

Document Cover Page

Official Title of the Study:

Do NSAIDS or Executing Exercise Decrease Local Erythema, Site Swelling & Pain After Inoculation: the NEED LESS PAIN Study

NCT Number: NCT02807623

Date of Document: October 1, 2018

EIRB Protocol Template (Version 1.10)

1.0 General Information

***Please enter the full title of your study:**

Do NSAIDS or Executing Exercise Decrease Local Erythema, Site Swelling & Pain After Inoculation: the NEED LESS PAIN Study

***Please enter the Protocol Number you would like to use to reference the protocol:**

Need Less Pain
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

☐ Yes ☒ No

2.0 Add Site(s)

2.1 List sites associated with this study:

**Primary
Dept?**

Department Name

☐

Army - Womack Army Medical Center (WAMC)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

HOUSEL, LAURIE A

Select if applicable

☐ Student

☐ Site Chair

☐ Resident

☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Collins, Limone C
Co-Investigator
Mcclenathan, Bruce M, MD

Associate Investigator Spooner, Christina Eve Associate Investigator		
B) Research Support Staff		
BRUNADER, Janet ANN, BSN Research Coordinator Beltran, Thomas A Team Member Collins, Gervon Teressa Team Member Hussain, Mary Team Member Lamberth, Sherry L, PharmD, MSCR Team Member Lohsl, Connie Lynn, BSN Research Coordinator Nivens, Arline G, MS, PA ASCP, CRP, CMA Research Coordinator Ritschl, Jennifer Lynn, BSN Team Member Ryder, Stephanie L Team Member Turnquist, Jacob Team Member		
3.3 *Please add a Protocol Contact:		
BRUNADER, Janet ANN, BSN HOUSEL, LAURIE A Hussain, Mary Lohsl, Connie Lynn, BSN Nivens, Arline G, MS, PA ASCP, CRP, CMA Spooner, Christina Eve The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).		
3.4 If applicable, please select the Designated Site Approval(s):		
Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).		
4.0 Project Information		
4.1 Has another IRB/HRPP reviewed this study or will another IRB/HRPP be reviewing this study? If Yes, answer the questions according to the IRB/HRPP Determination.		
<input type="radio"/> Yes <input checked="" type="radio"/> No		

IRB Name	Review Date	Determination
No records have been added		
4.2 Is this a research study or a Compassionate Use/Emergency Use/HUD project?		
<input checked="" type="radio"/> Yes <input type="radio"/> No		
4.3 What type of research is this?		
<input checked="" type="checkbox"/> Biomedical Research <input type="checkbox"/> Clinical trial (FDA regulated) <input type="checkbox"/> Behavioral Research <input type="checkbox"/> Educational Research <input type="checkbox"/> Psychosocial Research <input type="checkbox"/> Oral History <input type="checkbox"/> Other		
4.4 Are you conducting this project in pursuit of a personal degree?		
<input type="radio"/> Yes <input checked="" type="radio"/> No		
4.6 Is this human subjects research? (As defined by 32 CFR 219) Human subject means a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.		
<input checked="" type="radio"/> Yes <input type="radio"/> No		
4.7 Do you believe this human subjects research is exempt from IRB review?		
<input type="radio"/> Yes <input checked="" type="radio"/> No		
5.0 Personnel Details		
5.1 List any Research Team members without EIRB access that are not previously entered in the protocol:		
<div>No records have been added</div>		
5.2 Will you have a Research Monitor for this study?		
<input checked="" type="radio"/> Yes <input type="radio"/> No <input type="radio"/> N/A		

Research Monitor Qualifications

Ensure the individual has expertise consistent with the nature of risk(s) identified within your study and is independent of the team conducting the research.

Research Monitor Role:

Responsibilities: The medical monitor will review the conduct of the protocol and ensure that the rights and health of all subjects enrolled in the study are adequately protected .

This will include:

1. Ensuring that the principal investigator notifies the monitor of new subject enrollments in the protocol on a routine basis.
2. Periodically reviewing documents to ensure that the approved protocol plan is being followed and informed consent has been obtained from all subjects.
3. Reviewing all addenda, all annual progress reports, and all adverse event reports.
4. Reviewing all unanticipated problems involving risk to the subjects or other serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event.
5. Reporting any concerns with the study promptly to the IRB.

If applicable, you may nominate an individual to serve as the Research Monitor:

No Users have been selected.

6.0

Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

☐ Yes ☒ No

7.0

Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
<input type="text" value="Other"/> DoD-Defense Health Agency- Immunization Healthcare Brance	<input type="text" value="Internally funded"/>	

Total amount of funding:

607000

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

☐ Yes ☒ No

If Yes, complete and attach Conflict of Interest forms for all key personnel

8.0 Study Locations

8.1 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

☒ Yes ☐ No

8.2 Study Facilities and Locations:

Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site
Army	Womack Army Medical Center	Lead site				WAMC IRB
DHA	WRNMMC	Performance site				WAMC IRB

Other:

Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site	
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No records have been added

8.3 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

☐ Yes ☒ No

8.4 Is this an OCONUS (Outside Continental United States) study?

☐ Yes ☒ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

☐ Yes ☐ No

9.0 Study Details

9.1 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

Vaccine, vaccination, or immunization AND one of the following: Pain, intervention, time, exercise, NSAID, paracetamol, acetaminophen, naprosyn, ibuprofen, nonsteroidal anti-inflammatory, steroid, injection, side effect, adverse event, physical activity, pushup, muscle conditioning.

9.2 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

The Brighton Collaboration ("Brighton") is an independent, global nonprofit vaccine safety research network for health care professionals. Brighton states, "attending to immunization pain supports immunization because it reduces suffering which improves the immunization experience, reduces subsequent non-compliance as a result of minimizing injection induced anxiety and pain and it also maintains the ethical principle of 'do no harm.'" (Gidudu, Walco, et al. 2012). Interventions to enhance vaccine comfort promote vaccine acceptability for all populations which may improve vaccine participation and thus herd immunity and/or population disease prevention.

Brighton has differentiated acute pain from the actual needle stick and vaccine injection which occurs upon vaccine receipt, from delayed pain which occurs within minutes to hours from inflammatory responses. Delayed pain has three distinct categories defined as persistent pain, including at rest, pain with movement or touch and the impact of pain on functioning. Per Brighton, these differing symptom groups may be independent or potentially related. Existing literature evaluates interventions to mitigate immediate pain with injection, but only minimal research has been performed evaluating interventions to decrease local site pain and inflammation symptoms for delayed pain after vaccine receipt, and for most of this work, pain evaluation was a secondary endpoint and the populations were mostly infants and children.

Influenza vaccine receipt is mandatory for military service members. We reviewed the package inserts of US manufacturers of inactivated injectable influenza vaccine (IIV), and all identified injection site pain as the most common adverse reaction in pre-license studies (Afluria, 2015, Fluarix, 2014, Flublock, 2014, Flucelvax, 2014, Flulavel, 2014, Fluvirin, 2014, Fluzone, 2014). Local site pain has also been specifically identified as a vaccine safety concern by military populations (Porter, Bowens, Tribble, Putnam, Sanders & Riddle 2008).

In practice, non-steroidal anti-inflammatory medications (NSAIDS) are frequently recommended by providers to mitigate delayed post vaccination local and systemic vaccine adverse effects (Defense Health Agency, 2004). There is some literature to evaluate the effectiveness of this practice, primarily with paracetamol, but little research has been performed in adult populations. Additionally, the impact on antigen immunogenicity not been adequately researched. It is known that paracetamol impairs immune response in children post vaccine receipt and for this reason, it is not recommended to routinely treat children for systemic adverse effects (Prymula, et al. 2009).

The Brighton Collaborative has published case definitions for immunization site pain both acute and delayed, and guidelines for collection, analyses, and presentation of immunization safety data (Gidudu, Walco et al. 2012). They have additionally provided the same resources for evaluation of swelling, induration and local site reaction. Pain evaluation differentiates persistent pain, pain with movement or touch and impact on function, which is particularly pertinent to a service member whose daily requirements include demanding physical activity. Within military lore, pushups are reputed to be an effective intervention to decrease post-vaccine local site discomfort. There currently is literature to support enhanced antibody response to exercise and the use of exercise as a vaccine adjuvant. However, little research has been performed to evaluate exercise as a nonpharmaceutical intervention for pain management. Multiple acute pain management interventions have been evaluated but little research has been performed for delayed pain. There also has been little evaluation on the immunologic impact on antibody formation with use of NSAIDS. Prophylactic use of oral analgesics are not endorsed for delayed pain management but it is commonly recommended in practice to patients who express concern or who report prior negative experiences (Gidudu, Walco et al. 2012). Clinical research to determine if antibody response in adults is affected by NSAIDS may elucidate best practice recommendations and as previously noted, interventions to address vaccine safety concerns could improve acceptability and participation thus leading to healthier populations.

Literature Review

The initial literature review search encompassed three topics of interventions for delayed pain from immunization, exercise as an adjunct for pain mitigation and serologic effects of NSAIDS, all which yielded sparse results. The search was widened to include any pain interventions, exercise effects on immunization and impact on immune response with NSAIDS or paracetamol. Only English language results were considered and article reference lists were also reviewed for pertinent articles.

Pain interventions

The interventions trialed to address pain can be categorized into three classes of interventions: pharmacologic, nonpharmacologic, or combined. Nonpharmacologic included psychological techniques, physical techniques and devices. Acute immediate pain associated with the injection has been primarily the target of research with limited information found on interventions for delayed pain. Multiple interventions have been trialed to address immediate pain during injection of vaccine, primarily with children and infants. These include topical gels, sprays or creams (Abuelkeir et al. 2014, Berberich & Landman, 2009, Cohen & Hulubkov 1997, Dilli, Kucek, Izzet, & Daller 2009, Mawhorter, Daugherty, Ford, Hughes, Metzger, & Easley, 2004; Taddio, Appleton et al. 2010; Taddio, Lord et al. 2010), manual pressure, breast feeding (Dilli et al., Shah, Taddio & Reider 2009) oral sucrose solutions (Dilli et al., Shah et. al.) sucking swaddling, positioning, singing, psychological interventions of breathing, suggestion, child or parent directed distraction, bubble blowing, nurse directed distraction, parent coaching, cognitive behavioral interventions (Sparks 2001). Distraction techniques including music (Krsitjansdottir, 2011), ipads, relaxation and guided imagery (Kristjandottir; Nillson, Forsner, Finnstorm & Morelius, 2015) holding of infants, tactile techniques (Nikashima, Harada, Okayama & Kajii 2013, Taddio & Lord et al.,), and rattles and devices such a "shot blocker" or various devices (Berberich et al., Cobb & Cohen 2009). Taddio, Ilserch et al. (2009) published review of injection techniques to reduce pain. Shah et al., Taddio, Appleton et al., Taddio, Chambers et al. 2009, Taddio, Ilersich et al., Chambers, Taddio, Uman & McMurtry (2009) published extensive review articles and practice guidelines for acute pain. Most research interventions were targeted towards children or infants and few trials included the adult population (Maiden, Benton & Bourne 2003, Nikashima et al. and Taddio, Lord et al.). A fourth article by Russell, Nicholson & Naidu (2014) assessed a pharmacologic and a nonpharmacologic intervention however this was for a nonvaccine intramuscular injection. Research articles with interventions for acute pain only for infant population only were not further reviewed.

