**Protocol with Statistical Analysis Plan Cover Page:**

| | |
|---|---|
| **Official Title:** | Discovery of Sirolimus Sensitive Biomarkers in Blood |
| **NCT number:** | NCT03304678 |
| **Document Type:** | Protocol with Statistical Analysis Plan (SAP) |
| **Document Date:** | November 1, 2021 |

**CLINICAL RESEARCH PROJECT** **Protocol #** 18-H-0003
**IND/IDE:** N/A

**Protocol Title:** Discovery of Sirolimus Sensitive Biomarkers in Blood

**Abbreviated Title:** Sirolimus Sensitive Biomarkers

**Principal Investigator:**
Joel Moss, M.D., Ph.D., PB, NHLBI (E), phone #301-496-1597, Bldg. 10, Rm. 6D05

**Accountable and Medically Responsible Investigator:**
Joel Moss, M.D., Ph.D., PB, NHLBI (E), phone #301-496-1597, Bldg. 10, Rm. 6D05

| **Subjects of study:** | **Number** | **Sex** | **Age range** |
|---|---|---|---|
| | 33 | F | 18 to 90 |

| | |
|---|---|
| **Project involves ionizing radiation?** | No |
| **Off site project?** | No |
| **Multi-Institutional project?** | Yes (Reliance Agreement(s): Brigham & Women's Hospital, University of Pennsylvania Medical Center, University of Cincinnati) |
| **DSMB involvement?** | No |
| **Tech Transfer: CRADA, MTA** | Yes |

**Non- NIH Non-Enrolling Multi-Site Individuals:**
**Brigham & Women Hospital, Boston, MA**
**Site PI: Elizabeth Henske, M.D.**

**University of Pennsylvania Medical Center, Philadelphia, PA**
**Site PI: Vera Krymskaya, Ph.D.**

**University of Cincinnati, Cincinnati, OH**
**Site PI: Francis X McCormack, M.D.**

Table of Contents

## 1.0 Précis:

Sirolimus (rapamycin), which acts as a targeted inhibitor of the protein mechanistic target of rapamycin (mTOR), has been shown to be effective in patients with lymphangioleiomyomatosis (LAM). It stabilizes lung function, resolves chylous effusions and lymphangioleiomas and shrinks angiomyolipomas. The current study is to understand better the short-term action of the drug by following the effects on potential biomarkers in blood and urine. Patients with LAM will have samples taken prior to administration of first dose of the drug, at 1 hr and then at 23 hours after the drug (trough level). At 3 and 9 months, samples will be obtained at trough and 1 hour after the dose. Molecular and cellular analyses will be performed to look for potential biomarkers.

## 2.0 Objectives

To determine the levels of sirolimus required to suppress known and candidate biomarkers of mTORC1 inhibition in LAM patients.

## 3.0 Background

Lymphangioleiomyomatosis (LAM) is a cystic lung disease characterized by proliferation of cells with mutations in the tuberous sclerosis complex (TSC) which leads to activation of the mTORC pathway (1). In LAM ~70% of patients have increased levels of VEGF-D which serves as a biomarker for diagnosis and potentially for therapeutic response (2). Additional biomarkers are needed. We have previously shown that Sirolimus regulates microRNA levels in vitro and in vivo. One of these "RapamiRs" is miR-21 is also regulated in vivo (3).

The central question of this research proposal is to identify if miRNA are responsive to sirolimus in patients with LAM, which will serve as a marker of therapeutic efficiency and dosing of sirolimus in patients.

## 3.1 Treatment Options

Sirolimus is an FDA-approved medication for the treatment of LAM. We plan to use sirolimus in our studies.

## 3.2 Clinical and Scientific justification

Sirolimus is an effective suppressive therapy for LAM that must be used chronically for sustained benefit. In a disease where therapy with a toxic drug is expected to be lifelong, determining the minimal effective dose is critical. Therefore, there remains an urgent unmet clinical need for biomarkers of response to Rapalogs and other targeted agents to streamline clinical trial design and enable personalized dosing. This project will investigate potential biomarkers of sirolimus response in humans, including microRNA, circulating LAM cells, mTOR pathway suppression, and lymphangiogenic factors.

