TRIAL OF RIGHT VENTRICULAR VS. MODIFIED BLALOCK-TAUSSIG SHUNT IN INFANTS WITH SINGLE VENTRICLE DEFECT UNDERGOING STAGED RECONSTRUCTION

F. Appendices

Appendix A.

Sample Informed Consent Form for Trial

SAMPLE **INFORMED CONSENT FOR RESEARCH**

CONSENT TO PARTICIPATE AS A SUBJECT
IN MEDICAL RESEARCH

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PI:

IRB #

The Nature and Purpose of this study

You are being asked to let your child take part in this research study because your child was born with a one-ventricle (lower chamber of the heart) instead of a two-ventricle heart that requires an operation. This operation is called a Norwood operation, and includes three parts: 1) the aorta, the major vessel that brings blood from the heart to the rest of the body, needs to be enlarged (made bigger), 2) the wall between the atria, the two top chambers of the heart, needs to be opened, and 3) the branch pulmonary arteries, which carry blood to the lungs, need to be disconnected from the main pulmonary artery and a shunt (a small connection) needs to be placed to deliver blood from the heart to the branch pulmonary arteries. The branch pulmonary arteries then bring blood to the lungs. In the lungs, the blood receives oxygen. This research study involves the positioning of this shunt. There are two positions for this shunt.

The standard position for the shunt has been from a branch off of the aorta, the major blood vessel that takes blood from the heart to the rest of the body. This standard shunt is called a modified Blalock-Taussig shunt (MBTS). While the MBTS has generally worked fairly well, it is understood that this connection is not perfect. If the pressures are low in the lungs then sometimes too much blood flow can be carried away from the aorta and the body may not receive enough blood flow. Because of this observation there has been an ongoing effort to determine the best way to improve the shunt. Recently, there has been some thought that placing the shunt from the right ventricle (pumping chamber of the heart), instead of from the branch of the aorta, may improve how patients do following this operation. It is unclear which of the two types of shunts is better. The purpose of this research study is to compare the shunt from the right ventricle to the branch pulmonary arteries (RV-to-PA shunt), to the standard MBTS. The aim is to find out if the RV-to-PA shunt, rather than the MBTS, will improve how patients do following the Norwood operation.

If you decide to participate in this research study then it will be randomly decided (similar to flipping a coin) if your child will have the MBTS or the RV-to-PA shunt. The remainder of the Norwood operation will be the same.

Approximately ____patients will be studied at _____. This study is also being conducted at up to 15 other medical centers across the U.S. and Canada and it is planned that about 554 patients will be enrolled from all of the centers. This study is part of the Pediatric Heart Network and is being funded by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health. Portions of Dr. _____and his(her) research team's salaries are being paid by this grant.

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Explanation of Procedures to be followed

In order for your child to participate in this study, he/she must meet certain specific criteria, and you must sign this Consent Form. Your child's primary cardiologist or cardiothoracic surgeon has been responsible for the review of the medical information and has determined that your child may be eligible for this study. If you agree to allow your child to participate in this study, we will review and record information from your child's medical chart to get background information about your child's heart problem, how the heart condition was treated, and what other medical problems your child has.

You are being asked to enroll your child in this study because your child is scheduled to undergo a Norwood operation on his or her heart, the first of three heart surgeries. This operation includes placement of a shunt (connection) to supply blood to the branch pulmonary arteries. If you agree to participate, a random process (similar to flipping a coin) will be used to determine which type of shunt, the standard MBTS, or the RV-to-PA shunt, will be placed in your child during surgery.

Your child will be monitored closely in the intensive care unit following surgery whether or not you decide to participate in this study. If you do decide to participate, a lot of the evaluation that is performed for clinical reasons will also be recorded for the purpose of this research. For instance, we will keep track of the number of days your child needs to be on the ventilator (breathing machine) and the number of days he/she is in the intensive care unit.

It is our hope to continue to follow the patients who participate in this study for years to come -- through childhood and into adolescence. However, by agreeing to participate in this study you are just giving permission for the investigators of this study to contact you by a brief telephone call or letter, until your child is 5 years of age to obtain information about how your child is doing, if this information is not available in the medical record and to describe further follow-up studies. This does not in any way commit you to any other studies.

Your child will be evaluated for the study at the following time points:

- At entry into the study
- During the hospitalization and at discharge following the Norwood operation
- Before the stage II surgery
- During the hospitalization and at discharge following the stage II surgery
- At 12 months of age
- At 14 months of age

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The evaluations may be performed while your child is in the hospital or during an office visit.

Your child will have several tests to evaluate how your child's heart is functioning during the 14 months your child is in the study. The next section explains these tests.

Echocardiogram: An echocardiogram is a painless test using sound waves that takes a 2-dimensional picture of your child's heart. In addition to the regularly scheduled echocardiograms that your child will have as part of his or her routine care, he or she will have an echocardiogram at the end of the study when he or she is 14 months old, if there is no regularly scheduled echocardiogram when your child is between 13 and 15 months of age. The echocardiogram will give us information about the function of your child's heart and the growth of the pulmonary blood vessels.

Questionnaires: As part of the study, you will be asked to fill out two questionnaires when your child is 14 months old. The first questionnaire, called the Functional Status IIR instrument, describes your child's general health and level of physical functioning. The second questionnaire is called the MacArthur Communicative Developmental Inventory. It measures your child's ways of communicating (talking and gestures). The study coordinator will explain the questionnaires to you and show you how to fill them out. You may ask him/her questions about how to complete the form, but he/she cannot help you decide what the answers are. The questionnaires will be given to you, and you can fill them out before your clinic appointment or during the time your child is at the center undergoing testing.

In addition, the Bayley Scales of Infant Development will be used to measure your child's level of development when he or she is 14 months old. This is a test that will be administered by a specially trained person to evaluate your child according to their developmental milestones -- how well your child is able to do different things related to how old they are. For example, the specialist will evaluate whether your child can walk and talk, and how they play with toys. You will be told the results of this evaluation and if your child has any delays in his/her development. The early identification of any delays will allow for early intervention. The specialist will also conduct a brief interview with you using the Hollingshead Four Factor Scale. This scale includes questions about your household, your education and your work outside the home.

Cardiac Catheterization: If your child has a routine cardiac catheterization ordered by your child's cardiologist before the stage II shunt surgery, the information from the test

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will be recorded for the study. A cardiac catheterization is not required for participation in this study.

Responsibilities of parents and subjects

During the study, you should tell Dr. _____or _____your child's medical and surgical history, all of the medicines your child is taking and about any pain or signs of illness experienced during the study. You are urged to keep all of your child's scheduled visits with the study doctor.