Pharmacologic interventions consisting of topical gels, creams and sprays and were generally found to be effective compared to placebo (Abuelkeir et al. 2014, Dilli et al. 2009) or superior to self-distraction (Taddio & Lord et al. 2010). Nonpharmacologic interventions included application of manual pressure (Nikashima et. al, 2013), prewarming of vaccine (Maiden et al. 2003), freezing needles (Hogan, Kikuta & Taddio, 2010), and devices such as shotblocker (Cobb & Cohen 2009), all which were ineffective. Psychological techniques such as distraction demonstrated benefit (Krsitjansdottir, 2011) although less than other techniques (Taddio and Lord, 2010).

Russell, Nicholson & Naidu's (2014) research demonstrated benefit of an intramuscular lidocaine (lignocaine) and "Mr. Buzzy" however this was with IM benzathine PCN receipt and was not randomized. Mr. Buzzy is a device which applies cold and vibration and is marketed for immunization pain, however the research data located for this device was related to venipuncture or for nonimmunization intramuscular injections, and none was found with key word searches or on the list cited on their own marketing product web site.

Exercise effects

Data on exercise as an adjunct to serological response to immunization is present. The results appear to vary based on the vaccine, age of the cohort, and the type of exercise tested.

Vaccines studied included influenza, pneumococcal, meningococcal, varicella, Tetanus/diphtheria.

Serological response to individual influenza vaccine strains varied within individual study Groups.

Elders, who have the most immunesenescence, were most likely to demonstrate enhanced antibody response to exercise interventions. In some studies with half dose vaccine given to younger participants, serologic response to exercise was more prominent. Younger healthy individuals receiving full doses of vaccine were less likely to demonstrate benefit from exercise interventions. Younger healthy individuals receiving half dose vaccine did demonstrate benefit. One study also demonstrated benefit to psychological stress. Gender differences in response were also noted in differing studies, but no single trend was consistent.

Types of exercises trialed included eccentric exercises such as arm curls and lateral raises, use of resistance bands, and aerobic forms with ergometers, walking programs, elite swimmers, triathletes, flexibility regimens and Tai Chi. Other variants included exercise intensity and timing, such as immediately preceding vaccine receipt vs. an overall program of fitness without specific temporal correlation to receipt.

Site pain was evaluated in some of the studies involving eccentric exercises. Of interest, in the study by Campbell, Edwards, Ring, Drayson Bosch, Inskip et al. (2010), the exercise group reported increased immediate and delayed pain at 48 hours compared to control group. In another study using similar exercise treatments, the exercise group reported more pain at every time interval of immediate, 6 hour and 24 hours than the control group (Edwards, Burns, Allen, McPhee, Bosch, Carroll et al., 2007). Another exercise intervention group who used arm bands for exercise and received pneumococcal vaccine also reported more pain compared to controls. (Edwards, Pung, Tomfohr, Ziegler, Campbell, Drayson, et al. 2012).

In another trial, young healthy adults performed three arm exercise movements with resistance bands or performed no exercise and then received either half dose or full dose of pneumococcal vaccine. The exercise groups demonstrated superior antibody levels compared to the either the half or full dose resting groups. (Edwards, Pung, et al. 2012).

Edwards, Kate M, Campbell, John P., Ring, Drayson, Bosch, & Downes et al. (2010) also evaluated exercise intensity as an adjuvant to half dose influenza vaccine. The participants were assigned to a 60%, 80% or 110% of their predetermined capacity to perform lateral arm raises and biceps curls. The antibody response to the half dose vaccine was demonstrated in some but not all groups, and the antibody response did not vary with exercise intensity.

Campbell et al. (2010) evaluated effects of vaccine timing on the efficacy of eccentric exercise with the lateral raises arm biceps curls in a young adult cohort who then received influenza vaccine. In this study, no serological benefit was noted and it was attributed to the age of the cohort.

Edwards, Burns, Reynolds, Tracy, Carroll, Drayson, & Ring (2006) also evaluated exercise via ergometer, vs. a psychological stress intervention of a series of complex arithmetic tasks in a competitive contest with rewards and aversions prior to IIV receipt. Compared to the control group, both the exercise stress group and the psychological stress group demonstrated enhanced immune response compared to the control group.

Edwards Burns Adkins, Carroll, Drayson & Ring (2008) evaluated the antibody response to meningococcal vaccine in young adult subjects who were exposed to either exercise or mental stress. Men but not women demonstrated enhanced effect to both interventions.

Kohut, Arntson, Wanglok, Rozebloom, Yoon, & McElhaney (2004) demonstrated moderate exercise 3 times a week for 10 months by a cohort over age 65 improved antibody titer response to influenza vaccine compared to age matched controls. Additionally antibody titers were comparable to young subjects for one serotype in this small study.

Shuler, Lloyd, Clapp, Abadie, & Collins (1999) studied found no differences in antibody response to two strains of influenza virus vaccine in college students categorized by fitness level.

In another trial healthy elders were randomized to perform Tai Chi for 25 weeks or receive health education. Prior to receipt of Varivax vaccine, the Tai Chi Group demonstrated levels of cell mediated immunity (CMI) comparable to levels induced by vaccine in the health education Group. After vaccine receipt, their varicella zoster specific CMI was comparable to levels previously observed in adults 30 years younger (Irwin, Olmstead, & Oxman, 2007).

Shuler, Leblanc, & Marzilli (2003) identified enhanced antibody response to influenza vaccine in elders who exercised based on a self-reported activity scale. Antigen formation was significantly greater for one component of the vaccine.

Randive, Cook, Kappus, Yan, Lane, Woods et al. (2013) evaluated an acute aerobic exercise intervention in an older adult population and its effect on influenza vaccine titers. A benefit was seen only in women and only to the H1N1 strain of the trivalent vaccine.

One study introducing a 16 week walking program as a lifestyle intervention to sedentary women who then received pneumococcal vaccine did not demonstrate benefit to antibody response (Long, Ring, Bosch, Eves, Drayson, Calver et al. (2013).

Long, Ring, Drayson, Bosch, Campbell, & Bhabra et al. (2012) evaluated brisk walking in a young cohort and an over age 60 cohort prior to receipt of pneumonia vaccine or influenza vaccine. Neither cohort demonstrated increased antibody response to either vaccine.

Kohut, Nickolaus, Russell & Cunnick (2002) evaluated lifestyle including exercise in elders. Serology for IgG and IgM were greater in the vigorous exercise group.

Woods, Keylock, Lowder, Viera, Zelkovich, Dumich et al. (2009) evaluated effects of aerobic exercise and a flexibility exercise group in a previously sedentary elderly population. The exercise intervention was started 4 months prior to vaccine receipt and continued for 6 months after and resulted in enhanced sustained antibody levels in the aerobic group. The vaccine receipt timing was correlated with exercise session.

Gleeson, Pyne, McDonald, Clancy, Cripps, Horn et al. (1996) evaluated antibody response to pneumococcal vaccine in elite swimmers in an intense training period. They found no decrease in immune response compared to age and sex-matched peers.

Whitman, & Blannin (2003) evaluated differences of heavy training vs. light training on a cycle ergometer to influenza vaccine resulted in no effect on the kinetics of the IgG response. The vaccine receipt timing was correlated with exercise session.

Bruunsgaard, Hartkopp, Mohr, Konradsen, Heron, Mordhorst, & Pederson, (1997) found no difference in antibody titers in men after Td and pneumococcal vaccine receipt immediately after completion of a one-half iron man compared to controls.

Keylock, Lowder, Leifheit, Cook, Mariani, Ross et al. (2007) found higher antibody, but not cell – mediated, responses to vaccination in high physically fit elderly to two of three strains of fluzone and Th2 response to tetanus toxoid.

Systemic pharmacologic interventions for delayed pain reduction

NSAIDS or acetaminophen class medications are routinely recommended to reduce local and systemic adverse effects of immunization (Defense Health Agency, 2004). Pharmacologic interventions have been evaluated for reduction of delayed adverse events including fever, fussiness, and local site reactions, but there is a paucity of data on serological response, adult populations and use of NSAIDS.

Ibuprofen was evaluated in infants who demonstrated decreased unusual crying in addition to decreased local reactions and some systemic reactions, but not fever in infants who received DTaP (Diez-Domingo, Planelles, Baldo, Ballester, Nunez, Jubert et al. 1998).

Jackson, Dunstan, Starkovich, Dunn, Yu, Nelson, et al. (2006) compared prophylactic treatment with acetaminophen or ibuprofen for local reaction adverse effect mitigation from the fifth dose of DTaP in children. The investigators found no benefit to either medication regimen. Pain and fever were secondary endpoints and also did not demonstrate benefit.

Hayat, H. Humera, Khan, Parwez, & Hayat, G. (2011) evaluated paracetamol in infants who received DTP which demonstrated decreased fever and fussiness but no impact on site reactions.

Rose, Jeurgens, Schmoele-Thoma, Gruber, Baker & Zielen (2013) demonstrated paracetamol starting at vaccine receipt decreased fever in infants but not toddlers who received HBV-IPV/Hib, PCV-7 & DTaP. The paracetamol also tended to prevent site reactions but the authors felt it was not significant compared to the controls. Yalcin et al. demonstrated a single prophylactic dose of acetaminophen had no benefit on systemic reactions, or local site reactions of swelling, pain or erythema.

Doedee, Boland, Pennings, de Klerk, Berbers, van der Klis et al. 2014 evaluated the serological effects of paracetamol in adults on hepatitis B vaccine receipt. paracetamol was given starting either at the time of vaccine receipt (prophylactic) or six hours later (therapeutic). A control group received none. The prophylactic group demonstrated a 26% reduction in antibodies compared to the control group. The therapeutic group was not different from the control group. All groups achieved protective levels.

Prymula, Siegrist, Chlibek, Zemlikova, Vacknova, Smetana et al. 2009, studied the effect of prophylactic paracetamol in infants receiving pneumococcal/H. flu protein D conjugate (PHiD-CV), and a diphtheria, acellular pertussis, hep B, inactivated polio virus, and H. flu type B (DTPa/-HBV-IPV-/Hib). The paracetamol group did demonstrated reduced frequency of significant fever, but this event was overall rare. The paracetamol group also demonstrated lower antibody responses compared to controls, which persisted after boosting for several of the vaccines.

Das, Panigrahy & Naik (2014) performed a systematic literature review and stated they felt there is a favorable benefit to prophylactic antipyretic administration for both local and systemic symptoms. They cited lack of sufficient RCT data or based on Prymula solitary research and cited four points related to clinical and epidemiologic data and known immunological processes.

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9.3

Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions/hypotheses

The purpose of this clinical investigation is to evaluate the efficacy and immunological effects of interventions to decrease local injection site inflammation symptoms of erythema, edema and pain after vaccine receipt.

Interventions to mitigate acute pain associated with vaccine have been studied but little research has been performed to quantitatively evaluate interventions for mitigation of local site effects and delayed pain associated with vaccine receipt. The clinical investigation would address gaps in the literature concerning both management and serological effects of the interventions.

HYPOTHESES/RESEARCH QUESTIONS:

1. At each time point, mean pain scores as indexed by the BPI will be equivalent across groups.
2. At each time point, mean objective signs of inflammation will be equivalent across groups.
3. At each time point, mean serologic response to immunization will be equivalent across groups.

