**3.1 Protection of Human Subjects**

*Attach as a PDF. Use the section numbers and headings shown below. Two samples follow.*

*For more information, refer to* [*Research Involving Human Subjects*](https://humansubjects.nih.gov/)*. Contact the OSCTR for research with local Tribal Nations or special populations*

**1. Risks to Human Subjects**

**a. Human Subjects Involvement, Characteristics, and Design**

* Briefly describe the overall study design
* Describe the subject population(s), procedures for assignment to a study group, and anticipated numbers in each group
* List collaborating sites and describe their role

**b. Study Procedures, Materials, and Potential Risks**

* Describe study interventions and interactions
* Indicate how samples, data, and records will be obtained, and if identifiable information will be collected
* Identify sources of previous collections, whether they can be linked with living individuals, and who will be able to link the materials
* Address risks related to study procedures, the risk level, and likely impact to subjects
	+ Risks may be physical, psychological, social, cultural, financial, or legal
	+ All genetic studies pose risks of loss of confidentiality
* Describe the risks and potential benefits of alternative treatments and procedures
	+ If alternatives are possible, state the rationale for the proposed approach

**2. Adequacy of Protection Against Risks**

**a. Informed Consent and Assent**

* Describe the recruitment and informed consent process
	+ Who will seek consent and under what circumstances
	+ Types of information given to prospective participants, and the method of documenting consent
	+ Include special consent processes for children and vulnerable populations, if applicable
* Do not submit informed consent document(s) with your application unless specifically requested

**b. Protections Against Risk**

* Describe strategies to minimize all potential risks identified, including privacy and confidentiality
* Discuss plans for ensuring necessary medical or professional intervention in case of adverse effects
* Describe plans for handling incidental findings (e.g., from imaging, screening tests, or paternity tests)

**c. Vulnerable Subjects, if relevant to your study**

* Explain the rationale for involving special vulnerable populations
	+ Fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others
* Describe the risk level and additional protections necessary to meet HHS regulatory requirements
	+ HHS [Subpart B - Additional Protections for Pregnant Women, Fetuses, and Neonates](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb)
	+ HHS [Subpart D - Additional Protections for Children](http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#subpartd)
	+ OHRP Guidance on Subpart D [Special Protections for Children as Research Subjects](https://www.hhs.gov/ohrp/regulations-and-policy/guidance/special-protections-for-children/index.html) and the [HHS 407 Review Process](https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-407-review-process/index.html)
	+ HHS' [Subpart C - Additional Protections Pertaining to Prisoners as Subjects](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc) and OHRP Subpart C Guidance on [Involvement of Prisoners in Research](http://www.hhs.gov/ohrp/regulations-and-policy/guidance/prisoner-research-ohrp-guidance-2003/)

**3. Potential Benefits of the Proposed Research to Research Participants and Others**

* Discuss the potential benefits of the research to the participants and others
* Financial compensation is NOT a benefit
* Explain why the risks to subjects are reasonable in relation to the anticipated benefits

**4. Importance of the Knowledge to be Gained**

* Discuss the importance of the knowledge gained and why the risks to subjects are reasonable

# SAMPLE 1: CLINICAL TRIAL WITH INVESTIGATIONAL DRUG

## I. RISKS TO HUMAN SUBJECTS

### Human Subjects Involvement, Characteristics, and Design

This will be a multicenter, double blind, placebo-controlled Phase 2 trial of 60 patients with SLE who will enter with significant symptoms, but no organ-threatening disease. Patients who qualify for the study will be randomized to receive either DRUG A or placebo for the first three months. For the first two weeks a scheduled “taper up” of DRUG A will take place. Patients will receive 500mg mg bid for 7 days, followed by 500mg and 1,000mg in divided doses for 7 days. They will then continue on at a stable dose of 1,000 mg bid. Visits to assess adverse events, clinical response and to obtain biomarker sampling will occur four weeks after screening and every four weeks thereafter.The treatment period will end at the Month 8 visit and there will be a safety follow-up visit 6 weeks after that.

This study will take place at SLE clinical trial centers within the United States where the site principal investigators are known to be highly qualified and have patient populations suitable for this study. Additional qualified sites may be added, as needed, depending on enrollment rates in the first 18 months of the project.

### Study Procedures, Materials, and Potential Risks

1. ***Investigational drugs***
2. **DRUG A**

**Hypersensitivity:** DRUG A is contraindicated in patients with a hypersensitivity to DRUG A or any component of the drug product.

**Pregnancy Warning:** DRUG A is a Category D drug. It has been associated with risk of first trimester pregnancy loss and congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and, according to the package insert, anomalies of the distal limbs, heart, esophagus, kidney and nervous system.

