Submit Consent Documents in **Microsoft Word ONLY** *Leave blank for IRB Office Use.*	***IRB Office Use Only:*** Approval Date: Approved Consent IRB Version No.: PI Name: IRB No.

National Institutes of Health (NIH)

Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)

INFORMED CONSENT DOCUMENT
(Parent Permission)

Study Title: Losartan for the Treatment of Pediatric NAFLD (STOP-NAFLD): A Phase 2, Randomized, Placebo-Controlled Clinical Trial

Principal Investigator:

PI Version Date: 18 February 19

IRB No.:

What you should know about this study

- Your child is being asked to join a research study.
- This consent form explains the research study and your child's part in the study.
- Please read it carefully and take as much time as you need.
- Your child is a volunteer. He or she can choose not to take part. If your child agrees to join, he or she may quit at any time. There will be no penalty if your child decides to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to allow your child to continue to be in the study.

Purpose of research project

Nonalcoholic fatty liver disease (NAFLD) is a common liver disease in children, is potentially serious, and is without an approved treatment. NAFLD can lead to severe liver disease in some children. The term NAFLD covers a range of liver disease progression. NAFLD is usually discovered by blood tests, or other tests such as liver ultrasound or CT scan. A liver biopsy (small amount of liver tissue removed by needle) is usually done to confirm liver disease. The biopsy results may show different amounts of fat, inflammation (swelling), and scarring in the liver. Your child has been asked to be in this research study because one of the liver tests noted above has shown your child has NAFLD. This is a nationwide study funded by the National Institutes of Health (NIH).

Why you are being asked to participate

The purpose of this study is to find out whether treatment with losartan improves NAFLD compared to treatment with a placebo (an inactive study drug). The placebo capsule looks just like the losartan capsule, but has no active ingredients.

Your child must be at least 8 years old and have had a liver biopsy in the past that showed NAFLD to join this study. Your child will not be allowed to join this study if he/she has poorly controlled diabetes or cirrhosis. Your child cannot have drunk significant amounts of alcohol. We will ask your child questions to check that he/she is not drinking significant amounts of alcohol during the study.

If your child is capable of becoming pregnant and is sexually active, she must use two effective forms of birth control during the study. Examples of birth control are: no sexual intercourse, hormonal contraceptives (oral, implant, transdermal patch, or injection) at a stable dose for at least 1 month prior to screening, and barrier (condom with spermicide, diaphragm with spermicide). We will do a urine pregnancy test to make certain that your daughter is not pregnant before she begins this study; a pregnancy test will also be administered at each study visit. If your daughter is nursing an infant, she may not enroll in the study.

If your child is eligible and your child agrees to join the study, he/she will be one of about 110 children nationwide enrolled in this study. Children will be randomly put into one of two groups by using a chance mechanism, similar to flipping a coin: (1) those taking losartan or (2) those taking placebo only. Neither you, your child, nor the study staff, will know which drug he/she is taking. The type of study drug your child is taking will be available to the study doctor if it is needed in an emergency. The masking of study drug is done so that the study gives fair and unbiased results. Your child will swallow one capsule each morning for one week and then increase to two capsules once per day, for 24 weeks during the study.

We intend to learn more about treating fatty liver in children. There will be an NIH database to store medical information collected during this study, and blood will be collected for serum and plasma analysis and storage (banking) in a NIDDK-sponsored biorepository.

Procedures

If you agree to have your child in this study, the following will happen:

Visit #1 - Screening ~ 3hours

You and your child will be asked to sign permission forms allowing us to look at your child's medical records. Your child needs to come to this visit fasting. This means that your child can drink only water for 12 hours before the visit. We will draw about five tablespoons (80 mL) of your child's blood for tests. We will interview you and/or your child and give him/her a physical exam. Your child's blood pressure, heart rate, temperature, and respiratory rate will be measured. We will measure your child's height, weight, waist, and hips. You and your child will complete surveys about alcohol use, beverage intake and quality of life.

The study doctor will conduct a detailed physical exam and review your child's medical history. The study doctor will listen to your child's heart and lungs, and check his/her eyes, limbs, and abdomen, skin, eyes, ears, throat, chest, extremities, and nervous system. We will ask about your child's health and any medicines your child is taking or has taken in the past.

The Study Coordinator will provide educational material regarding diet and exercise. Your child may not be pregnant during this study, if she is able to become pregnant, we will perform a urine pregnancy test.