Foreseeable Risks and Discomforts

Your child has a serious heart abnormality that includes serious risks that are not related to this research study. Without surgery, your child will not live very long. He or she will need three heart surgeries, all of which also have serious risks not related to the research study. Risks related to participating in this study are related to the placement of the shunt (connection) your child will receive: standard MBTS or the RV-to-PA shunt. At this time, we do not know which has more risks associated with it. We do know that the risks for each are slightly different.

It can be difficult to create the perfect size shunt. For the MBTS, there is a risk of the shunt allowing too much or too little blood to be directed away from the body and directed to the pulmonary (lung) arteries. Patients with a MBTS shunt that is too big may have low blood pressure or poor blood circulation to the heart muscle and the body. If the shunt is too small the patient's blood oxygen level may be too low. The MBTS can also become narrowed over time or may clot off.

The RV-to-PA shunt can also be made too large or too small. However, it is hoped that the RV-to-PA shunt may help to avoid the problem of too much blood flow going away from the heart and the body. This shunt too has other potential problems. Patients who have a RV-to-PA shunt are at risk for some narrowing or clotting of that shunt just like a MBTS, which may cause a patient to have low oxygen levels. Also some surgeons have seen an out-pouching or aneurysm develop where the shunt is positioned from the right ventricle. Such an out-pouching would place a patient at risk for clot formation or rupture (burst open). For each of the shunts there is some risk that the position of the shunt may result in some narrowing of the branch pulmonary arteries, resulting in narrowing of the blood vessels carrying blood to lungs. The RV-to-PA shunt involves an incision in the heart muscle which may affect heart function and/or rhythm later in your child's life.

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In some cases where the structure of your child's heart or blood vessels does not permit a particular type of shunt, the surgeon will place the best shunt for your child.

The evaluation performed by the pediatric psychologist and pediatric neurologist at one year of age does not involve any invasive testing. This portion of the study will take approximately three hours of your time: approximately one hour with the psychologist, one hour with the neurologist and one hour to complete the questionnaires. There are no risks associated with these questionnaires.

Echocardiography has no risk. To obtain the echocardiographic pictures needed for this study, your child may need to be sedated. The risks of sedation are outlined in the consent that you will receive before the echocardiogram. The heart rate, blood pressure and oxygen saturation will be monitored during the examination, and your child will be closely observed by his/her caretakers during the examination. The sedation medicine is a standard medication used to sedate infants for echocardiograms.

Benefits

You child may not receive any personal benefits from being in this study. The aim of this study is to determine which of the two types of shunts, the MBTS or the RV-to-PA shunt, will be the best for patients who have hypoplastic left heart syndrome or similar single ventricle conditions. We hope that this research will be able to help children born with these abnormalities in the future.

You will be told if your child is found to have a delay in his/her development after the Bayley Scales of Infant Development evaluation is completed. You may then choose to arrange intervention for your child.

Alternative Treatments

The alternative to participating in this study is to have your child receive standard treatment for patients with a single ventricle (one lower chamber) heart as determined by your child's cardiothoracic surgeon and cardiologist.

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Voluntary Participation/Withdrawal

You may choose not to have your child be in the study, or, if you agree to have your child be in the study, you may withdraw your child from the study at any time. If you withdraw your child from the study, no new data about your child 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 child's entire medical record. All data that have already been collected for study purposes and any new information about an adverse event related to the study will be sent to the study sponsor.

Your decision not to have your child participate or to withdraw your child from the study will not involve any penalty or loss of benefits to which your child is entitled and will not affect your child's access to health care at _____. If you do decide to withdraw your child, we ask that you contact Dr. [PI] in writing and let [him/her] know that you are withdrawing your child from the study. [His/her] mailing address is [address].

Your child's participation in this study will be stopped if at any time it is determined by your doctor to be in your child's best interest.

A copy of this consent form will be provided to you for your records.

New findings

Any important information about how this shunt affects children, or any new information that we learn during this study which may affect your child's condition or your decision to have your child continue taking part in this study will be given to you by Dr. ____or _____.

Confidentiality and Privacy of Information

The study results will be retained in your research record for at least six years or until after the study is completed, whichever is longer. Your child's medical record may also be reviewed in the six-year period after the study is completed to add medical events and measurements related to your child's heart condition to the research record. At that time either the research information not already in your medical record will be destroyed or information identifying you will be removed from such study results at _____. Any research information in your medical record will be kept indefinitely.

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Study records that identify you and your child will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, you and your child will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of_____. All study information sent outside of _____ will be linked to your child through a study identification (ID) number and through a combination of your child's initials. The link between the study ID and your child will be kept in locked files at _____.

The tapes or disks with your child's echocardiogram and catheterization studies will be sent to the Pediatric Heart Network Data Coordinating Center (New England Research Institutes, in Watertown, Massachusetts) for submission to laboratories outside of _____ for reading. These tapes or disks, which may have your child's name on them, will be kept in locked files at these laboratories. Your child's name will not be recorded in any other records kept outside of _____.

Information gathered during this study and your child's medical records may be inspected and verified by staff representatives of the study sponsor (the National Institutes of Health), _____ Institutional Review Board, or the Pediatric Heart Network Data Coordinating Center. Medical records for this study and medical records from other institutions that contain your child's identity will be treated as confidential by the National Institutes of Health and will be shared only with these agencies, or as required by law. The results of this study may be published for all the subjects as a group, but will not identify your child individually.

<u>Costs</u>

There will be no additional costs to you as a result of your child's participation in this study. Tests required by the study and not part of your child's standard care such as the evaluation by the pediatric psychologist and pediatric neurologist, will be provided to your child free of charge. You will be responsible for all other costs related to your child's medical care such as hospitalization, surgery, drugs, laboratory tests, diagnostic procedures and physician fees which are considered standard medical care for patients with your child's condition.

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The following paragraph will be modified by each study site according to local guidelines. The study investigators will pay for travel expenses and food for your child and two family members/others on the days your child is scheduled for tests related to the study. If you live far away from the study center and an overnight stay is necessary to complete the study testing, you will be reimbursed for one night's lodging and meals. You will receive $_____ for the time required by your family to participate in the study.

Responsibility for Research-Related Risks

Immediate necessary medical care is available at _____ in the event that your child is injured as a result of your participation in this research study. However, there is no commitment by _____, or your [Institution] physicians to provide monetary compensation or free medical care to you in the event of a study-related injury. Further information concerning this and your child's rights as a research subject can be obtained from the _____ Office of Risk Management at _____.