MicroRNA (miRNA) are small RNA molecules that regulate gene expression. We have found that sirolimus regulates the expression of microRNA (3). miRNA are highly stable and many can be detected in the blood. MicroRNA have been identified as biomarkers of many human diseases, including COPD and several types of cancer. Therefore, biomarkers can be used to establish personalized sirolimus dosing levels, ultimately allowing therapeutic efficacy to be maximized while minimizing the adverse effects of continuous treatment (4). There is already evidence that lower doses may be sufficient but currently there is no proven metric other than lung function testing (which is inherently variable and slow to reflect changes) to guide optimal dosing. Our long-term goal is to correlate the impact of sirolimus on serum microRNA, lymphangiogenic factors, circulating LAM cells, and indicators of mTORC1 activity with the effect of sirolimus on VEGF-D, leading to the preliminary design of a combinatorial biomarker score of sirolimus efficacy in LAM and enabling future studies of personalized dosing.

## 4.0 Subject Recruitment and Registration

Recruitment: Subjects will be recruited from investigative sites (University of Cincinnati, Brigham and Women's Hospital, University of Pennsylvania). In addition, the study will be listed on clinicaltrials.gov,

Clinical Center research studies, the NHLBI patient recruitment websites. Patients will also be recruited through direct calls to LAM Clinic Directors in the largest cities, direct mailings to physicians, postings on the LAM Foundation and Tuberous Sclerosis Web site, and by mailings and eBlasts from the LAM Foundation. Currently the LAM Foundation Clinic Network comprises 30 LAM clinics in the US, and 19 international LAM clinics with a total of about 2750 LAM patients. It is expected that approximately 8 patients will be recruited per year for 3 years, drawing on existing patients who are already enrolled plus additional recruitments.

## 5.0 Study Design

Patients with LAM, whose treating physicians have decided that they need to start treatment with sirolimus will be referred to the NIH Clinical Center for these studies. This is a single center study with all subjects being enrolled at the NIH Clinical Center. The extracted LAM cells and serum, and other samples and data will be sent to the non-NIH associate investigators to identify the LAM biomarkers.

The first dose of sirolimus given will be a 2mg tablet per day. This is the typical starting dose as established by the Multicenter International Efficacy of Sirolimus (MILES) study (5). Once daily dosing is typical for sirolimus, which has a half-life of 60 hrs.

The amount of blood that may be drawn from adult patients (i.e., those persons 18 years of age or older) for research purposes shall not exceed 10.5 mL/kg or 550 mL (approximately 2 cups), whichever is smaller, at each study visit.

Each patient will have three study visits (0, 3, and 9 months from the start of therapy). Three blood samples will be drawn at Visit #1 and two samples at Visit #2 and Visit #3, totaling 7 samples/patient. Urine will also be collected during these visits. Urine or blood pregnancy test (if of childbearing potential) will be verified at the time of each visit.

**Visit#1** (Month 0): Urine or blood pregnancy test. Three blood samples will be drawn: a) a pretreatment level, b) 1 hr (± 15 min) after the first dose of 2 mg of sirolimus, representing a Cmax timepoint when we expect to see repression of mTORC1 targets, and c) 23 hr (± 15 min) after the first dose of 2 mg sirolimus, representing a trough level to look for de-repression of mTORC1 targets. Urine will be collected pretreatment and approximately 23 hours (± 1 hr) after the first dose of sirolimus. Subjects will be asked to complete a drug diary to document taking sirolimus.

**Visit #2** (Month 3 ± 2 weeks): Urine or blood pregnancy test. Two blood samples will be drawn: a) 23 hrs (± 15 min) after the prior dose of 2 mg of sirolimus, b) 1 hr (± 15 min) after the next dose of 2 mg. Urine will be collected approximately 23 hours (± 1 hr) after the prior does of sirolimus.

**Visit #3** (Month 9 ± 2 weeks): Urine or blood pregnancy test. Two blood samples will be drawn: a) 23 hrs (± 15 min) after the prior dose of 2 mg of sirolimus, b) 1 hr (± 15 min) after the next dose of 2 mg. Urine will be collected approximately 23 hours (± 1 hr) after the prior does of sirolimus.. Subjects will be considered off study after the completion of Visit 3.

