Marshfield Clinic
Personalized Medicine Research Project (PMRP)

Data and Tissue Access Guidelines

1 July 2010

1. PMRP purpose

The purpose of the PMRP is to establish a resource that will facilitate research in pharmacogenetics, genetic epidemiology and population genetics, with the ultimate goal of improving human health and medical treatment.

2. PMRP resources currently available

a. DNA
b. Plasma
c. Serum
d. Questionnaire
e. Electronic medical records to construct phenotypes
f. Ability to recontact subjects for additional information (where they have given consent for recontact)
g. Stored pathology specimens collected for clinical purposes
h. 51 clinically relevant polymorphisms
i. Illumina 660 quad for ~4200 subjects aged 50+

3. PMRP resources that will be available in the future

a. **Additional** Genotypes
b. Established phenotypes
c. Environmental data

4. Core principles of access:

a. Wishes of participants are respected
b. Elements of informed consent and ethical use of human biological samples are maintained
c. Collaboration, rather than competition, is strongly encouraged
d. Data will be made available to other scientists

5. Intellectual Property

Standard agreements between external investigators and the Marshfield Clinic will be reached prior to sharing of data and/or resources. These agreements may cover intellectual property and/or materials transfer. The opportunity to participate as an author should be offered to at least one Marshfield Clinic investigator on all publications arising from use of the PMRP database for phenotypes or genotypes developed by Marshfield Clinic investigators.

6. Institutional Review Board (IRB) review

PMRP subjects gave written informed consent under the understanding that the Marshfield Clinic Research Foundation (MCRF) IRB would review requests to use the database and decide whether additional consent would be required for a particular study. For minimal risk **data only** studies, an expedited review is often possible. Investigators must complete an IRB application and have written approval before commencing any studies with the PMRP database. The MCRF IRB would serve as the IRB of record for non-affiliated investigators where the conditions in the IRB policy in the Appendix A are met.

7. Process for accessing DNA samples

We anticipate that requests for access to the PMRP samples and established phenotypes and genotypes will come from both external and internal investigators and that scientific merit may or may not have been received prior to application to access the samples. The DNA samples were stored in three aliquots.

Scientific protocols that have undergone adequate scientific merit review (external peer-reviewed mechanism such as NIH, NSF or the MCRF Research Committee as defined in Appendix B) and include Marshfield Clinic investigators can request access to DNA samples without further scientific review.

Scientists will be encouraged to include the cost of whole genome amplification of the DNA in their budgets. After the first DNA aliquot is depleted, whole genome amplification will be required so that the original DNA sample is not exhausted. The third DNA sample will be archived in a separate location and rarely used as directed by the oversight committee. Cost estimates of whole genome amplification are available from the Molecular Diagnostics Laboratory, for inclusion in budget estimates.

For protocols that have **not** undergone adequate peer review elsewhere, the MCRF Research Committee will review the proposal for scientific merit. The Oversight Committee (Appendix C) will give final approval for access to DNA specimens. Once projects have been approved by the Oversight Committee, the Committee will provide a letter of support for grant applications if necessary. **PMRP samples ARE NOT to be used for assay development.**

8. Process for accessing plasma and/or serum samples

The Research Committee will review all proposals to use plasma and/or serum samples for scientific merit if they have not had a formal assessment of scientific merit from an outside body (see Appendix B). The Oversight Committee will give final approval for all requests to use plasma or serum samples. This committee will be appointed by and report to the Director of Medical Research at the Marshfield Clinic. This committee will give consideration to how much sample is being requested. Once projects have been approved by the Oversight Committee, the Committee will provide a letter of support for grant applications if necessary. Where additional subject samples or quantity of biological material is desired by an investigator, additional IRB approval may be necessary (for additional subjects), and an amendment and additional approval is required by the Oversight Committee. This approval can be accomplished electronically. **PMRP samples ARE NOT to be used for assay development.**

9. Process for accessing pathology samples (normal and tumor collected in the course of routine healthcare procedures)

We anticipate that requests for access to the PMRP samples and established phenotypes and genotypes will come from both external and internal investigators and that scientific merit may or may not have been received prior to application to access the samples. The tissue samples are routinely fixed and embedded and stored in blocks.