Offer to answer questions about this study:

If you have any questions about this study, you should contact:
Dr. _____ Phone_____ Pager_____
Study nurse_____ Phone_____ Pager_____

For information or questions regarding your child's rights as a study subject you may contact:

_____

_____

To obtain information about study procedures, report a research related injury or ask questions about this research study, you should contact:

_____	_____	_____
Contact Name	Phone	Pager
_____	_____	_____
Contact Name	Phone	Pager

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Agreement to Participate in the Study:

"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 additional questions. I have read this consent form and agree for my child to be in this study with the understanding that I may withdraw my child at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____ _____
Parent/Legal Guardian Signature Date

_____ _____
Signature of Person Obtaining Consent Date

****

Appendix B

Sample Informed Consent Form for Genotyping and Clinical Evaluation by a Geneticist

The purpose of this consent form is to provide the information you need in considering whether to allow your child to participate in this research study.

STUDY TITLE: TRIAL OF RIGHT VENTRICULAR VS. MODIFIED BLALOCK-TAUSSIG SHUNT IN INFANTS WITH SINGLE VENTRICLE DEFECT UNDERGOING STAGED RECONSTRUCTION: GENOTYPING SUB-STUDY

IRB study number:

Study Purpose

We are asking you to let your child take part in this research sub-study because your child has a heart abnormality – a one-ventricle (lower pumping chamber of the heart) instead of a two-ventricle heart and he or she is participating in the "Trial of Right Ventricular vs. Modified Blalock-Taussig Shunt in Infants with Single Ventricle Defect Undergoing the Norwood Procedure." The type of genes (the materials that are needed to construct and operate the human body) that a person carries can change his or her response to a disease or to the medications and procedures used to treat the disease. The gene to be studied for this portion of the study makes a protein called apolipoprotein E or APOE. This sub-study will help to determine whether this gene contributes to the way the brain develops in infants with single ventricle hearts. The brains of adult patients have been shown to respond differently to disease and injury, depending on the type of APOE that is present. This knowledge will help us understand the genetics of human disease, and may lead to progress in treating children with congenital heart disease.

Approximately ____patients will be studied at _____. This study is also being conducted at up to 15 other medical centers across the U.S. and it is planned that up to 466 patients will be enrolled from all of the centers. This study is part of the Pediatric Heart Network and is being funded by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health. Portions of Dr. _____and his(her) research team's salaries are being paid by this grant.

Study Procedures

DNA sampling: If you decide to participate, a test will be performed which requires rubbing a swab on the inside of your child's cheek. This is a simple way to look at some information about your child's genes. This swab will be rubbed on a slide and the information will be analyzed at the Children's Hospital of Philadelphia. This test is not painful. It is thought that some genes may put patients at higher risk for some poor neurological development. As we interpret the types of complications that some

patients have, it may be valuable to see if patients have certain genes. The information that is collected from this portion of the study will not affect the way your child is treated in any way.

Clinical evaluation by a geneticist: Your child will also undergo a evaluation by a Pediatric Geneticist. This evaluation will include a physical examination of your child and speaking to you about your family history. The evaluation will be performed prior to the Norwood procedure and at the 14-month neurological evaluation. Should any abnormalities be detected by the Geneticist, counseling will be available for you and your family.

You may choose to participate in either the DNA sampling, or the evaluation by a geneticist , or both. The following check boxes allow you to choose whether or not you agree to allow your child to have his/her DNA tested and/or a evaluation by a Geneticist. Please read the following statements and check and initial one or more of the following:

- ❑ I AGREE to allow my child's DNA sample to be tested for APOE.

_____ Initials of Parent or Legal Guardian

- ❑ I AGREE to allow my child to undergo an evaluation by a Geneticist.

_____ Initials of Parent or Legal Guardian

Additional Procedures

None

Study Risks

None

Informational Risk

Your child's cheek swab sample will be examined for genes that affect how his/her brain responds to injury. Your child's name and other identifying information will not be sent to the laboratory performing the analyses. The sample will be analyzed along with samples from other children. The results of your child's DNA tests will not be released to you or your family and no formal genetic counseling can be provided regarding the gene analysis, because the clinical importance of the genes being tested is not known.

The evaluation by the Geneticist is a separate test from the APOE DNA test, and may be able to detect other abnormalities. Unlike the APOE genes, we know more about the significance of some of these genetic problems. If the evaluation by the Geneticist reveals any problems, counseling will be available for you and your family.

Your child's medical management will not be changed based on these results. At the end of the study, the results of the genetic testing may be published for all the subjects as a group, but it will not identify your child individually.

You should be aware that insurance companies sometimes use information on genetic testing to deny coverage to applicants. This study involves research in genetics that could be used to develop such genetic testing in the future. The information on APOE obtained in this research study cannot provide any meaningful information about individual participants. Since this is the case, if you are asked, your child has not had a genetic test.

Under some circumstances, medical research, including genetic research, can lead to the association of a specific medical illness with a particular group of persons. This association could be viewed as harmful, but may also benefit the group if such research ultimately leads to earlier detection and treatment of the condition.

Study Benefits

Your child may not benefit personally from this study. He/she will not receive immediate medical benefit from participation, but the information will help us learn more about genes that may affect your child's neurological development. He/she and your family may be helped by the discovery of an abnormality on the evaluation by the Geneticist, which would allow your child and your family to have the benefit of genetic counseling. It is possible that the study could help children in the future with a similar heart condition by improving the way we treat children with heart disease.

Alternatives

The alternative would be not to participate in this study. Your child's future care will not be affected by your decision.

Costs and Compensation

There will be no costs to you or payments made to you for participation in this study. All procedures related to APOE testing and the evaluation by the geneticist as required by the study will be provided to you free of charge. Should your cardiologist request a genetics consultation on the basis of clinical need, and not simply as a part of this study, you will be responsible for the cost of the clinically-indicated genetics consultation. (Institution) does not have any program to provide compensation for persons who may experience injury while participating in research projects. Further information about research-related injuries is available from the Office of the Institutional Review Board (Phone:_____).

Confidentiality

Confidentiality is a central concern of this sub-study of "Trial of Right Ventricular vs. Modified Blalock-Taussig Shunt in Infants with Single Ventricle Defect Undergoing Staged Reconstruction". Any genetic information obtained during this study and associated with your child will remain strictly confidential. Once we take your child's swab sample, we will assign the specimen a unique identifier (a combination of letters and numbers). We will separate your child's name and any other information that points to your child's specimen. The results of the testing will only be sent to the Data Coordinating Center (New England Research Institutes, in Watertown, Massachusetts). Genetic information will not be part of your child's medical record. Your child's identity will not be revealed when research findings are presented or published.

Study records that identify your child will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, your child will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of {Institution}. For records disclosed outside of {Institution}, your child will be assigned a unique code number. The key to the code will be kept in a locked file in Dr. _____'s office.

