APPENDIX B-1

CONSENT FORMS

PARTICIPANT INFORMED CONSENT

IRB #

Informed Consent to Participate in Research

***If you are a parent**, as you read the information in this Consent Form, you should put yourself in your child's place to decide whether or not to allow your child to take part. Therefore, for the rest of the form, the word "you" refers to your child.*

***If you are a child, adolescent or adult** who is reading this form, the word "you" refers to you.*

You are being asked to take part in a research study. This form tells you about the study. The Principal Investigator (the person in charge of this research) or a co-worker of the Principal Investigator will also describe this study to you and answer all of your questions. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. Your taking part is entirely your choice.

1. Name of the Subject ("Study Subject")

2. Title of Research Study

A Randomized Double-blind Trial of Fluconazole Versus Voriconazole for the Prevention of Invasive Fungal Infections in Allogeneic Blood and Marrow Transplant Patients

3. Principal Investigator Contact Information

Contact information for emergencies after hours or on weekends or holidays:

Call (xxx) xxx-xxxx, the in-patient Bone Marrow Transplant Unit. Ask to speak to the Charge Nurse.

4. Sponsor and Source of Funding or Other Material Support

The sponsor of this study, The National Institutes of Health (NIH), is providing the study drugs and research tests free of charge to study subjects through the Blood and Marrow Transplantation Clinical Trials Network (BMT CTN), a group of 32 U.S. transplant centers.

5. What is the purpose of this study?

You are being asked to take part in this research study because you are having a blood or bone marrow transplant (BMT) using cells from another person.

One of the most common side effects of BMT is a decrease in the number or strength of infection fighting cells (white blood cells) in the body. Infections are caused by bacteria, viruses or fungi. When white blood cell numbers are low or the cells are weak, the body can't fight infections. For this reason, all BMT patients take drugs to prevent infection by these germs.

Fungal infections are one of the worst forms of infection. One of the drugs used to both prevent and treat fungal infections is called fluconazole. Fluconazole prevents some, but not all, types of fungal infections. Voriconazole is a newer antifungal drug that can treat more types of fungal infections than fluconazole. But, voriconazole has more side effects than fluconazole. Although voriconazole is used to treat severe fungal infections, it has not yet been tested for the prevention of fungal infections.

The purpose of this study is to compare fluconazole and voriconazole in the prevention of fungal infections in blood or marrow transplant patients where another person is the donor. About 600 patients will take part in this study at many centers around the country.

6. What will be done if you take part in this research study?

Before starting treatment in this study, your doctor will check your general health. This will include a physical exam and taking blood (about 3 teaspoons or 10-20 mL for adult patients). A CT scan of the chest will be required if the results of the baseline galactomannan blood draw are not available. A CT scan is a type of x-ray that takes many detailed pictures. A chest CT scan results in an estimated dose of 0.8 rem, equivalent to 2.25 years of naturally occurring background radiation in the United States. A CT scan of the abdomen and/or sinuses may be required. An abdomen CT results in 1.1 rem, equivalent to 3 years. A head (sinus) CT results in 0.55 rem, equivalent to 1.7 years of background. If you are a female able to have children, a pregnancy test will also be performed. If you are pregnant, you will not be able to take part in this study.

If you choose to take part in this study, you will be randomly assigned (much like the toss of a coin) to receive either fluconazole or voriconazole. You and your study doctor will not know whether you are receiving fluconazole or voriconazole. This is called a double-blind study. In an emergency, the name of your drug can be obtained quickly. Treatment will begin on the day of your transplant (Day 0).

Since voriconazole is given twice per day and fluconazole only once per day, a placebo (a pill with no active drug or a salt water infusion) will be used to keep us from knowing which drug you are receiving. You will take the assigned drug twice a day. Whenever possible, the drug will be given as pills. If you are unable to take pills, the drug will be given over two hours by an IV infusion through your catheter. If you have been assigned to fluconazole, one of the pills (or infusions) will be a placebo since fluconazole is normally taken once daily.

You will continue the study drug until 100 days after your transplant. At around 90 to 100 days, your doctor will test your immune function and review your immunosuppressive drugs. If your risk of fungal infection is high, you will stay on study drug until 180 days. The study drug will stop by 180 days. But your doctor can give you an antifungal drug for longer if he/she believes you need it.

