Weekly Steroids in Muscular Dystrophy

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PROTOCOL TITLE: Open label safety and efficacy of once weekly steroid in patients with LGMD and Becker muscular dystrophy

SHORT TITLE: Weekly Steroids in Muscular Dystrophy (WSiMD)

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	Oral prednisone
IND / IDE / HDE #	N/A
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	30
Funding Source	Kurt+Peter Foundation
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☒ Yes ☐ No
DSMB / DMC / IDMC	☐ Yes ☒ No

OBJECTIVES:
The purpose of this study is to evaluate the safety and efficacy of oral weekly glucocorticoid steroids in patients with Becker Muscular Dystrophy (BMD) and Limb Girdle Muscular Dystrophy

(LGMD). The primary objective is safety which we will measure using laboratory testing and forced vital capacity (FVC). The secondary objective is efficacy which will be measured by a change in MRI muscle mass, improved muscle performance, and quality of life.

We hypothesize that patients who receive oral weekly glucocorticoid steroids will have clinically significant improvements in strength and quality of life compared to their baseline. Furthermore, we anticipate that oral weekly glucocorticoid steroids will not have a significant adverse impact on patients.

BACKGROUND:

Glucocorticoid (GC) steroids are a mainstay of therapy for Duchenne Muscular Dystrophy, where they have been shown to prolong ambulation in for DMD in random clinical trials (Gloss et al., 2016). Dosing regimen vary for DMD, but most trials utilized oral daily dosing at 0.75- 1 mg/kg of prednisone or deflazacort (Birnkrant et al., 2018). The age at which to begin oral glucocorticoids and the age at which to cease steroid use are not well established by clinical trial investigation. High dose weekend dosing of oral glucocorticoid steroids has also been suggested to be noninferior to daily dosing when evaluated in a year-long study in DMD, and this approach is preferred in some settings since related to a reduced side effect profile, particularly with respect to behavioral changes which can occur with daily GC steroid dosing in children (Escolar et al., 2011). The use of GC steroids for other forms of muscular dystrophy, including Becker Muscular Dystrophy (BMD) and the Limb Girdle Muscular Dystrophies (LGMDs) is not considered standard of care and has insufficiently been investigated by RCTs. An RCT of GC steroids in LGMD 2B (DYSF mutations) was associated with unfavorable outcomes in the steroid treated group (Walter et al., 2013).

Recently, weekly steroid dosing was investigated in preclinical mouse models of muscular dystrophy, including the mdx mouse model of DMD/BMD and two models of LGMD, including LGMD 2B (DYSF) and 2C (SGCG) (Quattrocelli et al., 2017a; Quattrocelli et al., 2017b). All three models showed improved strength and reduced fibrosis with weekly GC steroid dosing. Moreover, in unpublished data, long term studies (24-52 weeks duration) in mice, showed favorable results with improved muscle strength in the mdx and DYSF models.

We propose to carry out an open label safety and efficacy trial of oral weekly GC steroids in patients with BMD and LGMD subtypes. Subjects will be recruited based on age, molecular diagnosis of BMD and LGMD subtypes, and willingness to participate. Both ambulatory and nonambulatory subjects will be included. Subjects will be excluded if they have diabetes mellitus, full time ventilator use, or severely compromised cardiac function, including symptoms referable to heart failure. Subjects must provide consent.

Subjects will be asked to take weekly GC oral prednisone dosed based on weight (1mg/kg for patients who weigh less than or equal to 70 kg and 0.75 mg/kg for patients who weigh more than 70 kg). Subjects will also be instructed to take their weekly prednisone on Mondays after their last meal between 7 and 9 PM. Prior to initiation, subjects will provide a blood sample for baseline screening including serum chemistries, HgbA1-C, creatine kinase, and lipid panel (HDL, LDL, triglycerides, and total cholesterol) and for exploratory biomarkers. Subjects will also provide a urine sample to analyze changes in metabolic biomarkers that are excreted. Subjects will have a physical exam and medical record review. Subjects will have strength testing and complete 10 meter timed run test in addition to a 6 min walk test (if ambulatory). Subjects will be asked to complete quality of life questionnaire. At 6 months, subjects will be evaluated with physical exam, strength testing, spirometry, 10 meter timed run test and 6 min