Although every reasonable effort will be made to protect the confidentiality of your child's records, such protection cannot be guaranteed. Government regulatory agencies such as the Food and Drug Administration (FDA) and the Office of Research Protections (OHRP) may inspect the research records if needed. Information gathered during this study and your child's medical records might be inspected and verified by staff representatives of the study sponsor (the National Institutes of Health), _____ Institutional Review Board, or the Pediatric Heart Network Data Coordinating Center. We remind all persons participating in this research that the maintaining of complete confidentiality is a responsibility of both the investigator and his/her staff, and the participant. You should consider these issues carefully before consenting to allow your child to participate in the study.

Participation is Voluntary

Your child's participation in this study is completely voluntary. You can refuse to participate or withdraw from the study at any time and such a decision will not affect your medical care at _____ (Institution) now or in the future. The investigator is also free to terminate the study, or your child's participation in it, at any time. You may at any time request that your child's blood sample collected (or the materials in it, including genetic materials) be removed from our collection and destroyed. Signing this form does not waive any of your legal rights.

Storage of Research Samples

In addition to the studies that are planned, we would like to keep any unused DNA for future research. We may want to use the sample you have provided for future studies of cardiovascular disease. The unused DNA sample will be given a unique genetic sample identifier (that is different from the identifier used for your child in the main study) and the sample will be stored at the Genetics Core Laboratory at _____. The Data Coordinating Center will have a list that links the main study identifier and the genetic sample identifier. Your child's name will only be stored at _____Hospital and therefore no hospital staff member or investigator will have information that links your child's name to the genetic sample identifier. You may choose not to have your child's sample stored for future research and still be part of the research study. Also, you may agree to have your child's specimen stored and later decide that you want to withdraw it from storage. If you make that decision, you should notify Dr. _____ in writing requesting that your specimen be discarded.

The following check boxes allow you to choose whether or not you agree to the storage of your child's sample for future research. Please read the following statements and check and initial one or more of the following:

- ❑ I AGREE to allow my child's DNA sample to be stored for future cardiovascular disease studies that are related to this research study.

_____ Initials of Parent or Legal Guardian

- ❑ I AGREE to allow my child's DNA sample to be stored for future cardiovascular disease studies that are not related to this research study.

_____ Initials of Parent or Legal Guardian

- ❑ I DO NOT AGREE to allow my child's DNA sample to be stored for future research.

_____ Initials of Parent or Legal Guardian

Questions

If you have any questions about this study, you can reach

Dr. _____ Phone_____ Pager_____

Study nurse _____ Phone_____ Pager_____

If you have any questions on your child's rights as a research subject, you can call the Institutional Review Board at _____ for information.

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 additional questions. I have read this consent form and agree for my child to be in this study with the understanding that I may withdraw my child at any time. Signing this form does not waive my legal rights. I have been told that I will be given a signed and dated copy of this consent form."

_____ _____
Parent/Legal Guardian Signature **Date**

_____ _____
Signature of Person Obtaining Consent **Date**

INVESTIGATOR'S STATEMENT

I have fully explained the nature and purpose of the above-described procedures and the risks involved in its performance. I have answered and will answer all questions to the best of my ability. I will inform the subject/family of any changes in procedure or the risks and benefits if any should occur during or after the course of the study. I have given a copy of the consent form to the subject/family. I have offered an opportunity for further explanation of this procedure to the individual whose signature appears above.

_____ _____
Investigator eliciting consent **Date**

The solicitation of subjects into this study has been approved by the _____(Institution) Institutional Review Board.

APPENDIX C

Observation

Sample Supplemental Consent to obtain limited information from those who chose not to participate yet are eligible to be randomized in the Trial of Right Ventricle versus Modified Blalock-Taussig Shunt in Infants with Single Ventricle Defect Undergoing staged Reconstruction.

SAMPLE
PEDIATRIC HEART NETWORK SUPPLEMENTAL INFORMED CONSENT FOR RESEARCH
This consent will be modified by each center according to local standards

The Nature and Purpose of this study

We are asking you to allow your child to take part in a research study because your child has a heart abnormality where instead of two pumping chambers or ventricles, there is only one. The surgery that will be done will involve creating one of two types of shunts (new connection) for blood flow. It is unclear at this time which type of shunt is best. This research study will permit us to obtain more information about how patients do after shunt placement.

Explanation of Procedures to be followed

Although your child is not participating in the full study, (The Single Ventricle Reconstruction Trial), as a part of this study, we would like to collect some information on all eligible patients until they are 5 years old. We will do this by using only the information that is written in your child's medical record. You will not be contacted. The only identifying information we will collect is your child's date of birth. Names will not be used, but a unique number will be given to each participant. The information collected will include how your child is doing at 12 months of age and yearly until he/she is 5 years old. We will also look at the type of shunt your child received information on the surgical and bypass time during your child's operation and other procedures done at the time of the Norwood surgery.

Alternative Procedures

You may choose not to allow us to collect this information. This will not affect the quality of the care you would otherwise receive.

Confidentiality and Privacy of Information

Study records that identify you and your child will be kept confidential as required by law. Federal (USA) Privacy Regulation provides safeguards for privacy, security, and authorized access. Except when required by law, you and your child will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of the xxxxx Hospital. All study information sent outside of the xxxxx Hospital will be linked to your child through a study identification (ID) number. The link between the study ID and your child will be kept in locked files at the xxxxx Hospital.

Costs

There will be no additional costs to you as a result of your child's participation in this study.

Compensation

You will not receive compensation for allowing your child to participate in this study.

Voluntary Participation

You may choose not to have your child in this study. If you agree to have your child be in this study, you may withdraw your child at any time. No new data will be collected. All data that had already been collected for study purposes will be sent to the study sponsor.

Agreement to Participate in the Study:

"The purpose of this study has been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have read this consent form and agree for my child to be in this study with the understanding that I may withdraw my child at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____ _____
Parent/Legal Guardian Signature Date

_____ _____
Signature of Person Obtaining Consent Date

APPENDIX D

MEASUREMENTS OF SOMATIC GROWTH

APPENDIX D. MEASUREMENTS OF SOMATIC GROWTH

Measurements of weight, recumbent height, and head circumference will be performed according to the guidelines developed by the U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau (MCHB) and the Centers for Disease Control and Prevention (CDC). All study personnel who will obtain height and weight measurements will complete the Growth Charts Training provided on the HRSA website:
http://128.248.232.56/mchbgrowthcharts/module4/text/mainintro.htm

Equipment to determine accurate and reliable recumbent height, weight and head circumference will conform to the MCH/CDC specifications described on the HRSA website:
http://128.248.232.56/mchbgrowthcharts/module4/text/page1a.htm

Weight, recumbent height, and head circumference will be normalized to the patient's age using data from the National Health and Nutrition Examination Survey available on the CDC website:
http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/zscore/zscore.htm