While you are in the study, your doctor will conduct routine and study-specific tests (such as x-rays, CT scans, or blood tests) and check you for a fungal infection. The table below shows when you will have study-required blood tests. The tests are described after the table.

Time	Amount of Blood per Draw (adults)*	Type of Test / Purpose** Standard of Care[S] / Investigational[I]
Pre transplant	1 teaspoon (5 mL) 1 teaspoon (5 mL) 1 teaspoon (5 mL)	Liver function tests[S]/ eligibility Galactomannan assay[S]/ eligibility Future testing[I]/ research
3x/week until engraftment	1 teaspoon (5 mL)	CBC[S]/ blood chemistry
1x/week until Day 100. Also on Day 120, 150 and 180 if patient remains on study drug	1 teaspoon (5mL)	Liver function tests[S]/ check for bad side effects
Day 14 and 28	1 teaspoon (5 mL)	Pharmacokinetics (PK) [I]/ test for drug levels
2x/week, Days 1 – 60	1 tablespoon (15 mL)	Galactomannan (GM) assay[S] and Investigational Fungal Diagnostics[I]/ tests for fungal infections
1x/week***, Days 61 – 100	1 tablespoon (15 mL)	GM assay[S] and Investigational Fungal Diagnostics[I]/ tests for fungal infections
If you have bad side effects	1 teaspoon (5 mL)	PK[I]/ test for drug levels
If doctor suspects you have a possible fungal infection	4 teaspoons (20 mL) at onset 1 tablespoon (15 mL) 2x/week for up to 14 days while on empirical antifungal therapy	PK[I]/ test for drug levels, GM assay[S] and Investigational Fungal Diagnostics[I]/ tests for fungal infections GM assay[S] and Investigational Fungal Diagnostics[I]/ tests for fungal infections
If you get a fungal infection	4 teaspoons (20 mL) at onset 1 tablespoon (15 mL) 2x/week for 4 weeks and then once every 2 weeks for 8 weeks, for a total of 12 samples	PK[I]/ test for drug levels, GM assay[I] and Investigational Fungal Diagnostics[I]/ tests for fungal infections GM assay[I] and Investigational Fungal Diagnostics[I]/ measure response to treatment

* Pediatric patients less than 12 years old will provide one-half of the required amounts of blood. The center may make adjustments in blood volumes collected from patients less than 12 years old to meet the institution's Human Investigation Committee Guidelines.

** Tests that are typically done for your care are considered standard of care. These tests will be charged to you. Tests that are done solely for research purposes are considered investigational and will not be charged to you.

*** Patients will be tested twice weekly from Days 61-100 if they (1) received a T cell depleted transplant (a transplant where certain white cells have been removed to reduce the risk of GVHD) and post transplant GVHD prophylaxis (medications designed to prevent GVHD), or (2) have or have had GVHD (a condition in which the donated cells recognize the recipient's cells as non-self and attack them) requiring systemic therapy, or (3) are taking steroids.

Blood (1 tablespoon or 15 mL) will be taken prior to the transplant to determine eligibility for the study. A small sample (1 teaspoon or 5 mL) will be saved for future testing.

Blood samples (1 teaspoon or 5 mL) will also be taken 3x/week to determine engraftment (when the infused stem cells begin to multiply its own cells in your bone marrow). Engraftment typically occurs within 1-4 weeks post-transplant.

Weekly blood tests (about 1 teaspoon or 5 mL) will be taken for the first 100 days (and on Day 120, 150 and 180 if you remain on study drug) to check for bad side effects. Blood (1 teaspoon or 5 mL) will also be taken to measure drug levels at about Day 14 and 28, plus if you develop any bad side effects possibly related to the study drug, and at the start of a fungal infection. Usually, blood can be taken from your central venous catheter. In addition, we will also take blood (about 1 tablespoon or 15 mL), twice a week for the first 60 days of the study, and extra samples if your doctor suspects you have an infection to see if new tests can detect a serious fungal infection earlier and more easily than current tests.

