DUKE UNIVERSITY HEALTH SYSTEM

# *Adaptive Pharmacotherapy Study*

**Pro00072077** Randomized-Controlled Smoking Cessation Trial on Adaptive Pharmacotherapy

*Concise Summary*

The purpose of this study is to evaluate a new method for using smoking cessation medications, each of which is FDA approved for use alone, but investigational when used together according to a study protocol. You will be asked to choose to take either the nicotine patch or varenicline (Chantix). You will be randomized (like flipping a coin) and you may receive active drug or placebo. Depending on how you respond (based on cigarettes smoked per day), you may be asked to take bupropion (Wellbutrin) or placebo for the remainder of your study visits. There will be a total of 5 study visits over a 16 week period. The screening visit may last up to 2 hour and the remainder of the study visits will last about 30-45 minutes. There will be 10 follow-up phone calls that will occur over a 1 year period (after target quit day). During study visits, you will be asked to complete self-report assessments and you will be asked to complete smoking diaries prior to study visits.

The most common side effects of the nicotine patch include insomnia and/or abnormal dreams. Less likely side effects of the patch include dizziness, nausea/vomiting, light headedness, and/or fainting. The most likely common side effects of varenicline (Chantix) are nausea/vomiting, gas, constipation, insomnia, and/or vivid dreams. Less common side effects of varenicline include changes in behavior, agitation, depressed mood and/or suicidal thoughts/actions. The most common side effects of bupropion are insomnia, agitation, headache, and/or dry mouth. Less common side effects of bupropion include changes in behavior, hostility, depressed mood, and/or suicidal thoughts/actions. You may also experience nicotine withdrawal when trying to quit. Symptoms are listed below in the consent form. There is also a risk to confidentiality, although we will take all steps to prevent this from happening.

If you are interested in learning more about this study, please continue to read below.

You are being asked to take part in this research study because you smoke cigarettes. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell study staff if you are taking part in another research study.

A grant from the National Institutes of Health (NIH) will sponsor this study. Portions of Dr. James Davis's and his research team's salaries will be paid by this grant. Pfizer will be supplying the active and placebo Varenicline. All other study drugs will be paid for by the grant.

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## WHO WILL BE MY DOCTOR ON THIS STUDY?

If you decide to participate, Dr. James Davis will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed. Dr. Davis or one of the Physician Assistants working on the study will perform your initial physical exam and follow your progress through the study. They may access your medical record if deemed medically necessary.

## WHY IS THIS STUDY BEING DONE?

The purpose of this study is to evaluate a new method for using smoking cessation medications, each of which is FDA approved for use alone, but investigational when used together according to a study protocol.

The medications used in this trial are Varenicline, Nicotine Patch, and Bupropion. All are approved individually by the U.S. Food and Drug Administration (FDA) for quitting smoking. Varenicline (Chantix) is considered standard of care. The investigational aspects of this trial are the use of two of these medications together, and the use of these medications before quitting smoking. The word "investigational" means that using these drugs in these ways is still being tested in research studies and are not approved by the U.S. Food and Drug Administration (FDA).

## HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

We will consent up to 780 subjects with the target of enrolling approximately 300 people. Participants consist of individuals who smoke cigarettes, are ages 18 and older, and meet our eligibility criteria.

## WHAT IS INVOLVED IN THE STUDY?

If you agree to be in this study, you will be asked to sign and date this consent form. After you sign the consent form, study staff will review your medical chart and physical exam results to make sure you are eligible. Study participation will be documented in your medical chart/record. You will have the following tests and procedures to make sure that you are eligible:

- *Self-report measures will be assessed on the following:* smoking heaviness, use of other tobacco products, depression, anxiety, drug and alcohol use, and willingness to take study medications.
- *Urine sample*: to be used to test for pregnancy (females only). If this test is positive, you will not be allowed to continue in this study.

Depending on the results of the screening procedures you may not be eligible for the study. If you are pregnant, you will not be allowed to participate in this study.