APPENDIX E

Determination of Apolipoprotein E Subclass

APPENDIX E. DETERMINATION OF APOE SUBCLASS

A buccal swab will be used to gather the DNA. Two swabs are stroked on either side of the child's cheek. This is then sent via routine mail to the Core Laboratory for DNA collection. Genomic DNA for analysis will be obtained from swab by standard techniques. High molecular weight DNA will be extracted via the Genepure™ automated nuclei acid extractor (Applied Biosystem Inc.) utilizing the supplied reagents and protocol. A sample of genomic DNA will be used to determine APOE genotypes as detailed below (1,2). The remaining DNA will be banked at –20 °C for the duration of the study. Determination of APOE genotype: the three major alleles of APOE differ by single nucleotide substitutions within two amino acid codons (112; Cys→Arg; $\in 3 \rightarrow \in 4$ and 158; Arg→Cys; $\in 3 \rightarrow \in 2$) and may be recognized by a polymerase chain reaction (PCR) based restriction enzyme isoform genotyping protocol. Briefly genomic DNA will be amplified using previously described primers. Each amplification reaction requires 20 ng genomic DNA, 1.0 pmol/μl of each primer, 10% dimenthylsulfoxide, 200 μm each dNTP, 1.0μCi[α^{32} P]dCTP, 0.05 U/μl Tag DNA polymerase and supplied buffer. An initial denaturation at 94°C for 5 minutes is followed by 35 cycles of annealing at 65°C for 0.5 minutes, extension at 70°C at 1.5 minutes, denaturation at 94°C for 0.5 minutes, and a final extension at 70°C for 10 minutes. Following amplification 5 U of the restriction enzyme Hha I are added directly to each well and the plates are incubated for at least 3 hours at 37°C. The fragments are resolved on a 6% nondenaturing polyacrylamide gel and electrophoresed for one hour under constant current (45 mA). Following electrophoresis, the gel is transferred to Whatman #M chromatography paper, dried, and autoradiographed.

Hha I cleaves the 244 bp PR product to yield smaller fragments that allow recognition of characteristic patterns on an autoradiograph gel electrophoresis. Hha I cuts the PCR product of $\in 3$ to generate 90-bp and 48-bp fragments. The $\in 4$ allele produces fragments of 72-bp and 48-bp length. The $\in 2$ allele generates a 91-bp doublet. All autoradiographs will be interpreted by two independent observers.

References:

1. Hixson JE, Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Apolipoprotein E polymorphisms affect atherosclerosis in the young male. Arterioscler Thromb 1991;11:1237-1244.
2. Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR (letter). Lancet 1991;337:1158-9.

APPENDIX F

NEURODEVELOPMENTAL AND FUNCTIONAL STATUS

APPENDIX F. NEURODEVELOPMENTAL AND FUNCTIONAL STATUS

Bayley Scales of Infant Development®—Second Edition **(BSID–II)** offers a standardized assessment of cognitive and motor development for children ages 1 month through 42 months (1). BSID–II was renormed on a stratified random sample of 1,700 children (850 boys and 850 girls) ages one month to 42 months, grouped at one-month to three-month intervals for the variables of age, sex, region, race/ethnicity, and parental education. BSID–II computes two scores, the Mental Development Index and the Psychomotor Development Index. A behavior rating scale is also incorporated into the testing to assess the degree of patient cooperation.

The Mental Development Index yields a normalized standard score evaluating a variety of abilities: sensory/perceptual acuities, discriminations and response; acquisition of object constancy; memory, learning, and problem solving; vocalization, beginning of verbal communication; basis of abstract thinking; habituation; mental mapping; complex language; and mathematical concept formation.

The Psychomotor Developmental Index yields a normalized standard score that assesses these skills: degree of body control, large muscle coordination, finer manipulatory skills of the hands and fingers, dynamic movement, dynamic praxis, postural imitation, and stereognosis. This score reflects a child's progress in large muscle activities (e.g., sitting, crawling, walking, climbing) and in prehension skills (e.g., visually-directed reaching, grasping).

The BSID-II will be administered by a trained developmental specialist at each institution using the standard kit available through the Psychological Corporation, San Antonio, Texas. The estimated time for performing the BSID-II ranges between 1-2 hours depending on patient cooperation.

MacArthur Communicative Development Inventory/Words and Gestures (CDI):
The MacArthur Communicative Development Inventory/Words and Gestures (CDI) is a parent-report instrument for assessing early language skills, designed for use in children 8 to 16 months of age (2). Use of the CDI will complement the Bayley Scales by providing a detailed assessment of several important aspects of early cognitive

development (specifically symbolic) that are difficult to measure in a brief developmental assessment. The instrument is attached. This instrument has been validated in both English and Spanish, and will be administered in both English and Spanish depending on the language preference of the parent/primary caregiver.

Functional Status II-Revised Questionnaire: The version of this questionnaire designed expressly as a parent report for parent/caregivers of children less than 5 years old is included in this Appendix (3). This questionnaire has been modified after consultation with the author of this instrument to be self-administered in this trial, rather than completed in an interview format, and requires 15-20 minutes to complete. This instrument will be administered in both English and Spanish depending on the language preference of the parent/primary caregiver.

References

1. Bayley N. Bayley Scales of Infant Development, Second Edition. San Antonio, TX: Psychol. Corp.; 1993.
2. Fenson L, Dale P, Reznick S, al. e. MacArthur Communicative Development Inventories: User's Guide and Technical Manual. San Diego, CA: Singular Publishing Group; 1993.
3. Stein REK, Jessop DJ Functional Status II(R): a measure of child health status. *Med Care* 1990; 28:1041-1055

Appendix G

CARDIAC CATHETERIZATION STUDIES

CINE-ANGIOGRAPHIC ASSESSMENT OF PULMONARY ARTERY GROWTH

Study Equipment:

Biplane cineangiography with a digital acquisition system

Timing of Studies:

Cardiac catheterization will be performed at the discretion of the attending cardiologist. One cine-angiocardiogram will be evaluated by the Core laboratory for the purpose of assessing pulmonary arterial growth. The angiocardiogram will be performed within 28 days prior to Stage II palliation (hemi-Fontan or bi-directional Glenn shunt).

