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The use of Methylsulfonylmethane (MSM) in the treatment of low back pain.

NCT02268305

PROTOCOL FOR CLINICAL INVESTIGATION – NON-EXEMPT HUMAN
(Wilford Hall Ambulatory Surgical Center – WHASC)

PROTOCOL SUMMARY

1. Title:

The use of Methylsulfonylmethane (MSM) in the treatment of low back pain.
FWH20140075H

2.0. Principal Investigator (PI): **NELLIS AFB PI:**

Name	Paul Crawford
Rank/Corps or Civilian Rating	Col, USAF, MC
Date of IRB Approved CITI Training & Date of Good Clinical Practice Training	12/28/2017
Branch of Service	USAF
AD Mil/DoD Civilian/Ctr/Non-DoD Civ	AD
Department & Base	Department of Medical Education, Nellis AFB
Phone & Pager #	(702) 653-3298
E-Mail Address & AKO/DKO E-Mail Address	Paul.F.Crawford.mil@mail.mil

3.0. Research Plan:

3.1. Purpose:
The purpose of this study is to assess whether Methylsulfonylmethane (MSM) plus standard of care naproxen improves symptoms of lower back pain versus standard of care naproxen plus placebo.

3.2. Hypotheses, Research Questions or Objectives:
Does the addition of MSM to standard of care treatment improve symptoms of lower back pain assessed by the Roland-Morris Disability Questionnaire (RMDQ) and Pain Impact Questionnaire (PIQ-6)?

4. Brief Summary of the study:
We are studying whether MSM plus standard of care naproxen improves symptoms of lower back pain compared to standard of care naproxen plus placebo. Subjects will be randomized into 1 of 2 groups. Group 1 will take by mouth 6000 milligrams (mgs) of MSM plus standard of care naproxen. Group 2 will take by mouth placebo capsules plus standard of care naproxen. Subjects will be instructed to take their study pills for 12 weeks and record on a study diary. They will then be followed up for one final visit 4 weeks later. RMDQ, PIQ-6, pain level, comprehensive metabolic panel (CMP), complete blood count (CBC) will be assessed at 4 week intervals for 12 weeks. Subjects' participation will last 16 weeks.

5. Subjects:
We will recruit male and female NELLIS AFB DoD beneficiaries between the ages of 18-65 years old with symptoms of lower back pain from the any of the clinics at the Mike O'Callaghan Military Medical Center at Nellis Air Force Base. Some subjects may be the patients of the PI or AI; however, the PI will have the AI, or Study staffs recruit their patients to prevent any misconception of coercion. No special populations (i.e. children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons) will be eligible for this study.

6. Inclusion/exclusion criteria:

- **Inclusion:**
  - DoD beneficiaries between the ages of 18-65 years old.
  - Symptoms of Low Back Pain greater than 12 weeks duration.
  - Patients with a history of lower back surgery may be included.
- **Exclusion:**
  - DoD beneficiaries less than 18 years old or greater than 65 years old.
  - Lower back pain caused by any of the following:
    - Infection
    - Tumor
    - Osteoporosis
    - Ankylosing spondylitis
    - Fracture
    - Deformity

        - Inflammatory process
        - Cauda equina syndrome
    - Treated or untreated central nervous system impairment.
    - Meeting the criteria for surgery, including:
        - progressive motor deficit
        - sphincter impairment from neurological cause
        - disabling sciatic pain (in the absence of backache) lasting 6 weeks or more that is attributed to a compromised nerve root and demonstrated by magnetic resonance imaging or computed tomography
    - Oncologic disease during the previous 5 years.
    - Unexplained weight loss, fever, or chills.
    - Diagnosed upper urinary tract infection within last 28 days.
    - Patients identified during standard of care interview to have a history of intravenous drug use.
    - Immunocompromised host.
    - A severe comorbidity to include:
        - a detriment to the subjects overall well-being (e.g. painful disabling arthritic hip joints)
        - Cirrhosis
        - Ongoing dialysis
    - Radiating symptoms to lower extremities (sciatica).
    - History of bleeding disorders.
    - History of high blood pressure.
    - History of heart, kidney, liver or ulcer disease.
    - Allergic to analgesics or Non-steroidal anti-inflammatory agents (NSAIDs).
    - Pregnant or breastfeeding.
    - Initial pain rating of greater than 8/10 on initial intake evaluation
    - If the comprehensive metabolic panel is reviewed by the PI, and any of the values are outside a range deemed safe for the subject to be included in study.
    - If any of these four components of the complete blood count is reviewed by the PI, and any of the values are outside a range deemed safe for the subject to be included in study:
        - White blood cell count
        - Hemoglobin
        - Hematocrit
        - Platelets
    - Patients taking any of the following medications are excluded from participating, unless they agree to wash out for two weeks prior to entering the study:
        - Muscle relaxers of any type
        - Tramadol
        - Gabapentin
        - Pregabalin
        - Glucosamine
        - Narcotic pain medications
        - Non-steroidal anti-inflammatory agents (NSAIDs)
          ***** Patients taking naproxen must agree to wash out for two weeks prior to entering the study, but can begin taking it again, as prescribed, after Visit 1 where a baseline pain assessment is performed.

7. Number of Subjects: TOTAL NUMBER OF SUBJECTS (nation-wide/study-wide): NELLIS AFB 100

8. Use of an Investigational New Drug:

a. Generic Name and IND Number: Methylsulfonylmethane (MSM), IND# 122180
b. Sponsor holder of the IND Number: Paul Crawford, MD, LtCol, USAF, MC
c. Justification for use: MSM plus standard of care naproxen improves symptoms of lower back pain.

