferator-activated receptor gamma (PPARγ) [54], increased IL-1β is observed above levels induced by LPS stimulation (red triangle) suggesting higher doses may be inducing general increases in transcriptional activity, a known function of PPARγ. As such, the pattern of THP1 activation in response to drug in the presence of stimulation can be used to indicate pramipexole-dependent actions in reducing the TLR4-NLRP3- IL-1β inflammatory pathway. As depicted in Figure 1, PAMPs and DAMPS can be applied to stimulate TLR4-NLRP3. Therefore, LPS and the DAMP, high mobility group box 1 (HMGB1) will be used to stimulate THP-1 cells. HMGB1 is relevant to the proposed study because it is released from damaged nerve terminals in the spinal

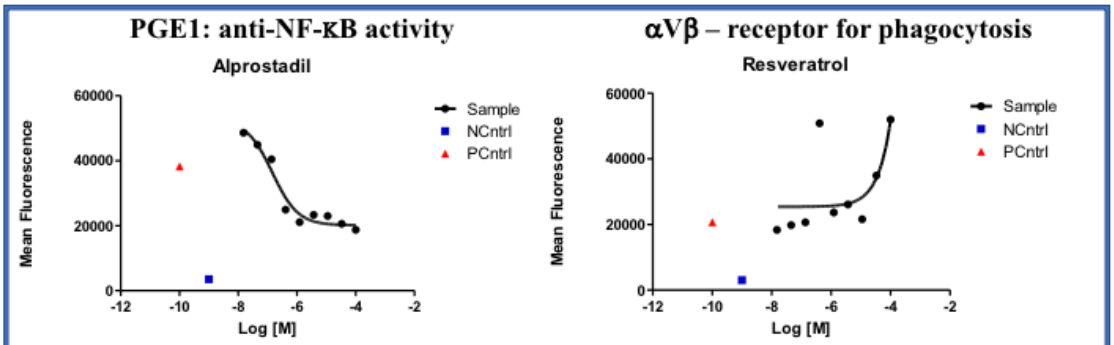


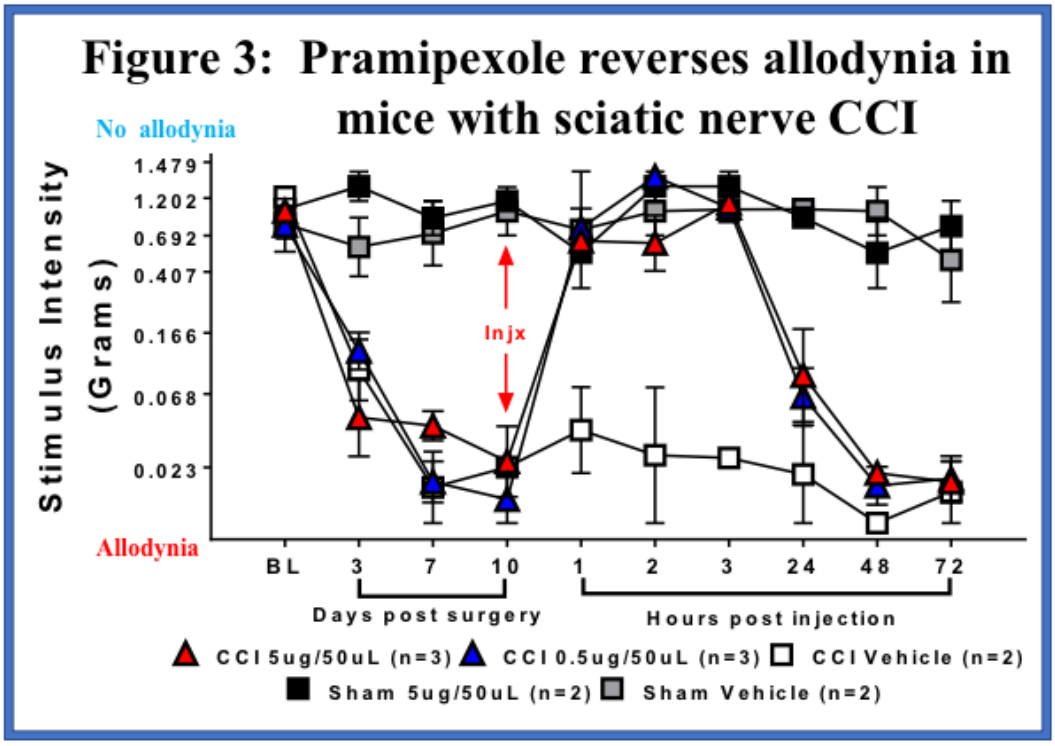
Figure 2: P = control with LPS; red triangle. N = control no LPS; blue square. Fluorescent measurement from bead-based antibody detection of IL-1β.

(L. Sklar; UNM Molecular Drug Discovery)

cord and characterized to mediate persistent pain [55].

Figure 3: Based on evidence demonstrating general anti-inflammatory effects of pramipexole (reduced IL-1β production, neutrophil accumulation and edema formation), a pilot study was performed in mice to examine the effects of an intravenous injection of pramipexole on pathological light touch sensitivity in a model of peripheral sciatic neuropathy. A widely-used and well-characterized rodent model of peripheral neuropathy was applied by loose ligation of 3 chromic gut sutures around one sciatic nerve (chronic constriction injury; **CCI**) that leads to hindpaw sensitivity to light touch, clinically referred to as allodynia. Allodynia is a hallmark of pathological sensory processing and is frequently a problem in pain patients. In this figure, compared to sham (no surgery) controls with vehicle or pramipexole treatment, mice with CCI and i.v.

vehicle/placebo treatment reveal stable allodynia (light touch responses from 0.023 – 0.068 g) throughout the timecourse (white squares). Conversely, those mice with CCI followed by i.v. pramipexole reveal a profound reversal from allodynia (0.5 or 5.0 ug; blue or red triangle, respectively) with allodynia returning by 24 hrs after drug injection in keeping with the reported half-life of pramipexole [43, 48]. These data support the exploration of pramipexole as a possible inhibitor of the TLR4-NLRP3-IL-1β pathway, and as such, a possible chronic pain therapeutic that is already FDA-approved for the treatment of other clinical conditions (explored in **Phase II** of the current proposal).



2.3. Additional Background and Rationale

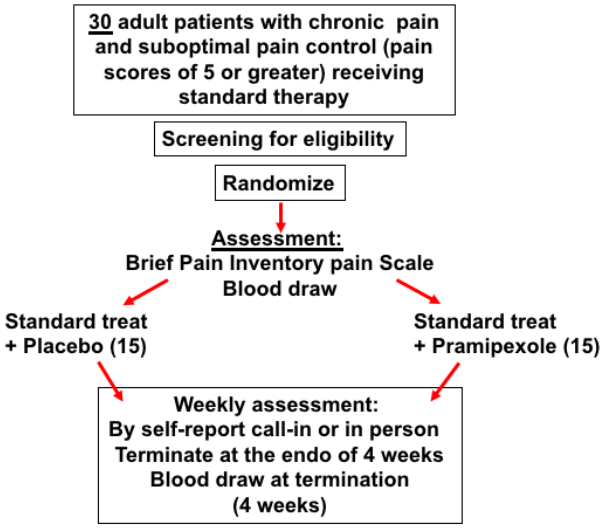
A growing body of evidence supports that repeated opioid exposure triggers TLR4-NLRP3-IL-1β activation and release, which may underlie the development of opioid-induced prolongation of pain and hyperalgesia [16, 28, 29, 39]. THP1 cells are characterized to respond to opioid stimulation by potentiating NFkB [56], and naloxone, a known antagonist at the mu opioid receptor, also blocks TLR4 activation [17, 33-35]. Indeed, naloxone prevents LPS-induced NLRP3 complex formation (NLRP3 + ASC) in THP-1 cells [49]. Results from these experiments could lead to (a) further support that pramipexole is a viable alternative to opioid as a pain therapeutic, and/or (b) co-administration of opioid compounds with pramipexole. The implications are far reaching.
To capture TLR4 immune cell activation by distinct mechanisms, PAMPs, DAMPs or opioids, THP-1 cells will be stimulated with either LPS, HMGB1 (a DAMP) or an opioid compound (either beta-endorphins or morphine). Increasing doses of pramipexole will be given, and levels of IL-1β will be analyzed. In addition, cell supernatant and lysates will

be collected to evaluate protein and mRNA for TLR4, p38, NFkB, NLRP3, Caspase-1, which is an enzyme activated only after NLRP3 complex formation with ASC that is required for mature IL-1β release, as well as the proinflammatory cytokines, IL-1β, TNF-α and HMGB1, and IL-10