Blood samples will also be taken once per week from Days 61-100 unless: (1) you received a T cell depleted transplant and received post-transplant GVHD prophylaxis or, (2) you are on steroids, or (3) you have or have had acute GVHD requiring systemic therapy. Then blood samples will be taken twice weekly from Days 61-100. Other tests will also be done to see which treatment is more effective in treating infections.

If your doctor suspects a fungal infection he/she may give you a drug (amphotericin B, Ambisome, Abelcet, Amphotec or Caspofungin) to treat it while he/she is reviewing your symptoms. You will continue to receive the study drug. If the tests do not show a fungal infection, your doctor will stop the other drug within 14 days. If your doctor believes that you need the other drug after 14 days, then he/she will continue it but the study drug will stop. You will continue to be tested as part of the study for the full year. Your doctor will still do the research tests, including the blood tests described above just as if you were taking the study drug.

If you get a fungal infection, the study drug will be stopped and another therapy will be discussed with you. This could include voriconazole if your doctor believes it to be the best choice. Your blood will be tested twice weekly for four weeks and then once every two weeks for eight weeks, for a total of 12 samples, to test your response to treatment.

This study will employ a new test approved by the FDA for detecting fungal infections in adults using blood samples. It is called the galactomannan test.

Galactomannan is a part of the fungus that gets into the blood of infected patients. Some (1 teaspoon or 5 mL) of the blood samples described above will be used for this test.

This galactomannan test will be used with other standard tests to check you for certain kinds of fungal infection. The results will be used along with your medical history, physical check up, and other laboratory tests to judge whether you have or may have an infection. If you have a procedure on your lungs known as a bronchoscopy to test for an infection, a small part of the fluid obtained will be saved for later testing by the galactomannan test and other investigational tests to see if these new tests are better than the tests used now. The galactomannan test will also be used to test response to treatment if you develop an infection.

It is not yet clear if the galactomannan test will be better than the old tests and it is possible that it may not be as good in patients receiving one of the study drugs and certain other antifungal drugs, including amphotericin B and caspofungin. One good thing about this new test is that it requires only a sample of blood rather than a biopsy of tissue or other more uncomfortable tests. It also may show infection earlier. However, it may not be as exact. This could mean that if the test is positive and you really are not infected, you may receive treatment you don't need or if the test is negative and you really are infected, you may not receive treatment you need. For these reasons, your doctor will be using several kinds of tests for your safety. Results from this study will be used to measure the new test's value.

After your treatment is complete, we would like to keep track of your progress until 12 months after your transplant. To do this, we will contact you or your local doctor.

7. Will You Provide Samples for Research?

Genetic material is any sample of blood, tissue, fluid, etc. that is obtained from you. You will be asked to provide samples of blood, tissue and fluid to be used solely for future research and testing in laboratories where we are studying fungal infections. These samples will not require additional procedures. Your name will not be on these samples. You do not have to agree to provide these research samples to participate in the study.

If you agree, a small blood sample (1 teaspoon or 5 mL) will be drawn pre-transplant and saved for future testing. Additional blood samples (2 teaspoons or 10 mL) will be taken, if you agree, each time samples are drawn to test for galactomannan. Usually the blood can be drawn from your central venous catheter at the time of other blood collections. If this is not possible, then it would be drawn directly from a vein.

If you agree, small samples of tissue or fluid (1 mL) will be collected post-transplant and saved for future testing. These samples will be taken from samples that are collected for diagnosis of potential fungal infections. Additional procedures are not required.

The samples collected for research purposes will be sent to laboratories that have contracts with the National Marrow Donor Program (NMDP) to conduct these research tests. They will be labeled with unique codes that do not contain information that could identify you. A link to this code does exist. The link is stored at the Data Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The staff at the laboratories where your samples are being tested do not have a link to this code. Your samples will be stored at these laboratories until the entire sample has been used for the research tests or until the end of the study.

If any of your samples are leftover after the research studies are completed, these samples will either be destroyed or be sent to the National Heart Lung and Blood Institute (NHLBI) sample repository in Maryland. If your leftover samples are sent to the repository, they will be given an anonymous code. These leftover samples stored at the repository can never be linked to you. Any research performed on these left-over samples must first be approved by an advisory panel at the NHLBI.

