Protocol Title

Comparison Between Cooled Radiofrequency Ablation (C-RFA), Standard Radiofrequency Ablation (t-RFA), and Control for Postoperative Pain Management Following Unilateral Knee Arthroplasty: A Double-Blinded, Parallel-Grouped, Placebo-Controlled Randomized Clinical Trial

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HALYARD HEALTH

LYMAN MEDICAL RESEARCH FOUNDATION, INC

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STUDY SYNOPSIS

<table>
<tr><td>TITLE</td><td colspan="2">Comparison Between Cooled Radiofrequency Ablation (C-RFA), Standard Radiofrequency Ablation (t-RFA), and Control for Postoperative Pain Management Following Unilateral Knee Arthroplasty: A Double-Blinded, Parallel-Grouped, Placebo-Controlled Randomized Clinical Trial</td></tr>
<tr><td>STUDY PHASE</td><td colspan="2">IV</td></tr>
<tr><td>OBJECTIVES</td><td colspan="2"><u>Primary Objective:</u> postoperative analgesic consumption [timeframe 0 - 48 hours to 3 weeks] and to cessation; hospital length of stay (LOS) [time frame 0 – 5 days]
<u>Secondary Objective:</u> pain scores (NRS and WOMAC) [time frame: before C-RFA/t-RFA/Control, pre-op; day of surgery; 3 (±1) days after surgery; 1week (±) 3 days after surgery via phone interview; 2 and 6 (±1) weeks after surgery; 12 (±1) weeks posts-op phone interview; 6 (±1) months; 12 (±1) months post-op]; [daily patient pain score and opioid pill count diary]
<u>Sub-study:</u> physical therapy rehabilitation milestones, ROM, WOMAC, numeric pain score [time frame: 2 (±1), 4 (±1), 6 (±1), 8 (±1), 10 (±1), 12 (±1) weeks] following surgery</td></tr>
<tr><td>STUDY DESIGN</td><td>Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Paralleled Assignment</td><td>Masking: Double Blinded (Subject, Outcomes Assessor)
Primary Purpose: Treatment (Decrease Opioid Utilization, Hospital Length of Stay)</td></tr>
<tr><td>NUMBER OF PATIENTS</td><td colspan="2">150-170</td></tr>
<tr><td>ELIGIBILITY</td><td><u>Inclusion Criteria</u>
<u>Ages Eligible for Study</u>
40 years and older (adult, senior)
<u>Genders Eligible for Study</u>
Both male and female
• osteoarthritis of the knee where unilateral knee arthroplasty is indicated by radiography; function decrease and/or pain
• readiness to undergo t-RFA, C-RFA or SHAM treatments
<u>Exclusion Criteria</u>
• acute illness/infection
• severe cardiac/pulmonary compromise
• bleeding disorder
• allergic reactions to local anesthesia, steroids or implant materials</td><td><u>Exclusion Criteria (Continued)</u>
• tobacco user within 2 months
• BMI > 40
• psychiatric disorders
• no documented narcotic dependency or recreational drug usage
• no major trauma hardware removals or prior TKA
• confounding inflammatory arthritis
• other confounding general chronic pain
• daily narcotic/opioid 5 weeks prior
• diagnosed thrombophilia
• neuropathy or neuro impairment
• pregnancy
• breastfeeding
• contraindicated thin body habitus</td></tr>
<tr><td>EVALUATION CRITERIA</td><td colspan="2">opioid consumption; pain scale (numerical rating Scale 0-10 where 0 is no pain and 10 is worst pain); Western Ontario and McMaster Universities Arthritis Index (WOMAC); hospital length of stay (LOS); physical therapy sub-study; need for manipulation under anesthesia (MUA) postoperatively</td></tr>
<tr><td>STATISTICAL CONSIDERATIONS</td><td colspan="2">Subjective Pain Scores; Provider Variance; Patient Drop Out; Delayed Treatment Effects</td></tr>
<tr><td>ENROLLMENT PERIOD</td><td colspan="2">Quarter I 2017 – Quarter IV 2018</td></tr>
<tr><td>FOLLOW-UP PERIOD</td><td colspan="2">Quarter I 2017 – Quarter IV 2019</td></tr>
</table>

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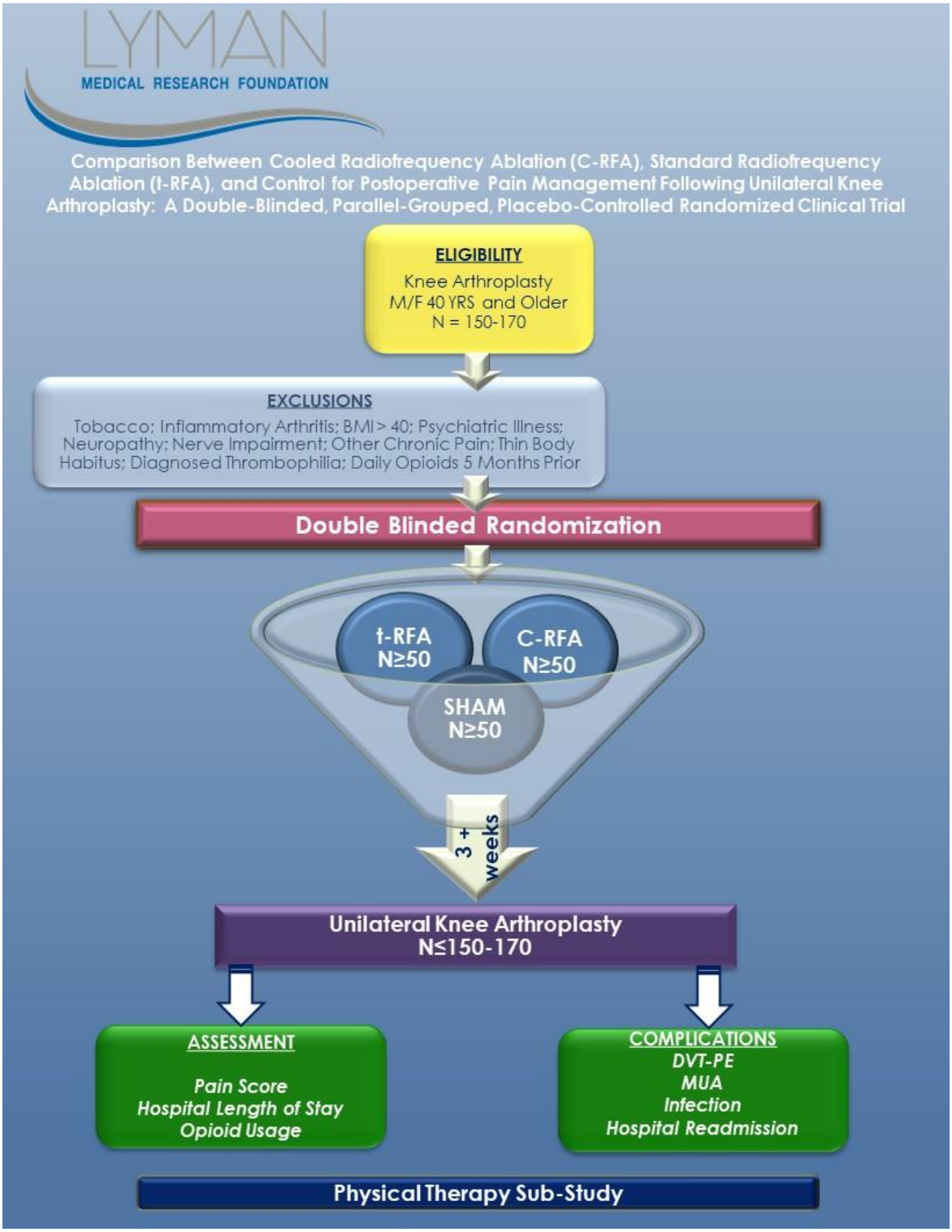
INDEX

00.0 SCHEMA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MEDICAL RESEARCH FOUNDATION
Comparison Between Cooled Radiofrequency Ablation (C-RFA), Standard Radiofrequency Ablation (t-RFA), and Control for Postoperative Pain Management Following Unilateral Knee Arthroplasty: A Double-Blinded, Parallel-Grouped, Placebo-Controlled Randomized Clinical Trial
ELIGIBILITY
Knee Arthroplasty
M/F 40 YRS and Older
N = 150-170
EXCLUSIONS
Tobacco; Inflammatory Arthritis; BMI > 40; Psychiatric Illness; Neuropathy; Nerve Impairment; Other Chronic Pain; Thin Body Habitus; Diagnosed Thrombophilia; Daily Opioids 5 Months Prior
Double Blinded Randomization
t-RFA N≥50
C-RFA N≥50
SHAM N≥50
3 + weeks
Unilateral Knee Arthroplasty N≤150-170
ASSESSMENT
Pain Score
Hospital Length of Stay
Opioid Usage
COMPLICATIONS
DVT-PE
MUA
Infection
Hospital Readmission
Physical Therapy Sub-Study

01.0 BACKGROUND AND RATIONALE

Total knee replacements are a leading orthopedic procedure in the United States totaling 600,000 in 2010, and are anticipated to grow to 3.48 million procedures by 2030 (Kurtz S, 2007) (Patel A, 2015). Three primary reasons prolong hospital stays following unilateral knee arthroplasty. Pain is the primary reason followed by opioid drowsiness and nausea/vomiting side effects (Husted H, 2011). Reducing opioid usage and decreasing hospital length of stays are paramount in improving patient care during recovery and rehabilitation, subsequently reducing overall costs associated with total knee replacement. Standard genicular radiofrequency ablation (t-RFA) has been effective pain management for non-operative knee pain associated with osteoarthritis (Choi WJ, 2011). Additionally, cooled radiofrequency ablation (C-RFA), which was previously used for spinal pain, is now available for knee pain management (Stelzer W, 2013). C-RFA, compared to t-RFA, causes large volume spherical lesions and potentially reduces time and fluoroscopic exposure with direct placement techniques. Both t-RFA and C-RFA offer minimally invasive, non-surgical, non-opioid pain relief options following surgery. Preliminary reports from Orthopedic Specialty Institute, involving 40 patients who underwent either C-RFA or t-RFA prior to unilateral knee arthroplasty, indicate both procedures improved postoperative pain assessments and decreased opioid utilization. A double-blinded, parallel grouped, placebo-controlled randomized study to compare three pain management paradigms involving preoperative C-RFA, t-RFA, and SHAM is proposed. The aim of this study is to establish if C-RFA and t-RFA, offered preoperatively to patients undergoing unilateral knee arthroplasty, provide postoperative pain relief, reduce hospital length of stays and decrease opioid utilization thereby improving patient outcomes and decreasing overall costs.

02.0 OBJECTIVES

The purpose of this study is to assess and compare the efficacy of preoperative t-RFA, C-RFA, and SHAM for unilateral knee arthroplasty post-surgical pain control. A priori outcome is reduced pain, decreased post-surgical opioid utilization, and decreased Hospital Length of Stay.

2.1 Primary Objective:

Postoperative Opioid Consumption [Timeframe: 0 - 48 hours to 3 weeks] and to cessation; Hospital Length of Stay (LOS)

2.2 Secondary Objective:

Pain Scores (NRS and WOMAC) [Time Frame: Before C-RFA/t-RFA/Control, Pre-Op Visit; Day of Surgery; 3 (±1) Days After Surgery; 1Week ± 3 Days After Surgery via Phone Interview; 2 and 6 (±1) Weeks After Surgery; 12 (±1) Weeks Posts-Op Phone Interview; 6 (±1) Months; 12 (±1) Months Post-Op]; [Daily Patient Pain Score & Opioid Pill Count Diary]

2.3 Sub-study:
Physical Therapy Rehabilitation Milestones, ROM, WOMAC, Numeric Pain Score [Time Frame: 2 (±1), 4 (±1), 6 (±1), 8 (±1), 10 (±1), 12 (±1) After Surgery

03.0 ELIGIBILITY CRITERIA

3.1 Written informed consent and HIPAA authorization for release of personal health information.

3.2 No daily opioid consumption 5 weeks prior to enrollment

3.3 No documented narcotic dependency or recreational drug usage

3.4 Males and Females > 40 years old

3.5 Must have a BMI < 40

3.6 Females must not be breastfeeding

3.7 Unilateral knee arthroplasty indicated by radiograph, function decrease and/or pain indication

3.8 No confounding major trauma hardware removals or prior TKA

3.9 Post-operative physical therapy is approved by Dr. Lyman or Dr. Lovell

3.10 No tobacco usage within 2 months prior to surgery

3.11 No confounding inflammatory arthritis diseases are present

3.12 No neuropathy or neuro impairment present

3.13 No significant acute illness or infection

3.14 No contraindicated body habitus

3.15 No diagnosed thrombophilia

3.16 No severe cardiac or pulmonary compromise

3.17 No bleeding disorder(s)

3.18 No allergic reaction to local anesthesia, steroids, or implant materials

3.19 Absence of other confounding chronic pain

3.20 No confounding psychiatric illnesses because of subjective pain evaluations

3.21 No treatment with any investigational agent within 3 months prior to enrollment

3.22 Negative pregnancy tests at time of radiofrequency ablation procedure which is a standard of care but will be paid for by the study.

3.25 The patient is to refrain from requesting their medical records following enrollment in the trial to 6 months postoperatively to remain blinded to their treatment protocol. If patients request their medical records during this period, then they will be excluded from the trial as indicated on the informed consent. Data obtained prior to discontinuing the trial may be used for research.

04.0 PATIENT REGISTRATION (ENROLLMENT PROCEDURES)

Potential study candidates seeing Jeffrey Lyman, MD, Adam Olscamp, MD, or Timothy Lovell, MD for knee pain, where unilateral knee arthroplasty is indicated, will be given the opportunity to participate in the clinical trial. Potential study candidates are defined as patients who are "eligible" candidates, thereby meeting the inclusion and exclusion criteria. The provider determines if the patient is eligible based on inclusion and exclusion criteria. If the patient is determined to be "eligible", the providers may inform and invite the patients by telephone or in clinic about the experimental nature of the trial regarding the advantages, risks, and objectives to minimize pain following surgery and subsequently reduce opioid utilization. The patient will be provided the "study packet' which includes recruiting materials (Appendix J), directions to the surgery center, participating physical therapy sites and copies of the informed consent (Appendixes A&B) to take home.

Telephone invitations may occur and follow the forthcoming steps.

1) Provider screens patients for Inclusion/Exclusion
2) Provider contacts eligible candidates and invites them to participate in the study [similar to clinical invites]
3) Interested patients are referred to study treatment
4) Provider documents patient telephone invitations
5) Study forms are faxed to the Lyman Medical Research Foundation (Enrollment Eligibility and Study Referral)

6) Providers' patients are mailed the "study packet" by Providers' study team members and recruitment will be sought from Providers' corresponding patients only.

Interested patients are referred to one of the three treatment providers (Greg Bauer, CRNA; Doran Thomas, CRNA; and Mike Ludwig, MD). Provider variances will be addressed using a random number generator (numbergenerator.org).

1) Dr. Lyman's site will use the numbergenerator.org when referring patients for treatment procedures. The Study Referral will be faxed accordingly.
    a. Greg Bauer is assigned (1)
    b. Doran Thomas is assigned (2)
    c. Mike Ludwig is assigned (3)
2) Drs. Lovell and Olscamp teams will authorize and fax the Study Referral, Enrollment Eligibility and Medical Release (for clinical invitations) to the Lyman Medical Research Foundation, Inc. (208) 620-3546.
    a. The Lyman Medical Research Foundation, Inc. will use the numbergenertor.org as outline in in 4.0 to assign the treatment provider.
    b. Lyman Medical Research Foundation, Inc. will fax the Study Referral accordingly.

