PROTOCOL TITLE:

"Evaluating the efficacy of micro-fragmented adipose tissue and intra-articular corticosteroid injections for symptomatic knee osteoarthritis: a randomized, placebo controlled study"

PRINCIPAL INVESTIGATOR:

Dustin Richter, MD
UNMH Department of Orthopaedics

VERSION NUMBER:

6

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REGULATORY FRAMEWORK:

Please indicate all that apply:

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

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

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1. Objectives

1.1. The purpose of this study is to evaluate the possible benefits of reduced joint pain and increased joint functionality in participants with knee osteoarthritis after the injection of Lipogems®. Based on limitations of prior research, intra-articular corticosteroids are included as a study group to be evaluated for impact on pain relief and joint functionality in comparison to placebo.

1.2. We hypothesize that participants who receive an injection of Lipogems® will experience a decrease in pain of the affected knee and an increase in joint functionality in comparison to placebo. We also hypothesize that participants who receive an intra-articular corticosteroid will experience decreased pain or improved functionality in the affected joint.

2. Background

2.1. Osteoarthritis (OA) causes patients considerable joint pain and leads to instability, reduced range of motion, and functional limitations. Pathologic findings of OA include decreased articular cartilage, joint space narrowing, osteophytes, subchondral sclerosis and bone cysts.[1] Currently, treatment options are confined to symptom management only. Options for treatment include: topical preparations, nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections, and, in severe cases, total knee arthroplasty. Review of recent recommendations shows limitations to all available treatments. Oral NSAIDs have shown relief, but is limited to patients without risk factors or contraindications. Topical NSAIDs are recommended in elderly patients or those with GI risk factors, rather than oral NSAIDs. However, pain improvement took 12 weeks and was not long-lived, potentially due to compliance issues in application.[2,3] A recent systematic review of intra-articular corticosteroids reported that, due to low-quality evidence, it is inconclusive whether intra-articular corticosteroids provided any short or long-term pain relief.[4] Taylor's review of hyaluronic acid treatment is hampered by the variability of preparations currently on the market and shortage of double-blind placebo controlled studies, but conflicting data is reported.[3] Osteoarthritis Research Society International currently recommends corticosteroid injections for short-term pain relief only, and is inconclusive in recommending hyaluronic acid.[5] The aforementioned treatment limitations have generated interest in alternative options to restore function and alleviate joint pain, some with the aim of healing damaged articular cartilage. It is well known that articular cartilage is avascular and lacks innervation, which limits its intrinsic healing and repair capabilities. Chondrocytes, derived from MSCs, have limited potential to replicate, which also limits the intrinsic healing and repair capabilities of articular cartilage.[6,7] The stromal vascular fraction, containing adipose derived mesenchymal stem cells (MSCs), has historically been isolated successfully via enzymatic processes.[8] There has been preliminary support in the literature for

reduced pain and improved functional performance in patients who received MSCs as part of treatment.[7,9,10] However, approaches to isolate MSCs are costly, time consuming, require extensive lab equipment, and are currently limited by complex regulatory issues.[11-13]
Thus, interest in an alternative isolation method lead to the development of Lipogems®. Lipogems® is a technique to harvest, process, and inject minimally manipulated adipose tissue. This procedure is enzyme free and requires no clonal expansion or manipulation. Lipoaspirate is harvested and washed in saline solution, then processed through a closed-system device that micro-fragments the adipose tissue. This mechanical process retains the vascular architecture, mature pericytes, and MSCs for autologous injection.[12,13]
As new technologies are becoming available for the treatment of OA, it is important that we gather high-quality data on their efficacy and outcomes. The goal of this study is to evaluate the possible benefits of reduced joint pain and increased joint functionality in participants with knee osteoarthritis after the injection of Lipogems®. In addition, given the limitations of prior research on the efficacy of intra-articular corticosteroids, we will also include this as an additional study group to compare to placebo. Although Lipogems® is relatively new to the United States, it has been used for a variety of orthopaedic arthroscopic applications overseas including the treatment of knee OA and is being used more frequently now in the United States. As of now, there are no published studies reporting the outcomes of patients who receive Lipogems® for knee OA. There have been case reports published showing favorable outcomes. Thus, this would be the first study reporting data on the efficacy of Lipogems® for pain relief in knee OA in a randomized, controlled clinical trial with a larger sample of participants. It would also be the only study to date comparing Lipogems® to intra-articular corticosteroids and placebo injections. We feel this study design will provide new insight into the efficacy of Lipogems® for pain relief of symptomatic knee OA as well as offer new data on the efficacy of intra-articular corticosteroids in this application.

2.2. *We do not have any preliminary data. There is, at this point, no study published explicitly evaluating the efficacy of Lipogems in patients with knee osteoarthritis, although Lipogems® has been used for this purpose and is acknowledged in case reports. One case study by Striano et al reports decreased knee pain and no adverse side effects following injection of Lipogems®.[14]*

2.3. *Estimates say that there are between 15-27 million US adults age 25 or older with clinical OA of at least one joint, and that 49.7% of people over the age of 65 report that they have diagnosed arthritis.[15-17] The lifetime risk of symptomatic knee osteoarthritis is estimated to be 13.8%, and an even higher risk is identified for obese persons (19.7%) and females (16.3%).[18]*
OA is not exclusive to patients over 65. Recent estimates show that approximately 6.6 million people between the ages of 45-64 had OA in 2011-

2012. Furthermore, it is estimated that 1.7 million adults under the age of 45 had OA in the same year.[17] Thus, the burden of OA is much more widespread than the elderly population.
Current therapies are limited to symptom management only, none curative or capable of stopping the progress of disease. Thus, a staggering number of Americans of all ages are living with a chronically painful joint condition. Furthermore, with the burden of an aging population and high rate of obesity in the United States, the management and treatment of OA will continue to be an important health concern.
As new technologies are becoming available for the treatment of OA, it is important that we gather high-quality data on their efficacy and outcomes. The goal of this study is to evaluate the possible benefits of reduced joint pain and increased joint functionality in participants with knee osteoarthritis after the injection of Lipogems®. In addition, given the limitations of prior research on the efficacy of intra-articular corticosteroids, we will also include this as an additional study group to compare to placebo. This would be the first study to evaluate the efficacy of Lipogems® for pain relief in knee OA in a randomized, controlled clinical trial with a large sample of participants. It would also be the only study to date comparing Lipogems® to intra-articular corticosteroids and placebo injections. We feel this study design will provide new insight into the efficacy of Lipogems® for pain relief of symptomatic knee OA as well as offer new data on the efficacy of intra-articular corticosteroids for this application. .