9. Use of an Investigational Device: N/A

10. Use of a Placebo: Yes. The placebo is a capsule filled with rice flour.

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Phone & Pager #	(702) 653-3298
E-Mail Address & AKO/DKO E-Mail Address	Paul.F.Crawford.mil@mail.mil

2.1. Associate Investigators (AI): See form A-2 Study Personnel

2.2. Research Assistants (RA) & Coordinators (RC): See form A-2 Study Personnel

2.3. The research relevance of this protocol focuses on:
[ ] Diagnosis [x] Treatment [ ] Medical Utilization/Managed Care [ ] Prevention [ ] Medical Readiness [ ] Other

2.4. Location(s):

a. Collaborating Facilities: None.
b. Air Force Sites seeking Regional IRB: Mike O'Callaghan Military Medical Center/Nellis Air Force Base, Jill Clark
c. List study sponsors: This study will be sponsored by Bergstrom Nutrition. The collaborative research will be executed in accordance with 15 USC 3710a through a Cooperative Research and Development Agreement, between the 99th MDG and Bergstrom Nutrition. The estimated fair market value of the support is $17,570.00.

3. Research Plan:

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3.2. Hypotheses, Research Questions or Objectives:
Does the addition of MSM to standard of care treatment improve symptoms of lower back pain assessed by Roland-Morris Disability Questionnaire (RMDQ), pain level, and Pain Impact Questionnaire (PIQ-6)?

3.3. Significance:
A lack of true clinical assessment of the usefulness of MSM in low back pain suggests that patients will continue to consume a product with a potential but unknown benefit. As a multidimensional approach to the treatment of low back pain is endorsed, the assessment of MSM on low back pain as an alternative or adjunctive therapy would be prudent. For this reason, we propose that a clinical trial be carried out to assess the impact of MSM on low back pain.

3.4. Military Relevance[81]:
Low back pain is a common complaint of Tricare beneficiaries. In 2012, chronic pain treatment accounted for an approximate annual cost of $560-635 billion in direct medical treatment costs and lost productivity in the United States. Despite these costs, the response of each individual to standard treatments varies greatly, often being under treated. Within the military, responses to traditional treatments and lost productivity are no different than the civilian communities but may have a far more reaching consequence as service men and women are often unable to perform their duties fully or deploy due to pain.

While the DoD has developed tools for physicians to assess and treat low back pain, treatment is not always successful. As such, additional treatments options are needed which may yield positive results, without producing adverse side effects which may limit a member from duty or deployment. The proposed study of MSM will help define this new potential treatment, specifically

measuring improvement of pain and function. If found to be effective, this treatment may represent a significant step forward in providing excellent care to service members, while ensuring a force which is fit for duty.

3.5. Background and Review of Literature:

Background: Low back pain has been identified to account for 40% of all work related compensations filed in the US[1]. Overall, the lifetime prevalence of experiencing at least one episode of low back pain is believed to be 70-80%[1]. The etiology of low back pain is often considered multidimensional, and as such often requires a multidimensional approach to its treatment[2,3]. Even when a multidimensional treatment plan is created or proposed for patients, many endorse the concurrent use of complementary and alternative medicines, either as adjunctive therapy or in place of offered treatment. This is especially true when patients have concerns about the cost or delayed receipt of conventional care[4]. While the true percent of patients who endorse the use of complementary or alternative medicines is unknown, reports suggest that 9% to 65% of the population has or currently uses treatments other than those prescribed by their physician[5]. Back pain has been noted to be the principle reason for using CAM[4,6] Top cited uses of CAM include prayer[5], nonvitamin, nonmineral, natural products, deep breathing exercises, meditation, chiropractic, or osteopathic manipulation, massage, and yoga[7].

Sources used by patients for acquiring information on various CAM therapies vary from internet, to personal testimonial, to books published by a variety of health professionals. Among the many published books, *H procumbens, S alba,* topical capsasin compresses, and methylsulfonylmethane (MSM) are often cited as a supplemental agent which can be used for a variety of orthopedic ailments ranging from arthritis to low back pain[8,9]. Specifically, MSM accounts for 4.1% of nonvitamin, nonmineral products used[4]. While several clinical trials and systematic reviews have been aimed at testing *H procumbens, S alba,* topical capsasin compresses for low back pain, clinical trials assessing the role MSM may play in the treatment of low back pain are largely lacking. Despite this, it remains widely cited as an agent which may be used in the treatment of low back pain[8,10] as well as many other illnesses[11].

Research of Interest: One area in which MSM has undergone some degree of investigation is its use as an adjunct therapy for osteoarthritis[12-19]. In each study of patients with OA, MSM was associated with decreased patient pain and increased function. Variation in method used to measure effectiveness was noted from study to study, the most frequent assessments used including Oswestry Disability Questionnaire, Roland-Morris Disability Questionnaire, Visual Analogue Scale (for pain intensity), and Western Ontario and McMaster University Osteoarthritis Index visual analogue scale (WOMAC). As pointed out by We et al, the variability of effect found in the use of MSM in osteoarthritis approaches 0% with studies noting a significant improvement in most measured symptoms. This suggests that the effect of MSM has on pain caused by osteoarthritis consistently improves symptoms from study to study. Because each study contained various shortcomings in terms of study design (small treatment groups, possible un-blinding, questionable open-label trials, possible co-interventions, unstated compliance the use of MSM in the treatment of osteoarthritis), MSM has not been recommended for treatment of OA in all patients. However, data currently are supportive of its use.

Pharmacology of MSM: Methysulfonylmethane [$(CH_3)_2SO_2$] is a largely tasteless, odorless, white, crystalline solid which is water soluble[20]. It occurs naturally in the environment and is synthesized in the human body[18] as a byproduct of dietary DMSO[21] where 15% of consumed DMSO is converted into MSM [11]. MSM is believed to have anti-inflammatory properties as demonstrated by in-vitro studies which suggest MSM may blunt inflammatory processes[22]. However, studies have demonstrated that MSM does not interact with the COX or PG synthesis pathways[23] or by decreasing ESR or CRP levels[13]. While DMSO and MSM are believed to block conduction of peripheral C-fibers[15], slow the proliferation of smooth muscle and endothelial cells, and decrease the binding, uptake, and degradation of LDL by fibroblasts[27,28], decrease urine MDA levels in humans, and delay chemically-induced colon cancer onset in rats[13], no clear anti-inflammatory mechanism of action has been elicited.

