APPENDIX I: INFORMED CONSENT TEMPLATE

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Affiliate	☒<Blank> Hospital	☐<Blank> Hospital
	☐<Blank> Hospital	☐<Blank> Hospital

Agreement to Participate in a Research Study

_____ _____
Committee # Name of Study Volunteer

Claudication: Exercise Vs. Endoluminal Revascularization (CLEVER)

You are asked to take part in a research study. All research studies carried out at <blank hospital/institutions> are covered by rules of the Federal government as well as rules of the State and <blank hospital/institution>. Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement. By signing this consent document, you agree that the study risks, benefits and procedures have been explained to you, that your questions have been answered, and that you agree to volunteer in this study.

The principal investigator for this study at <institution> is <blank>. His/her telephone number is <blank>. The lead research coordinator for this study at <blank> is <blank>, and her telephone number is <blank>. If you have a medical problem during nonworking hours, please contact your doctor, go to the emergency room, or call 911.

This study is sponsored primarily by the National Institutes of Health National Heart, Lung, and Blood Institute. Support for this study was also received by Otsuka Pharmaceuticals, Boston Scientific, Cordis/Johnson&Johnson, and Guidant Corporation.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Notify your physician or research

coordinator if you are pregnant, planning on becoming pregnant, or lactating. If so, you are not eligible for this study. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

1. Nature and Purpose of the Study

You have been diagnosed as having blockages in your arteries due to a medical problem called "peripheral arterial disease". These blockages are causing symptoms such as pain or cramping in your leg muscles when you walk, called "claudication". The most effective treatment for claudication is unknown. Treatment options may include vascular surgery (replacing a portion of your artery), stent placement (a metal tube placed through the catheter into your artery), exercise therapy, or medications. At the current time, it is not clear which of these treatments is most beneficial and safe. The purpose of this study is to evaluate the use of stents compared to supervised exercise therapy (exercise rehabilitation), and to also compare each of these treatments to optimal medical care. Optimal medical care for most people with claudication includes encouragement to stop smoking, use of home-based unsupervised exercise, and use of claudication medications. If you agree to join the study, the total commitment to this study is 18 months. During that time, data will be collected at 3 intervals: baseline, 6 months, and 18 months. The baseline data collection requires 2 visits separated by at least 7 days.

Approximately 130-150 participants will be enrolled in the research study.

The following description of the study and study procedures is provided so that you can clearly understand the information about this study before agreeing to participate and signing your name on the final page. Your doctor will also explain all treatment procedures to you.

2. Explanation of Procedures

To determine your eligibility for this study, you will be asked to have screening tests. You will undergo a brief history and physical exam, and your local investigator may review some of your imaging tests. You will undergo measurement of the blood pressure in your arms and legs. To obtain blood pressure in the legs, blood pressure cuffs will be applied and inflated on your upper thighs and at your ankles. If these values are abnormal, you may have an ultrasound exam (an exam using sound waves to form images of the body that involves placing a gel on your legs, and a sensing device (a wand or "probe") across the skin to examine the blood vessels). Depending on the results of all of these evaluations, you may then undergo a specialized exercise treadmill test. The screening tests should take about 2 hours to complete.

If the results of the screening tests show that you are eligible to participate in this study, you will be given a pedometer to wear for 7 consecutive days during your waking hours. You will be asked to return in 1-2 weeks to complete brief questionnaires about your walking ability and about your quality of life. During this visit, the following procedures

will be done. You will undergo a 2nd exercise treadmill test and repeat ankle-brachial pressure measurements (blood pressure cuffs applied and inflated on your legs and arms). A blood sample of approximately 3 teaspoons will be taken. Your height, weight, and waist circumference will be measured.

After completing the questionnaire and the treadmill tests you will be randomly assigned (like the toss of a coin) to one of three treatment groups: placement of a stent in a leg artery(ies), supervised exercise therapy in a rehabilitation program, or optimal medical care (defined as encouragement to stop smoking and walk regularly). All study participants will receive study medication, cilostazol (Pletal, Otsuka Pharmaceuticals), known to improve symptoms of claudication without charge throughout the study if tolerated.

All procedures and treatments being evaluated in this study are considered accepted standard of care therapy that are routinely provided by doctors in the U.S. and elsewhere for people with claudication. The purpose of this study is to compare commonly provided treatments for intermittent claudication to determine which is the most effective. Some of the stents used in this study are investigational devices when used in iliac arteries (i.e. they are biliary stents indicated for use in the liver instead of in blood vessels such as the iliac artery). However, it is very common for doctors in the United States to use biliary stents to treat blockages in blood vessels, including iliac arteries. The devices to be used in this study have been approved by the FDA and therefore available for vascular use by physicians since between April 12, 2001 and June 1, 2004.