SPECIFIC AIMS/SIGNIFICANCE:

Interventions to mitigate acute pain associated with vaccine have been studied but little research has been performed to evaluate interventions for mitigation of local site inflammation effects and delayed pain associated with vaccine receipt in adults. Delayed site pain has been specifically identified as a vaccine safety concern by military populations (Porter et al., 2008) and use of the pushup type compound exercise to decrease delayed pain is reputed to be part of military folklore.

Addressing concerns of safety and comfort promotes acceptance of both required and optional vaccines. This could increase vaccine rates achieving public health immunization and disease prevention goals. Previous clinical studies support exercise enhances antibody response in some populations. Little research has been performed on the serologic impact of systemic pharmaceuticals after immunization receipt. Paracetamol has been demonstrated to decrease immune response in children but little research has been performed on the serological impact in adult populations. Additionally the serological impact of NSAIDS, a medication class with much greater anti-inflammatory effects than paracetamol, has had little evaluation. Serologic data could provide guidance for best practices.

9.4 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

This study utilizes a prospective randomized control trial design. Participants will be randomized to one of three treatment arms and both study personnel and study participants will be blind as to the type of medication received (NSAID or placebo). Participants will be assessed during 3 visits, over a 3 to 4 week period.

9.5 Target Population:

Describe the population to whom the study findings will be generalized

Male and female active duty service members who will be receiving influenza vaccine as required per DoD policy.

9.6 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

MILITARY RELEVANCE: Address gaps in current literature related to:

1. Interventions to decrease signs of inflammation, which could impair activity performance
2. Interventions to decrease delayed pain concerns of soldiers which have potential to
 - a. increase vaccine acceptability
 - b. decrease vaccine anxiety
 - c. decrease vaccine hesitancy for optional vaccines for other populations for whom other vaccine is optional such as dependents . For example HPV is recommended for all males and females through age 26, and it is an optional vaccine for military service members. This vaccine is a very effective anticancer vaccine, but currently full series completion rates remain low.

Reference: <http://www.cdc.gov/vaccines/who/teens/vaccination-coverage.html>

10.0

Study Procedures, Data Management, and Privacy

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

Study briefing and consents to be performed by IHB staff prior to study enrollment as follows:

1. Recruitment

WRNMMC site: Recruitment posters will be placed at influenza drive sites and on the WRNMMC Intranet.

WAMC site: The principal investigator, associate investigators, study nurse, and DHA-IHB research staff will recruit and enroll subjects, presenting the study content to potential participants. Investigators at WAMC will retain original signed consents. Participants will be counseled that a decision not to enroll will not affect their standard of care and is independent of their decision to receive the influenza vaccine.

Recruitment Process Details:

Recruitment posters (see attachment A) will be placed at influenza drive sites. At Fort Bragg this will be the 82nd SRC. The research staff will contact the NCOIC at the 82nd SRC to identify scheduled dates of influenza vaccinations. The research staff will be present at the 82nd SRC during scheduled dates of influenza vaccinations. The research staff will provide a briefing at the 82nd SRC just prior to or during influenza vaccination drive. The briefing will notify individuals who will be receiving influenza vaccine per their military requirements of the opportunity to participate in the voluntary study. The research staff will meet with soldiers at the SRC and query if any senior enlisted (E5-E9) or officers (O1-O-10) are present. The potential subjects will be briefed in 3 separate groups consisting of lower enlisted (E1-E4), senior enlisted (E5-E9) and officers (O1-O-10) to eliminate potential for coercion, and the groups not being currently briefed will be requested to leave the immediate area for the duration of the brief. The research staff will sequentially rotate the order of groups briefed to decrease the potential for inadvertent introduction of age or socioeconomic bias as there will be a limited number of participants accepted each day. The research staff will then read the briefing script (see attachment: k).

The briefing will describe the following study details:

- The study description stating that we will assess pain at the injection site after flu vaccination to develop methods of decreasing vaccination pain.
- Participants receiving an influenza vaccine today may qualify.

Participation includes:

- One (1) initial visit prior to receiving your flu shot and two (2) follow-up visits.
- Vaccination site pain and appearance assessments.
- Random assignment to Ibuprofen, placebo or exercise intervention.
- One venous blood draw for visit #1 and #3 (two total) and #1 or #2 POC finger sticks for the exercise intervention group (first POC will attempted to be collected from the venous specimen blood draw).
- Abstinence from pain relief medications and alcohol for 2-3 days after receipt of vaccine, until the second visit is completed.

- Participants who complete the study will receive financial compensation for the lab draws.

Screening & Consent: WAMC & WRNMMC

Prior to recruitment, as part of Standard of Care, the individuals who volunteer to be considered for this clinical study will likely have completed the WAMC Adult Influenza Screening form which will be reviewed per standard organizational procedures to determine if the subject is appropriate to receive IIV. This form will not be collected or reviewed by the research staff until after the subject is consented.

Individuals who are scheduled for influenza vaccine receipt and are interested in the study will meet with the research staff at the IHB research office adjacent to the SRC prior to receipt of vaccine to obtain informed consent. The research staff will provide a description of the study requirements including three assessment visits, receipt of one of three interventions of oral medication, oral placebo, or performance of pushups at a minimum of 80% of their last APFT in one session, completion of 2 symptom diaries, and collection of two blood specimens for serology and 1-2 POC finger stick specimens for the exercise intervention group. Persons wishing to be considered for participation will be screened for eligibility by the research staff by completion of the Study Eligibility Screening Form (see attachment #B). The Eligibility Screening Form does not contain identifying information. All sections of the form will be completed prior to consent with the exception of the question regarding pregnancy testing. Females of childbearing age will be required to complete a pregnancy test after being consented. After the subject is consented, the previously completed Adult Influenza Screening forms will be reviewed by the research staff to ensure congruence with the Study Eligibility Screening Form and confirm no contraindication to vaccination exists. In the event no influenza screening form was completed at the SRC, the research staff will complete such screening form after informed consent is obtained. Also following consent, the research staff will review the candidates' current medication list for medication classes as cited in the exclusion criteria and counsel the candidates on any medications they will need to abstain from for the first 2-3 days of the study, until Visit 2 is completed. Prescription pain medications ordered on a routine basis will be considered necessary and the medication benefits to the patient will supersede study participation, thus making the candidate ineligible. Prescription pain medications ordered on an as needed basis are acceptable if the participant states they anticipate they would not be requiring the medication or accept abstinence from the medication for the first 2-3 days of the study, until Visit 2 is completed. Any question by the study staff concerning the appropriateness of a current subject medication will be discussed with the principal investigator and /or associate investigator to determine if patient can continue in the study.

The research staff will also advise the candidate that all over-the-counter medications need to be avoided or reviewed and approved by research staff for anti-inflammatory or pain relieving properties prior to use. The research staff will contact the PI or AI for any questions or clarification as needed. Any new prescription medications started after the start of the study will be considered necessary and the benefits to the patient will supersede the study. Enrolled subjects identified as having exclusion criteria after reviewing the screening forms will be counseled they are ineligible for continuation in the trial and referred to back to SRC providers to follow their usual protocols for influenza vaccine receipt.

Subjects will receive counseling from the research staff to meet the established guidelines for informed consent: to include a statement of the purpose, randomization process, use of placebo control, use of prescription dose ibuprofen, foreseeable risks, potential benefits, research staff contact information, rights and responsibilities, and that participation is voluntary. After consent, subjects will be asked for contact information and consent to contact by telephone or email for clarification of medical history, and /or prior immunizations and/or adverse events and to remind subjects of follow-up visits. During the consent process the research staff will also provide counseling and the participant will complete the HIPAA form. The data and specimens collected may be of significant utility for future studies. Subjects will be asked for consent for future study to include use of collected specimens and use of data collected. Subjects will be asked for permission to be contacted for future studies and the participant will have the option to consent or refuse permissions for future studies without effect on participation in this proposed study. Subjects interested in study participation will complete the study consent/HIPAA form (see attachment C.) with required initials, signature, and date.

3. Randomization and Treatment Arms: WAMC & WRNMMC

Once fully enrolled, the participants will then be randomized to treatment arms Group A, Group B or Group C. A random number sequence will be generated via SPSS. The first third of the random number sequence will be assigned to Group A, the second third to Group B and the remaining third to Group C. The sequence will then be reordered in ascending order (i.e. 1 = Group C, 2 = Group A, 3 = Group A, 4 = Group B...). As individuals are recruited and consented they will be given the next number in the sequence and thus are randomly assigned. Should dropouts occur, replacement participants will be assigned to the same group as the participant whom they are replacing. The replacement participant's Study ID number will be the next available after the required 216. For example, if participant 35 drops out prior to completion and the individual was assigned to group C, then a replacement will be recruited and assigned the study ID number 217 and group C.

Complete data set will be defined as completion of the three evaluations, all laboratory specimen collection, reported receipt of a minimum of four doses of study drug for Groups A&B, and the exercise intervention at 80% or above APFT for Group C in a single session or a lactate measurement of 15mmol/L or greater 3-15 minutes post exercise should the 80% threshold not be achieved.

Group A and Group B will receive either ibuprofen 800 milligrams orally three times a day for 48 hours (6 doses) or a placebo starting immediately after vaccine receipt and the initial dose will be observed by the research staff (the participants will self-dose subsequent doses and record in a diary time of receipt). Group C will perform the exercise intervention.

The research staff will provide the study drug to the participants enrolled in the pharmacologic treatment arms Group A and Group B. The medication will be blinded into Group A or Group B and dispensed by the research pharmacist. Only the research pharmacist will know which is ibuprofen and which is placebo. The research staff will provide instruction on the oral medication dosing, frequency and a recommendation to take with food or milk. The participant will be provided with a snack such as crackers for receipt of the first dose of study drug. The Group C will also be provided the same snack opportunity. The participants will be given the Visit 1 Vaccination Diary Card (attachment D) measurement tools, how to measure and the documentation requirements will be explained by the r. The participants will also be instructed not to take any topical or oral over the counter medications for 2-3 days of the study, until Visit 2 is completed unless they verify the medication does not contain a pain relieving and anti-inflammatory medication with a pharmacist and/ the study staff. This includes counterirritants such as menthol, methylsalicylate, camphor menthols, capsiacins, acetaminophen, opioids, tramadol, NSAID or salicylate containing products.

Initial Evaluation: Visit 1 (time 0)

The research staff will complete the Visit 1 Site Evaluation and Vaccination Capture Form (attachment E), Demographic and Military History Survey (attachment F), a Brief Pain Inventory (attachment G), and visit 1 Health Status Questionnaire (attachment H). The subjects will be provided computer use to access their previous APFT score which will be visually confirmed by the research staff. The data collected will be consistent with the Brighton standards for immunization research for subjective pain assessment and objective site assessment for local reaction swelling and induration. Subjects will identify their non-dominant arm for assessment and vaccine receipt. In the event the assessment reveals the non-dominant arm is unsuitable for vaccine receipt (new tattoo, abrasion, etc.) then the opposite arm will be assessed and used for vaccination. If the subject states they are ambidextrous and do not have an identifiable arm dominance, the left arm will be used. The research staff will perform assessments of the patient arm to include site inspection, arm circumference measurement at mid deltoid of the upper arm to receive vaccine, and a site photograph. An identifying label with the subject number will be included in the site photograph. To facilitate data reliability, arm assessment and measurement will be performed by the same research staff for a given participant when possible at the follow-up visits #2 & #3. Laboratory specimen of 10 milliliters for baseline serology will be collected by the research staff or lab personnel and baseline POC testing for lactate for the exercise Group will be performed. Residual blood from the serum collection will be used for the POC lactate if possible, however a fingerstick specimen may be required if this is not successful. The participants will be given the current Influenza Vaccine Information Statement per CDC and provided opportunity for review and to ask any questions.

