STUDY: Swine Flu Vaccine in Healthy Children
PROTOCOL NO: V112_02
STERLING IRB ID: 3276-023
DATE OF IRB REVIEW: 07/30/09
DATE REVISED: 08/10/09, 08/27/09

PARENTAL PERMISSION FORM AND AUTHORIZATION TO USE AND DISCLOSE MEDICAL INFORMATION

STUDY TITLE: A Pivotal Randomized, Single-Blind, Dose-Finding Study to Evaluate Immunogenicity, Safety and Tolerability of Different Formulations of an Adjuvanted and Non-Adjuvanted Egg-Derived, Inactivated Novel Swine Origin A/H1N1 Monovalent Subunit Influenza Virus Vaccine in Healthy Pediatric Subjects 3 to < 9 Years of Age

PROTOCOL NO: V112_02

STUDY DOCTOR: Isaac R. Melamed, M.D.

STUDY SITE: 1st International Clinical Research Centers
3260 E. 104th Avenue
Thornton, CO 80233

TELEPHONE: 303-224-4700

SPONSOR: Novartis Vaccines and Diagnostics

GENERAL INFORMATION

You and your child are being asked to participate in a clinical research study, sponsored by Novartis Vaccines and Diagnostics. You and your child's participation in this research study is strictly voluntary, meaning that you may or may not choose to take part. Before you decide whether or not you are willing to participate, this form will provide information about what you and your child will be asked to do before, during and after the study as well as the risks and possible benefits of the study. You may have a copy of this form to review at your leisure or to ask advice from others.

The study doctor or study staff will answer any questions you may have about this form or about the study. Please read this form carefully and ask any questions that might help you decide if you would like to take part in this clinical research study. This form may contain words that you do not understand. Please ask the study doctor or study staff to explain the words or information that you do not understand. If you decide that you and your child will take part in this study, you will be asked to sign this Parental Permission Form and Authorization to Use and Disclose Medical Information. A copy of this signed form will be given to you to keep.

BACKGROUND AND PURPOSE OF THE STUDY

Influenza (also called the flu) is a highly contagious disease caused by a virus. Influenza is still a major health concern and is one of the leading causes of death in the world. Vaccination is the most common way to prevent a disease like influenza and its complications. Vaccines contain substances that help your immune system fight off the virus. The immune system works to protect the body against infection and disease. This vaccine is a shot.

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The novel swine origin influenza virus is a new influenza virus (also called A/H1N1) first detected in April 2009. This is a new flu virus that comes from Influenza A and is found in swine, but is different from the swine flu virus of 1977. In the United States, as of mid-July 2009, 40,617 confirmed or probable cases of A/H1N1 influenza and 263 deaths have been reported. Worldwide (including the U.S.), as of early June, there have been 94,512 cases of A/H1N1 influenza and 429 deaths. The World Health Organization (WHO) declared a pandemic (a worldwide outbreak) due to the rapid worldwide spread of the virus from person to person.

Many people have been exposed to different human influenza viruses since their childhoods. This means that their immune system (body's defense system) contains antibodies (substances within your body that fight off germs) that recognize these types of viruses. Because this swine flu virus is a new virus, most people's immune systems won't recognize this virus, and therefore they might not be able to fight off the virus and will become ill with influenza. As more people become ill with influenza, the virus will be spread to more people, and the number of cases of influenza will greatly increase.

The sponsor of this study is developing a vaccine against this A/H1N1 influenza virus. To develop a suitable vaccine, it is important that studies are done with vaccines containing antigens (substances that cause the body to make antibodies) that will protect against this virus.

The purpose of this study is to evaluate the side effects from the vaccine and how the vaccine helps your immune system to create antibodies against this A/H1N1 influenza virus. The vaccines in this study are investigational. That means they have not been approved by regulatory agencies such as the US Food and Drug Administration (FDA).

In this study, investigators will also examine if increasing the dose of the A/H1N1 antigen in the vaccine with or without additives (substances added to improve medicine, also called "adjuvants") will improve the body's ability to respond to this virus. An adjuvant may increase the effect of the influenza vaccine. This means it may help your body to develop more antibodies. MF59 is an adjuvant which is used in influenza vaccines licensed for the adults and/or elderly in many countries worldwide, but it is not contained in any vaccines currently approved in the United States.