If you agree to allow your blood, tissue and fluids to be kept for research, you are free to change your mind at any time. We ask that you tell [the Principal Investigator] in writing and let him/her know you are withdrawing your permission for your samples to be used for research. The mailing address is on the first page of this form. Any unused samples will be destroyed. **You are free <u>not</u> to take part in this future research and still take part in the other parts of the study. There will be no change in your care if you decide not to give these extra samples. Please mark your choice below for each sample:**

(1) <u>Pre-transplant 5 mL blood sample</u>

- ❑ **I agree to have a blood sample drawn pre-transplant for future research and testing.**
- ❑ **I do not agree to have a blood sample drawn pre-transplant for future research and testing.**

(2) <u>Post-transplant 10 mL blood samples taken each time blood samples are taken for the galactomannan (GM) assay</u>

- ❑ **I agree to have blood samples drawn post-transplant for future research and testing.**
- ❑ **I do not agree to have blood samples drawn post-transplant for future research and testing.**

(3) Post-transplant tissue and fluid samples each time samples are taken post-transplant for diagnosis of fungal infections

- ☐ **I agree to have tissue and fluid samples collected post-transplant for future research and testing.**
- ☐ **I do not agree to have tissue and fluid samples collected post-transplant for future research and testing.**

_____ _____

Signature Date

8. What are the possible discomforts and risks?

Cancer treatments can cause bad side effects, some of which may be life threatening or could kill you. The drugs used in this study may cause all, some, or none of the side effects listed below. Also, there is always the chance of unexpected new side effects.

The most common side effect in patients who have received voriconazole has been a change in eyesight that was often described as a "brightness" in vision that usually lasts less than one hour. Some patients treated with voriconazole have reported temporary glare or blurred vision. The effect may begin within 30 minutes after taking a dose of voriconazole and lasts an average of one-half hour but may last up to one hour. You should not drive or operate machinery during these periods. The next most common side effect was abnormal liver tests.

The following side effects have been reported in more than 1% of patients who have received voriconazole: a reaction at the site of injection, photosensitivity (a rash caused by sunlight), weakness, dizziness, headache, trouble sleeping, dry mouth, nausea, stomach pain, and low potassium levels. Other side effects that have been reported in at least one patient that was treated with voriconazole include: skin rash, skin erythema (redness), psoriasis (scaling) with eosinophilia (an abnormal blood condition), hypoglycemia (low blood sugar), hepatitis (liver disease), nausea, vomiting and jaundice (yellow skin), pancreatitis (a disease of the pancreas with pain in the stomach), decrease in the number of cells in the bone marrow (this was reported in a patient who had leukemia before starting voriconazole), and irregular heartbeat. An irregular heartbeat resulting in death occurred during treatment in a patient who had a history of an irregular heartbeat before entering the study. The patient also had a history of cancer and was on chemotherapy and many other drugs (including a potassium infusion, which may have affected the heart beat). In addition, an irregular heartbeat possibly related to taking voriconazole with the medications pimozide,

quinidine, dofetilide, and quinupristin-dalfopristin (an antibiotic) has been reported. One patient with leukemia, who was also taking this antibiotic, was hospitalized because of faintness and palpitations (rapid heartbeats).

Voriconazole may increase or decrease levels of other commonly prescribed drugs and non-prescription drugs. Drugs known to interact with voriconazole include warfarin, phenytoin, cyclosporine, tacrolimus, sirolimus, rifabutin, ompreazole and rifampin. Other drugs that may interact with voriconazole include ritonavir, lovastatin (and other statins), benzodiazepines, sulfonylureas, clarithromycin, terfenadine, astemizole, cisapride, dihydropyridine calcium channel blockers (verapamil, diltiazem), certain chemotherapy drugs (vinca alkaloids) and cabamazepine. We ask that you consult with your doctor before starting new drugs or increasing the dose of any drug including non-prescription drugs or herbs such as St. John's Wort. Grapefruit juice should be avoided. Other drugs that you may be taking may need to be changed or stopped in order for you to receive voriconazole.