While MSM has not received FDA approval for any specific ailment, DMSO, the parent compound of MSM (see above) has been FDA approved for the treatment of intersitital cystitis when infused as a 50% solution[71]. MSM continues to be used (CAM) for illnesses including OA, back pain, fibromyalgia, tendinitis, carpal-tunnel syndrome, dental pain, asthma, food allergies, asthma, rheumatoid arthritis, SLE, scleroderma, hypertension, and elevated serum cholesterol among others[20,24].

Safety: MSM is rated as "Probably Safe" by the Natural Medicines Comprehensive Database when given in 2.6 to 6 grams/day, up to 12 weeks[24]. Studies in rats given 1.5-2.0 g/kg/day orally showed no mortality, adverse effects or clinical signs of toxicity, effects on body weight gain, or gross lesions[68]. In a study by Kim et al[15] on MSM and osteoarthritis, no change or adverse event was noted in liver or renal function, hematology studies (CBC), stool assessment for occult bleeding or lipid profile, or urinalysis. In a similar study, Vidyasagar et al[78] found similar results with no CBC, Serum Glucose, Urea, Creatinine or AST/ALT. Taking all of this into consideration, the FDA previously labeled MSM as Generally Recognized as Safe in 2008[79]. The LD50 is currently unknown due to the fact that maximum dose given to date (20g/kg/day) failed to produce death in animal studies[69]. MSM should be avoided during pregnancy and lactation due to insufficient reliable information available (no studies have specifically

looked at its use during pregnancy). Prior to the recommendation to limiting the daily dose to 6 grams/day in humans, some physicians recommended up to 20 g/day, which approximates to 300 mg per kg/day[70].

Adverse Reactions[13,24]: When dosed orally, nausea, diarrhea, bloating, headache, fatigue, insomnia, and difficulty concentrating have been reported. These adverse reactions however, do not appear to occur any more frequently in groups exposed to MSM than placebo in clinical trials[13]. There is no known drug-food, drug-drug, or drug-lab test interactions known[24].

Proposed use of MSM in Low Back Pain: As noted previously, MSM accounts for 4.1% of all nonvitamin, nonmineral CAM therapies used and is often cited as a remedy for back pain. Tant et al note that in a trial of glucosamine containing MSM, both yield symptomatic relief in patients with low back pain, individually and when taken together[25]. Interestingly, trials such as that performed by Usha et al included MSM in the formulation of Glucosamine when assessing its impact on osteoarthritis[14]. However, additional information on the impact MSM may have on low back pain is lacking. Furthermore, of the 462 trials for low back pain registered with clinicaltrials.gov, none is designed to assess the impact of MSM on low back pain[26].

Patients continue to access information on CAM through a variety of sources. A lack of true clinical assessment of the usefulness of MSM in low back pain suggests that patients will continue to consume a product with a potential but unknown benefit. As a multidimensional approach to the treatment of low back pain is endorsed, the assessment of MSM on low back pain as an alternative or adjunctive therapy would be prudent. For this reason, we propose that a clinical trial be carried out to assess the impact of MSM on low back pain.

Selection of Outcome Measurements in Low Back Pain: Clinical outcome measurements for low back pain have been studied by many groups. Reviews of various outcome measurements for low back pain have identified up to 36 distinct outcome measurements[36]. However, only a select number of them are considered valid or reliable. Studies may be unidimensional, focusing only on pain, or multidimensional where focus is placed not only on pain but on the extent to which the severity of pain impacts activity or emotional function[30,35]. No Gold Standard exists for evaluating disability in low back pain[34] though authors suggest that prospective[32], patient/self-reported[31,33,35] measures of pain are ideal. Some authors suggest that surrogate markers such as analgesic use should not be used when assessing a patient's clinical status[32]. However, because the etiology of low back pain is often multifactorial, multiple measurements of low back pain are often recommended when measuring the impact any given intervention has on low back pain[29].

Three general areas of assessment common to low back pain include pain, function, and quality of life[29]. Of these areas, assessment of pain itself is often the focus of studies due to the belief that a prerequisite to the management of pain is the accurate assessment of the same[47]. This focus is further supported by the finding that the correlation between self-reported pain and self-reported function and objective measures of function are significant but weak[48,49,50]. The other areas are assessed as they give insight into the overall impact the treatment has on the patient (clinical significance). Studies commonly used to assess these areas include:

-Pain: Visual Assessment Scale (VAS)[29, 31, 37], Verbal Rating Scales (VRS)[32], and Numerical Rating Scale (NRS)[32,38]
-Function: Oswestry Low Back Pain Disability Questionnaire/Index (ODI) [29,37], Roland-Morris Disability Questionnaire (RMDQ)[29,37], Quebec Back Pain Disability Scale[34,37]
-Quality of Life: SF-36, 12, or PIQ-6[29,35,37,67], Patients Global Assessment of Response to Therapy (PGART)[31]

Pain: We recommend the VAS. The VAS appears in most studies of low back pain and has specifically been recommended[29]. Mannion et al also suggest that most patients treat the VRS and NRS as a VAS by simplifying each respective numerical scale to approximate that seen in the VAS. When the scale is properly explained, it has been shown to be reproducible and easy to interpret[35]. However, this choice may be considered arbitrary as studies measuring the variance between various numerical scales suggest any numerical scale may be used with expected reproducible results[35]. One advantage of using the NRS is that the Minimally Clinically Important Difference (MCID) has already been calculated as 2[35,38]. With respect to expected outcomes, Farrar suggests that a relative treatment difference in pain level of 33-50% on any scale is considered clinically meaningful[40].

