Title: Connectivity Affecting the Antidepressant Response (CAARE)
Consent form for depressed participants

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This informed consent applies to depressed adults age 60 or above

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study. Anyone you authorize to receive your medical record will also get this note.

1. What is the purpose of this study?

You are being asked to take part in this research study because you have depression and are age 60 years or older. We have known for a long time that individuals with depression respond differently to antidepressant medications. For example, one individual may do very well with a given medication, while another individual may not respond at all. There is currently no way to determine how an individual will respond to any given medication.

We think that differences in how people respond to medication are related to differences in brain function and connections between brain regions. When someone is depressed, we see on brain imaging that their brain may work differently than people who are not depressed. When depression improves with treatment, brain function appears to become normal. We think that individual differences in brain function and brain connections during depression may contribute to why people respond differently to antidepressant medications.

The purpose of the study is to better understand the relationship between brain function and brain connectivity and how adults over the age of 60 years respond to antidepressant medications. For this study, we will examine two different antidepressant medications that have different ways of working. We will examine escitalopram, also known as Lexapro, and bupropion, also know as Wellbutrin. Both medications are commercially available and approved by the U.S. Food and Drug Administration for the treatment of depression. We plan to enroll up to 200 depressed individuals and 55 non-depressed controls for this study over five years.

2. What will happen and how long will you be in the study?

If you agree to be in this study, you will first be asked to sign and date this consent form. The study has two phases. Phase 1 will last at least 8 weeks, and Phase 2 will last an additional 9 weeks. Before starting the study medication, you will have a clinical assessment, memory testing, and a brain MRI scan. If you are currently depressed and taking an antidepressant, we will need to stop it before you can start the study medication.

Phase 1 'Assessment Visit': During the initial visit, you will meet both with the study coordinator and the study doctor. Your medical and psychiatric history will be carefully reviewed to make sure that you are eligible for the study. Additionally, we will assess your current depression symptoms as well as your current and past medication use. You do not have to answer any questions you do not feel comfortable answering. The interview with the study coordinator will take about 90 minutes. Your visit with the study doctor will take about an hour.

For your safety, you must tell your study doctor about all the medications you are taking, including over-the-counter drugs and herbals, before you start the study and before taking any new medications while you are on the study.

As part of this visit, we will carefully evaluate you to determine if you have any metal in your body that could stop you from having the MRI. If you have had surgeries that used implanted metal objects, we will need to request medical records to assure your safety before you could proceed to MRI. If you have had surgeries where records are not available and you do not think those surgeries included metal, we may ask you to have an x-ray of that part of your body to make sure there is no metal in that site.

During this visit, you will also have an option to complete a "mock" MRI scan. Although no actual scan is taken, you will be able to experience the process (getting on and off the table, being inside the scanning tube, hearing the sounds the machine produces during a scan) to make sure you are comfortable with having an MRI scan.

Stopping Current Antidepressants: If eligible and willing to participate, and you are taking a medication for depression, your study doctor will work with you on a plan to safely stop that medication. He will develop a schedule that will slowly reduce and stop your current antidepressant. Depending on your individual medical history, this may take several days or a few weeks. During this time, we will speak to you at least weekly by telephone to make sure that you are not having any problems coming off the medication and that your depression is not worsening. If you want to come for in-person visits, we can do this as well. Once you are off your current antidepressant, you will return for the Phase 1 'Testing Visit'.

Phase 1 'Baseline Visit': This will be an in-person visit with your study doctor who will again assess your depression symptoms. During this visit, you will complete the memory testing and MRI scan. This visit can last about half of the day. Due to scheduling, we may need to spread these procedures over two days.

Memory Testing: We will ask you to complete some tasks that measure your memory, concentration, and problem-solving abilities. Some of these will be done using pencil-and-paper while other tests will be done on a computer. The memory testing will take about two hours.

MRI: You will complete a brain scan using Magnetic Resonance Imaging (MRI). This will be a one-hour long session. An MRI scan is taken in a large machine that is shaped like a tunnel. This scan does not use x-rays. Instead, they use a strong magnet and radio waves, like those used in an AM/FM radio, to make pictures of your body.

You may not be able to have this scan if you have a device in your body, such as aneurysm clips in the brain, heart pacemakers or defibrillators, and cochlear (inner ear) implants. Also, you may not be able to have this scan if you have iron-based tattoos or pieces of metal (bullet, BB, shrapnel) close to or in an important organ (such as the eye). If we determine you cannot safely complete the MRI, we will withdraw you from the study.

