



IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at <http://intranet.mayo.edu/charlie/irb/>

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this template to the protocol section.

Modification: To modify this template after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes"..
3. Revise the protocol template to reflect the modification points, save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Eva Morava-Kozicz, MD

Study Title: Large-scale metabolomic profiling for the diagnosis and treatment of inborn errors of metabolism

Protocol version number and date: V3, 11/7/2019

Purpose

Hypothesis: We hypothesize that large-scale metabolomics profiling on dried blood spots (DBS), in fibroblasts, urine, stool, and serum will allow more discriminate screening and diagnosis of inborn errors of metabolism and lead us to better understanding the pathophysiology in metabolomic abnormalities). We will also utilize different culturing and measuring conditions to help us to develop new therapies. The overall goal of this study is to develop a novel high-throughput screening and diagnostic platform for understanding the pathology of inborn errors of metabolism and assessing different conditions through spiking samples with sugars or mimicking changes in diet during measurement by using global metabolomic profiling. Metabolomic profiling is a technique that provides a comprehensive view of metabolic pathways and therefore allows for more discriminate evaluation of analyte abnormalities. To perfect this platform, different human samples including fibroblasts, serum, urine and DBS are required. In particular, samples with known disease states have significant utility as they will aid in the mapping of metabolic pathway perturbations in their respective diseases.



Aims, purpose, or objectives:

Aim 1: To evaluate the metabolic background of disorders by using dried blood spots, fibroblasts, serum and urine from clinical residual samples stored in BGL and from patients collected under IRB 19-005187.

- a. Current disorders using stored blood spots, fibroblasts, serum and urine that need improvement in diagnostics

Aim 2: Improve follow-up and accurate diagnosis of inborn errors of metabolism.

- a. Better understanding of biomarkers
- b. Better understanding culturing and measuring conditions

Aim 3: Measurement of samples under different conditions (mimicking dietary intake and changes or adding sugars to the samples prior measurement)

- a. Standardize measurements
- b. Asses the effect of dietary conditions on measurements to evaluate dietary therapy

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc.*):

Current metabolic disagnostics employs procedures such as tandem mass spectrometry (MS/MS), fluorometric assays and enzymology testing to test for inborn errors of metabolism. These tests may produce false positives and require further testing before a diagnosis can be made, costing families additional time and money before being provided answers about the health of their child. Using global metabolomic profiling, metabolic pathways can be examined more comprehensively to evaluate any irregularities in analyte levels. We hypothesize that global metabolomics profiling can provide improvements to the process of finding and diagnosing inborn errors of metabolism.

Data in this study will be taken from anonime residual samples from Mayo Clinic patients with known diseases, available through BGL, and from patients consented under IRB 19-005187. The DBS will be the primary identifier, Based on the prior diagnosis of the samples, metabolomics data will be collected and will be analyzed to see if the metabolomics profile can pick up the abnormality using the DBS, serum, urine or fibroblast samples. It has already been shown that metabolomics profiling can detect an array of inborn errors of metabolism with more details on pathophysiology under different conditions.

Subject Information – charts, records, images, or specimens are considered ‘subjects’

Target accrual: *Proposed number of subjects to be included in your study at your site. “Subjects” may include Mayo Clinic charts, records, or specimens, and/or charts, records, or specimens received at Mayo Clinic from external sources for collaborating analysis by the investigator under this IRB application: 160*



Subject population: The target population for this study includes anonime residual samples of individuals affected by inborn errors of metabolism.

Inclusion Criteria: All individuals with specimens in BGL or consented to future research under IRB 19-005187..

Exclusion Criteria: None..