walk test (if ambulatory), blood draw for serum chemistry, HgbA1-C, creatine kinase, lipid panel and for exploratory biomarkers. Subjects will also provide a urine specimen to be analyzed for any changes in excretion of metabolic markers as an exploratory endpoint. Subjects will be asked to complete a quality of life questionnaire. An MRI/ MRS will be performed before starting GC oral prednisone and at 6 months.

STUDY ENDPOINTS:
Primary Outcome: Safety

Safety monitoring:

- Comprehensive chemistry panel, hemoglobin A1C, CK, lipid panel at screening and after 6 months of GC steroid dosing
- FVC (sitting, supine) at screening and at 6 months
- Phone calls to each patient each month to determine their state of health and study drug compliance.

Secondary Outcomes: Change in MRI muscle mass, improved muscle performance, improved quality of life, blood and urine metabolic biomarker changes.

Functional Assessments

- NSAD (Northstar Assessment for Dysferlinopathy)—AMB
- 6 min walk test and 10 meter timed run test, if patient ambulatory
- PUL (Performance of Upper Limb)
- Brooke Scale
- Vignos Scale

Strength assessments

- MMT MRC

Patient Reported Outcome Measures

- PROM: ACTIVLM
- Quality of life questionnaire

Blood and urine for exploratory biomarkers

Imaging

- MRI/ MRS of leg and arm muscles to measure muscle volume, T2 value and fat fraction
- DEXA scan at screening and at 6 months

Outcome measures:

- Comparing MRI/MRS changes the leg and arm muscles at screening and 6 months
- Change in 6 min walk test and 10 meter timed run test for ambulatory patients
- Change in strength assessment
- Change in FVC measurements

Strength assessment:

- MRC scale: Shoulder abduction, elbow flexion, knee extension and knee flexion, hip flexion, foot dorsiflexion.
- Grip strength (Jamar dynamometer)

- Hand held dynamometry

Functional testing:
- Lift arm above head
- Lift arm above head using 50g/100g/200g/500g weight
- Bring arm to the mouth
- Bring weight to mouth using 50g/100g/200g/500g weight

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):
Oral prednisone is a synthetic glucocorticoid that is FDA-approved medication for the treatment of various inflammatory and allergic conditions.

In this study, subjects will be asked to take weekly GC oral prednisone, dosed based on weight (1mg/kg for patients who weigh less than or equal to 70 kg and 0.75 mg/kg for patients who weigh more than 70 kg). Subjects will be instructed to take weekly prednisone on Mondays after their last meal between 7 and 9 PM. Study drug, oral prednisone, will be stored under the secure and controlled environment of the Investigational Drug Pharmacy at Northwestern Memorial Hospital. The Investigational Drug Pharmacy will follow its current SOP regarding the storage and handling of investigative drugs. The study drug will be dispensed from the Pharmacy and administered to subjects once they have signed informed consent, passed screening, on Day 0 of their treatment. Subjects will return home with 6 months of study drug treatment. They will be educated on dosing, storage, and return of unused study drug by the study staff. Subjects will be contacted on a monthly basis to assess medication and dosing adherence. They will be asked to confirm their medication and the dosing instructions and re-educated if not adhering.

PROCEDURES INVOLVED:
This is an open label study that evaluates the safety and efficacy of oral weekly glucocorticoid steroids in patients with BMD and LGMD over 6 months. The study is comprised is three visits; screening to determine eligibility, initial dosing (Day 0), and final dosing (Month 6).