A sample of the blood taken during the study may be frozen to allow for potential future research. Any such research using these samples will be approved by an Institutional Review Board, like the one that has approved this study. When such research is done, the investigators using these samples will not receive any information that would identify you (like your name, medical record number, or social security number). You can change your mind about the use of these samples at any time. The results of this testing will not be told to you and will not be placed into your medical record, unless you request that at the end of this form. If you do so, your results will be transmitted back to your local researchers and they will match your results to your identity and contact you with the results. Your samples will only be used for research and will not be sold.

This study also contains a health economics review (analysis of costs) that will be done to compare medical care costs for the three treatment strategies being tested in this study. As part of this study, you will be asked to sign a Medical Billing Release Form. This form will be used by the Economic and Quality of Life Assessments Group of the Harvard Clinical Research Institute (HCRI) to collect hospital bills from the patient accounting department at any hospital to which you are admitted, from the time of your enrollment in CLEVER through the study follow-up period. Subject diaries will also be a part of the economic study. You will be asked to keep this diary and enter health care interactions that you may have during follow up period. All health economic information

will be kept strictly confidential and be used solely to assess the medical expenses that occur as a direct result of participating in the CLEVER trial.

Also, as part of this study, your research coordinator will have you, or a person you permit (your proxy) complete a questionnaire called a Quality of Life Survey during your enrollment in the study. Part of this survey will also be completed with your research coordinator at the 6 and 18 month follow-up visits. You will be asked to sign a Patient Address Form as part of this study. This form will be used by the Economic and Quality of Life Assessments Group, at the Harvard Clinical Research Institute (HCRI), to contact you or your proxy via mail or telephone to answer questions regarding your overall health status. You will answer questions about your general health, and symptoms that you may or may not have (i.e. leg pain, shortness of breath, ability to walk, etc). All of your responses to the questions will remain completely confidential and you may choose not to answer any question. The time points of contact will be at 6 months and 18 months.

2.1 Procedures for those randomized to optimal medical care:
If you are randomized to "optimal medical care" group, you will receive the care that many of those with intermittent claudication receive: advice and referral if needed for smoking cessation, verbal recommendations to exercise by walking as much as possible (at least three times a week) and free supplies of the drug cilostazol. You will be contacted monthly, by a member of the study, to identify any health concerns you may have.

2.2 Procedures for those randomized to stenting:
If you are randomized to stent placement, you will receive care similar to that described in the optimal medical care section above, plus you will undergo a diagnostic test known as an arteriogram, which is an x-ray of your blood vessels of your abdomen and leg arteries (iliac, femoral and/or popliteal) that uses a dye (also called "contrast") to see your blood vessels. The arteriogram is done by placing a catheter (tube) into the artery in your groin and passing it through the arteries in your pelvis and abdomen, to the artery to be examined. The "contrast" is administered via this catheter to permit the physicians to see your arteries on x-rays.

If you agree to have a stent(s) placed, the stent(s) will be placed via a small tube or catheter into an artery in your abdomen (aorta) or pelvis (iliac artery). The stent(s) will support the walls of the artery and allow the blood to pass freely through the artery. A balloon may be used to enlarge the opening within the stent after it is placed in the artery. This angioplasty (balloon inflation) and stent procedure will be done in a radiological suite to permit x-ray guidance for the placement of the catheters and the stent(s).

After the stent(s) is (are) in place, x-ray pictures will be taken to decide if the artery is open and if the stent needs to be enlarged with a balloon. Once the stent is in place and the artery is open, all the catheters (tubes) will be removed and pressure will be applied to your groin area. Your x-ray images from your arteriogram, or other vascular tests,

will be sent to the clinical coordinating center for this study at Rhode Island Hospital. All of these tests will be maintained strictly confidential in the clinical coordinating center and identifiable information will not be sent from the clinical coordinating center to any data center, site, or other person outside of the clinical coordinating center.

At any time after treatment, you may be asked to have a repeat arteriogram, if your symptoms or test results worsen and your doctor and feels that it is necessary to re-evaluate your artery(ies) or the stent. Repeat angioplasty or stent placement, in your artery (ies), may be done again to treat your artery(ies).

Bypass surgery for a blockage in your artery(ies) is not a study treatment but may be needed clinically if your peripheral arterial disease severely worsens, and your symptoms progress beyond claudication and result in foot pain at rest, skin ulceration, or gangrene. If your doctor decides that you require bypass surgery of your leg artery(ies), your research doctor or nurse should be told immediately, so that you may have some repeat tests done before the surgery is performed. This possibility is described below in section 2.5.