**GI Disturbances:** Diarrhea is common but gastrointestinal bleeding and perforations have been reported.

**Other Concerns:** Renal impairment may lead to increased blood levels of DRUG A.

***2. Risks of Investigational Products Cited in the Medical Literature***

The best summary of adverse events in lupus patients with DRUG A comes from the international X trial. Although this trial did not meet its primary endpoint of superior efficacy, N patients on DRUG A were directly compared to N patients on Drug Z. The treatments were equally effective, and it was possible to compare a range of side effects**.** The most common adverse events in the DRUG A group were infections and diarrhea. The number of deaths was comparable with both drugs.

Below are data from two trials combining Drug Y with DRUG A. The table below compares two Drug Y doses and DRUG Z (Group C, n = 400), all taken in combination with DRUG A. The main finding in the Drug Z/DRUG A group was an increased incidence of diarrhea. This trial took place outside the US.

Table 1. Adverse Reactions Occurring in ≥ 10% of Patients Treated with Drug Y combined with DRUG A

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Drug Z (Group C)** | **Drug Y (Group A)** | **Drug Y (Group B)** |
|  | **(N = 400)** | **(N = 300)** | **(N = 500)** |
| Diarrhea | % | % | % |
| Urinary Tract Infection | % | % | % |
| Anemia | % | % | % |
| Hypertension | % | % | % |
| Leukopenia | % | % | % |
| Edema Peripheral | % | % | % |
| Hyperlipidemia | % | % | % |

The best data we have from the package inserts and clinical trials are evaluating patients after organ transplant or with lupus nephritis, including some very ill patients. Nevertheless, the data underscores the potential for DRUG A to create additive side effects. Patients will be monitored monthly for blood pressure, blood sugar, renal function and adverse events, andwe are choosing to use low (but known effective) doses of each agent in this trial.

***3. Blood Collection***

Only experienced personnel will perform phlebotomy. This protects subjects from errors attributable to incompetence or inexperience and has proven to be effective. Phlebotomy is performed in a setting where it is possible to lay the subject down if fainting occurs. This is effective in minimizing trauma from falling and provides blood flow to essential organs during the period of hypotension during the vasovagal reaction. Pressure is applied to the phlebotomy site to reduce subsequent bruising. This is at least partially effective. There is a theoretical possibility of infection from phlebotomy since a foreign body is being introduced into the vascular space. Most subjects will provide ~100 ml of blood. From the blood, RNA, serum, plasma, DNA and cells will be isolated for use in subsequent analysis.

***4. Biospecimen storage and analysis***

Under IRB approval, blood and urine samples from all sites will be centrally stored in the biorepository. Proteomic, transcriptomic, flow cytometry and cell culture assays will be performed on these samples. Additional samples will be banked for future IRB approved projects.

***5. Clinical Data/Information***

Under a central study IRB at our institution, clinical/demographic identifiable information data collected from the patients will be send and stored centrally via electronically encrypted devices. We will obtain clinical data (relevant to ensure that patients meet criteria and measure of disease progression/response to treatment) and demographic data (sex, age, race, etc.) from samples for the purposes of this project. Patients enrolled in this study and under the central IRB will have identifiable private information kept at the institution. Only those investigators and colleagues directly involved in this study will have access to this information.

## II. ADEQUACY OF PROTECTION AGAINST RISKS

### A. Informed Consent and Assent

Potential participants will sign an informed consent form before undergoing any study procedures. Patients will be consented, enrolled, and collected by the each clinical collaborator under the central IRB. Clinical information is obtained from questionnaires, by face-to-face interviews with study personnel and by review of the patient’s medical records. Study personnel administer an informed consent interview with each participant, which includes a verbal explanation of the study in lay terms. Participants also receive a written informed consent form. Potential participants are told that they need not participate in this research study, that the study may or may not benefit them directly, that they would be contributing toward a better understanding of treatments for lupus, and that they may decline participation. The consent process also describes alternative options for the person considering research participation (including the right to decide not to participate in any research), privacy protections, potential circumstances involving loss of privacy, and what to do in case of adverse events. All potential participants are given adequate time to make a decision, have a chance to have their questions answered prior to making a decision, and are encouraged to include trusted relatives, friends, and/or other healthcare providers when making a decision. Once the informed consent has been signed, the participant is considered enrolled in the study and will be assigned a unique participant number. At this time study-specific procedures may be performed. Assent will not be required, as patients will be adults and will not have cognitive deficiency that would hinder giving consent.