Study Acquisition:

1. Height and weight: Patient length in centimeters and weight in kilograms will be measured at the time of cardiac catheterization.
2. Moderate (conscious) sedation or general anesthesia according to local practice.
3. Biplane contrast angiography: (i) To assess branch pulmonary artery anatomy, angiocardiographic measurements will be obtained in the antero-posterior or anterior oblique projections, usually with cranial angulation of the camera. To calculate Nakata index, the diameters of the right and left pulmonary arteries will be measured distal to the insertion of the shunt, but proximal to the division of the individual pulmonary artery into lobar branches. The catheter size will be used for calibration of vessel caliber. (ii) To assess PA stenosis, the proximal branch PA diameter will be measured from the images obtained at cardiac catheterization. "Proximal" will be defined as the portion of the pulmonary arteries closest to the source of pulmonary blood flow. Imaging should be done to optimize the long axis view of the pulmonary arteries. The narrowest portion of the PA within 1.0 cm of the shunt insertion will be used as the definition of the proximal PA. The vessel diameter at this point will be measured using standard off-line techniques available at the core lab facility. A second measurement using the same technique will be made at the widest portion of the pulmonary artery prior to the take-off of the lobar branches. This will be the distal pulmonary artery diameter. The area of the pulmonary artery that constitutes "proximal" pulmonary artery will differ between the two groups, but the ratio of proximal to distal vessel diameter should be a comparable variable.

Core Laboratory Data Processing and Analysis:

Nakata Index: The individual PA diameters will be expressed as Z-scores relative to body surface area (BSA) in normal subjects. Z-scores indicate the position of each measurement relative to the normal population expressed as the number of standard deviations from the population mean. Reporting the data as Z-scores adjusts for the effects of variation in body size or age. The echocardiographic Nakata index will be calculated using the following formula (1):

Nakata index (mm^2/m^2 body surface area) = (Cross-sectional area of the RPA + Cross-sectional area of the LPA) / BSA

or

Nakata index = [{3.14 x (RPA diameter (in mm)^2}/4 +{3.14 X (LPA diameter (in mm)^2}/4] / BSA.

Pulmonary artery stenosis: The site(s) of PA stenosis will be recorded. The ratio of the distal to proximal PA diameter will be used as a measure of severity of PA stenosis. PA stenosis will be graded as follows:

- Severe stenosis is defined as a ratio of 0.49 or less.
- Moderate stenosis is defined as a ratio of 0.65-0.50.
- Mild stenosis is defined as a ratio of 0.85-0.66.

In subjects with long –segment narrowing of the branch PAs (i.e hypoplastic PAs), the PA diameter Z-scores will be used as an index of PA size.

Pulmonary artery distortion: The appearance of the branch PAs will be recorded i.e., normal in appearance, diffusely narrowed, discretely narrowed or “stretched” because of distortion. The narrowest portion of the three segments of the pulmonary artery defined as a) the anatomic LPA just distal to the MPA bifurcation, b) the anatomic RPA as it passes anterior to the aorta, and 3) the anatomic RPA just to the right of the aorta and prior to the RPA bifurcation will be measured.

References

1. Nakata S, Imai Y, Takanashi Y, Kurosawa H, Tezuka K, Nakazawa M, Ando M, Takao A. A new method for the quantitative standardization of cross-sectional areas of the pulmonary arteries in congenital heart diseases with decreased pulmonary blood flow. J Thorac Cardiovasc Surg 1984;88:610-619.

APPENDIX H

ECHOCARDIOGRAPHIC STUDIES

APPENDIX H. ECHOCARDIOGRAPHIC STUDIES

Study Equipment:

1. Echocardiographic imaging system equipped with transthoracic transducers appropriate to patient size.
2. Studies will be recorded in either sVHS format with standard 1/2" sVHS videotape or in any of the several full-motion digital formats in common use (MPEG-I, MPEG-II, MPEG-IV, motion JPEG, AVI) with an optimal clip length of 10 seconds (mininal clip length 3beats). Recordings must be deidentified prior to shipment to the Data Coordinating Center. Videotapes will be deidentified and archived to a CD or DVD using the Echo Trace equipment supplied by the Data Coordinating Center.
3. For three-dimensional echocardiography, full volume datasets will be recorded in digital format. Because deidentification of three-dimensional datasets is not possible, we will obtain informed consent to send these data to the core laboratory and will establish a data use agreement between the core laboratory and NERI.

Timing of Studies:

Four echocardiograms per subject will be evaluated by the Core Laboratory. All studies will be performed according to the acquisition protocol below and obtained prior to randomization, after the first stage (randomized) surgery, prior to the second stage surgery, and at the 14 month study visit.

Study Acquisition

1. Height and weight: Patient length in centimeters and weight in kilograms will be measured at the time of echocardiography (1).
2. Sedation may be required to obtain high quality echocardiographic images that are adequate for analysis. Sedation will be performed according to the Sedation Policy at each study center and will conform to the "Practice guidelines for sedation and analgesia by non-anesthesiologist" (2).
3. Two-dimensional echocardiography: In addition to complete orthogonal sweeps from subxiphoid, apical, parasternal, and suprasternal notch windows, the following specific information pertinent to derivation of the indices of systolic and diastolic ventricular function is required:

A. *Two-dimensional recording of the right ventricular short axis:* The short-axis coronal image will be obtained at the position of the largest short-axis cross-sectional area in a plane parallel to the plane of the tricuspid valve and orthogonal to the long-axis of the right ventricle from subxyphoid or parasternal windows.

B. *Two-dimensional recording of the right ventricular long axis:* The long-axis image will be recorded in the transverse plane transecting both atrioventricular valves (if both are present) and intersecting the true apex of the right ventricle from apical windows.

C. *Two-dimensional recording of the right ventricular inflow-outflow view.* The image of the para-sagittal plane intersecting the apex of the right ventricle, the tricuspid valve, and the pulmonary valve will be recorded from subxyphoid, apical, or parasternal windows.

D. *Two -dimensional recording and measurement of the semilunar annulus(es) :* Parasternal long-axis images of the semilunar root(s) will be recorded with zoom mode activated to maximize resolution of the semilunar annulus(es).

E. *Color Doppler assessment of the severity of atrioventricular valve regurgitation:* In subjects with atrioventricular valve regurgitation, color Doppler images of the proximal jet width including the *vena contracta* are to be recorded from apical transverse and parasternal long-axis views (3,4).

F. *Color Doppler assessment of the semilunar valve(s):* From apical and parasternal long-axis views, color Doppler samples of the ventricular outflow tract(s) are recorded with the color sector placed in the ventricular outflow tract below the semilunar valve(s).

G. *Spectral Doppler recording of the tricuspid or right atrioventricular valve regurgitant jet:* 2D color Doppler mode is used to align the spectral Doppler sample parallel with the regurgitant jet. Gain should be adjusted to provide the sharpest Doppler envelope.

H. *Spectral Doppler recording of the atrioventricular valve inflow jet:* 2D color Doppler mode is used to direct spectral Doppler recording of the atrioventricular valve inflow. If two atrioventricular valves are present, the assessment is carried out on each.

I. *Spectral Doppler recording of the pulmonary vein inflow jet:* Color Doppler directed 2-dimensional Doppler sample aligned parallel with pulmonary vein flow just proximal to the point at which the jet emerges within the left atrium.