After completion of these assessments the participants will receive their inactivated injectable influenza vaccine using standard of care technique (see below). For consistency in technique, when possible, all participants will receive their vaccine injection by the same nurse. The research staff will complete vaccine documentation sections of the Adult Influenza Screening Form. The research staff will provide the subject with a completed documentation card for proof of vaccine receipt. All participants will complete a modified Brief Pain Inventory (BPI) for data collection of acute pain during the vaccine receipt. The participants assigned to Group A and Group B will take their study medication immediately after vaccine receipt and this will be observed by the research staff. Study medication will be labeled with subject identification number (SID) and contain 6 doses for 48 hours of medication. The last 5 doses will be taken home for self-administration approximately every 8 hours. The research staff will direct and assist these participants in logging the first dose in the Visit 1 Vaccination Diary Card.

The participants assigned to Group C (exercise) will perform pushups as immediately as possible, but within 15 minutes of IIV receipt and observed by the research staff. The goal will be 80% or above of the subjects reported last APFT score in one session. The number of pushups will be recorded. A finger stick lactate will be collected from the hand opposite to the vaccination arm. within 3-8 minutes, but no more than 15 minutes, of completion of the pushups.

The research staff will notify the research pharmacist of the names and Social Security numbers of participants within 24 hours of enrollment, so the pharmacist may enter into the participant's medical record prescription list they are taking a study medication.

Second Evaluation: Visit 2 (time 48-72 hours)

The subjects will return to the IHB research office within the time frame of 48-72 hours of vaccine receipt. The staff will collect the Visit 1 Vaccination Diary Card and receive receipt of any returned study medication, which they will document the number of missed doses. The subject will complete the Brief Pain Inventory and the staff will complete the Visit 2 Health Status Questionnaire (attachment I). The research staff will perform objective site assessment to include measurement of arm circumference, injection site inspection and measurement any erythema or induration and a site photograph. An identifier with the subject number will be included in the site photograph. For interrater reliability, when possible, the assessment will be performed by the same research staff member who performed the initial assessment.

The subject will receive compensation in the amount of \$50 per blood draw (\$100 total); payments will be made via direct deposit to the subject's banking account or via a \$50 gift card. No compensation will be provided for visit #2 which does not include any type of blood sampling. In the event of significant immunization adverse reaction the patient will be referred by the research staff to follow-up with DHA-IHB as needed. Also the patient may self-refer to DHA-IHB by calling the Fort Bragg office 910-432-4015 or the 24/7 DOD call center number 1-877-438-8222. The 24/7 DOD call center card will be provided to each patient as a contact number for vaccine specific concerns.

Third Evaluation: Visit 3 (time 21-28 days)

The subjects will return to the IHB research office within the time frame of 21-28 days of vaccine receipt. The research staff will collect the symptom diary, and the subject will complete The Visit 3 Health Status Questionnaire (attachment J) and a BPI. The research staff will perform objective site assessment to include measurement of arm circumference, injection site inspection and measurement any erythema or induration and a site photograph. An identifier with the subject number will be included in the site photograph. For inter-rater reliability, as possible, the assessment will be performed by the same research staff member who performed the previous assessments. Serology #2 following the same procedure as visit #1 will be collected. The subject will receive compensation for visit #3. A debriefing by staff will be completed.

Study Medications:

The study medications will be obtained from a national compounding pharmacy for consistency in appearance and to enhance blinding and the medications will be shipped to the research staff. The 800 milligram ibuprofen dose will be dispensed in units of 400 milligrams each. The research staff will then transport the study drugs to Womack research pharmacist who will repackage them and dispense as medication Group A or medication Group B. Only the research pharmacist will be aware of which medication is ibuprofen and which is placebo. The research staff will pick up the study medications from the pharmacist prior to enrollment and will repeat this process as needed to have adequate supplies available. Medication will be batched if needed to ensure potency within manufacturer expiration dates. Medication and placebo containers shall be counted and logged in a spreadsheet upon receipt from the pharmacy. Medication and placebo will remain in the original, pharmacy labeled, tamper resistant container and stored at the research office in a locked cabinet away from moisture, at room temperature (20- 25°C or 66-77°F) until administered by the research nurse. The investigational pharmacy will perform site visits to monitor inventory, storage conditions and documentation. Study medications not used or returned by subjects to the research staff will be returned to pharmacy for destruction. The pharmacist will notate and certify the receipt and destruction of any expired, unused or returned study medications. At the end of the study, the pharmacist will unblind the study and certify the identification of treatment A and B.

Per Micromedex, all of the NSAIDs possess anti-inflammatory, antipyretic, and analgesic properties with overall therapeutic equivalence. Ibuprofen was selected due to its ubiquitous use both prescription and over-the-counter in lower doses such that allergy or intolerance would likely already be known. Although the FDA no longer uses pregnancy categories, ibuprofen was last categorized as Pregnancy Category C in first and second trimester in pregnancy and D during the third trimester. Ibuprofen is used for fever and pain control and for the treatment of several rheumatologic conditions. The mechanism of action most likely produces anti-inflammatory, antipyretic, and analgesic effects by inhibiting the cyclooxygenase enzyme, leading to decreased prostaglandin production and decreased pain and inflammation. The dosing ranges vary by indication from 1200-3200 milligrams/day. The dosing was selected due to the anti-inflammatory effects are more prominent in higher doses enhancing this clinical trials' potential to measure endpoints. The adverse effect potential is minimal due to the short duration of therapy and the safety profile of the medication. The most common adverse effect in an open-label study given to a population with rheumatoid arthritis was epigastric pain in 15% of participants. Those subjects received 3000 mg/day for four weeks duration. A recent FDA advisory raised concerns for increased cardiovascular risks for heart attack and stroke with use of NSAIDs. We consider this risk in the study population to be minimal because compared to general populations this population is overall a young, fit, non-obese cohort who receive consistent recommended preventive care such as lipid screening and management. Additionally, the treatment regimen is only a two day course. The FDA warning states cardiovascular events can occur early in a treatment regimen, the cited course is still in "weeks" not days. Due to the concerns of this risk we will exclude any applicant with a history of cardiovascular disease. In the unlikely event of a clinical emergency requiring the clarification if the

subject received NSAIDs or placebos, the PI or AI can be contacted and discuss if unblinding is necessary and can work with the research pharmacist for unblinding.

The influenza vaccine is not a study medication and participant receipt is per their active duty requirements. During the influenza season, the FDA licensed trivalent or quadrivalent injectable influenza vaccine will be used for all study participants at the Fort Bragg site. The same trivalent or quadrivalent vaccine chosen for a given flu season will be administered throughout the season to maintain consistency of vaccine product for study subjects.

Multisite: WRNMMC-Recruitment, Screening and Consent summary

Recruitment posters will be placed at influenza drive sites and on the WRNMMC Intranet. Active duty males and females age 18 and older.

Prior to recruitment the individuals who volunteer to be considered for this clinical study will have completed the WRNMMC Adult Influenza Screening form which will be reviewed per standard organizational procedures to determine the subject is appropriate to receive IIV. Individuals who are scheduled for influenza vaccine receipt will meet with the research staff at the IHB research office prior to receipt of vaccine for eligibility screening and counseling to obtain informed consent. The IHB Study Nurses will provide a description of the study requirements including three assessments visits, receipt of one of three interventions of oral medication, oral placebo, performance of pushups at a minimum of 80% of their last APFT in one session, completion of 2 symptom diaries, and collection of two blood specimens for serology and 1-2 POC finger stick specimens for the exercise intervention group. Persons wishing to be considered for participation will be screened for eligibility by the IHB Study Nurses by completion of the Study Eligibility Screening Form (see attachment #B). Females of childbearing age will be required to complete a pregnancy test. The previously completed Adult Influenza Screening forms which will be reviewed by the IHB Study Nurses to ensure congruence with the Study Eligibility Screening Form and confirm no contraindication to vaccination exists. The IHB Study Nurses will review the candidates' current medication list for medication classes as cited in the exclusion criteria and counsel the candidates on any medications they will need to abstain from for the first 2-3 days of the study, until Visit 2 is completed. Prescription pain medications ordered on a routine basis will be considered necessary and the medication benefits to the patient will supersede study participation, thus making the candidate ineligible. Prescription pain medications ordered on an as needed basis are acceptable if the participant states they anticipate they would not be requiring the medication or accept abstinence from the medication for the first 2-3 days of the study, until Visit 2 is completed. Any question by the IHB Study Nurses concerning the appropriateness of a current subject medication will be discussed with the principal investigator and /or associate investigator prior to enrollment in the study.

The IHB Study Nurses will also advise the candidate that all over-the-counter medications need to be avoided or reviewed and approved by research staff for anti-inflammatory or pain relieving properties prior to use. The IHB Study Nurses will contact the PI or AI for any questions or clarification as needed. Any new prescription medications started after the start of the study will be considered necessary and the benefits to the patient will supersede the study. Ineligible candidates will be counseled that they are ineligible for participation in the trial and referred to back to their providers to follow their usual protocols for influenza vaccine receipt.

Reference

Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: <http://www.micromedexsolutions.com/> (cited July 10, 2015) Retrieved from : http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/B29A35/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/ABCEE6/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=Ibuprofen&fromInterSaltBase=true&false=null&false=null&=null#

U.S. Food and Drug Administration, (07/17/2015) FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm>

Vaccine Injection Technique:

Injectable immunobiologics should be administered where local, neural, vascular, or tissue injury is unlikely. Use of longer needles has been associated with less redness or swelling than occurs with shorter needles because of injection into deeper muscle mass. Appropriate needle length depends on age and body mass. Injection technique is the most important parameter to ensure efficient intramuscular vaccine delivery. For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. Vaccinators should be familiar with the anatomy of the area into which they are injecting vaccine. Intramuscular injections are administered at a 90-degree angle to the skin, preferably into the anterolateral aspect of the thigh or the deltoid muscle of the upper arm, depending on the age of the patient. A decision on needle size and site of injection must be made for each person on the basis of the size of the muscle, the thickness of adipose tissue at the injection site, the volume of the material to be administered, injection technique, and the depth below the muscle surface into which the material is to be injected. Aspiration before injection of vaccines is not necessary because no large blood vessels are present at the recommended injection sites. All adults who weigh <

130 lbs. (< 60 kg), a 1/2-inch needle is sufficient to ensure intramuscular injection in the deltoid muscle if the injection is made at a 90-degree angle and the tissue is not bunched. For men and women who weigh 130-152 lbs. (60-70 kg), a 1-inch needle is sufficient. For women who weigh 152-200 lbs. (70-90 kg) and men who weigh 152-260 lbs. (70-118 kg), a 1- to 1½ -inch needle is recommended. For women who weigh >200 lbs. (>90 kg) or men who weigh >260 lbs. (>118 kg), a 1½-inch needle is recommended.