The protocol involves no more than minimal risk, since it only includes blood draws, since initiation of rapamycin is clinically indicated. Information gathered from other NIH Intramural IRB approved protocols that subjects may have participated in, may be used as part of this study.

## 6.0 Eligibility Assessment

### 6.1 Inclusion Criteria

1- Female 18 to 90 years of age

2- Diagnosis of LAM
3- Initiation of sirolimus therapy (2mg daily) based on standard-of-care pulmonary indications and the advice of the patient's local physician

**6.2 Exclusion criteria**

1- Unable to travel to the NIH
2- Unable to provide informed consent
3- Advanced stage of a pulmonary or a systemic illness in which the risk of the study is judged to be significant even in the absence of a clear contraindication to the procedures.
4- Women who are pregnant or lactating

## 7.0 Sample Collection, Storage, and Biospecimen and Data Management Plan

***Biospecimen Management:*** Specimens and their derivatives (e.g., genomic material, cell lines) will be coded and stored in conformity with DIR Policy (e.g., BSI). Coded biospecimens may be sent to collaborators outside of the NIH with IRB approval in accordance with applicable NIH and DIR Policy for sharing research resources, including an executed material transfer agreement. Biospecimens with subject personal identifiers may be sent to associate investigators and collaborators outside of the NIH only after approvals of both NHLBI and local IRBs, an executed reliance agreement with NIH Intramural IRB, or an extension of the NIH's FWA through an Individual Investigator Agreement.

***Data Management:*** The principal investigator, associate investigators, and research nurses will assist with the data management efforts. Data will be abstracted from Clinical Center progress notes as well as intake forms. Laboratory data from NIH will be reviewed using CRIS. The principal investigator and associate investigators/research nurses will assist with the data management efforts to ensure that data is verifiable and evaluable. Data will be abstracted from Clinical Center progress notes as well as from progress notes forwarded from the subjects' home physician.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. Laboratory values from referring home physicians will not be entered into the system. The principal investigator and associate investigators/research nurses will assist with the data management efforts to ensure that data are verifiable and evaluable.

Any pertinent supplementary information obtained from outside laboratories, outside hospitals, radiology reports, laboratory reports, or other patient records will be used as additional sources for data collection.

We will maintain the confidentiality of identifiable private information collected in this clinical trial and protect the privacy of the individual human subjects. Primary data containing individually identifiable information obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH information security standards. Identifiable data will not be sent outside NIH without prior IRB approval or appropriate conditions for disclosure outlined in the executed CTA or MTA.

***Storage:*** All samples will be stored in the laboratory of Dr. Moss. Collected samples will be de-identified prior to storage in the laboratory of the principal investigator following current NHLBI DIR BSI Policy. Efforts to ensure protection of patient information include;

- Each sample is assigned a unique number.
- Vials holding patient samples are labeled with the sequential laboratory accession ID number that does not contain any personal identifier information.
- An electronic database is used to store patient information related to the coded samples.

- The laboratory is located in a controlled access building and laboratory doors are kept locked. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Hard copy records or electronic copies of documents containing patient information are kept in the locked laboratory or other controlled access locations.

***Intended use:*** During the course of participating on this study, blood and data may be collected for correlative laboratory research studies. Specimens collected strictly for research purposes will not be read by a pathologist.

***Tracking:*** Samples will be ordered and tracked through the CRIS Research Screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the medical record. Samples will not be sent outside NIH without appropriate institutional approval and an executed MTA or CTA.

***End of study procedures:*** At a minimum, data collected at the NIH will be stored in locked cabinets and in a password protected network servers until it is no longer of scientific value. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. A file note will be made to document the withdrawal / destruction, and existing data will not be used in future studies.

***Loss or destruction of data/samples:*** Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the Institutional Review Board (IRB) will be notified.

***Publication Policy:*** Given the research mandate of the NIH, patient data including the results of testing and responses to treatment will be entered into an NIH-authorized and controlled research database. Any future research use will occur only after appropriate human subject protection and institutional approval.