3. Study Design

3.1. This is a proof-of-concept randomized placebo-controlled clinical trial.

Figure 4: Study Design



3.2. Describe blinding, if applicable.

All subjects will pick up the allotted capsules from the UNMH Clinical Pharmacy that will dispense either pramipexole or placebo. A randomization table will determine which subject will receive pramipexole or placebo.

4. Inclusion and Exclusion Criteria

4.1. Recruitment of Subjects and Inclusion

Subjects who qualify for inclusion will be those potential subjects identified by Dr. Koshkin being seen at the UNM Pain Clinic who are experiencing pain with “suboptimal” pain relief (defined as discussed below in this section) by standard pain treatment. A randomization table for all subjects receiving pramipexole vs. placebo will be generated such that the Clinical Research Coordinator will use as a template when dispensing drug at the time of consent. All types of chronic pain will be considered, and thus, specific types of chronic pain will not be part of the inclusion or exclusion criteria. Non-English, Spanish speaking subjects will be included. Adults 18 yrs. or older will be included. Women who are not post-menopausal or have not undergone an oophorectomy/hysterectomy will be excluded.

Initial screening will occur at the time when Dr. Koshkin is evaluating the patient in the pain clinic. The Electronic Medical Record database is up-to-date and will be viewed at the time of the clinical evaluation. Data that will be evaluated and collected are: sex, weight, height, age, race/ethnicity, years post-menopausal, prior oophorectomy/hysterectomy, years under pain treatment, pain diagnosis (etiology), and type of insurance.

At the time Dr. Koshkin is evaluating a patient that meets the inclusion criteria, 3 standardized questions will be asked:
(1) Are you happy with the amount of pain relief so far?
(2) Would you like to try something else to improve your pain relief?
(3) Are you able to do everything you want to do with the current treatment?

At this time, systemized exclusion criteria will be evaluated as noted in the table below.

Based on the Electronic Medical Record, Dr. Koshkin will have access to information regarding prior history of renal impairment. If Dr. Koshkin suspects the possible presence of renal impairment, a blood panel will be evaluated prior to potential patient participation.
As indicated in the Inclusion/Exclusion Criteria table, Patients with Parkinson's Disease or patients who are taking prescription medications that act as dopamine agonists are excluded from the study.

Note that only those patients who are pregnant will be excluded. A pregnancy test at the time of enrollment and at mid-term (end of 2 weeks of the 4 week study) when subjects check in with the Clinical Research Coordinator. The second pregnancy test will act to mitigate risks of false negative pregnancy test results at the time of enrollment..

4.2. children, a particular racial or ethnic group, etc. and provide justification.

We will attempt to enroll an equal number of males and females. There are no race- or ethnic specific questions in this protocol. However, in an attempt to include a balanced approach for enrolling non-Caucasian and Caucasian populations participating in this clinical trial, approximately 50% of the study subjects will make up these two populations. An attempt to enroll African American and Native American (American Indian) populations that will make up the remaining 50% of the study population will be planned to reflect the unique cultural and ethnic diversity of Albuquerque. A review of this targeted enrollment progress in this area will be made quarterly, and if minority recruitment is not meeting expectations by the end of the 2nd quarter, further guidance from the CTSC will be utilized.

Diverse socioeconomic backgrounds will also be an important factor for inclusion. The UNM Clinical Neuroscience Center serves a diverse population, and recruitment will occur among all represented groups.

INCLUSION OF CHILDREN

This research study will include only individuals 18 years of age and older because chronic pain is rare in pediatric populations. The mechanism underlying its development is not typically expressed until adulthood. Any pediatric chronic pain cases encountered are thus likely to have a substantial idiopathic component. This factor along with the small sample would make results interpretation difficult or impossible for pediatric patients.

"Suboptimal pain relief/ scores" is vague because the Brief Pain Inventory address two discrete aspects of pain: (1) pain severity and (2) pain interference that are subjectively evaluated (Tan, Jensen et al. 2004, Walton, Beattie et al. 2016). The scores obtained from aspects of the scale (items 1-6) that evaluate pain severity and the quality of the pain (burning vs. aching) focuses on current or recent pain. However, the scores obtained from aspects that target affective and physical interference (item 9 with 7 subscales) of pain experience and provides a more complete evaluation of issues surrounding quality of life that are frequently (but not always) considered more critical to patient's pain experience. Item #8 of the pain scale ("In the past 24 hours, how much pain relief have pain treatments or medications provided? Please circle the percentage that most shows how much relief you have received") targets the key issue of "suboptimal" pain relief, but only in the past 24 hrs, and provides a "snapshot" of the patient's chronic pain relief. Therefore, while it may seem to oversimplify the patient's level of pain relief, patient scores 5 or greater on most items in the Brief Pain Inventory will be considered "suboptimal".

5. Number of Subjects

5.4. All subjects will be recruited from the UNMH outpatient population from the UNMH Pain Center.

5.5. The target sample size is 30 subjects with complete data. The investigators may recruit up to 45 patients to allow for any dropouts.

5.6. All subject recruited will participate. There will be no screening after recruitment.

6. Study Timelines

6.4. Describe:

- The duration the subject will participate in the study is 4 weeks
- The duration anticipated to enroll all subjects may require 10-11 months
- The expected duration for the investigators to complete the study analyses will be 12 months, with most of the analysis occurring in the final months 11-12.

7. Study Endpoints

7.4. The primary endpoint is the paper-and-pencil survey, the Brief Pain Inventory. The secondary study endpoints will be mRNA and protein analysis from blood samples provided at the initiation and terminal of the study.

7.5. Safety endpoints of the study will include the following: (1) Worsening of pain score or increased verbal dissatisfaction with pain relief, (2) sudden onset of sleep without warning, (3) intense urges, (4) hallucinations and/or psychotic-like behaviors, (5) fever, and (6) orthostatic hypotension. While the patients who experience these adverse events, dosing with pramipexole will require a 50% step-wise reduction over a period of two weeks. Given the maximal allowable dose is 0.75 mg, this prescribed step-wise reduction is well within the manufacturer's recommended tapering of pramipexole, which the recommended dose reduction is 0.375 per day.

7.6. No exploratory endpoint are in the current study.

8. Research Setting

8.4. Patients interested in participating in the study will be gided by a Clinical Research Coordinator who will collect information from the Brief Pain Inventory (short form) questionnaire and will also collect and store a blood sample for assay at the termination of the project period.

8.5. All patients will be recruited from the UNMH Pain clinic and examined by Dr. Koshkin (co-I).

8.6. All research procedures will be conducted in the CTSC clinical laboratory. All analytics will be conducted in the Center for Molecular Drug Discovery, a CTSC translational lab directed by Dr. Sklar (co-I).