You will be contacted monthly, by a member of the study, to identify any health concerns you may have and to inquire about changes in your health status.

2.3 Procedures for those randomized to supervised exercise/exercise maintenance:

If you are randomized to the supervised exercise/adherence to physical activity group, you will receive a free supply of the drug cilostazol and you will be asked to attend free supervised exercise therapy classes for one hour three times a week for 26 weeks. Usually, these sessions will be conducted at rehabilitation centers used for cardiac or pulmonary rehabilitation. Facilities will be staffed by nurses, doctors, and often exercise specialists. At exercise classes, you will exercise on a treadmill in the presence of an instructor. In addition to being monitored by this staff, a central study committee also will monitor your progress and increase your exercise regimen based upon the results of each exercise session. At month 5, you will be assigned a health educator, who will contact you by telephone once a month in months 5 and 6, then every 2 weeks during months 7-12, and then once a month in months 13-18. The purpose of this health educator is to help motivate you to maintain a healthy, physically active lifestyle. Each call will take about 10 minutes. You will also receive educational and motivational materials by mail, and will be asked to complete a specially designed exercise log book to review on the telephone with your health educator.

2.4 Follow-up Procedures for all treatment groups:

Cilostazol medication will be provided throughout the study without charge. You will receive a telephone call every month during the study to review any health changes and to see if you have any questions about your participation. If you experience any new symptoms during this study, you should tell your research doctor or nurse. If at any time the symptoms are severe you can go to the emergency room, or call 911.

You are asked to return every 3 months to receive a new supply of cilostazol. During your 6 and 18 month follow-up visits you will also have a repeat exercise treadmill test, and have repeat ankle-brachial pressures on your legs performed. Brief demographic and medical information will be gathered, and blood work will be repeated. You will also be asked to complete one additional questionnaire in person with your research coordinator. During these visits you will also be asked about hospital admissions or hospital treatments, your use of other medical resources for example at your doctor's office, and will answer health-related questionnaires similar to your screening visit.

The total length of your participation in this study is 18 months. After you have completed all follow-up visits, you will be reimbursed $250.00 for your time and travel. If you are in the supervised exercise group, you will receive up to an additional $15 per exercise training session for time, travel, and expenses (up to $1,170 total).

Finally, if you have any questions during this study, you can contact your research coordinator or principal investigator at the telephone numbers listed at the beginning of this form. Should you have any questions concerning this project you may call <Principal Investigator> at <phone number>.

2.5. Procedures for Subjects with Disease that Worsens to Critical Limb Ischemia

During this study, it is possible that your peripheral arterial disease may worsen and you will have more frequent or more severe symptoms. ***If you agree to participate in this study, you are specifically asked to not undergo vascular bypass surgery or other artery procedure (angioplasty, stent placement) outside of this study during the study period unless your symptoms progress beyond claudication to symptoms such as pain in the foot at rest, skin ulceration, or gangrene. If these symptoms arise, you are asked to contact your local investigator to discuss necessary treatment.*** The need to open blocked arteries when these conditions are present is usually not an emergency. If such conditions are detected, you will be informed that your disease has worsened and will be offered recommendations for additional treatment, including revascularization either by surgery or catheter-based means, like stent placement. You will be asked to have a study visit to provide data prior to having this additional recommended treatment. All study data collected at baseline, including treadmill testing, will be collected if possible.

3. Discomforts and Risks

The discomfort and risks associated with screening procedures and study participation are: the time lost in undergoing a brief physical examination, performing multiple treadmill tests, undergoing Doppler ultrasound testing, blood sampling, leg blood pressures, having an invasive procedure with exposure to contrast dye in order to balloon and stent a blockage in the artery(ies) of the leg, increasing regular exercise activity and answering health questionnaires and quality of life questionnaires. Specific risks and discomforts for the more invasive and challenging tests performed in this study are described below in further detail:

Treadmill Test

Lightheadedness, dizziness, shortness of breath and chest pain can be associated with the treadmill test and you will be monitored closely to try and avoid any of these problems. In addition, very rare (3-4 out of 10,000) patients may have a heart attack or die during the treadmill test.

Segmental Leg Pressures and Doppler pressures
You may experience pressure in your legs (from the blood pressure cuffs) as the pressure evaluations are being performed similar to when blood pressure is obtained from the arm. You may feel mild pressure as the ultrasound wand is passed over your abdomen.