Visit #2 - Randomization (Treatment Assignment) ~45 minutes

The randomization visit occurs after the screening evaluations are complete. We will review that eligibility criteria continue to be met. A brief physical exam will be done and any changes in medication use will be documented. Your child's blood pressure, heart rate, temperature, and respiratory rate will be measured. Height, weight, hip, and waist measurements will be made. The study doctor will listen to your child's heart and lungs, and check his/her eyes, limbs, and abdomen. You will be asked about your child's health. Girls who have started having periods will have a urine pregnancy test.

If your child is still eligible for the study, we will use a computer to randomly choose the study drug your child will be given. This is random, like a flip of a coin. Neither your child nor the study team will know whether your child is receiving losartan or placebo. Once the assignment has been generated, the study staff will provide the assigned study drug (in person) and teach you and your child about starting the drug. Your child will swallow one capsule each morning for one week and then increase to two capsules once per day, for weeks 2-24 during the study. The study staff will teach you and your child how to use an automated blood pressure monitor. You will be asked to take your child's blood pressure each morning for the first 14 days and record it on a blood pressure log. The study staff will discuss possible side effects and teach you how to complete the blood pressure log. Patients and/or parents should call the clinic if your child's blood pressure drops below < 90 mmHg systolic **or** < 60 mmHg diastolic and for symptoms of hypotension (dizziness, fainting, and lightheadedness). The log will be reviewed with you over the telephone during the second week and checked for hypotension. Study drug will be given with written instructions to reach the prescribed dose. Your child will return in approximately 4 weeks for the next clinical follow-up visit.

Telephone Visit – Week 2

We will arrange a telephone visit after your child has started the higher dose (100 mg) to review your child's blood pressure log, the dosing instructions, and any adverse effects he or she may be experiencing.

Visit #3 – Week 4 Follow-Up Visit ~1 hour

We will interview you and/or your child. Your child's blood pressure, heart rate, temperature, and respiratory rate will be measured. We will measure your child's height, weight, waist, and hips. You and your child will answer questions about alcohol use. We will ask about your child's health and any changes in medicines your child is taking and how well they followed their study drug dosing schedule. You will be given information to maintain diet and exercise. We will collect all study drug bottles for capsule counts. Females who are of child bearing potential will have a urine pregnancy test. Approximately 1 teaspoon (4 mL) of blood will be drawn for lab tests to monitor your child's response to and tolerance of the study drug.

The study doctor will review your child's medical history. The study doctor will listen to your child's heart and lungs, and check his/her eyes, limbs, and abdomen. The study doctor will discuss any side effects with you and your child. The study doctor may change study drug dosing as needed. Your study doctor or study coordinator will review dosing instructions. You will return in approximately 8 weeks for your next follow-up visit.

Visit # 4- Week 12 Follow-Up Visit ~1 hour

Your child needs to come to this visit fasting and bring his/her study medication bottle(s). This means that your child can drink only water for the 12 hours before to the visit. We will interview you and/or your child. Your child's blood pressure, heart rate, temperature, and respiratory rate will be measured. We will measure your child's height, weight, waist, and hips. We will ask about your child's health and any changes in medicines your child is taking and how well they followed their study drug dosing schedule. You will be given information to maintain diet and exercise. We will collect all study drug bottles for capsule counts. Females who are of child bearing potential will have a urine pregnancy test. Approximately 4 tablespoons of blood (60 mL) will be drawn for lab tests, to monitor your child's response to the study drug and for serum and plasma sample storage.

The study doctor will review your child's medical history. The study doctor will listen to your child's heart and lungs, and check his/her eyes, limbs, and abdomen. The study doctor will discuss any side effects with you and your child. The study doctor may change study drug dosing as needed. Your study doctor or study coordinator will review dosing instructions. You will return in approximately 12 weeks for your next follow-up visit.

Visit # 5- Week 24 End of treatment visit ~1 hour

Your child needs to come to this visit fasting and bring his/her study medication bottle(s). This means that your child can drink only water for the 12 hours before to the visit. We will interview you and/or your child. Your child's blood pressure, heart rate, temperature, and respiratory rate will be measured. We will measure your child's height, weight, waist, and hips. You and your child will complete surveys about alcohol use, beverage intake and quality of life. We will ask about your child's health and any changes in medicines your child is taking and how well they followed their study drug dosing schedule. You will be given information to maintain diet and exercise. We will collect all study drug bottles for capsule counts. Females who are of child bearing

potential will have a urine pregnancy test. We will draw about four tablespoons (60 mL) of your child's blood for lab tests, to monitor your child's response to the study drug and for serum and plasma sample storage.

