Consent Form

Study Title: A Phase I/II Study of Decitabine in Combination with Sequential Rapamycin or Ribavirin in High Risk AML Patients

Clinical trials.gov # NCT02109744

Principal Investigator: Jane Liesveld, MD

This is a clinical research study. Clinical research studies include only those patients who choose to take part. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. Please take your time to make your decision. Discuss it with your family and with people who are important to you.

What is the usual approach to my leukemia?

Acute myelogenous leukemia in those above 65 years of age can be treated with chemotherapy or other agents called hypomethylating agents. Some patients choose to have no therapy at all or transfusions and chemotherapy by mouth only. In younger patients, when leukemia relapses or does not respond to treatment, it is often treated with different types of chemotherapy or in suitable patients with well matched donors, a stem cell transplantation. There is no one chemotherapy regimen which is considered standard or best in this setting.

You are being asked to take part in this study because you are older than 65 years of age and have recently been diagnosed with acute myelogenous leukemia OR you have previously been treated for acute myelogenous leukemia, and you have not had a complete response to therapy or your disease responded and has now returned. People who are not in a study are usually treated with other combinations of chemotherapy drugs or with stem cell transplantation. Your doctor can explain why these options may or may not be appropriate or available to you at the present time. Previous studies that have used decitabine by itself have shown response rates of 25 to 40% in newly diagnosed patients.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for leukemia, but you may want to receive transfusion support or comfort care to relieve symptoms.

Why is this study being done?

The purpose of this study is to evaluate the response to chemotherapy with the drug decitabine combined with rapamycin in the treatment of relapsed or refractory acute myeloid leukemia in patients of all ages and in the treatment of newly diagnosed leukemia in those are older than 65 when diagnosed. The safety of this combination has been previously studied but it is considered investigational for the treatment of refractory or relapsed leukemia. The study will determine whether this combination is not only safe but has benefit in reducing the amount of leukemia present in these patients. There will be up to 24 patients taking part in this portion of the study. Both decitabine and rapamycin have approval from the FDA but not when used in this combination for leukemia.

Because some patients who have M4 and M5 leukemia (types that are determined by the pathology doctor who reviewed the blood and marrow at diagnosis) may have changes in their cells that would make it more difficult for rapamycin to inhibit their leukemia, in those cases, we will combine decitabine with ribavirin which has also been shown to have ability to inhibit leukemia cells. The purpose of this portion of the study will be to determine the highest dose of ribavirin that can be given safely in combination with decitabine in M4and M5 types of leukemia. Up to 18 patients with M4 and M5 leukemia will participate in this study. Both decitabine and ribavirin have approval from the FDA but not when used in this combination for leukemia.

The study will also look at the effects of the treatment on your leukemia and other cells in your blood and bone marrow. These studies will be done by researchers at the University of Rochester. As part of this study, blood and bone marrow samples may be frozen for experiments that cannot be done immediately but will only be used for studies that are related to this research study or to leukemia and other types of cancer.

What are the study groups?

All study participants will get the same study drug, decitabine, given intravenously daily over 60 minutes for 10 days in the first cycle and for 5 days in subsequent cycles. The dose given will depend on your height and body weight. Cycles will be repeated very 28 days.

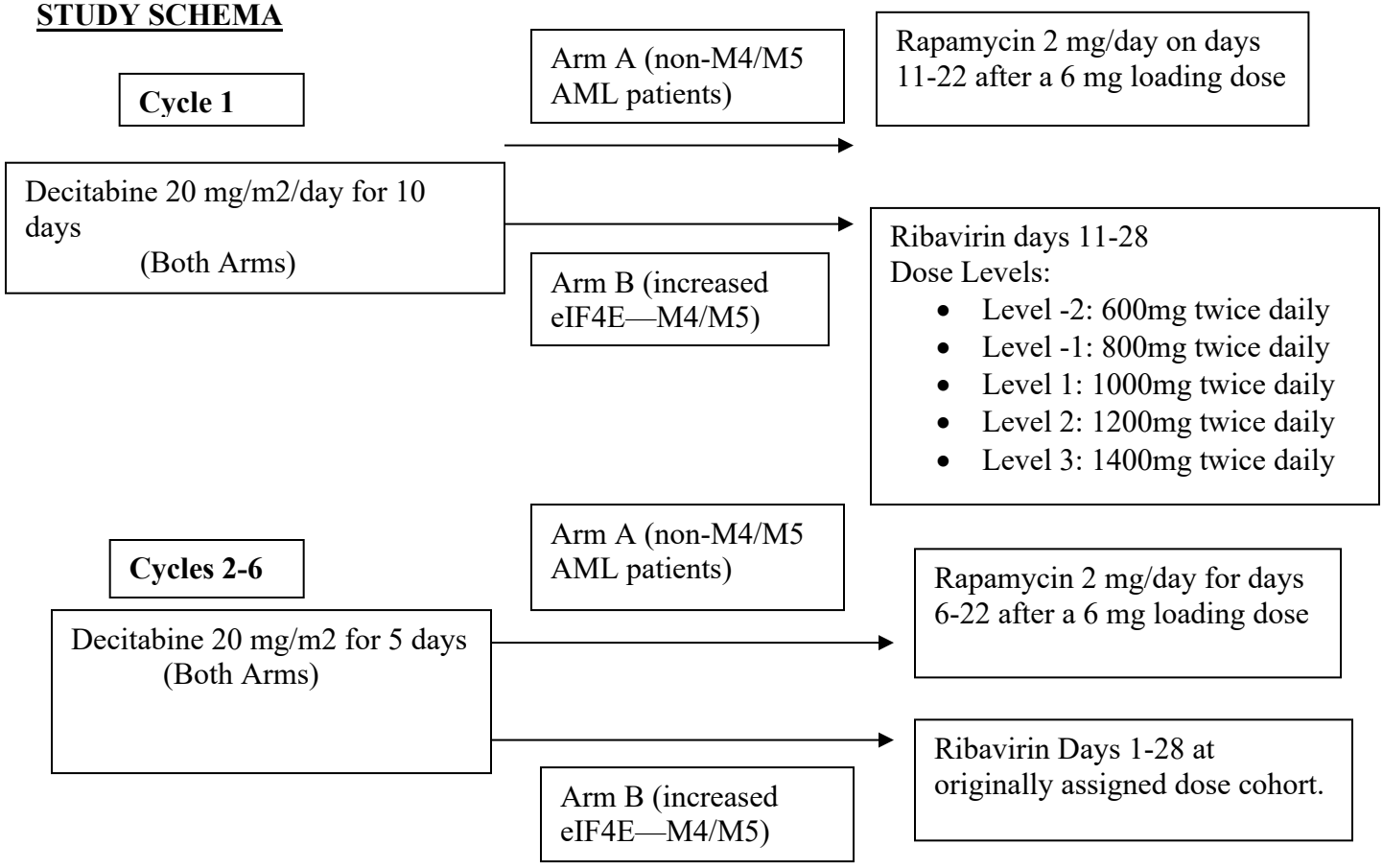
If your leukemia is of a subtype called M4 or M5 which will be determined by your pathology report (study group Arm B), after you finish decitabine, you will receive a drug called ribavirin, orally twice per day, from day 11 on through the duration of the study. Different doses of the study drug will be given to several study participants. The first several will receive the lowest dose, and if ribavirin does not cause serious side effects when given after decitabine, it will be given to other participants at a higher dose. Three doses are planned, but if side effects occur, the dose will be lowered, and this part of the study will be stopped. You will be informed which dose you will be receiving. M4 and M5 leukemias express a protein that may make those types more susceptible to ribavirin than rapamycin which other study subjects will be receiving.

If your leukemia is not the M4 or M5 subtype as determined by your pathology report (study group Arm A), after you finish decitabine, you will receive a drug called rapamycin, orally, at a fixed dose of 2 mg per day after a dose of 6 mg on day 11. You will take this from days 11 through 22 in the first cycle and 6 through 22 in subsequent cycles.

Irrespective of which arm of the study you are on, you will be asked to write down in a small note pad the number of pills you take each day and when, and your doctor will order the pills for you during your clinic visits.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.

STUDY SCHEMA



How long will I be in this study?

You may receive decitabine followed by rapamcycin or ribavirin for up to 6 cycles of 28 days (about 6 months). After you finish these cycles, your doctor will continue to watch you for side effects and follow your condition for up to 2 years. Your doctor may or may not continue other treatments when the 6 cycles are concluded.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your leukemia. However, there are some extra tests or procedures that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following extra tests and procedures to find out if you can be in the study beyond what might be performed if you chose alternate treatments:

- Blood sample (approximately 2 tablespoons) for future research purposes only

- A bone marrow aspirate and biopsy (within 2 weeks prior to treatment). If you had a biopsy within 2 weeks, only an aspirate will need to be repeated to determine baseline blasts and to obtain a sample for future research purposes

Blood and bone marrow collection for the study
Blood and marrow research specimens are required for you to take part in this study because the research on the sample is an important part of the study. The blood and marrow draws will be done just as they would for diagnosis and followup, and most would need to be done in any case to monitor the status of your leukemia. The extra amounts taken for research will help to understand if the decitabine and rapamycin or ribavirin are working on blood and marrow cells as expected but will not determine your treatment course on this study.

Risks and side effects of blood sample collection
Obtaining blood samples may cause pain and bruising. Fainting, and in rare cases infection, may also occur. If you have an indwelling central line or port, every effort will be made to use that for blood testing during the study.

Risks and side effects of bone marrow aspirate and biopsy
Possible side effects of bone marrow aspirate and biopsy include bleeding, infection, bruising, discomfort at the biopsy site and possible side effects from the local anesthetic (pain or bruising at the site where the aspirate or biopsy occurs). During the bone marrow biopsy and aspiration, you may have a reaction to the local anesthetic.

Left over specimens
If there is specimen left over after the needed tests are completed, the specimen can be stored for future research. This is optional, and will be discussed in the section on optional studies. Your privacy is very important and the researchers will make every effort to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and from your health care information. The research results of individual participants will not be available to study subjects but will be available to study doctors, although this will not influence planned treatment on the study.

Neither you nor your health care plan/insurance carrier will be billed for the collection of the blood and marrow used for this study that are not part of standard of care.

During the study:

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra tests and procedures which are not part of the usual approach to your type of cancer.

- All study subjects will have a marrow aspirate (not biopsy) on day 10 or 11.
- For those receiving rapamyin, blood tests for rapamycin levels on days 14 and 21 and a triglyceride level at the start of cycles 2 through 6.
- Bone marrow aspirate and biopsy when you end the study. This might be done even if you were not on the study but not in all cases.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- The combination of decitabine with ribavirin or rapamycin may not be better, and could possibly be worse, than the usual approach for your cancer.

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Arms A and B- Possible side effects of DECITABINE, which is a usual approach for this type of cancer:

Possible Side Effects of DECITABINE

COMMON, SOME MAY BE SERIOUS In 100 people receiving DECITABINE, more than 20 and up to 100 may have:

• Changes to blood composition (including one to three of the following)
  • Low number of white cells: may increase the chance of infections, including pneumonia, fever of unknown origin, urinary tract infection, infection or irritation of the mouth, sinusitis and sepsis, a blood-stream infection caused by the presence of bacteria or other infectious organisms or their toxins in the blood.
  • Low number of platelets: increases the chance of bleeding; this may show up as small bleeding spots in the skin, bleeding from the nose or gums and, rarely, bleeding in the stomach or brain.
  • Low number of red cells (anemia): this may lead to pallor, fatigue, shortness of breath, dizziness or worsening of the function of the heart.
• Headache
• Nausea
• Vomiting
• Diarrhea
• Constipation
• Fever
• Hyperglycemia (elevated blood sugars)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving DECITABINE, from 4 to 20 may have:
▪ Ulceration of the tongue or lip ▪ Loss of appetite ▪ Sleeplessness ▪ Cough ▪ Hair loss ▪ Redness of skin ▪ Changes in liver or kidney function ▪ Back pain, joint pain or muscle pain

RARE, AND SERIOUS In 100 people receiving DECITABINE, 3 or fewer may have:
• Seizures • Septic shock • Death may occur due to infection or bleeding.

ARM A: Possible side effects of rapamycin which those on this arm could expect in addition:

Possible Side Effects of RAPAMYCIN

COMMON, SOME MAY BE SERIOUS In 100 people receiving RAPAMYCIN, more than 20 and up to 100 may have:
• Trouble sleeping • Nervousness • Increased appetite • Indigestion • Inflammation of espophagus (food pipe) • Excess hair growth • Diabetes (blood sugar elevations) • Joint pain • Cataracts • Too much fat or cholesterol in the blood • Suppression of immune system

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving RAPAMYCIN, from 4 to 20 may have:
• Joint pain • Cataracts • Nosebleeds • Headache • Fluid and water retention • Increased glucose levels in blood

RARE, AND SERIOUS In 100 people receiving RAPAMYCIN, 3 or fewer may have:
• Seizures • Mood swings • Delirium or hallucinations • Thinning of skin • Bruising • Darkening of skin • Acne • Loss of menstrual periods in females • Suppression of bone growth • Swelling of the abdomen • Ulcers in the esophagus • Inflammation of the pancreas • Scarring in the lungs

Arm B- In addition to side effects outlined above, people who are in Arm B may also experience the possible side effects of ribavirin listed below.

Possible Side Effects of Ribavirin

COMMON, SOME MAY BE SERIOUS In 100 people receiving ribavirin, more than 20 and up to 100 may have:
• Anemia due to breakdown of red blood cells (seen mostly in patients with hepatitis)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ribavirin, from 4 to 20 may have:
• Anemia of other types which may require blood transfusion • Low white cell count • Low platelet count • Itching of skin • Low calcium • Low magnesium • Shortness of breath • Pneumonia

RARE, AND SERIOUS In 100 people receiving ribavirin, 3 or fewer may have:
• Liver failure (only seen in patients with hepatitis C) • Serious skin reactions • Acute allergic reaction • Increased pressure in the lungs • Inflammation of the pancreas

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. *Decitabine, rapamycin, or ribavirin* used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What possible benefits can I expect from taking part in this study?

You might not benefit from participation in this study. The potential benefit to you from being in this study might be that your cancer would be controlled longer.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is voluntary. You are free not to take part or to withdraw at any time, for whatever reason. No matter what decision you make, there will be no penalty or loss of benefit to which you are entitled. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

If we discover anything that might make you change your mind about continuing in the study, we will let you know.

For questions about your rights while in this study, call the University of Rochester Institutional Review Board at (585) 276-0005. For long-distance you may call toll-free: (877) 449-4441.

What are the costs of taking part in this study?

The decitabine and its preparation and administration will be charged to you and/or your insurance company. You and/or your insurance company will be charged for rapamycin or ribavirin, both commercially available drugs.

You and/or your health plan/insurance company will need to pay for all of the other costs of caring for your leukemia while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are directly injured by the drugs that are being studied, or by clinical procedures solely required to participate in the study, you may need to pay for treatment of your injuries, but you will not be required to pay for emergency medical treatment provided at Strong Memorial Hospital or Highland Hospital. The University may seek payment for this care from your health insurer or third parties. Decisions regarding care and compensation for any other research related injury will be made on a case-by-case basis.

Who will see my medical information?

Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes

The University of Rochester makes every effort to keep the information collected from you private. In order to do so, we will restrict access of study materials only to those personnel directly involved in the research, ensure all staff involved has been properly trained, and keep matierials in proper storage. Sometimes, however, researchers need to share information that may identify you with people that work for the University, regulators or the study sponsor.

If you have never received a copy of the University of Rochester Medical Center (URMC) and Affiliates Notice of Privacy Practices, please ask the investigator for one.

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Past and present medical records related to the study (only if you will be collecting information from the medical record)
- Results of medical tests (only if you will be conducting medical testing, labs, imaging, etc.)

Who may use and give out information about you?

- The study doctor and the study staff
- URMC and Affiliates

Your information may be given to:

- The Department of Health and Human Services;
- The University of Rochester
- The U.S. Food and Drug Administration (FDA) may also need to inspect study records at some point during the study or even after it has been completed. In the event that this should occur, every effort will be made to keep identifying information about you private.

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

How long will this be permission be valid?
This permission will last indefinitely. [If you will destroy the records at a definite point that should be stated instead and should be consistent with what is listed in both your protocol and application.]

May I cancel my permission to use and disclose information?
You may cancel your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. Upon receiving the written notice, the study team will no longer use or disclose your health information and you will not be able to stay in this study. Information that has already been gathered may need to be used and given to others for the validity of the study.

May I withdraw from the study?
Yes. If you withdraw your permission to be in the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
No. There is a risk that your information will be given to others without your permission.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

For more information concerning this research or if you feel that your participation has resulted in any research related injury, emotional or physical discomfort, please contact the study doctor, Dr. Jane Liesveld, at *585-275-5863 (24 hours).*

The University of Rochester Research Subjects Review Board can also be contacted for any of the following reasons:

- You wish to talk to someone other than the research staff about your rights as a research subject;
- To voice concerns about the research;
- To provide input concerning the research process;
- In the event the study staff could not be reached.

The University of Rochester Research Subjects Review Board can be reached at:

University of Rochester Research Subjects Review Board
265 Crittenden Blvd., CU 420315
Rochester, NY 14642

Telephone (585) 276-0005 or
For long-distance you may call toll-free: (877) 449-4441

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional Storage and Use for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment. If a genetic study is being done, DNA (inherited material) will be isolated from the sample. A variety of tests may be used to examine the genes we think may be related to your disease or condition. The exact testing that will be done is not known at this time, so we cannot give you more details right now. Even if your samples are used for this kind of research, the results will not be put in your health records. Records about you and the genetic testing results will be kept in a coded fashion. We may need to contact you to obtain your consent to future genetic testing of your samples. If you want to obtain genetic counseling to understand more about what genetic testing is, please let us know so we can refer you to a genetic counselor.

For the optional studies portion of this clinical study, no extra blood or marrow material will be obtained beyond that required in the study itself, but if there are extra cells remaining in these samples after tests for this study are completed, the researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by the leukemia research group at the James P. Wilmot Cancer Center at the University of Rochester.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

- It will be determined that there is leftover tissue from the samples collected for this trial and that they are no longer needed to assess your progress or response to the study medications.
- Your sample and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.

- Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization will review each request. There will also be an ethics review to ensure that the request is necessary and proper. All requests will be part of an approved research study. Researchers will not be given your name or any other information that could directly identify you.
- Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
- Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

- The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
- There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
- There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

- When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
- The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank staff or reserachers with access to the list must sign an agreement to keep your identity confidential.
- Researchers to whom the University of Rochester sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
- Information that identifies you will not be given to anyone, unless required by law.
- If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part in the optional portion of this study.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, Dr. Jane Liesveld, at 585-275-4099 who will let the researchers know. Then, any sample that remains in the bank will no longer be

used and related health information will no longer be collectd. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, Dr. Jane Liesveld, at 585-275-4099.

Please circle your answer to show whether or not you would like to take part in each option (*include only applicable questions)*:

LEFTOVER SAMPLES FOR THE LABORATORY STUDIES:

I agree to have my leftover specimens collected and I agree that my specimen sample(s) and related information may be used for the laboratory study(ies) described above.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to learn about results from this(ese) study(ies).

YES NO

LEFTOVER SAMPLES FOR FUTURE RESEARCH STUDIES:

My leftover samples and related information may be kept in a Biobank for use in future health research.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other future research related to my participation in this study.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Subject's name (printed):_____

Subject's signature:_____

Date of signature:_____

Person Obtaining Consent

I have read this form to the subject and/or the subject has read this form. I will provide the subject with a signed copy of this consent form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information. I have given the subject adequate opportunity to read the consent before signing.

Investigator's (or approved designee's) name & title (printed):_____

Investigator's (or approved designee's) signature:_____

Date of signature:_____