There are designated days and times, for informed consent and randomized treatment procedures, which may be adjusted during the study to accommodate patients. The patients will meet with an authorized study representative Pleasant View Surgery Center wherein the patient will be informed about the study in plain language and the written information will be reviewed. Then the patients' informed consents will be obtained by an IRB authorized study representative prior to being randomized to one of the three treatments. Enrollment occurs after written consent is obtained. Patients may be referred to and scheduled for a procedure at Pleasant View Surgery Center, whereat Informed Consent will transpire prior to treatment. Patients requiring total knee replacement, who are ineligible or decline enrollment, will be offered the same treatment and pain management choices as those who are enrolled. No data will be obtained from non-enrolling patients. Documentation for qualifying non-participants will be noted in the physicians' dictations. Documentation for non-qualifying non-participants and reason(s) for exclusion will be noted in the physicians' dictations.

- Treatment providers' schedulers and Pleasant View Surgery Center will coordinate with an authorized clinical study representative for study subject schedules. An authorized study representative will receive information regarding scheduled patients and their corresponding providers. This information may be used to predetermine the randomized arm for each patient. Predetermined randomization is possible due to the randomization being determined by the date order of subject recruitment and electing to be referred to pain management for a RFA study treatment. on a rotating basis. When a patient is scheduled for a treatment procedure at the surgery center then we know the day anticipated for them providing informed consent and therefore, randomization can be

"predetermine" based on date and order of invitation and agreement to be referred to pain management for a RFA study treatment. This predetermined randomization may be different in select cases where patients cancel or reschedule their originally scheduled treatment or do no consent upon arrival to the study. In these cases, the organized randomization will reflect the recruitment and referral date order of the subjects that enroll by signing their informed consent(s).

Enrollment	Jeffrey Lyman, MD	Timothy Lovell, MD	Adam Olscamp, MD
Average Weekly Total Knees	5.5	5.5	4
Monthly Average Total Knees	22	22	20
Estimated Eligible Candidates/Month	11	11	9
Estimated Willing to Participate/Month	9.9	4	7
Estimated Participant Study Retention after Dropout Rate/Month	8.4	3.0	6.0
Estimated Enrollment Start Date	Jan-17	Aug-17	March-18
Total Candidate Rate/Month	**8.4**	**3.0**	**6.0**
Enrollment Population Total	**130**	**30**	**10**
Total Enrollment Duration (Months)	**15.4**	**10**	**1.7**

Estimated Enrollment Completion Quarter IV 2018

- After patients check in at Pleasant View Surgery Center, they will be given a formal consent form to sign describing the study, outlining risks and benefits, and what is required throughout the duration of the trial. Patients will be able to read and receive verbal information about the trial. An authorized clinical study representative will go over the informed consents and answer all questions and concerns related to the study. After full disclosure and understanding, the patient will sign the informed consent.

- If an eligible candidate is vulnerable and unable to provide consent, they will be offered the standard of care relating to unilateral knee arthroplasty and options for radiofrequency ablation. However, they will not be enrolled in the study because of the possibility of receiving the SHAM procedure.

4.1 Randomization

Randomization will be confirmed by the Clinical Research Director/Study Coordinator and/or treatment providers at Pleasant View Surgery Center after informed consent is obtained.

4.1.1 A proportionate randomization is identified dividing the study population into three equal groups (≥50 t-RFA; ≥50 C-RFA; & ≥50 SHAM). The randomization will be based on a numeric number generator (numbergenerator.org) or as outlined in the table below.

Control SHAM may conclude before 50 subjects are treated when statistical significance between SHAM and the two RFA arms is reached ($p \leq 0.025$) (see *sample* table *Randomization Procedure*).

4.1.2 The Clinical Research Director and/or authorized study representative will fill out a study form for the patient indicating the specific treatment assigned to the subject, the provider performing the treatment, the date, and the referring surgeon (Appendix I). This form will be stored and locked primary study file located in a locked cabinet at the Clinical Study Administrative office.

Randomization Procedure				
Enrollment Date	**Surgeon**	**Reference #**	**Treatment**	**Treatment Provider**
01/02/17	Jeff Lyman, MD	0001	C-RFA	Greg Bauer, CRNA
01/03/17	Jeff Lyman, MD	0002	t-RFA	Doran Thomas, CRNA
01/15/17	Tim Lovell, MD	0003	SHAM	Greg Bauer, CRNA
01/15/17	Jeff Lyman, MD	0004	t-RFA	Mike Ludwig, MD
01/16/17	Jeff Lyman, MD	0005	t-RFA	Doran Thomas, CRNA
01/16/17	Tim Lovell, MD	0006	SHAM	Mike Ludwig, MD
01/30/16	Jeff Lyman, MD	0007	C-RFA	Doran Thomas, CRNA
02/01/17	Jeff Lyman, MD	0008	C-RFA	Mike Ludwig, MD
02/01/17	Jeff Lyman, MD	0009	SHAM	Greg Bauer, CRNA
02/01/17	Jeff Lyman, MD	0010	C-RFA	Greg Bauer, CRNA

4.1.3 Upon recruitment and pain management referral, patients will be assigned a *Study Reference Number*.

4.1.4 Treatment arm allocation is random and not based on diagnostic or demographic values.

4.1.5 Enrollment date is determined by the date the candidate is recruited and agrees to be referred to one of the RFA study treatments.

4.1.6 Treatment providers are randomly predetermined by the referring physician and/or the clinical study representative who will use the random number generator for numbers 1, 2, 3 which corresponds to each provider. All three providers are experienced with radiofrequency ablation and qualified to perform all three treatment arms (t-RFA, C-RFA, SHAM).

4.1.7 Pleasant View Surgery Center (PVSC) is the treatment location for randomization (t-RFA, C-RFA or SHAM) treatments.

4.2 Double Blinded Patient Record Management

4.2.1 Investigators will not have access to the hard copy files pertaining to their patients and the treatments they receive. Neither patients nor study investigators will have access to patients' randomized treatment information.

4.2.2 Authorized study representatives and the Administrator at Pleasant View Surgery Center will have access to the clinical study participant locked file cabinet.

4.2.3 If patients submit a request to view their treatment records or if patient records pertaining to the t-RFA, C-RFA, SHAM are sent to any other provider during the blinded portion of the primary study (from consent to 6 months following total knee arthroplasty), the patient will be removed from the clinical study (see 3.25).

4.2.4 Treatment providers will implement a standard generic dictation that will not specify which procedure the study participant received. "The study patient underwent one of three clinical trial procedures at PVCS…"

4.2.5 The digital record will not specify which treatment arm the patient received. The digital file will be kept as a patient hard copy file at Pleasant View Surgery Center.

4.2.6 Treatment providers will specify that a copy of the dictation and specific treatment is on file at Pleasant View Surgery Center where it will be kept in a secured file cabinet.

4.2.7 Drs. Lyman, Olscamp, and Lovell (study investigators) may receive a copy of the digital record that does not specify the specific treatment received as indicated in 4.2.4.

4.2.8 There will be no charge for the randomized treatments. Neither patients nor insurances will be billed for the randomized study treatment procedures. Therefore, this research phase will bypass incidental patient or investigator awareness through billing records at PVSC.

05.0 TREATMENT PLAN

The clinical study is divided into preoperative, operative, and postoperative stages. The operative and postoperative stages are adherent to industry standard of care.

Preoperative

The preoperative radiofrequency treatments have been used as a standard of care for knee pain associated with osteoarthritis. However, the preoperative intent to relieve knee pain, following total knee replacement, is a novel application. Comparative studies with all three treatment groups have not been published, and therefore this is the research

component of the trial. The t-RFA, C-RFA and SHAM procedures will be performed by three Halyard trained providers at PVCS. The estimated procedural time is 45 minutes.

Operative

The operative unilateral knee arthroplasty is an industry standard of care routinely performed by the study investigators at Northwest Specialty Hospital, Pleasant View Surgery Center and Providence Sacred Heart Medical Center. Institutional standards will be followed for hydration, pre-medications, postoperative wound care, rehabilitation, and pain management as needed. This is a multi-provider, multi-center clinical investigation.

Postoperative

The postoperative rehabilitation phase is an industry standard of care including physical therapy, pain management and routine office visits. The study subjects will maintain a pain and opioid pill count diary until cessation. Phone interviews will conclude after 12 months.

PROVIDER PROCEDURE CHART				
PROVIDER	**Pleasant View Surgery Center**	**Northwest Specialty Hospital**	**Providence Sacred Heart Medical Center**	**Participating Physical Therapy Clinics**
Jeffrey Lyman, MD	**Total Knee Replacement**	**Total Knee Replacement**		
Adam Olscamp, MD	**Total Knee Replacement**	**Total Knee Replacement**		
Timothy Lovell, MD			**Total Knee Replacement**	
Mike Ludwig, MD	***t-RFA; C-RFA, SHAM***			
Greg Bauer, CRNA	***t-RFA; C-RFA, SHAM***			
Doran Thomas, CRNA	***t-RFA; C-RFA, SHAM***			
Participating Physical Therapy Clinics				**SUB STUDY Physical Therapy**

5.1 Preoperative Treatment Plan

Treatment: t-RFA; C-RFA; or SHAM

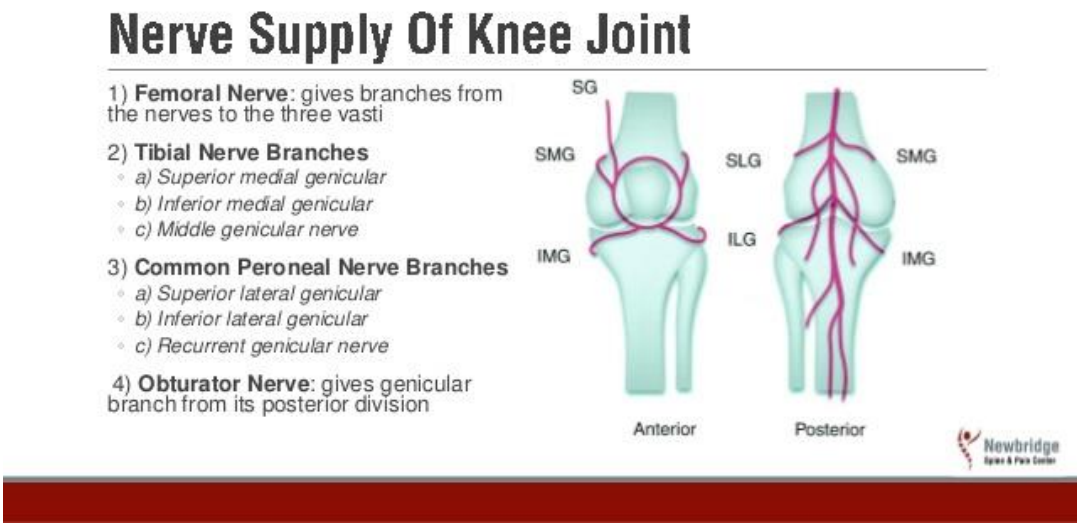
Location: Pleasant View Surgery Center

Treatment Providers: Mike Ludwig, MD; Greg Bauer, CRNA; Doran Thomas, CRNA (Certified Training Provided by Halyard Health)
Treatment Category: Research for Unilateral Knee Arthroplasty Pain Management
Cost: Patient Incurs NO Cost; Funding Provided by Dr. Lyman, Pleasant View Surgery Center, Lyman Medical Research Foundation, INC, and Halyard Health. Investigators will receive no compensation for the clinical trial.

The preoperative treatment plan involves patients that were randomized into three study arms (t-RFA, C-RFA, SHAM).

Pregnancy testing will be performed by urine dip for any female who is regularly or irregularly menstruating. If pregnant, the procedure will not be performed, and the patient is ineligible to enroll in the trial at that time.
The providers will evaluate the skin and musculature for patients' body habitus as it relates to the exclusion criteria. If the body habitus is contraindicative, they will not be enrolled but can receive the standard thermal t-RFA if they choose. Appropriate insurance and patient billing for the costs will transpire.

All patients will be prepared with an IV to administer total intravenous anesthetic to provide comfort. The treatment instruments will be turned on but not in the patient's

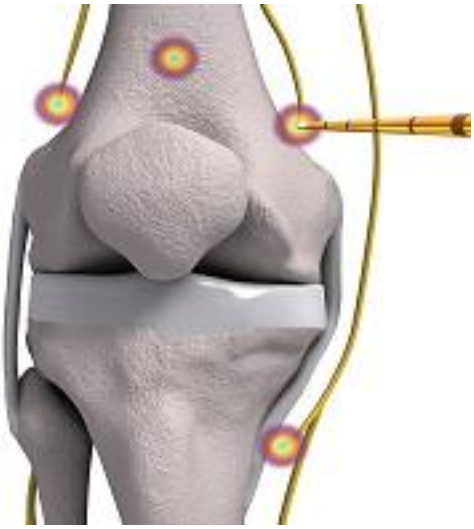


view. Once the patient is affected by the anesthetic, the procedure will be initiated. Patients will be sedated and unaware of the procedure that is performed and will remain blinded.

5.1.1 Cooled Radiofrequency Ablation (C-RFA) *Coolief by Halyard*

Subjects randomized to C-RFA will be placed in a supine position on a fluoroscopy table with a pillow under the popliteal fossa to alleviate discomfort. The true AP fluoroscopic view of the tibiofemoral joint will be obtained to show the tibiofemoral joint space with equal width interspaces on both sides.

Note: An exclusion criteria exists for body habitus. Extremely thin patients and those with minimal subcutaneous tissue thickness, that would not accommodate a lesion of up to 14 mm in diameter, will be excluded to limit the risk of skin burns. The treatment provider will examine the patient at Pleasant View Surgery Center. If the patient is excluded, they will be offered the standard thermal t-RFA and will not participate in the study. If the patient elects to proceed with the t-RFA and is not enrolled, the patient and the patient's insurance will be billed for the treatment costs.



An appropriately sized (17 gauge) cooled radiofrequency needle will be placed overlying the affected knee joint and using fluoroscopic guidance the needle will be advanced to a bony endpoint on the superior lateral portion of the femoral condyle of the affected knee. A second needle will be advanced to a bony endpoint on the superior medial portion of the femoral condyle. A third needle will then be placed over the inferior medial portion of the tibial condyle until a bony endpoint is met. A fourth needle will be placed 2 cm cephalad to the epiphyseal line of the distal femur and 50% diaphysis of the femur anteriorly. Care should be taken to avoid inserting the RF probe into the inferolateral area of the knee to avoid the common peroneal nerve and potential foot drop. Watch for pooling of blood or fluid in the stylet. If seen, aspirate and reposition as necessary.

Lateral x-ray views taken during the procedure should show all the needles with probes in place at 50% depth of the femur and tibia. Motor stimulation must be tested at 2.0 volts with no leg movement. Sensory stimulation should be conducted at < 0.5 volts in all four locations with concordant pain reproduction. All images must be saved in AP and lateral views and become part of the source documentation for the study. A mixture consisting of 1cc lidocaine 1% and 1cc Marcaine 0.5% with a maximum volume of 2 cc should then be slowly injected. Then a radiofrequency ablation of each of the four targeted nerves will be conducted at 60° C for 2 minutes and 30 seconds at each of the 4 anatomic

locations. One burn will occur at the four sites just past the midline. The treatment is removing the myelin from the Delta A fibers and causing axonal injury of the C fibers, thus impeding the pain signal. Upon conclusion, the needles will be removed, the insertion sites will be treated with appropriate closure, and the subject will be allowed to properly recover prior to discharge home. Instillation of postoperative analgesic pain medication is permissible per institutional standard of care.