J. *Spectral Doppler recording of the semilunar outflow jet(s).*

K. *Spectral tissue Doppler recording of the tricuspid or right atrioventricular valve annular velocities.* From apical views, 2D images are used to orient the transducer in the transverse plane transecting the plane of the tricuspid valve. The pulsed sample volume is positioned within the myocardium just proximal to the valve lateral annular junction and adjusted until the sample volume remains within myocardium throughout the cardiac cycle. Tissue Doppler mode is activated and at least ten to fifteen cardiac cycles should be recorded. This data acquisition is then repeated from the septoannular junction.

L. *Spectral Doppler assessment of the RV to PA shunt:* Using color Doppler guidance, pulsed Doppler will be used to sample shunt flow. Velocity time integrals will be obtained for both forward and reverse signals.

M. *Spectral Doppler assessment of the aorta:* Using color Doppler guidance, pulsed Doppler will be used to sample flow in the descending aorta at the level of the diaphragm. Velocity time integrals will be obtained for both forward and reverse signals.

N. *Two-dimensional and Spectral Doppler assessment of the neoaortic arch:* The narrowest segment of the reconstructed aortic arch post surgical reconstruction will be recorded from suprasternal notch long-axis imaging. Using color Doppler guidance, the maximum peak Doppler gradient will be recorded through the narrowest segment of the arch by continuous wave Doppler.

O. *Measurement of pulmonary artery growth*: To assess PA anatomy, the narrowest diameters of the right and left pulmonary arteries will be measured at the following 3 locations: a) the anatomic LPA distal to the MPA bifurcation, b) the anatomic RPA as it passes posterior to the aorta, and c) the anatomic RPA to the right of the aorta and prior to the RPA bifurcation. These measurements will be obtained using two-dimensional imaging, profiling the individual pulmonary arteries in their long axis.

P. *Assessment of atrial septal shunting:* Using color Doppler guidance, the mean gradient across the atrial septal defect will be recorded by pulsed Doppler from the imaging window that provides the best alignment with the flow across the atrial septum.

Q. *Assessment of ascending aorta size:* The diameter of the ascending aorta will be obtained at level where it passes before the pulmonary artery by two-dimensional recording from a parasternal or suprasternal window.

4. Three-dimensional echocardiography: The following datasets are required:

A. 3D Full Volume black and white recording of the right ventricle: From apical views, the 3D transducer is initially used to obtain a 2D image in a plane that is midway between the planes of right ventricular inflow and outflow. The full volume mode is then activated. The resulting display of two orthogonal 2D images is used to adjust transducer position to optimize definition of right ventricular endocardium. Acquisition of 3D Full Volume is activated. The acquisition is completed in 8 cardiac cycles. This data acquisition is then repeated from the subcostal long axis view.

B. 3D Color Doppler assessment of the tricuspid valve: From apical views, the 3D transducer is initially used to obtain a 2D color flow image of tricuspid valve inflow and regurgitation (if present). The 3D color Doppler full volume mode is then activated. The resulting display of two orthogonal 2D color Doppler images is used to adjust transducer position to optimize visualization of tricuspid valve flow. Acquisition of 3D color Doppler is activated. The acquisition is completed in 14 cardiac cycles.

<u>Core Laboratory Data Processing and Analysis:</u>

1. Original recording of analog recordings will be converted to digital format at the PHN clinical center using the analog-to-digital conversion system supplied by the Data Coordinating Center. Patient identification data will be masked on screen and the echocardiogram ID number supplied by the Data Coordinating Center will be entered as an overlay image. The image processing system will be used to write the converted images to CDROM or DVD disk (one study per disk). Centers using digital image storage can transfer the digital images directly to

CDROM or DVD. The disks are to be labeled on the exterior with labels supplied by the DCC and transferred to the Data Coordinating Center semi-monthly.

2. Measurements will be performed on a microcomputer-based workstation custom programmed for electronic caliper overlay of captured digital images for recording

The following measured and derived parameters will be obtained:

Ventricular size and function: The diameter of the tricuspid valve annulus will be measured from leading edge to leading edge using orthogonal views (parasternal long-axis and apical). End-diastolic (frame at which atrioventricular valve closure occurs) and end-systolic (frame preceding atrioventricular valve opening) endocardial and epicardial borders of the ventricle on long and short axis images, excluding the papillary muscles but including outflow tract(s), will be used to compute volumes using a modified Simpson's rule algorithm (5) to provide end-diastolic and end-systolic volumes, ejection fraction, ventricular mass, and mass:volume ratio. In patients with two ventricles that contribute to systemic outflow (for example, mitral atresia with ventricular septal defect), the ventricular volumes will be calculated separately and subtracted from total epicardial volume to obtain total ventricular mass. The shape of the ventricle(s) is quantified as eccentricity from the end-diastolic long axis dimension (L) and short axis area (A) as Eccentricity = $[L^2 - (4A/L)^2]^{0.5}/L$ [2]. RV dP/dt will be calculated by dividing the difference in the pressures corresponding to 3 and 1 m/s (using the simplified Bernoulli equation) or 32 mm Hg by the time interval between 1 and 3 m/s velocities (Figure 8) as $dP/dt = [4(3)^2 – 4(1)^2]/time$ (6).

Right Ventricular Doppler Stroke Volume. The Doppler-derived right-ventricular stroke volume will be calculated as the neo-aortic time-velocity integral times the neo-aortic valve annulus.

Nakata Index: The individual PA diameters will be expressed as Z-scores relative to body surface area (BSA) in normal subjects. Z-scores indicate the position of each measurement relative to the normal population expressed as the number of standard deviations from the population mean. Reporting the data as Z-scores adjusts for the effects of variation in body size or age. The echocardiographic Nakata index will be

calculated using the following formula (7). The delta change in Nakata index from Stage I to Stage II palliation will be compared between the two groups.

Nakata index (mm^2/m^2 body surface area) = (Cross-sectional area of the RPA + Cross-sectional area of the LPA) / BSA
or
Nakata index = [{3.14 x (RPA diameter (in mm)^2}/4 +{3.14 X (LPA diameter (in mm)^2}/4] / BSA.

Tissue Doppler indices of systolic and diastolic function: Tissue Doppler velocities for both systolic longitudinal contraction (annular displacement toward the apex) and for diastolic recoil (annular displacement away from the apex) will be averaged from at least three consecutive cardiac cycles for each of the sample sites. The isovolumic acceleration will be measured from the lateral annulus recording. The isovolumic contraction and relaxation times and the ejection time will be recorded from the lateral annulus recording and the Tei index will be calculated as (8):

$$\frac{\text{isovolumic contraction time + isovolumic relaxation time}}{\text{ejection time}}$$

Doppler indices of diastolic function: Numerous derived variables have been reported from these tracings, but those that are considered of most interest are the ratio of peak early velocity (E_P) to peak atrial velocity (A_P), the early deceleration time, and the duration of the atrial contraction-related retrograde pulmonary vein Doppler signal (9).