Study Design

Methods: *Describe, in detail, the research activities that will be conducted under this protocol:* The work we propose involves the analysis of existing DBS, fibroblast, serum, stool, and urine samples of Mayo Clinic patients provided by the BGL lab or by the IRB 19-005187. Mayo Clinic will perform untargeted global analysis of metabolites present in the samples. We will then use the analysis to diagnose the inborn errors of metabolism in these individuals as well as identify biomarkers for these disorders.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.):* We will utilize DBS, fibroblasts, serum, stool, and urine provided by the BGL clinical laboratory. Specimens will also come from IRB 19-005187. Metabolomic analysis will be performed by staff members at Mayo Clinic.

Check all that apply. If none apply, leave blank:

- This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:
- Mayo Clinic staff will be engaged in research activity at a non-Mayo Clinic site. *When checked, provide the location and a detailed description of the Mayo Clinic research staff involvement.*
- This study is to establish and/or maintain an ongoing database or registry for research purposes only.
- The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw.
- The study involves audiotaping or videotaping



Blood Collection

If this study involves prospective blood collection by finger, heel, ear stick or venipuncture, complete the following:

From healthy, non pregnant, adult subjects who weigh at least 110 pounds. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

From other adults and children considering age, weight, and health of subject. For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

Review of Chart, Images, Specimens

Provide the date range for collection of data and/or specimens that will be included in your research dataset. (Example: 01/01/2000 to 12/31/2012)

Date range: 01/01/1980 to present

Check all that apply:

This study involves only data and/or specimens that exist at the time this application is submitted to the IRB (IRB submission date). No data or specimens will be collected beyond this date.

This study involves only data and/or specimens that will be collected after submission to the IRB.

The study involves data and/or specimens that exist at the time of submission to the IRB **and** data and/or specimens that will be collected after submission to the IRB, for example a study that includes collection of existing data and prospective collection of specimens.

Data and/or specimens used in this study are collected under another IRB protocol. *When checked, provide the IRB number(s) from which the research material will be obtained and check the box below to attest that subjects have provided consent for future use of their data and/or specimens, as described in this protocol.*

19-005187



Subjects have provided consent for use of their data and/or specimens, as described in this protocol.

Other data sources will be utilized in this study. When checked, provide all data sources:

Data Confidentiality, HIPAA Subject Identifiers

Review the list of subject identifiers below and, if applicable, check the box next to each subject identifier being recorded at the time you are collecting/abstracting data/specimens for use in this study.

Subject Identifiers: Individually identifiable information, including demographic data, that identifies the individual or for which there is reasonable basis to believe it can be used to identify the individual. NOTE: Identifiers apply to subjects enrolled in your study and to the subject’s relatives, household members, employers, etc.

Internal refers to subject identifiers that will be included in the dataset maintained by the study team.

External refers to subject identifiers that will be shared with persons outside of the immediate study team, for example, sent to an external collaborator or shared with a national registry.

SUBJECT IDENTIFIERS Check all that apply	INTERNAL IDENTIFIER	EXTERNAL IDENTIFIER
Name		
Social Security number		
Medical record/patient registration number, lab accession, specimen or radiologic image number		
Study number, subject ID, or any other unique identifying number, characteristic or code that can be used to link the identity of the subject to the data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual. Their birth date, date of death, date of diagnosis, etc. Note: Recording a year only is not a unique identifier.		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
If None of the above identifiers will be recorded or maintained in the	<input type="checkbox"/> None	<input type="checkbox"/> None



dataset and/or sent outside of the study team, please check “None”.

Statistical Information

Note: Power analyses and study endpoints are not needed for a pilot or feasibility studies.

No statistical information. *If checked, please explain:* Due to this study being a chart review study, no statistical analysis will be performed.

Statistical Considerations

Power Statement: The results will be compared directly with the known results of the DBS (negative or positive for an inborn error of metabolism) therefore it will be clear for each sample whether the analysis showed the correct result.

Data Analysis Plan: As above.

Endpoints

Primary: To evaluate whether untargeted metabolomics profiling on dried blood spots can detect inborn errors of metabolism

Secondary: Can untargeted metabolic profiling give a comprehensive and discerning view of the patient’s metabolism to aid interpretation of equivocal results.