5.1.2 Traditional Radiofrequency Ablation (t-RFA) *supplied by Halyard*

Subjects randomized to t-RFA will be placed in a supine position on a fluoroscopy table with a pillow under the popliteal fossa to alleviate discomfort. The true AP fluoroscopic view of the tibiofemoral joint will be obtained to show the tibiofemoral joint space with equal width interspaces on both sides. An appropriately sized (16 gauge) radiofrequency needle will be placed overlying the affected knee joint, and using fluoroscopic guidance, the needle will be advanced to a bony endpoint on the superior lateral portion of the femoral condyle of the affected knee. A second needle will be advanced to a bony endpoint on the superior medial portion of the femoral condyle. A third needle will then be placed over the inferior medial portion of the tibial condyle until a bony endpoint is met. A fourth needle will be placed 2 cm cephalad to the epiphyseal line of the distal femur and 50% diaphysis of the femur anteriorly. Care should be taken to avoid inserting the RF probe into the inferolateral area of the knee to avoid the common peroneal nerve and potential foot drop. Watch for pooling of blood or fluid in the stylet. If seen, aspirate and reposition as necessary.

Lateral x-ray views taken during the procedure should show all the needles with probes in place at 50% depth of the femur and tibia. Motor stimulation must be tested at 2.0 volts with no leg movement. Sensory Stimulation should be conducted at < 0.5 volts in all four locations with concordant pain reproduction. All images must be saved in AP and lateral views and become part of the source documentation for the study. A mixture consisting of 1cc lidocaine 1% and 1cc Marcaine 0.5% with a maximum volume of 2cc should then be slowly injected. Then a radiofrequency ablation of each of the four targeted nerves will be conducted at 80° C for 90 seconds actual burn time at each of the 4 anatomic locations. One burn will occur the four sites just past the midline (Santana Pineda MM1, 2016). The treatment is removing the myelin from the Delta A fibers and causing axonal injury of the C fibers, thus impeding the pain signal. Upon conclusion, the needles will be removed, the insertion sites will be treated with appropriate closure, and the subject will be allowed to properly recover prior to discharge home. Instillation of postoperative analgesic pain medication is permissible per institutional standard of care.

5.1.3 Simulated Radiofrequency Ablation (SHAM)

Subjects randomized to SHAM will be placed in a supine position on a fluoroscopy table with a pillow under the popliteal fossa to alleviate discomfort. The true AP fluoroscopic view of the tibiofemoral joint will be obtained to show the tibiofemoral joint space with equal width interspaces on both sides. An appropriately sized (22 gauge) radiofrequency needle will be placed overlying the affected knee joint and using fluoroscopic guidance the needle will be advanced to a bony endpoint on the superior lateral portion of the femoral condyle of the affected knee. A second needle will be advanced to a bony endpoint on the superior medial portion of the femoral condyle. A third needle will then be placed over the inferior medial portion of the tibial condyle until a bony endpoint is met. A fourth needle will be placed 2 cm cephalad to the epiphyseal line of the distal femur and 50% diaphysis of the femur anteriorly. Care should be taken to avoid inserting the RF probe into the inferolateral area of the knee to avoid the common peroneal nerve and potential foot drop. Watch for pooling of blood or fluid in the stylet. If seen, aspirate and reposition as necessary.

Lateral x-ray views taken during the procedure should show all the needles with probes in place at 50% depth of the femur and tibia. A mixture consisting of 1cc lidocaine 1% and 1cc Marcaine 0.5% with a maximum volume of 2 cc should then be slowly injected. At the conclusion of the procedure, the needles will be removed, the insertion sites will be treated with appropriate closure, and the subject will be allowed to properly recover prior to discharge home. Instillation of post-operative analgesic pain medication is permissible per institutional standard of care.

The t-RFA and C-RFA treatment procedures may provide pain relief benefits that may last from 6-9 months. The duration of pain relief benefits depends upon the healing time and regeneration of the nerve. It may take 4-6 weeks or sooner to experience the pain relief benefits from the RFA treatment. The SHAM group will undergo a simulated procedure wherein the nerve will be undisturbed. The SHAM RFA will receive no additional pain relief benefits associated with RFA because an ablation will not be performed on the nerves. All three groups will receive total knee replacement surgery, and a routine standard of care in the hospital and after surgery. All three groups will have access to pain medication after surgery as needed.

5.2 Operative Treatment Plan: Total Knee Arthroplasty

Treatment: Unilateral Knee Arthroplasty
Location: Northwest Specialty Hospital; Pleasant View Surgery Center; and Providence Sacred Heart Medical Center
Treatment Providers: Jeffrey Lyman, MD; Adam Olscamp, MD; Timothy Lovell, MD
Treatment Category: Routine Standard of Care for Knee Replacement Surgery
Cost: Patients are responsible and insurances will be billed

Dr. Lyman, Dr. Olscamp, and Dr. Lovell may or may not use a computer assisted knee modality with an industry standard implant. The total knee arthroplasty procedures are a routine standard of care for both physicians.

Anesthesia may be either General Anesthesia or a Spinal with intrathecal Bupivacaine with Morphine. The Bupivicaine and Morphine form a compound that binds to the receptor for 24-hour pain relief. No systemic Morphine or Exparel is used.

Ketamine may be used by the physicians as indicated by standard of care protocol.

5.3 Postoperative Treatment Plan

Treatment: Knee Replacement Physical Therapy Rehabilitation
Location: Multi-Clinic Regional Locations
Treatment Providers: Multi-Clinic Regional Providers
Treatment Category: Routine Standard of Care for Knee Replacement Rehabilitation
Cost: Patients are responsible and insurances will be billed

The postoperative treatment plan includes access to traditional pain management as needed *(see Pain Management and Drug Administration 5.3.1)*, postoperative office visits/phone interviews, and physical therapy rehabilitation (Sub-study).

- Postoperative Radiographs
- Physical Therapy
- Routine Standard Analgesic Orders

5.3.1 Pain Management and Drug Administration

The three treatment arms will have access to traditional pain management as it relates to the industry standard of care. The preoperative, operative, and postoperative medications will be used by both treating physicians.

Prior to the total knee arthroplasty surgery, patients may be counseled on medication usage and may receive a medication usage instructions sheet from the providers that prescribe the medications as a standard of care (see Appendix J) at providers' discretion. The medication usage sheet is not required to be provided to the subject for all investigators, but is available for those providers' subjects who are prescribed the medications in Appendix J. Providers who do not prescribe all of the medications on the medication usage instruction sheet may not provide the subjects with the sheet in Appendix J. The following medications may be available.

Preoperatively
MS Contin 15 mg tablets 12-hour release

Transderm-Scopalamine 1.5 mg Patch

Operatively
60 cc 0.25 % Ropivacaine dilute with 40 cc normal saline to total volume of 100 cc
Patients > 70 yrs and Creatinine Normal 15 mg Toradol
Patients < 70 yrs and Creatinine Normal 30 mg Toradol
(Toradol is determined by age and renal function)
4 mg morphine

Postoperatively
MS Contin 15 mg tablets 12-hour release
Oxycodone 5 mg tablets
Hydrocodone 5 mg/325 mg tablets
Aspirin 325 mg twice a day for 5 weeks (for prevention of deep vein thrombosis/clots)
Hibiclens (cleaning the night before and morning of surgery)
3 grams Tylenol daily/oral
10 mg Ambien Q6 PRN sleeplessness/anxiety
Zofran for nausea
Multivitamins; iron supplements; constipation medication

5.3.2 Postoperative Office Visits and Telephone Pain Score Interviews

Industry standard of care will be implemented for all postoperative office visits. Study subjects will maintain a daily diary for pain and opioid pill usage. Phone interviews will be conducted periodically for pain scores and opioid pill count. No additional office visits and associated costs will be imposed on the patient for research purposes. Follow-up interactions will occur at study time-points *(see Evaluations 6.0).*

5.3.3 Sub-Study: Physical Therapy Rehabilitation

The sub-study will include rehabilitation program using an industry standard of care for postoperative knee arthroplasty physical therapy. This will be a multi-clinic investigation where all clinics will adhere to the predetermined industry standard rehabilitation protocol (see Appendix C). Clinics will sign an agreement to participate in the study (see Appendix D).

5.3.3.1 During enrollment, patients who consent to the primary study will be offered the opportunity to enroll in the physical therapy sub-study. A separate consent form (see Appendix B) will be provided to the patient for their participation in the physical therapy sub-study.

5.3.3.2 Participating physical therapy clinics will be presented to the study subjects from which they will choose their preferred study site.

5.3.3.3 An industry standard physical therapy protocol will be implemented (see Appendix C).

5.3.3.4 Participating physical therapy sites will sign a *Participation Agreement* with Lyman Medical Research Foundation, Inc. (see Appendix D).

5.3.3.5 Patients wanting to enroll in the physical therapy sub-study and who wish to see a non-participating physical therapy provider will be unable to enroll in the physical therapy sub-study. However, they will receive physical therapy standard of care during their rehabilitation.

06.0 STUDY SCHEDULE & EVALUATIONS

Pre-study > 3 Weeks Prior to Surgery

Office visit by potential candidates seeking medical care for knee pain. Routine assessments are taken for all patients seeking medical care for knee pain. If the patients meet the enrollment criteria, then the provider may invite the patient to participate in the study and if interested will be referred to the study treatment. Invitation may be during the clinical appointment or telephone. Interested patients will be referred to the study treatment as outlined in section 4.0 of this protocol. The patient will receive the "study packet' which includes recruiting materials (Appendix J), directions to the surgery center, participating physical therapy sites and copies of the informed consent (Appendixes A&B) to take home. Interested patients will be referred to one of the three treatment providers. The referring provider will complete an enrollment eligibility form for the subjects file

Consent and Randomization Treatment 3-12 Weeks Prior to Surgery

The patient will be scheduled for a procedure with a randomly selected treatment provider at the Pleasant View Surgery Center. Before the procedure, the patient will meet with an authorized clinical study representative to review the information about the trial, review the informed consents, and sign the informed consent. The informed consent verification form will be completed and placed in the subjects file. After consent is obtained, the authorized clinical study representative will inform the provider which randomization (t-RFA, C-RFA, SHAM) the subject will undergo. The WOMAC and Numeric Pain scores, and medical release will be obtained from the subject. Selected physical therapy clinic will be confirmed. *If the surgery occurs more than 12 weeks after the randomized RFA study treatment, the patient may remain in the study with an out-of-window surgery.*

Pre-Operative Office Visit with Surgeon

During this office visit the patient will be evaluated for any RFA complications, pain scores will be documented and information will be provided regarding medication usage and standard of care information for TKA. The patient pain medication usage and pain

diary will be given to the subject for post-surgical documentation. The subject travel reimbursement form will be given at this time for the subject to complete and return to the study for mileage reimbursement to and from Pleasant View Surgery Center. The WOMAC scores will be obtained from the subject.

Day of Surgery
The patient will be admitted to either Northwest Specialty Hospital, Pleasant View Surgery Center, or Providence Sacred Heart Medical Center to undergo unilateral knee arthroplasty with either Dr. Lyman, Dr. Olscamp, or Dr. Lovell.

Day 1 After Surgery
The patient will receive routine medical care, including pain assessment and traditional pain relief medication as indicated.

Day 3 (±1) Day After Surgery
The patient will receive routine medical care including but not limited to pain assessment and traditional pain relief medication as indicated while admitted to the hospital. Discharge assessments may occur. If patients discharge early, then a phone interview will assess their pain and opioid use.

Week 1 (± 3) Days After Surgery
The patient will be contacted by phone for a pain score assessment and interviewed for opioid pill consumption counts.

Week 2 (± 3) Days After Surgery
The patient will have a routine postoperative appointment with the surgeon and a pain score will be assessed along with pain medication usage. The WOMAC scores will be gathered from the patient. The pain medication usage and pain score diary will be collected from the subject and additional diaries will be provided as needed.

Week 6 (±1) Weeks After Surgery
The patient will have a routine postoperative appointment with the surgeon and a pain score will be assessed along with pain medication usage. The WOMAC scores will be gathered from the patient. The pain medication usage and pain score diary will be collected from the subject and additional diaries will be provided as needed.

Week 12 (±1) Weeks After Surgery
The patient will be contacted by phone for a pain score assessment and interviewed for pain medication use and frequency.

Month 6 (±1) Month After Surgery
The patient will be contacted by phone for a pain score assessment and interviewed for pain medication use and frequency.

Month 12 (±1) Months After Surgery

The patient will have a routine postoperative appointment with the surgeon and a pain score will be assessed along with pain medication usage.

Study Timeline and Costs										
ACTIVITY	Office VISIT	*STUDY*	Office VISIT	SURGERY	*STUDY PHONE*	Office VISIT	Office VISIT	*STUDY PHONE*	*STUDY PHONE*	Office VISIT
	Initial	≥ 3 weeks before surgery	Pre-Op for TKA	3 - 12 weeks after study treatment	Interview 1 week (± 3 days) after surgery	Post-Op 2 weeks (± 3 days) after surgery	Post-Op 6 (± 1) weeks after surgery	Interview 12 (± 1) weeks after surgery	Interview 6 (± 1) months after surgery	Post-Op 12 (± 1) months after surgery
TKA Medical History	S									
TKA Labs Ordered	S									
TKA Brief Physical	S									
TKA X-Ray Ordered	S									
TKA MRI Ordered	S									
TKA Pre-Op Office Visit			S							
Informed Consent; Randomized Treatment; *Pregnancy Screening		R								
Total Knee Arthroplasty (TKA)				S						
TKA Post-Op Office Visit						S	S			S
Opioid Usage and Pain Score Phone Interviews					R			R	R	
Physical Therapy	N/A				S					

6.1 Trial Treatment Discontinuation

A patient will be discontinued from trial treatment under the following circumstances:

- If there is evidence of progressive exclusion criteria.
- If the physician determines a change of treatment would be in the best interest of the patient.
- If the patient requests discontinuation.
- If the treatments exhibit an unacceptable adverse event.
- If a patient becomes pregnant.
- Patients may discontinue their trial enrollment and treatment at any time.
- If patients discontinue enrollment they will continue to be treated routinely for postoperative knee arthroplasty.
- If patients request or release their medical records from time of consent to 6 months after surgery.

6.2 Clinical Trial Follow

Follow-up Procedures
Patients will be followed according to the routine standard of care after completion of, or early withdrawal from study treatments.

07.0 REPORTING ADVERSE EVENTS & SERIOUS ADVERSE EVENTS

7.1 Definitions of Adverse Events

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a study procedure and which does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the t-RFA, C-RFA or control SHAM treatment, whether or not related to the preoperative treatment.

7.1.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Results in death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

7.1.3 Unexpected Adverse Event (UAE)

An adverse event not mentioned in the preoperative treatment consent, or operative consent or the specificity or severity of which is not consistent with the performed standard of care procedures.

7.2 Adverse Event (AE) Reporting

Adverse events (AE) will be recorded from the time of consent and for at least 30 days after unilateral knee arthroplasty, regardless of whether or not the event(s) are considered related to trial procedural application. All AEs considered related to trial procedural applications will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

7.2.1 Requirements for Reporting SAEs

Investigators and other personnel must report any SAEs occurring during the course of the study within one business day of discovery of the event. This includes events both related and unrelated to the trial treatments. The definition of "related" being that there is a reasonable possibility the randomized treatment caused the adverse experience.