8.7. A community advisory board will not be involved

8.8. No research will be conducted outside of UNMH and UNM-CTSC

9. Resources Available

9.4. The PI and study staff have received training for clinical trials. Dr. Milligan (PhD) is a basic scientist conducting the cell assays and interpreting the data results. Dr. Sklar(PhD) is a basic scientist directing the CTSC core for conducting the cell assays and interpreting the resultant data. Dr. Petersen (PhD) is a statistician and familiar with clinical trials designs, and Dr. Koshkin (MD) is a physician who specialized in pain treatment at the UNMH Pain Clinic.

9.5. Dr. Koshkin, MD will be responsible for medical decision-making and ordering and evaluation of necessary diagnostics and therapeutics.

9.6. Dr. Koshkin treats 15-30 patients daily at the UNMH Pain Clinic. With this high access to patients, the goal of enrolling 30 patients during an 11 month period is predicted to be very feasible.

All 30 recruited patients will be needed with no further screening.

An estimated 6 hrs per patient will be devoted to consent, completing surveys, blood draw, scheduling and dispensing the pramipexole or placebo by the Clinical Research Coordinator.

- The facilities used will be at the CTSC where consent, enrollment, scheduling visits, obtaining blood samples, completion of the Brief Pain Inventory survey, dispensing drugs at initiation and at midterm (end of week 2,) and collecting unused drug at termination. For the biological assays from human cell lines or from blood samples, the clinical laboratory arm of the CTSC, Center for Molecular Drug Discovery, will be used.
- The availability of medical and/or psychological resources that subjects might need as a result of an anticipated consequences of the human research will be avaialve by Dr. Koshkin or by referral from Dr. Koshkin. The anticipated consequences of the research will be (1) improved pain relief, (2) no change in pain relief, or (3) a worsening of pain. Dr. Koshkin will continue to monitor patients after the study is terminated, as these patients will continue to receive outpatient care from the pain clinic.
- All persons assisting with the research will have group meetings once every 3 months in the conference room in the Dept of Anesthesiology. Goals of each meeting will include research progress updates, preliminary findings of the pain scores derived from the Brief Pain Inventory, problems or unanticipated adverse events, how these adverse events were managed, and action items for continued progress or needed to adjust to potential changes. Dr. Koshkin will provide updates on his clinical observations from his pain patients, Dr. Sklar will provide updates with regard to progress or impediments of cell assays, Dr. Milligan will provide a summary of data collected from the cell based assay from Phase I (Specific Aim I) and Dr. Petersen will provide input for preparation of appropriate statistical analysis, manuscript preparation and future NIH NIDA grant preparation should the data support the research hypothesis.
- If CTSC resources are being accessed, the signed CTSC resources attachment must be uploaded on the CTSC Submission page in Click.

10. Prior Approvals

10.4. A waiver from IND from the FDA will not be required because pramipexole is FDA-approved for other indications (Restless Legs Syndrome, Parkinson's Disease), with no contraindications and no change in recommended dosing and route of delivery, and no increased risk to subjects.

10.5. The required Departmental Review Form signed by PIs Department Chair has been added.

10.6. N/A

10.7. The package insert for pramipexole hs been attached.

11. Multi-Site Research

11.4. This is not a multi-site study.

12. Study Procedures

The goal of Phase II will be to determine the therapeutic benefit of pramipexole for pain, which is a repurposing of this FDA-approved drug with a good safety profile. In collaboration with Dr. Koshkin (co-I at UNMH Pain Clinic), patients from the UNM pain clinic will be recruited who are experiencing modest or suboptimal pain relief. The patient will meet the CTSC Clinical Research Coordinator, who will escort the patient to the Clinical Research Lab. At the time, an explanation of the study, consent, the Brief Pain Inventory survey will be completed, blood draw and Clincard will be given to the patient ($15/visit). Scheduling for the midterm visit to the CTSC (at the end of two weeks) will be determined. At the time of consent, all patients will be under standard pain treatment and will be randomized into two groups: (1) patients receiving pramipexole in addition to their standard ongoing pain treatment, or (2) no pramipexole but will continue to receive the standard pain treatment. Patients will be followed up in the morning at weekly intervals to provide pain scores either by phone (for week 1 and 3), or by return visit (for end of week 2 and at the end of week 4) until study termination which is at the end of week 4.. At the initiation of the study and at the end of 4 weeks, blood will be collected and analyzed for mRNA for TLR4, p38, NFkB, NLRP3-ASC, Caspase-1, IL-1β, TNF-α, HMGB1, and IL-10. The dose and route of administration of pramipexole will be identical to that previously approved for the treatment of Restless Legs Syndrome and according to manufacturer's recommended prescribing protocol (Mirapex, Boehringer Ingelheim Int. GmbH). Briefly, oral dosage will be titrated each week to achieve a weekly total daily dose of 0.125 (mg), 0.250, 0.5 or 0.750. Patients will take one capsule containing pramipexole of placebo 2-3 hours before bedtime.

Patient recruitment, assessment of Brief Pain Inventory (BPI): Pain scores and blood draws will be conducted at the CTSC Participant Clinical Interactions Unit with the CTSC Clinical Research Coordinator. Blood samples collected by the CTSC Clinical Research Coordinator will be analyzed at the Center for Molecular Discovery by personnel from Dr. Milligan's lab, trained by personnel from the Center for Molecular Drug Discovery (Director; Dr. Sklar, co-I). Personnel from the Milligan lab have expertise in inflammatory marker analysis from PBMCs [57, 58]. All freshly collected blood samples will be frozen and stored by the Clinical Research Coordinator at the CTSC Clinical Laboratory and will be transported to the Center for Molecular Drug Discovery once ALL of the samples for the study (all 30 patients) have been collected. This is to allow for assay to be conducted at the same time to avoid potential effect of 'time of assay' that may impact data.

All subjects will therefore meet with the CTSC Clinical Research Coordinator for a total of 3 times; at the initiation of the study, at mid-term when the second batch of drug is dispensed and unused drug is returned, and at termination for a second and final blood draw and providing all completed Brief Pain Inventory surveys (5/patient). At the termination of the study, patients will turn in their paper copies of the Brief Pain Inventory questionnaire completed for each week of the study (total 4 weeks). Original data records are important to demonstrate all necessary physical documentation of the study.

Pramipexole: FDA approved drugs that demonstrate an excellent safety profile in humans while also demonstrating the above-noted anti-inflammatory profile could be explored **as repurposed drugs for non-opioid pain therapeutics**. One such compound that satisfies this profile is pramipexole, which is now documented to reduce inflammation in several preclinical animal models of peripheral inflammatory pain [41]. While this study did not examine rodent pain behaviors, the classic hallmarks of hindpaw edema and neutrophil accumulation were assessed, with pramipexole significantly blunting these inflammatory processes. In a separate study examining brain inflammatory cytokines in mice following low-dose LPS inflammation, IL-1β mRNA levels were blunted following treatment with pramipexole [42]. Pramipexole is well-documented as a preferred dopamine-2/3 (D2/D3) receptor agonist that is FDA approved for alleviating movement disorders in Parkinson Disease and for treating restless leg syndrome, with modest therapeutic outcomes [43-48]. Therefore, based on the documented safety profile of pramipexole, we propose to explore whether it exerts anti-inflammatory (anti- IL-1β actions) resulting in therapeutic pain suppression in people. Our ***overarching hypothesis*** is that pramipexole will control clinical pain by suppressing the activation of the TLR4-NLRP3-IL-1β pathway and prevent IL-1β release from peripheral immune cells. These findings have provided the current impetus to examine pain therapeutic drugs targeting immune-related factors either upstream or downstream of IL-1β signaling.

Below is a table and brief description of the planned dispensing pattern. The goal for patients is to achieve improved pain control which will be a score 3 points lower on the BPI scale. However, in some subjects, a requirement of titrating dose-increases will be needed to achieve improved pain control.