The study doctor will conduct a detailed physical exam and review your child's medical history. The study doctor will listen to your child's heart and lungs, and check his/her eyes, limbs, abdomen, skin, eyes, ears, throat, chest, extremities, and nervous system. The study doctor will discuss any side effects with you and your child. The study doctor may change study drug dosing as needed. You will return in approximately 12 weeks for your final study visit to assess any duration of treatment response, and to evaluate for any adverse effects of treatment.

Visit # 6- Week 36 Follow-Up Visit
(Completion of the study)

Your child needs to come to this visit fasting and bring any remaining study medication bottle(s) to the visit. This means that your child can drink only water for the 12 hours before to the visit. You and your child will complete surveys about alcohol use, beverage intake and quality of life. The study doctor will conduct a focused physical exam and review your child's medical history. The study doctor will listen to your child's heart and lungs, and check his/her eyes, limbs, abdomen, skin, eyes, ears, throat, chest, extremities, and nervous system. The study doctor will discuss any side effects with you and your child. We will draw about two tablespoons (42 mL) of your child's blood for lab tests, to monitor your child's response to the withdrawal of study drug and for serum and plasma sample storage.

Risks/discomforts

Are there risks if my child gets pregnant? There are risks to an unborn baby if your daughter becomes pregnant during the STOP-NAFLD Trial. The use of losartan in pregnancy is contraindicated. Use of losartan during the second and third trimesters of pregnancy can cause injury and death to the developing fetus. Potential adverse effects to the baby include skull and lung hypoplasia (incomplete development), anuria (kidneys do not make urine), hypotension (low blood pressure), kidney failure, and death. If your daughter decides to take part in this study, and she has periods, she must be as sure as possible that she is not pregnant. It is important that you contact the study doctor right away if you think your daughter may be pregnant, if she has missed a period or if it is late, or if she has had a change such as heavier bleeding than usual or bleeding between periods. If your daughter becomes pregnant during the study she will stop taking the study drug.

Blood Draws: Blood drawing is mildly painful and can cause bruising and very rarely, dizziness or fainting, blood clots, bleeding or an infection at the site. If numbing cream is used for blood draws, it may cause pain, skin irritation, or the skin temporarily turning red, white or developing a rash. This usually doesn't last very long. During the entire study period, your child will have approximately 17 tablespoons of blood drawn (246 mL).

Losartan: This drug is an "angiotensin 2 receptor antagonist", used primarily to treat high blood pressure in both children and in adults. It keeps blood vessels from narrowing, which lowers blood pressure and improves blood flow. It is also used to lower the risk of stroke in certain adults with heart disease. Losartan is used also to slow long-term kidney damage in people with type 2 diabetes who also have high blood pressure. The most common side effects are dizziness and lowered blood pressure. Other side effects are listed below:

- Low blood pressure – Losartan is a medicine that is commonly used to treat children with high blood pressure so it can lower the blood pressure in children with NAFLD. It may make the blood pressure too low and could cause dizziness, fainting and lightheadedness. This is more likely to happen if your child is not drinking enough water and becomes dehydrated. You will be instructed to measure your child's blood pressure each morning for 14 days after starting losartan to monitor for low blood pressure. During the study, it will be important for your child to drink water regularly and avoid becoming dehydrated.
- Cold or flu symptoms such as cough, stuffy nose, sore throat or fever. Tell the study staff if your child experiences these.
- High potassium levels – Medications such as losartan can rarely cause the potassium level in the blood to become elevated. Do not give your child a potassium supplement or potassium based salt substitutes while on the study medication. Your child's potassium levels will be checked regularly during the study.
- High acid levels – Losartan can rarely elevate acid levels in the blood. This will be checked at each appointment.
- Kidney injury - Losartan can rarely cause injury to the kidneys, especially if taken with other medications that can injure the kidneys. Your child's kidney function will be monitored closely through the blood work during the study. If your child is prescribed new medications while in the study, tell the study coordinator or investigator right away.
- Muscle pain - In rare cases, losartan can cause a condition that results in the breakdown of skeletal muscle tissue. Call the study doctor or the study staff right away if you have unexplained muscle pain, tenderness, or weakness; especially if you also have fever, unusual tiredness, and dark colored urine.

If you want more information about these risks you should ask the study doctor before you sign this consent.

If your child has any illness or discomfort as a result of using the study drug call your study doctor immediately. If necessary, your child might need to stop taking the study drug.

Other risks:

• Your child's condition may not improve, it may stay the same, or it may get worse

while in this study.