Unrelated	The Adverse Event is *clearly not related* to SHAM, t-RFA or C-RFA
Unlikely	The Adverse Event is *doubtfully related* to SHAM, t-RFA or C-RFA
Possible	The Adverse Event *may be related* to SHAM, t-RFA or C-RFA
Probable	The Adverse Event is *likely related* to SHAM, t-RFA or C-RFA
Definite	The Adverse Event is *clearly related* to SHAM, t-RFA or C-RFA

The completed SAE Report Form must be faxed to Dr. Lyman within 1 working day of discovery of the event. The principal investigator (PI) is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.
The original copy of the SAE Report and the fax confirmation sheet must be kept within the secured primary clinical study file at the Executive Director Clinical Research's office.

Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

7.2.2 Death and Immediately Life-Threatening Events

Any death and immediately life-threatening event from any cause while a patient is receiving trial treatment on this protocol or up to 30 days after standard of care unilateral

knee arthroplasty, or any death and immediately life-threatening event occurring more than 30 days after trial treatment but which is felt to be SHAM, t-RFA, or C-RFA treatment related must be reported **within one working day of discovery of the event**. All deaths must be reported primarily for the purposes of SAE reporting; however, deaths due unequivocally to issues unrelated to preoperative SHAM, t-RFA, or C-RFA are not SAEs.

The IRB should be notified and their reporting procedure followed. The completed SAE Reporting Form should be faxed to Dr. Lyman **within one working day of discovery of the event**.

08.0 STATISTICAL CONSIDERATIONS

8.1 Numeric Rating Scale (NRS) is an 11-point numeric scale with 0 representing "no pain" and 10 representing the "worst pain". The WOMAC consists of 24 items divided into 3 subscales to assesses pain, stiffness, and physical function in patients with knee osteoarthritis (OA). The WOMAC and NRS will be used for the three treatment arms of the study for patients who received standard thermal radiofrequency ablation (t-RFA), cooled radiofrequency ablation (C-RFA) and SHAM. These scores will be measured as outlined in section 0.60, study schedule and evaluations.

NRS

t-RFA

0 No Pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Worst Pain**

C-RFA

0 No Pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Worst Pain**

SHAM

0 No Pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Worst Pain**

Statistical analyses for the three variables (t-RFA, C-RFA, SHAM) will be performed using appropriate analyses by a third party contracted statistician, Sterling McPherson, Ph.D., as a Providence Medical Research Center Employee. To enhance the credibility and appeal in the greater scientific community, a third-party unbiased statistician will perform all statistical analyses. Additionally, the SHAM group and double-blinded masking attributes to the validity of the study.

INTERIM & Final ANALYSES

The hypotheses will be tested using Bonferroni (α/m) where *alpha* (α) is the desired overall significance ($p \leq 0.05$) and *m* is the number of hypotheses. An interim analysis will be performed when there are 50-80 subjects with completed TKAs. Applicable data will be analyzed for the two RFA treatment arms, t-RFA and C-RFA, may be collapsed together and their scores will be compared to the SHAM treatment arm (thus *m* is 2). Bonferroni correction $p = 0.05/2 = 0.025$ will be applied for the t-test analysis of SHAM versus RFA treatment arms. This will determine significance in SHAM versus combined RFA treatments. ANOVA may also be used for the first interim analysis. If the interim analysis determines the cessation of SHAM treatments, the informed consent will be revised and submitted for IRB approval to proceed with the two RFA treatment arms (t-RFA and C-RFA).

Justification for the interim analysis prioritizes patient care and therefore an interim analysis penalty may be waived and discussed in the analyses. The motive and priority for the interim analysis is to implement best practices for study patients and avoid unnecessary SHAM procedures when significance is reached. If evidence comparing RFA to SHAM treatments is statistically significant during the interim analysis the SHAM treatment arm will stop. Enrollment for the two remaining RFA treatment arms will continue and a revised protocol will be submitted to the IRB for approval upon discontinuation of the SHAM arm.

If final analysis of data reveals no significance at primary endpoints, then data collection for the 1 year timepoint will cease and subjects will be notified with a Providence-IRB approved letter. Subjects will have access to standard of care from their physicians.

8.2 Opioid utilization will be assessed for continuous daily use postoperatively from day of surgery [0 – 48 hours] through three weeks after surgery and until cessation. The opioid use measurements will be determined for the three treatment arms of the study for patients who received standard thermal radiofrequency ablation (t-RFA), cooled radiofrequency ablation (C-RFA) and SHAM. The statistician will assess "morphine equivalent" analysis for in-hospital medication use. This calculates the equivalent morphine dosage for other pain relief medications used.

Opioid utilization for quantity of pills taken daily will be assessed from day of surgery through 3 weeks after surgery and until cessation if available. Patient recorded daily amounts of opioid pills taken from day of surgery through 3 weeks after surgery will be used to assess the quantity of discharged opioid usage, if patient diary integrity is available. If comprehensive opioid consumption is unavailable from the diaries then analysis will be deferred to opioid cessation dates where available. The patient diaries will be collected from the patients.

In-hospital opioid medication usage will be obtained from the patient release of medical records and/or from pharmacy billing records.

Morphine equivalents may be calculated for in-patient opioid usage. Inpatient NRS will be analyzed accordingly. Opioid daily utilization and opioid quantity utilization statistical analyses for the three variables (t-RFA, C-RFA, SHAM) will be performed by a third party contracted statistician, Sterling McPherson, Ph.D. with Providence Medical Research Center.

8.3 Hospital Length of Stay (LOS) will be documented for the three treatment arms (t-RFA, C-RFA, SHAM), and statistical analysis will be performed by a third party contracted statistician, Sterling McPherson, Ph.D. with Providence Medical Research Center.

Three-day timepoint for discharge are based on CMS regulations and will be distinguished between assisted nursing home release and independent home release with outpatient physical therapy. Industry standard discharge criteria will be followed see (Appendix L). Examples of physician home discharge criteria include but are not limited to oxygen saturation, stable hemodynamic, independently mobile, and stable hemoglobin that is appropriate for age.

8.4 SUB-Study statistical analyses will consist of Western Ontario and McMaster Universities (WOMAC) score, numerical pain, range of motion (ROM) and milestones.

8.4.1 WOMAC (Appendix H)
Score Range: On the Likert Scale version, the scores are summed for items in each subscale, with possible ranges as follows: pain=0-20, stiffness=0-8, physical function=0-68. Most commonly, a total WOMAC score is created by summing the items for all three subscales.

8.4.2 Range of Motion (ROM)
ROM will be measured by degrees for the three groups. The mean will be determined for three groups and statistical analyses will be performed.

WOMAC and ROM scores for the three variables (t-RFA, C-RFA, SHAM). Statistical analyses will be performed by a third party contracted statistician, Sterling McPherson, Ph.D. with Providence Medical Research Center

8.4.3 Milestones
Milestones will be measured at weekly intervals following the physical therapy protocol.

Statistical analyses for milestones for the three variables (t-RFA, C-RFA, SHAM) will be performed by a third party contracted statistician, Sterling McPherson, Ph.D. with Providence Medical Research Center.

Data Sets for Protocol Endpoints

Data Set/Endpoint	Criteria
Pain Scores	Numerical Pain Scores 0-10 where 0 is no pain and 10 is worse pain and WOMAC
Diary Opioid Usage	Quantified by opioid pills per day (if available) to cessation of opioid utilization
Morphine Equivalent	In-Hospital Morphine equivalent usage may be calculated using the patient hospital records
Hospital Length of Stay (LOS)	Quantified by a 24-hour day where one day equals 24 hours after surgery completion, independent ambulatory discharge criteria applied
Physical Therapy	Sub-Study: WOMAC, Pain, ROM, Milestones

09.0 TRIAL MANAGEMENT

9.1 Quality Controls and Quality Assurance

9.1.1 Study Monitoring

The Principal Investigator and/or authorized clinical study representative will perform periodic monitoring visits to the participating sites during the trial, to ensure all aspects of the protocol are followed. An authorized clinical study representative will visit Pleasant View Surgery Center monthly to review source documents for verification of agreement and with data. The Executive Director Clinical Research will oversee appropriate randomization and documentation of the treatment procedures. Neither the PI nor patients will have access to source documents or any documents obtaining patient identifiers to adhere to the double-blinded masking. The interim analysis, absent of patient identifiers, may be reviewed by the PI when considering SHAM cessation. Source data that include patient identifiers will be stored and locked and inaccessible by the PI or Co-PI as outlined in section 4.2. Spreadsheet data without patient identifiers may be available as desired by the PI and Co-PI. The investigator and institution guarantee access to source documents by Lyman Medical Research Foundation, INC or its designee and appropriate regulatory agencies. The trial site may also be subject to quality assurance audits by Spokane-IRB, Halyard Health, Lyman Medical Research Foundation, Inc., Dr. Lyman or its designee as well as inspection by appropriate regulatory agencies.

The investigator and/or their relevant personnel will be available during the monitoring visits, possible audits and sufficient time to be devoted to the process.

9.1.2 Data Collection and Quality Assurance

Data Collection Forms

Data will be recorded by authorized clinical study representatives. All data will be secured in a locked file cabinet, password protected computer file, and hard copy files will be locked in research office. Electronic data will be backed up routinely to an encrypted external network.

Quality Assurance

Protocol Deviations: Deviations from the protocol, unless immediately life threatening, will require approval by the Principal Investigator and Co-Investigator and will be sent to the IRB as an RNI and possible revision to the protocol subject to IRB review and approval.

Monitoring: Routine monitoring of the participating sites, personnel, recording keeping, record storage, confidentiality, blinded status and follow-up will be done by the Executive Director Clinical Research and documented in the in the Quality Assurance (QA) file.

9.2 Changes to the Protocol

Study procedures will not be changed without the mutual agreements between Halyard Health, Investigator, and Co-Investigator and until a revision to the protocol has been reviewed and approved by the IRB.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by the Principal Investigator and must be approved by the IRB.

If a protocol amendment requires a change to the Written Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB will be obtained before the revised form is used.

The Principal Investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled accordingly.

9.3 Ethics

9.3.1 Ethics Review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved in writing by an IRB.

The principal investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit patients for the study. Annual protocol IRB approval is required, as local regulations require.

Progress reports and notifications of serious unexpected adverse events will be provided to the IRB as specified by local regulations and guidelines.

The investigator is also responsible for providing the IRB with reports of any serious adverse event from any other study conducted using the SHAM, t-RFA, or C-RFA treatments. Jeffrey Lyman, MD is the Primary Investigator. These reports may be reviewed by Halyard Heath. Those considered unexpected and possibly related to preoperative treatment plus all deaths within 30 days after surgery will be forwarded to participating sites for submission to their Institutional Review Board per their guidelines. All other events will be held and submitted to the sites for continuing review.

9.3.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

9.4 Written Informed Consent

The investigator will ensure patients are given full and adequate oral and written information about the nature, purpose, possible risks, and benefits of the study. Patients must also be notified they are free to discontinue from the study at any time. The patient will be given the opportunity to ask questions and allowed time to consider the information provided.

The patients' signed and dated informed consents must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed Written Informed Consent Form. A carbon copy of the signed Written Informed Consent Form will be given to the patient.

9.5 Grant Funding

Halyard Health is the grantor for the study costs including but not limited to patient preoperative treatment costs for t-RFA, C-RFA, and SHAM; financial management, statistical analyses; DVD Informational and Informed Consent video and print materials,

trial management personnel; patient travel reimbursement (see APPENDIX N); and conference attendance. The investigators, Drs. Lyman, Olscamp, and Lovell, will receive no compensation for the research trial.

10.0 REFERENCES

Choi WJ, H. S. (2011). Radiofrequency treatment relieves chronic knee oseoarthritis pain: A double-blind randomized controlled trial. *Pain*, 481-487.

Husted H, L. T.-L. (2011). Why still in hospital after fast-track hip and knee arthroplasty? *Acta Orthopaedica*, 679-684.

Kurtz S, O. K. (2007). Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *American Journal of Bone Joint Surgery*, 780-785.

Patel A, P. G.-M. (2015). The epidemiology of revision total knee and hip arthroplasty in Engalnd and Wales: a comparative analysis with projections for the United States. A Study using th national Joint Registry dataset. *The Bone and Joint Journal*, 1076-1081.

Santana Pineda MM1, V. L. (2016, November). Analgesic Effect and Functional Improvement Caused by Radiofrequency Treatment of Genicular Nerves in Patients With Advanced Osteoarthritis of the Knee Until 1 Year Following Treatment. *American Society of Regional Anesthesia and Pain Medicine*.

Stelzer W, A. M. (2013). Use of cooled radiofrequency lateral branch neurotomy for the treatment of sacroiliac joint-mediated low back pain: A large case series. *Pain Medicine*, 29-35.

LYMAN
MEDICAL RESEARCH FOUNDATION

APPENDIX A

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

TITLE OF STUDY

Comparison Between Cooled Radiofrequency Ablation (C-RFA), Standard Radiofrequency Ablation (t-RFA), and Control for Postoperative Pain Management Following Unilateral Knee Arthroplasty: A Double-Blinded, Parallel-Grouped, Placebo-Controlled Randomized Clinical Trial

PRINCIPAL INVESTIGATOR *Jeffrey Lyman, M.D.*

CO-INVESTIGATOR *Timothy Lovell, M.D.*

SUB-INVESTIGATOR *Adam Olscamp, M.D.*

24-HOUR EMERGENCY PHONE NUMBERS *(208) 758-0716 | (509)838-7100 | 208.457.4211*

CLINICAL STUDY CONTACT

Lyman Medical Research Foundation, Inc.
1875 N Lakewood Drive STE 200 | Coeur d'Alene, ID 83814
Phone (208) 902-9029 | Fax (208) 620-3546 | E-mail elliciacoyne@lymanmfr.org
Website LYMANMRF.ORG

INTRODUCTION

- You are being asked to volunteer to take part in this research study because you have *knee arthritis known as osteoarthritis and will be undergoing a total knee replacement*.
- Before deciding whether you want to participate in this research study or not, it is important that you read and understand the following explanation of the study procedures. This consent describes the purpose, procedures, benefits, risks, discomforts, and precautions of the study. It also describes the alternative procedures, if any, that are available to you and your right to withdraw from the study at any time. No promises can be made about how you will be affected if you consent to be in the study.
- This consent may contain words you do not understand. You should ask the study doctor or research staff to explain any words or information you do not clearly understand. Please review this informed consent carefully and, if possible, discuss with your family or friends before agreeing to participate.

- For your safety, it is important that you be completely honest with your study doctor about your health history to provide a complete and accurate understanding of your health condition.

WHY IS THIS STUDY BEING DONE?

Total knee replacements have routinely been done using opioid pain medications after surgery to decrease pain. The purpose of this study is to see if a procedure called radiofrequency ablation (RFA) performed on the nerves of the knee before surgery help reduce pain after total knee replacement.

Historically, RFA has been done to relieve pain in patients who have osteoarthritis but who did not require knee replacement. This clinical trial is experimental because now we are going to study if RFA treatment before knee replacement surgery helps reduce pain after surgery. RFA is commonly done, however, this use of RFA to help manage pain after knee replacement is new.