Function: We recommend the Roland-Morris Disability Questionnaire. While both the ODI and RMDQ are reliable, valid, and require only 5 minutes to complete, the RMDQ is the most studied of all functional outcome assessments[35]. Published Mean Detectable Change (MDC) is available for both of these studies though it varies from study to study, based on the initial measured level of function. Generally, a low initial score indicates that less than a 5 point difference is needed to identify a detectable change. Higher baseline scores may necessitate as much as a 8-9 point difference to identify a change. Roughly, a 5 point difference correlates to a 20% change on the scale[35]. Other authors such as Bombardier et al suggest that a 2-3 point difference is a MCID[41].

Quality of Life: We propose the use of the PIQ-6/R. While the SF-36 and SF-12 has been well studied and approved by the Medical Outcome Trust[51], shorter questionnaires which measure the impact of pain on the quality of life have been developed and include the SF-6D and PIQ-6/PIQ-R[35,51,67] which may provide reliable information. While the SF-36 has been more widely published[35], the SF-12 and PIQ-6/R are routinely used. Limited data has been published on the MDC or MCID for the SF-36 but has been described by Walters et al[65]. The PIQ-6 is ideal for the current study due to its high internal validity and correlation with pain visual analog and numerical rating scales[67]. An additional reason for using the PIQ-6 rather than the SF-6 includes concerns that the SF-6 may overestimate baseline values and underestimate change[66]. Sheldon et al[31] suggest that the correlation between RMDQ and VAS ranged from 0.657 and 0.703, and the VAS and PGART from 0.677 and 0.738, suggesting that results are similar enough that assessments may be simplified (eliminate one of these studies). Because the PIQ-6 also highly correlates with VAS, it was selected in place of the PGART. Similar correlation results have been reported by Kovacs et al at days 15 and 60 of follow up, but not on initial (day 1)[52] making long term follow up important. The PIQ-6/R satisfies this time course as it is designed for a 4 week follow up. Reasons for including a measure of quality of life (vs pain only) is that measuring the quality of life helps determine the clinical significance of statistical findings[39].

Patient Selection: It has been noted that the natural course of acute low back pain is such that rapid improvement of pain, disability, and return to work is experienced in the majority of patients by 4 weeks[56]. Further improvement is then noted up to 3 months[55,56]. Of the patients who go on to develop chronic low back pain, 90% endorse stable pain and disability[55]. Kovacs et al note that the extent to which disability can be attributed to pain itself (vs psychosocial and cognitive measures) is highest in the acute setting (pain <14 days)[53]. Disability from chronic low back pain (pain >12 weeks in duration[33]) is also influenced by multiple factors to include both pain itself and psychosocial facotrs[42]. Despite this finding, attempts to address the psychosocial aspects with antidepressants have inconsistently shown true benefit[58,60]. Even though chronic low back pain is a multidimensional problem, authors such as Kovacs et al agree that the enduring presence of pain can predict disability, and disability in turn may predict quality of life. Treatment plans for patients with chronic low back pain encompass a variety of treatments from advice/continued activity to pain medications to use of complementary and alternative medicine[43-46,49,54]. Yet despite this multifaceted approach, a substantial number patients continue to experience pain and disability, albeit at a stable level[55,56]. Because of this stability, patients with chronic low back pain would be ideal study population to assess the impact of MSM on low back pain.

MSM has not been well studied in low back pain. Tant et al report that it may be helpful in the treatment of chronic low back pain[57] when coupled with glucosamine complex. However, their study used a small number of patients and did not include a true placebo control for glucosamine/MSM. Further information on MSM and chronic low back pain is otherwise lacking.

Adverse Side Effects: As noted above, Kim et al[13]. reported adverse side effects of bloating, constipation, indigestion, fatigue, decreased concentration, insomnia and headache, though these symptoms were not any more prevalent in the group taking MSM than the placebo group.

Proposal of Materials and Methods: Selection of proper follow up time has been based on studies of MSM in osteoarthritis. Follow up time ranges from 2[13] to 12 weeks[12]. In the study by Kim et al[13], efficacy was not noted until 4 weeks into the study. This improvement was even more notable at 8 and 12 weeks than at 4 suggesting that improvement in symptoms may require longer exposure MSM. For this reason, the impact MSM on low back pain, function and quality of life should be carried out to at least 12 weeks.

The use of 4 week intervals for reassessment mirrors the protocol by Kim et al. This is convenient considering the PIQ-6/R was designed for a 1(acute) or 4 week (chronic) follow up.

Inclusion and Exclusion Criteria for this study will be similar to the common criteria from various studies on Low Back Pain[42-44,52,55, 58, 61].

Studies of MSM and osteoarthritis have recommended MSM dosing ranging from 500mg TID to 3 g BID[12,13]. Doses of 6 g daily are considered safe[13,24]. As noted above, studies in rats found that doses 5-7 times the maximum recommended daily amount may be given without any appreciable toxicity[15,68]. Human studies using >6gm/day have not been performed. MSM will be given in the dose of 1500mg x2 Tabs, BID. Standard of care naproxen is typically defined as a dose of 225-550 mgs twice a day although it may vary depending on the provider.

3.5.1. Bibliography:

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3.6. Research Design and Methods:

We will recruit male and female NELLIS AFB DoD beneficiaries between the ages of 18-65 years old with symptoms of lower back pain from any of the clinics at Nellis Air Force Base. Patients taking Muscle relaxers of any type, Non-steroidal anti-inflammatory agents (NSAIDs), Tramadol, Gabapentin, Pregabalin, agree to wash out for two weeks prior to entering the study. Randomization will be performed by the research coordinator. Both Investigators and subjects will be blinded to study assignments.