Week 1
1 Red at 0.125mg/day

Week 2
1 Red at 0.125 mg/day OR 2 Red to achieve 0.250 mg/day.

Week 3
1 Red at 0.125 mg/day OR 1 green at 0.250 mg/day OR 2 green to achieve 0.5 mg/day.

Week 4
1 Red at 0.125 mg/day OR 2 Red at 0.125 mg/day to achieve 0.250/day, OR 1 green at 0.250 mg/day OR 2 green to achieve 0.5 mg/day, OR 3 green to achieve 0.750 mg/day.

	Week 1	Week 2	Pills needed/ Dispense @ enrollment visit	Week 3	Week 4	Pills needed/ Dispense at midterm
Scenario 1	1 Red	1 Red	14 Red	1 Red	1 Red	14 Red

Scenario 2	1 Red	1 Red	14 Red	1 Red	2 Red	21 Red
Scenario 3	1 Red	2 Red	21 Red	1 Green	1 Green	14 Green
Scenario 4	1 Red	2 Red	21 Red	1 Green	2 Green	21 Green
Scenario 5	1 Red	2 Red	21 Red	2 Green	2 Green	28 Green
Scenario 6	1 Red	2 Red	21 Red	2 Green	3 Green	35 Green

Yellow highlight indicates number of pills at Dispense time.
1st Dispense (week 1)
21 Red pills

2nd Dispense (week 3)
Either 21 Red pills (week 3 subject still at 1 Red)
OR 35 Green pills (any other scenario)

13.Data Analysis

Experimental Design for Phase I (Aim I). The goal of these experiments is to examine the specific anti-inflammatory mechanisms of pramipexole on PAMP, DAMP and opioid stimulated immune cells, THP-1 cells will be used.

A growing body of evidence supports that repeated opioid exposure triggers TLR4-NLRP3-IL-1β activation and release, which may underlie the development of opioid-induced prolongation of pain and hyperalgesia [16, 28, 29, 39]. THP1 cells are characterized to respond to opioid stimulation by potentiating NFkB [56], and naloxone, a known antagonist at the mu opioid receptor, also blocks TLR4 activation [17, 33-35]. Indeed, naloxone prevents LPS-induced NLRP3 complex formation (NLRP3 + ASC) in THP-1 cells [49]. Results from these experiments could lead to (a) further support that pramipexole is a viable alternative to opioid as a pain therapeutic, and/or (b) co-administration of opioid compounds with pramipexole. The implications are far reaching.
To capture TLR4 immune cell activation by distinct mechanisms, PAMPs, DAMPs or opioids, THP-1 cells will be stimulated with either LPS, HMGB1 (a DAMP) or an opioid compound (either beta-endorphins or morphine). Increasing doses of pramipexole will be given, and levels of IL-1β will be analyzed. In addition, cell supernatant and lysates will be collected to evaluate protein and mRNA for TLR4, p38, NFkB, NLRP3, Caspase-1, which is an enzyme activated only after NLRP3 complex formation with ASC that is required for mature IL-1β release, as well as the proinflammatory cytokines, IL-1β, TNF-α and HMGB1, and IL-10

Statistical Analysis. The experimental design is 2 (vehicle vs. drug) X 4 (TLR4 stimulants) X 6 (doses of pramipexole), and therefore will require a 3-way repeated measure ANOVA (using IBM SPSS Statistics version 24 (IBM; RRID:SCR_002865). All biological wells will be conducted in triplicate.

Experimental Design for Phase II (Aim II). At the time of consent, all patients will be under standard pain treatment and will be randomized into two groups: (1) patients

receiving pramipexole in addition to their standard ongoing pain treatment, or (2) no pramipexole but will continue to receive the standard pain treatment. Patients will be followed up in the morning at weekly intervals to provide pain scores by phone for a total of 4 weeks. At the initiation of the study and at the end of 4 weeks, blood will be collected and analyzed for mRNA for TLR4, p38, NFkB, NLRP3-ASC, Caspase-1, IL-1β, TNF-α, HMGB1, and IL-10. Dr. Escalona from the Dept of Psychiatry at the VA will be a consultant, as he is currently using pramipexole to treat depression in pain patients (see letter of support), and can provide valuable feedback on interpretation.

The dose and route of administration of pramipexole will be lower to that previously approved for the treatment of Parkinson's Disease and Restless Legs Syndrome and according to manufacturer's recommended prescribing protocol (Mirapex, Boehringer Ingelheim Int. GmbH). Briefly, oral dosage will be titrated each week to achieve effective pain control, with increases occurring at weekly total daily dose of 0.125 (mg), 0.250, 0.500 mg for weeks 1-2, and 3-4, respectively. The highest daily dose will not exceed 0.5 mg. Patient recruitment, assessment of BPI pain scores, and blood draws will be conducted at the CTSC Participant Clinical Interactions Unit, where monetary compensation for participation will also be provided. Blood samples collected by staff at the CTSC will be analyzed at the Center for Molecular Discovery by personnel from Dr. Milligan's lab who have expertise in inflammatory marker analysis from PBMCs [57, 58].

Study drug compounding: Pramipexole and placebo. The following operating procedure has been recommended by the UNM Clinical Pharmacist, Susan Kunkel:

1. Both active and placebo doses will be compounded into capsules. Both types are prepared in 100-count batches by packing powdered material into empty, usually gelatin-based, capsule shells. To make active capsules, a quantity of tablets equal to 100 doses is pulverized and then blended with a sufficient quantity of microcrystalline cellulose, a pharmacologically inert powder, to fully pack each capsule in the batch. The filler (cellulose) is necessary to ensure each capsule contains a uniform dose. Each placebo capsule will be fully and uniformly packed with plain microcrystalline cellulose.
2. Each equivalent active dose will look identical to its corresponding placebo. Because the intent of the study is NOT to conceal the timing of dose changes from subjects, it has been strongly recommended that different colored capsules for different dose levels (keeping active/placebo pairs identically matched, of course) be maintained. Based on prior experience, not color-coding dose levels (and similarly placebo) will greatly increase the chance for medication errors. Given it is very common for manufactured medications to have different colors at different dose levels, most subjects will likely be familiar with this practice. The alternative would be for all active capsules to contain 0.125 mg of pramipexole and have subjects take more capsules for a higher dose level. Those subjects who end up at the highest dose level (0.75mg) would then have to take three capsules per dose.
3. IDS' operating hours are Monday through Friday from approximately 8:00 to 4:30, excluding UNMH holidays. Dispensing times will occur during these periods. Most days, staffing consists of an IDS pharmacy technician (John Cocanower) and an IDS pharmacist. There are two trained IDS backup pharmacists (Susan Meoli and Audrey Dettwiller) to cover Susan Kunkel's leave periods. Accordingly, trained IDS staff will be available during the IDS operating hours barring rare exceptions when, for example, the IDS pharmacy technician is out on vacation and the IDS pharmacist needs leave for a meeting. Dispensing during evenings, nights, weekends, and holidays, will not occur.

14.Provisions to Monitor the Data to Ensure the Safety of Subjects

This section is required when research involves more than Minimal Risk to subjects. Describe:

Contact Information

Standard procedures, which are comprised of in-person description of the study and consent, completion of the Brief Pain Inventory (short form), and electronic communication, which is used to track pain scores via phone call on weeks 1 and 3. We will identify all subjects with a sequentially assigned subject ID number and subject initials. The subject ID number will be utilized for data collection (questionnaires, blood specimens, and database entry). To ensure subject confidentiality, no names, social security numbers, or UNM pain clinic numbers will be included in any communication external to UNM. Names, addresses, telephone numbers, and any other information needed for recruitment, study involvement, and tracking will be obtained and maintained locally by the study staff (UNM CTSC Clinical Research Coordinator). All computer files and systems will be password protected and accessible by authorized Informatics study staff only (CTSC Analyst/Programmer).