Atrioventricular valve regurgitation

1. The proximal jet width will be measured directly.

Semilunar valve regurgitation: The degree of semilunar valve regurgitation will be graded by the width of proximal color Doppler jet at the level of the semilunar valve.

3. For 3D echocardiography, each study will be saved onto a separate CD or DVD disk. These disks will be labeled on the exterior with labels supplied by the DCC.

4. The following 3D measured and derived parameters will be obtained:

Ventricular size and function: End-diastolic (frame at which atrioventricular valve closure occurs) and end-systolic (frame preceding atrioventricular valve opening) endocardial and epicardial borders of the ventricle on subcostal long axis and apical images, excluding the papillary muscles but including outflow tract(s), will be used to compute volumes, using 8 planes for tracing (11,12). This will provide end-diastolic and end-systolic volumes, ejection fraction, ventricular mass, and mass:volume ratio that are based on actual anatomic borders with no assumptions regarding chamber geometry. In patients with two ventricles that contribute to systemic outflow (for example, mitral atresia with ventricular septal defect), the ventricular volumes will be calculated separately and subtracted from total epicardial volume to obtain total ventricular mass.

Atrioventricular valve regurgitation: Tricuspid regurgitation orifice area will be measured directly from 3D color Doppler tricuspid valve datasets (13,14).

References

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APPENDIX I

CODE LIST M: COMPLICATIONS

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CODE	COMPLICATION
	Cardiac General
	Arrhythmia (only record if requires medication or treatment)
M-0001	Atrial fibrillation
M-0002	Atrial flutter
M-0003	Supraventricular tachycardia
M-0004	Junctional ectopic tachycardia
M-0005	Sinus node dysfunction (requiring pacing)
M-0006	Atrioventicular block (second or third, not first)
M-0007	Ventricular tachycardia
M-0008	Ventricular fibrillation
	Mediastinum
M-0020	Hemopericardium (requiring intervention, includes post-op mediastinal hemorrhage, N.B. hemorrhage requiring restenotomy = SAE)
M-0021	Pericardial effusion (requiring drainage)
M-0022	Post-pericardiotomy syndrome (requiring treatment)
	Cardiac Performance
M-0030	Hypotension (<40 mmHg for neonates; < 50 mm Hg after Stage II)
M-0031	Hypertension (requiring chronic [>30d] post-discharge therapy, therapy should be at therapeutic doses and specifically prescribed for the treatment of hypertension)
M-0032	RV dysfunction- (requiring escalation or initiation of therapy, not to include immediate post-op dysfunction routinely associated with CPB)
	Valves
M-0033	Semi-lunar valve insufficiency or stenosis (requiring treatment initiation or escalation)
M-0034	Atrioventricular valve insufficiency or stenosis (requiring treatment initiation or escalation)
M-0035	Prosthetic valve dysfunction
	Great Vessels
M-0036	SVC stenosis (anatomic, symptomatic, “SVC syndrome”)
M-0037	SVC occlusion
M-0038	IVC occlusion
M-0099	Other cardiovascular
	Respiratory
M-0101	Chronic respiratory failure (intubated for > 2 weeks after surgery)
M-0102	Chylothorax (Postoperative accumulation of chylous fluid in the pleural space requiring intervention whether by evacuation, dietary change and / or medical treatment)
M-0104	Hemothorax (requiring drainage)
M-0105	Phrenic nerve injury/ diaphragmatic paralysis (newly elevated diaphragm on CXR)
M-0106	Pleural effusion (requiring drainage >7 days post- op, other)
M-0107	Pneumothorax (requiring tube insertion)

M-0108	Tracheal injury
M-0109	Vocal cord injury (direct visualization)
M-0110	Airway obstruction- requiring a significant intervention
M-0111	Hypoxia (requiring readmission or escalation of care)
M-0199	Other respiratory
	Neurological
M-0203	Choreoathetosis/posturing (moderate involuntary movements interfering with function)
M-0204	Coma
M-0205	Intracranial bleeding (confirmed by imaging)
M-0206	Seizure(s) - definite (EEG or obvious motor)
M-0207	Stroke (confirmed by imaging study)
M-0209	Hydrocephalus (report if CTCAE ≥2 or higher)
M-0210	Neurological deficit persisting at discharge not attributed to any of above diagnoses
M-0299	Other neurological
	Gastrointestinal
M-0301	Direct bilirubin > 4
M-0303	Liver failure (AST, ALT or GGT >500)
M-0304	NEC, confirmed (pneumatosis or free air)
M-0305	NEC, suspected (NPO, antibiotics started)
M-0306	Other esophageal or bowel perforations not associated with NEC
M-0307	Upper GI bleed, requiring treatment
M-0309	Stricture/stenosis/GI (CTCAE ≥ grade 2)
M-0399	Other gastrointestinal
	Infectious
M-0401	Empyema
M-0402	Endocarditis
M-0414	Gastroenteritis or Enteritis
M-0408	Line infection, Bacterial (+ blood cultures)
M0409	Line infection, Fungal (+ blood cultures)
M-0410	~~Pneumonia~~, Respiratory infection, Bacterial (Requiring the initiation of therapy)
M-0411	~~Pneumonia~~, Respiratory infection, Viral (Requiring the initiation of therapy)
M-0404	Mediastinitis/ Wound Infection, deep (requires I & D, sternal instability)
M-0407	Wound infection, superficial (erythema, possible tissue separation and drainage)
M-0405	Sepsis, confirmed (positive blood culture, not line infection)
M-0412	Sepsis, clinical with negative cultures
M-0413	Urinary tract infection
M-0499	Other infection
	Renal
M-0501	Acute renal failure (creatinine > 1.5 mg/dl (133 micromole/L) or tripling of baseline value for ≤ 7 days) temporary dialysis
M-0502	Chronic renal failure (creatinine > 1.5 mg/dl (133 micromoles/L) or tripling of baseline value for >7 days) chronic dialysis
M-0599	Other renal

	Hematologic
M-0601	Anemia (Hemoglobin < 10 gm/dl)
M-0602	Thrombocytopenia (platelets < 50,000)
M-0604	Hematoma (CTCAE grade ≥2)
M-0605	Hemorrhage, GI (CTCAE grade ≥2) [heme + stools]
M-0606	Hemorrhage, GU (CTCAE grade ≥2)
M-0607	Hemorrhage, pulmonary/upper respiratory (CTCAE grade ≥2)
M-0699	Other hematologic
	Vascular
M-0603	Thrombus/thromboembolism
M-0799	Vascular, other
	Other Complication
M-9999	Other