The three procedures being studied are standard (t-RFA), cooled (C-RFA), and control (simulated RFA). A primary outcome is to compare pain and opioid medication utilization between the 3 groups. This study is called double-blind. This means that neither the patient nor Drs. Lyman, Olscamp, or Lovell know which treatment is performed. This aids in the unbiased comparison of the three groups. ***The t-RFA and C-RFA will be compared to each other to determine if one is more effective than the other, and both RFA treatments will be compared to SHAM to see if RFA is effective pain management for total knee replacement.*** *This study will determine if RFA treatment reduces pain, reduces opioid use, and decreases hospital length of stays.*

Because it is important to the validity of the study, patients enrolled may not request to see their medical records from any provider or facility until 6 months after the knee replacement surgery. If a patient requests access to their medical records during the time of consent to 6 months after total knee replacement surgery, their enrollment in the study will be discontinued, however routine care and treatments will continue.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of about **150-170** local participants will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

You are eligible to participate in the study because of your knee osteoarthritis, indication for a total knee replacement, and you meet the eligibility criteria. Here is a summary of the study and your involvement.

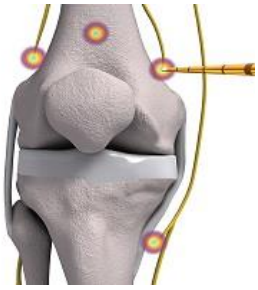
1. Initial Office Visit

You will be invited to participate in this clinical trial. You will receive informed consent forms, a clinical study brochure, and a DVD Informational and Informed Consent video and/or a link to view the video online. You will be referred to the study and one of the treatment providers at Pleasant View Surgery Center in Post Falls, ID.

2. You will receive ONE of the three treatment procedures

After your surgeon sends a study referral, you will be called to schedule your treatment procedure. Your treatment procedure will occur 3 - 12 weeks before your total knee replacement surgery. At Pleasant View Surgery Center, an authorized study representative will review the information, and will answer any questions. After you have received thorough information and have a clear understanding, you may sign the informed consent and enroll in the clinical trial. You will be asked to complete a medical release form and two questionnaires.

You will be randomly assigned to one of the three procedures that are being evaluated in this clinical trial. The three procedure groups being examined are genicular standard thermal (t-RFA), cooled (C-RFA), and a control simulated RFA control group. You will not know which procedure you are assigned. If you receive one of the RFA treatments, pain relieving benefits may be experienced. The nerves receiving the ablation will heal in approximately six to nine months. If you receive a control simulated RFA procedure, then no ablation will occur and the nerves will be undisturbed with no additional pain relief benefits. Your total knee replacement surgery must be scheduled at least three weeks after the treatment procedure to allow time for healing and treatment assessment. It is acceptable if more than three weeks occur between the treatment and total knee replacement.



Genicular refers to the specific name of the nerves in the knee. Four nerves will be targeted for treatment. Randomized means that patients will be assigned to one of the three treatment groups through a process that is unbiased and random, like the flip of a coin. Neither you nor the surgeon will know which group you are in, therefore categorized as "double-blinded".

Treatment Procedure: Standard thermal radiofrequency ablation (t-RFA)

You will receive an IV to administer total intravenous anesthetic, which will make your feel sleepy. You will be asleep during the procedure and unaware of which treatment is being performed. The t-RFA is a procedure used to remove the myelin sheath surrounding the delta A-nerve fibers and cause axonal injury of the C-nerve fibers that register pain. A needle will be inserted, and the four nerves will receive this treatment. This treatment will take approximately 45 minutes. You will be evaluated as the sedation wears off. Then your designated driver may

drive you home after treatment that same day. You will be given a form by your provider to record your pain following the ablation.

> ***NOTE*** *An exclusion criteria exists for body habitus. Extremely thin patients and those with minimal subcutaneous tissue thickness, that would not accommodate a lesion of up to 14 mm in diameter, will be excluded to limit the risk of skin burns. The treatment provider will examine the patient at Pleasant View Surgery Center. If the patient is excluded they will be offered the standard thermal t-RFA and will not participate in the study. If the patient elects to proceed with the t-RFA and is not enrolled, the patient and the patient's insurance will be billed for the treatment costs.*

Treatment Procedure: Cooled radiofrequency ablation (C-RFA)

You will receive an IV to administer total intravenous anesthetic, which will make you feel sleepy. You will be asleep during the procedure and unaware of which treatment is being performed. The C-RFA is very similar to the t-RFA, however it has larger precise removal of the myelin sheath surrounding the delta A-nerve fibers and larger precise axonal injury of the C-nerve fibers for all four nerve sites. A needle will be inserted, and the four nerves will receive the treatment. This treatment will take approximately 45 minutes. You will be evaluated as the sedation wears off. Then your designated driver may drive you home after treatment that same day. You will be given a form by your provider to record your pain following the ablation.

Treatment Procedure: Control simulated radiofrequency ablation (Control)

You will receive an IV to administer total intravenous anesthetic, which will make your feel sleepy. You will be asleep during the procedure and unaware of which treatment is being performed. During the simulated procedure, you will experience all parts of the procedure except the probe will not be used and the ablation of the nerve will not occur. A small puncture in the skin will be made but RFA will not be performed on the nerve. The nerve will be left undisturbed during the control procedure. You will be evaluated as the sedation wears off. Then your designated driver may drive you home after treatment that same day. You will be given a form by your provider to record your pain following the ablation.

3. Pre-Op Appointment at Your Orthopedic Office

You will be scheduled for total knee replacement surgery 3 - 12 weeks after the randomization treatment of t-RFA, C-RFA, or control. Before your surgery and after your treatment you will be scheduled for a pre-op office visit at your surgeon's orthopedic office. During your pre-op appointment, follow-up assessment of your treatment procedure will occur. Any complications from the treatment procedure will be addressed. During this appointment, you will receive a numeric pain scale and opioid pill count diary to record in daily after surgery. You will be interviewed periodically during your recovery about your pain level on a scale of 0-10, with zero being no pain and 10 being the worst pain you've experienced, and opioid daily pill counts. Two questionnaires will be completed (WOMAC and Pain).

Study Timeline and Costs										
ACTIVITY	Office VISIT	*STUDY*	Office VISIT	SURGERY	*STUDY PHONE*	Office VISIT	Office VISIT	*STUDY PHONE*	*STUDY PHONE*	Office VISIT
	Initial	≥ 3 weeks before surgery	Pre-Op for TKA	3 - 12 weeks after study treatment	Interview 1 week (± 3 days) after surgery	Post-Op 2 weeks (± 3 days) after surgery	Post-Op 6 (± 1) weeks after surgery	Interview 12 (± 1) weeks after surgery	Interview 6 (± 1) months after surgery	Post-Op 12 (± 1) months after surgery
TKA Medical History	S									
TKA Labs Ordered	S									
TKA Brief Physical	S									
TKA X-Ray Ordered	S									
TKA MRI Ordered	S									
TKA Pre-Op Office Visit			S							
Informed Consent; Randomized Treatment; *Pregnancy Screening		R								
Total Knee Arthroplasty (TKA)				S						
TKA Post-Op Office Visit						S	S			S
Opioid Usage and Pain Score Phone Interviews					R			R	R	
Physical Therapy	N/A				S					

R "Research" | paid by the study
S "Standard of care services" | patient responsibility and billed to insurance

4. Total Knee Replacement Surgery

Your total knee replacement surgery may occur 3-12 weeks after the randomization treatment. Surgery may occur more than three weeks after your treatment depending on your surgeon's scheduling availability. If your surgeon's average surgery schedule is less than three weeks, then your surgery may be delayed due to the necessary 3-week waiting period after your treatment. If your surgery occurs more than 12 weeks after the randomized RFA study treatment, you may remain in the study with an out-of-window surgery. ***The total knee replacement surgery <u>is not</u> part of this study and is being performed as standard of care. However, all information related to the total knee replacement surgery, including but not limited to pain scores, medication usage, hospital length of stay, will be collected from your hospital medical records when you sign the medical release.***

5. Post-Op Follow-Up

You will have a pain and pill count diary to record in daily after your total knee replacement surgery. You will also be asked your pain level during routine office visits by completing a WOMAC and Numeric Pain Score questionnaire. You will be contacted by phone and asked your pain and medication usage at specific time-points following your surgery. The standard

follow-up for knee replacement surgery is 12 months and your participation in this study will be concluded at 13 months after your informed consent.

PROVIDER PROCEDURE CHART				
PROVIDER	**Pleasant View Surgery Center**	**Northwest Specialty Hospital**	**Providence Sacred Heart Medical Center**	**Participating Physical Therapy Clinics**
Jeffrey Lyman, MD	**Total Knee Replacement**	**Total Knee Replacement**		
Adam Olscamp, MD	**Total Knee Replacement**	**Total Knee Replacement**		
Timothy Lovell, MD			**Total Knee Replacement**	
Mike Ludwig, MD	***t-RFA; C-RFA, SHAM***			
Greg Bauer, CRNA	***t-RFA; C-RFA, SHAM***			
Doran Thomas, CRNA	***t-RFA; C-RFA, SHAM***			
Participating Physical Therapy Clinics				**SUB STUDY Physical Therapy**

Your prior medical records may be reviewed to determine if you are able to participate in this study. A separate medical release form authorizing the clinical study to access your medical records will be used to obtain medical records from Providence Sacred Heart Medical Center, Northwest Specialty Hospital, Pleasant View Surgery Center, Providence Orthopedics, Olscamp Orthopedics, Orthopedic Specialty Institute, Lyman Medical Research Foundation, INC, Physical Therapy Clinics, and other clinical trial participating sites.

Physical therapy is necessary after total knee replacement and this clinical trial will also assess if radiofrequency ablation has any effect on physical therapy rehabilitation. After consenting to the main study, you will be offered participation in the physical therapy sub-study. We have several physical therapy sites to choose from, where you will receive a standard of care that is recommended for total knee replacement therapy. Additional consent and a release of records form will be provided to enroll in the sub-study. Your participation in the main clinical trial and the sub-study provides a comprehensive evaluation for this clinical trial.

HOW LONG WILL YOU BE IN THE STUDY?

You will be in the study for approximately 13 months.

WHAT ARE THE RISKS OF THE STUDY?

Complications from RFA of the nerves in the knee are rare. This procedure is a safe, non-surgical option for treating chronic knee pain. Bleeding, infection, nerve damage and muscle weakness are all possible complications; however, these risks are minimized with a proper technique and correct needle placement. Neuritis is another infrequent but potential side effect whereby the skin near the area of the radiofrequency ablation can become irritated or overly sensitive for a short period of time. Some individuals report mild soreness and/or spasm in the area of the procedure; both of which are easily controlled with oral medications the treatment provider can prescribe upon discharge after the treatment procedure. In some cases, pain relief may take up to 4-6 weeks to be noticeable however this is less common and not considered a complication.
Complications will be distinguishable between the treatment and total knee replacement surgery because the treatment ablations occur at least three weeks prior to total knee replacement. Complications due to the treatments are commonly detectible within three weeks after the treatment and during the "wait period" between the treatment and total knee replacement surgery. These potential complications or side effects include nerve inflammation, soreness, spasm, bleeding, infection, nerve damage, and muscle weakness.

Complications associated with the three treatments (t-RFA, C-RFA, Control) are anticipated to be discovered prior to your pre-op visit with your orthopedic surgeon and addressed at such visit accordingly. Any long-term risks associated with genicular radiofrequency ablation are unknown. *The control/simulated RFA will receive no additional pain relief benefits associated with RFA because an ablation will not be performed on the nerves.*

Reproductive Risk in Women

If you are of childbearing age, you must not be pregnant at the time you enter the study. A negative pregnancy test is required to enter the study. This study could potentially harm your unborn child. You should not nurse your baby during this study. You must not become pregnant during the study. Before you enter the study, the study doctor will talk with you about appropriate methods of family planning, which you must use for the entire time you are in the study. If you become pregnant during the study, you must tell the study doctor immediately. After your participation in the study is complete, if you plan to become pregnant you should speak with your study doctor regarding when it safe to proceed.

Possible adverse effects and safety of the study have not been fully determined. That is one of the purposes of this study.

It is possible in any research study that harmful things can happen that are unknown at this time. There is also a risk that the treatment may not be effective.

The side effects we know about so far are listed below. You could have some, all, or none of them.

<u>Traditional post-surgical pain medications will be available as needed.</u>

The side effects to the t-RFA, C-RFA and control treatments we know about so far are listed in the following table. You could have some, all, or none of them.

RISKS		
More Likely (Greater than 10%)	**Less Likely (1 - 10%)**	**Rarely (Less than 1%)**
Pain or Discomfort Around the Area Treated (13.43%)	Swelling (1.49%) Inflammation of the Nerves Bruising (1.49%) Infection (1.49%)	Allergy IV Anesthetic Muscle Weakness Nerve Damage Worsened Pain Muscle Spasm Numbness of Skin Bleeding
https://www.asra.com/content/documents/2940_prospective-multi-center-rando_1609300829.pdf Halyard Health unpublished data from 67 patients receiving COOLIEF cooled radiofrequency ablation.		

WHAT ARE THE BENEFITS TO TAKING PART IN THE STUDY?

- You may have less than average pain following total knee replacement surgery
- There may be no direct benefit to you
- Knowledge may be gained that may benefit others undergoing total knee replacement

The t-RFA and C-RFA treatment procedures may provide pain relief benefits that may last from 6-9 months. The duration of pain relief benefits depends upon the healing time and regeneration of the nerve. It may take 4-6 weeks or sooner to experience the pain relief benefits from the RFA treatment. The control group will undergo a simulated procedure wherein the nerve will be undisturbed. All three groups will receive total knee replacement surgery, and a routine standard of care in the hospital and after surgery. All three groups will have the availability to pain medication after surgery as needed.

WHAT OTHER POSSIBLE OPTIONS ARE THERE?

You will continue to be followed for your condition. Other options include:

1. Not to participate in the study and instead receive standard treatment for your condition.
2. You can receive t-RFA or C-RFA even if you don't participate in this study.

WHAT ARE THE COSTS?

There will be no charge for the study treatment (t-RFA, C-RFA, SHAM). The preoperative office visit, knee replacement and physical therapy rehabilitation are all routine standards of care and not research. You will be charged for all costs associated with routine office visits, knee replacement and physical therapy rehabilitation following surgery. These will be billed to insurance and you are responsible for these costs. Participation in this study is not a substitute for health insurance. You and/or your insurance company must pay for routine medical care, including services, supplies, and procedures. You will be responsible for any co-payments and/or deductibles, or for any portion of the bill that your insurance does not cover that are associated with industry standard of care including but not limited to office visits, hospital charges associated with your surgery, post-surgical care, pain management medications, physical therapy, and ambulatory devices. You may want to discuss these costs with your insurance company before agreeing to participate in the study. (Please refer to the Study Timeline and Costs table) You will not be paid for your participation in this study.

You may receive reimbursement to cover travel expenses associated with driving to and from Pleasant View Surgery Center for care associated with the t-RFA, C-RFA, or Control treatment you received. The study will reimburse qualifying travel at .50 cents per mile to and from Pleasant View Surgery Center for the study treatment. A travel reimbursement form, pain and pill count diaries will be provided with your pre-op clinical trial pain and pill count log. Please fill out the paperwork and return it along with the completed pain and pill count logs. The travel reimbursement form will reimburse travel to and from Pleasant View Surgery Center for the research treatment procedure that occurs before total knee replacement. The travel reimbursement form is required to receive compensation for your travel to and from Pleasant View Surgery Center. The form lists your home address as the from location and your approximate mileage. The mileage may be confirmed with a computerize mapping system to assure accurate reimbursement. Upon receipt of the travel reimbursement form, a check will be mailed to you within 60 days. If you have questions, the Clinical Research Director will review the travel reimbursement process with you.

