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CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

A Phase 2b, Multicenter, Randomized, Double Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy of Short-Course Antimicrobial Therapy for Young Children with Acute Otitis Media (AOM) and Impact on Antimicrobial Resistance

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University Of Pittsburgh Institutional Review Board
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Evening/Weekend Phone Number	412-999-3277 (EARS)

SOURCE OF SUPPORT: National Institutes of Health

Who is being asked to take part in this research study?
We invite you and your child to take part in our research study because your child has an ear infection. Before you decide whether to participate, it is important for you to know why the research is being done and what it will involve. Ask us if there is anything that is not clear or if you would like more information. Please read this information and feel free to ask any questions before you agree to take part in the study. The purpose of this consent form is to help you decide if you want to have your child participate in this research study. This consent form contains information about why the study is being conducted, what will be involved if you agree to have your child participate, and what the risks and benefits are. You will be provided a copy of this consent document. Please read this consent form carefully before making your decision. Please ask the study doctor or study staff to explain anything you do not clearly understand.

This is a research study. The purpose of this study is to find out how many days of antibiotics (a medicine that kills bacteria) should be given to children with ear infections. Ear infections are one of the most common illnesses in children. About 30 million cases are diagnosed yearly, making it the most common reason for children to get antibiotics. In recent years, sometimes the usual antibiotics don't work. Using antibiotics when there is not an infection (for example, for colds or fluid in the middle ear), and taking too many days of antibiotics are two reasons why a germ may change so that it is not killed by the antibiotic. Some children are more likely than others to develop infection with resistant germs: children under 2 years old, children who have received antibiotics in the last 60 days, children in daycare or those who are around many other children, and children who have had many ear infections. Your decision regarding your child's participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh, medical care at Children's Hospital of Pittsburgh of UPMC or affiliated health care provider or your relationship with a health care insurance provider.

As this research study includes children, the following applies: Title 45, Code of Federal Regulations, Part 46, Subpart D
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd.

What will happen at today's visit?
Today, if you decide to have your child participate in the study and you sign the informed consent, we will ask you about your child's

- date of birth, current and past medical history, including medications
- sibling ages, day care attendance,
- parent contact information, smoking history, and indicators of socioeconomic status such as education level and type of insurance.

A limited physical exam will be done by a nurse, nurse practitioner or physician and will include a temperature, pulse, breathing rate and ear exam. For research only, we will collect a little bit

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of mucous from the back of your child's nose with a flexible soft-tipped swab. The results of the back-of-the-nose culture will help us understand how germs in the back of your child's nose change when a child is taking antibiotics. The test may also help us to choose a new antibiotic if your child does not get better. The cost of the nose cultures will be paid by the study. The swab will then be frozen for future research on the germs that cause ear infections. The swab will be labeled with the study identification number. No personal identifying information will be used. Your child will need to sign a new consent form at age 18 for the continued use of their research specimen.

When possible, we will get a picture of your child's ear drums that may help us see if the ear infection is getting better or not. We have a very small otoscope (an instrument used to look at the eardrum) attached to a camera and TV monitor. You may be able to see your child's ear drum and ear infection. We will also be able to share this picture with your child's doctor. The whole visit will take about 1 hour.

Study Procedures

About 600 children overall, including 300 children in Pittsburgh, between the ages of 6 and 23 months, with an ear infection will be enrolled in the study. Your child will be given the antibiotic amoxicillin-clavulanate, one of the generic forms of Augmentin, for either 5 or 10 days. He/she will be assigned by chance, like the flip of a coin, to one of those groups. The actual dose will be based on your child's weight. Amoxicillin-clavulanate is approved by the Food and Drug Administration (FDA) for 10 days for the treatment of ear infections. The study medicine will be supplied in 2 bottles. The bottle for the first 5 days will be antibiotic for everyone. The second bottle for days 6-10 will be antibiotic for half of the children and placebo (non-active medicine) for the other half of the children. This is so everyone is taking something for 10 days. Neither you nor your child's doctor will know to which group your child has been randomly assigned. The study pays for the study medicine and placebo.

We want to follow your child for the entire cold and ear infection season until next September. We will call you on day 4-6 and examine your child on day 12-14 to see if the ear infection is getting better. Then, we will see your child every 6 weeks until May 31. The last study visit for everyone is in September. Study visits will be in the same office where your child was enrolled.