All vaccinators will have a completed Injectable Influenza Vaccine Administration Competency assessment. Needle selection will be based on CDC weight recommendations. The vaccine will be shaken thoroughly and administered immediately using aseptic technique. Intramuscular injections are administered at a 90-degree angle to the skin to the deltoid muscle of the upper arm. No aspiration will be performed.

Reference

Centers for Disease Control and Prevention. General Recommendations on Immunization. MMWR 2011;60 (2):15-16.

Human Biological Specimens:

Tissue (blood, blood cells) specimens will be collected at study site(s) under informed consent. Approximately 20mL (1.5 tablespoon) of whole blood will be drawn over two time points from each study participant. Whole blood will be collected in red top vacutainer tubes with clot activator. Each tube will be spun down in the centrifuge to separate the serum from red blood cells. Serum will be collected and aliquots will be prepared for laboratory testing. Hemagglutinin Inhibition Antibody Titer testing will be performed by the Viral and Rickettsial Diseases Department at Naval Medical Research Center (NMRC) in Silver Spring, MD. Any remaining serum at NMRC will be destroyed following completion of assay testing and analysis.

At time of enrollment, a unique study identification number (SID) will be assigned to each participant. Personal identifiers will not be included on any specimen labels to protect the identity of all participants. The label will include the SID, date of specimen collection, visit number, and Need Less Pain Study ID number. DHA-IHB study staff will transport frozen serum samples to Womack Army Medical Center (WAMC) Laboratory. WAMC laboratory staff will receive, package, and ship frozen serum samples on dry ice to NMRC via courier service (e.g., FedEx).

Participants can give an informed consent to approve or disapprove the use of their specimens for future clinical investigation studies. If a study participant gives permission for their serum to be stored and used for future research studies, the study must be an IRB approved addendum, amendment, or protocol. Subjects that give approval for future use will not be contacted or re-consented. The specimens will be stored at a DHA-IHB study site repository. Specimens from a study participant who does not give consent for future will not be stored at a DHA-IHB study site repository after study is complete. These specimens will be destroyed after all testing for this study is complete. Participants, under informed consent, are advised as to how they may have their sample destroyed at any time by contacting the Principal Investigator or other designated study team members. All participants have the right to withdraw from the study at any time. If this occurs, any specimens that are available will be destroyed. Data that has been collected will be maintained in the study records.

When the laboratory testing is complete, results will be sent, listed by subject ID number, to DHA-IHB study staff via email or fax. Identifying information will not be shared with NMRC.

Serum Testing

Hemagglutinin Inhibition Assays (HAI) will be run on serum collected at Visit 1 and Visit 3 at Naval Medical Research Center (NMRC) under the direction of Maya Williams, Ph.D. LCDR, MSC, or her replacement. Specimens from both time points will be paired to run on the same assay. HAI testing will utilize strains matching those included in the inactivated influenza virus vaccine that year (strains will change annually to match IIV vaccine strains).

Influenza virus particles have an envelope protein called hemagglutinin which binds to sialic acid receptors on cells. The virus will also bind to red blood cells causing the formation of a lattice. This process is called Hemagglutination, and is the basis of a rapid assay to determine levels of influenza virus present in a sample. To conduct the assay, two-fold serial dilutions of a virus are prepared, mixed with a specific amount of red blood cells, and added to the wells of a plastic tray. The red blood cells that are not bound by influenza virus sink to the bottom of a well and form a button. The red blood cells that are attached to the virus particles form a lattice that coats the well. (Influenza hemagglutinin inhibition assay, 2009, par 2).

The basis of the hemagglutinin inhibition assay is that antibodies to influenza virus will prevent attachment of the virus to red blood cells. The highest dilution of serum that prevents hemagglutinin is called the HI titer of the serum. If the serum contains no antibodies that react with the influenza strain, then hemagglutinin will be observed in all wells. Likewise, if antibodies to the virus are present, hemagglutinin will not be observed until the antibodies are sufficiently diluted. (Influenza hemagglutinin

inhibition assay, 2009, par 5). Hemagglutinin measures the relative concentration of antibody in serum and is expressed as Titer. (Immunology Laboratory: Hemagglutinin).

Whole Blood Lactate Testing (DHA-IHB Study Site)

A Lactate meter will be used to test the exercise group for lactate readings. Two lactate tests will be performed for the exercise group at Visit 1, both pre and post Influenza vaccination. The first lactate reading will be taken after the blood draw. Residual blood from the serum collection will be used for the lactate testing if possible; however, a finger stick specimen may be required if this is not successful. Approximately 5uL of blood is collected for the lactate test. The second lactate reading will be obtained from a fingerstick from the hand opposite to the vaccination arm, ideally within 3-8 minutes after the study subject completes pushups.

Lactate is mainly produced in muscle cells, erythrocytes and brain cells and is metabolized by the liver. Lactate, presented as an anion in blood, is an end product of anaerobic glucose metabolism and plays an important role in acid-base balance in the body. Lactate is used as a biochemical indicator of lactic acidosis. As lactate concentration increases in blood during exercises due to lack of oxygen, lactate can be measured to evaluate physical performance or to establish a proper intensity of exercise. (Kawachi 1989, Kinoshita 1995, Westgren 1995, and Shimojo 1993).

Change in lactate can be found in light and moderate exercise. In performing a maximal exertion effort lasting 30-120 seconds peak values of 15-25mmol/L may be observed 3-8 minutes post-exercise with POC testing (Goodwin, Harris, Hernandez & Gladden, 2007). The lactate analyzer, which uses microliters of blood, will help provide a measure of muscle exertion by the exercise intervention group.

Specimen Tracking and Storage at Study Site

Study participants that give informed consent for future use of serum will be stored at a DHA-IHB repository. Electronic inventory of samples will be maintained in the DHA-IHB Specimen Tracker application. Specimens will be identified by the unique SID assigned to the participant. Specimen Tracker will capture the location of each tube by SID and display each specimen's freezer location, specimen type, visit number 1 or 3, date of collection and consent for future use.

Specimens will be stored indefinitely after the completion of this study unless a subject requests the destruction of his/her specimens. A subject may request in writing to the Principal Investigator his/her desire to have specimens destroyed.

Sample Shipment

As mentioned above, Womack Army Medical Center Laboratory will ship specimens to Naval Medical Research Center Head, Viral and Rickettsial Diseases Department at Naval Medical Research Center (NMRC) in Silver Spring, MD, annually for the duration of the protocol. The specimens will be shipped frozen on dry ice via courier service. Each specimen will be labeled with a unique study ID number and protocol study code.

Reference

Virology.ws. Influenza hemagglutinin inhibition assay. (2015). Available at: <http://www.virology.ws/2009/05/27/influenza-hemagglutinin-inhibition-assay/>. Accessed August 12, 2015.

Medicine.mcgill.ca. Immunology Laboratory: Hemagglutinin. (2015). Available at: <http://www.medicine.mcgill.ca/physio/vlab/immun/hemag.htm>. Accessed August 12, 2015.

Goodwin, M., Harris, J., Hernandez, A., & Gladden, L. (2007). Blood Lactate Measurements and Analysis during Exercise: A Guide for Clinicians. *Journal of Diabetes Science and Technology*, 1(4), 558-569.

Owles, W. (1930). Alterations in the lactic acid content of the blood as a result of light exercise, and associated changes in the co₂-combining power of the blood and in the alveolar co₂ pressure. *The Journal of Physiology*, 69(2), 214-237.

Lactate Pro Test Strip Instructions:

Kawachi M, (1989). Lactate. *Japanese Clinical Medicine*, 47:439-495.

Kinoshita K, Maeda E., & Yoshida S. (1995). The measurements of blood lactate concentration and its age change in days on healthy infant. *Japan Journal of Clinical Pathology*, 43: 1071-1076.

Westgren, M., Divon, M., Horal, M., Ingemarsson, I., Kublickas, M., Shimojo, N., & Nordström, L. (1995). Routine measurements of umbilical artery lactate levels the prediction of perinatal outcome. *American Journal Of Obstetrics And Gynecology*, 173(5), 1416-1422.

Shimojo N, Naka K., Uenoyama H., Yoshioka K, & Okuda K (1993). Electrochemical assay system with single use electrode strip for measuring lactate in whole blood. *Clinical Chemistry*, 39: 2312-2314.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, and how the data will be operationally measured.

Brighton's case definition of pain describes pain that develops in response to a vaccine at or near an injection site as "immunization site pain" (Gidudu, Walco et al., 2012). This includes "acute" pain in response to the needle and "delayed" which develops in minutes to hours following vaccination and acute pain. It does not include myalgia or arthralgia pain.

There are three levels of diagnostic certainty and pain is differentiated as:

1. Persistent including at rest
2. Pain with movement or touch
3. Pain with impact on functioning.

Specific pain assessment tools which vary by age Group are recommended by Brighton for evaluation and study of immunization pain. Brighton acknowledges these tools have limited validation for delayed pain but they state they are currently the best available and would be useful for this application. The Brief Pain Inventory (BPI) is a recommended numerical pain scale tool and Su, et al., (2000) validated the tool for measuring injection site pain in a randomized double blind placebo controlled clinical trial. This study randomized participants to one of five vaccine regimens including a saline control. Pain assessment was made at eight time points over a two day period after injection.

The Brighton Collaboration also has developed case definitions for swelling, induration and local reactions differentiated into 3 levels of diagnostic certainty. (Gidudu, Kohl, et al., 2008, Kohl, et al. 2007, Kohl, et al., 2007). The measurement tools the collaboration developed for collecting data for each case definition developed by Brighton will be utilized. The tools have been adapted to reduce redundancy.

References:

Gidudu, Jane, Kohl, Katrin S., Halperin, Scott, Hammer, Sandra Jo, Heath, Paul, Hennig, Renald et al. (2008). *A local reaction at or near injection site: Case definition and guidelines for collection, analysis and presentation of immunization safety data*. Vaccine 26 (2008) 6800-6813.

Gidudu, Jane F., Kohl, Katrin S., Halperin, Scott A., Hammer, Sandra Jo, Heath, Paul, Hennig, Renald et al. (2008). *A local reaction at or near injection site: Case definition and guidelines for collection, analysis and presentation of immunization safety data*. Vaccine 26(2008) 6800-6813.

Gidudu, Jane F., Walco, Gary, A., Taddio, Anna, Zempsky, William T., Halperin, Scott A., Calugar, Angela et al. (2012). *Immunization site pain: Case definition and guidelines for collection, analysis, and presentation of immunization safety data*. Vaccine 30(2012) 4558-4577.

Kohl, Katrin S., Walop, Wikke, Gidudu, Jane, Ball, Leslie, Halperin, Scott, Hammer, Sandra Jo et. al. (2007). *Swelling at or near injection site: Case definition and guidelines for the collection, analysis and presentation of immunization safety data*. Vaccine 25 (2007) 5858-5874.

Su, L., Tucker, R., Frey, S.E., Gress, J.O., Chan, I. S.F., Kuter, B.J., Guess, H.A. (2000). *Measuring injection-site pain associated with vaccine administration in adults: a randomized, double-blind, placebo-controlled clinical trial*. Journal of Epidemiology and Biostatistics. 2000, 5(6):359-365.