3. Study Design

3.1. This study will be conducted as a randomized, placebo-controlled clinical trial. Participants will be randomized to receive either Lipogems®, intra-articular corticosteroids, or a placebo injection of saline. Lipogems® is cleared for use by the FDA in orthopaedics and arthroscopy and is offered as a treatment option for knee osteoarthritis. This study will be evaluating the effectiveness (not safety) of Lipogems® when compared to corticosteroids and placebo. Thus, no information will be submitted to the FDA.

3.2. It is not feasible to blind participants who are randomized to receive Lipogems®, as adipose tissue must be obtained from the participant. However, participants randomized to receive intra-articular corticosteroids or placebo injections will be blinded.

3.3. Randomization will be stratified according to baseline pain severity as defined here, ethnicity, and age to ensure a balanced assignment across the three groups with respect to important determinants. Stratification will not be based on radiographic severity as previous studies have shown no correlation between the radiographic severity of knee osteoarthritis and the pain experienced by the patient.

4. Inclusion and Exclusion Criteria

4.1. Participants will be recruited from the patient population at the clinics of Dustin Richter, MD, Robert Schenck, MD, Andrew Veitch, MD and Suki Pierce, PA-C at the University of New Mexico's Orthopaedic Department. Since all potential participants will be independently seeking care for osteoarthritis, the participating clinicians and research staff will screen the patients for inclusion criteria during their standard examination. Qualifying patients will be offered enrollment into the study at that time.

4.2. Inclusion criteria include being the age of eighteen or older, diagnosed symptomatic knee osteoarthritis, and radiographic evidence of knee osteoarthritis. For the purposes of this study, radiographic evidence of knee osteoarthritis is defined at any one or more of the following: osteophytes, joint space narrowing, loss of articular cartilage thickness, subchondral sclerosis or cysts. Patients will also meet inclusion criteria if their intake sheet pain score is at least a 3 out of 10, as pain scores less than 3 are unlikely to show a clinically meaningful improvement from any treatment option. Patients will be excluded from the study if they have a history of treatment with any intra-articular knee injection or have current ligament instability as demonstrated by a positive Lachman Test, Anterior or Posterior Drawer Test, or positive Valgus or Varus Stress Test.[19] Patients with a known allergy to lidocaine will also be excluded from the study. Patients will be excluded if they do not meet our above-mentioned severity criteria with a pain score of at least 3 on the intake sheet.

4.3. This study will only include English or Spanish speaking adults over the age of eighteen who are capable of independently consenting to participate in a research study. This study will not include any children, pregnant women, or prisoners. Women of childbearing age will be included only after they have had a negative urine pregnancy test at point of care.

4.4. Individuals under the age of 18 will be excluded from this study. As osteoarthritis is largely considered a degenerative joint disease, this population is highly unlikely to have osteoarthritis of the knee and thus will not be eligible for the study.

5. Number of Subjects

5.1. This study will take place solely at the University of New Mexico Hospital.

5.2. Based on our power analysis, we need 75 participants to complete the study. All subjects will have been pre-screened for eligibility by the participating clinicians.

5.3. We will take advantage of the 5-repeated measurements of joint pain and functionality from each patient, and compare the post-treatment trajectory of joint pain and functionality over follow-up between a pair of treatment groups. This approach facilitates group comparisons (1) at individual follow-up times, (2) life course of effects over the entire follow-up period. This will be done by means of mixed-effects regression models which incorporate both within-patient

(over time) and between-patient variations, and are more flexible in making inference on group differences. The method also allows for the inclusion of multiple covariates (see below) in the model to quantify effects attributable to the treatments. We will also consider repeated measurement analysis of covariance and pairwise comparison (e.g. t-tests) to validate our analysis with respect to robustness and sensitivity. We will follow LaPrade's recent recommendations of minimal reporting requirements for treatments that potentially include mesenchymal stem cells, such as Lipogems®. This includes age, gender, diabetes status, inflammatory conditions, pre-existing joint problems, and current NSAID use.[19] Since patient perception of post-treatment pain as measured by the VAS scale is a main variable of interest in our hypothesis, we searched the literature for previous studies in which the variability of pain using a VAS scale was investigated.[20-23] We estimated that the standard deviation likely to be found for our own observations will be approximately 35 on a 100 point scale, conservatively. We assume that most clinicians will consider a difference in post-treatment pain of about 15 points to be clinically important, as supported by Tashjian et al, who estimated 1.4 cm as the minimal clinically important difference on a 10 cm scale. To determine an adequate sample size for our pilot, we assumed average change in pain score over the follow-up to be 10-15, and standard deviation to be 10-20. To have 80% power with a 5% Type I error rate, an approximate 2-way ANOVA model suggest sample size in the range of 18-49 per group. We adopt n=22 as our minimum sample size per group based on the assumption of 15-point change in pain score over time on average and a 20-point standard deviation over time. Within the recruitment time window, we will aim to enroll n=25 or more participants in each of the three treatment arms so long as the logistics permit. We expected the mixed-effect model will increase the power by utilizing the longitudinality of the data, compensating potential loss of power due to drop-outs and serial correlation.