When your child is taking study medicine for an ear infection, we will ask you to write in a memory aid diary so that we understand how your child is feeling. We want to know if your child is pulling his ears, crying, fussy, having trouble sleeping or eating less. You will also write down when you give the study medicine, acetaminophen (Tylenol), and the number and type of bowel movements. Please do not give ear drops to your child during the study. You may give your child acetaminophen (Tylenol) for pain or fever. The correct dose of acetaminophen for your child will be written on your child's memory aid diary. In general, we recommend avoiding the use of ibuprofen in young children; however, you may give your child an appropriate dose of ibuprofen for pain or fever that is not relieved by Tylenol. All medications given to your child should be recorded in the memory aid diary. Please bring the memory aid diary with you to visits two and three.

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You can call us on the study phone anytime (412-999-3277). We want to see your child anytime she/he is not better or is worse. Some reasons that we want you to call us are continued fever, waking up at night, continued crying or if you are worried about your child. We will see your child within 24 hours if necessary and we will reimburse you for transportation as at the other visits. A sick visit would be very similar to a regular visit.

If your child's ear infection is not better, worse or comes back before day 17 of the study, we will give him/her either amoxicillin-clavulanate or cefdinir for 10 days; or an injection (a shot) in the thigh muscle of ceftriaxone (Rocephin®) , 1-3 doses (each on a different day). We will examine your child about 14 days afterwards to see how the ear infection is responding to the medication.

If your child's ear infection gets better, but comes back on or after day 17, we will give your child the same study treatment that he/she received on day 1 because this is probably a new infection. If your child is treated with more study medication, we will ask you to complete another memory aid diary and bring it to the follow-up visit. If your child has had an allergic reaction (hives) to amoxicillin-clavulanate, we will change the antibiotic to cefdinir (Omnicef™). Ceftriaxone, cefdinir and amoxicillin-clavulanate are FDA-approved for the treatment of ear infections. The dose for these medications is based on your child's weight. If your child is taken off amoxicillin-clavulanate and prescribed one of the antibiotics described above, your child will not be withdrawn from the research study. You may withdraw your consent for your child's participation in this research study at any time.

The following table explains all of the visits in the study, which will be very similar to the first visit described in detail above. Your child will be in the study for 6 months to a year, depending on the month of enrollment.

Visit	Description
Day 1	AOM-SOS scale, medical history; temperature; exam; ear drum picture; 1 nose swab; receive medication & diary.
Day 4-6 Phone Visit	Review diary and discuss compliance.
Day 12-14	AOM-SOS scale, medical history since last visit; exam; temperature; ear drum picture; 1 nose swab; collect diary; assessment of parental satisfaction of therapy.
Day 16-30 (if needed)	AOM-SOS scale, medical history since last visit; exam; temperature; ear drum picture; 1 nose swab
Every 6 weeks until May 31	AOM-SOS scale, medical history since last visit; exam; temperature; ear drum picture; 1 nose swab.
Unscheduled-Sick visit	AOM-SOS scale, medical history since last visit; exam; temperature; 1 nose swab (if your child has a recurrent ear infection).

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End-of-Study in September	AOM-SOS scale, medical history since last visit; exam; ear drum picture; temperature; 1 nose swab.

What are the possible risks, side effects and discomforts of this research study?
All participants will take amoxicillin-clavulanate for days 1 – 5. About half of the participants will also take amoxicillin-clavulanate days 6 – 10. The most common side effect is diarrhea. Infrequently, children may have vomiting, nausea, yeast diaper rash, stomach pain, gas and/or headache. Rarely, there can be an increase in liver enzymes, allergic reactions including hives, joint pain and shock or anaphylaxis (a severe form of allergy which may lead to death). Most of the reported side effects have been mild to moderate and stop when the medicine is stopped.

Placebo - There is no active medicine in the placebo. The same flavoring, coloring and powder mixers used in regular amoxicillin-clavulanate are in the placebo to make it look and taste like the real medicine. A child could rarely be allergic to one of these powders.

Ear Wax Removal – It may be necessary to remove ear wax in order to see the ear drum or take a picture. This can infrequently cause a red area or irritation in the ear canal or minor bleeding. The physician or nurse practitioner looking at your child's ears has had expert training.