Certain metal objects like watches, credit cards, hairpins, writing pens, etc. may be damaged by the machine or may be pulled away from the body when you are getting the scan. Also, metal can sometimes cause poor pictures if it is close to the part of the body being scanned. For these reasons, you will be asked to remove these objects before going into the room for the scan.

You will hear "hammering", clicking, or squealing noises during the scan. You will be given earplugs to reduce the noise. You will also be told how to alert the staff if you need them.

In this study, the MRI scan is for research only. But, if we see something that is not normal, you will be told and asked to consult your doctor.

As part of the MRI, we will ask you to complete a visual task. In this task, you will be presented with pairs of pictures presented on the left and right side of a screen. After seeing a pair of pictures, and asterisk (*) will appear on either the right or left side of the screen. You will be asked to indicate which side of the screen the asterisk appears by pressing a button, as quickly as possible.

After the MRI is complete, the study drug or placebo will be delivered to your home. You will be randomly assigned to receive either escitalopram (the study drug) or a placebo. A placebo is not a drug. It looks like the study drug but is not designed to treat any disease or illness. It is designed to be compared with a study drug to learn if the study drug has any real effect. Neither you, the study staff, nor the study doctor will know if you are receiving the placebo, although this can be determined in an emergency.

Study participants will be randomly assigned to either escitalopram or placebo at a 2-to-1 ratio. That means, for every two people assigned to escitalopram, 1 will be assigned to placebo. You will have a 67% chance of receiving escitalopram and 33% chance of receiving placebo.

You will initially start on 10mg of study medication. This is the usual starting dose for escitalopram.

Phase 1 Follow-Up Visits: We will schedule a telephone visit 2 weeks later. We will assess your depression symptoms and see if you are having any side effects. You will have a clinic visit at weeks 4 and 8 and another telephone visit at week 6. At each contact we will assess your depression and any side effects. You and the study doctor may discuss increasing the dose of escitalopram depending on how you tolerate it and how you are doing. If you are not doing well, the telephone visits may be changed to in-person clinic visits or additional visits could be added. Additionally, if you are having any side effects, concerns, or feel that your depression is worsening, you should contact us at any time to discuss how to proceed.

End of Phase 1/ Phase 2 Baseline Visit (Week 8): During the final Phase 1 visit, your study doctor will work with you to determine whether to end study participation or continue to Phase 2:

> If your symptoms have significantly improved, your study participation will end. We will discuss continued antidepressant treatment and offer up to two free follow-up visits to ease transition back to clinical care. Your study doctor will provide prescriptions during this time, but medication will no longer be provided or reimbursed by the study.
>
> If you decide to stop the study at this point for any reason and not proceed to Phase 2, we will also offer the two free follow-up visits and discuss other antidepressant treatment options with you. Again, medication will not be provided or reimbursed.

If your symptoms have not significantly improved, or you could not tolerate the study drug and had to stop it early, you may continue to Phase 2 of the study. During Phase 2, all participants will receive the antidepressant bupropion. There is no placebo involved, so both you and the study staff will know what you are taking. Your study doctor will work with you to stop the Phase 1 medication before starting bupropion.

The bupropion dose will start at 150mg in the morning for two weeks. If tolerated, you will then increase the dose to 300mg daily. This is the dose most people do well on; however, if you do not respond well to the medication, your study doctor may discuss increasing it to the maximum dose of 450mg daily.

Optional 8 Week MRI Scan: For your Week 8 Visit, you have the option to participate in an additional MRI scan. This MRI will be a repeat of the MRI scan that was performed on you during your Phase 1 Baseline Visit. This MRI carries no additional risks to you.

_____Initial here if you want to participate in this optional 8 week MRI Scan

_____Initial here if you do NOT want to participate in this optional 8 week MRI Scan

If you determine that you are uncomfortable with the MRI scan during the Baseline Visit, you can always change your mind about taking part in this optional scan.

Phase 2 Follow-Up visits: We will schedule a telephone visit 2 weeks later at week 11. We will assess your depression symptoms and see if you are having any side effects. You and the study doctor will discuss possibly increasing the dose of bupropion depending on how you tolerate it and how you are doing. You will have a clinic visit at weeks 13 and 17 and a telephone visit at week 15. At each contact we will assess your depression and any side effects. If you are not doing well, the telephone visits may be changed to clinic visits or additional visits could be added. Additionally, if you are having any side effects, concerns, or feel that your depression is worsening, you should contact us at any time to discuss how to proceed.

End of Phase 2 (Week 17): Two free follow-up visits will be offered to transition to clinical care. Medication will no longer be provided or reimbursed.