Variables/Data Points:

Figure 1. Table of Variables/Data Points

Variable	Data Source
Pain	BPI
Erythema	Collection tool, photo
Edema	Collection tool, photo

Induration	Collection tool, photo
Serological response to antigens	Lab serology
Exercise	Lactate, collection tool

10.3 At any point in the study, will you request, use, or access health information in any form, including verbal, hard copy and electronic?

☒ Yes ☐ No

10.4 Review the definitions below and respond to the following two questions. If you are not sure of the answers, email DHA.PrivacyBoard@mail.mil for assistance.

The *Military Health System (MHS)* is defined as all DoD health plans and DoD health care providers that are organized under the management authority of, or in the case of covered individual providers, assigned to or employed by, the Defense Health Agency (DHA), the Army, the Navy, or the Air Force

***MHS workforce members* are employees, volunteers, trainees, and other persons whose conduct, in the performance of work for the MHS, is under the direct control of the MHS, whether or not they are paid by the MHS.**

***MHS business associates* are persons or entities that provide a service to the MHS and require protected health information (PHI) to provide the service.**

Are you an MHS workforce member?

- ☒ Yes, I am an MHS workforce member
☐ No, I am not an MHS workforce member

Are you an MHS business associate?

- ☐ Yes, I am an MHS business associate
☒ No, I am not an MHS business associate

10.5 Have you consulted with an MHS data expert to determine the data elements required for your study?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (DHA.PrivacyBoard@mail.mil)

- ☐ Yes, then complete the questions below according to the data consult
☒ No, then complete the questions below according to the best of your knowledge

10.6 Indicate how you will request data from the MHS. Select all that apply.

- ☐ Talking with MHS health care providers or MHS health plans about specific research participants
☐ Obtaining MHS hard copy records specific to research participants
☒ Obtaining data from an MHS information system(s)

10.7 If you are obtaining data from an MHS information system(s), indicate whether you plan to receive a data extract or whether you plan to access an MHS information system directly to create a data set.

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should

be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

- ☐ Data Extract
☒ Access

10.8 Do you intend to request de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:

- 1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
- 2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

☐ Yes ☒ No

10.9 Indicate the MHS information system(s) from which you will seek to obtain data

If you do not know which system(s) contains the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or request guidance from an MHS data expert at: **DHA.**

PrivacyBoard@mail.mil.

Below is a list of commonly used MHS systems. If the system from which you seek to obtain data is not listed below, list the name of the system in the "Other MHS Systems" category below

PHI Systems:

MHS Information System	Requesting Data
: AHLTA	

PII-Only Systems:

MHS Information System	Requesting Data	
No records have been added		

De-Identified Data & Other Systems:

Information System	Requesting Data	
No records have been added		

10.10 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- ☐ Yes, will merge data
☒ No, will not merge data

10.11 Indicate the data elements about research participants or relatives, employers, or household members of the research participants that you will request from MHS hard copies or from MHS information systems.

If you will merge data, also indicate non-MHS data elements about research participants or relatives, employers, or household members of the research participants that you will have access to in any form or medium.

Data Element(s)	MHS	Non-MHS Systems	MHS Hard Copies
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1. Names	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Postal address with only town, city, state and zip code	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Telephone numbers	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Fax numbers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Electronic mail addresses	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Social Security numbers (SSNs)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Medical record numbers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11. Health plan beneficiary numbers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Account numbers	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Certificate/license numbers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Vehicle identifiers and serial numbers, including license plate numbers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Device identifiers and serial numbers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Web Universal Resource Locators (URLs)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Internet Protocol (IP) address numbers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Biometric identifiers, including finger and voice prints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Full-face photographic images and any comparable images	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Any other unique identifying number, characteristic, or code (Diagnosis, DEERS ID, EDI-PI, Rank)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

The study subject's Social Security number is required to process blood draw compensations through the military payroll system.

10.12 Do you believe it is possible for the MHS data to become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would use rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30, so the rank category may need to be expanded to include lower ranks.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 20 of the table above (in Section 10.10), but that could be used to identify an individual. Unique data elements include characteristics that are not themselves identifying, such as the rank of general or admiral, or a race or gender, but within the context of other information could be identifiable.

- ☐ Yes, I believe there is a reasonable possibility the MHS data will become identifiable
- ☒ No, I believe there is no reasonable possibility the MHS data will become identifiable

10.13 Have you completed and uploaded an appropriate HIPAA document (i.e. HIPAA Authorization will be obtained or Waiver/alteration of HIPAA Authorization is being requested)?

- ☐ Yes
- ☐ No
- ☐ N/A

10.14 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

PHI/PII:

PHI requested is to enable the following:

1. Adult Influenza Screening Form to determine subject is able to receive IIV (collected after subject is consented)
2. Documentation and tracking for safety of the subject
 - to include medical record documentation the subject is taking a study medication should a clinical event occur
 - Identification of the subject should an issue with the medication lot be identified in the future.
3. Callback as reminder to facilitate completion of the protocol or notification of unanticipated issues

Specimens will be assigned a unique study identification number and will not contain any personal identifiers. Electronic information will be stored on the DHA-IHB SharePoint database and is password protected. The SharePoint firewalls are securely managed at Fort Detrick MD. Laboratory results will be sent from the Naval Medical Research Center laboratory to study research staff for linkage and reporting. Thus, only research staff and Investigators will be able to link blood specimens and data to a specific individual. Although personal identifiers will be kept to ensure proper linkage, they are protected such that no individual is identified in any report. Records and computer files will be maintained securely in accordance with DoD regulations (NMRDCINST 5870.4). Although subjects will not directly benefit from their involvement in this study, the findings may guide public health and DoD policies that will in turn benefit future service members.

The following procedures are in place to ensure that confidential information will not be used or abused in ways that might directly or indirectly harm the individuals involved:

Administrative:

- a) All Investigators and study staff will receive training in HIPAA regulation and procedures. Will obtain and maintain Citi-training and follow ICH-GCP and the Belmont Report.
- b) The PI will monitor employees to ensure that they are following proper confidentiality procedures by performing, at a minimum, quarterly research site visits.
- c) A quarterly review of confidentiality routines will be conducted;
- d) If employees leave the program, they will remain under obligation to protect the confidentiality of all data collected as part of the program.

Procedural:

- a) Access to PHI will be restricted to DHA-IHB investigators or by DoD provider/co-investigators as part of treatment, and these data will not be re-used or re-disclosed to any other entity.

- b) Subject consent forms and records from each data source will be collected and assimilated by study staff in paper-based files and/or electronic files maintained at the clinical sites and on WAMC and DHA-IHB servers.
- c) Subject laboratory specimens being tested will be sent by the DHA-IHB research staff to Naval Medical Research Center Laboratory, Silver Spring, MD, with a non-personal identifier (SID#) assigned by DHA-IHB investigators. Results will be sent from the lab to the research staff/investigators in conjunction with the SID# via encrypted email or secure fax. The testing laboratory will not have access to any identifiable data.
- d) Data utilized for this proposal consist of the minimum necessary PHI needed to accomplish the study goals; however, all data is assumed to be, and is treated as, PHI.
- e) All data is entered on password-protected computers.
- f) Findings will only be released as an aggregate; no individuals will be identified with the possible exception of any requirement to report if required by law, e.g. the financial remuneration if required for tax purposes or reportable abuse.

Physical safeguards:

- 1. The research office is located on an access controlled military installation. Study staff /investigators will store study files in locked metal cabinets in building C-5537 Tullidge Way, Ft Bragg NC 28310.
- 2. The locked cabinets are located inside the office behind locked doors. There is a security gate surrounding the research office that is kept locked after hours and on weekends and holidays.
- 3. Key control procedures include file keys remain in a locked box when not in use and a key signature accountability form is maintained.
- 4. Only investigators and research staff have access to the files.

Technical safeguards:

- a) All study databases will be stored on the existing DHA-IHB information systems network, which requires a DoD issued Common Access Card (CAC) in conjunction with a unique personal identification number (PIN) for access. The DHA-IHB network security system will prevent all others from accessing these files. This system meets current DoD data security requirements.
- b) The Principal Investigator will grant access to the confidential database only to those staff members who require it.
- c) All data will be carefully guarded and used only to meet the stated study objectives.
- d) Data are analyzed using only de-identified analytic data files, which will be retained for six years after the close of the study.
- e) There will be periodic review of the computer security procedures by DHA-IHB network managers including challenges of the security firewall erected to assure its integrity.

This study uses participant provided demographic and health data (data collection form), electronic military data obtained from AHLTA and laboratory results. These data consist of the minimum necessary Protected Health Information (PHI) needed to accomplish the study goals; however, all data is assumed to be, and is treated as, PHI.

We will request permission from potential participants to collect PHI. The PHI that will be collected for the study will be specified in the Informed Consent Form (ICF) and used with authorization from the subject as stipulated in the ICF. The ICF includes the following required information: a description of the information to be used; the name of the person(s) requesting the use; the name of the person(s) who may use the requested PHI, i.e., the intended recipients; a description of each purpose of the requested use; the length of time that the data will be maintained, tied to an expiration date or an expiration event; a statement regarding the individual's right to revoke authorization for use of PHI and whom to contact in writing to revoke the authorization; a statement regarding the individual's right to inspect hard copies of any PHI collected and who to contact in writing to inspect the contributed data. Original ICFs and data collection forms will be maintained in a locked file at the research office. The study coordinators will maintain study electronic files and the master enrollment file on a CAC enabled WAMC imaged computer. These files will be maintained and backed up on the Z:/ drive and remain under WAMC firewall protection.

Our use of PHI involves no more than minimal risk to the individuals since we will implement procedures to control access to the information collected. The analytic database will not contain identifiers; instead, the data will be stored in conjunction with a randomly assigned subject identification number. A separate database will contain the data in conjunction with PHI, which is necessary for linking data. The SharePoint database is located on secure servers located at Fort Detrick, MD. Access to files containing PHI is restricted to approved IRB investigators and research staff.

Identified data will be maintained securely at DHA-IHB both within the physical environment and IT environment. Hard copies of any records will be stored in a locked file cabinet as mentioned above. All data are stored as password-protected files that are stripped of personal identifiers, to the extent possible for the research and will retain study-specific subject identification numbers. Data are managed and analyzed using only these de-identified data files, which will be destroyed by shredding and degaussing, for paper files and electronic files respectively, six years following completion of the study, or longer as dictated by any future required retention periods, whichever is longer. Findings will only be released as an aggregate; no individuals will be identified. Blood specimens without consent for long term storage will be destroyed after testing.

10.15 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens /data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed.

Specimen Tracking and Storage at Study Site

Study participants that give informed consent for future use of serum will be stored at a DHA-IHB repository. Electronic inventory of samples will be maintained in the DHA-IHB Specimen Tracker application. Specimens will be identified by the unique SID assigned to the participant. Specimen Tracker will capture the location of each tube by SID and display each specimen's freezer location, specimen type, visit number 1 or 3, date of collection and consent for future use.

Specimens will be stored indefinitely after the completion of this study unless a subject requests the destruction of his/her specimens. A subject may request in writing to the Principal Investigator his/her desire to have specimens destroyed.