Data collected from this study will help identify a vaccine that may protect individuals from getting A/H1N1 influenza, and thus may reduce the rapid spread of the virus or may reduce or prevent hospitalization and deaths during a severe outbreak.

OVERVIEW OF THE STUDY

Eight investigational vaccine formulations with different amounts of A/H1N1 antigens and with or without adjuvant will be tested in this study. Your child will be assigned by chance (like flipping of a coin) to one of the study vaccine formulations. Your child has equal chances of getting any one of the 8 vaccine formulations. You will not know which vaccine your child receives until he or she completes the study.

Approximately 1,360 healthy children 3 to 8 years of age will take part in this study. There are two parts to this study: Enrollment/Vaccination Period and Follow-up Period.

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If you choose to have your child will take part in this study, you will be asked to sign this Parental Permission Form and Authorization to Use and Disclose Medical Information. After you sign this document, your child will undergo an enrollment visit. During this enrollment visit, the study doctor will evaluate your child's health to determine whether he or she meets the eligibility criteria and can participate in the study. Your child will have approximately 2 teaspoons of blood collected from a vein in his or her arm at visits 1, 2, 3, 4 and 5. The blood samples will be used to evaluate how your child's defense (immune) system responds to the vaccine and for laboratory tests (routine blood chemistry tests).

If your child meets the study requirements and is eligible to receive the study vaccine, he or she will receive two doses of the assigned vaccine, 3 weeks apart. The vaccinations will be given in the upper part of the arm your child uses the least.

You and your child will be in the study for approximately 13 months after the first study vaccine. In addition, you and your child will need to come into the clinic 5 times, and you must be available for up to 11 monthly telephone calls from the study staff. You and your child may return to the clinic if additional blood needs to be collected for re-test. You and your child must also follow all instructions given by the study doctor or by his/her staff. Detailed study procedures are described in the section below.

STUDY PROCEDURES

Before any study procedures are performed you will be asked to review and sign this Parental Permission Form and Authorization to Use and Disclose Medical Information indicating that you have been told about you and your child's involvement in the study and the risks of participating in the study, and you agree to take part.

The study staff will schedule the clinic visits during the Enrollment/Vaccination Period described in the table below and telephone calls (during the Follow-Up Period) monthly for 12 months following your child's last study vaccination. The study staff will remind you to complete the diaries and memory aids. You must bring the diary card with you when you bring your child in for clinic visits. Memory aids will be used for the telephone calls you will receive monthly, but you should not give or send these to the clinic. You should call the study clinic as soon as possible if your child experiences any medical problem that prevents him/her from performing his/her usual activities, causes you to take him/her to visit a physician or hospital, or that may lead you to end your child's participation in the study early.

The table below describes the activities to be performed during the Enrollment/Vaccination period.

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Overview of Study Procedures for Enrollment/Vaccination Period

	Enrollment/Vaccination Period (Days)				
Study Day	1	8	22	29	43
Study Visit	1	2	3	4	5
Visit Type	Clinic	Clinic	Clinic	Clinic	Clinic
You will be asked about the health of your child and his/her recent medication use	x	x	x	x	x
Brief Physical Examination	x	x	x	x	x
Measurement of vital signs and body temperature	x	x	x	x	x
Blood sample collection for immune response	x		x	x	x
Blood sample collection for laboratory tests	x	x	x		
Investigational vaccine administered	x		x		
Take home diaries	x	x	x	x	
Complete diaries	x	x	x	x	x
Review diaries with the staff in person		x	x	x	x
Review any changes in your child's health, serious medical problems, and/or visits to a healthcare provider		x	x	x	x
Review of medications	x	x	x	x	x

As outlined in the Table above, the study staff will conduct the following procedures:

- **Review of your child's health status and brief physical examination** - During the enrollment visit, you will be asked to provide information about your child's health. You may be asked to get medical records from other doctors. You will be asked to confirm whether or not your child has previously received a flu vaccine and whether or not your child has experienced the flu or signs of the flu within the past 6 months. You will be asked to describe all medications including prescription and non-prescription (over-the-counter) with the exception of vitamins and minerals your child is currently taking. Your child will have a brief physical examination performed by the study staff at each clinic visit.