Supervised exercise
For those assigned to perform exercise training, there is the potential risk of exercise precipitating a heart attack. The incidence of death among participants in cardiac rehabilitation programs is about 1/750,000 hours patient hours of participation, the incidence of cardiac arrest is 1/117,000 patient hours and the incidence of non-fatal myocardial infarction is 1/220,000 patient hours. Other potential complications that can be seen with exercise training are: heart rhythm problems, which could be life-threatening or fatal, heart attacks, heart failure, low blood pressure and shock, musculoskeletal trauma, severe fatigue sometimes persisting for days, dizziness, fainting, body aches, or delayed feelings of illness.

Stent Placement
For those assigned to stent placement, there are risks related to both the diagnostic arteriogram and stent placement (including balloon angioplasty). The procedure to place the stents in the artery have the same potential risks of complications as those encountered during routine arteriography (injection of contrast or “dye” into the artery and taking x-rays). These risks include but are not limited to: blood clots on the wall of the blood vessel, a blood clot traveling in the vessel that needs treatment with medication or surgery, a tear in the wall of the vessel, an infection at the site where the catheter is placed or at the site where the stent is placed, clotting of the artery after stent placement and/or failure of the stent to open the artery, spasm (tightening), pain, bleeding at the site where the catheter is placed which sometimes causes a small collection of blood around the blood vessel, a weakness in the wall of the blood vessel, an abnormal rhythm of the heart beat, heart failure, damage to the heart muscle tissue, stroke, limb loss, and death. A reaction to the x-ray dye is rare, but it may cause brief or permanent damage to your kidneys, cause heart and lung problems or rarely death. If serious bleeding or other complications occur, an emergency operation may be required to control the problem. You may also experience burning as numbing medicine is injected at the site where the tube will be placed into the artery in your groin; and possible pressure as the stent(s) is(are) being placed.

On long-term follow-up, if you receive a stent there is a chance that the artery could become narrowed again. It is estimated that fewer than one in 5 will have this complication. If it occurs, it may be treated by your doctors by catheter-based procedures like the one you had initially to place the stent.

The approximate rate that study procedure adverse events may occur is summarized below:

Adverse Event	Severity	Expected rate of event occurrence
Bleeding from access site	Low to High	1%
Blood vessel injury or rupture	High	1%
Pseudoaneurysm	Moderate	<1%
Permanent renal failure	High	<<1%
Transient renal failure	Low	<5%
Need for surgery	Moderate to High	<1%
Death	High	<0.1%
Amputation	High	<0.5%
Artery thrombosis/occlusion	Moderate	<2%
Allergic reaction	Low to Serious	<1%
Distal embolization	Moderate	<3%
Fever	Low	<0.1%
Hypotension (low blood pressure)	Low	<1%
Hypertension (high blood pressure)	Moderate	<1%
Infection	High	<0.5%
X-ray exposure	Very Low	100%
Cardiac event related to exercise test	Very Low	<<<1%
Cardiac event related to exercise training	Very Low	<<<1%

The greatest risk associated with the storage of these blood samples for genetic testing is a possible loss of confidential information that you may not want disclosed. However, this risk has been minimized by storing your samples so that they will be identified only by code, so that they remain private and confidential. Investigators utilizing the stored samples will not have access to the code that links them to any study participant. Most narrowings can be treated with one stent; according to this protocol your doctor should use no more than two stents per narrowing, but your doctor will make the final determination based on what is needed for you.

Risks to Pregnant Women

This research represents a significant risk to unborn children. Namely, complications of the procedure could result in early termination of pregnancy, and radiation exposure to fetuses or children has been associated with increased risk of childhood cancer. Therefore, all women of childbearing age will be screened for pregnancy. This screening is standard procedure for all women of childbearing age prior to undergoing an angiogram. This screening may include a blood or urine pregnancy test. If you think that you may be pregnant or plan to become pregnant you should not participate in this study. If you become pregnant during this study, immediately contact your research physician.

4. Benefits

There are few if any benefits to undergoing the screening procedures and not enrolling in the study. You may gather some information about the status of blood flow to your extremities, blood pressure, or learn other health information. If your ability to walk, exercise and/or improve activity levels long-term is improved due to involvement in this study, you may experience improved quality of life. Although it is possible that you will benefit from this project, it is also possible that no such improvements will occur.

The potential benefit of the use of the stored samples is to identify new information about claudication and peripheral arterial disease that may improve the care of patients in the future.