Screening Visit:

- Obtain signed Informed Consent Document and HIPAA Authorization.
- Review inclusion/exclusion criteria.
- Record: name, race ethnicity, race, date of birth, age, sex, height (in inches), weight (in pounds), blood pressure, email address, phone number, history of lower back surgeries, medical history, concomitant medications, and record the amount of naproxen prescribed as standard of care.
- Subjects will have the following research-driven blood test drawn via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood drawn for each test) which include:
  - Women of childbearing potential will have a serum pregnancy test.
  - Comprehensive metabolic panel (liver function, renal function, plasma glucose tests).
    **Subjects who have had a comprehensive metabolic panel test within the one week prior to this visit will not need to have this test repeated unless they are abnormal.*
  - Complete Blood Count.
    **Subjects who have had a complete blood count test within the one week prior to this visit will not need to have this test repeated unless they are abnormal.*

Visit 1/Day 1 (within 1 week of Screening Visit):

- Subjects will be randomized by the research coordinator. Both subjects and investigators will be blinded to the study group assignments:
  - Group 1 will take by mouth three 1000 mg capsules twice a day (6000 mgs) of MSM plus standard of care naproxen.
  - Group 2 will take by mouth three placebo capsules twice a day plus standard of care naproxen.
- Subjects will be asked to complete the following questionnaires:
  - RMDQ
  - PIQ-6
- Subjects will be asked "On a scale of 0-10, with 10 being the worst pain, what is your current level of pain".
- Subjects will be asked if they are undergoing any other treatment for back pain, when the last treatment was, and whether or not they were satisfied.
- Subjects will be given a 12 week supply of the study pills and reminded to take the pills as instructed.
- Subjects will be given a Study Diary and will be instructed to record any missed dose of their study pills, record how much standard of care naproxen taken, and to bring the Study Diary to next visit.

Visit 2/Week 4:

- Record: Weight (in pounds), blood pressure, history of lower back surgeries, medical history, and concomitant medications.
- Subjects will be asked to complete the following questionnaires:
  - RMDQ
  - PIQ-6
- Subjects will be asked "On a scale of 0-10, with 10 being the worst pain, what is your current level of pain".
- Research staff will record whether subject had any side effects to report.
- Subjects will have their study medications refilled.
- Research staff will collect the subject's Study Diary, issue them a new one, and remind them to bring it with them to the next study visit.
- Research staff will remind subjects to take the pills as instructed.
- Subjects will have the following research-driven blood test drawn via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood drawn for each test) which include:
  - Comprehensive metabolic panel (liver function, renal function, plasma glucose tests).
    **Subjects who have had a comprehensive metabolic panel test within the one week prior to this visit will not need to have this test repeated unless they are abnormal.*
  - Complete Blood Count.
    **Subjects who have had a complete blood count test within the one week prior to this visit will not need to have this test repeated unless they are abnormal.*

Visit 3/Week 8:

- Record: Weight (in pounds), blood pressure, history of lower back surgeries, medical history, and concomitant medications.
- Subjects will be asked to complete the following questionnaires:
  - RMDQ
  - PIQ-6
- Subjects will be asked "On a scale of 0-10, with 10 being the worst pain, what is your current level of pain".
- Research staff will record whether subject had any side effects to report.
- Subjects will have their study medications refilled.
- Research staff will collect the subject's Study Diary, issue them a new one, and remind them to bring it with them to the next study visit.
- Research staff will remind subjects to take the pills as instructed and to return the bottle to the research staff at the next visit.
- Subjects will have the following research-driven blood test drawn via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood drawn for each test) which include:
  - Comprehensive metabolic panel (liver function, renal function, plasma glucose tests).
    **Subjects who have had a comprehensive metabolic panel test within the one week prior to this visit will not need to have this test repeated unless they are abnormal.*
  - Complete Blood Count.
    **Subjects who have had a complete blood count test within the one week prior to this visit will not need to have this test repeated unless they are abnormal.*

Visit 4/Week 12 *SUBJECTS STOP TAKING STUDY PILLS AT THIS VISIT:

- Record: Weight (in pounds), blood pressure, history of lower back surgeries, medical history, and concomitant medications.
- Subjects will be asked to complete the following questionnaires:
  - RMDQ
  - PIQ-6
- Subjects will be asked "On a scale of 0-10, with 10 being the worst pain, what is your current level of pain".
- Research staff will record whether subject had any side effects to report.
- Research staff will collect the subject's Study Diary.
- Research staff will collect the study pills.
- Subjects will have the following research-driven blood test drawn via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood drawn for each test) which include:
  - Comprehensive metabolic panel (liver function, renal function, plasma glucose tests).
    Subjects who have had a comprehensive metabolic panel test within the one week prior to this visit will not need to have this test repeated unless they are abnormal.
  - Complete Blood Count.
    Subjects who have had a complete blood count test within the one week prior to this visit will not need to have this test repeated unless they are abnormal.

Final Visit 5/Week 16:

- Record: Weight (in pounds), blood pressure, history of lower back surgeries, medical history, and concomitant medications.
- Subjects will be asked to complete the following questionnaires:
  - RMDQ
  - PIQ-6
- Subjects will be asked "On a scale of 0-10, with 10 being the worst pain, what is your current level of pain".
- Subjects will be asked if they are undergoing any other treatment for back pain, when the last treatment was, and whether or not they were satisfied.
- Subject will be asked if they have taken any medications for pain since their last visit.
- Research staff will record whether subject had any side effects to report.
- Subjects will have the following research-driven blood test drawn via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood drawn for each test) which include:
  - Comprehensive metabolic panel (liver function, renal function, plasma glucose tests).
    Subjects who have had a comprehensive metabolic panel test within the one week prior to this visit will not need to have this test repeated unless they are abnormal.
  - Complete Blood Count.
    Subjects who have had a complete blood count test within the one week prior to this visit will not need to have this test repeated unless they are abnormal.

DIRECTIONS FOR TAKING MEASUREMENTS:

Directions for weighing subjects: Have subject remove his/her shoes and empty pockets of any items prior to stepping on the scale. Weight should be recorded to the nearest ½ pound (for example 150.5#).

Directions for taking height: Have subjects remove their shoes before taking their height. Height should be recorded to the nearest 1/2 inch (for example 60.5").