***Privacy and Confidentiality:*** All efforts, within reason, will be made to keep subjects' protected health information (PHI) and private identifiable information (PII) private. Using or sharing ("disclosure") such data must follow federal privacy rules. Under certain circumstances, the United States Office of Human Research Protections (OHRP), and the NIH Intramural Institutional Review Board (IRB), will be able to inspect and copy confidential study-related records which identify participants by name. Therefore, absolute confidentiality cannot be guaranteed.

***Data sharing and future use of data***
Research data may be shared with qualified non-collaborator recipients following publication of the primary research results after removal of PII and an executed MTA, and or DTA.. Future research use of data not defined in the research protocol may occur only after the appropriate institutional approval and an executed MTA and or DTA. Refusal of a research subject participant to permit future use of data--other than required in the protocol --will be honored. Limitations in data sharing and future use of data due to contractual obligations (e.g., CRADAs) or intellectual property proceedings (such as patent filings) will be honored.

***Future use of biospecimens***
Following analyses of biospecimens for primary research purposes, remaining samples suitable for future research will be stored in manner that conforms with DIR policy (such as BSI) or in a publicly accessible research biospecimen repository following IRB or OHSRP approval, as applicable. Biospecimens may be destroyed only when permitted by the Clinical Director and the IRB.

Any future research use of biospecimens not defined in the protocol in which NHLBI investigators are engaged in research (e.g., they are undertaking research activities and hold the key that identifies research subjects) requires IRB review and approval. Coded biospecimens (NHLBI investigators hold the key that identifies research subjects) to be shared outside of NIH for future research use requires IRB review and approval (for research collaborations), and an executed transfer agreement. Unlinked biospecimens (no key to identify research subjects exists) to be shared outside of NIH for future research use requires appropriate institutional approval and an executed transfer agreement. There are a few types of biospecimens that do not require IRB or OHSRP approval for future research use outside of NIH, such as specimens from deceased individuals (refer to OHSRP SOP5, Appendix 1 for complete list); an executed transfer agreement is required in these special cases. Refusal of a research subject participant to allow for future use of identifiable biospecimens--other than required in the protocol or for appropriate regulatory purposes --will be honored.

Reliance Agreements are in the process of being executed between the external research sites associated with the protocol and NHLBI for identifiable data and samples to be sent for analysis in accordance with the U01 grant. Sample and data analysis will only address those questions pertaining to the primary and secondary objectives/endpoints of the study. The review of samples and data with identifiers will only start upon execution of a reliance agreement. Until such time, the external sites may receive deidentified samples upon execution of an MTA at each site.

### 7.1 Intended use

Biomarkers including miRNA, VEGF-D, circulating LAM cells, peripheral lymphocyte phosphor-S6 and phospho-S6K will be drawn.

## 8.0 BIOSTATISTICAL CONSIDERATIONS

**microRNA.** In a pilot study, we profiled 185 serum microRNA in 5 women with LAM (2 sporadic LAM and 3 TSC-LAM) and 5 healthy controls using the miRCURY LNA RT microRNA PCR Serum/plasma Panel. Based on this five sample/group pilot experiment, a power-analysis was performed. If we assume that at least a similar level of difference in microRNA will be observed with sirolimus treatment vs. the prior comparison of LAM patients vs. healthy women, the top nine miRNA should be validated with 18 samples per group ($p=0.05$ after B-H correction, 95% confidence interval). For this project, we will test 24 women treated with sirolimus. Therefore, we should have sufficient statistical power to detect sirolimus-dependent changes in microRNA.

**Lymphangiogenic factors.** In the MILES trial, VEGF-D levels decreased more than 2 folds with sirolimus treatment. Our planned enrollment of 24 women with LAM will ensure that a two-sided test with $\alpha=0.05$ has 80% power to detect a 2-fold change using a paired Wilcoxon signed-ranked test.

## 9.0 Data and Safety Monitoring and Reporting

**Safety Monitoring:**
Accrual and safety data will be monitored by the Principal Investigator who provides oversight to the conduct of this study, Joel Moss, M.D., Ph.D.

**NIH Intramural IRB:** Accrual and safety data will also be monitored and reviewed annually by the IRB. Prior to implementation of this study, the protocol and the proposed subject consent form will be reviewed and approved by the properly constituted IRB operating according to 45 CFR 46. This committee will approve all amendments to the protocol or informed consent and conduct continuing annual review so long as the protocol is open to accrual, follow-up of subjects, or data analysis continues.