6. Study Timelines

6.1. Describe:

- *Individuals who agree to participate in this study will be enrolled during an initial screening visit which they will have independently sought and scheduled. Their participation will involve one procedure visit, two brief follow-up visits, and three online completion of surveys. We anticipate that it will take approximately 15 months from date of enrollment to complete each individual subject's procedure and follow-up visits, allowing time for flexibility in scheduling based on the clinician and subject's schedules.*
- *We estimate that it should take approximately three months to enroll 75 subjects. We anticipate this being feasible based on the four participating clinicians' current schedules. Roughly, an orthopaedic surgeon may see upwards of 50 patients a day. Approximately 10% of these patients have knee OA and potentially qualify for the study.*

- *We anticipate the data analysis to take a maximum of two months following the completion of all data collection.*

7. Study Endpoints

7.1. This study will conclude once all active, enrolled participants have completed their one-year follow-up.

7.2. Participants will be followed via standard of care and monitored at follow-up appointments. After we have had 10 participants enrolled in each group, we will do a preliminary evaluation of the available data.

7.3. Not applicable. We will not have exploratory endings.

8. Research Setting

8.1. Research will be conducted at the University of New Mexico Hospital Orthopaedic Clinics of Dustin Richter, MD, Robert Schenck, MD, Andrew Veitch, MD and Suki Pierce, PA-C. Research, including all patient visits and procedures, will also be conducted at the CTSC.

8.2. Participants will be recruited from the patient population at the clinics of Dustin Richter, MD, Robert Schenck, MD, Andrew Veitch, MD and Suki Pierce, PA-C at the University of New Mexico's Orthopaedic Department. Since all potential participants will be independently seeking care for osteoarthritis, the participating clinicians and research staff will screen the patients for inclusion criteria during their standard examination.

8.3. Procedures and follow-up visits will be performed at the CTSC facilities on North Campus.

8.4. Not applicable. There will be no community advisory board

8.5. Not applicable. No research will be conducted outside of UNM HSC or CTSC.

9. Resources Available

9.1. Dustin Richter, MD (PI):
As an Assistant Professor in the Department of Orthopaedics at the University of New Mexico in Albuquerque, Dr. Richter practices Orthopaedic surgery with an emphasis on care of the athlete. He is new faculty and has been in practice since 2016. He is fellowship trained in sports medicine (University of Virginia, 2016) and has worked as a team physician for most of his training. In addition, he has worked at a level I trauma center throughout his Orthopaedic career. In addition to managing complex traumatic injuries and fractures, he performs routine and complex surgeries treating athletic injuries (for example, ACL tears of the knee, rotator cuff tears of the shoulder, shoulder dislocations, and fractures of all types) and utilizes arthroscopy for many of his surgeries. His practice is divided between shoulder, knee sports surgeries, and hip arthroscopic procedures.
As a sports surgeon, he routinely sees patients of all ages with knee pain. Many

of these patients have pain as a result of osteoarthritis which has not been previously diagnosed. He pursues a conservative treatment algorithm with these individuals that consists of activity modification, weight loss, oral anti-inflammatories, and intra-articular knee cortisone injections or hyaluronic acid injections prior to referring the patient to any of his colleagues for consideration of a reconstructive procedure (knee replacement). His research interests have included: Multi-ligamentous knee injuries, knee cartilage repair, and evidence-based medicine with a focus on quality and value-added care. Specifically related to this proposal, he recently published a comprehensive review in Sports Health evaluating the efficacy of knee articular cartilage repair and restoration techniques. He has also studied and published on the psychosocial and demographic factors influencing pain scores of patients with knee osteoarthritis (UNMORJ 2016). Lastly, he also recently published on looking at the value in healthcare regarding inpatient versus outpatient partial knee replacements. For this proposal, he will serve as the Principal Investigator and will be the primary contact for all correspondence related to the study. He will be responsible for contributing to the overall design and conduct of the study. He will oversee subject recruitment and follow-up for and will be responsible for supervision of the research support staff at the University of New Mexico. He will assure integrity and security of the data and will be responsible for timely completion of progress reports as well as preparation of abstracts and manuscripts to disseminate the results. He will use his collective research and administrative experience to ensure that the study is completed within budget and in compliance with all federal and University of New Mexico regulations.

Lauren Faber, MS1:

Lauren Faber is a first-year medical student at the University of New Mexico School of Medicine. She graduated from the University of New Mexico in 2011, earning her Bachelor of Arts in Psychology with Summa Cum Laude honors. She has previous bench research experience at UNM's Center for Evolutionary and Theoretical Immunology. She has also worked closely with the Research Coordinator at Southwest Women's Health, assisting in clinical studies by consenting patients, monitoring implantation of study protocols, and managing and reporting data. She is currently in good standing at UNM SOM and was selected for an honors research track, "Community of Scholars," for demonstrating a passion for research.

Robert Schenck, MD:

Dr. Schenck, current Professor and Chair in the Department of Orthopaedics and Rehabilitation at the University of New Mexico, has been a full-time academic physician since starting orthopaedic career as an instructor at the University of Texas. After his medical training at Johns Hopkins, he pursued fellowship training in sports medicine with subspecialty training in foot and ankle surgery. He has also served as an athletic team physician for most of his career. As Chair for the last 10 years, he has mentored faculty and created a department which has seen three-fold growth in both faculty size and revenues.

He is a member of numerous orthopaedic groups and associations and has served the American Board of Orthopaedic Surgery for 10 years as an Oral Examiner and a Question Writing Task Force participant for Part I of the written ABOS examination. He was selected to be an accompanying "godfather" for the 2017 Latin American Society of Knee Arthroscopy and Sports Medicine fellowship. He has substantial research experiencing and has contributed over 150 articles to medical publications.

Andrew Veitch, MD:

Dr. Veitch is a board certified orthopaedic surgeon who is fellowship trained in orthopaedic sports medicine. He is an associate professor at the University of New Mexico and has been the Head Team Physician for Varsity Lobo Athletic Teams since 2004. The focus of his medical practice is on sports injuries, knee injuries, and shoulder injuries. He also performs fracture care. His prior research experience results in publications on ankle arthrodesis to treat arthritis, tendon repair, and fractures. He has also given multiple lectures on knee injuries and articular cartilage injuries.