Directions for taking blood pressure: Have subjects sit for 5 minutes before taking blood pressure.

VISIT WINDOWS: Visits will have a 1 week visit window. If a subject fails to come in within this visit window, they will be instructed to bring in any unused study pills and removed from the study.

ADHERENCE TO STUDY ASSIGNMENTS: Adherence to study medication will be assessed via review of the "Study Medication Diary". Compliance will be recorded both in paper format and in the electronic data collection tool. If a subject misplaces their Study Medication Diary, they will be asked to reproduce it from memory to the best of their ability. Subjects will be instructed to bring back all of the bottles regardless of whether there are empty or contain missed doses.

If a subject misses a dose, regardless of the amount, they will be encouraged to document this in their study diary and resume taking their pills. All subjects will remain in the study and continue with all the study related visits.

If a subject misplaces or loses their study medication, they will be instructed to return to the research department and will be given a new bottle of their assigned study medication. Since the research coordinator is not blinded, they will be able to give the medication that the subject was assigned.

If a subject forgets to bring their study medication in for their visit, they will be instructed to bring it in at their earliest convenience.

WITHDRAWAL PROCEDURES: If at any time during the study, the subject decides to withdraw consent or if the subject is withdrawn from the study by the investigator, they will be referred to their Primary Care Manager (PCM) to continue with standard of care treatment.

PREGNANCY: Subjects must agree to take precautions to prevent pregnancy during the course of this study due to the possible effect MSM may cause an unborn child. The only completely reliable methods of birth control are total abstinence or surgical removal of the uterus. Other methods, such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy. In addition, women who are breastfeeding may not participate in this study.

If a subject unintentionally becomes pregnant, they will be instructed to cease taking their study pills, return their pill bottle and will be removed from the study.

DISPOSAL OF STUDY RELATED PILLS: Subjects will return any remaining study-related pills directly to the Research Coordinator or Principal Investigator. The Research Coordinator or Principal Investigator will be responsible for disposing of the study-related pills. The preferred method of disposal is to have the Pharmacy dispose of them. If the Pharmacy is unable to dispose of them, they will provide directions on safe disposal for the Research Coordinator or Principal Investigator to follow.

OTHER: Subjects will take their study pills daily and will be permitted to have the usual medical care for other co-morbid and acute conditions if applicable. Analysis described above using intention-to-treat principles for any missing data will be used (we will use the carry-forward method to impute missing data).

The placebo will be a capsule filled with rice flour, which does not increase the risks to subjects.

This study involves the use of an investigational product (IP) called Methylsulfonylmethane (MSM). This means that the product has not been approved by the Food & Drug Administration (FDA) for treating lower back pain. It is being given in a dose that does not increase the risk to the research subjects. There are no known risks associated with MSM as it is a compound granted GRAS (Generally Recognized As Safe) status by the United States Food and Drug Administration (more information can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=582.20). The Sponsor-Investigator will report unexpected SAEs associated with the use of the drug to the FDA as specificed at 21 CFR 312.32(c).

3.6.1. Interventions, Observations, or Data Sought:
We will assess the effect of 6000 mgs of MSM plus standard of care naproxen taken for 12 weeks plus one follow up visit on RMDQ, PIQ-6, pain level, comprehensive metabolic panel (CMP) and complete blood count (CBC) will be assessed at 4 week intervals.

3.6.2. Data Collection and Processing:
Data will be collected and recorded in a spreadsheet. At the conclusion of the study, all personally identifying information will be removed prior to analysis based on AFI 33-332, "The Air Force Privacy and Civil Liberties Program" and the "National Institute of Standards and Technology Special Publication (NIST SP 800-88) for the approved methods to destroy PII".

3.6.3. Setting: Mike O'Callaghan Military Medical Center at Nellis Air Force Base.

3.6.4. Date(s): June 2014-June 2016

3.6.5. Source of Research Material:

Source of Research Material per Participant (Procedures)	# Routine Care	# Research Driven	# Total Procedures
PIQ6	0	5	5
RMDQ	0	5	5
Study Diary	0	5	5

Serum pregnancy test for women of child-bearing potential	0	1	1
Comprehensive metabolic panel	0	5	5
Complete Blood Count	0	5	5

All specimens kept at NELLIS AFB will be handled and disposed of in accordance with federal regulations.

3.6.6. Subjects:
We will recruit male and female NELLIS AFB DoD beneficiaries between the ages of 18-65 years old with symptoms of lower back pain from any of the clinics at the Mike O'Callaghan Military Medical Center at Nellis Air Force Base. Some subjects may be the patients of the PI or AI; however, the PI will have the AI, or Study staffs recruit their patients to prevent any misconception of coercion. No special populations (i.e. children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons) will be eligible for this study.

3.6.7. Inclusion/Exclusion Criteria:

- **Inclusion**:
  - DoD beneficiaries between the ages of 18-65 years old.
  - Symptoms of Low Back Pain greater than 12 weeks duration.
  - Patients with a history of lower back surgery may be included.
- **Exclusion**:
  - DoD beneficiaries less than 18 years old or greater than 65 years old.
  - Lower back pain caused by any of the following:
    - Infection
    - Tumor
    - Osteoporosis
    - Ankylosing spondylitis
    - Fracture
    - Deformity
    - Inflammatory process
    - Cauda equina syndrome
  - Treated or untreated central nervous system impairment.
  - Meeting the criteria for surgery, including:
    - progressive motor deficit
    - sphincter impairment from neurological cause
    - disabling sciatic pain (in the absence of backache) lasting 6 weeks or more that is attributed to a compromised nerve root and demonstrated by magnetic resonance imaging or computed tomography
  - Oncologic disease during the previous 5 years.
  - Unexplained weight loss, fever, or chills.
  - Diagnosed upper urinary tract infection within last 28 days.
  - Patients identified during standard of care interview to have a history of intravenous drug use.
  - Immunocompromised host.
  - A severe comorbidity to include:
    - a detriment to the subjects overall well-being (e.g. painful disabling arthritic hip joints)
    - Cirrhosis
    - Ongoing dialysis
  - Radiating symptoms to lower extremities (sciatica).
  - History of bleeding disorders.
  - History of high blood pressure.
  - History of heart, kidney, liver or ulcer disease.
  - Allergic to analgesics or Non-steroidal anti-inflammatory agents (NSAIDs).
  - Pregnant or breastfeeding.
  - Initial pain rating of greater than 8/10 on initial intake evaluation
  - If the comprehensive metabolic panel is reviewed by the PI, and any of the values are outside a range deemed safe for the subject to be included in study.
  - If any of these four components of the complete blood count is reviewed by the PI, and any of the values are outside a range deemed safe for the subject to be included in study:
    - White blood cell count
    - Hemoglobin
    - Hematocrit
    - Platelets