Data Safety: The risk of breach of confidentiality is considered to be similar or even less than a data safety compromise of non-research clinical electronic health records. To minimize potential breach of confidentiality, all electronic data will be maintained in a password-protected database to which only study staff with a legitimate need will have access. All paper documentation will be kept in a secure file cabinet in a locked office. The CRC will be responsible for keeping the data in a password protected database with hard copies of the BPI kept in a locked file cabinet in the CTSC during the study period. Monitoring will occur daily or when needed while enrolling subjects and collecting BPI scores. After the study period, Drs. Milligan and Petersen will maintain the study records (electronic version of the BPI scores, mRNA and protein analysis from cell-based assays) in Dr. Petersen's office in a password protected databased and hard copies of the BPI well be kept in a locked file cabinet in a locked room (Dr. Milligan's and Dr. Petersen's offices).

Safety Monitoring Plan:

While there are no contraindications associated with pramipexole, the collection and reporting of adverse are as follows:

The collection and reporting of adverse events will occur at: (1) the time of the phone conversation at the end of weeks 1 and 3 with the CRC who will collect the Brief Pain Inventory scores, (2) at the end of week 2, the time of the mid-term in-person meeting with the CRC when the subject will provide the scores of the BPI for that week and will pick up drug dispense #2, (3) At the final in-person with the CRC, at the termination of the study at week 4, and (4) at any point during the study when the subject calls the CRC to report an adverse event or when the subject calls Dr. Koshkin. All adverse events will be recorded by the CRC and kept with the subject's study records.

Symptomatic orthostatic hypotension and other adverse reactions will be monitored during dose escalation during weeks 1-2, as well as throughout the 4-week study, as part of the routine contact with participants.

The HRRC will be notified as per usual rules within five business days after the PI becomes aware of any severe adverse events, as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, published 11/27/2017 by the National Cancer Institute. The CTCAE defines adverse events of grade 3 or higher as "severe."

Safety monitoring will occur in two tracks. In one track, monitoring will occur as part of the routine (weekly) study-related contact. Study personnel will include screening for adverse events as noted in the included script. The PI will be notified promptly of any moderate or severe adverse events identified in this screening process. All screening information will be provided to the PI for review in the second track of the monitoring procedure, and for entry in a Non-Reportable Log, as appropriate.

The second track of safety monitoring will be an interim review conducted shortly (within one week) after enrollment of the 15th participant. All relevant study information, including but not limited to pain and dosage data, any adverse events identified in screening (regardless of CTCAE grade), and any direct adverse-event reports to investigator Dr. Koshkin, will be included in this review. PI Dr. Erin Milligan will conduct this review with assistance from investigators Dr. Koshkin and Dr. Petersen. The HRRC will be notified if adverse events of CTCAE grade $\geq$2 have been identified in three or more patients in the active (pramipexole) arm at the time of this review. As noted above, the HRRC will be notified within five business days of any adverse events of grade 3 or higher, regardless of timing with respect to this interim review.

Stopping rules: Enrollment will be at least temporarily suspended if any of the following conditions are met:

- Instructions from the HRRC to suspend or terminate enrollment.
- A second adverse event of CTCAE grade 3 or higher among study participants. As with any first one, this event would be reported to the HRRC.
- Any event that, in the opinion of the PI, represents substantial unanticipated risk (i.e. a risk not included in the FDA pramipexole package insert or consent documentation) to study participants.

After any suspension, enrollment would only be resumed on instructions from the HRRC.

If enrollment is suspended, study-related treatment will continue as normal for any active study participants, except in the case of the third (substantial unanticipated risk) bullet point above. If study enrollment is suspended for that reason, participants will be advised to taper off or terminate study drug use as soon as possible.

Adequacy of Protection Against Risks

A. Recruitment and Informed Consent

Recruitment of Subjects

Subjects who qualify for inclusion will be recruited for the study. Potential subjects will be identified by Dr. Koshkin who are experiencing pain with suboptimal pain relief by standard pain treatment. A randomization table for all subjects receiving pramipexole vs. placebo will be generated such that the Clinical Research Coordinator will use as a template when dispensing drug at the time of consent.

B. Protections Against Risk

Confidentiality of Subjects

Subjects will be assigned a study ID number. Linkage to name and other personal identifying information will be kept in a password-protected master database of enrolled subjects that will include subject name, date of birth, address, telephone numbers, race/ethnicity. The Brief Pain Inventory survey and records will be kept in a locked cabinet in a secure room by the CTSC Clinical Research Coordinator and will be accessible only to study staff. The computerized study database will only be accessible to study personnel using a password-protected system. For this study, we will utilize REDCap Survey, a secure, password protected data collection and management tool hosted by UNM's CTSC. Patients will use a study ID number to complete the electronic surveys to further ensure patient confidentiality. No personal identifying information will be used in data analysis or study reports. Subjects will sign also sign a HIPAA authorization as part of the informed consent process.

Dose escalation risks

Dose titration will increase by double if efficacy has not been achieved by the end of one week at the lower initial dose. A dose of 0.125 mg pramipexole once per night for 1 week is initiated for all subjects. At the end of week one, subjects will either increase the dose by double, 0.25 mg if pain relief is not satisfactory, or will remain at 0.125 mg if relief is satisfactory. A 2nd titration may occur at the end of week 2, with the dose escalating from 0.25 mg to 0.75 mg per night. Please see flow chart indicating the 'Dispensing Guideline', as an illustration.

Safety will be monitored either at the time the CRC asks the subject to provide their scores on the Brief Pain Inventory, or when the subject calls Dr. Koshkin reporting adverse experiences as indicated in safety endpoints. Upon consent, subjects will be instructed to call Dr. Koshkin should any adverse experiences noted in the 'safety endpoints' occur during the study period. After the study period is terminated, subjects will continue to see Dr. Koshkin in follow-up visits as needed.

All risks associated with pramipexole (Mirapex; Boehringer Ingelheim Pharmaceuticals) according to the manufacturer are:

1. Falling asleep during activities of daily living. Sudden onset of sleep may occur without warning. Somnolence is a common occurrence in patients receiving pramipexole at *doses above 1.5 mg/day (0.5 mg three times a day).* In controlled clinical trials in Restless Leg Syndrome, patients treated with MIRAPEX tablets *at doses of 0.25-0.75 mg once a day*, the incidence of somnolence was 6% compared to an incidence of 3% for placebo-treated patients.

2. Symptomatic orthostatic hypotension: Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to pramipexole tablets than among those assigned to placebo.

   Symptomatic orthostatic hypotension will be monitored during dose escalation during weeks 1-2, as well as throughout the 4-week study. Monitoring will occur as detailed in "Collection and Reporting of Adverse Events".

3. Impulse control/Compulsive behaviors: Patients may experience compulsive behaviors and other intense urges taking one or more of the medications, including pramipexole, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. For this reason, Parkinson's Disease patients are not included in this study. However, if patients or their caregivers experience increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with pramipexole, subjects will be asked to report this to Dr. Koshkin and/or the CRC. Dr. Koshkin will consider dose reduction.
4. Hallucinations and Psychotic-like Behavior: The following symptoms are associated with patients with Parkinson's Disease. In the three double-blind, placebo-controlled trials in early Parkinson's disease, hallucinations were observed in 9% (35 of 388) of patients receiving pramipexole tablets, compared with 2.6% (6 of 235) of patients receiving placebo.