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

DATA ANALYSIS: The primary outcome of interest for this study is self-reported delayed pain post vaccine. Thus we plan to analyze differences in mean pain scores among the 3 Groups using ANOVA with planned comparison between the exercise condition (Group C) and the other Groups. Repeated measures ANOVAs will be used to analyze pre and post vaccine differences in lactate, serological response to antigens, edema, and erythema. If data fail to satisfy test assumptions such as normality, a log transformation or non-parametric test will be used as appropriate. Statistically significant effects will be followed-up with Tukey's HSD post hoc mean comparison. In the event that pain data show a bimodal distribution, appropriate cut offs will be determined so as to create dichotomized (pain / no-pain) scores. In this scenario, 2 pair-wise comparisons will be made between Groups C&A and C&B using Chi square tests. Demographic characteristics will be compared among Groups using a one-way ANOVA or Chi square test, as appropriate. A significance level of $p \leq 0.05$ will be used for all analyses.

Figure 2. Data Analysis Table

Statistical Test	Independent Variable/ Predictors Variables	Dependent Variable/ Outcome Variables
ANOVA, Chi Square	Treatment condition	Pain

Repeated Measures ANOVA	Treatment condition	Edema, Erythema, Lactate, Serology
11.2 Sample Size:		
<input type="text" value="350"/>		
11.3 Total number of subjects requested (including records and specimens):		
<input type="text" value="350"/>		
11.4 If you are recruiting by study arm, please identify the arms of the study and how many subjects will be enrolled in each arm		
<input type="text" value="N/A"/>		
11.5 Please provide a justification for your sample size		
<ol style="list-style-type: none"> Sample Size: We will enroll up to 350 participants with a goal of approximately 216 with complete data sets Power Analysis: A sample size of 216 is needed for the study to yield an 86% chance of rejecting the null hypothesis ($p < 0.05$), assuming a moderate effect size of 0.25. 		
11.6 Data Analysis Plan: Complete description: Background, Objectives, Design, Step by Step how the project is going to be done, Data analysis plan:		
<p>DATA ANALYSIS: The primary outcome of interest for this study is self-reported delayed pain post vaccine. Thus we plan to analyze differences in mean pain scores among the 3 Groups using ANOVA with planned comparison between the exercise condition (Group C) and the other Groups. Repeated measures ANOVAs will be used to analyze pre and post vaccine differences in lactate, serological response to antigens, edema, and erythema. If data fail to satisfy test assumptions such as normality, a log transformation or non-parametric test will be used as appropriate. Statistically significant effects will be followed-up with Tukey's HSD post hoc mean comparison. In the event that pain data show a bimodal distribution, appropriate cut offs will be determined so as to create dichotomized (pain / no-pain) scores. In this scenario, 2 pair-wise comparisons will be made between Groups C&A and C&B using Chi square tests. Demographic characteristics will be compared among Groups using a one-way ANOVA or Chi square test, as appropriate. A significance level of $p \leq 0.05$ will be used for all analyses.</p>		
12.0 Participant Information		
12.1 Subject Population:		
Active-duty men and women who meet the study criteria at WAMC and WRNMMC will be considered for enrollment.		
12.2 Age Range:		
<p>Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.</p> <p> <input type="checkbox"/> 0-17 <input checked="" type="checkbox"/> 18-24 </p>		

- ☒ 25-34
- ☒ 35-44
- ☒ 45-54
- ☒ 55-64
- ☐ 65-74
- ☐ 75+

12.3 Gender:

- ☒ Male
- ☒ Female
- ☐ Other

12.4 Special categories, check all that apply

- ☐ Minors /Children
- ☐ Students
- ☐ Employees - Civilian
- ☐ Employees - Contractor
- ☐ Resident/trainee
- ☐ Cadets /Midshipmen
- ☒ Active Duty Military Personnel
- ☐ Wounded Warriors
- ☐ Economically Disadvantaged Persons
- ☐ Educationally Disadvantaged Persons
- ☐ Physically Challenged (Physical challenges include visual and/or auditory impairment)
- ☐ Persons with Impaired Decisional Capacity
- ☐ Prisoners
- ☐ Pregnant Women, Fetuses, and Neonates
- ☐ Non-English Speakers
- ☐ International Research involving Foreign Nationals - Headquarters Review is necessary

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

12.5 Inclusion Criteria:

Order Number	Criteria
1	<ul style="list-style-type: none"> 18 years of age old and older
2	<ul style="list-style-type: none"> Active Duty Service Members
3	<ul style="list-style-type: none"> Requiring and eligible for inactivated influenza vaccine receipt
4	<ul style="list-style-type: none"> Be willing and able to complete the study protocol requirements

- | | |
|---|---|
| 5 | <ul style="list-style-type: none"> Have a current completed Flu Screening Form to receive the influenza vaccination. |
|---|---|

12.6 Exclusion Criteria:

Order Number	Criteria
1	<ul style="list-style-type: none"> Previous receipt of the current seasonal influenza vaccine.
2	<ul style="list-style-type: none"> Receipt of any vaccine 72 hours before influenza vaccine receipt.
3	<ul style="list-style-type: none"> Medical profile resulting in current profile exemption from PT of U2 or U3.
4	<ul style="list-style-type: none"> Have preexisting symptoms of injury or infection or other local symptoms that require medical evaluation or treatment to either upper extremity
5	<ul style="list-style-type: none"> Pregnancy
6	<ul style="list-style-type: none"> Have a history of allergy, intolerance, stomach bleeding or other medical exclusion for ibuprofen?
7	<ul style="list-style-type: none"> A history of stroke or heart disease, such as uncontrolled high blood pressure, heart attack or abnormal heart beat.
8	<ul style="list-style-type: none"> Taking any topical or oral pain medications from the following medication classes in the past 24 hours prior to the start of the study: oral acetaminophen, opioids, tramadol, NSAID or ASA or topical pain relievers or counterirritants of menthol, methyl salicylate, camphor menthols, and capsaicins.
9	<ul style="list-style-type: none"> Currently participating in any other study that asks participant to take a medicine or exercise.
10	<ul style="list-style-type: none"> Any acute or chronic illness or treatment causing immunological suppression, as defined by Infectious Disease Society of America (IDSA) definitions of High and Low level Immunosuppression (Rubin, et.al, 2013). Any participant whose status is unclear or potentially immunosuppressed in the clinical judgement of the PI or AI will not be enrolled.

13.0

Recruitment and Consent

13.1 Please describe the recruitment process, including how subjects will be identified and selected for the study.

Active duty males and females 18 years of age and older eligible for annual influenza vaccine receipt.

(Please see section 10.1 for additional information.)

13.2 Compensation for Participation:

The subject will receive compensation in the amount of \$50 per blood draw (\$100 total); payments will be made via direct deposit to the subject's banking account or via \$50 gift card. No compensation will be provided for visit #2 which does not include any type of blood sampling.

13.3 Please describe the pre-screening process. If no pre-screening, enter Not Applicable in the text editor

Persons wishing to be considered for participation will be screened for eligibility by the study personnel by completion of the Study Eligibility Screening Form (see attachment B). Females of childbearing age will be required to complete a pregnancy test after being consented. The previously completed Adult Influenza Screening forms will be reviewed by the study personnel, after completion of the consent form, to ensure congruence with the Study Eligibility Screening Form and confirm no contraindication to vaccination exists.

13.4 Consent Process:

Revised Common Rule, Section 219.116: General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens.

Are you requesting a waiver or alteration of informed consent?

☐ Yes ☒ No

Please explain the consent process:

Persons who are eligible for participation will receive counseling from the study personnel to meet the established guidelines for informed consent: to include a statement of the purpose, randomization process, use of placebo control, use of prescription dose ibuprofen, foreseeable risks, potential benefits, research staff contact information, rights and responsibilities, and that participation is voluntary. During the consenting process, subjects will be asked for contact information and consent to be contacted by telephone or email for clarification of medical history, and/or prior immunizations and/or adverse events. The subject will be informed that use of their unsecure personal email account is not recommended due to the potential risks of inadvertent disclosure of their personal health information. They will be advised that their personal email may only be used as a last resort and with their written permission. The study personnel will also provide counseling and the participant will complete the Consent/HIPAA form.

Since the data and specimens collected may be of significant utility for future studies, subjects will be asked for consent for future study to include use of collected specimens and use of data collected. Subjects will be asked for permission to be contacted for future studies and the participant will have the option to consent or refuse permissions for future studies without effect on participation in this study. Subjects interested in study participation will complete the study consent/HIPAA form with required initials, signature, and date.

13.5 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

☒ N/A
☐ Propose ombudsman

13.6 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

All participants have the right to withdraw from the study at any time. If this occurs, any specimens that are available will be destroyed. Data that has been collected will be maintained in the study records.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

RISKS TO SUBJECTS

The risk to human subjects is likely minimal because:

1. The NSAID intervention is of minimal duration in a low risk group for receipt of this pharmacologic agent.
2. The vaccine is not part of the study, however an adverse event to the vaccine may occur, and the subject will be referred to DHA-IHB for evaluation and management.
3. The participants could experience increased pain associated with performance of compound exercise of pushups.
4. The participants could experience an adverse effect associated with the POC finger stick, or venipuncture including pain, or infection which is rare.
5. The participants could experience a decrease in expected immune response, in particular those assigned to the oral NSAID arm, potentially decreasing influenza disease protection. The clinical significance in terms of actual disease risk due to decreased titers is unknown and has not been studied. In previous trials which measured serological response to full dose vaccine, participants still achieved protective titers. Serological markers are also only one component of the immune response to antigen and a decrease may not represent increased disease risk.
6. The participants assigned to the exercise arm could potentially sustain physical injury from engaging in the pushup type compound exercise. This risk is no more likely than the participant's everyday routine fitness activities as the pushup type compound exercise is routinely performed by the participants and part of themilitary PFT.
7. The participants assigned to the oral NSAID arm could experience an adverse effect associated with this medication, such as a hypersensitivity reaction. Ibuprofen was selected due to its ubiquitous use both prescription and over- the- counter in lower doses such that allergy or intolerance would likely already be known. The adverse effect potential is minimal due to the short duration of therapy and the safety profile of the medication. Most significant reactions are associated with longer term use than the 48 hour protocol or in higher risk populations such as elderly. See section 7.34 study medications for additional discussion

h. **Pregnancy** testing will be completed as part of eligibility screening.

RISKS:

1. An inadvertent disclosure could occur.

The individuals participating in this RCT could experience a loss of privacy/confidentiality of enrollment in the study, particularly the exercise intervention group who could be observed performing pushups post vaccine re

14.2

Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

Vaccine Injection Technique:

Injectable immunobiologics should be administered where local, neural, vascular, or tissue injury is unlikely. Use of longer needles has been associated with less redness or swelling than occurs with shorter needles because of injection into deeper muscle mass. Appropriate needle length depends on age and body mass. Injection technique is the most important parameter to ensure efficient intramuscular

vaccine delivery. For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. Vaccinators should be familiar with the anatomy of the area into which they are injecting vaccine. Intramuscular injections are administered at a 90-degree angle to the skin, preferably into the anterolateral aspect of the thigh or the deltoid muscle of the upper arm, depending on the age of the patient. A decision on needle size and site of injection must be made for each person on the basis of the size of the muscle, the thickness of adipose tissue at the injection site, the volume of the material to be administered, injection technique, and the depth below the muscle surface into which the material is to be injected. Aspiration before injection of vaccines is not necessary because no large blood vessels are present at the recommended injection sites. All adults who weigh <130 lbs. (<60 kg), a 1/2-inch needle is sufficient to ensure intramuscular injection in the deltoid muscle if the injection is made at a 90-degree angle and the tissue is not bunched. For men and women who weigh 130-152 lbs. (60-70 kg), a 1-inch needle is sufficient. For women who weigh 152-200 lbs. (70-90 kg) and men who weigh 152-260 lbs. (70-118 kg), a 1- to 1 1/2 -inch needle is recommended. For women who weigh >200 lbs. (>90 kg) or men who weigh >260 lbs. (>118 kg), a 1 1/2-inch needle is recommended.