The most frequent side effects after treatment with fluconazole affect the gastrointestinal tract (stomach and intestines) such as nausea and vomiting. Other side effects include dizziness, headache, skin rash, and liver problems. Serious side effects which have been reported with fluconazole include: liver damage which included deaths primarily in patients with serious medical conditions; elevated liver tests; severe skin disorders; hepatitis (liver disease), jaundice (yellow skin), irregular heartbeats or heart function changes; and acute allergic reactions.

The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely, an infection; and, uncommonly, faintness from the procedure.

Only you, the person for whom it has been prescribed, can take the study drug. If the drug is not packaged in a childproof container, you should keep it out of the reach of children and persons who have limited ability to read or understand. By federal law, this drug cannot be given or transferred to anyone for whom it is not prescribed.

As noted earlier, a new test, the galactomannan test, will be used along with other tests to see if you have an infection and will be used to test your response to treatment if you develop an infection. It is possible that this test may be less exact in patients taking one of the study drugs (voriconazole) when compared to the other (fluconazole). It is hoped that information from the study will help show that the new test can quickly and easily detect fungal infections.

Throughout the study, the researchers will tell you of new information that might affect your decision to remain in the study.

If you wish to discuss the information above or any other discomforts you may experience, you may ask questions now or call the Principal Investigator or contact person listed on the front page of this form.

9a. What are the possible benefits to you?

Although this study cannot be guaranteed to be of benefit to you, it is hoped that your taking part may prevent you from getting a fungal infection. A possible advantage of this study is that one antifungal treatment may prevent fungal infections better than the other. However, you may not benefit from this treatment. The use of the galactomannan test along with other diagnostic tests may allow us to more quickly and more easily diagnose fungal infections and determine how well you respond to treatment if you develop an infection. However, there is no guarantee that this test is better than the currently available tests.

9b. What are the possible benefits to others?

Future patients may benefit from the results of this study.

10. If you choose to take part in this study, will it cost you anything?

Your cost for care on this research study will not be higher than for standard treatment for this disease. The BMT CTN will cover the cost of the study drug. You will remain responsible for the costs of standard treatment for your disease. Your insurance provider may not cover all or part of these costs. You or your family will have to pay installments based on your verified ability to pay. Any questions about these charges should be discussed with the Principal Investigator of the study.

11. Will you receive payment for taking part in this research study?

No.

12. What if you are injured because of the study?

If you experience an injury that is directly caused by this study, only the professional medical care you receive at the [participating clinical facility] will be provided without charge. You or your insurance provider will pay hospital expenses. No other compensation is offered. If you have any questions about study-related injuries, you may call [insert name of person at institution] at [insert phone number].

13. What other options or treatments are available if you do not want to be in this study?

Taking part in this study is entirely up to you. You are free to refuse to be in the study, and your refusal will not affect current or future health care you receive at this institution. You and your doctor will discuss any other treatment options available to you.

The current standard therapy for preventing fungal infections in patients receiving bone marrow or stem cell transplant is fluconazole. Your doctor will review other treatments with you.

14a. How can you withdraw from this research study?

If you agree to be in this study, you are free to change your mind. At any time you may withdraw your consent to be in this study and for us to use your data. If you withdraw from the study, you will continue to have access to health care at [participating clinical facility]. If you decide to withdraw, we ask that you tell [the Principal Investigator] in writing; his/her mailing address is on the first page of this form. If you do withdraw your consent, there will be no penalty and you will not lose any benefits to which you are otherwise entitled. You will be asked to return any unused study drug. You will also be asked to return for a checkup before you stop your study drug. Even if you withdraw, or your doctor withdraws you, from the study, you are asked to have research tests conducted and allow the study investigators to collect that information.

If you have any questions about your rights as a study subject, you may call the Institutional Review Board (IRB) office at (xxx) xxx-xxxx.

14b. If you withdraw, can information about you still be used and/or collected?

If you withdraw from the study, we ask that you agree that we can continue using all information about you that has already been collected as part of the study prior to your withdrawal, and to continue to allow your doctor to tell us about your progress until 12 months after your transplant. You may, of course, say no.