Nose Swab – Obtaining mucous from the nose with a soft swab can commonly cause minor discomfort and gagging.

Ear Photograph - We have a very small otoscope attached to a camera and a TV monitor. You may be able to see your child's ear drum and the ear infection. Children commonly cry while being held for an ear exam or a picture.

Confidentiality - Rarely, there is a risk of loss of confidentiality. All of the study data will be stored in locked file cabinets that are kept in the research area and computer records are password protected. The study staff are trained and experienced in protecting health information (date of birth, medical record number, names) as confidential information. Ear photographs will be stored in computer files on computers that are locked in the research rooms. Each computer has a password only available to the study staff. Pictures that are published or used for teaching purposes will not have any identifying information attached. Identifying codes will be kept in a locked file cabinet in the research office.

What are the possible benefits of this study?
Your child may benefit from early detection of ear infections that come back, but no benefits are guaranteed from your child being in the study. The results of this study may be of benefit in the future to other children with ear infections. The results of this study will assist health care providers in making decisions regarding the use of antibiotics for treating children with ear infections and may benefit the health of the general community by slowing the spread of resistant germs. By reducing the occurrence of resistant germs, society may benefit through

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easier treatment of this common infection and may result in fewer side effects of antibiotic therapy.

What treatments or procedures are available for my child if I decide not to take part in this study?
Amoxicillin-clavulanate for ten days is one of the antibiotics usually prescribed for ear infections. If your child is not in the study, your child may receive a prescription for it or other common antibiotics such as amoxicillin, cefdinir or ceftriaxone to treat your child's ear infection for the recommended number of days as prescribed by your child's doctor to properly treat your child's ear infection.

Will we be told of any new risks that may be found during the course of the study?
We will tell you as soon as possible if significant new information is found during the study which may cause you to change your mind about your child staying in the study.

Will our insurance be charged for costs of any procedures in the study?
You and/or your insurer will be billed for any routine care services that are provided. You will be responsible for any applicable co-pays, coinsurances, and deductibles. There will be no costs to you or your insurance company for the study visits. The cost of the study medication will also be covered by the study.

Will my child be paid for participating in the study?
Your child will not be paid. There will not be any bills sent to you or your insurance company for participation in this study. You will be reimbursed $20 for each study visit to help cover travel expenses. At the last visit, you will be reimbursed $40 if you have attended most of the scheduled study visits. In addition, you will receive free parking for each visit at our facility.

Who will pay if my child is injured as a result of this study?
If you believe that the research procedures have resulted in an injury to your child, immediately contact the Principle Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your child's participation in this research study will be provided to your child by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your child's research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

Confidentiality: Who will know about my child's participation in this research study?
Any identifiable information about your child obtained from this research will be kept as confidential (private) as possible. All records related to your child's involvement in this research study will be stored in a locked file cabinet. Your child's identity will not be recorded in study data, but will be indicated by a case number rather than by name, and the information linking these case numbers with the identity will be kept separate from the research records. Your child will not be identified by name in any publication of the research results.

Will this research study involve the use or disclosure of my child's identifiable medical information?

We may review your child's past, current and future medical information. The information that will be recorded will be limited to information concerning ear infections and will be used to help us find out how many days of antibiotics children should take for ear infections. We will use your child's medical information for an indefinite period of time. If we use any of the information for other studies, we will never provide personal identifiers that would allow them to learn your child's identity. Dr. Hoberman and his study staff will be permitted to use your child's identifiable health information indefinitely if you decide to have you child participate in this study.

Who will have access to identifiable information related to my child's participation in this study?

In addition to the investigators listed on the first page of this consent form and their research staff, the following individuals may have access to identifiable information related to your child's participation in this research study:

- Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your child's identifiable research information for the purpose of monitoring the appropriate conduct of this research study.

- In unusual cases, the investigators may be required to release identifiable information related to your child's participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies. Research investigators may be required under Pennsylvania law to report any suspicion of child abuse to child protection services.

- Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information related to your child's participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g. laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) assessing internal hospital operations (i.e. quality assurance).

