Dear sir/madam:

Your child is being invited to take part in a research study: An open-label, single-arm, multicentre clinical study to evaluate the efficacy and safety of rituximab in the first episode of paediatric idiopathic nephrotic syndrome (RTXFIRPedINS).

Before you decide, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information carefully. This document explains the purpose of this study, what it means to participate in it, and what your child can expect. Ask your child’s study doctor if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to have your child take part in this study.

This is a multicentre clinical study on the nephrotic syndrome in children led by professor Xu hong from the Children’s Hospital of Fudan University.

1. What is the purpose of the study?

Idiopathic nephrotic syndrome (INS) is one of the most common paediatric glomerular diseases. Although 80%–90% of children achieve complete remission after initial steroid therapy (steroid-sensitive nephrotic syndrome; SSNS); however, relapses are common after the reduction or discontinuation of corticosteroids. Half of these children will experience frequent relapses (FRNS) or become steroid-dependent (SDNS). They may experience serious side effects from further steroid treatment or other immunosuppressive drugs (including mycophenolate mofetil, calcineurin inhibitors, etc.). In addition, up to 15%–25% of childhood relapses persist into adulthood, and some may develop late-onset steroid resistance (SRNS) with a higher risk of progression to kidney failure and relapse after kidney transplantation. Long-term side effects of steroids and non-corticosteroid immunosuppressive medications are common and may include: poor growth, obesity, hypertension, cataracts, glaucoma, psychological disturbances, osteoporosis, nephrotoxicity, diabetes mellitus, dyslipidaemia, gonadal toxicity, and carcinogenicity, which significantly affect the prognosis and quality of life. In recent years, many high-quality clinical studies have shown that the use of anti-CD20 monoclonal antibody-rituximab (RTX) in FRNS/SDNS can effectively reduce relapse and promote better growth catch-up, even when steroids and other immunosuppressants are discontinued. The 2020 Kidney Disease Improving Global Outcome (KDIGO) guidelines are recommended to be used for children with FRNS/SDNS. Our centre is the first in China to report the efficacy and safety of RTX for treating FRNS/SDNS. The primary objective of our study is to assess whether RTX is effective and safe for children to maintain remission when initiated at the first episode of SSNS with the guideline-recommended corticosteroids. Exploratory endpoints include changes in immunologic factors, to be studied as predictors of response to RTX and relapse of INS.
2. **What will happen in the study?**

Forty-four subjects will take part in the study from eight hospitals. This study will use competitive enrolment, and the follow-up period will be one year.

You and your child should attend all study visits as scheduled.

**Screening**

The study will begin, after signing this informed consent form, with a screening visit. The purpose of the screening visit is to find out if your child meets the requirements to participate in this study.

What needs to be done during the screening visit: 1. Routine pre-enrolment examinations: demographic information, medical history collection, physical examination, vital signs (blood pressure and heart rate), height, and weight. 2. Laboratory tests: complete blood count, C-reactive protein, urine and urine sediment, urine protein/creatinine, 24-hour urine protein (child >3 years old), urinary microprotein concentrations, serum creatinine, blood urea nitrogen, albumin, alanine aminotransferase, aspartate aminotransferase, cholesterol, triglycerides, serum electrolyte levels (sodium, potassium, chloride, calcium, and phosphorus), blood gas analysis, EBV/CMV DNA and antibodies, HBsAg, HBsAb, HBeAg, HbcAb, HCV, syphilis, HIV, tuberculosis, antinuclear antibodies, cluster of differentiation, immunoglobulin, pre-steroid blood samples. 3. Ophthalmological evaluation, urinary system ultrasound, electrocardiogram, echocardiography, and chest X-ray.

Nephrotic syndrome is treated with a standard course of steroids. If complete remission is achieved within 4 weeks, steroid-sensitive nephrotic syndrome is diagnosed. The study doctor will determine if your child is eligible to continue in the study. Medical history collection, physical examination, vital signs (blood pressure, heart rate), height, weight, urine routine, urine sediment, urine protein/creatinine, complete blood count, C-reactive protein, liver and kidney function, cluster of differentiation, immunoglobulin, and blood samples will be repeated before administration of RTX. To prevent infection, trimethoprim-sulfamethoxazole (SMZ) will be used for 3 months, starting with RTX treatment initiation.

Later, if your child is not required in the study, the study doctor will explain the reason for it and discuss other treatment options with you.

**Treatment Visit**

Your child will have to follow the prescribed schedule for routine observations and examinations.

At month 1, medical history collection, physical examination, vital signs (blood pressure and heart rate), height, weight, urine and urine sediment, urine protein/creatinine, complete blood count,
C-reactive protein, liver and kidney function, cluster of differentiation, immunoglobulin, and blood, and urine specimens will be collected.

At month 3, medical history collection, physical examination, vital signs (blood pressure and heart rate), height, weight, urine and urine sediment, urine protein/creatinine, complete blood count, C-reactive protein, liver and kidney function, cluster of differentiation, immunoglobulin, blood and urine specimens will be collected. Additionally, the ophthalmological evaluation will also be conducted.