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- **Measure your child's vital signs and body temperature** - Your child's blood pressure, heart rate (beat) and body temperature will be measured during each clinic visit.

If your child is eligible to take part in the study, the study doctor or member of the study staff will:

- **Collect a blood sample** -Approximately 1 teaspoon of blood will be drawn from a vein in your child's arm at the Enrollment Visit (Visit 1), Visit 3, Visit 4 and Visit 5 for immune response measurement. Your child will have an additional 1 teaspoon of blood drawn at the Enrollment Visit (Visit 1), Visit 2 and Visit 3 for laboratory tests. Approximately 1 teaspoon of additional blood may be drawn if your child has a lab test result that is abnormal, so that a repeat test can be performed to confirm the abnormal result.

- **Perform vaccination** - At the Enrollment Visit (Visit 1) and on Day 22 (Visit 3), your child will receive the study vaccination in the upper part of the arm he or she uses the least. After the vaccination, your child will need to stay in the clinic for at least 30 minutes so that the study staff can observe if your child has any reactions.

  30 minutes after the vaccination, the study staff will check the place where your child received the vaccination and ask you and your child about any reactions since the vaccination was given. They will also ask if your child has pain where the vaccination was given. If your child has pain, the study staff will ask about it's intensity.

- **Diary Cards** - Study staff will give you a diary card and show you how to complete it. You will be asked to complete diary cards throughout the Enrollment/Vaccination period of the study. On diary cards covering the 7 days after each vaccination, you will record your child's temperature starting 6 hours after vaccination on the evening of the day of vaccination and for each of the following 6 days. On these days you will also record how the skin around your child's vaccination site looks (including making measurements of any changes you see), whether or not your child is having specific side effects from vaccination, whether or not your child is showing any other signs of illness and any prescription and non-prescription (over the counter) medications your child is taking. At times outside of the 7 days after each vaccination, you will complete the diary cards for any signs of illness your child is having, prescription medications you have given your child to treat these signs of illness, and any serious medical problems, such as hospitalizations or life-threatening medical problems, your child may have.

  Study staff will also provide you with a digital thermometer and ruler and show you how to use them. The study staff will answer any questions you may have about the diary card.

Overview of Study Procedures for Follow-Up Period

Following the Enrollment/Vaccination period, you have monthly telephone contact for approximately 12 months after the last study vaccination (for a total of 11 phone contacts after your child's last clinic visit).

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- **Memory Aids** - The study staff will give you a memory aid at the last clinic visit and will show you how to complete it for the remainder of the time that your child participates in the study. You will be asked to complete the memory aid throughout the Follow-up period of the study for review during each telephone contact. You will be asked to have the memory aid out and ready for review when the study staff calls you to check on your child's health status. You will be asked to record on the memory aid information about any time your child is taken to a medical office for a medical problem or a routine check-up, emergency room visits, any medical condition that is serious (requires hospitalization or is life-threatening), and any medical condition that results in ending your child's participation in the study.

POSSIBLE RISKS AND SIDE EFFECTS

There are possible risks or side effects your child might experience from participating in the study. Your child will be monitored for the risks and side effects throughout his/her participation in the study. You should contact the study doctor if you think your child is having side effects or experiencing a change in his/her medical condition. Possible risks and discomforts are detailed below; however, as this is a new vaccine, there may be other risks and side effects that are not yet known.

Risks of vaccination

The most common side effects at the site of injection (shot) reported for flu vaccines include:

- redness of the skin
- hardness of the skin
- swelling and pain at the injection site

Other general side effects that may commonly occur following use of influenza vaccines include:

- general feeling of being unwell (malaise)
- muscle pain and joint pain (arthritis)
- headache
- tiredness (fatigue)
- fever

All of these side effects are usually mild and generally last for 1 to 4 days.