All tissues must be accessed in consultation with a pathologist to make sure adequate tissue exists and remains for future patient medical needs.

The requester should include budget time and cost for retrieval and access of samples.

PMRP Oversight Committee approval will allow up to 5% of the tissue sample (not needed for patient medical needs) to be processed for the investigators to a given research project. Additional tissues over the 5% threshold will require additional PMRP Oversight approval.

PMRP Samples ARE NOT to be used for assay development.

10. Process for documenting data only requests

OSC approval is not necessary for data-only request, however, these requests need to be documented. A data-only request should be completed using the on-line form.
http://sharepoint01/is/teams/researchis/PMRPRequests/default.aspx

Access for GWAS Data must be obtained from the Principal Investigator and the grant must be acknowledged (Genome-Wide Study of Cataract and Low HDL in the Personalized Medicine Research Project 1U01HG004608-01).

11. Creation of phenotypes from the Marshfield Clinic electronic medical record and PMRP questionnaire

IRB approval is required to use the Marshfield Clinic electronic medical records to create phenotypes for studies. Feasibility requests can be made without prior IRB approval. Data requests are made to Marshfield Clinic Information Systems (IS) using their online request form. The results from ongoing phenotyping pilot projects (type II diabetes, osteoporosis, open angle glaucoma, breast cancer, pancreatic cancer) indicate that although electronic algorithms can be used to identify cases and controls for some diseases such as type II diabetes, manual chart abstraction will be needed to verify case and control status for many diseases. Cost estimates for IS time and Research Coordinator time to develop and execute the electronic algorithms and conduct manual chart abstraction can be developed for budget preparation.

IS can also assist investigators in accessing phenotypes created for other studies. These phenotypes will be maintained in a central database and an index will be created to mange them.

12. Process for recontacting PMRP participants to collect additional information

The consent form for enrollment into the PMRP provided an option for participants to indicate if they did not want to be contacted for possible recruitment into subsequent studies that require additional data collection. More than 99% of PMRP participants agreed to allow recontact.

When additional data need to be collected for a particular study, the Marshfield Clinic investigator(s) will obtain from Marshfield Clinic IS a file with the names and addresses of relevant PMRP participants who have agreed to allow recontact; IS can also provide mailing labels, as needed. For external investigators, contact with PMRP participants will be undertaken by Marshfield Clinic staff and any questionnaires will be returned to the Marshfield Clinic for data entry. This process will be used to protect the privacy of PMRP participants.

Marshfield Clinic PMRP staff will maintain a database of contact with PMRP participants and the Oversight Committee will regulate contact as necessary so that individual PMRP participants are not unduly bothered by requests for participation in sub-studies. Where possible, mailings will be coordinated to save time and inconvenience for PMRP participants.

13. Approval for presentation/publication of results

Prior approval is not required, but authors are requested to reference and refer to the basic PMRP methods paper **and acknowledge support from the Clinical and Translational Science Award (CTSA).**

McCarty CA, Wilke RA, Giampietro PF, Wesbrook SD, Caldwell MD. Marshfield Clinic Personalized Medicine Research Project (PMRP): design, methods and recruitment for a large population-based biobank. Personalized Med 2005;2:49-79.

Supported by grant 1UL1RR025011 from the Clinical and Translational Science Award (CTSA) program of the National Center for Research Resources, National Institutes of Health.

14. Statistical analyses

Statistical support is available through the **Biomedical Informatics Research Center (BIRC)** at the Marshfield Clinic Research Foundation. They can also provide assistance when developing appropriate allowance for statistical analyses in budget preparations. Investigators are not required to have their statistical analyses conducted by the **BIRC.**

15. Transfer of data to PMRP database

We recognize that research results could result in the creation of intellectual property and patent or copyright applications. We encourage investigators to pursue intellectual property protection where applicable. However, all investigators will be expected to return their data and analyses to the PMRP database for other investigators to use within 6 months after final data analysis. Exceptions may be considered by the Oversight Committee.

16. Fees

Feasibility requests for internal investigators can be made free of charge through IS data requests. IS should be consulted during grant budget preparation to determine the resources necessary for phenotyping and to create and manage the de-identified datasets. Funds will also be required for laboratory staff to pull samples and perform genotyping, biochemical and molecular analyses. These costs will vary by disease, test and number of samples being requested.