Screening
All subjects will be recruited to the study through the Muscular Dystrophy (MDA) Clinic at Northwestern Memorial Hospital. Prior to any study procedures, the study team will complete the full informed consent process with each patient. Upon obtaining informed consent, the study team will collect information from the patient including: demographics, vital signs, weight, height, medical history, concomitant medication, genetic mutation test results, EKG and Echocardiogram test results. If the subject does not have EKG or Echocardiogram results within the last 2 and 6 months, respectively, they will not be screened until they complete these two procedures as part of their standard of care. The principal investigator will review this information and determine whether the subject is eligible to participate in the study. If the subject is ineligible, he/she will be notified and continue to seek treatment through their treating physician.

Data will be retained in paper source materials by members of the study team at Abbott Hall, 1109, 710 N. Lake Shore Dr., Chicago, IL 60611.

Day 0
Subjects will return to the MDA Clinic at Northwestern Memorial Hospital for the Day 0 procedures. If on a separate day from the screening visit, the study team will review concomitant medications, medical history, and collect vital signs with height and weight.

The following laboratory tests will be collected for safety purposes: A comprehensive chemistry panel, hemoglobin A1C, CK, and lipid panel. A blood and urine sample will be taken for exploratory biomarkers. Samples will be collected by members of the study team and processed by the Northwestern Memorial Hospital Main Laboratory. Records will be populated in the patient's medical charts and stored by members of the study team in the subject binders.

A member of the study team will also collect forced vital capacity in a sitting and supine position.

The subject will be asked to undergo an MRI through the study team at the Center for Translational Imaging at Northwestern University. Before the study participant completes the MRI, he or she must answer questions about their medical and surgical history on a MRI safety questionnaire to determine whether it will be safe for them to complete the MRI. If not, they will not be eligible to participate in this study. No contrast will be administered. The MRI images will be de-identified and electronically transmitted to a secure file transfer (SFT) system to the University of Florida for interpretation.

Before dosing occurs, a member of the study team (physical or occupational therapist) will complete the following functional assessments: Northstar Assessment for Dysferlinopathy (NSAD) –AMB, 10 meter timed run test and 6-minute walk test if the patient is ambulatory, performance of upper limb (PUL) evaluation, Brookes and Vignos scales. A member of the study team will also collect the strength assessment, MMT MRC.

Subjects will be asked to complete two questionnaires; ACTIVLM and a Quality of Life Questionnaire.

The subject will also complete a bone density (DEXA) scan at Northwestern Memorial Hospital.

Monthly Phone Calls
Between Day 0 and Month 6, a member of the study team will call the subjects on a monthly basis to determine their state of health and whether they are taking the medication correctly. State of health will be determined by assessed by asking if the subject has experienced any changes to their physical health (adverse events). He or she will also ask the subjects about how they are taking the medication and if you are doing so correctly. If the subjects are not, the study member will help the subjects by providing additional instructions on how to correctly take the study drug.

Month 6
After 6 months of treatment, subjects will return to the MDA Clinic at Northwestern Memorial Hospital. A member of the study team will collect vital signs, weight and height, medical history, concomitant medication information, and review adverse events. The subject will also provide a sample for safety laboratory analysis (Comprehensive chemistry panel, hemoglobin A1C, CK, and lipid panel). A blood and urine sample will be taken for exploratory biomarkers.

A member of the study team will also collect forced vital capacity in a sitting and supine position.

A member of the study team (physical or occupational therapist) will complete the following functional assessments: Northstar Assessment for Dysferlinopathy (NSAD) –AMB, 10 meter timed run test and 6-minute walk test if the patient is ambulatory, performance of upper limb (PUL) evaluation, Brookes and Vignos scales. A member of the study team will also collect the strength assessment, MMT MRC.

Subjects will be asked to complete two questionnaires; ACTIVLM and a Quality of Life Questionnaire.

The subject will also complete a bone density (DEXA) scan at Northwestern Memorial Hospital.

An MRI will be conducted at the Center for Translational Imaging at Northwestern University within 2 weeks before or after the subject's final visit. No contrast will be administered.