**Enrollment and Randomization:** If you sign consent and pass screening criteria, you may enroll in the study. If you enroll in the study you will be randomized to one of two groups. Randomization is like flipping a coin; there is a 50/50 chance of ending up in either group. All participants will be able to choose a smoking cessation drug: either Varenicline or Nicotine Patch. One randomization group will receive a single active medication, guided by their choice, and placebo Bupropion. The other group will receive the

medication they choose in combination with Bupropion if they do not respond to their chosen medication. During the study you will not be told if you are receiving active or placebo Bupropion. The dose of Varenicline, Bupropion, and the Nicotine Patch will follow accepted FDA guidelines. All tablets must be swallowed whole, and not crushed, divided, or chewed. You may also be given placebo medications during the first few weeks of your treatment. A placebo looks like the real drug but has no effect on the body, and is used to maintain the integrity of the study. All drugs will be provided in unmarked containers. Study staff will call you within the first week of starting study drugs to assess effects and address questions you may have. However, please call us immediately if you have questions or concerns.

You will be blinded to what medications you are taking. Blinding means you will not know if the drug you have been prescribed is active or a placebo. The study staff will also be blinded to what treatment group you are in, unless there is an emergency and they need to know if the medication you are taking is active or a placebo. After the end of the study, you can contact the study physician for information on which active medications you were taking during the study. In the case of a health care need during the study, your healthcare provider can also contact the study physician for information on the active medications you are taking.

You will be assigned a Quit Smoking Day that is approximately four weeks from your Enrollment Visit. You will also be required to attend four study visits, each lasting approximately 30 minutes.

- **Study Visit 1** will occur approximately 1 week after your Screening Visit. At this visit, study staff will review the results of your urine tests to determine whether you are eligible to participate. If you are able to participate, you will be enrolled in the study, and randomized to a study group. Study staff will also provide you with active and placebo medications (study drugs).

- **Study Visit 2** will occur approximately 2 weeks after Study Visit 1 (about 2 weeks before your Quit Day). At this Visit, study staff will give you additional medications and instructions on how to take them. Study staff will also collect any of your empty prescription medication bottles.

- **Study Visit 3** will occur 2 weeks after your Quit Day. During this visit, you will be asked to complete questionnaires that will take approximately 20 minutes. You will receive the remainder of your medications. Study staff will also collect your empty prescription medication bottles.

- **Study Visit 4** will occur 12 weeks after your Quit Day. During this visit, you will be asked to complete questionnaires that will take approximately 20 minutes. Study staff will also collect any empty prescription medication bottles that you have.

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A member of the study staff will call you at the following times:

| **Call Timing** |
|---|
| 1-2 Days after Study Visit 1 |
| 1-2 Days before Study Visit 2 |
| 1-2 Days prior to Quit Day |
| 1-2 Days After the Quit Day |
| 1 Week after the Quit Day |
| 1-2 days before Study Visit 3 |
| 6 Weeks after Quit Day |
| 1-2 Days before Study Visit 4 |
| 26 Weeks after Quit Day |
| 52 Weeks after Quit Day |

During these calls, we will answer any further questions you may have. However, please call us immediately if you have any questions or concerns.

We will also ask you to complete a 7 day diary before your Study Visits. This diary will include information on how many cigarettes you have smoked and if you are taking the medications you are given through the study.

Participation in this trial is voluntary and refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. If you choose not to participate or wish to withdraw from the study, we encourage you to talk to study staff. If you do not sign this consent form, you will continue to receive care, but not as part of this study.

**HOW LONG WILL I BE IN THIS STUDY?**

You will be in this study for 13 months; but you will only receive the study drugs for 16 weeks, 4 weeks before your Quit Date and 12 weeks after your Quit Date. Follow-up will be conducted up to 1 year after your Quit Day if you are abstinent at Study Visit 4. Your entire study participation, including one-year follow-up, will last approximately 13 months. If you are still smoking at Study Visit 4, you will be in the study for approximately 16 weeks, and we will not call you after the last study visit. You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to study staff first.

**WHAT ARE THE RISKS OF THE STUDY?**

There is in any study a potential risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed. Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, and you may take a break at any time during the study. You may stop your participation in this study at any time.

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As a result of your participation in this study, you are at risk for the side effects described below. You should discuss these with the study doctor or nurse practitioner and your regular health care provider if you choose. Since Varenicline has been associated with severe mood changes, if either you or your family notices any changes in mood or behavior, or if you develop suicidal thoughts or actions, you should stop taking your tablets and capsules and report these side effects to study staff. If medical study staff is not immediately available then you should call your primary physician or go to the nearest emergency department. Any other side effects should be reported to study staff immediately before making any changes to your use of these drugs. Symptoms will be evaluated by the study medical staff. Depending on how severe the side effects are, you may be given a reduced dose of the study drugs or given the option of discontinuing use of these study drugs entirely.