WHO PAYS FOR STUDY–RELATED ILLNESS OR INJURY?

If you have suffered a complication, illness, or injury during this study, treatment will be provided to you by Jeffrey Lyman, MD, Adam Olscamp, MD, Timothy Lovell, MD or appropriate providers and their associates at Pleasant View Surgery Center, Northwest Specialty Hospital, or Providence Sacred Heart Medical Center. If the complication, illness, or injury is a direct result from the treatment received at Pleasant View Surgery Center, care will be provided to you at no cost. You should contact the study investigators Jeffrey Lyman, MD at (208) 758-0716, Adam Olscamp, MD at (208) 457-4211or Timothy Lovell, MD at (509) 838-7100. If these complications are not related to randomization treatments (control, t-RFA, C-RFA) at Pleasant View Surgery Center and are a result of routine care, your insurance will be billed for necessary care and you will be responsible for all non-study treatment related costs. No funds have been set aside for payment of expenses for medical treatment, or for lost wages or other

expenses, either as a direct or indirect result of your participation in this study. Such expenses will be billed to you or your insurance company. If you have questions regarding illness or injury related to this study, please discuss this with the study doctor.

WHAT ABOUT CONFIDENTIALITY?

Your records will be available to all those caring for you at Providence Sacred Heart Medical Center, Pleasant View Surgery Center, Northwest Specialty Hospital, Orthopedic Specialty Institute, Olscamp Orthopedics, Inland Northwest Anesthesia, Coeur d'Alene Spine, Providence Inland Orthopedics and Lyman Medical Research Foundation, INC. A medical release will be provided to sign and the hospital records from the knee replacement surgery will be accessed for purpose of data and billing collection information along with treatment provider, physician, and all related clinical trial medical information.

The following people will have access to review and/ or copy your medical records as they relate to your participation in this study:

1. Medical personnel associated with the study
2. Research personnel associated with the study
3. Halyard Health and their representatives
4. Providence Health Care Institutional Review Board
5. Lyman Medical Research Foundation
6. Olscamp Orthopedics
7. Providence Inland Orthopedics
8. Orthopedic Specialty Institute

We will not share these records with persons not involved in your care or in this research study, except as required by law. Although, we cannot guarantee absolute confidentiality, your records relating to this study will be kept confidential and publication of general study results will not personally identify you. You will be required to read and sign an addendum to this consent that explains in detail how your health information will be used and protected.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Participation in this study is voluntary and refusal to participate will not affect your current or future relationships with your primary care physician, study doctor, participating hospitals. There will be no penalty or loss of benefits to which you are otherwise entitled if you decide not to participate.

You have the right to know about new information that may affect your health, welfare, or your willingness to continue participating in the study. Your study doctor will give you this information in writing as soon as it becomes available.

The study doctors, Orthopedic Specialty Institute, Olscamp Orthopedics, Lyman Medical Research Foundation INC, Spokane Providence Sacred Heart Medical Center, Providence Inland Orthopedics Northwest Specialty Hospital, and Pleasant View Surgery Center will not profit or receive payments for the clinical research trial. Research grant funds from Halyard Health will provide necessary funds to pay for research study costs that are not billed to the patient including randomized treatment costs, research personnel costs, and other study related expenses. The study doctor and research staff do not hold a financial interest in this research study, however, Dr. Lyman, Dr. Ludwig, Greg Bauer, CRNA and Doran Thomas, CRNA do have ownership at Pleasant View Surgery Center. They do not believe that this will affect how the study is being conducted or the results. If you have any questions regarding this, any aspect of your illness, your treatment, or your patient rights you may contact Dr. Lyman at (208) 758-0716. Should you have further questions regarding your rights as a research participant or complaints regarding this research study you may contact the Providence Health Care Institutional Review Board at 509-474-3640

CAN I STOP PARTICIPATING IN THIS STUDY?

You may withdraw from this study at any time without prejudice or loss of benefits to which you are entitled. Withdrawing from the study will have no impact on your standard of care.

WHAT COULD END YOUR PARTICIPATION?

The study doctor can withdraw you from the study if:

- It is necessary for your safety
- You do not follow instructions
- You access your medical records from time of consent to 6 months after surgery
- You do not meet the conditions of the study
- The study is closed for any reason

PARTICIPANT CONSENT

I have read, or have had read to me, the information describing the study and it is written in a language that I understand. All my questions have been answered to my satisfaction. I am signing this form voluntarily, indicating my willingness to be in this study. I understand that I am not giving up any of my legal rights by signing this form and I will receive a copy of this signed consent form.

SIGNATURE OF PARTICIPANT	PRINTED NAME	DATE & TIME (AM/PM)

SIGNATURE OF AUTHORIZED PERSONNEL	PRINTED NAME	DATE & TIME (AM/PM)

If this consent form is read to the participant because the participant is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood, by the participant. The participant freely consented to participate in the research study.

Printed Name of Impartial Witness	*Signature*	*Date*

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.

Addendum to Informed Consent Form

Authorization to Use, Create, and Share Health Information for Research

This attachment provides additional information about how your medical records and health information (together, your "records") will be used and disclosed for this research study. Your records may include information about your lab tests, physical examinations, x-rays, scans, interviews, physical therapy rehabilitation and medical history. It may also include any other health information created, collected, or reviewed during the course of the research study as described in the consent form. In addition, it may include your demographic information, your initials and date of birth.

This form allows the study doctor(s) identified in the consent to use your records to carry out the study described in the consent form. If you do not sign this form, you cannot participate in the study.

By signing this form, you allow the study doctor to disclose your records to the sponsor identified in the consent and the sponsor's representatives. The sponsor will use the information to review the results of the study. The information sent by the study doctor to the sponsor usually does not include your name, address or social security number. However, the sponsor might review or copy all of your records to assure the quality of the study or for other uses allowed by law.

All of your records, the signed consent form(s) and this form might be reviewed or copied by Spokane Providence Sacred Heart Medical Center, Providence Health Care Institutional Review Board or by other regulatory agencies. These agencies might review your records to check the information collected in this study, to check how the study was conducted or for other uses allowed by law.

Federal and state laws require the study doctor(s) to protect the privacy of your records. However, absolute confidentiality cannot be guaranteed because of the need to disclose information as described above. After the study doctor(s) discloses your records to others, the law may no longer protect the privacy of the information. If you would like to know how the sponsor will protect the privacy of your records, ask your study doctor(s) how to obtain this information.

You have the right to see and copy your records related to the study for as long as the study doctor has this information in his or her possession. However, by signing this form you agree that you might not be able to review some of your records related to the study until after the study has been completed, at which time your right of access will be restored.

If you move you agree to allow the study doctor to access your medical records at other healthcare facilities.

As required by Washington State Law RCW 70.02.030 Patient Authorization of Disclosure must contain an expiration date or event. Your authorization will expire when the goals of the study have been met.

You can cancel this authorization at any time and cancellation will be noted by the post-mark date on the letter. Cancellation must be given by written notice to:

Lyman Medical Research Institute, INC
Ellicia Coyne, Clinical Research Director
Clinical Study Cancellation
1875 North Lakewood Drive, Suite 200
Coeur d'Alene, ID 83814

Please call (208) 902-9029 if you have any questions.

If you cancel this authorization, then you no longer will be able to participate in the study and any health information collected prior to your cancellation will be retained by the study doctor and sponsor.

I am not giving up any of my legal rights by signing this form. I understand that I will receive a signed copy of this authorization for my records.

SIGNATURE OF PARTICIPANT DATE

PRINTED NAME

APPENDIX B

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY
SUB-STUDY

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY
PHYSICAL THERAPY SUB-STUDY

TITLE OF PRIMARY STUDY

Comparison Between Cooled Radiofrequency Ablation (C-RFA), Standard Radiofrequency Ablation (t-RFA), and Control for Postoperative Pain Management Following Unilateral Knee Arthroplasty: A Double-Blinded, Parallel-Grouped, Placebo-Controlled Randomized Clinical Trial

SUB-STUDY OBJECTIVE

The purpose of the physical therapy sub-study is to compare three different pain treatments utilized in the primary study and their effects on total knee replacement physical therapy rehabilitation.

PRINCIPAL INVESTIGATOR *Jeffrey Lyman, M.D.*

CO-INVESTIGATOR *Timothy Lovell, M.D.*

SUB-INVESTIGATOR *Adam Olscamp, M.D.*

24-HOUR EMERGENCY PHONE NUMBERS *(509)838-7100 or (208) 758-0716*

CLINICAL STUDY CONTACT

Lyman Medical Research Foundation, Inc.
1875 N Lakewood Drive STE 200 | Coeur d'Alene, ID 83814
Phone (208) 902-9029 | Fax (208) 620-3546 | E-mail elliciacoyne@lymanmfr.org
Website LYMANMRF.ORG

INTRODUCTION

- **You are being asked to volunteer to take part in this research study because you have** *osteoarthritis of the knee and will be undergoing a total knee replacement, participating in the primary study, receiving one of three randomized treatments, and will undergo physical therapy rehabilitation.*

- **Before deciding whether you want to participate in this research study or not, it is important that you read and understand the following explanation of the study procedures. This consent describes the purpose, procedures, benefits, risks,**

discomforts, and precautions of the study. It also describes the alternative procedures, if any, that are available to you and your right to withdraw from the study at any time. No promises can be made about how you will be affected if you consent to be in the study.

- **This consent may contain words you do not understand. You should ask the study doctor or research staff to explain any words or information you do not clearly understand.** Please review this informed consent carefully and, if possible, discuss with your family or friends before agreeing to participate.

- **For your safety, it is important that you be completely honest with your study doctor about your health history to provide a complete and accurate understanding of your health condition.**

WHY IS THIS STUDY BEING DONE?

The purpose of this sub-study is to further compare the effects of t-RFA, C-RFA, and control/placebo for total knee replacement physical therapy rehabilitation.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of about ***150-170*** participants will take part in the primary study and will be offered the opportunity to participate in this physical therapy sub-study. A potential of 150-170 patients may participate throughout the region.

WHAT IS INVOLVED IN THE STUDY?

You are eligible to participate in the sub-study because of your knee osteoarthritis, being scheduled for a total knee replacement, enrolling in the primary study and willingness to enroll in the physical therapy sub-study. Here is a summary of the study and your involvement.

- *Concurrent to your enrollment with the primary study, you will be offered this consent form to participate in the physical therapy sub-study.*
- *We will offer a list of our participating physical therapy clinics for your rehabilitation.*
- *If you wish to participate and your physical therapy clinic is not on the list of participating providers, we will offer your preferred clinic the option to participate in our study.*
- *Following surgery, the surgeon will order routine physical therapy rehabilitation for your recovery.*
- *A standard physical therapy rehabilitation protocol will be given throughout your recovery phase.*

- *Routine chart notes and assessments will be made during your physical therapy and those records will be used by the Sponsor Investigator, Co-Investigator, Executive Director Clinical Research and the OSI clinical research department.*
- *A routine schedule of care will be provided by the participating physical therapy provider during 3 (±1) months following your surgery.*
- *Additional physical therapy will be available if indicated.*

Your medical records and physical therapy records will be reviewed throughout the sub-study. A separate medical release form is included with this consent for physical therapy patient records from participating providers in addition to other study records.

HOW LONG WILL YOU BE IN THE STUDY?

You will be in the sub-study for 3 (±1) months which is concurrent with your enrollment in the primary study.

WHAT ARE THE RISKS OF THE STUDY?

The physical therapy sub-study follows a standard routine of care for knee replacement rehabilitation. The sub-study provides the opportunity to evaluate the effects of preoperative t-RFA and C-RFA pain management on rehabilitation and recovery and will compare those results to the control/placebo group. The sub-study allows for the data collection from the patient records.

Reproductive Risk

There is no reproductive risk associated with the sub-study relating to physical therapy rehabilitation.

It is possible in any research study that harmful things can happen that are unknown at this time. Traditional physical therapy rehabilitation will be done.

WHAT ARE THE BENEFITS TO TAKING PART IN THE STUDY?

- You will receive a standard of care that has proven results.
- There may be no direct personal benefits other than contributing to the health care improvements.

WHAT OTHER POSSIBLE OPTIONS ARE THERE?

You will continue to be followed for your condition. Other options include:

1. Not to participate in the study and instead receive standard treatment for your condition.
2. You can receive t-RFA or C-RFA even if you don't participate in this study.

WHAT ARE THE COSTS?

Participation in this study is not a substitute for health insurance. You and/or your health insurance must pay for all physical therapy care. This sub-study is an industry standard of care and services provided by your physical therapy clinic will be your and/or your health insurance responsibility. These are routine services following a total knee replacement, however you may want to discuss these costs with your insurance company before agreeing to participate in the study.

WHO PAYS FOR STUDY–RELATED ILLNESS OR INJURY?

The Sponsor Investigator, Co-Investigator, and Sub-Investigator and associated research personnel are not responsible for any injury, illness or complication arising from your physical therapy rehabilitation. Those circumstances are between you and your physical therapy provider. The sub-study has no legal authority between you and your physical therapy provider and only collects data from your physical therapy provider that is associated with routine industry standard physical therapy care.

WHAT ABOUT CONFIDENTIALITY?

Your physical therapy records will be available to all those caring for you at your chosen physical therapy clinic, the Sponsor Investigator, Co-Investigator, Sub-Investigator, Executive Director Clinical Research and associated clinical research representatives.

The following people will have access to review and/ or copy your medical and physical therapy records as they relate to your participation in this study:

- Medical personnel associated with the study
- Research personnel associated with the study
- Halyard Health and their representatives
- Providence Health Care Institutional Review Board
- Lyman Medical Research Foundation
- Olscamp Orthopedics
- Providence Inland Orthopedics
- Orthopedic Specialty Institute

We will not share these records with persons not involved in your care or in this research study, except as required by law. Although, we cannot guarantee absolute confidentiality, your records relating to this study will be kept confidential and publication of general study results will not personally identify you. You will have an assigned participant number that does not identify you

in the data analysis records. You will be required to read and sign an addendum to this consent that explains in detail how your health information will be used and protected.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Participation in this study is voluntary and refusal to participate will not affect your current or future relationships with your primary care physician, study doctor or participating physical therapy clinics. There will be no penalty or loss of benefits to which you are otherwise entitled if you decide not to participate. You have the right to know about new information that may affect your health, welfare, or your willingness to continue participating in the study. Your study doctor will give you this information in writing as soon as it becomes available.

The study doctors, Providence Sacred Heart Medical Center, Northwest Specialty Hospital, Pleasant View Surgery Center, and participating physical therapy clinics will not receive payment from the study sponsor. There is no research associated with the physical therapy sub-study. The study doctor and research staff do not hold a direct financial interest in this research study. If you have any questions regarding this, any aspect of your illness, your treatment, or your patient rights you may contact Dr. Lyman at (208) 758-0716 Should you have further questions regarding your rights as a research participant or complaints regarding this research study you may contact the Providence Health Care Institutional Review Board at 509-474-3640.

CAN I STOP PARTICIPATING IN THIS STUDY?

You may withdraw from this study at any time without prejudice or loss of benefits to which you are entitled. Withdrawing from the study will have no impact on your standard of care.

WHAT COULD END YOUR PARTICIPATION?