Jory Wasserburger, MD:

Dr. Wasserburger is a resident in the Department of Orthopaedics and Rehabilitation at the University of New Mexico. He began his education at the University of Wyoming earning a Bachelor of Science in Nursing with honors. In 2012, he entered medical school at the University of Washington. At Washington, he gained clinical research experience exploring heterotopic ossification prevention in elbow fractures and propionibacterium acnes infection of total shoulder arthroplasty. During his residency he has continued clinical research by publishing case series, case reports, and posters. Additionally, he volunteered to be the team physician for the Valencia High School football team.

Carina Suki Pierce, PA-C:

Suki is a certified physician assistant who specializes in orthopaedic sports medicine. She completed her medical education at the University of New Mexico in 2009. She runs an injection clinic and has substantial experience with injections for knee osteoarthritis.

9.2. Dustin Richter, MD, Robert Schenck, MD and Andrew Veitch, MD will be responsible for making medical decisions during procedures and at follow-up visits. Suki Pierce, PA-C, will be responsible for medical decision making for injections and visits done at her clinic.

9.3. Other resources available to conduct the research include:

- *We anticipate needing 75 total subjects enrolled who have finished the study to completion. Based on the current clinic schedules of Dr. Richter, Dr. Schenck, Dr. Veitch, and Pierce, PA-C, we feel it is reasonable to expect to enroll the necessary number of participants in the study time period.*
- *We anticipate that this study will approximately one year from date of onset to complete. All study subjects are expected to have completed their*

requirements within 15 months of enrollment. We anticipate needing two months for data analysis.

- *The facilities available for the research include: University of New Mexico Hospital including clinics and operating facilities for patient recruitment, the facilities made available for the Orthopedic Department, the CTSC facilities for participant procedures and follow-up, and the UNM IDS Pharmacy for drug storage and handling.*
- *Subjects that may desire further medical attention may request to be removed from participation in the study and can then choose to pursue further care with the physician of their choice.*
- *All persons assisting with the study will be trained on the protocol, consent process, and data collection by Dustin Richter, MD, the principal investigator, prior to participating in the study.*
- *We will also be utilizing the CTSC research facility and resources for conducting this study, including their statistical department, rooms and facilities, and their study coordinators to help gather survey data.*

10. Prior Approvals

10.1. We will be awaiting funding approval and IRB approval prior to conducting the research. We have already received departmental approval.

10.2. Departmental Review Form.

10.3. Not applicable. No x-rays are required during participation in the study. Patients who qualify for the study will have obtained standard of care x-rays prior to enrollment in the study as part of their provider's evaluation.

10.4. Drug attachment.

11. Multi-Site Research

11.1. Not applicable. This study will be conducted at the University of New Mexico Hospital and CTSC and will not include any other sites

11.2. Not applicable. This study will be conducted at the University of New Mexico Hospital and CTSC and will not include any other sites.

11.3. Not applicable. The treatments used in this study are FDA approved and being used in the manner intended.

12. Study Procedures

12.1. In chronological order, all research procedures and interventions being performed and when they are performed.

1. Participants will be screened prior to enrollment. Depending on their medical history and prior consultations, they will likely have a physical exam and x-rays of the affected knee(s). This is standard of care and will happen prior to enrollment in the study. X-ray images and medical data from these visits may be used for the purposes of analyzing statistical data.

2. Upon enrollment, participants will be randomized to a treatment group and scheduled for their injection procedure.
3. At their injection visit, participants will complete the Western Ontario and McMaster Universities Osteoarthritis Index, a Visual Analog pain scale, and the Knee Injury and Osteoarthritis Outcome Score scales to establish a baseline. They will also fill out a medication log to document any medications that they take, including oral pain medications, although we will not be intervening with oral medications. They will complete these surveys and the log again at 2 weeks, 6 weeks, 3 months, 6 months, and 1 year after the injections
4. Participants will receive their assigned injection. Participants who are randomized to the placebo group will receive an injection of 7cc of sterile saline. Participants who are randomized to the corticosteroid group will receive an injection of 2cc (80mg) of Kenalog®-40 (triamcinalone acetonide injectable suspension, USP) mixed with and 5 cc of 1% plain lidocaine for a total of 7cc of fluid injected. Kenalog® injections are part of the current standard of care for patients with osteoarthritis of the knee. Participants who are randomized to the Lipogems® treatment group will undergo a lipoaspiration from their abdomen and autologous injection of the harvested adipocytes into their knee. It is standard to harvest three to four times more adipose tissue than is planned to be injected to account for tissue processing by the Lipogems® device. We plan to inject 7cc of autologous adipose tissue. Thus, we will harvest between 25 and 30 cc of adipose tissue from each patient. The tissue will be processed immediately and 7cc will be injected. Any remaining adipose tissue will be disposed of immediately in biohazardous waste. Lipogems® is currently approved for orthopedic and arthroscopic procedures; thus, this would be an on-label use. All injections will be performed in the clinic by Dr. Richter, Dr. Schenck, and Pierce PA-C as an in-office procedure.
5. Participants will be scheduled to return for in-person follow-up visits with a research staff member at 6 weeks and 6 months after their injection, where they will again complete a medication log, Western Ontario and McMaster Universities Osteoarthritis Index, a VAS pain scale, and the Knee Injury and Osteoarthritis Outcome Score scales. They will also complete the above surveys and log at 2 weeks, 3 months, and 1 year post injection, but these will be completed online. The above mentioned surveys and medication log will be generated in RedCap and emailed securely to participants for their completion. If participants do not have email or access to the internet, these surveys will be completed over the phone and entered into RedCap by research staff.
6. Upon completion of their 1-year questionnaires, participants who were randomized to receive Lipogems® or Corticosteroid injections will be finished participating in the study.
7. Upon completion of their 1-year questionnaires, participants who were randomized to receive placebo injections will be offered the choice to cross-over to the corticosteroid group. Whether they choose to have the injection or not, their participation in the study will be completed.