5. Alternative Therapies

The alternatives available to you include surgery to bypass a portion of your diseased artery(ies). This surgery is major surgery and is usually not advised as an initial treatment for individuals with only claudication symptoms (leg pain while walking). If you agree to participate in this study, you are specifically asked to not undergo vascular surgical bypass or other artery procedure during the study period unless your symptoms progress beyond claudication to very severe symptoms that threaten your leg and then require opening of the blood vessel (see section 2.5 above).

6. Costs and Payments

You will be billed in the standard fashion for routine medical care for which you are scheduled and either you or your insurance provider will be responsible for this payment. Neither you, nor your third-party insurance provider will be billed for any research procedures that are not part of your routine medical care.

7. Payment for Research-Related Injuries

<Institution> and the study sponsor(s), the National Heart, Lung, and Blood Institute (NHLBI), have made no provision for monetary compensation to you in the event of physical injury resulting from this study. Should physical injury occur, treatment is available, but treatment <may not be> provided free of charge. <Insert Institution policy>

8. Confidentiality

All of your records from this study will be treated as private health care records. The records will be protected according to the rules of <blank hospital/institution>. The <blank hospital/institution> privacy practices and policies are based on the rules about protection of private health care information contained in <State> law and in the Federal Health Insurance Portability and Accountability Act of 1996 and its regulations ("HIPAA"). The privacy practices of <blank hospital/institution> and of the people who provide services at or with <blank hospital/institution> are explained in more detail in the <blank hospital/institution> Joint Privacy Notice (the "Privacy Notice') which will be given to you.

As required by HIPAA, you will be given a separate Research Authorization Form that will tell you the people and organizations that may use, receive and share information learned about you during the Study. Signing the Authorization Form means you give permission for your health care information to be used and shared for study purposes.

You should also know that there are times when the law might require or permit <blank hospital/institution> to release your health information without your permission. The Privacy Notice explains when this might happen. To give you some examples, state law often requires health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF). State law often also requires health care workers to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

9. Refusal/Withdrawal

You decide whether or not you want to be in the study. Participation is voluntary. If you decide now to participate, you can change your mind later and quit the study.

If you decide not to participate, or if you quit the study, it will not affect the health care services that you normally receive. If the researcher or your doctor feels it is in your best interest, they may choose to take you out of the study at any time before you complete the study.

As soon as it becomes available, the researcher will give you new information about the study that may or may not affect your decision to stay in the research study

In addition, the sponsor may choose to end the study at any time, for reasons unrelated to health care.

10. Rights and Complaints

If you have any complaints about your taking part in this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies, you may contact <blank>, in the <blank hospital/institution> Office of Research Administration, at <blank>.

CONSENT AND SIGNATURES

I HAVE READ THE ABOVE DESCRIPTION OF THIS STUDY. ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

_____ _____
Signature of study volunteer/authorized representative* Date/Time (24 hour clock)

I was present during the consent process and signing of this agreement above by the study volunteer or authorized representative.

_____ _____
Signature of witness (required if consent is given orally or at the request of the IRB) Date/Time (24 hour clock)

Blood samples will be stored for future potential studies. These studies will be approved by institutional review boards. Potential future research includes the possibility of genetic or DNA studies. The purpose of this part of the consent is to give you information so that you can decide whether you want to allow these tests in the future. The specific testing to be performed on the blood samples has not been established at this time. Techniques have been developed which allow evaluation of the inherited factors called genes, as well as of the genetic make-up of your cells, called DNA. By studying material obtained from your blood sample, researchers might identify the gene(s) that carry the trait(s) for peripheral artery disease. Participation in this genetic research study is entirely voluntary. If you agree to participate, blood samples used for biochemical analysis will be saved and stored for possible future genetic testing. These samples will be stored indefinitely or until the genetic material (DNA) used for testing is no longer useful.

Please answer the following three questions by circling the response at the right:

1.	Samples of my blood may be stored for future testing?	**Yes**	**No**
2.	Samples of my DNA may be stored for future **genetic** testing?	**Yes**	**No**
3.	I wish to be contacted about information pertaining to my Health if genetic information is obtained and if my study doctor believes it would alter my care.	**Yes**	**No**

I ASSURE THAT I HAVE FULLY EXPLAINED TO THE ABOVE STUDY VOLUNTEER/AUTHORIZED REPRESENTATIVE, THE NATURE AND PURPOSE, PROCEDURES AND THE POSSIBLE RISK AND POTENTIAL BENEFITS OF THIS RESEARCH STUDY.

_____ _____

Signature of researcher or designate Date

Consent form copy: ☐ study volunteer ☐ medical record ☐ researcher ☐ other(specify)
*If signed by agent other than study volunteer, please explain below.