14c. Can the Principal Investigator withdraw you from this research study?

You can be taken off the study (with or without your consent) for any of the following reasons:

- You do not qualify to be in the study because you do not meet the study requirements. Ask your doctor if you would like more information about this.
- You need a medical treatment not allowed in this study.
- The investigator decides that continuing in the study would be harmful to you.
- The study treatments have a bad effect on you.
- You become pregnant and the study treatment could be harmful to the fetus.
- You are unable to keep appointments or take study drugs as directed.
- Other study-specific reasons; for example, if the dose of study drug you are taking has been found to be unsafe.
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH).

15. How will your privacy and the confidentiality of your research records be protected?

Study records that have your name will be kept private as required by law. You will not be identified by name in the central study records. Your records will be given a unique code number. The key to the code will be kept in a locked file in the Principal Investigator's office. Authorized persons from [the participating clinical facility], the hospital or clinic (if any) involved in this research, and the Institutional Review Board have the legal right to review your research records and will protect their confidentiality to the extent permitted by law. This research study is sponsored by and conducted with funds from the National Institutes of Health; therefore, the sponsor, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), the investigators conducting this study and the FDA also have the legal right to review your research records. Otherwise, your research records will not be shown to anyone without your consent unless required by law or a court order.

If the results of this research are published or presented at scientific meetings, your name will not be disclosed.

Information related to or resulting from your stem cell transplant will be reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a voluntary organization of basic and clinical scientists working together in an effort to gather

information on results of stem cell and marrow transplants. This information is used to guide clinical decisions and identify ways to improve transplant outcomes. Scientific data or medical information (not identifiable with you) that could be useful to others may be presented at meetings and/or published in medical journals.

16. Expiration date for retention of records

The study results will stay in your research record at (*insert Institution*) for at least six years or until after the study is completed, whichever is longer. At that time either the research information not already in your medical record will be destroyed or your name and other identifying information will be removed from such study results. Research information in your medical record will be kept indefinitely.

17. How will the researcher(s) benefit from your being in this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator may benefit if the results of this study are presented at scientific meetings or in the scientific press. In addition, the sponsor is paying the Principal Investigator to conduct this study.

18. HIPAA[2] authorization to use and disclose individual health information for research purposes

a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *A Randomized, Double-blind, Trial of Fluconazole vs. Voriconazole for Prevention of Invasive Fungal Infections in Allogeneic Blood and Bone Marrow Transplant Patients*.

b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., CT scan, blood tests, biopsy results).

[2] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from:

(*list hospitals, clinics or providers from which health care information can be requested)*

_____

_____

_____

d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff
- Dr. John Wingard, Study Chairperson and staff/laboratories at University of Florida College of Medicine
- Dr. Thomas Walsh, Study Chairperson and staff/laboratories at NIH/NCI/POB
- Staff/laboratories identified in the protocol for the evaluation of other laboratory samples; e.g., Dr. Patricia Fraser/Harvard
- National Heart, Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data coordinating center
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

e. Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this

authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

g. Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

h. This authorization does not have an expiration date.

19. Consent and Assent Instructions

Consent: Subjects 18 years and older must sign on the subject line below. For subjects under 18, consent is provided by the Legally Authorized Representative

Assent: Is required for subjects under the age of 18, using the Assent Section on the following page.

I have been informed about this study's purpose, procedures, possible benefits and risks. I have been given the chance to ask questions. My questions have all been answered satisfactorily. I understand that I can ask other questions at any time.

I voluntarily agree to take part, or to allow my child to take part, in this study.

By signing this consent form, I have not given up any of the legal rights that I (my child) otherwise would have as a subject in a research study.

_____ _____
Subject's Signature Date

If you are not the subject, please print your name_____
and indicate one of the following:

_____	The subject's parent	_____	The subject's guardian
_____	A surrogate	_____	A durable power of attorney
_____	A proxy	_____	Other, please explain:

_____ _____
Legally Authorized Representative Signature Date

As a representative of this study, I have explained the purpose, the procedures, the benefits, and the risks that are involved in this research study:

_____ _____
Signature of person conducting informed consent Date

ASSENT SIGNATURES: For subjects under the age of 18 years.