13. Data Analysis

13.1. We will take advantage of the 5-repeated measurements of joint pain and functionality from each patient, and compare the post-treatment trajectory of joint pain and functionality over follow-up between a pair of treatment groups. This approach facilitates group comparisons (1) at individual follow-up times, (2) life course of effects over the entire follow-up period. This will be done by means of mixed-effects regression models which incorporate both within-patient (over time) and between-patient variations, and are more flexible in making inference on group differences. The method also allow for the inclusion of multiple covariates (see below) in the model to quantify effects attributable to the treatments. We will also consider repeated measurement analysis of covariance and pairwise comparison (e.g. t-tests) to validate our analysis with respect to robustness and sensitivity.

13.2. Since patient perception of post-treatment pain as measured by the VAS scale is a main variable of interest in our hypothesis, we searched the literature for previous studies in which the variability of pain using a VAS scale was investigated.[20-23] We estimated that the standard deviation likely to be found for our own observations will be approximately 35 on a 100 point scale, conservatively. We assume that most clinicians will consider a difference in post-treatment pain of about 15 points to be clinically important, as supported by Tashjian et al, who estimated 1.4 cm as the minimal clinically important difference on a 10 cm scale. To determine an adequate sample size for our pilot, we assumed average change in pain score over the follow-up to be 10-15, and standard deviation to be 10-20. To have 80% power with a 5% Type I error an approximate 2-way ANOVA model suggest sample size in the range of 18-49 per group. We adopt n=22 as our minimum sample size per group based on the assumption of 15-point change in pain score over time on average and a 20-point standard deviation over time.

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

14.1. Corticosteroids are standard of care. Lipogems® is approved for use in orthopaedics and arthroscopic procedures. Participants will be closely followed by the participating clinicians/investigators through the follow-up visits required for participation. All measures will be taken to ensure that participants receive appropriate care.

14.2. Patients will be informed of the risks of participating prior to enrolling in the study and may choose to enroll or not enroll. They will be reminded of expected post-procedural findings and will be monitored for adverse reactions by the participating clinicians at their follow-up visits.

14.3. The data monitoring committee will consist of Dr. Dustin Richter, Dr. Daniel Wascher [Orthopaedic Sports Medicine], Dr. Gehron Treme [Orthopaedic

Sports Medicine]; this committee will conduct a preliminary review of the existing data once 10 participants have been enrolled in each group.

14.4. The existing literature has been reviewed regarding Lipogems®. A board certified plastic surgeon was consulted regarding adverse effects of lipoaspiration procedures and the adverse risks are detailed in this protocol and the consent form.

14.5. N/A. Safety data is not collected in this study.

14.6. The research will be suspended and/or terminated if there is an unexpected serious adverse event that requires further investigation.

15. Withdrawal of Subjects

15.1. We do not anticipate any medical reasons to withdraw subjects from the study without their consent. If participants are not adherent and miss follow-up appointments, refuse to be scheduled, or do not respond to scheduling requests, they will be withdrawn from the study.

15.2. Participants may withdraw at their request and continue to seek standard of care treatments with the physician of their choice. No labs/tapering of meds/or physical exams are necessary to withdraw.

15.3. Partial withdrawal will be permitted if a patient desires to continue participating in data collection but no longer wishes to be seen for follow-up. The questionnaires would be completed online only. All previously collected data will still be used for research purposes unless the patient explicitly asks for data to be excluded.

15.4. If a patient withdraws, all previously collected data will still be used for statistical analysis unless the participant explicitly asks for their previous data to be excluded from further consideration. Describe the disposition of existing data/specimens when a subject withdraws.

15.5. If a patient requests to be withdrawn, Dustin Richter, MD, the principal investigator, must be made aware. If the patient requested that their data be destroyed and not used for analysis, then the data will be properly destroyed. Otherwise, data that was collected prior to withdrawal from the study may be used for analysis.

16. Data Management/Confidentiality

16.1. Members of the research team will be permitted to access the participants' medical records through PowerChart to confirm participant eligibility and document procedures and follow-up visits. PHI will be reviewed as part of the normal screening process in clinic.

16.2. Members of the research team will have access to direct identifiers only as necessary to confirm participant eligibility and document procedures and follow-up visits.

16.3. The research team will have access to the patient's PHI, as data may be needed from their consultation visits prior to enrollment in the study. Furthermore, they will have access to the medical record as procedures and follow-up visits will be documented in their medical records.

16.4. Not applicable. The study team may only know of any sensitive PHI if noted in medical chart.

16.5. Not applicable.

16.6. Participants will fill out questionnaire at their procedure and their 6 week and 6 month visits. These questionnaires will be filled out on paper and will only have the participant's unique identifier number on them. The data will be entered into RedCap by a member of the research staff. These paper copies will be kept in a locked file cabinet in Dustin Richter, MD's office behind a locked door. In addition, each participant will be assigned a number from 001-100. This code will be kept on a password protected excel file on Dustin Richter, MD's password protected computer located in his office behind a locked door. Only the PI and research staff will have access to any of these documents. No data is to be transported or transmitted to any other computer or location. Participants will also complete the questionnaires via RedCap (or phone if the patient doesn't have email or internet access) at 2 weeks, 3 months, and 1 year post injection. If a patient has internet access and email, surveys will be sent and completed securely via RedCap. If performed by phone, the member of the research staff will collect the data on paper and it will then be transcribed into RedCap.

Data will be kept for one year after full completion of data collection to allow time for data analysis and manuscript writing. Paper files, such as consent forms and questionnaires, will be appropriately shredded and disposed of. Excel files will be deleted. As no additional copies will be stored, this will destroy all of the identifiers and excel logs.

16.7. Each participant will be assigned a number from 001-100. This code will be kept on a password protected excel file on Dustin Richter, MD's password protected computer located in his office behind a locked door. There will only be patient names and unique identification numbers on this document. Only the PI and research staff will have access to the document.

16.8. Not applicable. As participants will be answering questionnaires and filling them out on their own, there is no need for quality control.