An overview of the study assessments may be found in Table 1.0 below:

	Screening (D0-2M)	**Day 0**	**M6 ±2 wks**
Informed Consent	**X**		
Demographics	**X**		
Vital Signs	**X**	**X**	**X**
Weight and Height	**X**	**X**	**X**
Medical History	**X**	**X**	**X**
Concomitant Medications	**X**	**X**	**X**
Genetic mutation Confirmation	**X**		
Review EKG*	**X**		
Review Echo**	**X**		
Safety Monitoring Labs***		**X**	**X**
Forced Vital Capacity (FVC)		**X**	**X**
NSAD		**X**	**X**
6-min Walk Test / 10 m Run		**X**	**X**
Performance of Upper Limb		**X**	**X**
Brooke Scale		**X**	**X**
Vignos Scale		**X**	**X**
MMT MRC		**X**	**X**
Grip Strength		**X**	**X**
ACTIVLM		**X**	**X**
Quality of Life Questionnaire (SF36)		**X**	**X**
MRI/MRS		**X**	**X**
DEXA Scan		**X**	**X**
Study Drug Dispensation		**X**	
Review of Adverse Events			**X**

Table 1.0: Schedule of Assessments from Screening, Day 0, and Month 6

* EKG – Results within 2 months of study initiation accepted

**Echo – Results within 6 month of study initiation accepted
*** Comprehensive chemistry panel, hemoglobin A1C, CK, lipid panel

SHARING RESULTS WITH PARTICIPANTS
Results of investigational diagnostic tests, and incidental findings, will be shared with the subjects through the MyChart patient portal. Once the laboratory samples are drawn and analyzed by the Northwestern Memorial Hospital Main Laboratory, the results will be posted to MyChart. If the results are abnormal and clinically significant, the Principal Investigator will notify the subject about further testing and treatment. Furthermore, the Principal Investigator will contact and inform the subject's primary care physician.

Results from questionnaires, functional assessments, blood / urine exploratory biomarkers, Dexa, and MRI imaging will not be shared with the patient.

STUDY TIMELINES
The study team will screen and enroll subjects for a period no longer than 1 year from IRB approval.

Screening will occur at one clinic visit that will last no more than 2 hours. If subjects have not had a MRI within the previous 6 months, they will return for a MRI (1 hour). Similarly, if subjects have not had a DEXA scan within the previous 6 months, they will return for a DEXA scan (1 hour).

Enrolled subjects will participate in the study for 6 months from their first dosing (Day 0). Subjects will schedule their MRI and DEXA scan on the final day of the study. If subjects are unable to complete a MRI or Dexa on that day, they will return to complete the required procedure within the next 2 weeks.

The investigators estimate the study's primary analyses will be completed by December 2019.

INCLUSION AND EXCLUSION CRITERIA
Inclusion criteria (Collected at screening):
1. Patients with Becker muscular dystrophy or LGMD2A (CAPN3), LGMD 2B (DYSF), LGMD 2C (SGCG), LGMD2E (SGCB), LGMD2F (SGCD), LGMD 2I (FKRP), LGMD (ANO5). Genetic mutation or muscle biopsy staining required to confirm genetic subtype
2. Ages 18-65 years
3. EKG without evidence of prior infarct or atrial fibrillation done within 2 months of study initiation.
4. Echocardiogram with LVEF >25% done within 6 months of study initiation.
5. Stable medications (same medication and dose) for the previous 3 months
6. Stable pulmonary status for the previous 6 months (No change in FVC by more than 20% in the past 6-months)

Exclusion criteria (Collected at screening):
1. Diabetes
2. BMI>35 kg/m^2
3. Cardiac transplantation
4. Myocardia Infarct in the past 2-years from screening
5. Any history of tuberculosis
6. Untreated or uncontrolled (medication and/or dose change in previous month from screening) hypertension

7. A diagnosis of congestive heart failure
8. A diagnosis of chronic kidney disease
9. A diagnosis of untreated hypothyroidism
10. The patient is believed to be at high risk of osteoporosis by the primary investigator
11. Inability to provide consent
12. Prior oral glucocorticoid steroid use for > than one month during a subject's life.
13. Full time ventilator dependency
14. Heart failure symptoms or LVEF <25%
15. Orthopedic surgery within the prior year or upcoming elective orthopedic surgery within the 6-months from Day 0.
16. Inability to complete MRI (claustrophobia, metal implants)
17. Pregnant women at screening, women seeking to become pregnant, or men seeking to father a child within 6-months from Day 0 should not participate in this study.