17. Questions

Questions can be directed to investigators through the PMRP web site (http://research.marshfieldclinic.org/pmrc/pmrc_contact_us.asp).

18. Return of samples/data

Remaining biological material must be returned to the main repository after all approved studies have been completed. **Data must be submitted to BIRC within six months after completing papers/security intellectual property. Researchers need to cover the cost of incorporating their data into the PMRP database. BIRC and provide estimates of the costs.**

Appendix A

Systemwide

Policy ID & Revision:	957.1
Title:	Marshfield Clinic Research Foundation as IRB of Record
Latest Eff. Date:	1/1/2010
Responsible Party:	Linda Jaros, Assistant Director, Office of Research Integrity & Protections

1. **Scope**
   System Wide

2. **Purpose**

   This policy provides details regarding when Marshfield Clinic Research Foundation (MCRF) IRB will serve as the IRB of record for research conducted by investigators in collaboration with, but external to, Marshfield Clinic (MC) or St. Joseph's Hospital (SJH).

3. **Background**

   Marshfield Clinic maintains an Institutional Review Board (IRB) established to review research conducted by investigators at MC and SJH and involving human subjects. MCRF IRB is given authority to review and approve, require modification in, disapprove, suspend or terminate any human subjects research in which either MC investigators are engaged in research or investigators at institutions for which MC is serving as IRB, per specific IRB Agreements, are engaged in research.

4. **Definitions**

   External Collaborator: Investigator who is not physician or staff member of MC or SJH. This is most often a student on site temporarily, or a researcher who is part of a multi-site research effort, and whose organizational IRB has deferred review to MCRF IRB via an IRB Authorization Agreement.

   IRB of Record: The IRB responsible for the initial and ongoing review and approval of a given research project.

Minimal Risk Research: Categories of research that present not greater than minimal risk and may be reviewed by the IRB through an expedited review procedure 45.CFR46.110(b)(1-2) and 63 FR 60364-60367 (1-7).

5. **Document Body**

A For greater than minimal risk research, MCRF IRB will serve as IRB of record when a qualified MC or SJH physician or staff member is principal investigator, and the research will be conducted at a location and under conditions that allow for the necessary MCRF IRB oversight of the research. Exceptions will be evaluated and decided upon a case-by-case basis.

B For minimal risk research, MCRF IRB will serve as the IRB of record when a qualified MC or SJH physician or staff member is principal investigator, or when all of the following conditions are met:

a. An external investigator has partnered with an appropriate co-investigator from MC or SJH;

b. The research involves access to MC and SJH shared patients, data, records or MC or SJH staff or facilities;

c. The external collaborator provides proof of human subjects protection training from an institution with an assurance from OHRP or completes MCRF's human subjects protection training requirement;

d. The external collaborator provides a current CV showing necessary credentials to conduct the research;

e. The external collaborator agrees to provide notice to MCRF IRB when they conclude their relationship with MC or the SJH. The notice must include contact information and details of how the investigator intends to complete the study and to keep up necessary communication with MCRF IRB.

C HMO Research Network(HMORN) and the Wisconsin IRB Consortium(WIC) involve separate, specific collaborative IRB deferral processes which supercede this policy and must be followed.

6. **Procedure**

A To request MCRF IRB review of a research project, an external investigator, must submit to the IRB:

a. An MCRF IRB Research Application;

b. A current curriculum vitae; and

c. Proof of human subjects protection training.

B If criteria set forth in Policy Section B (above) are met, the IRB will process the application

C The external collaborator will receive written correspondence regarding the ongoing IRB oversight of the project. The internal collaborator will receive copies.

7. Revision History

10/1/05: Clarification regarding greater than minimal risk research.

9/12/06: editorial revision

5/4/07: Updated Keyword

10/1/07: minor editorial revision

10/31/07: reflects changes to MHC contract

5/16/08: Updated title of Policy to reflect that Marshfield Clinic Research Foundation is the IRB of Record, defined External Collaborator

1/1/10: Updated Background and Policy section to reflect that MCRF IRB will serve as IRB of record for MC or SJH physicians or staff members

8. Keywords

IRB of Record, External Collaborator, IRBWEB, Deferral

Appendix B

Systemwide

Policy ID & Revision:	934.0
Title:	Scientific Merit Review Requirements
Latest Eff. Date:	5/20/2009
Responsible Party:	Linda Jaros, Assistant Director, Office of Research Integrity & Protections
Approved By:	Humberto Vidaillet, MD, Director of Medical Research

1. **Scope**
   System Wide

2. **Purpose**

   To outline requirements for scientific merit review of research submitted to the IRB.