   Patients with a major psychotic disorder should ordinarily not be treated with dopamine agonists, including pramipexole, because of the risk of exacerbating the psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of pramipexole. If a subject experiences hallucinations while taking pramipexole, pramipexole will be discontinued or reduced step-wise, pending the dose.
5. Dyskinesia: May be caused or exacerbated by pramipexole.
6. Renal impairment: Since pramipexole is eliminated through the kidneys, caution will be exercised in the current study.
7. Rhabdomyolysis, a condition in which the skeletal muscle rapidly breaks down leading to muscle pains, weakness, vomiting and confusion. A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with Pramipexole tablets. The patient was hospitalized. The symptoms resolved with discontinuation of the medication.
8. Events reported with dopaminergic therapy: Include hyperpyrexia and confusion, fibrotic complications, and melanoma.

   Most common adverse reactions (incidence >5% and greater than placebo):

1. Early PD without levodopa: nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations.

2. Advanced PD with levodopa: postural (orthostatic) hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, and urinary frequency.
3. RLS: nausea, somnolence, fatigue, and headache

In the event of an adverse event, the HRRC will be notified. An adverse event case report from will be completed. The CRC will notify Dr. Koshkin and Dr. Milligan as well as the appropriate personnel in the HRRC. It is important to note that a standardized form will be used for adverse event reporting. The form will ask the following questions:

1.Have you experienced any unusual events since you were last seen here? If yes, the CRC will probe further and ask:
2.What exactly did you experience?
3. Did you seek treatment for this experience?
4. Were you given any medications. What was the dose and date started? Are you still taking this medication? If no, when did you stop taking this medications?

and should specifically

5. Have you been feeling dizzy and have you experienced any falls?

In addition, the opinion of Dr. Koshkin will note on the adverse event case report from if this adverse event was associated with the study drug, pramipexole.

15.Withdrawal of Subjects

Anticipated circumstances where subjects may be withdrawn from the research without their consent may be if their pain scores worsen for longer than a week.

In the event of early withdrawal, patients will be tapered from 0.5 (if currently taking that dosage) to 0.250 for 1 week. However, according to the manufacturer's (Boehringer Ingelheim, Inc) packet information, pramipexole at doses of up to 0.75 once daily can be discontinued without taper.

While there are no contraindications associated with pramipexole, the collection and reporting of adverse are as follows:

The collection and reporting of adverse events will occur at: (1) the time of the phone conversation at the end of weeks 1 and 3 with the CRC who will collect the Brief Pain Inventory scores, (2) at the end of week 2, the time of the mid-term in-person meeting with the CRC when the subject will provide the scores of the BPI for that week and will pick up drug dispense #2, (3) At the final in-person with the CRC, at the termination of the study at week 4, and (4) at any point during the study when the subject calls the CRC to report an adverse event or when the subject calls Dr. Koshkin. All adverse events will be recorded by the CRC and kept with the subject's study records.

See actions upon evidence of symptomatic orthostatic hypotension above (Section 14, "*Provisions to monitor the data to ensure the safety of subjects"),* and other adverse

reactions will be monitored during dose escalation during weeks 1-2, as well as throughout the 4-week study. Monitored will occur as detailed in "Collection and Reporting of Adverse Events".

16. Data Management/Confidentiality

16.4. Data will be shared only among the study team members. Data will not be shared to an external source.

16.5. To minimize potential breach of confidentiality, all electronic data will be maintained in a password-protected database to which only CTSC study staff with a legitimate need will have access. All paper documentation will be kept in a secure file cabinet in a locked office in the CTSC or in Drs. Milligan or Petersen's office at UNMH.

17. Data and Specimen Banking

Blood samples will be banked locally only for the study period. All unused blood samples will be destroyed at the termination data of the study, which is 1 year after the study period begins.

Potential Risks

This study includes multiple elements designed to reduce the risk for the subject. For example, the lowest recommended dose for the study drug, Pramipexole is being used, with a careful monitoring of escalating dosages if needed to achieve pain suppression. Potential research risks to the subjects in this study include those associated with answering questions on the Brief Pain Inventory and blood draws (conducted twice; once at the initiation of the study and at the termination of the study).

1. Discomfort Answering Questionnaires: The subject may feel uncomfortable answering questions regarding their symptoms and quality of life, or may feel encumbered by the number of questions asked in the survey instrument. The number and content of the questions to be included have been carefully considered in order to minimize subject burden.
2. Blood Draws: Subjects may suffer pain, discomfort, or bruising from the daily blood draws.
3. Pediatric Use: Subject under 18 years will be excluded
4. Geriatric Use: Pramipexole total oral clearance is approximately 30% lower in subjects older than 65 years compared with younger subjects, because of a decline in pramipexole renal clearance due to an age-related reduction in renal function. The resultant increase in elimination half-life from approximately 8.5 hours to 12 hours. In clinical studies with Restless Legs Syndrome patients, 22% of patients were at least 65 years old, and no apparent differences in efficacy or safety between older and younger patients was observed.
5. Renal Impairment: Patients with renal impairment will be excluded.

Pramipexole (a.k.a. Mirapex) vs. Placebo: will be taken orally by capsule (2-3 hours before bedtime, with an initial starting dose of 0.125 mg /day for 1 week, and increased to 0.25 mg/day beginning the second week if pain relief remains suboptimal. Maximal doses of up to 0.75 mg/day for weeks 3 and/or 4 will be taken as needed to achieve maximal pain relief. The recommended doses and titration steps are derived from the manufacturer (Boehringer Ingelheim Pharmaceuticals, Inc) for treating Restless Legs Syndrome. Pramipexole is predicted to be well tolerated in the current pilot study because the dose range is much lower (by 60%) than documented doses noted as well-tolerated (1.5 to 4.5 mg/day).

Adverse reactions occur at doses greater than 0.75 mg/day. However, the following precautions will be discussed: patients may have the potential to develop drowsiness and an increased risk for somnolence with Pramipexole tablets may occur when also using sedating medications or alcohol, or if there is the presence of sleep disorders.

Drug Interactions: Dopamine antagonist drugs may diminish the effect of pramipexole.
Contraindication: None.

18. Potential Benefits to Subjects

Potential Benefits of the Proposed Research to Human Subjects and Others

There is potential direct benefit of the proposed research to the study subjects. The benefit may come from the treatment of pramipexole for improving pain conditions. The benefit to others will be a possible new approach using a non-opioid drug 'repurposed' for the treatment of chronic neuropathic pain. Further, the application of pramipexole for pain treatment has the potential of rapid clinical application because the compound is FDA-approved with a very good safety profile.

19. Recruitment Methods

Recruitment of Subjects

Subjects who qualify for inclusion will be recruited for the study. Potential subjects will be identified by Dr. Koshkin who are experiencing pain with suboptimal pain relief by standard pain treatment. A randomization table for all subjects receiving pramipexole vs. placebo will be generated such that the Clinical Research Coordinator will use as a template when dispensing drug at the time of consent.

20. Provisions to Protect the Privacy Interests of Subjects

Confidentiality of Subjects

Subjects will be assigned a study ID number. Linkage to name and other personal identifying information will be kept in a password-protected master database of enrolled subjects that will include subject name, date of birth, address, telephone numbers, race/ethnicity. The Brief Pain Inventory survey and records will be kept in a locked cabinet in a secure room by the CTSC Clinical Research Coordinator and will be

accessible only to study staff. The computerized study database will only be accessible to study personnel using a password-protected system. For this study, we will utilize REDCap Survey, a secure, password protected data collection and management tool hosted by UNM's CTSC. Patients will use a study ID number to complete the electronic surveys to further ensure patient confidentiality. No personal identifying information will be used in data analysis or study reports. Subjects will sign also sign a HIPAA authorization as part of the informed consent process.