### B. Protections Against Risk

***1. Treatment protocol***

All study procedures will follow good clinical practice. We abstain from interventions, including blood draws for research purposes, in participants who are tachycardic, under duress for any reason, or considered by the clinic physician to have significant or unstable anemia, require transfer to an emergency room due to acute illness, or have any other condition that makes them unsuitable candidates for study procedures. Blood will be drawn using standard clinical techniques by trained and well-experienced personnel in a certified location for blood drawing.

Participants may be terminated from the study for the following reasons to minimize risk of the intervention: (i) the participant elects to withdraw consent from all future study activities, including follow-up, (ii) the Investigator no longer believes participation is in the best interest of the participant, (iii) individual safety stopping rules will include severe adverse events.

***2. Confidentiality***

Participant confidentiality is and will be protected by our strict adherence to HIPAA guidelines. As specified in the informed consent process, it is not possible to ensure complete protection of a subject’s identity. However, any breaches of good clinical practice in this regard would be taken extremely seriously, with appropriate reporting and regulatory actions.

To protect participant privacy, all recruited individuals will receive a barcode on entry. Codes will be used to link specimens to de-identified clinical database information. All samples and paperwork will be barcoded at the point of collection and stored without direct links to identifiers. Our personnel have extensive experience with this process. Identifying information is only available to the clinical coordinator, principal investigators and database administrator for local collections. Participant consents, subject encounters, detailed clinical data, experimental data, and details of biorepository activities associated with each sample are stored in an electronic health records system. This system is highly secured with a strict role-based security system for electronic access, and the servers are kept in physically secured locations.

The PI will be responsible for steps to protect against risks, including but not limited to training in Protection of Human Subjects for all study personnel, security of database systems, locking of any areas containing medical records, and protection of vulnerable populations.

### C. Vulnerable Subjects

This is not relevant. No pregnant women, incarcerated persons, or children will be enrolled in this study.

## III. POTENTIAL BENEFITS OF THE RESEARCH TO RESEARCH PARTICIPANTS AND OTHERS

If this treatment regimen can improve control of active, but not organ-threatening, SLE disease and reduce the risk of flares, it could have an important impact on the reduction of active manifestations and quality of life of patients with SLE.

## IV. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study will provide new knowledge about the efficacy and specific immune processes influenced by the specific proposed intervention. The additional biomarker studies will also give valuable information about the basic biology of SLE flares and response to specific therapies, thus reducing the chances of prescribing ineffective therapies to treat acute manifestations. The procedures in this study, including blood and urine collection, will provide a comprehensive understanding of the impact of DRUG A and further help identify patients who may potentially benefit (or not) from this therapy. The risks to the subjects involved in these studies are similar to how acute manifestations of non-organ threatening disease are managed in routine clinical practice. These risks are far outweighed by the potential knowledge gained in improved management of SLE disease flares. Given that many of the processes to be studied in this project are shared with other autoimmune diseases, knowledge gained from this study is likely to provide insight into basic mechanisms of autoimmunity.

# SAMPLE 2: MECHANISTIC STUDY USING NEW AND EXISTING SAMPLES FROM AN ESTABLISHED COHORT

**1. RISKS TO HUMAN SUBJECTS**

**1a. Human Subjects Involvement and Characteristics**

This study will use existing samples from 200 subjects in the Oklahoma Cohort for Rheumatic Diseases. Expected demographics for this study group are described in the planned enrollment table, and are based on the demographics of the Oklahoma Cohort for Rheumatic Diseases. The Oklahoma Cohort for Rheumatic Diseases serially follows 1,568 patients with rheumatic diseases. Over 135,000 samples are available from >9,000 subject visits, with >15 years of follow-up for some patients.

In addition, this study will procure new blood samples from 30 of the 200 SLE patients described above and 10 unaffected controls from the Oklahoma Immune Cohort, who have given consent for re-contact. In addition to blood, we will collect demographic information, medication use, and major diagnoses. The newly procured samples will come from only female subjects. This is because these analyses will not have sufficient power to perform the subset analyses that would be required with unrestricted enrollment (see Research Strategy and Inclusion of Women, Minorities, and Children).

The Oklahoma Immune Cohort provides unaffected controls for a variety of immune studies and is housed at the Oklahoma Medical Research Foundation. This cohort has enrolled over 1,000 individuals who reported no major autoimmune disease. New samples will be collected at the Oklahoma Medical Research Foundation. Individuals will be seen within space and by personnel of the Clinical Characterization and Biorepository Core of the Oklahoma Rheumatic Disease Research Center.

**1b. Study Procedures, Materials, and Potential Risks**

After consent, participants will provide basic medical information, including major medical diagnoses, recent hospitalizations, a list of medications and brief demographic information using standard forms in place for our Oklahoma Cohort for Rheumatic Diseases and Oklahoma Immune Cohort. No more than 80 mL of blood will be collected per draw, and individuals will not provide blood more than twice per month. Blood will be processed as described in the Research Strategy.