Other side effects that have been reported in clinical studies with other influenza vaccines or have been reported by people who received influenza vaccines may include:

Reactions at the site of injection:

- bruising
- itchiness
- rash
- warmth

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- lump or irritation at the site where the vaccine was given
- sharp pain in or along nerves or tingling of pins and needles (paresthesia)
- pain limiting movement of the limb where the vaccine was given
- infection
- muscle ache

Other general reactions:

- hot flashes or flushing
- chills or shivering
- dizziness
- generalized weakness
- fainting shortly after vaccination
- nausea
- vomiting
- diarrhea
- loss of appetite
- abdominal pain
- back pain
- lymph node enlargement
- temporary decrease in the number of blood platelets, which may increase the risk of bleeding
- bleeding
- decrease in red blood cells, or anemia, which may make you feel tired.
- high blood pressure (hypertension)
- shortness of breath
- wheezing
- chest tightness
- chest pain
- cough
- sore throat
- runny nose
- "pins and needles" in the skin
- sweating
- skin disorders related to allergic reaction (which can lead to rash and skin loss)
- inflammation of blood vessels (including inflammation of blood vessels that may cause short-term effect on kidneys)
- confusion
- headaches similar to those described as migraine
- seizures associated with fever
- spinal cord or brain inflammation (encephalomyelitis)
- paralysis
- muscle weakness
- infection
- life-threatening and/or debilitating disorders of the nervous system

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These other general conditions have occurred in people who received influenza vaccines:

- autoimmune disorders (these are disorders in which the body's tissues are attacked by its own immune system and include liver injury or nerve injury)
- arthritis (joint pain)

In addition, study vaccines, like any medication, may cause an allergic reaction. These allergic reactions may be mild, such as mild rash or hives or, rarely can be severe or life-threatening such as difficulty breathing, swelling of the face or tongue, a sudden drop in blood pressure with loss of consciousness and/or associated with seizures, including the possibility of death. The study staff is aware of this possibility of allergic reaction and have appropriate emergency treatment available for immediate use in the event of severe allergic reactions. **If you think your child is having a severe allergic reaction after you leave the study center, call 9-1-1 and seek medical attention immediately.**

Your study doctor or study nurse will check you closely for these side effects. This is why you will be asked to stay at the clinic for at least 30 minutes after each vaccination. There may be unexpected side effects that may occur during the study that have so far not been reported.

If your child has had an allergic reaction in the past to eggs, egg products, neomycin or polymyxin (antibiotics), sodium ethylmercurothiosalicylate or thimerosal (compounds containing mercury that are frequently used as preservatives in vaccines), beta propriolactone (substance that inactivates a virus), or nonoxynol 9 (substance commonly used in cleaners, cosmetics, and spermicides), you must tell the medical staff before you decide to sign this Parental Permission Form and Authorization to Use and Disclose Medical Information. If you have any questions about your child's allergies, you should check with the study doctor. **If your child has an allergy to any of these products, your child will not be able to take part in this study.** Serious allergic reactions can be life-threatening.

Symptoms having other causes may appear to be side effects of the vaccination. For this reason your child will be kept under close observation during the study. Please contact your study doctor immediately if you are concerned about anything or your child experiences any unusual symptom.

Risks of blood sample collection

Blood will be drawn from a vein in your child's arm using a needle. There is a minor risk associated with taking blood, including temporary soreness, and possible bleeding, bruising, injury to a nerve and discoloration. Your child may feel faint or light-headed for a short period of time. There is a rare possibility of infection.

Other risks

If your child has any unusual symptoms, report them immediately to the study doctor or study nurse. Your child will be monitored and treated promptly and adequately.

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If your child experiences a change in health during the study (even if not related to the study vaccine) and needs a medical intervention, you will be asked to give a copy of any clinical documents related to this event to the study doctor. This information will be part of the study results. To ensure confidentiality, any personal information that might identify your child will be removed.

POSSIBLE BENEFITS

There may or may not be a direct medical benefit to your child as a result of taking part in this study. Information from this study may help us learn more about the study vaccine and the body's defense (immune) system.

ALTERNATIVES TO STUDY PARTICIPATION

This swine flu virus is different from the seasonal influenza viruses that circulate each year. There are currently no vaccines against this swine flu influenza virus. Although new antiviral agents have improved the ability to treat new influenza infections, vaccination remains the most suitable method of controlling global influenza.

Your child does not have to participate in this study. You should discuss other treatment alternatives that may be right for your child with your child's doctor.