21. Economic Burden to Subjects

The anticipated burden to subjects will be transportation to the CTSC to visit the CTSC Clinical Research Coordinator at mid-term and the termination of the study. No study-related burden is anticipated upon consent and initiation, as the subject will be seeing Dr. Koshkin at the UNMH Pain Clinic at a self-initiated doctor's visit.

Research Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐

Subjects will NOT be charged for investigational drugs.

No financial related adverse events are anticipated as a result of participating in the study.

22. Compensation

Subjects will be compensated for their participation in the study via a ClinCard provided to the subject by the Clinical Research Coordinator. Subjects will be compensated $15/visit to a total of 3 visits. We predict each visit will be approximately 1hr on the first visit, a 30 min for the following two visits to ask

questions if any, provide a completed Brief Pain Inventory Survey and blood draw at the initiation and termination. We do not consider the amount of time that each subject is devoting to the study a full compensation of their effort. However, the compensation amount is considered to be an expression of appreciation of their participation.

23. Compensation for Research-Related Injury

This research project involves minimal risk to the subjects. However, If you are injured or become sick as a result of this study, UNMHSC will provide you with emergency treatment, at your cost

24.Consent Process

Consent will be obtained by the CTSC Clinical Research coordinator at the CTSC. obtaining consent, and if so describe:

Each subject will be informed at the time of consent:
Subject name and other identifying information will be maintained in locked files, available only to authorized members of the research team, for the duration of the study. For any information entered into a computer, the only identifier will be a unique study identification (ID) number. Any personal identifying information and any record linking that information to study ID numbers will be destroyed 3 years after the study completion. Information resulting from this study will be used for research purposes and may be published; however, the subject will not be identified by name in any publications.

Information from the subject's participation in this study may be reviewed by the investigators only, and by the UNM Human Research Review Committee (HRRC), which provides regulatory and ethical oversight of human research. The subject's name will not be used in any published reports about this study.

A discussion with each subject will include ensuring that the subject can withdraw from this study at any time without affecting your access to healthcare.
The investigators may end subject's participation in this study if determined that it is in the subject's best interest or the study's best interest to stop subject participation.

Each subject will be informed of their right to withdraw from the study and related information. Their authorization for the use and disclosure, within the research team, of health information (subject name, date of birth, address, telephone numbers, race/ethnicity. The Brief Pain Inventory survey) for this study shall not expire unless subject cancels this authorization. Health information will be used or disclosed within the research team as long as it is needed for this study. Subjects will be informed that they may withdraw authorization at any time, but will need to be done in writing.

Subjects not fluent in English

English and/or Spanish speaking subjects will be enrolled. Subjects who do not understand or have limited fluency in English will have a translator with the CTSC Clinical Research Coordinator. Consent documents in Spanish will be made available for unanticipated enrollments of persons who don't understand or have limited fluency in English, with translation of the consent document with a scheduled translator, also coordinated by the CTSC Clinical Research Coordinator.

An alternative consent from will be prepared in the Spanish language as needed and submitted as a modification to the IRB.

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative

Adults unable to consent will not be enrolled in the current pilot study.

Subjects who are not yet adults (infants, children, teenagers)

Subjects who are <18 yrs. Will be excluded from the study.

Waiver or Alteration of Consent Process (consent will not be obtained, required element of consent will not be included, or one or more required elements of consent will be altered)

A waiver of Alteration of Consent Process is not required/applicable.

25. Documentation of Consent

A consent form to document consent will be used per template from the UNM-HSC. It has been attached. .

The study is collecting and/or storing tissue samples. A Tissue Banking Consent Form is attached.

26. Study Test Results/Incidental Findings

Individual Results: The results of the Brief Pain Inventory will be self-evident to the subject, and results from the blood samples will be shared with the test subjects by the CTSC Clinical Research Coordinator on study termination. The findings from these studies will be shared between the team members of the study (Milligan, Petersen, Sklar and Koshkin). Pending the results, the work will be reported in a peer-reviewed scientific journal.

Incidental Findings: Based upon the nature of the research, incidental finding are not anticipated.

27. Sharing Study Progress or Results with Subjects

27.4. The design of the study will not allow for results to be shared with the subjects during the course of study. In addition, all of the blood samples will not be analyzed until after all subjects have completed the study. A summary of the study results will be disclosed at the study termination (end of month 12) via written communication and a copy of the manuscript submitted for peer review in a science journal.

27.5. Inclusion of Vulnerable Populations

27.5.1.1. It is not anticipated that the research will involve subjects who are unduly susceptible to coercion other than the desire to achieve full pain relief. All of the subjects will review and will provide assurance that they fully understand the risks and benefits of participation, and can change their mind at any point during the study.

27.5.2. The research may include students or employees, which the CTSC Clinical Research Coordinator will ensure that the study is entirely voluntary and confidential, and will not impact expectations and ongoing work at UNMH.

27.5.3. The research may include economically disadvantaged persons, which the CTSC Clinical Research Coordinator will ensure that the study is entirely voluntary and will not impact the ongoing treatment that is being received from the UNMH Pain Clinic.

27.5.4. The research may include educationally disadvantaged persons, for which the CTSC Clinical Research Coordinator will ensure that the Consent form will be read aloud, stopping to ask if there are questions. In addition, the CTSC Coordinator will make sure all words that may be unfamiliar with the subject will be defined in a manner that the subject understands. If the research includes seriously or terminally ill patients

N/A

27.5.5. If the research involves pregnant women

N/A

27.5.6. If the research involves neonates

N/A

27.5.7. If the research involves prisoners.

N/A

27.5.8. If the research involves persons who have not attained the legal age

N/A

27.5.9. If the research involves cognitively impaired adults

N/A

28.Community-Based Participatory Research

28.4.1. Describe involvement of the community in the design and conduct of the research. Members of the community will not be part of the study in the capacity of fulfilling key research responsibilities.

29.Research Involving American Indian/Native Populations

29.4. Because all subjects will be recruited from the UNMH Pain Clinic based on voluntary appointment and treatment by Dr. Koshkin for a routine appointment, and the nature of the Brief Pain Inventory, the subject participation is not intrusive nor probing sensitive cultural issues related to American Indian/Native Populations. However, we do plan to enroll a balanced cultural/racial population that attempts to capture the populations in New Mexico.

30.Transnational Research

Transnational research is not being conducted in this study.

31.Drugs or Devices

Pramipexole of placebo capsules will be dispensed from the UNMH Clinical Research Pharmacy and utilizing a randomization table to guide drug condition to each subject. Capsules can be stored at room temperature.

Consenting randomized patients will receive either oral pramipexole to be added to ongoing routine treatment for chronic pain, or placebo with routine treatment. Oral pramipexole will be administered in capsule once daily dose starting with 0.125 (mg), and titrating as needed to 0.25 mg by end of week 1 and/or week 2, and further titrating up to 0.75 mg if needed for weeks 3-4. *This is the entry-level dose for Restless Legs Syndrome without kidney issues.*

Subject's Final dose/day	Week 1	Week 2	Dispense 1 Final Dose	Week 3	Week 4	Dispense 2 Final Dose
Scenario 1	1Red/ 0.125MG	1Red/ 0.125MG	14 Red/ 0.125MG	1 Red/ 0.125MG	1 Red/ 0.125MG	14 Red/ 0.125MG
Scenario 2	1 Red/ 0.125MG	1 Red/ 0.125MG	14 Red/ 0.125MG	1 Red/ 0.125MG	2 Red/ 0.250MG	21 Red/ 0.250MG
Scenario 3	1 Red/ 0.125MG	2 Red/ 0.250MG	21 Red/ 0.250MG	1 Green/ 0.250MG	1 Green/ 0.250MG	14 Green/ 0.250MG

Scenario 4	1 Red/ 0.125MG	2 Red/ 0.250MG	21 Red/ 0.250MG	1 Green/ 0.250MG	2 Green/ 0.500MG	21 Green/ 0.500MG
Scenario 5	1 Red/ 0.125MG	2 Red/ 0.250MG	21 Red/ 0.250MG	2 Green/ 0.500MG	2 Green/ 0.500MG	28 Green/ 0.500MG
Scenario 6	1 Red/ 0.125MG	2 Red/ 0.250MG	21 Red/ 0.250MG	2 Green/ 0.500MG	3 Green/ 0.750MG	35 Green/ 0.750MG

Pramipexole has a relatively benign side effect profile. Chronic pain, conversely, presents substantial challenges to affected patients' quality of life. If it proves effective as an adjunct to more routine chronic pain therapy, it will mitigate suffering and potentially permit dosage reduction for other medications (e.g. opioids) with more serious side effects. Laboratory evidence indicates that it may also mitigate the unintended hyperalgesic and neuroimmune inflammatory consequences of prolonged opioid treatment, which paradoxically exacerbate pain. This knowledge would be of great importance in the field of chronic pain treatment.