16.9. Not applicable. Data will not be transferred or transmitted to outside locations or entities. Any paper copies of questionnaires will be collected within CTSC facilities and will be input into RedCap. Paper copies will be stored as outlined in this protocol.

16.10. There will be data collected via a secure RedCap survey. Participants will be emailed a link to complete the questionnaires. This secure email will be sent

through RedCap and all data will be gathered through RedCap. RedCap is a secure web application frequently utilized to collect data for research, including HIPAA compliant information.

16.11. Not applicable. Data will not be collected by audio or video recording.

16.12. Not applicable. No photographs of participants will be taken at any point during the study.

17. Data and Specimen Banking

17.1. Not applicable. There will not be any data or specimen banking.

17.2. Not applicable. This is not a multi-center study, nor will any data or specimens be banked.

18. Risks to Subjects

18.1. This study involves risks to the participants as corticosteroids and Lipogems® are both used by clinicians as part of the current standard of care for knee osteoarthritis. One potential risk that may arise is a breach in patient confidentiality. Although such a breach is unlikely to occur and should not negatively impact patient health or well-being, we will take precautions to minimize this risk. All investigators and members of the study team will strictly adhere to the HIPAA and patient confidentiality guidelines set forth by the hospital. All research staff will adhere to the guidelines set forth in the Data Management/Confidentiality portion of this protocol.
Intra-articular knee injections, such as corticosteroids and Lipogems®, are employed in routine clinical practice for the treatment of knee osteoarthritis. With any injection, there is a risk of local adverse reaction such as pain or swelling, and a risk of infection. In addition to an injection, Lipogems® requires a lipoaspiration procedure from the patient's abdomen. Some risks of lipoaspiration include seromas and hematomas requiring drainage, infections, changes to the skin including hyperpigmentation, scarring, or induration. Very rarely, more serious complications (including skin necrosis or local anesthetic toxicity) may arise. [24,25]

18.2. We have received input from a board certified plastic surgeon on the risks of lipoaspiration. We have also reviewed the existing literature. Corticosteroid injection is part of the standard of care for treating knee osteoarthritis. As Lipogems® is still a relatively new treatment option, there may be unforeseen risks.

18.3. Patients who are pregnant will not be eligible for participation. Patients must verbally confirm they are not pregnant prior to enrollment in the study and prior to receiving their injection.

18.4. Not applicable. There are no risks to others who are not subjects.

18.5. To minimize risk, all injections will be performed following standard of care sterile techniques and treatment guidelines. We will have a board certified plastic surgeon trained in lipoaspiration train the study investigators accordingly. To protect patient confidentiality, we will take the necessary precautions to protect patient data. All electronic files will be password protected and stored on a password protected computer behind a locked door. All paper documents will be kept in a locked filing cabinet in a locked office.

19. Potential Benefits to Subjects

19.1. Potential benefits include the possibility of reduced pain and/or increased functionality of the affected knee after injection with Lipogems® or corticosteroids.

20. Recruitment Methods

20.1. Upon funding and IRB approval, participants will be recruited from the patient population at the clinics of Dustin Richter, MD, Robert Schenck, MD, and Suki Pierce, PA-C at the University of New Mexico Hospital's Orthopaedic Department. Patients at these clinics are independently seeking evaluation of orthopaedic problems. The participating clinicians and research staff will screen the patients for inclusion during their standard examination.

20.2. Review of relevant prior medical records (x-ray's, primary care/referring physician evaluations, and orthopaedic records including current visit findings and imaging) will be conducted to screen for eligible participants.

20.3. Subjects will be recruited by participating physicians and research staff via word of mouth at pre-existing patient visits. If we are having difficulty with subject recruitment, we may consider advertising.

Additionally, a non-publically-displayed patient flyer will be created to relay brief, informative details about the study design to surgical staff (eg, patient inclusion/exclusion criteria, follow-up length, etc).

21. Provisions to Protect the Privacy Interests of Subjects

21.1. All discussion of the study, including the informed consent process, will be conducted in a private exam room with only the clinician, relevant research staff, and patient in the room. All procedures and follow-up visits will be performed in private exam rooms with only the patient, the clinicians, necessary medical personnel, and necessary research staff present. Investigators will abide by standard patient confidentiality practices and will adhere to HIPAA protocols.

21.2. All discussion of the study, including the informed consent process, will be conducted in a private exam room with only the clinician, relevant research staff, and patient in the room. All procedures and follow-up visits will be

performed in private exam rooms with only the patient, the clinicians, necessary medical personnel, and necessary research staff present. Investigators will abide by standard patient confidentiality practices and will adhere to HIPAA protocols.

22. Economic Burden to Subjects

22.1. See below table.

Research Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
Lipogems® Injection 7cc of autologous adipose tissue	1 (randomization dependent)	☒	☐
Lipoaspiration 25-30cc of adipose tissue harvested	1 (randomization dependent)	☒	☐
Intra-articular corticosteroid injection 2cc (80mg) of Kenalog®-40 (triamcinalone acetonide injectable suspension, USP) plus 5 cc 1% lidocaine	1 (randomization dependent)	☒	☐
Placebo saline injection 7cc sterile saline	1 (randomization dependent)	☒	☐
Procedure Visit	1	☒	☐
Follow-Up Visits (6 weeks, 6 months)	2	☒	☐
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
Evaluation by clinician prior to participation	1	☐	☒
Routine x-rays prior to participation	Varies by clinician	☐	☒
_____	_____	☐	☐

22.2. There are no additional costs to participants.

22.3. The study will pay for all procedures and drugs involved in the study, including: corticosteroids and Lipogems®. Lipogems® has agreed to cover the costs of the kits for all study participants randomized to receive Lipogems®.

22.4. While we do not anticipate any serious adverse events, there are risks involved with undergoing medical procedures. Corticosteroid injections are currently included as part of the standard of care for treating osteoarthritis of the knee, and Lipogems® is FDA approved for autologous use in orthopaedic surgery. Thus, any adverse events experienced by the patient will fall under insurance coverage for standard of care procedures. All adverse events will be reported as required by the University. Depending on the severity of event, the investigators will consider the adverse event and reserve the right to hold enrollment or close the study early.