3. Costs to you if you take part in this study:

There is no cost to you for taking part in this study. If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. We will provide study medication to you free of charge.

However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance. You have the

right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

4. Side effects and risks that you can expect if you take part in this study:

Risks of Escitalopram: Although generally well tolerated, escitalopram does carry the risk of side effects. Common side effects include dry mouth, nausea, diarrhea, constipation; dizziness, lifelike dreams; fatigue, tiredness, or difficulty sleeping; appetite change with potential weight gain or loss; increased sweating; and loss of interest in sex or difficulty having sex. Clinically, most people find these side effects mild and it does not cause them to stop the medication. Rarely, escitalopram may increase the risk of bleeding in your stomach or bowels. This risk is high for participants who are taking aspirin, NSAIDs, warfarin, other anticoagulants, or have a prior history of bleeding from the stomach or bowels.

Risks of Bupropion: Common side effects include nausea, diarrhea, constipation; dizziness, headache, ringing in the ears, tremor / shakiness, lifelike dreams; increased anxiety or agitation; difficulty sleeping, decreased appetite and/or weight loss, dry mouth, and increased sweating. Bupropion is also associated with the rare risk of seizures, but only in people who have other reasons to have seizures.

All antidepressants have the risk of increasing thoughts of suicide. This risk is primarily in teenagers and young adults. It does not appear to be an issue with older adults. However, as people respond differently to medication, you will be monitored for suicidality at each study contact. If you develop any thoughts of wanting to harm yourself, you should contact your study doctor immediately.

Risks of stopping antidepressants: Stopping antidepressants too quickly can also result in side effects. This could occur when and if you stop escitalopram or bupropion. Individuals who suddenly stop an antidepressant or cut it down too quickly can develop symptoms of nausea, dizziness, tremor, or unusual sensations like tingling in the hands. Feeling tired and having mild muscle aches can also occur. Finally, you could see irritability, worsening anxiety or worsening mood. If you need to stop an antidepressant you are currently taking, or if you wish to stop escitalopram or bupropion at the end of your study participation, we will try to avoid these problems by slowly reducing the dose of the antidepressant over time. If you decide to leave

the study early and stop the study medication suddenly, you may also be at risk for these side effects.

Risks of Memory Testing: It is not uncommon to experience some stress or frustration during the memory testing. However, you may stop the testing at any time if you wish.

Risks of x-ray: As part of this research, you might have x-ray images of parts of your body before you have your MRI studies. These x-ray procedures employ radiation and will be used to see where a metal object is located in your body. Depending on which part of your body is x-rayed, you could receive a dose that is about 3% (0.03 times) the dose a radiation worker is allowed to receive in a year or you could receive a lower dose.

Risks of MRI: There are no known major risks with an MRI scan. But, it is possible that harmful effects could be found out in the future. Even though the tunnel is open, it may bother you to be placed in a tight space (claustrophobia), and to hear the noise made by the magnet during the scan. You will be given earplugs to reduce the noise. You may also feel the table vibrate and/or move slightly during the scan. It may be hard to lie on the table during the scan. If you have any metal pieces in your body, they could move during the scan and damage nearby tissue or organs. If you have tattoos, these could result in skin injury.

If you use a transdermal patch (medicated patches applied to the skin), you may need to take it off during the MRI scan. Transdermal patches slowly deliver medicines through the skin. Some patches have metal in the layer of the patch that is not in contact with the skin (the backing). You may not be able to see the metal in the backing of these patches. Patches that contain metal can overheat during an MRI scan and cause skin burns in the immediate area of the patch. Tell the study doctor that you are using a patch and why you are using it (such as, for pain, smoking cessation, hormones). Ask your doctor for guidance about removing and disposing of the patch before having an MRI scan and replacing it after the procedure. Tell the MRI facility that you are using a patch. You should do this when making your appointment and during the health history questions you are asked when you arrive for your appointment.

Loss of Confidentiality: There is also the potential risk of loss of confidentiality. Every effort will be made to keep your information confidential, however, this cannot be guaranteed.

5. Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided at Vanderbilt to treat the injury. There are no plans for Vanderbilt to pay for the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

6. Good effects that might result from this study:

a) The benefits to science and humankind that might result from this study: We anticipate that this study will provide more information about how differences in brain function and brain connections influence how people respond to different antidepressant medications. This may lead to better ways of making decisions about what antidepressant medications to use for each individual and so benefit others with your condition in the future.

b) The benefits you might get from being in this study: By receiving an FDA approved medication for treating depression, you may experience an improvement in your condition. However, as people respond differently to medications, personal benefit cannot be guaranteed.