Assent of Minor
I have been told what I will be asked to do if I am in this study. I have been told that I don't have to be in this study. I may quit the study at any time, and no one will be mad at me. I have had a chance to discuss the study and ask questions. My questions have been answered. I agree to be in the study and do what I am asked to do so long as I continue in the study.

_____ _____ _____
Signature of Minor Date Age (years)

Study Personnel

I have explained the purposes, procedures, and risks involved in this research study in detail to:

_____
Print name(s) of Parents/Authorized Consenting Party, **and**

_____, who in my opinion_____IS/___IS NOT capable of assenting to participate in this study.

Print child's name

_____ _____
Signature of Person Conducting Assent Date

APPENDIX B-2

CONSENT FORMS

DONOR INFORMED CONSENT FOR SNP ASSAY

CO-PRINCIPAL INVESTIGATORS: John R. Wingard, M.D. and Thomas J. Walsh, M.D.

STUDY TITLE: **A Randomized, Double-blind, Trial of Fluconazole vs. Voriconazole for Prevention of Invasive Fungal Infections in Allogeneic Blood and Bone Marrow Transplant Patients**

INTRODUCTION

We invite you to take part in a research study sponsored by the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with your family, friends, or your personal physician or other health professional.

PURPOSE

During the course of this study, we will attempt to learn about genetic factors that may have an influence on infections due to invasive fungal infections. This type of infection occurs in individuals with a breakdown in the body's immune system, due to either medications, (such as corticosteroids) or in those who have had bone marrow transplantation. We are interested in studying the small variations or differences in genes, called polymorphisms or variants that could effect the body's ability to fight off invasive fungal infections. We also will study genes that help the body eliminate fluconazole and voriconazole from the blood stream. We have identified a collection of genes (twenty-six), each of which has one or more polymorphism. We would like to analyze your DNA for these twenty-six genes to see if any of these genes are associated with fungal infections. We invite you to participate in this study so that we can learn more about these genetic

factors that may influence the susceptibility and severity of fungal infections in those who undergo blood or marrow transplantation.

PROCEDURES

Five (5) milliliters of blood or stem cell product will be used for the genetic analysis. We ask that you submit a sample of no more than 5 mL, equivalent to one teaspoon. It may be necessary to perform a buccal swab of the inside of your mouth to obtain genomic DNA if blood is unable to be drawn. If you withdraw from the study, your samples will not be used for other research studies or tested further.

Clinical information (e.g., HLA typing) about you/your child will be collected. NIH will not have access to the names of the patients enrolled in this study. The clinical information will be coded and compared to the genetic analysis of the twenty-six genes chosen for our study: *MBL2, CCR5, IL1RN, IL1A, IL1B, IL6, IL8, IL8RA, IL8RB, IL10, TNFA, TNFB, MPO, NRAMP1, CHIT1, FCGR2A, FCGR3A, FCGR3B*, MICA, MICB, TLR4, CD14, HBD-1, IL-18 and two cytochrome P450 genes (3A4 and 2C19). In the laboratory, we will isolate DNA from your blood or stem cell product and test for each of these genes by standard techniques. We shall determine normal and variant sequences in DNA and compare this information to the clinical information collected.

ALTERNATIVES

You may choose not to participate in this part of the study. The decision to participate in this study will not affect the care given to you by your physicians.

RISK AND DISCOMFORT

It is possible that the information from this study could be important for family members (even though no blood and no analysis of family members are proposed). However individual results will not be reported directly to you.

There is a small risk of an infection or fainting from the blood draw. If blood is not available, a buccal swab from the inside of your mouth needs to be performed by a health care provider. This may result in minimal discomfort in the mouth during the time the cotton swab is rubbed against the inside of the cheek of your mouth.

At no time will this information be made available to those not directly involved in the study without your written consent. Patient information will not be made public. Only the results of the proposed analysis will be collected, presented and published. At no time, will

the name or an identifier of patients be available to anyone except those conducting the study. The investigators who will conduct the genetic analysis will not have access to the names of the patients enrolled in this study. The clinical information will be coded and compared to the genetic analysis of the twenty-six genes chosen for the study.