The risks involved in the procedures for this study are minimal. Potential risks to the newly recruited subjects include minor discomfort, bruising, local infection, or fainting from blood drawing.

The research project will not include any private identifiable information. However, personnel in the research clinics who are directly involved in assessing participants and acquiring and/or verifying data will have access to the participants’ personal information, as will potentially, any government regulatory agencies who monitor our clinical study units. Therefore, there is a potential risk to privacy. As specified in HIPPA protocols included in the informed consent process for the Oklahoma cohorts, it is not possible to ensure complete protection of a subject’s identity. However, based on the mechanisms in place to protect participant private information (see 2b, below), this concern is very minimal. Any breaches of good clinical practice in this regard would be taken extremely seriously, with appropriate reporting and regulatory actions.

**2. ADEQUACY OF PROTECTION AGAINST RISKS**

**2a. Informed Consent and Assent**

Prior to undergoing study-specific procedures, individuals will be given an IRB-approved informed consent form which fully describes the study, study procedures, the rights of study participants, and alternatives to research participation. Our trained clinical research staff go over these forms with all potential research participants. Our written informed consent forms and our informed consent process address possible side effects, issues related to privacy protections, potential loss of privacy, HIPAA disclosures, what to do in case of adverse events, and how to register problems or issues with the investigator or institution if needed. Our informed consent forms and process also address the right to decide not to participate in research and the right to withdraw from research at any time without penalties or loss of benefits to which a person is otherwise entitled. Consent is documented by the signatures of a potential participant, person obtaining consent and a witness.

All individuals who participate in the informed consent process will have adequate time to make a decision, will have a chance to have their questions answered prior to making a decision, and will be encouraged to include close family members and/or other healthcare providers and/or trusted friends when making a decision. Our clinic is open to having informed consent discussions that include people who provide a support system for our potential research participants, when they wish to do this.

**2b. Protections Against Risk**

Research investigators and staff at the OMRF are required to take the initial Collaborative IRB Training Initiative (CITI) Course in the Protection of Human Subjects within the first three months of their employment and before beginning any human subject-related research. This initial course includes HIPAA training and satisfies institutional IRB, NIH and HIPAA requirements for research involving human subjects. Investigators and staff must maintain certification every three years through the CITI course on protection of human subjects, and due to our active participation in company-sponsored clinical trials, our personnel are continuously re-trained well beyond that minimal requirement in the elements of good clinical practice and informed consent procedures.

All study procedures will follow good clinical practice. We abstain from interventions, including blood draws for research purposes, in participants who are tachycardic, under duress for any reason, or considered by the clinic physician to have significant or unstable anemia, require transfer to an emergency room due to acute illness, or have any other condition that makes them unsuitable candidates for study procedures. Blood will be drawn using standard clinical techniques by trained and well-experienced personnel in a certified location for blood drawing.

To protect participant privacy, all recruited individuals will receive a barcode on entry. Codes will be used to link specimens to de-identified clinical database information. All samples and paperwork will be barcoded at the point of collection and stored without direct links to identifiers. This process has been in place for many years at OMRF, where our personnel have substantial experience in managing NIH-funded repositories. Identifying information is only available to the clinical coordinator, principal investigators and database administrator for local collections. Participant consents, subject encounters, detailed clinical data, experimental data, and details of biorepository activities associated with each sample are stored in an electronic health records system. This system is highly secured with a strict role-based security system for electronic access, and the servers are kept in physically secured locations.

The PI will be responsible for steps to protect against risks, including but not limited to training in Protection of Human Subjects for all study personnel, security of database systems, locking of any areas containing medical records, and protection of vulnerable populations.

**2c. Vulnerable Subjects**

Pregnant women and individuals under the age of 18 years are excluded from this study. Prisoners are excluded from medical research in the state of Oklahoma. However, our study may include people from a variety of cultural backgrounds and with a variety of potential socioeconomic vulnerabilities. Care will be taken to ensure that all participants are treated respectfully and given adequate time to consider research participation, with procedures that are transparent and clearly understood.

**3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO RESEARCH PARTICIPANTS AND OTHERS**

No direct benefits are anticipated for the subjects included in the proposed study. Others, particularly future lupus patients and their families, may benefit from the knowledge gained through the proposed project. This study is designed to XXXXXXXXXXXXXXXXX. This goal justifies any potential associated risks from extra blood donations, especially since the current standard of care for these diseases are not optimal and many patients experience poor quality of life, extensive morbidity, and early mortality.

**4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED**

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