- Authorized representatives of the National Institutes of Health (NIH), the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) may review and/or obtain your child's identifiable medical information for the purpose of monitoring the accuracy and completeness of the research data, for performing required scientific analyses of the research, and re-analyses of the research data at a later date and to be sure that the research is being conducted according to the guidelines of each institution. These organizations review research studies to be sure that participants are safe. While these organizations have provided their assurance that they will not release

your child's identifiable medical information to anyone else, Children's Hospital of Pittsburgh cannot guarantee this.

- The Privacy Act applies to the information collection per Privacy Act System of Records Notice (SORN) #09-25-0200 http://oma.od.nih.gov/ms/privacy/pa-files/0200.htm which covers clinical, basic and population-based research studies of the NIH. The authority to collect this information is under 42 USC 285f National Institute of Allergy and Infectious Diseases (NIAID).

How long will the investigators be permitted to use and share identifiable information related to my child's participation in this study?
Dr. Hoberman and his study staff will be permitted to use your child's identifiable health information indefinitely. In addition, they will contact you a few months after your child completes the study to share information about the study findings and to discuss other research opportunities you might find of interest.

May I have access to the medical information that results from my child's participation in this study?
In accordance with the Children's Hospital of Pittsburgh of UPMC Notice of Privacy Practices document which you have been provided, you are allowed to look at information (including information resulting from your child's participation in this research study) contained within your child's medical records unless specifically stated. In this study, neither the researcher nor you will know which treatment course your child is receiving (continued antibiotics or placebo). After the study is finished and the results have been studied, we will send you a letter that tells you which treatment course your child received.

Is my child's participation in this study voluntary?
Yes, your child's participation in this research study is completely voluntary. The study will include the use and disclosure of your identifiable information for the purposes described above. If you do not provide your consent, your child will not be allowed to participate in the research study. Your decision regarding your child's participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh, medical care at a UPMC hospital or affiliated health care provider or your relationship with a health care insurance provider nor will there be any penalty or loss of benefits if you decide to not have your child participate.

Your child's doctor may be involved as an investigator in this research study. As both your child's doctor and a research investigator, s/he is interested both in your child's medical care and the conduct of this research study. Before agreeing to participate in this research study or at any time during your study participation, you may discuss your child's care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

May I withdraw my consent for my child's participation in this study at a future date?
Yes, you may withdraw your consent for your child's participation in this research study at any

time. The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your child's identifiable medical information) related to your child's participation in this research study. Any identifiable research or medical information recorded for, or resulting from, your child's participation in the research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above and will continue to be kept confidential. If you decide to withdraw before any procedures have occurred, your child will be replaced in the study.

To withdraw your consent for your child's participation in this research study you should provide a written and dated notice of this decision to Dr. Hoberman at the address listed on the first page on this form. If you decide to withdraw your consent while your child has an untreated ear infection, you should call your child's primary care provider for an appointment. If you withdraw your consent at any time, there is no penalty or loss of benefits to which your child is otherwise entitled.

Can my child be removed from the study without my consent?

The researchers also have the right to stop your child's participation if your child has had an unexpected reaction, if you have failed to follow instructions, for other reasons that the investigator is concerned about your child or because the entire study has been stopped. The University of Pittsburgh Institutional Review Board (IRB), FDA or NIH may stop the study if there are concerns about the safety of the enrolled subjects. The primary purpose of the IRB is to protect the rights and welfare of participants involved in research activities being conducted at any University of Pittsburgh facility.

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Voluntary Consent

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation. Dr. Hoberman (412-999-3277) will be available for questions about this research, my child's rights, and any possible research-related injury. By signing this form I agree to participate in this research study. I will receive a signed copy of this consent form.

_____
Printed Name of Child (Research Subject)

I understand that, as a minor (age less than 18 years), the above named child is not permitted to participate in this research study without my consent. Therefore, by signing this from I give my consent for his/her participation in this research study and allow the use and sharing of my child's medical record information for the purposes described above.

_____	_____
Printed Parent's Name	Relationship to Child
_____	_____
Signature of Parent	Date

Certification of Informed Consent

I certify that I have explained the nature and purpose of this research study to the above-named individual and I have discussed the potential benefits and possible risks of study participation. Any questions the individual has about the study have been answered and we will always be available to address future questions as they arise. I further certify that no component of this protocol was begun until after this consent form was signed.

_____	_____
Printed Investigator's Name	Role in Research Study
_____	_____

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Signature of Investigator Date

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