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Total:	50 adults	40 adults	30 adults

RECRUITMENT METHODS

All subjects will be recruited through the Muscular Dystrophy (MDA) clinic at Northwestern Memorial Hospital. The MDA clinic is located in the Lavin Family Pavilion, 259 E. Erie St., Suite 1900, Chicago, IL 60611 and is held on Wednesday mornings from 08:00-12:00.

Participants will be selected by the neurologists in the MDA clinic, primarily the Principal Investigator. They will be selected for screening based on their clinical exam, medical history, and willingness to participate in the study. The Principal Investigator will review the patient's medical chart to determine pre-eligibility. A member of the study team will conduct the informed consent process once pre-eligibility is confirmed by the Principal Investigator.

No external methods will be used for recruitment purposes.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Subjects will not be compensated for participating in this study. Furthermore, subjects will not be reimbursed for expenses related to travel, lodging, or accommodation.

If patients become ill or are injured as a result of this study (medications, devices or procedures), they should seek medical treatment through their doctor or treatment center of choice. The subject should promptly tell his/her study doctor about any illness or injury.

The hospital [university, researchers] will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.

WITHDRAWAL OF PARTICIPANTS

Subjects may be withdrawn from the study if the Principal Investigator believes that participating places them at risk of harm. Subjects may also be withdrawn if it is found that they are not complying with the study's required dosing instructions.

In the event that a subject is to be withdrawn, the Principal Investigator will inform the subject regarding the reason for withdrawal. The Principal Investigator will make recommendations for seeking additional testing and prompt medical care, if necessary. A member of the study team will indicate that the subject was withdrawn in the subject binder.

RISKS TO PARTICIPANTS

Participating in this study places subjects at minimal risk of the following:

Risks from glucocorticoid steroids

- The risks associated with glucocorticoid steroids include: glaucoma (elevated pressure in the eyes), edema (fluid retention in lower legs), hypertension (high blood pressure), weight gain, problems with mood and memory, alterations in endocrine function, increased risks related to infections, decrease in bone density, and possible damage to your vision. These risks are seen when people take glucocorticoid steroids daily for extended periods of time. Based on preclinical studies in animals and limited studies in humans, it is expected these risks are much less when taking glucocorticoids steroids once per week.

Since the subjects will be taking glucocorticoid steroids once weekly, for 6 months, their risk of side effects is low, with short duration, and reversible.

Risk from blood draws

The risks of taking blood include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

Risk from MRI

Some people cannot have an MRI because they have certain types of metal in their body. For instance, if you have a heart pacemaker, artificial heart valves, metal implants such as metal ear implants, bullet pieces, chemotherapy or insulin pumps or any other metal such as metal clips or rings, you cannot have an MRI. During this test, subjects will lie in a small closed area inside a large magnetic tube. Some people are scared or anxious in small places (claustrophobic). The MRI scanner makes loud banging noises while taking a measurement, so either ear plugs or specially designed headphones will be used to reduce the noise.

Risks from DEXA bone scans

Procedures such as CT scans, X-rays and/or radioactive drugs will be used during this research study to see how subjects are doing. The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect subjects or their disease. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to subjects' risk of injury or disease. When deciding to enter this study, subjects will think about their past and future contact with radiation. Examples of contact with radiation include x-rays taken for any reason or radiation therapy for cancer treatment.

Background radiation is present on Earth (soil, air, water, food) and also includes cosmic radiation. Exposure to radiation from natural sources is a feature of everyday life. Your

participation in this study will involve additional exposure to radiation. The radiation dose received for one DEXA scan is approximately equal to 4.5 days of background radiation.