- There may be side effects or discomforts from the use of the study drug that we don't know about yet.

Benefits

Your child may receive no benefit from being in this study. He/she may receive benefit from the counseling on diet and exercise offered in this study. Your child's liver disease may improve because of treatment with the study drug. He/she may benefit from health information obtained during the physical exams, laboratory tests, and other study procedures. Your child's participation may help future patients by providing important information about the treatment of NAFLD.

Payment

You/your child will be compensated $50 for time and travel for each of the clinic visits completed. You/your child will receive up to $300 if he/she completes all aspects of the study.

Data Sharing

Representatives of the National Institutes of Health, Data Coordinating Center, or other experts may review your consent document, your child's records at visits to the clinic as part of the ongoing monitoring of the progress of the study. In addition, representatives from the United States Food and Drug Administration (FDA), Office for Human Research Protections (OHRP) or the <<insert your Institution>> Institutional Review Board may review your child's records, including your child's medical records.

Protecting data confidentiality

Your child's health and medical information will be labeled with only an identifying number and a random three letter code that cannot be linked to your child's name or other personal identifiers except at the clinical center where your child completes visits. Your child's health and medical information will be sent to the Data Coordinating Center currently located at The Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, and at the end of the study to the NIDDK Central Data Repository. Your child's name, address, social security number, date of birth and other personal identifiers will not be sent to the data Repository, and hence the Repository will not be able to give out your child's name or other information that identifies your child to the researchers who use your child's data.

A Data and Safety Monitoring Board will have access to the research records including your health information.

All research projects carry some risk that information about a participant may become known to people outside of a study. Every reasonable effort will be made to keep your child's records confidential. Your child's participation in this study will be kept confidential, and your child's name, address, and other personal identifying information will not be made known to anyone other than study staff at this clinic. When results from

this study are published in medical literature, your child will not be identified by name.

Per NIH Notice NOT-OD-17-109 (Notice of Changes to NIH Policy for Issuing Certificates of Confidentiality https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html) this research is deemed to be issued a Certificate through this Policy and is therefore required to protect the privacy of individuals who are subjects of such research in accordance with subsection 301(d) of the Public Health Service Act.

A certificate of confidentiality from the U.S. Department of Health and Human Services has been provided for this study so that research staff can avoid disclosing your child's records in Federal or State courts if requested by outside organizations or individuals without your written consent (involuntary disclosure). You, your child's legal representative, or government agencies (FDA, NIH, DHHS) may still request your child's study information from the research staff and it will be provided (voluntary disclosure). This Certificate does not mean that the government approves or disapproves of this study. This Certificate adds special protection for research information that identifies your child. It allows us, in some circumstances, to refuse to give out study information about your child without your consent when it is sought in a legal action. Still, we may disclose identifying information about your child if, for example, you need medical help.

We may also give out information about your child if the government audits us. The research team will also give information to local or state authorities:

- If they suspect abuse or neglect of a child or dependent adult;
- If certain communicable diseases are present; and
- If the team learns that you or your child plan to harm someone. In this case, the team also may warn the person who is at risk.

Protecting subject privacy during data collection

Your child's records will not be released without your consent to the extent the law allows. As a way to establish and maintain a trusting relationship with your child, it is necessary that we keep confidential any discussion that we have with him/her about certain sensitive subjects (e.g., alcohol or drug use, sexual activities) unless your child permits otherwise, or unless there is a strong compelling medical reason for doing differently.

Alternatives to procedures or treatments

You have the option not to allow your child to participate in this study. There are no approved treatments for NAFLD in children. You may discuss other alternatives with your child's gastroenterologist.

Biological specimens

The blood (plasma, serum), and data collected from your child during this study are important to science. You will not own the plasma and serum samples, or data after it is given to the study. You will not receive any financial benefit from any product or idea

created by the investigators using the data or samples collected from your child.

Your child's specimens – the serum and plasma samples collected as part of this study – will be sent to the NIDDK Biosample Repository. At the end of the study, the data collected on your child will be sent to the NIDDK Data Repository. The Repositories are a research resource supported by the NIH. The Repositories store and distribute samples and study data from people with many kinds of disorders, from unaffected family members, and from other healthy people. The purpose is to make samples and data available for use in health research. Your child's samples and data will be used by the researchers carrying out the STOP-NAFLD Trial, but they also may be used by other researchers, both during the study and after it ends. Your child's samples and data may be stored indefinitely.