BENEFITS

This study will increase our understanding of the factors that influence the risk for developing and treating fungal infections during bone marrow transplantation. We hope that it will eventually contribute to improvements in medical care, treatment and prevention of these types of infection. There may be no direct benefit to you or your family from this study. If there are any questions, we will attempt to answer them with the most recent information.

SAMPLES FOR RESEARCH AND FUTURE TESTING

Genetic material is any sample of blood, tissue, fluid, etc. that is obtained from you. You will be asked to provide a sample of blood, stem cell or buccal product to be used solely for future research and testing in laboratories where we are studying fungal infections. This sample will not require additional procedures. You do not have to agree to provide this research sample to participate in the study.

A portion of your 5 mL blood sample, stem cell product or buccal swab product, if you agree, will be saved for future testing and research related to infectious diseases or the immune system. These tests may include genetic analysis of your DNA beyond the 26 genes identified in this document.

The samples collected for research purposes will be sent to laboratories that have contracts with the National Marrow Donor Program (NMDP) to conduct these research tests. They will be labeled with unique codes that do not contain information that could identify you. A link to this code does exist. The link is stored at the Data Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The staff at the laboratories where your samples are being tested do not have a link to this code. Your samples will be stored at these laboratories until the entire sample has been used for the research tests or until the end of the study.

If any of your samples are leftover after the research studies are completed, these samples will either be destroyed or be sent to the National Heart Lung and Blood Institute (NHLBI) sample repository in Maryland. If your leftover samples are sent to the repository, they will be given an anonymous code. These leftover samples stored at the repository can never be linked to

you. Any research performed on these leftover samples must first be approved by an advisory panel at the NHLBI.

If you agree to allow your blood, stem cell or buccal product to be kept for research, you are free to change your mind at any time. We ask that you tell [the Principal Investigator] in writing and let him/her know you are withdrawing your permission for your sample to be used for research. The mailing address is on the first page of this form. Any unused sample will be destroyed. **You are free <u>not</u> to take part in this future research and still take part in the other parts of the study. There will be no change in your care if you decide not to give this extra sample. Please mark your choice below:**

- ❑ I agree to use of a sample of my blood, stem cell or buccal swab product for additional research or future testing.
- ❑ I do not agree to use a sample of my blood, stem cell or buccal swab product for any additional research or future testing.

_____ _____

Signature Date

HIPAA[3] AUTHORIZATION TO USE AND DISCLOSE INDIVIDUAL HEALTH INFORMATION FOR RESEARCH PURPOSES

1. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *A Randomized, Double-blind, Trial of Fluconazole vs. Voriconazole for Prevention of Invasive Fungal Infections in Allogeneic Blood and Bone Marrow Transplant Patients*.

2. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: Demographic information (e.g., age, date of birth, sex, weight), medical history, physical examination findings, and genetic test results.

[3] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

3. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from (*list hospitals, clinics or providers from which health care information can be requested):*

_____

_____

_____

4. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item 3 and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff
- Dr. John Wingard, Study Chairperson and staff/laboratories at University of Florida College of Medicine
- Dr. Thomas Walsh, Study Chairperson and staff/laboratories at NIH/NCI/POB
- Staff/laboratories identified in the protocol for the evaluation of other laboratory samples; e.g., Dr. Patricia Fraser/Harvard
- National Heart, Lung and Blood Institute (NHLBI) and National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data coordinating center
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

5. Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

6. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

7. Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

8. This authorization does not have an expiration date.

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. **Payments.** The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. **Problems or Questions.** If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator at (xxx) xxx-xxxx.

5. **Consent Document.** Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM BELOW, A or B

A. Adult Patient's Consent.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

_____
Signature of Adult Patient & Date Signed

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM _____ THROUGH _____.

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable)

_____
Signature of Parent(s)/Guardian & Date Signed

If other than parent, specify relationship: _____

Child's Verbal Assent (if applicable).

The information in the above consent form has been adequately described to my child in language that my child can understand, and my child willingly agrees to participate in the study.

_____
Signature of Parent(s)/Guardian & Date Signed

_____
Signature of Investigator & Date Signed

_____
Signature of Witness & Date Signed