The effective dose for one DEXA scan (lumbar spine and total hip) is 4 mrem. The total effective dose of all research related radiation procedures is 8 mrem.

POTENTIAL BENEFITS TO PARTICIPANTS
There may be benefit from participating in this research. Potential benefit may include increased strength and muscle mass.

DATA MANAGEMENT AND CONFIDENTIALITY
This is a pilot study to determine safety and tolerability of the intervention. All subjects will receive once weekly prednisone, and no placebo arm is planned for this study. Data will be compared between study entry and 6 months of once weekly steroids. The data from this study will be used to plan for a larger trial. In preclinical animal models, a 25% improvement in muscle strength and function was observed.

During the trial, study team members with access to Northwestern Memorial Hospital's electronic medical records System, Epic, will have access to the subject's medical chart. The study team will print, redact, and store all study-specific test results in the subject binders. All medical records will be de-identified and labeled with the subject identification number. The tests obtained from Epic include: genetic test results, medical history, concomitant medications, safety laboratory results, EKG results, Echo results, DEXA results, and MRI results. The remaining tests will be performed during the study visit and documented on case report forms (source documentation) located in the subject binders.

MRI images that are collected as part of this research study will be obtained at the Center for Translational Imaging and Northwestern University. The study team will obtain a de-identified copy of the MRI images for all study participants that contains the participant's study number. A member of the study team will transmit the images to the University of Florida through a secure file transfer (SFT) system. Copies of the images will also be secured by the study team in the subject binders.

The Principal Investigator and study team will have access to the data and be responsible for data transmission and storage.

The study binders will be secured in Abbott Hall 1109, 710 N. Lake Shore Dr., Chicago, IL 60611 and, upon completion of the trial, O'Hare Storage Facility. Study data will be stored for a period no longer than 5 years. After this period, unless otherwise notified by the study team, all study records will be shredded or disposed through HIPAA-compliant document bins.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS
The Principal Investigator and study team will make every effort to ensure that the subjects' privacy is protected. As mentioned above, subjects will only share personal information with the Principal Investigator and members of the study team. The study team will be permitted to access sources of information about the participant through the consent. During the consent process, and throughout the study, subjects will be given the opportunity to ask questions about the study and voice their concerns. Contact information will be provided to the subjects in the consent.

COMPENSATION FOR RESEARCH-RELATED INJURY
Subjects will not be compensated for research-related injury.

ECONOMIC BURDEN TO PARTICIPANTS
This study does not pose a large economic burden to participants because they will not have to pay for the study treatment and study procedures. Furthermore, subjects will be seen during their routine, standard-of-care visits to minimize additional costs of travel. Patients will not be seen until an EKG and ECHO are collected as part of their standard of care to prevent these costs being transferred to the patient.

CONSENT PROCESS
The consent process will take place in the MDA clinic at Northwestern Memorial Hospital, 259 E. Erie St., 1900, Chicago, IL 60611. Subjects will be given time to read the informed consent form, ask questions, and have them answered satisfactorily (sufficient time to consult with family members and outside physician will be granted). A member of the study team will perform the consent process as follows:

- Read the Informed Consent Guidelines
- Ensures that consent form given to subject is the current version with approval stamp
- Administers the informed consent form explaining the following:
    - Anticipated benefits of the trial
    - Attendant discomforts and risks
    - Appropriate alternative procedures that might be advantageous for the subject
    - The extent to which confidentiality of records identifying the participant will be maintained
    - Compensation
    - Contacts for questions or in case of injury
    - Voluntary participation
    - Summary of the study including interventions and assessment visits
    - Specific assessments scheduled for the current visit
- Optional elements
    - Changes to protocol (and consent document) since last visit
- Allows time for Subject to read the consent
- Asks if Subject has any questions, answers adequately
- Collects completed consent from Subject
- Does not begin visit until consent is obtained from Subject and photocopy returned to Subject
- Files original copy of consent in Subject's personal information file.

The Consent Process will take place in the Neurology Clinic.
Will be following "SOP: Informed Consent Process for Research (HRP-090)