- Patients taking any of the following medications are excluded from participating, unless they agree to wash out for two weeks prior to entering the study:
  - Muscle relaxers of any type
  - Tramadol
  - Gabapentin
  - Pregabalin
  - Glucosamine
  - Narcotic pain medications
  - Non-steroidal anti-inflammatory agents (NSAIDs)

***** Patients taking naproxen must agree to wash out for two weeks prior to entering the study, but can begin taking it again, as prescribed, after Visit 1 where a baseline pain assessment is performed.

3.6.8. Instrumentation: N/A

4.0. Human Subject Protection:

4.1. Recruitment:
All potentially eligible patients will be offered an opportunity to participate. Primary Care Managers (PCMs) who are not part of the research team will be informed about the study and provided information on the inclusion/exclusion criteria. PCM referrals and posted advertisements will be utilized for recruiting subjects to the study. Some patients may be patients of the PI or AI, however, they will have the study staff recruit their patients to prevent any misconception of coercion or undue influence. If a potential subject is identified by the treating PCM and is interested in obtaining more information about the study, the patient will either be provided a contact number to the Research Staff, the Research Staff will be given the potential subject's contact information by the PCM with the patient's oral or written authorization, or the PCM will come and get the Research Staff to speak with the patient directly.

4.2. Consent Processes:
The PI, AI, or Research Coordinators will obtain Informed Consent on this study. Informed consent and HIPAA Authorization will be sought in advance from each prospective subject. Informed consent will be appropriately documented. [32 CFR 219.117] After discussion with one of the investigators, the subject will be given the opportunity to consent. The investigator will provide a written copy of the consent form and allow the subject to read it, review it with the subject, and answer questions. The subject may decline to consent, and no pressure will be applied. If the subject consents to be enrolled in the study, the proper signatures will be obtained, and a copy given to the subject.

4.3 Participation Compensation: Subjects will not be paid for participation in this study.

4.4. Assent Process: N/A

4.5. Benefits: The benefits to the subjects may include a decrease in lower back pain and increase in function.

4.6. Risks: Risks to the subject are minimal.

Since the interaction between MSM and the medications in the exclusion list that require a washout period (Muscle relaxers of any type, Non-steroidal anti-inflammatory agents (NSAIDs), Tramadol, Gabapentin, Pregabalin, Glucosamine, Narcotic pain medications) have not been studied, patients will be asked not to resume taking these medications while participating in this study.

Less likely and not serious:

- <u>Risks related to Blood Draws:</u>
  - Bleeding
  - Feeling light-headed
  - Bruising at the blood draw site
  - Infection
- <u>Risks related to MSM:</u>
  - Bloating
  - Constipation
  - Indigestion
  - Fatigue

- Decreased concentration
- Insomnia
- Headache

Rare and serious:
There may be a risk that the subject has an allergy to MSM that they are not aware of currently. The signs and symptoms of an allergic reaction include:

- Shortness of breath
- Hives (itchy rash)
- Runny nose
- Watery eyes
- Sore eyes
- Asthma
- Lip swelling
- Tongue swelling
- Nausea
- Bronchospasm (a bronchial spasm is a sudden constriction of the muscles in the walls of the bronchioles)
- Anaphylaxis (whole-body allergic reaction that has the following signs and symptoms):
    - Abdominal pain or cramping
    - Abnormal (high-pitched) breathing sounds
    - Anxiety
    - Confusion
    - Cough
    - Diarrhea
    - Difficulty breathing
    - Difficulty swallowing
    - Fainting, light-headedness, dizziness
    - Hives
    - Itchiness
    - Nasal congestion
    - Nausea, vomiting
    - Palpitations
    - Skin redness
    - Slurred speech
    - Wheezing

*****If the subject experiences any of these symptoms, they are instructed to stop taking the study pills and seek urgent medical treatment.

There is also a potential risk of an inadvertent disclosure of personal health information.

4.7. Costs: N/A

4.8. Safeguards for Protecting Information:
The research consents will be stored in a locked cabinet in a locked room. Medical records will be annotated with ICD-10 code Z00.6 to reflect the subject's participation in a research study.All research data including patient demographics will be kept in an electronic database, which will be encrypted, double password protected and the access will be restricted. The research data will be de-identified and any links to identifiable data will be destroyed as soon as possible. The research data will not be utilized for further research activity beyond the protocol stipulations without additional IRB approval.

4.9. Safeguards for Protecting Subjects:
The principal investigator will be responsible for the protocol safety monitoring. The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and over sight staff for confirmation of the study data.

4.9.1. Minimizing Risks:
If a subject experiences any injury, adverse event, or unexpected clinical finding, a PI, AI, or Primary Care provider will be available to assess the subject and initiate proper clinical care

4.9.2. Vulnerable Populations: N/A

4.9.3. Clinical Care:
If a subject experiences any injury, adverse event, or unexpected clinical finding, a PI, AI, or Primary Care provider will be available to assess the subject and initiate proper clinical care.