**Nicotine Skin Patch**
The use of nicotine patches for the thirty days of the study, prior to quitting smoking, is investigational and is not standard practice. Risks of nicotine from the patch as well as from smoking include cardiovascular risks such as high blood pressure and increased heart rate as well as stroke. Using the patch at the same time as you continue smoking may also increase your risk of experiencing the side effects listed below. The amount of nicotine you receive from the patch will be less than you would receive from smoking one or two medium strength cigarettes every 30 minutes. The rate at which the nicotine will enter your system will be slower than the rate from smoking cigarettes. Nicotine skin patches may cause some, all or none of the side-effects listed below:

More likely
- Insomnia
- Abnormal dreams

If you experience either, please call us so that we can determine whether you should remove the patches at bedtime and apply new ones in the morning upon waking. Please do not make any changes to your use of the patches without contacting study staff. Skin irritation may occur, although the likelihood of this will be reduced by changing the site of the patch application daily. Notify us if you have skin irritation so that we may recommend treatment to help reduce the irritation.

Less likely
- Dizziness
- Light Headedness
- Nausea/Vomiting
- Fainting

There is no evidence that normal healthy smokers will be exposed to a major risk of the nicotine toxicity side effects listed above when using nicotine patch.

**Bupropion:**
Bupropion may cause some, all or none of the side-effects listed below:

More likely
- Insomnia
- Headache
- Agitation
- Dry mouth

Less likely
- Changes in behavior
- Hostility
- Depressed mood
- Suicidal thoughts or actions

Some people had these symptoms when they began taking Bupropion, and others developed them after several weeks of stopping Bupropion.

**Varenicline:**
Varenicline may cause some, all or none of the side-effects listed below:

More likely
- Nausea
- Vomiting
- Gas
- Constipation
- Insomnia
- Vivid dreams

Less likely
- Changes in behavior
- Agitation
- Depressed mood
- Suicidal thoughts or actions

Some people had these symptoms when they began taking Varenicline, and others developed them after several weeks of stopping Varenicline.

If you develop thoughts of wanting to hurt yourself, you should contact the study doctor immediately. The study doctor or one of the physician assistants will evaluate you, and may refer you for further treatment if needed. If you develop strong thoughts of suicide, and feel you cannot keep yourself safe, you should immediately go to your local emergency room.

If you develop heart problems during your participation in this study, you should contact the study doctor immediately. The study doctor or one of the physician assistants will evaluate you, and may refer you for further treatment if needed. Get emergency medical help right away if you have any symptoms of a heart attack.

If you are receiving Varenicline with Bupropion the side effects may be greater. In addition, there may be side effects that are currently not known with the use of this combination.

When quitting smoking you may experience some, all or none of the withdrawal symptoms listed below:
- Headache
- Nausea
- Constipation or diarrhea
- Decrease in heart rate and blood pressure
- Fatigue, drowsiness, and insomnia
- Irritability
- Difficulty concentrating
- Anxiety
- Depression
- Tobacco cravings
- Increased desire for the taste of sweets
- Increased hunger and caloric intake leading to weight gain

**Female**
Being a part of this study while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. If you are a woman of childbearing potential, a urine pregnancy test will be done, and it must be negative before you can continue in this study. If sexually active, you must agree to use appropriate contraceptive measures for the duration of the study and for one week after the last dose. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you do become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

Risk to the fetus if you become pregnant include the following: nicotine has been shown to lead to pre-term delivery, low birth weight, and birth defects. Varenicline and bupropion have not been approved or studied for use during pregnancy, and risks to the fetus are unknown.

**Drug and Food Interactions:**
For your safety, you must tell the study doctor or staff about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study. There may be risks, discomforts, drug interactions or side effects that are not yet known.

## ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may be a direct medical benefit to you. A possible benefit from participation in this study is quitting smoking. We also hope the information learned from this study will benefit people that smoke in the future.

## WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THE STUDY?
If you do not wish to participate in this study, there are other alternatives to treat tobacco use. You can talk with your doctor about prescription medicines that may help you quit (including Varenicline or Bupropion), or nicotine-replacement products offered outside of this study, both over-the-counter and by prescription. You can also participate in other quit-smoking programs, such as the Duke Smoking Cessation Program, which can be reached by calling 919-613-7848. Information about these resources is available through the North Carolina Tobacco Use Quit line at http://www.quitnownc.org or by calling (800) 784-8669.

## WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal

information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests, x-rays, and procedures may be reported to research staff and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, the Duke University Health System Institutional Review Board, the Duke Cancer Institute, the Duke Office of Audit, Risk and Compliance, NIH, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

As part of this study, you will be asked to have certain tests or procedures performed. Some of these would have been done as part of your regular care. The study doctor will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record and will be reported to the representatives and affiliates of NIH. Results of tests and studies done solely for this research study and not as part of your regular care will also be included in your medical record.

The study results will be retained in your research record for at least seven years after the study is completed. At that time either the research information not already in your medical record may be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations. If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

A representative from the sponsor may be present at certain study visits/procedures.

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);
2) you have consented to the disclosure, including for your medical treatment; or
3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.
4) Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.
Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

**WHAT ARE THE COSTS?**
You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. Not all services are covered by insurance. Some procedures or scans may require pre-authorization by your insurance plan. We will notify you if we learn that a service is not covered by your insurance plan as part of the pre-authorization process. If it is not covered, you will be responsible for paying for it. The amount of your out-of-pocket expense will depend on your insurance plan. For beneficiaries with Medicare Advantage Plans, traditional Medicare is billed for the routine cost of a research study. You may have more or higher co-pays than with a Medicare Advantage plan. Please discuss the costs of the study with Dr. James Davis. At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

The study sponsor, NIH, has agreed to pay for services and procedures that are done solely for research purposes. Please talk with the PI/study team about the specific services and procedures that the sponsor will pay for, and the ones for which you or your insurance will be responsible.

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

NIH and Pfizer will provide the study drug/biologic free of charge to you. At the end of the study, or if you decide to withdraw from the study before it ends, you may be asked to return all unused study drug. Your study doctor may request that you return for a checkup before you stop your study drug/biologic if he/she thinks that stopping it suddenly may harm you and may ask you to complete the tests that would ordinarily occur when a person completes the study.

**WHAT ABOUT COMPENSATION?**
You will be compensated up to $210 for your participation in the study. After completing Visit 1, you will be compensated $20. After completing Visit 2, you will be compensated $20. After Visit 3, you will be compensated $50, and after Visit 4, you will be compensated $100. You will also receive $20 at the end of the study for completion of the phone call assessments ($2 for each of the 10 calls). You will receive payment through a rechargeable debit card called ClinCard.

**WHAT ABOUT RESEARCH RELATED INJURIES?**
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. James Davis at (919) 668-5055 during regular business hours. After hours and on weekends and holidays, please call Dr. Davis at 608-217-9405.

**WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?**
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. James Davis in writing and let him know that you are withdrawing from the study. His mailing address is 2424 Erwin Road, Suite 201, Durham, NC 27705.

Nonparticipation or withdrawal from this study will not affect your job status if you are a Duke employee and will not affect your grades if you are a Duke student. If you do decide to withdraw, we

ask that you contact study staff by phone or Dr. Davis in writing and let him know that you are withdrawing from the study. His mailing address is 2424 Erwin Road, Suite 201, Durham, NC, 27705. The study may be stopped at any time without your consent. If this occurs, you will be notified and your study doctor or nurse practitioner will discuss other options with you. In addition, you must return all unused study drug to Dr. Davis or his staff. Dr. Davis may ask you to return for a checkup before you stop your study drug if he thinks that stopping the drug suddenly may harm you. We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at any time without your consent. Reasons why this might occur include difficulty in study recruitment or retention that will significantly impact the ability to evaluate the study endpoints or any new information becomes available during the study that necessitates stopping the study. If this occurs, you will be notified and your study doctor will discuss other options with you.

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

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. James Davis at (919) 668-5055 during regular business hours. After hours and on weekends and holidays, please call Dr. Davis at 608-217-9405.
For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

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**STATEMENT OF CONSENT**

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

| _____ | _____ | _____ |
|---|---|---|
| Signature of Subject | Date | Time |
| _____ | _____ | _____ |
| Signature of Person Obtaining Consent | Date | Time |