The study doctor can withdraw you from the study if:

- It is necessary for your safety
- You do not follow instructions
- You access your medical records during the study period
- You do not meet the conditions of the study
- The study is closed for any reason

PARTICIPANT CONSENT

I have read, or have had read to me, the information describing the study and it is written in a language that I understand. All my questions have been answered to my satisfaction. I am signing this form voluntarily, indicating my willingness to be in this study. I understand that I am not giving up any of my legal rights by signing this form and I will receive a copy of this signed consent form.

SIGNATURE OF PARTICIPANT	PRINTED NAME	DATE & TIME (AM/PM)

SIGNATURE OF AUTHORIZED PERSONNEL	PRINTED NAME	DATE & TIME (AM/PM)

If this consent form is read to the participant because the participant is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood, by the participant. The participant freely consented to participate in the research study.

Printed Name of Impartial Witness	Signature	Date

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.

Addendum to Informed Consent Form

Authorization to Use, Create, and Share Health Information for Research

This attachment provides additional information about how your medical records and health information (together, your "records") will be used and disclosed for this research study. Your records may include information about your lab tests, physical examinations, x-rays, scans, interviews, physical therapy rehabilitation and medical history. It may also include any other health information created, collected or reviewed during the course of the research study as described in the consent form. In addition, it may include your demographic information, your initials and date of birth.

This form allows the study doctor(s) identified in the consent to use your records to carry out the study described in the consent form. If you do not sign this form, you cannot participate in the study.

By signing this form, you allow the study doctor to disclose your records to the sponsor identified in the consent and the sponsor's representatives. The sponsor will use the information to review the results of the study. The information sent by the study doctor to the sponsor usually does not include your name, address, or social security number. However, the sponsor might review or copy all your records to assure the quality of the study or for other uses allowed by law.

All your records, the signed consent form(s) and this form might be reviewed or copied by the Providence Health Care IRB, or by other regulatory agencies in this country or in other countries. These agencies might review your records to check the information collected in this study, to check how the study was conducted or for other uses allowed by law.

Federal and state laws require the study doctor(s) to protect the privacy of your records. However, absolute confidentiality cannot be guaranteed because of the need to disclose information as described above. After the study doctor(s) discloses your records to others, the law may no longer protect the privacy of the information. If you would like to know how the sponsor will protect the privacy of your records, ask your study doctor(s) how to obtain this information.

You have the right to see and copy your records related to the study for as long as the study doctor has this information in his or her possession. However, by signing this form you agree that you might not be able to review some of your records related to the study until after the study has been completed, at which time your right of access will be restored.

If you move you agree to allow the study doctor to access your medical records at other healthcare facilities.

As required by Washington State Law RCW 70.02.030 Patient Authorization of Disclosure must contain an expiration date or event. Your authorization will expire when the goals of the study have been met.

You can cancel this authorization at any time and cancellation will be noted by the post-mark date on the letter. Cancellation must be given by written notice to:

Lyman Medical Research Institute, INC
Ellicia Coyne, Clinical Research Director
Clinical Study Cancellation
1875 North Lakewood Drive, Suite 200
Coeur d'Alene, ID 83814

Please call (208) 902-9029 if you have any questions.

If you cancel this authorization, then you no longer will be able to participate in the study and any health information collected prior to your cancellation will be retained by the study doctor and sponsor.

I am not giving up any of my legal rights by signing this form. I understand that I will receive a signed copy of this authorization for my records.

CHOSEN PHYSICAL THERAPY CLINIC AND LOCATION

SIGNATURE OF PARTICIPANT DATE

PRINTED NAME

APPENDIX C

PHYSICAL THERAPY PROTOCOL FOR UNILATERAL KNEE REPLACEMENT

ROUTINE ASSESSMENTS

EVERY VISIT	INITIAL AND BIWEEKLY
PATIENT COMPLETED SCORE SHEET Patient Pain Scale Numeric 0 – 10 PLEASE NOTE IN PATIENT DAILY CHART OR WRITE ON PATIENT PAIN SCORE SHEET ACTIVE Range of Motion	PATIENT COMPLETED SCORE SHEET INITIAL WOMAC Week 2 WOMAC Week 4 WOMAC Week 6 WOMAC Week 8 WOMAC Week 10 WOMAC Week 12 WOMAC

PHASE 1

Post Op Time Frame	Goals	Milestones	Strategies	Exercises
0-2 weeks	• Decrease pain and swelling • WBAT • Return and improve muscle function and reactivation with no quad lag • Normalize gait pattern	• 10-90 deg knee flexion ROM • Pain <5/10	• RICE • Electrical stim for muscle activation, biofeedback, and/or pain control • Manual therapy to reduce edema	• Supine knee flexion (heel slides) • Short-arc knee extensions Standing bilateral squats • Sidelying hip external rotation, with hips flexed to 45° and knees flexed to 90° (clams) • Sidelying hip adduction • Supine ankle plantar flexion and dorsiflexion (ankle pumps • Straight leg raise

PHASE 2

Post Op Time Frame	Goals	Milestones	Strategies	Exercises
2-4 weeks	• Control inflammation and swelling • Decrease pain • Improve ROM • Progress balance • Progress strength	• 5-100 deg knee flexion ROM • Pain <5/10 • Ambulates without assistive device	• RICE • Electrical stim for muscle activation, biofeedback, and/or pain control • Manual therapy to	• Phase 1 exercises as appropriate • Seated single-leg knee extension* • Straight leg raise* • Standing hamstring curls* • Sidelying hip adduction* • Sidelying hip abduction* • Standing bilateral calf raises • Repeated sit-to-stand transfers • Marching or single-limb stance

	• Normalize gait pattern	• Sit to stand with use of hands and no assistive device	reduce edema • Joint mobilization	• Multidirectional stepping
PHASE 3				
Post Op Time Frame	Goals	Milestones	Strategies	Exercises
4-6 weeks	• Control inflammation and swelling • Decrease pain • Improve ROM • Progress balance and proprioception • Progress strength • Normalize gait pattern • Return to low- to mid- level functional activities	• 0-110 deg knee flexion ROM • Pain <3/10 at rest • Able to don/doff shoes independently • Sit to stand without use of hands • Ambulates community distances	• Ice as needed • Electrical stim for muscle activation, biofeedback, and/or pain control • Manual therapy to reduce edema • Joint mobilization	• Phase 1 and 2 exercises as appropriate • Seated single-leg knee extension* • Seated single-leg knee flexion* • Single-leg press* • Single-leg calf press* • Standing hip extension, flexion, abduction, and adduction* • Step-ups, side step-ups, step-downs • Forward lunging • Single-limb stance progression (shoe to sock to foam, with eyes open, then with eyes closed) • Tilt board squats • Wall slides for knee flexion • Stability ball supine hip extension
Phase 4				
Post Op Time Frame	Goals	Milestones	Strategies	Exercises
6-12 weeks	• Control inflammation and swelling • Decrease pain • Attain pain-free knee ROM • Improve activity tolerance	• 0-120 deg knee flexion ROM • Pain <2/10 • Ascend and descend stairs with alternating gait pattern	• Ice as needed • Electrical stim for muscle activation, biofeedback, and/or pain control • Manual therapy to reduce edema	• Phase 1, 2, and 3 exercises as appropriate • Seated single-leg knee extension (eccentric)* • Seated single-leg knee flexion (eccentric)* • Single-leg press (eccentric)* • Single-leg calf press (eccentric)* • Standing hip extension, flexion, abduction, and adduction* • Step-ups, side step-ups, step-downs

	• Progress balance and proprioception • Progress strength • Return to all functional activities	• Transfer from floor to standing	• Joint mobilization	• Multidirectional lunging • Star excursion balance reaching • Wall slides with 5- to 10-second endurance holds at 90° • Stability ball supine combined hip extension with knee flexion • Agility exercises: side-shuffle, backward walking, and braiding • Single-limb stance progression

General Progressions: When able to complete 2 × 8 reps without fatigue; NPRS score <5/10 and ROM goals have been met

Abbreviations

ROM= total active arc of knee range of motion; NPRS = numeric pain rating scale, RICE = Rest, Ice, Elevation, and Compression *Resistive exercise utilizing ankle weight, resistive band, cable column or machine.

Adapted From

Early High-Intensity Rehabilitation Following Total Knee Arthroplasty Improves Outcomes

Michael J. Bade, Jennifer E. Stevens-Lapsley

Journal of Orthopaedic & Sports Physical Therapy 2011 41:12, 932-941

Acknowledgement

We want to thank North Idaho Physical Therapy for drafting this total knee arthroplasty industry standard of care protocol for the purposes of this clinical trial.

APPENDIX D

PHYSICAL THERAPY PARTICIPATION AGREEMENT
SUB-STUDY

Comparison Between Cooled Radiofrequency Ablation (C-RFA), Traditional Radiofrequency Ablation (t-RFA), and Control for Postoperative Pain Management Following Unilateral Knee Arthroplasty: A Double-Blinded, Parallel-Grouped, Placebo-Controlled Randomized Clinical Trial

Participation Agreement

By signing this document, I agree to adhere to the parameters of the attached protocol for the treatment of all patients identified to me and/or my clinic as research study subjects.

I understand that deviating from the approved protocol may jeopardize the outcome of the study.

If I have any concerns about the patient or the protocol, I will notify Dr. Lyman, Dr. Lovell or Ellicia Coyne, Clinical Research Director, at (208) 902-9029.

I agree to allow Lyman Medical Research Foundation, Inc. to obtain the records pertaining to the WOMAC; pain scores; milestones; documentation; evaluation documentation; plan of care; progress notes; and discharge summaries for study participants upon request.

Physical Therapy Clinic Name and Location

Physical Therapy Clinic Name and Location

Physical Therapy Clinic Name and Location

	Ellicia F. Coyne
Printed Name of Authorized Therapist	Printed Name of Clinical Research Director
	Ellicia F. Coyne
Signature of Authorizing Therapist	Signature of Clinical Research Director
Date	Date

APPENDIX E

PATIENT PAIN SCALE AND OPIOID PILL COUNT DIARY

STUDY PATIENT NAME

Clinical Study Patient Diary
Numeric Pain Scale & Pain Pill Count

NUMERIC PAIN SCALE

On a scale of 0 to 10, how would you rate your pain RIGHT NOW?

0 being no pain
10 being the worst possible pain

0	2	3	4	5	6	7	8	9	10
NO PAIN									WORST POSSIBLE PAIN

PAIN PILLS TAKEN PER DAY

Please count the number of pain medication pills taken per 24-hour day (example: 8:00 AM – 8:00 AM *the next day*).

PLEASE USE THE ATTACHED FORMS FOR YOUR
NUMERIC PAIN AND PAIN PILL COUNT DAILY DIARY
THANK YOU!

DATE	TIME AM / PM	PAIN LEVEL #	MS CONTIN 15 MG	OXYCOD ONE 5 MG	HYDROCOD ONE 5 MG/325MG	TRAMAD OL 50 MG	TYLEN OL	OTHER

APPENDIX F

NUMERIC PAIN SCALE

Clinical Trial Questionnaire

PATIENT NAME **DATE**

NUMERIC PAIN SCORE

On a scale of 0 to 10, how would you rate your pain RIGHT NOW for just your treatment knee?

0	1	2	3	4	5	6	7	8	9	10
NO PAIN										WORST POSSIBLE PAIN

PAIN MEDICATION CONSUMPTION IN LAST 24 HOURS

(please list all prescription and non-prescription pain medicine taken in last 24 hours)

Usage Date	Medication Name	Dosage/mg	Number of Pills Consumed

STUDY NOTES

APPENDIX G

WOMAC

LYMAN
MEDICAL RESEARCH FOUNDATION

Name: _____ Date: _____

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely Circle *one number for each activity*

Pain

1. Walking	0	1	2	3	4
2. Stair Climbing	0	1	2	3	4
3. Nocturnal	0	1	2	3	4
4. Rest	0	1	2	3	4
5. Weight bearing	0	1	2	3	4

Stiffness

1. Morning stiffness	0	1	2	3	4
2. Stiffness occurring later in the day	0	1	2	3	4

Physical Function

1. Descending stairs	0	1	2	3	4
2. Ascending stairs	0	1	2	3	4
3. Rising from sitting	0	1	2	3	4
4. Standing	0	1	2	3	4
5. Bending to floor	0	1	2	3	4
6. Walking on flat surface	0	1	2	3	4
7. Getting in / out of car	0	1	2	3	4
8. Going shopping	0	1	2	3	4
9. Putting on socks	0	1	2	3	4
10. Lying in bed	0	1	2	3	4
11. Taking off socks	0	1	2	3	4
12. Rising from bed	0	1	2	3	4
13. Getting in/out of bath	0	1	2	3	4
14. Sitting	0	1	2	3	4
15. Getting on/off toilet	0	1	2	3	4
16. Heavy domestic duties	0	1	2	3	4
17. Light domestic duties	0	1	2	3	4

Total Score: _____ / 96 = _____%
Comments / Interpretation (to be completed by therapist only):

APPENDIX H

RANDOMIZED TREATMENT ARM ASSIGNMENT

Randomized Treatment Arm Subject Assignment

Comparison Between Cooled Radiofrequency Ablation (C-RFA), Standard Radiofrequency Ablation (t-RFA), and Control for Postoperative Pain Management Following Unilateral Knee Arthroplasty: A Double-Blinded, Parallel-Grouped, Placebo-Controlled Randomized Clinical Trial

Subject Name

Subject Identifier

Referring Physician

- ☐ Jeffrey Lyman, MD
- ☐ Timothy Lovell, MD
- ☐ Adam Olscamp, MD

Treatment Arm Assignment

- ☐ C-RFA
- ☐ SHAM
- ☐ t-RFA

Treatment Arm Provider

- ☐ Greg Bauer, CRNA
- ☐ Dorn Thomas, CRNA
- ☐ Mike Ludwig, MD

APPENDIX I

RECRUITMENT BROCHURE

- **Clinical Study Treatment Center**
  Pleasant View Surgery Center, Post Falls ID
- **Cost to participate:**
  There is no cost for the RFA treatment
- **Clinical Study Investigators**
  Jeffrey Lyman, MD (208) 758-0716
  Timothy Lovell, MD (509) 838-7100
- **Clinical Research Director**
  Ellicia Coyne
  elliciacoyne@lymanmrf.org

Dr. Jeffrey Lyman, MD
Orthopedic Specialty Institute

Coeur d'Alene
1875 North Lakewood Dr. Ste 200
Coeur d'Alene, ID 83814
Phone: 208.758.0716
Fax: 208.667.7717

Spokane
26 E. 5th Ave.
Spokane, WA 99202
Phone: 509.747.5615
Fax: 509.747.5133

Dr. Timothy Lovell, MD
Providence Orthopedics

Spokane
820 S. McClellan St. Ste 300
Spokane, WA 99204
Phone: 509.838.7100
Fax: 509.838.0721

For information, contact:
Ellicia Coyne, Clinical Research Director
elliciacoyne@lymanmrf.org

www.lymanmrf.org

A clinical trial of the **Lyman Medical Research Foundation, Inc.**

Total Knee Replacement
Pain Reduction Clinical Trial

If you are experiencing knee pain associated with osteoarthritis and require total knee replacement surgery, you may be eligible to enroll in a clinical trial investigating treatments to reduce pain following surgery.