4.9.4. Injury Compensation: N/A

4.9.5. Data Safety Monitoring:
The trial will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), and any applicable national and international regulatory requirements. The principal and associate investigators will be monitoring all aspects of the study in accordance with the appropriate regulations and will have regular meetings with periodic quality control of data documentation and collection. The objectives of the monitoring meetings will be:

1) To verify the prompt reporting of all data points, including reporting Serious Adverse Events (SAEs) and checking availability of signed informed consent,
2) To compare individual subject records, data pulls and/or the study source documents/case report forms (supporting data, laboratory specimen records and medical records to include physician progress notes, nurses' notes, subjects' hospital charts),
3) To ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records.

The principal investigator will be responsible for the protocol safety monitoring. The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and over sight staff for confirmation of the study data.

David Moss, DO, Maj (Primary) and Matthew Hawks, Capt (Alternate) will be the research monitors assigned to this study.

5.0. Alternatives: The alternative is not to participate in this study.

6.0. Data Analysis:

6.1. Outcome Measures:
We will be utilizing stratified random sampling with proportionate allocation which will ensure that all parts of the population are represented in the sample.

Factors:

1. Subject Characteristics
   a. Subject identification: nominal variable (1 … n)
   b. Gender: binomial variable (male, female)
   c. Age: interval variable (years)
   d. Height: interval variable (inches)
   e. Weight: interval variable (pounds)
2. Treatment: nominal variable (Naproxen + MSM, Naproxen + placebo)
3. Time (5 repeated measures for each subject): nominal variable (0wk, 4wk, 8wk, 12wk, 16wk)
4. Outcomes
   a. VAS: interval variable [72,73] (1-10 cm)
   b. RMDQ: interval variable (0-11,18, or 24 depending on instrument used)
   c. PIQ-6: interval variable (20-80)

6.2. Sample size estimation/power analysis:
The power for the rANCOVA was assessed using G*Power Version 3.0.10 [76] . The investigators anticipate there will be large effect size as determined by a 50% improvement in clinical outcomes. The results shown below indicate 34 subjects per Treatment group with 5 repeated measures will achieve a power of 0.80 to detect a large effect size of 0.40 at $\alpha = 0.05$.

Input:

Effect size f	=	0.4
β/α ratio	=	4
Total sample size	=	68
Number of groups	=	2
Repetitions	=	5

Corr among rep measures = 0.8

Output:

Critical F = 2.524097
Numerator df = 4.000000
Denominator df = 63.000000
α err prob = 0.049538
β err prob = 0.198150
Power (1-β err prob) = 0.801850

Software R Version 2.13.1 (R Foundation for Statistical Computing) [77]

6.3. Statistical Analysis:

Descriptive statistics: Sample means, standard deviations and standard errors of measurement for interval variables and frequency distributions for nominal variables will be calculated for the total sample and for the Treatment groups.

Hypothesis Testing: H_{01} and H_{02}: interval outcome data will be tested by a mixed effects repeated measures analysis of co-variance (rANCOVA

Post Hoc Tests: In the event H_{02} is rejected, contrasts will used to investigate differences among means.

6.4 Number of Subjects:

Number of subjects planned for NELLIS AFB	Enrolled in Study	100	to result in	68	completing the study.

TOTAL NUMBER OF SUBJECTS (nation-wide/study-wide): 100

7. Duration of Study: Approximate duration of the study: 2 years

8. Local and External Support Services: None

9. Intramural (GME) and Extramural Funding Support:

This study will be sponsored by Bergstrom Nutrition. The collaborative research will be executed in accordance with 15 USC 3710a through a Cooperative Research and Development Agreement, between the 99th MDG and Bergstrom Nutrition. The estimated fair market value of the support is $17,570.00. We received a grant from AFMSA/SG5 in the amount of $50,000 in support of purchasing supplies and a research coordinator.

10. Conflict of Interest: None

a. Financial Conflict of Interest: No financial conflicts of interest exist.
b. Personal Conflict of Interest: No personal conflicts of interest exist.
c. Current Off-Duty Employment: None

11. Use of an Investigational New Drug, use of a Drug for a non-FDA approved purpose, use of an investigative device or use of a placebo:

This research uses an Investigational New Drug **[x] YES [] NO**
This research uses a FDA approved drug for a non-FDA approved purpose **[] YES [x] NO**
This research uses an Investigational Device **[] YES [x] NO**
This research uses a placebo. **[x] YES [] NO**

12. Medical Research Area for the Study: (Pick as many as appropriate)

[] Analytical Chemistry	[] Anatomy	[] Anesthesiology	[] Biochemistry
[] Cardiovascular Surgery	[] Cardiology	[] Cell Biology	[] Dentistry
[] Dermatology	[] Dietetics	[] Electrophysiology	[] Endocrinology
[] Emergency medicine	[] Gastroenterology	[] General Surgery	[] Hematology
[] Histology	[] Immunology/Allergy	[] Infectious Disease	[] Microbiology
[] Molecular Biology	[] Neonatology	[] Neurology	[] Neurosurgery
[] Nursing	[] OB/GYN	[] Occupational Medicine	[] Occupational Therapy
[] Oncology	[] Ophthalmology	[] Oral/Maxillofacial Surgery	[] Orthopedics
[] Pathology	[] Pediatrics	[] Pharmacology	[] Physical Therapy
[] Mental Health	[] Radiology/Imaging	[] Urology	[] Wellness
[] Other (state):			

13. Attachments:

1. Certificate of Compliance
2. Informed Consent Document
3. HIPAA Authorization Document
4. Use of an Investigational New Drug (IND) in Research
5. Use of a Placebo in Research
6. Intramural and Extramural Funding Support Appendix
7. FDA Correspondence
8. Pharmacy Letter of Support
9. Laboratory Letter of Support
10. Pain Impact Questionnaire
11. Roland Morris Disability Questionnaire
12. Study Medication Diary
13. Form A2-Study Personnel