Adverse reactions occur at doses greater than 0.5 mg/day. However, the following precautions will be discussed: patients may have the potential to develop drowsiness and an increased risk for somnolence with Pramipexole tablets when also using sedating medications or alcohol, or if there is the presence of sleep disorders. Fatigue and/or headache may also occur.

Drug Interactions: Dopamine antagonist drugs may diminish the effect of pramipexole.
Contraindication: None.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

None of the following sections apply to this pilot project.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

A. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

1. Describe the data source that you need to review (e.g., medical records):

2. Describe the purpose for the review (e.g., screening):

3. Describe who will conducting the reviews (e.g., investigators, research staff):

4. Do all persons who will be conducting the reviews already have permitted access to the data source?

   ☐ Yes

   ☐ No. Explain:

5. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

   a) The activity involves no more than minimal risk to the subjects because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

      ☐ True

      ☐ Other justification:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

      ☐ True

☐ Other justification:

c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

☐ True

☐ Other justification:

d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*

☐ True

☐ Other justification:

Partial Waiver of HIPAA Authorization for Screening/Recruitment
Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

6. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☐ Yes. Describe:

   ☐ No

7. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

8. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

B. Waiver of Documentation of Consent

Complete this checklist if you intend to obtain consent verbally but will not be obtaining signatures from subjects on a consent form to document consent. Waivers of documentation of consent are commonly requested when using scripts, information sheets, or email or survey introductions to present the elements of consent instead of using a traditional consent form.

1. Are you requesting a waiver of documentation of consent for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for <u>one</u> of the following:

   a) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

   b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

3. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?

   ☐ Yes. Please attach a copy to your submission in Click.

   ☐ No

C. Alteration of Consent

Complete this checklist if you intend to obtain consent but will be eliminating or altering one or more of the required elements of consent. Alterations of consent are commonly requested for research involving deception or for minimal risk research when an abbreviated consent is desired and one or more of the required element are not relevant to the research.

<u>Note: FDA-regulated research is not eligible for an alteration of consent.</u>

1. Which element(s) of consent do you wish to eliminate <u>and</u> why?

2. Which element(s) of consent do you wish to alter and why?

3. Provide justification for each of the following regulatory criteria:
   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

   c) The research could not practicably be carried out without the waiver or alteration:

   d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

D. Full Waiver of Consent/Parental Permission

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of consent are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

Note: FDA-regulated research is not eligible for a full waiver of consent using these criteria. If you believe that your FDA-regulated research may be eligible for a waiver under another mechanism, such as planned emergency research, contact the HRPO for assistance in determining what information to provide to the HRRC.

1. Are you requesting a waiver for some or all subjects?
   ☐ All
   ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:
   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

c) The research could not practicably be carried out without the waiver or alteration:

d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

E. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort) and the research involves the evaluation of a public benefit or service program.

1. Are you requesting a waiver for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:

   a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs:

   b) The research could not practicably be carried out without the waiver or alteration.

F. Full Waiver of HIPAA Authorization

Complete this checklist if you are requesting a full waiver of the requirement to obtain HIPAA authorization for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of HIPAA authorization are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

1. Are you requesting a waiver of authorization for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Describe your plan to protect health information identifiers from improper use and disclosure:

3. Describe your plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so):

4. Describe why the research could not practicably be conducted without the waiver or alteration:

5. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

G. Other Waiver Types

If you are seeking another waiver type (e.g., Planned Emergency Research, Waiver of Parental Permission to Protect Child Participants, Enforcement Discretion for In Vitro Diagnostics, etc. contact the HRPO office for assistance in determining what information to submit for the HRRC's consideration.

II. Vulnerable Populations

A. Adults with Cognitive Impairments

Complete this checklist if the subject population will include adults with cognitive impairments.

<u>This checklist does not need to be completed if the research doesn't involve interactions or interventions with subjects and will be conducted under a waiver of consent.</u>

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

2. Describe how capacity to consent will be evaluated.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

B. Children

Complete this checklist if the subject population will include children.

1. Select the category of research that you believe this research falls within and provide justification for any associated criteria. If there are different assessments for different groups of children or arms (e.g., placebo vs. drug), include a memo to provide an assessment for each group.

   ☐ Research not involving greater than minimal risk. *(Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*

☐ Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Provide justification for each of the following criteria:

(1) The risk is justified by the anticipated benefit to the subjects:

(2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

☐ Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Provide justification for each of the following criteria:

(1) The risk represents a minor increase over minimal risk:

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

C. Pregnant Women and Fetuses

Complete this checklist if the subject population will include pregnant women and fetuses.

This checklist does not need to be completed if the research is both minimal risk and is not conducted, funded, or otherwise subject to regulation by DHHS, DOD, EPA, or VA.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ***or***, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

3. Any risk is the least possible for achieving the objectives of the research.

D. Neonates of Uncertain Viability or Nonviable Neonates
Complete this checklist if the subject population will include neonates of uncertain viability.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, ***or***, the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research

E. Nonviable Neonates
Complete this checklist if the subject population will include nonviable neonates.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

Verify each of the following:

5. Vital functions of the neonate will not be artificially maintained

   ☐ True

   ☐ False

6. The research will not terminate the heartbeat or respiration of the neonate

   ☐ True

   ☐ False

7. There will be no added risk to the neonate resulting from the research

   ☐ True

   ☐ False

F. Biomedical and Behavioral Research Involving Prisoners

Complete this checklist if the subject population will include prisoners.

Note: Minimal risk for research involving prisoners is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

1. Select and justify which allowable category of research involving prisoners this research falls within:

   ☐ Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

☐ Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

☐ Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults)

☐ Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject

☐ Epidemiologic studies in which the sole purpose is to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease, the research presents no more than Minimal Risk and no more than inconvenience to the subjects, and Prisoners are not a particular focus of the research.

2. Provide justification for each of the following regulatory criteria:

    a) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired

    b) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers

    c) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless justification is provided, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project

d) The information is presented in language which is understandable to the subject population

e) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole

f) When appropriate, adequate provision has been made for follow up examination or care after research participation, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact

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III. Medical Devices

Complete this checklist if the research evaluates the safety or effectiveness of a medical device. If more than one medical device is being evaluated, provide the requested information for each.

A. Device Name:

B. Manufacturer:

C. Does the research involve a Significant Risk Device under an IDE?

☐ Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*

☐ No

D. Is the research IDE-exempt?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

☐ No

E. Does the research involve a Non-Significant Risk (NSR) Device?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☐ No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

IV. Export Control:

Indicate if there will be export control concerns (i.e., select agents or select toxins involved in the project, collaboration with foreign institution or foreign nationals, publication restrictions, foreign travel, etc.). If so, please upload and complete Export Control Exclusion Screening Form.

EC-Screening-Form-FILLABLE 12-1-14.pd