A clinical trial of the **Lyman Medical Research Foundation, Inc.**

LYMAN
MEDICAL RESEARCH FOUNDATION

Lyman Medical Research Foundation, Inc.
LEADING
THE WAY IN
MEDICAL
RESEARCH
About the Clinical Trial
This study is designed to compare traditional knee replacement pain management with a novel preoperative nerve ablation technique. The goal is to improve pain control and make recovery easier.
Radiofrequency ablation (RFA) has been used to reduce osteoarthritis in non-operative patients. This trial will investigate RFA usage before total knee replacements to help manage pain after surgery.
Radiofrequency Ablation Treatments
Radiofrequency ablation is a minimally invasive, non-surgical outpatient procedure to treat nerves causing knee pain. RFA involves no incision. The treatment is performed at least three weeks prior to surgery. General anesthesia is not required, therefore patients should be able to return home shortly after the treatment.
Treatment procedure:
IV sedation administered
Small needle placed at four nerve sites
One of the three treatments performed
Your designated driver may take you home shortly after the treatment
Post treatment:
You will receive routine follow-ups for up to a year, as is standard with all total knee replacement patients.
Your Participation
Once enrolled, you will receive one of three study treatments at no cost. You may experience additional pain relief benefits after surgery.
Standard radiofrequency ablation (S-RFA)
Cooled radiofrequency ablation (C-RFA)
Control (Simulated Treatment)
Benefits:
You may receive decreased pain after total knee replacement surgery
Participating in a ground breaking study for RFA for total knee replacement
Risks:
Patients may experience pain or discomfort around the area treated. Patients are less likely to experience swelling, bruising or infection. Rarely patients can experience muscle weakness, nerve damage, worsened pain, muscle spasm, numbness of skin or bleeding.

APPENDIX J

MEDICATION USAGE SHEET

MEDICATIONS PRESCRIBED TO YOU AT YOUR PRE-OPERATIVE VISIT

NARCOTIC (OPIOID) PAIN MEDICATIONS: The medications are arranged in order of most potent to least potent. Use the single medication of lowest potency that treats your pain well enough at rest and when needed for activity and physical therapy. You will be able to gradually decrease the potency of pain medication. Please call us with any questions regarding medications. **USE CAUTION IF COMBINING MEDICAITONS**

NARCOTIC (OPIOID) PAIN MEDICATIONS

MS Contin 15 mg tablets 12-hour release
Prescription: paper prescription given to you to take to your pharmacy to fill before your surgery
Instructions: TAKE ONE TABLET THE MORNING OF SURGERY
Leave the remaining pills at home for after surgery and take as directed only when needed for pain

Oxycodone 5 mg tablets
Prescription: paper prescription given to you to take to your pharmacy to fill before your surgery
Instructions: Leave this medication at home for after surgery and take as directed only when needed for pain

Hydrocodone 5 mg/325 mg
Prescription: paper prescription given to you to take to your pharmacy to fill before your surgery
Instructions: Leave this medication at home for after surgery and take as directed only when needed for pain

Tramadol 50 mg tablets
Prescription: paper prescription given to you to take to your pharmacy prior to surgery
Instructions: Leave this medication at home for after surgery and take as directed only when needed for pain

OTHER MEDICATIONS

Transderm-Scopalamine 1.5 mg Patch (anti-nausea medication for postoperative nausea)
Prescription: prescription sent to your pharmacy
Instructions: APPLY 1 PATCH BEHIND THE EAR THE NIGHT BEFORE SURGERY

Aspirin 325 mg twice a day for 5 weeks after surgery (for prevention of deep vein thrombosis/clots)
Prescription: this can be purchased as an over the counter medicine at your pharmacy
Instructions: take twice a day (morning and night) for 5 weeks after surgery

Hibiclens (for skin cleansing the night before and morning of surgery)
Prescription: this can be purchased as an over the counter cleanser at your pharmacy)
Instructions: USE HIBICLENS TO CLEAN YOUR SKIN THE NIGHT BEFORE AND MORNING OF SURGERY SEE SKIN PREP SHEET

Zofran 4 mg; multivitamins; iron supplements; constipation medication
Prescription: these will be called into your pharmacy at the time of hospital discharge to be picked up

APPENDIX K

SAMPLE DISCHARGE CRITERIA

DISCHARGE SAMPLE

The below Standards of Post Anesthesia Care have been adopted as generally accepted practice at the Facility.

STANDARD I:

All patients who have received general anesthesia, regional anesthesia or monitored anesthesia care shall receive appropriate post anesthesia management.

1. A Post anesthesia Care Unit (PACU) or an area that provides equivalent post anesthesia care shall be available to receive patients after anesthesia care.
2. All patients who receive anesthesia care shall be admitted to the PACU or its equivalent except by specific order of the anesthesia provider responsible for the patient's care.
3. The medical aspects of care in the PACU or its equivalent shall be governed by policies and procedures that have been reviewed by the Department of Anesthesiology.
4. The design, equipment, and staffing of the PACU shall meet requirements of the Facility's accrediting and licensing bodies.

STANDARD II:

A patient transported to the PACU shall be accompanied by a member of the anesthesia care team who is knowledgeable about the patient's condition. The patient shall be evaluated continually and treated during transport with monitoring and support appropriate to the patient's condition**.**

STANDARD III:

Upon arrival in PACU, the patient shall be re-evaluated and a verbal report provided to the responsible PACU nurse by the member of the anesthesia care team.

1. The patient's status on arrival to PACU shall be documented.
2. Information concerning the preoperative condition and the surgical/anesthetic course shall be transmitted to the PACU nurse.
3. The member of the anesthesia care team shall remain in the PACU until the PACU nurse accepts responsibility for the nursing care of the patient.

STANDARD IV:

The patient's condition shall be evaluated continually in the PACU.

1. The patient shall be observed and monitored using methods appropriate to the patient's medical condition.
2. Particular attention shall be given to monitoring oxygenation, ventilation, circulation, level of consciousness, and temperature.
3. During recovery from all anesthetics, a quantitative method of assessing oxygenation, such as a pulse oximetry shall be employed in the initial phase of recovery.
4. An accurate written report of the PACU period shall be maintained.
5. Use of an appropriate PACU scoring system is encouraged for each patient on admission, at the appropriate intervals prior to discharge and at the time of discharge.
6. General medical supervision and coordination of patient care in the PACU should be the responsibility of an anesthesia provider.
7. There shall be a policy to assure the availability in the facility of a physician capable of managing complications and providing cardiopulmonary resuscitation for patients in the PACU.

STANDARD V:

A physician is responsible for the discharge of a patient from the PACU.

1. Before discharge from the center, each patient must be evaluated by a physician for proper anesthesia recovery.
2. When discharge criteria are used, they must be approved by Director of Anesthesia and the Governing Board.
3. Discharge criteria may vary depending on where the patient is being discharged to go (e.g., home, extended care facility, short stay unit, etc.).
4. In the absence of the physician responsible for the discharge, the PACU nurse shall determine that the patient meets the discharge criteria.
5. The name of the physician accepting responsibility for patient discharge shall be noted on the medical record.
6. All patients are discharged in the company of a responsible adult, except those exempted by the attending physician.

APPENDIX L

MEDICAL RELEASE AUTHORIZATION

MEDICAL RECORDS RELEASE AND AUTHORIZATION FOR USE OR DISCLOSURE OF PROTECTED HEALTH INFORMATION

I_____herby authorize **Lyman Medical Research Foundation, INC, Orthopedic Specialty Institute, and their associated medical and clinical research personnel** to receive information from:

- **Providence Sacred Heart Medical Center**
- **Northwest Specialty Hospital**
- **Pleasant View Surgery Center**
- **Orthopedic Specialty Institute**
- **Providence Orthopedics**
- **Participating Physical Therapy Clinic**

contained in _____ Medical Record, including alcohol and drug abuse records, if any; social services records, if any; records of Human Immunodeficiency Virus (HIV) testing including results, if any; records of Acquired Immunodeficiency Syndrome (AIDS), ARC (AIDS related Complex), if any; and records of communicable diseases, if any; to the individuals or organizations listed below.

NAME OF INDIVIDUAL(S)/ORGANIZATION(S) Ellicia Coyne, Clinical Research Director; Lyman Medical Research Foundation; Orthopedic Specialty Institute; Jeffrey Lyman, MD; Timothy Lovell, MD; Halyard Health; Providence Health Care IRB and other regulatory agencies associated with the clinical research trial

ADDRESS 1875 N Lakewood Drive STE 200

CITY/STATE/ZIP Coeur d'Alene, ID 83814

TELEPHONE (208) 758-0716 **FAX** (208) 667-7717

I. PATIENT IDENTIFICATION

PATIENT'S DATE OF BIRTH	SOCIAL SECURITY NUMBER
NAME USED AT TIME OF TREATMENT	DATE(S) OF TREATMENT

II. RECORDS TO BE RELEASED

☒Inpatient Medical Records ☒Outpatient Treatment or Testing ☒Physical Therapy Rehabilitation

☒Entire Record

III. PURPOSE OF DISCLOSURE

THE INFORMATION BEING DISCLOSED IS FOR THE PURPOSE OF:

Clinical Research Trial (Principal Investigator: Dr. Lyman, Co-Investigator: Dr. Lovell)/Investigational Study

IV. SIGNATURE

SIGNATURE	DATE
RELATIONSHIP TO PATIENT	IDENTIFICATION

V. RIGHTS

- The information listed here above is to be release for the stated purpose only. Any other use is forbidden.
- I may inspect and receive a copy of the information to be used pursuant to this authorization.
- This authorization is voluntary and I may refuse to sign this form. I will not be refused treatment if I refuse to sign this form.
- This authorization is valid for a period of 180 days. I understand that I may also revoke authorization at any time by contacting Lyman Medical Research Foundation. My revocation must be in writing. However, the hospitals, providers, research and medical personnel, and treatment facilities are not responsible for actions already taken based upon this authorization. I may not be able to revoke this authorization if its purpose was to obtain insurance.
- I understand that information used or disclosed pursuant to this authorization may be subject to re-disclosure by the recipient and may no longer be protected by federal and state law.

APPENDIX M

TRAVEL REIMBURSEMENT FORM

Clinical Research Trial
Patient Travel Reimbursement Form for
Treatment at Pleasant View Surgery Center

Patient Name
Patient Address
Patient Phone Number
Estimated Mileage to and from PVSC

Pleasant View Surgery Center (PVSC)
4171 W Expo Pkwy
Post Falls, ID 83854

Official Office Use Only
Total Mileage to and from PVSC
Calculated Reimbursement to Patient
Date Payment is Mailed
Signature of Executive Director Clinical Research

APPENDIX N

ENROLLMENT ELIGIBILITY FORM

Enrollment Eligibility

RFA for TKA Clinical Study

INCLUSION

- MALES AND FEMALES
- 40 YEARS OF AGE AND OLDER
- BMI < 40
- UNILATERAL KNEE ARTHROPLASTY INDICATED BY RADIOGRAPH, FUNCTION DECREASE AND/OR PAIN INDICATION
- READINESS TO UNDERGO A RESEARCH TREATMENT

EXCLUSION

- NO DAILY OPIOID CONSUMPTION 5 WEEKS PRIOR TO ENROLLMENT
- NO DOCUMENTED NARCOTIC DEPENDENCY OR RECREATIONAL DRUG USE
- NO TOBACCO USAGE WITHIN 2 MONTHS PRIOR TO SURGERY
- NO CONFOUNDING INFLAMMATORY ARTHRITIS DISEASES ARE PRESENT
- NO NEUROPATHY OR NEURO IMPAIRMENT PRESENT
- NO SIGNIFICANT ACUTE ILLNESS OR INFECTION
- NO OTHER CONFOUNDING CHRONIC PAIN
- NO INVESTIGATIONAL AGENT WITHIN 3 MONTHS PRIOR TO ENROLLMENT
- NO DIAGNOSED THROMBOPHILIA
- NO SEVERE CARDIAC OR PULMONARY COMPROMISE
- NO BLEEDING DISORDER(S)
- NO ALLERGIC REACTION TO LOCAL ANESTHESIA, STEROIDS, OR IMPLANT MATERIALS
- NO BREASTFEEDING
- NO PREGNANCY
- NO CONFOUNDING PSYCHIATRIC ILLNESSES
- NO CONFOUNDING MAJOR TRAUMA HARDWARE REMOVALS OR PRIOR TKA

**NO CONTRAINDICATED BODY HABITUS TO BE DETERMINED BY A TREATMENT PROVIDER*

I assessed the patient for inclusion and exclusion criteria. The patient is eligible to enroll in the clinical trial. The study was discussed with the patient including the RFA treatment randomization to SHAM, C-RFA or t-RFA. The patient was invited to participate and accepted consideration to enroll in the study. The patient was referred to a randomized study RFA treatment. The informed consents and recruitment materials were provided to the patient.

PROVIDER

○ JEFFREY LYMAN, MD	○ KIRA SANDON, PA
○ TIMOTHY LOVELL, MD	○ VINCINT SPRUNG, PA
○ ADAM OLSCAMP, MD	○ RYAN SMITH, PA

(SIGNATURE) (DATE)

APPENDIX O

SITE REFERRALS

LYMAN
MEDICAL RESEARCH FOUNDATION

Timothy Lovell, MD
Clinical Study Pain Management Referral Order

TO	FROM
LYMAN MEDICAL RESEARCH FOUNDATION	PROVIDENCE ORTHOPEDICS
JEFFREY LYMAN, MD	TIMOTHY LOVELL, MD
ELLICIA COYNE, CLINICAL RESEARCH DIRECTOR	820 S MCCLELLAN ST #300
1875 N LAKEWOOD DRIVE STE 200	SPOKANE, WA 99204
COEUR D'ALENE, ID 83814-7717	PHONE: (509) 838-7100
PHONE: (208) 902-9029	FAX: (509) 838-0721
FAX: (208) 620-3546	

REFERRAL ORDER INFORMATION			
DIAGNOSIS	OSTEOARTHRITIS		
	PLEASE INDICATE LOCATION	R KNEE	L KNEE
ORDER NAME	OSTEOARTHRITIS PAIN MANAGEMENT REFERRAL (RFA STUDY)		
REASON FOR REFERRAL	PLANNED TOTAL KNEE ARTHROPLASTY		

PATIENT INFORMATION			
PATIENT ID			
PATIENT NAME			
	LAST	FIRST	MI
SEX – DOB - AGE			
	SEX	DOB	AGE
ADDRESS			
	STREET		
	CITY	STATE	ZIP
PHONE			
	HOME	MOBILE	

CLINICAL STUDY ADMINISTRATIVE USE	
RFA TREATMENT PROVIDER RANDOMIZATION	(1) GREG BAUER (2) DORAN THOMAS (3) MIKE LUDWIG, MD

AUTHORIZATION **DATE**

LYMAN
MEDICAL RESEARCH FOUNDATION

Clinical Study Pain Management Referral Order

TO
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REFERRAL ORDER INFORMATION			
DIAGNOSIS	**OSTEOARTHRITIS**	**R KNEE**	**L KNEE**
ORDER NAME	**OSTEOARTHRITIS PAIN MANAGEMENT REFERRAL -STUDY RFA TREATMENT**		
REASON FOR REFERRAL	**PLANNED TOTAL KNEE ARTHROPLASTY**		

PATIENT INFORMATION			
PATIENT EMR#			
PATIENT NAME			
	LAST	**FIRST**	**MI**
SEX – DOB - AGE			
	SEX	**DOB**	**AGE**
ADDRESS			
	STREET		
	CITY	**STATE**	**ZIP**
PHONE			
	HOME		**MOBILE**

CLINICAL STUDY ADMINISTRATIVE USE	
RFA TREATMENT PROVIDER RANDOMIZATION	(1) **GREG BAUER** (2) **DORAN THOMAS** (3) **MIKE LUDWIG, MD**