22.5. See consent form for discussion of costs.

23. Compensation

23.1. Participants will be compensated for their participation by receiving a reloadable gift card. They will receive $25 at each in person follow-up visit. They will be compensated $10 each time they complete the online surveys. Each participant will be asked to return for 2 follow-up visits (6 weeks and 6 months, post-procedure) and complete the online surveys 3 times for a total of $80 compensation for participating.

24. Compensation for Research-Related Injury

24.1. If a patient elects to withdraw from the study, i.e. for further treatment/care elsewhere, the patient may withdraw. We do not anticipate any more risk than standard of care would provide to the patient. The patient can elect to pursue standard of care treatments as determined by the patient and their physician.

24.2. Study subjects will be monitored at follow-up appointments. If a subject is unhappy with their treatment outcome throughout the course of the study, they may elect to withdraw from the study and pursue their own care with the physician of their choice.

25. Consent Process

25.1. Participants must provide research staff with informed consent prior to enrolling in the study.

25.1.1. Consent may be obtained by Dr. Richter, Dr. Schenck, Dr. Veitch, Dr. Wasserburger, and Lauren Faber and any other approved investigators listed in the Click IRB record. The process for obtaining informed consent and consent form will be reviewed with each member of the research staff responsible for obtaining consent by Dustin Richter, MD.

25.1.2. Consent will take place at the various clinics/hospitals associated with the University of New Mexico Hospital and the Orthopedics Department. Consent will only be obtained in a private patient room. No one besides the patient and study staff will be in the room at the time of consent. If the patient requests a family member or friend be in the room during the time of their appointment/consent, the patient's request will be honored.

25.1.3. The study, possibly treatment outcomes, and follow-up requirements will be explicitly stated at the time of consent. The patient will be made aware of their standard of care treatment options and will also be invited to participate in the study. The consent process will emphasize that patients have the right to accept or deny entry into the study with no consequences on their care.

25.1.4. Potential subjects will be offered the choice to participate if they meet eligibility criteria at visits with their provider prior to enrollment in the

study. The study will be explained at that time. If the patient is interested, informed consent will happen at that time.

25.1.5. Patients will provide consent for participation prior to enrolling in the study. This consent covers the injection and all follow-up visits. At each visit, participants will be asked if they wish to continue in the study and will provide verbal consent.

25.1.6. During informed consent, the person obtaining consent will utilize teach-back and ask the patient to explain, in their own words, what the study entails and what they are consenting to.

25.1.7. People obtaining consent will utilize teach back to make sure that patients understood the study, what possible treatment outcomes are, and what follow-up is required of study participants.

Subjects not fluent in English

25.1.8. This study will also include Spanish speaking participants.

25.1.9. For informed consent, explanation of the study, and all visits thereafter, a translator will be available to translate for the patient and the clinician. The informed consent document will be translated to Spanish.

25.1.10. Not applicable. No short-form consent documents will be used. There will be one standard informed consent document that must be explained to the patient and read by the patient prior to enrollment.

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

25.1.11. Not applicable. This study will only be enrolled individuals with full, independent ability to provide legally effective consent.

25.1.12. All subjects are required to have full, independent ability to provide legally effective consent.

25.1.13. During the consent process, those obtaining consent will utilize teach-back to ensure that the individual understands what participation in the study entails. Individuals will be asked to explain, in their own words, what they are agreeing to before giving informed consent. For individuals who are Spanish speaking, an interpreter will be made available to help with the consent process. If an individual is unable to explain the study or verbalize what they are agreeing to, he/she will not be enrolled.

25.1.14. As above, teach-back and asking the individuals to explain what their agreement to participate entails will be utilized during the consent process to ensure that individuals understand the study prior to providing informed consent. The research staff member obtaining consent are responsible for confirming that an individual can provide consent.

Research staff members will document this process by signing their respective portion of the informed consent document.

25.1.15. The participant's decisional capacity will be assessed at each visit (procedure, where consent is given, and four follow-up exams) by the participating clinicians.

25.1.16. Not applicable. Patients will have full capacity to provide consent prior to enrolling in the study.

25.1.17. Not applicable. This study will only enroll participants who can independently give informed consent.

25.1.18. Not applicable. No research will be conducted outside of New Mexico for this study.

25.1.19. Not applicable. Consent to participate in this study must be given by the participant.

25.1.20. Not applicable. If a patient is unable to provide informed consent they will be excluded from the study.

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

25.1.21. Not applicable. No individuals under the age of 18 will be enrolled in this study.

25.1.22. Verification of patient's date of birth will allow selection of participants over the age of eighteen.

25.1.23. Not applicable. No parental permission will be obtained as all study participants are required to be eighteen years of age or older and capable of providing independent, legally effective consent.
Describe whether parental permission will be obtained from:

25.1.24. Not applicable. No permissions from individuals other than the patient will be required as all study participants are required to be eighteen years of age or older and capable of providing legally effective consent.

25.1.25. Not applicable. Children will not be enrolled in this study.

25.1.26. Not applicable. Children will not be enrolled in this study.

25.1.27. Not applicable. Children will not be enrolled in this study.

26. Documentation of Consent

26.1. This study will utilize an informed consent document in order to maintain documentation that the patient has given consent to participate in the study.

26.2. Not applicable. This study will not require the use of stored tissue samples.

26.3. Consent for this study will be obtained verbally and in-person by the participating clinicians, medical students, or research staff.

27. Study Test Results/Incidental Findings

27.1. ***Individual Results:*** *Participants will be made aware of any physical findings in-person at their follow-up visits. Participants will still be kept blinded to their treatment group, as this is a single-blinded study. Once they have completed their one year follow-up questionnaire, the participants will be unblinded and those in the placebo group will be offered the opportunity to cross-over and receive a corticosteroid injection.*

27.2. ***Incidental Findings:*** *We do not anticipate coming across any incidental findings. If found, they will be disclosed to the patient.*

28. Sharing Study Progress or Results with Subjects

28.1. Not applicable. Subjects will not be provided with trial progress while the study remains underway.

28.2. Participants will be made aware of what arm of the study they were assigned to. Lipogems® participants will have known since assigned to that group, as the procedure cannot be blinded. However, as this is a single-blinded study, placebo and corticosteroid participants will be made aware of their treatment at the conclusion of the study. Placebo participants will be given the option to receive a corticosteroid injection after they complete their 1 year questionnaire.