## 9.1 Assessment of Safety

**Definitions**
Please refer to Policy 801 for current definitions**.**

## 9.2 Adverse Event Management

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The AEs will be attributed (unrelated, unlikely, possibly, probably or definitely) to study procedure and graded by severity utilizing CTC version 4.0. A copy of the criteria can be downloaded from the CTEP home page at http://ctep.cancer.gov/reporting/ctc.html.

Patients entered onto this protocol will only be subject to blood and urine collection.. Therefore any observed or volunteered adverse events not related to these research study procedures will NOT captured in the research data base.

Adverse events that are deemed possibly, probably or definitely related to the subject's underlying disease(s), prior therapies, or concurrent non-protocol treatments will be captured in the subject's medical records, but will not be captured in the research database.

## 9.3 NIH Intramural-IRB and CD reporting

Only adverse events, SAEs, and UPs that occur solely as a result of participation in this research study, such as those due to blood draws, will be captured in the research database.

NIH Intramural IRB and CD reporting:
Expedited Reporting:

Events requiring expedited reporting will be submitted to the IRB per Policy 801 "Reporting Research Events".

Reports to the IRB at the time of Continuing Review:
The PI or designee will refer to HRPP Policy 801 "Reporting Research Events", to determine IRB reporting requirements.

Reports to the CD:
The PI or designee will refer to NHLBI DIR guidelines to determine CD reporting requirements.

***Data reporting*:**
The following Adverse Events will captured in the subject's medical records, but will not be captured in the research database..

- Adverse events that are deemed possibly, probably or definitely related to the subject's underlying disease(s), prior therapies, or concurrent non-protocol treatments.
- **Phlebotomy:** Transient discomfort, minor bleeding and/or bruising may occur at the phlebotomy site. Vasovagal symptoms can occur during blood drawing.

# 10.0 Human Subjects Protection

## 10.1 Rationale for Subject Selection

**Study population:** Female patients ages 18 to 90 will be considered for the protocol. No patient will be excluded from participation based on race or ethnicity. Patients may self refer, be recruited through the NIH office of recruitment and may include patients participating on NIH Clinical Center Protocols and NIH employees and/or children of NIH employees. Women who are pregnant or lactating are excluded due to the risk to the developing fetus or nursing babies.

### 10.2 Participation of children

We are limiting the protocol to participants who are 18 to 90 years old because LAM is primarily a disease of young to older women but not children.

### 10.3 Risks and Discomforts

Risks associated with phlebotomy and/or blood draws include symptoms related to a fear of blood drawing, temporary lowering of blood pressure, dizziness, lightheadedness, fainting, and rarely seizures.

### 10.4 Informed Consent Processes and Procedures

Informed consent will be conducted following OHSRP Policy 301- Informed Consent.
An IRB-approved consent form will be provided to the participant electronically or by hard copy for review prior to consenting. The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved platforms). The investigational nature and objectives of this trial, the procedures, and their attendant risks and discomforts and potential benefits will be carefully explained to the participant in a private setting. The participant will be given as much time as they need to review the document and to consult with their family, friends, and personal health care providers. In addition, a study team member will be available to answer any questions.

A signed and dated informed consent document will be obtained by any investigator authorized to consent (See Key Study Personnel Page) prior to entry onto the study. Consent may be obtained with required signatures on the hard copy of the consent or on the electronic document.
When a document that is in electronic format is used for obtaining consent, this study may use the iMed platform which is 21 CFR, Part 11 compliant, to obtain the required signatures.
During the consent process, participants and investigators may view the same approved consent document simultaneously when participant is being consented in person at the Clinical Center or both may view individual copies of the approved consent document on screens in their respective locations remotely. Signatures may be obtained either by both directly signing on the device that the consenting investigator is using (when in person) or through iMed Mobile Signature Capture (remotely) which allows texting or emailing a link to the participant. That link allows the participant to review the consent, then proceed to sign on the device they are using.