7. Other treatments you could get if you decide not to be in this study:

You do not have to participate in this study to receive treatment for depression. There are many antidepressants, including escitalopram and bupropion, that are commercially available and may be prescribed by your physician. Talk therapy is also available, which is a treatment for depression that does not require medications. If you have questions about these options, your study doctor will discuss them with you.

8. Research Results

In the event new information becomes available that may affect the risks and/or benefits associated with this study or your willingness to participate in it, you will be notified so you can make a decision whether or not to continue your participation in this study.

If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent.

9. Payments for your time spent taking part in this study or expenses:

You will be compensated for your participation based on how many visits/assessments you attend.

For Phase 1, you will be given:

Visit	**Amount**
Assessment	$50.00
Baseline	
• MRI	$100.00
• Memory Testing	$50.00
Week 4	$50.00
Week 8	$50.00
Total:	**$300.00**
Optional Week 8 MRI	$100.00
Total (including optional Week 8 MRI)	**$400.00**

If you end the study at Phase 1 and complete all visits/assessments, you will receive $300. If you complete the Optional Week 8 MRI scan, you will receive an additional $100.00. If you are unable to complete the study, or miss study visits/assessments, you will only be compensated for those visits/tasks completed.

If you continue to Phase 2, you will given:

Visit	**Amount**
Baseline	$50.00
Week 13	$50.00
Week 17	$50.00
Total:	**$150.00**

If you end the study with both Phases complete, you will receive $450. If you choose to complete the optional Week 8 MRI scan, you will receive an additional $100.00. Again, if you are unable to complete the study, or miss study visits, you will be compensated only for those visits completed. Additionally, during Phase 2, you have the option to receive the study medication free of charge through the Vanderbilt pharmacy or through a pharmacy of your choice. We will reimburse you for any out-of-pocket expenses related to your bupropion prescription if you choose to use a non-Vanderbilt pharmacy. You will need to provide us with receipts in order to be reimbursed.

We may ask you for your Social Security number and address before you are compensated for taking part in this study.

For individuals that have extreme difficulty with transportation (to where it stops them from attending study visits), we have limited funds to assist with transportation. If this applies to your situation, please let the study doctor and the study coordinator know so we can discuss this. We do not have funds available to reimburse for gas or mileage.

10. Reasons why the study doctor may take you out of this study:

The study doctor may withdraw you from study participation if they determine that, based on the initial study interview, you are not eligible to continue in the study. They may also withdraw you if you are having difficulty completing study procedures, if you need an immediate referral for clinical care, or if he decides it is not in your best interest to continue. If you are taken out of the study, you will be told the reason.

11. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should first talk with your study doctor. We may ask you to come in for a final study visit. Because you will be taking medication, it is important to discuss a safe and effective plan for continuing, altering, or stopping the medication. If you withdraw or are withdrawn from the study early, you will be compensated for the parts of the study you have completed.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact the study coordinator Katie Anders, at (615) 322-1030, or the main study doctor, Dr. Warren Taylor, at (615) 322-1073. If you cannot reach the research staff, you can page the study doctor at (615) 835-0217.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Clinical Trials Registry.

A description of this clinical trial will be available on 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 this website at any time.

14. Confidentiality:

All reasonable efforts will be made to keep the personal information in your research record private and confidential but absolute confidentiality cannot be guaranteed. Your information may be shared with institutional and/or governmental authorities, such as the Vanderbilt University Institutional Review Board, if you or someone else is in danger or if we are required to do so by law.

During the research, if we learn you are having thoughts about suicide or hurting yourself or others, the research staff will ask you more questions about your thoughts. Based on your response, the staff may provide you with help to get treatment. This may include:

- working with you to contact your doctor,
- contacting a trusted family member, or a therapist to discuss your thoughts,
- working with you on a plan that may include getting you to a hospital for safety.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Warren Taylor and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

15. Authorization to Use/Disclose Protected Health Information:

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been, gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Warren Taylor and his study team may share the results of your study and/or non- study linked evaluations, memory testing, and MRI, as well as parts of your medical record, to the groups named below. These groups may include Vanderbilt University Institutional Review Boards. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Taylor in writing and let him know that you withdraw your consent. His mailing address is 1601 23rd Avenue South, Nashville, TN 37212. At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date _____ Signature of patient/volunteer _____

Consent obtained by:

Date _____ Signature _____

Printed Name and Title _____ Time _____