Your child's samples and data will be labeled with a code number before they are sent to the Repositories. Your child's name, address, social security number, date of birth, and other personal identifiers will not be sent to the Repositories, and hence the Repositories will not be able to give out your child's name or other information that identifies your child to the researchers who use your child's samples and data.

If you do not agree to have your child's samples and data sent to the Repositories, your child may not join the STOP-NAFLD Trial. If you agree to have your child's samples and data sent to the Repositories, you can change your mind up until the end of the trial. When study researchers receive written instructions from you, they will destroy your child's samples and all information that identifies them. You may withdraw unused samples during the study. After this study ends, you will not be able to withdraw your child's sample because the Repository will not know which one is your child's. The sample will stay in the Repository indefinitely.

Because researchers will not have access to your child's identity, you will not get the results of any studies that might be performed on your child's samples. Sometimes research results in findings or inventions that have value if they are made or sold. These findings or inventions may be patented or licensed, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits may be paid back to the researchers and the organizations doing this study, but you or your child will not receive any financial benefits.

Cost of participation in the study

There are no costs to you regarding this study

What happens if you leave the study early?

Participation in research is entirely voluntary. Your child may refuse to participate or decide to stop participating at any time without jeopardy to the medical care they receive.

We will tell you about new information that may affect your child's health, welfare, or willingness to stay in this study. Your decision will not result in any penalty or loss of benefits to which your child is entitled. If you have questions about your child's rights, or to report research related problems, please contact: << insert contact info>>

Conflict of Interest

The study staff does not have any conflict of interest in conducting the study.

Payment of treatment costs for injury or illness from study participation

If your child is injured as a direct result of participation in this research, the <<Insert your Institution>> will provide any medical care needed to treat those injuries. The <<Insert your Institution>>> will not provide any other form of compensation to you or your child if he/she is injured. You may call the <<insert your Institution>> Human Research Protections Program office to inquire about your child's rights as a research subject or to report research-related problems at (xxx) xxx-xxxx.

Clinical Trial Registration

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

Authorization for Disclosure of Protected Health Information for Research

We are asking you to authorize the disclosure and use of your child's private health information for this research study. By signing this authorization, you agree that the following health care providers may release your child's private health information to us for use in this research study:

<<List Providers)>> to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Demographic information (name, date of birth, age, gender, race, etc.)

The people who may receive or use your child's private health information include the researchers and their staff.

The Health Care Providers listed above are required by the Federal Privacy Rule to protect your child's private health information. By signing this Authorization, you permit them to release your child's information to the researchers for use in this research study. The

researchers will try to make sure that everyone who needs to see your child's private information for this research keeps it confidential, but we cannot guarantee this. The people who may receive or use your child's private health information include the researchers and their staff.

Some other people may see your child's private health information outside of the research team. They may include the sponsor of the study (NIH: National Institutes of Health), study safety monitors, government regulators, and legal compliance staff. All these people must also keep your child's information confidential.

You do not have to sign this Authorization, but if you don't, your child will not join the study. It is your choice.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, NIH: NATIONAL INSTITUTES OF HEALTH and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, data coordinating center, Data and Safety Monitoring Board, may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research (for example, to account for a subject's withdrawal from the research study, to conduct investigations of scientific misconduct, or to report adverse events). If you revoke this Authorization, you will no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: <<insert PI name and contact info>>

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other research purposes.

Ending Consent

You may end your permission at any time. Information obtained and used before you end your permission will continue to be used for research. If you wish to end your permission allowing your child to participate, let us know.

Who do I call if I have questions or problems?

- Call the principal investigator, <<insert name>>, at <<telephone number>> if you have questions, complaints, or get sick or injured as a result of being in this study.

- Call or contact the <<institution>> IRB Office if you have questions about your rights as a study participant. Contact the IRB if you feel you have not been

treated fairly or if you have other concerns. The IRB contact information is:

Address:

Telephone:
Toll Free: 1-xxx-xxx-xxxx
Fax: xxx-xxx-xxxx
E-mail:

What does your signature (or thumbprint/mark) on this consent form mean?

Your signature below means that you have read the above information about this study and have had a chance to ask questions to help you be informed about what your child will do in this study. Your signature also means that you have been told that you can change your mind later if you want to. You will be given a copy of this consent form to keep. By signing this consent form you are not giving up any of your legal rights or those of your child. You agree to let your child participate.

Print name of Parent/Legal Guardian	Signature of Parent/Legal Guardian	Date

Print name of child participant _____

Print name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

Print name of Witness	Signature of Witness	Date

Give one copy to the participant and keep one copy in study records