NEW FINDINGS

Any new information or findings that develop during the study, that may affect your decision on allowing your child to continue participation in this study will be made available to you in a timely manner.

PARTICIPANT RESPONSIBILITIES

If you agree for your child to participate in the study, you are agreeing that you and your child will come to the clinic for the scheduled visits and will be available for the monthly and final telephone contacts. You are agreeing to follow the study doctor's and staff's instructions, including instructions to complete and return Diary Cards (when asked). You must tell the study doctor and study staff about any changes in your child's medical condition or medicines during the study.

COST OF PARTICIPATING IN THE STUDY

There will be no cost involved in taking part in this study. Your child will receive the study vaccines at no cost to you.

COMPENSATION FOR PARTICIPATION

Yes, you will be compensated for your time and travel for your child's study participation. You will receive $50.00 for completing each study office visit (visits 1-5) and $15.00 for completing each telephone visit (visits 6-16) to help you cover your expenses (e.g., travel, parking, and meals). If

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you and your child do not complete the entire study, you will be compensated for the visits and telephone calls that you and your child do complete.

RESEARCH-RELATED INJURY

If your child is injured as a direct result of a study related procedure or because he/she received the study vaccine, appropriate medical care for the immediate treatment of the illness or injury will be given. If the study site or someone who works for them caused your child an injury, Novartis Vaccines and Diagnostics will not pay your child's medical bill. If you or your child did not follow study instructions, Novartis Vaccines and Diagnostics will not pay your child's medical bill.

If your child experiences an injury or if you or your child have any questions or concerns, you should contact the study doctor.

By signing this Parental Permission Form and Authorization to Use and Disclose Medical Information you will not waive the legal rights to which you are entitled as a participant in a research study.

VOLUNTARY PARTICIPATION / RIGHT TO WITHDRAW

Taking part in this study is voluntary. That means that you and your child can decide not to participate or if you and your child agree to take part, you can change your mind at any time without penalty or loss of any benefits to which you or your child may be otherwise entitled. Your decision to not participate will not affect the care that your child would normally get from his or her doctor.

If you decide to withdraw from the study, please inform the study doctor or member of the study staff right away and inform them of any medical problems your child experienced or medications your child took since the last study contact.

Your child's participation in this study may be stopped at any time by the study doctor or the sponsor without your consent. This may happen if:

- Your child requires a medication that is not allowed during the study,
- Your child develops a condition which may negatively affect his or her health.
- You or your child do not follow the study instructions given by the study staff,
- You withdraw consent to participate,
- The sponsor decides to suspend or terminate the study or the participation of this site in the study,
- Other unanticipated circumstances

CONFIDENTIALITY AND AUTHORIZATION TO USE AND DISCLOSE MEDICAL INFORMATION

During this study the study doctor or study staff will record information about your child, your child's health, and your child's participation in the study on forms provided by Novartis Vaccines and Diagnostics. These are known as case report forms. Your child will not be able to participate in this study if you do not agree to the collection of this information about him/her.

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The information collected about your child, will be held by 1st International Clinical Research Centers and Novartis Vaccines and Diagnostics. To ensure that your child's personal information is kept confidential, your child's name, and any other information that allows your child to be identified, will not be entered on the case report forms or included in any records or samples the study doctor provides to i3 Research or Novartis Vaccines and Diagnostics. Instead, your child will only be identified by a code. The code is used so that the study doctor can identify your child if necessary.

Novartis Vaccines and Diagnostics and its representatives will analyze and use the information they receive for the purposes of this study and to help establish whether the study vaccine is safe and effective. If necessary for these purposes, they may communicate information to affiliates of Novartis Vaccines and Diagnostics, Sterling Institutional Review Boards (IRB: an independent group that evaluates the study and the safety of the people participating in the study), people and companies with whom Novartis Vaccines and Diagnostics works with and regulatory agencies. These people, companies, and regulatory agencies may be located in other countries. Your child's participation in this research study will remain confidential. After the research clinic gives the information in your child's study records or medical records to the Sponsor or its employees, the information will no longer be protected by federal law. Because of the need to give information to the company, absolute confidentiality cannot be guaranteed. Novartis Vaccines and Diagnostics will keep any information it receives as confidential as possible within the limits of applicable law.