All vaccinators will have a completed Injectable Influenza Vaccine Administration Competency assessment. Needle selection will be based on CDC weight recommendations.

The vaccine will be shaken thoroughly and administered immediately using aseptic technique. Intramuscular injections are administered at a 90-degree angle to the skin to the deltoid muscle of the upper arm. No aspiration will be performed.

14.3

Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e.g., child or spouse abuse

Specimens will be assigned a unique study identification number and will not contain any personal identifiers. Electronic information will be stored on the DHA-IHB SharePoint database and is password protected. The SharePoint firewalls are securely managed at Fort Detrick MD. Laboratory results will be sent from the Naval Medical Research Center laboratory to study research staff for linkage and reporting. Thus, only research staff and Investigators will be able to link blood specimens and data to a specific individual. Although personal identifiers will be kept to ensure proper linkage, they are protected such that no individual is identified in any report. Records and computer files will be maintained securely in accordance with DoD regulations (NMRDCINST 5870.4).

14.4

Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

BENEFITS:

1. Although there are no direct benefits to the participants, the information may assist in
determining best practice recommendations concerning use of exercise or NSAIDS
associated with vaccine receipt for mitigation of common adverse effects and serologic
impact of those recommendations
1. Addressing vaccine concerns may decrease vaccine hesitancy, increase acceptability and
tolerability increasing overall vaccine rates, especially for optional vaccines. This improves and
promotes public health goals of increased vaccination rates and improves health of populations.

MEDICAL APPLICATION: Address gaps in current literature concerning:

1. Efficacy of exercise as an intervention to decrease post immunization site local inflammation
effects
2. Efficacy of NSAIDS as an intervention to decrease post immunization site local inflammation
effects
3. Serological effects of exercise on immunization response
4. Serological effects of NSAID on immunization response

14.5

Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

Subjects will be consented and complete all study documents in one of the study nurse's private offices and all other procedures will be performed in the study team's examination room behind closed doors. Recruitment will be done via Intranet advertisement with DRP approved flyer, through posting of same study flyers in WRNMMC clinics, during open recruitment in lobby of building 19, and through word of mouth referrals.

14.6

Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

Findings will only be released as an aggregate; no individuals will be identified with the possible exception of any requirement to report if required by law, e.g. the financial remuneration if required for tax purposes or reportable abuse.

15.0

Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).

- ☒ DSMP
- ☐ DSMB
- ☐ Both
- ☐ Not Applicable

A DSMP should describe the plan to monitor the data to verify that the data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored, and the frequency of monitoring. It should also include the plan to ensure the safety of subjects

Safety Review Plan and Monitoring

Purpose: Oversight of participant safety includes review of adverse events as well as study progress, data integrity and study outcomes.

Safety and study progress reviews

1. The Principal Investigator and/or his/her designee will review the adverse events log on a semi-annual basis to ensure adverse events are being reported to the WRNMMC IRB in accordance with the IRB-approved protocol and in a timely manner. Furthermore, the Principal Investigator will review adverse events to determine whether rates are consistent with pre-study assumptions.
2. The Principal Investigator and/or his/her designee will review study progress, to include recruitment and enrollment rates, retention, data integrity, and protocol adherence, on a semi-annual basis. This individual will offer recommendations for improving enrollment and retention, when applicable.

What precautions will you take to protect the confidentiality of research source documents (Case Report Forms, questionnaires, etc.), the research data file, and the master code (if any)?

To protect the confidentiality of these data, unique study identification numbers will be created and assigned to each subject. The linkage of study identification numbers with personal identifiers will be stored in the master data roster and will only be accessible by the Principal Investigator and designated Associated Investigators/Team Members.

The datasets used for purposes of review and analysis will contain the study identification number without personal identifying information. Paper copies will be stored in secure, locked file cabinets within the IHB offices.

At time of enrollment, a unique study identification number (SID) will be assigned to each participant. Personal identifiers will not be included on any specimen labels to protect the identity of all participants. The label will include information such as the SID, date of specimen collection, and visit number. Tissue (blood, blood cells) specimens will be collected at study site(s) under informed consent. Hemagglutinin Inhibition Antibody Titer testing will be performed by the Viral and Rickettsial Diseases Department at Naval Medical Research Center (NMRC) in Silver Spring, MD. Protocol laboratory staff will package and ship frozen serum samples on dry ice to NMRC via courier service (e.g., FedEx). Any remaining serum at NMRC will be destroyed following completion of assay testing and analysis.

Participants can give informed consent to approve or disapprove the use of their specimens for future clinical investigation studies. If a study participant gives permission for their serum to be stored and used for future research studies, the study must be an IRB approved addendum, amendment, or protocol. The specimens will be stored at a DHA-IHB tissue repository. Specimens from a study participant who does not give consent for future will not be stored at a DHA-IHB study site repository after study is complete. These specimens will be destroyed after all testing for this study is complete. Participants, under informed consent, are advised as to how they may have their sample destroyed at any time by contacting the Principal Investigator or other designated study team members. All participants have the right to withdraw from the study at any time. If this occurs, any specimens that are available will be destroyed. Data that has been collected will be maintained in the study records.

When the laboratory testing is complete, results will be sent, listed by subject ID number, to DHA-IHB study staff via email or fax. Identifying information will not be shared with NMRC.

Reportable Events

16.1 Reportable Events: Consult with the research office at your institution to ensure requirements are met. Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event.

Consult with the research office at your institution to ensure requirements are met

- Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)
- Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

Reportable Events include adverse events (AE), serious adverse events (SAE), unanticipated problems involving risks to subjects or others (UPIRTSO), and protocol deviations occurring at the WRNMMC or the WAMC study site will be reported IAW RHC-A P & P. All reporting requirements are listed in the PI agreement.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

☐ Yes ☒ No

18.0 FDA-Regulated Products

18.1 Will any drugs, dietary supplements, biologics, or devices be utilized in this study?

- ☒ Drugs
☐ Dietary Supplements
☐ Biologics
☐ Devices
☐ N/A

18.2 Drugs, Dietary Supplements and Biologics/Vaccines details:

- ☒ Are drug(s) in this research being used in accordance to the approved labeling?
☐ Are drug(s) in this research being used in a manner other than its approved labeling?

Enter Dietary Supplements and Biologics/Vaccines in the Drug Information table. Complete all relevant fields in the table ("Protocol Drug Details" screen). If the question is not relevant, leave the question blank and/or do not change the default selection.

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
	Trade Drug Name: IBUPROFEN			

<input type="checkbox"/>	Generic Drug Name: Investigational Drug Name:	Yes	No
Trade Drug Name:	IBUPROFEN		
Generic Drug Name:			
Investigational Drug Name:			
Identify the name of the manufacturer or source of investigational drug/biologic:	US Compounding		
Is the drug supplied at no cost?	Yes		
Is the Drug FDA Approved:	Yes		
Is this a new drug or a new use of an already approved drug	No		
Is an IND necessary	No		
IND Number			
Who holds the IND:	N/A		
IND details:			
If FDA Approved and an IND is not required, Please provide a rationale for exemption:			
Are you currently using this IND in another research project?	No		
If yes, list the IRB Number(s):			
Dose Range:			
Frequency:	every 8 hrs x 48 hrs		
Route of administration:	by mouth		
Will the investigational pharmacy be dispensing?	Yes		
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	US Compounding is an FDA registered 503b outsourcing facility with P-CAB accreditation.		
Identify who will be preparing the investigational drug/biologic for administration and describe in detail how it will be prepared:	The research pharmacist at WAMC, Sherry Lamberth, will receive and prepare the ibuprofen and placebo from US Compounding. She will utilize the SID enrollment list to randomize the products.		
Indication(s) under Investigation:	Pain		
Where will the drug be stored	WAMC pharmacy and the research office		
Drug Storage Restrictions (including temperature, etc.):	Product is stored in a pharmacy bottle with a child proof cap inside a locked cabinet in a clean and environmentally controlled atmosphere at ambient temperature between 64-72 degrees Fahrenheit. (+ or - 5 degrees)		
Administration Instructions:	The study drug is used in accordance with it's FDA approved labeling. (2) 400mg capsules will be taken by mouth with food 3 times a day for 48 hours.		
Possible Untoward Effects, Their Symptoms & Treatment:	See ibuprofen/placebo package insert and investigators brochure.		
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	See ibuprofen/placebo package insert and investigators brochure		
Contraindications and	See ibuprofen/placebo package insert and investigators		

Interactions, If Known:		brochure		
Investigators Authorized to Prescribe:		Laurie Housel, FNP and Bruce McClenathan, MD		
<input type="checkbox"/>	Trade Drug Name: Placebo capsule Generic Drug Name: Investigational Drug Name:	No	No	

Trade Drug Name:	Placebo capsule
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	US Compounding
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	No
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Placebo
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	every 8 hours x 48 hours
Route of administration:	by mouth
Will the investigational pharmacy be dispensing?	Yes
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	US Compounding is an FDA registered 503b outsourcing facility with P-CAB accreditation.
Identify who will be preparing the investigational drug/biologic for administration and describe in detail how it will be prepared:	The research pharmacist at WAMC, Sherry Lamberth, will receive and prepare the ibuprofen and placebo from US Compounding. She will utilize the SID enrollment list to randomize the products.
Indication(s) under Investigation:	Pain
Where will the drug be stored	WAMC pharmacy and research office
Drug Storage Restrictions (including temperature, etc.):	Product is stored in a pharmacy bottle with a child proof cap inside a locked cabinet in a clean and environmentally controlled atmosphere at ambient temperature between 64-72 degrees Fahrenheit. (+ or - 5 degrees)
Administration Instructions:	Placebo contains no lactose and no active ingredients. It will be randomized by SID. Two capsules will be given by mouth at the study site with a snack and water. Subjects will be advised to

	take two capsules every 8 hours until gone.
Possible Untoward Effects, Their Symptoms & Treatment:	None (Placebo contains no lactose)
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	None
Contraindications and Interactions, If Known:	None
Investigators Authorized to Prescribe:	Laurie Housel, FNP and Dr. Bruce McClenathan, MD

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

N/A; this is not a FDA-regulated research under IND and IDE.

18.5 Sponsor (organization/institution/company):

☒ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

- ☐ Registration is not required
- ☐ Registration pending
- ☒ Registration complete

"NCT" number:

NCT02807623

19.2 Defense Technical Information Center Registration (Optional):

- ☒ Registration is not required
- ☐ Registration pending
- ☐ Registration complete

20.0 References and Glossary

20.1 References:

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20.2 Abbreviations and Acronyms: