The Ohio State University Combined Consent to Participate in Research and HIPAA Research Authorization

Study Title: **Sirolimus for Cowden syndrome with colon polyposis**

Principal Investigator: **Peter P. Stanich, MD**

Sponsors: **PTEN Research Foundation and Pfizer Inc.**

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

Patients with Cowden syndrome commonly have colon polyps. Colon polyps are extra tissue or nodules within the large intestine. Some colon polyps have the potential to turn into cancer and we know that removing this kind of colon polyp can reduce the risk of colon cancer in the general population. In the general population, about 25% of people will have a pre-cancerous type of colon polyp at age 50 when they get their first screening colonoscopy. This is usually only 1-2 polyps and they can be removed during the procedure. In Cowden syndrome, many patients have a great number of colon polyps (also called polyposis) when they get their colonoscopy. This can be as many as 50-100 polyps or many more. Cowden syndrome patients also have an increased risk of colon cancer in comparison to the general population. This presents a difficult situation clinically since there are too many polyps to remove them all at colonoscopy. The aim of

this study is to assess the effect of the medication sirolimus on the number of colon polyps.

2. How many people will take part in this study?

This study will include 10 patients.

3. What will happen if I take part in this study?

Patients in this study will take the medication sirolimus for 1 year. There will be a colonoscopy at study onset and then again at study close after 1 year of sirolimus usage. These colonoscopy images will be recorded (both as a recording of the procedural video through the colonoscope as well as still images from the procedure). The visual images of the colon will be used by multiple study investigators to compare any changes in polyp number and polyp characteristics (size, appearance). We will also biopsy and remove colon polyps and assess any changes in their histology (microscopic characteristics). This may include specialized staining of the tissue to see if the sirolimus affected the levels of proteins associated with Cowden syndrome. During the study, there will also be frequent laboratory monitoring (including 4 days after starting medication, at 2 weeks after starting medication, then every 4 weeks for 3 months, then every 3 months until completing the year of therapy) and 5 office visits with physical and well-being assessments to assess any additional changes. For the labs, we estimate up to 8 tubes of blood (~ 100 ml or ~ 7 tablespoons of blood) will be obtained each time as well as urine samples. The office visits will likely be 45 minutes in length.

The colonoscopies and treatment of samples obtained at the time of colonoscopy will be consistent with the usual standard of care with the exception of the recording of the endoscopic video of the procedure. The usual standard of care includes inspecting for colon polyps, removal or biopsy of colon polyps and sending these to the pathology department for interpretation and a report on the histology of the polyp. The recording of the procedure as well as medication usage, laboratory monitoring, physical and well-being assessments, and further analysis of the polyp tissue for Cowden syndrome-associated proteins will be done for research purposes.

4. How long will I be in the study?

This study is planned for 1 year. Each clinic visit will last an estimated 45 minutes. Each colonoscopy will include 3-4 hours of time, with a planned 60 minutes of procedural time and the additional time allotted for pre-procedure evaluation and preparation and post-procedure recovery.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

Sirolimus (also known as rapamycin or Rapamune) is a specific inhibitor of mTOR (mechanistic target or rapamycin, a protein involved in cell growth, replication and life cycle). Sirolimus is United States Food and Drug Administration (FDA)-approved for immunosuppression and use in several types of cancers as chemotherapy. Sirolimus has also been used successfully in hamartomatous syndromes such as lymphangioleiomyomatosis as a treatment. Hamartomous syndromes are diseases which are characterized by the development of a type of tumor known as a hamartoma. These are overgrowths of cells and tissue native to the anatomic location in which they occur and can occur throughout the body. Importantly for this study, Cowden syndrome is a hamartomatous syndrome.

Sirolimus can have significant side effects. There are reports of interstitial pneumonitis (inflammation of the lungs) occurring. This also includes increased susceptibility to infection, lymphoma (blood cancer) and malignancy (cancer), hypersensivity reactions or allergic reactions, dermatitis (severe skin irritation), angioedema (swelling) and fluid accumulation, high cholesterol levels, decline in kidney function, protein in the urine and interstitial lung disease among others. When used in lymphangioleiomyomatosis, the most common adverse reactions (incidence ≥ 20%) are stomatitis (severe mouth sores), diarrhea, abdominal pain, nausea, nasopharyngitis (upper respiratory tract infection), acne, chest pain, peripheral edema (swelling), headache, dizziness, myalgia (muscle pain), and hypercholesterolemia (high cholesterol). In clinical trials for patients with lymphangioleiomyomatosis, 11% of subjects discontinued due to adverse reactions, with no single adverse reaction leading to discontinuation in more than one patient being treated. When used in patients with renal transplants, the most common adverse reactions (incidence ≥ 30%) were peripheral edema (swelling), hypertriglyceridemia (high triglycerides), hypertension (high blood pressure), hypercholesterolemia (high cholesterol), creatinine increased (worsened kidney function), abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia (low blood counts), nausea, arthralgia (joint pains), pain, and thrombocytopenia (low platelet levels which may lead to risk of bleeding). The following adverse reactions resulted in a rate of discontinuation of > 5% in clinical trials for renal transplant rejection prophylaxis: creatinine increased (worsened kidney function), hypertriglyceridemia (high triglycerides), and thrombotic thrombocytopenic purpura (severe disorder which can cause low platelets and blood clots).

Also of note, a short clinical trial involving sirolimus use in Cowden syndrome for 2 months was previously completed at an outside institution. They reported no serious adverse effects, but did have a high rate of minor adverse effects including: stomach pain, diarrhea, constipation, fatigue, headache, dry skin, mucositis (mouth sores), nausea, insomnia, rash, and gastritis (inflammation of the stomach lining). Common laboratory abnormalities included low phosphate (12%), low white blood cell count (6-12%), change in hemoglobin (45%), change in platelets (6%), low protein levels (12%), liver function test abnormalities (11-33%), change in magnesium (11%), high cholesterol and triglycerides (22-28%), high calcium (6%), and change in glucose (6-11%).

There is also a low risk associated with each of the blood and urine collections, which are performed to monitor for adverse reactions to the medication. This includes pain, bleeding and bruising.

The colonoscopies performed during the course of this trial will include the standard risks of lower endoscopy, polyp biopsy and removal and procedural sedation. This includes risk of perforation (poking a hole in the colon), bleeding, post-procedural pain and adverse reaction to the medications used for sedation among others. An intravenous line will also be placed prior to the procedure. These would be the same risks as the standard of care colonoscopies you would be receiving.

7. What benefits can I expect from being in the study?

The potential benefit of the study is the possibility of reduction in number of colon polyps.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

9. What are the costs of taking part in this study?

The potential costs to be in this study include travel and lodging as needed prior to clinic visits. No additional costs for study procedures are anticipated (the colonoscopy procedure and bowel preparation, biopsies and pathology assessment, clinic visits, laboratory testing and study medications will be covered by the study).

10. Will I be paid for taking part in this study?

To assist with the potential costs of travel and lodging, you will be paid $400 after each research visit. This will be paid to you via ClinCard, a research debit card.

Payment received as compensation for participation in research is considered taxable income. If your total payments exceed $600 in any one calendar year, this must be reported to the Internal Revenue Service (IRS). The Ohio State University will issue you an IRS Form 1099.

11. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center. The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

13. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

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

14. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and present medical records;
- Research records;
- Records about phone calls made as part of this research;
- Records about your study visits;
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual;
- Information gathered for this research about:

Physical exams
Colonoscopy results
Pathology results
Laboratory, x-ray, and other test results

- Records about any study drug you received;

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician's office record;

IV. Your information may be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities;
- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported; and
- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

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

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your authorization will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, 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.

VIII. 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 and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

15. Who can answer my questions about the study?

For questions, concerns, or complaints about the study, or if you feel you have been harmed as a result of study participation, you may contact:

- Peter P Stanich MD (Principal investigator)
    - Phone: (614) 293-6625
    - Email: peter.stanich@osumc.edu

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact:

- HIPAA Privacy Officer
    - Address: Suite E2140, 600 Ackerman Road, Columbus, OH 43201
    - Phone: 614-293-4477

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact:

- Ms. Sandra Meadows (Office of Responsible Research Practices)
    - Phone: 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact:

- Peter P Stanich MD (Principal investigator)
    - Phone: (614) 293 -6625
    - Email: peter.stanich@osumc.edu

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**
Relationship to the subject	**AM/PM**
	Date and time

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time