Representatives from government agencies, Sterling Institutional Review Board, Novartis Vaccines and Diagnostics or its agents (e.g., auditors, monitors), and representatives may also need access to your child's medical records and study records for the purpose of checking data collected for the study. By signing the Parental Permission Form and Authorization to Use and Disclose Medical Information, you authorize this access.

The following groups may inspect the study records and your child's medical records, without violating your child's confidentiality:

- Novartis Vaccines and Diagnostics employees or representatives
- Health Authorities Representative from other countries
- The United States Food and Drug Administration (FDA)
- Sterling Institutional Review Board (IRB) - A group that oversees the conduct of human research and assures the protection of subject's rights and welfare.

When you sign this Parental Permission Form and Authorization to Use and Disclose Medical Information, you give permission for any of the groups listed above to look at your child's medical records

Blood samples obtained in the study will be labeled with your child's study code (also referred to as initials) and number, but not your child's name. The blood samples will be stored in a freezer until the tests looking at your child's immune response to the study vaccine are performed. These blood samples may be stored by Novartis Vaccines and Diagnostics beyond the duration of this study, and may be used for additional laboratory tests to further characterize the response to vaccines administered in this study. By signing this Parental Permission Form and Authorization

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to Use and Disclose Medical Information you allow Novartis Vaccines and Diagnostics to store your child's blood samples for this purpose. Under no circumstances will your child's blood be used for any human genetic testing.

You have certain rights to gain access and to correct any inaccuracies in information about your child. As explained above, you and your child will not know which study vaccine he/she has received until the study is over. While this is the case, the study is referred to as being "blinded". This study needs to be blinded to ensure its scientific integrity, so it is important that it remains this way until the study is over. By signing the Parental Permission Form and Authorization to Use and Disclose Medical Information you agree that you and your child will not be able to have access to information about the study vaccine your child received until the study is over and Novartis Vaccines and Diagnostics can find out which vaccine your child received. After that, you can obtain access to information through the study doctor.

If the results of the study are published in medical publications, nothing will identify your child. If you or your child has any questions about the collection and use of information about you or your child would like to exercise rights that you may have with respect to this information, you should ask your study doctor. This authorization will not expire. You may withdraw your authorization to use and disclose your child's health information at any time. You can do this by writing a letter to the study doctor, saying that you are taking away your authorization to use and disclose your child's medical information. If you withdraw your authorization, your child will no longer be able to participate in the study. No new information will be required after the study doctor receives the notice withdrawing your authorization, but any information collected up to that time will be used in the study.

WHOM TO CONTACT FOR QUESTIONS

If you have any medical or study related questions or feel your child has been hurt or injured as a result of taking part in the study, you should contact Dr. Melamed or the study staff at 303-224-4700.

If you have questions regarding your rights as a research participant, or if you have questions, concerns, complaints about the research, would like information, or would like to offer input, you may contact: Sally P. Green, M.D., Chairman of Sterling Institutional Review Board, 6300 Powers Ferry Road, Suite 600-351, Atlanta, Georgia 30339 (mailing address) at telephone number 1-888-636-1062 (toll free).

If you agree to participate in this study, you will be given a copy of this Parental Permission Form and Authorization to Use and Disclose Medical Information after both you and the study doctor or his/her delegate have signed it.

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Parent(s)/Guardian(s) Statement of Consent

Before you sign this consent form, please ask any questions about any part of this study that is not clear to you. By signing below, you are confirming that you have read the information provided in this document, that you have been told about the study and risks, and that you and your child agree to be in this study. You are also documenting that you have been given enough time to ask questions about the study and that the questions have been answered to your satisfaction. By signing this document you are giving permission to review, disclose and use your confidential information, as described above. By signing this consent, you and your child are not giving up any of your legal rights.

You will receive a signed copy of this document.

_____
Child's name (print)

_____
Parent/guardian's name (print)

_____ _____
Parent/guardian's signature Date

By signing this below, you confirm that you have conducted the informed consent process and have been available to answer any questions by the parent/guardian of the participant.

_____
Study doctor or designee (print)

_____ _____
Study doctor or designee's signature Date

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