3. **Background**
   The IRB, the institution, and the investigator share an obligation to ensure that any research to be conducted has significance and is adequately designed to answer the question being posed. The IRB believes it is unethical to expose subjects to research of no significance or research that is poorly designed. To obtain assurance of the scientific merit of a proposal, the IRB requires others to assist in the review.

4. **Definitions**

   Minimal risk – the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in the daily life of a healthy individual or during the performance of routine physical or psychological examinations or tests.

   Scientifically meritorious –significant and adequately designed to answer the question being posed by the research.

5. **Document Body**

   Prior to review, the IRB will require peer review of proposed research to determine whether the project is scientifically meritorious. This will be required for both minimal risk and greater than minimal risk projects.

   When research is conducted at a Marshfield Clinic center that has a departmental

structure, scientific peer review should be conducted by the principal investigator's department.

When research is proposed by an investigator at a center without a departmental structure, review should normally be conducted by a group determined by the regional center director to be adequate to conduct such a review. In some cases, it may be more appropriate to defer this review to a department with expertise in the area discussed in the protocol. This decision may be made by the regional center director.

In some cases, the IRB may also request review by another department if another department has significant involvement in the proposed protocol or when expertise on certain protocol aspects is not available within the principal investigator's department or regional center.

As part of the application process, the department chair or regional center director will be asked to certify that scientific peer review took place and that the project was determined to be of adequate scientific merit. Each department or regional center may determine the appropriate mechanism for conducting this review. Some suggestions include review of the protocol at department or regional center meetings, distributing the protocol to department or regional center members for comment, designating a representative subgroup of the department or regional center to conduct the review, etc. For projects involving greater than minimal risk to subjects, responsibility for conducting departmental scientific merit review should not be assigned to one individual.

The IRB also requires a formal scientific merit review by the Research Committee or an external scientific merit review body:

- when any part of the proposal could be considered greater than "minimal risk", or
- if the IRB questions whether the project is adequately designed to provide meaningful results.

EXCEPTION: emergency use protocols

A formal assessment of scientific merit will be considered adequate if performed by:

- federal or other extramural funding agencies who do not have a financial interest in the success of the product/process under study (e.g., NIH, American Heart Assoc.)
- Marshfield Clinic Research Foundation's Research Committee
- other groups without conflicting financial interest who can demonstrate adequate peer review structure by providing to the IRB:

a. the group's mission statement, and

b. the composition of the group, which must include experts in the field under study

If the scientific merit of a proposal is disapproved by a peer review group, the

project will not be reviewed by the IRB until the proposal has been revised to satisfy scientific merit reviewers.

If a project is not supported by a department or regional center for reasons other than scientific merit, the IRB will, at the investigator's request, review the project. However, the decision to proceed with the project, if approved by the IRB, will be made at the departmental and/or institutional level.

6. **Keywords**
Scientific Merit Review, IRBWEB, Scientific Merit, RCWEB

Appendix C
Oversight Committee

Purpose:
The overall purpose of the Oversight Committee is to serve as a steward of the PMRP resources for the Marshfield Clinic Research Foundation. The Oversight Committee will give final approval for access to PMRP DNA, plasma**,** serum and pathology specimens.

Composition:
Director of Medical Research, Chair of Oversight Committee
Principal Investigator of the Personalized Medicine Research Project
Department Chair of Medical Genetics
Director of the Center for Human Genetics
Director of the Marshfield Clinic Laboratories, or his/her designee
Director of Biomedical Informatics Research Center, or his/her designee
Director of Clinical Pathology

The Director of Medical Research has discretion to add additional ad hoc, permanent or ex-officio members as necessary.

Appointed by:
Director of Medical Research

Term of Appointment:
1 year, renewable annually

Frequency of Meetings:
Monthly

Review Format
The Oversight Committee will determine the format for review of proposals to access PMRP tissue specimens.