29. Inclusion of Vulnerable Populations

29.1. Not applicable. The study does not involve individuals who are vulnerable to coercion or undue influence.

30. Community-Based Participatory Research

30.1. Not applicable. There will not be any community involvement in this study.

31. Research Involving American Indian/Native Populations

31.1. This is neither an inclusion or exclusion criteria for the study. Participants will be offered the chance to participate and the study will be explained at length to potential participants. Participants are free to decline the study if would prefer not to participate. They will continue to receive the standard of care.

32. Transnational Research

32.1. Not applicable. Our study will not involve transnational research.

33. Drugs or Devices

33.1. All drugs and devices are approved and cleared by the FDA.

Lipogems® (brand name: Lipogems System, manufacturer: Lipogems International S.p.A., no generic currently on the market) device kits will be sent to Dustin Richter, MD at the University of New Mexico Hospital after a participant has enrolled in the study and been randomly assigned to receive

Lipogems®. Treatment drugs and devices will be stored, handled, and dispensed by a licensed pharmacist at UNM IDS Pharmacy. Drugs will be stored under proper conditions of sanitation, temperature, light, moisture, ventilation, segregation, safety, and security. These items will be stored in accordance with existing hospital policy and storage requirements. Dustin Richter, MD, Robert Schenck, MD, and Andrew Veitch, MD will be authorized to perform Lipogems procedures. Dustin Richter, MD, Robert Schenck, MD, Andrew Veitch, MD and Suki Pierce, PA-C are authorized to give corticosteroid or placebo injections.

33.2. Not applicable. No drugs or devices in this study are investigational. They are all marketed and none are being used off-label.

33.3. Not applicable.

Checklist Section

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

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

A. Partial Waiver of Consent for Screening/Recruitment

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

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

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

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

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

   ☐ Yes

   ☐ No. Explain:

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

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

      ☐ True

      ☐ Other justification:

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

☐ True

☐ Other justification:

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

☐ True

☐ Other justification:

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

☐ True

☐ Other justification:

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

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

   ☐ Yes. Describe:

   ☒ No

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

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

   ☒ True

☐ False

B. Waiver of Documentation of Consent

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

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

   ☐ All

   ☐ Some. Explain:

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

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

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

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

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

   ☐ No

C. Alteration of Consent

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

Note: FDA-regulated research is not eligible for an alteration of consent.

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

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

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

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

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

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

D. Full Waiver of Consent/Parental Permission

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

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

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

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

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

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

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

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

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

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

   ☐ All

   ☐ Some. Explain:

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

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

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

F. Full Waiver of HIPAA Authorization

Complete this checklist if you are requesting a full waiver of the requirement to obtain HIPAA authorization for all subjects or certain subject groups (e.g.,

retrospective cohort). Full waivers of HIPAA authorization are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

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

   ☐ All

   ☐ Some. Explain:

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

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

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

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

   ☐ True

   ☐ False

G. Other Waiver Types

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

II. Vulnerable Populations

A. Adults with Cognitive Impairments

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

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

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

2. Describe how capacity to consent will be evaluated.

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

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

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

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

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

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

B. Children

Complete this checklist if the subject population will include children.

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

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

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

Provide justification for each of the following criteria:

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

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

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

Provide justification for each of the following criteria:

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

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

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

vital importance for the understanding or amelioration of the subjects' disorder or condition

C. Pregnant Women and Fetuses

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

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

Provide justification for each of the following:

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

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

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

D. Neonates of Uncertain Viability or Nonviable Neonates

Complete this checklist if the subject population will include neonates of uncertain viability.

Provide justification for each of the following:

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

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

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

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

E. Nonviable Neonates

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

Provide justification for each of the following:

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

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

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

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

Verify each of the following:

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

☐ True

☐ False

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

☐ True

☐ False

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

   ☐ True

   ☐ False

F. Biomedical and Behavioral Research Involving Prisoners

Complete this checklist if the subject population will include prisoners.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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III. Medical Devices

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

A. Device Name: *Lipogems System*

B. Manufacturer: *Lipogems International S.p.A.*

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

☐ Yes.

☒ No

D. Is the research IDE-exempt?

☒ Yes.

Lipogems® is marketed as an autologous adipose tissue transfer system. It has been cleared by the FDA twice, most recently on November 4th, 2016. In the most recent clearance, Lipogems® has been approved for harvest, concentration, and transfer of autologous adipose tissue for use in orthopaedic and arthroscopic procedures. Thus, it is considered on-label for those applications. The term "stem-cell" is not used as the device does not separate cells and tissue and all original components of the adipose tissue are present in the final concentrate after processing. In the clearance, it is stated that the cells and tissue microarchitecture are preserved, constituting a minimally manipulated product. With the existing FDA clearance, injection into the knee for arthritis or pain relief is considered within the scope of Lipogems®.

☐ No

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

☒ Yes.

Lipogems® is marketed as an autologous adipose tissue transfer system. It has been cleared by the FDA twice, most recently on November 4th, 2016. In the most recent clearance, Lipogems® has been approved for harvest, concentration, and transfer of autologous adipose tissue for use in orthopaedic and arthroscopic procedures. Thus, it is considered on-label for those applications. The term "stem-cell" is not used as the device does not separate cells and tissue and all original components of the adipose tissue are present in the final concentrate after processing. In the clearance, it is stated that the cells and tissue microarchitecture are preserved, constituting a minimally manipulated product. With the existing FDA clearance, injection into the knee for arthritis or pain relief is considered within the scope of Lipogems®.

☐ No

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

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

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