Whether hard copy or electronic, both the investigator and the participant will sign the document with a hand signature using a pen (if using hard copy), finger, stylus, or mouse (if electronic). When done remotely, if the participant prefers to sign a hard copy, they may be instructed to sign and date the consent document during the discussion and mail, secure email or fax the signed document to the consenting investigator.

Whether in person or remotely, the privacy of the participant will be maintained.

Finally, the fully signed informed consent document will be stored in the electronic medical record, and the participant will receive a copy of the signed informed consent document.

## 11.0 Conflict of Interest

The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf.

None of the members of the research team reported a potential conflict of interest.

This protocol may have investigators who are not NIH employees. Non-NIH investigators are expected to adhere to the principles of the Protocol Review Guide but are not required to report their personal financial holdings to the NIH. Investigators at Brigham and Women's Hospital, University of Cincinnati, and University of Pennsylvania Medical Center will have a Reliance Agreement with the NIH.

## 12.0 Compensation

Subjects will not be paid for their participation in this study.

### Reimbursement for Travel

Reimbursement for travel will be in accordance with NHLBI travel policy. Reimbursement for food and lodging will be consistent with NIH and NHLBI guidelines.

## 13.0 References


1. Carsillo T, Astrinidis A, & Henske EP (2000) Mutations in the tuberous sclerosis complex gene TSC2 are a cause of sporadic pulmonary lymphangioleiomyomatosis. *Proc Natl Acad Sci U S A* 97:6085-6090.
2. Young L, Lee HS, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, Barker AF, Chapman JT, Brantly ML, Stocks JM, Brown KK, Lynch JP, 3rd, Goldberg HJ, Downey GP, Swigris JJ, Taveira-DaSilva AM, Krischer JP, Trapnell BC, & McCormack FX (2013) Serum VEGF-D a concentration as a biomarker of lymphangioleiomyomatosis severity and treatment response: a prospective analysis of the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial. *Lancet Respir Med* 1:445-452.
3. Trindade AJ, Medvetz DA, Neuman NA, Myachina F, Yu J, Priolo C, & Henske EP (2013) MicroRNA-21 is induced by rapamycin in a model of tuberous sclerosis (TSC) and lymphangioleiomyomatosis (LAM). *PLoS One* 8:e60014.
4. Trelinska J, Dachowska I, Kotulska K, Fendler W, Jozwiak S, & Mlynarski W (2015) Complications of mammalian target of rapamycin inhibitor anticancer treatment among patients with tuberous sclerosis complex are common and occasionally life-threatening. *Anticancer Drugs* 26:437-442.
5. McCormack FX, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, Barker AF, Chapman JT, Brantly ML, Stocks JM, Brown KK, Lynch JP, 3rd, Goldberg HJ, Young LR, Kinder BW, Downey GP, Sullivan EJ, Colby TV, McKay RT, Cohen MM, Korbee L, Taveira-DaSilva AM, Lee HS, Krischer JP, & Trapnell BC (2011) Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *N Engl J Med* 364:1595-1606.

| *UO1: Discovery of Sirolimus Sensitive Biomarkers in Blood* | **Study Drug Diary** |
|---|---|
| Participant: | Local ID: |

Please complete this Study Drug Log daily while on Sirolimus providing the date it was taken, the time of day, reason if medication was not taken and any symptoms related to taking Sirolimus. Please report any changes to dosage or if you need to stop the medication.

| Date (MM/DD/YYYY) | Time (circle AM or PM) | Dosage | Reason if medication not taken | Report any symptoms related to taking Sirolimus |
|---|---|---|---|---|
| ____/____/_____ | _____ AM or PM | ___2mg_____ | | |
| ____/____/_____ | _____ AM or PM | ___2mg_____ | | |
| ____/____/_____ | _____ AM or PM | ___2mg_____ | | |
| ____/____/_____ | _____ AM or PM | ___2mg_____ | | |
| ____/____/_____ | _____ AM or PM | ___2mg_____ | | |

| | | | | |
|---|---|---|---|---|
| ____/____/_____ | _____AM or PM | ___2mg_____ | | |
| ____/____/_____ | _____ AM or PM | ___2mg_____ | | |

Signature of staff member reviewing form:_____Date___/___/ _____