At months 4.5, medical history collection, physical examination, vital signs (blood pressure and heart rate), height, weight, urine routine, urine sediment, urine protein/creatinine, complete blood count, C-reactive protein, liver and kidney function, immunoglobulin, and blood and urine samples will be collected.

At months 6, 9, and 12, medical history collection, physical examination, vital signs (blood pressure and heart rate), height, weight, urine routine, urine sediment, urine protein/creatinine, complete blood count, C-reactive protein, liver and kidney function, cluster of differentiation, immunoglobulin, and blood and urine samples will be collected.

In case of relapse, medical history, physical examination, vital signs (blood pressure and heart rate), height, weight, complete blood count, C-reactive protein, urine and urine sediment, urine protein/creatinine, 24-hour urine protein (child >3 years-old), urinary microprotein concentrations, serum creatinine, blood urea nitrogen, albumin, alanine aminotransferase, aspartate aminotransferase, cholesterol, triglycerides, serum electrolytes (sodium, potassium, chloride, calcium, and phosphorus), blood gas analysis, EBV/CMV DNA and antibodies, HBsAg, HBsAb, HBeAg, HbcAb, HCV, syphilis, HIV, tuberculosis, antinuclear antibodies, cluster of differentiation, immunoglobulin, and blood and urine specimens will be recorded. Ophthalmological evaluation, urinary system ultrasound, electrocardiogram, chest X-ray, and echocardiography will also be performed.

Follow-up visits are required to be conducted on the prescribed schedule. The doctor will measure your child’s height, weight, and blood pressure at each visit, with urine and blood samples collection. Dipsticks for proteinuria determination will be evaluated daily. In case of relapse, you should contact us immediately. The treatment will progress according to the treatment instructions. Physical examination and urine and blood samples will be taken at each visit and relapse.

The amount of blood drawn each time will be about 10–20 mL, which is similar to the amount drawn in routine clinical treatments. Since this test needs to detect morning urine, liver, and kidney functions, you will have to refrain your child from eating and drinking plenty of water before visiting the doctor.

3. Are there other treatment options for my child?
The other treatment plan for this disease includes paying close attention to the urine protein levels; if there are one or more relapses within 1 year of treatment, steroids and non-corticosteroid immunosuppressive medications may be required following renal biopsy and other examinations, to reach long-term remission.

4. **What issues should be paid attention to during the study?**

Provide truthful information about your medical history and current medical condition. At each visit, you should convey to your child’s study doctor any changes in your child’s health or condition. You must also communicate with the child’s study doctor immediately if there are any major changes in your child’s health or condition between visits or if you have any concerns regarding the study. Notify the study doctor about any discomfort and other treatments your child has had during this study. Tell the doctor if your child has recently participated or is currently participating in other studies.

5. **What are the side effects or risks of participation?**

The drugs used in this trial are approved drugs that have been marketed in China and are also used in routine clinical treatment. The associated adverse reactions are similar to those observed in current clinical therapies and are detailed below:

- **Adverse consequences of glucocorticoid medication** (prednisone, prednisolone or methylprednisolone) include: (1) Fluid and electrolyte disturbances: sodium retention, congestive heart failure in some sensitive patients, hypertension, fluid retention, potassium loss, hypokalaemic alkalosis; (2) Musculoskeletal system: steroid myopathy, muscle weakness, osteoporosis, aseptic necrosis, compressive vertebral fractures, pathological fractures, tendon ruptures, especially the Achilles tendon; (3) Gastrointestinal tract: peptic ulcer that may perforate or bleed, gastrointestinal bleeding, pancreatitis, esophagitis, intestinal perforation; (4) Skin and subcutaneous soft tissue: poor wound healing, petechiae and ecchymosis, brittle skin, thin skin, acne; (5) Metabolism: negative nitrogen balance due to protein breakdown; (6) Nervous system: elevated intracranial pressure, pseudo-brain tumour, confusion; (7) Endocrine: menstrual disorders, triggers Cushing's symptoms, affects the pituitary-adrenal axis, impairs glucose tolerance, triggers latent diabetes, increases the demand for insulin and oral hypoglycaemic drugs in diabetic patients, and stunts growth (8) Allergic reactions: angioedema, severe anaphylaxis; (9) Eye: long-term use can cause subcapsular cataracts, glaucoma, and possible damage to the optic nerve, and increase the risks of secondary fungal or viral infections in the eyes. To prevent corneal perforation, glucocorticoids should not be used in children with herpes simplex and herpes zoster with ocular symptoms, increased intraocular pressure, or proptosis; (10) Cardiovascular symptoms: myocardial rupture after myocardial infarction, high doses may cause tachycardia; (11) Immune system: decreased ability to detect infection, the onset of underlying infections, opportunistic infections, may suppress skin test reactions.
The use of RTX, as an immunosuppressive agent, may be dangerous in the presence of an infection. We will conduct clinical screening for detecting serious or underlying infections. Your child will receive a careful physical examination. Complete blood count, urine and urine routine, liver and kidney function, immune function, infection indicators, electrocardiogram, and chest radiograph will be assessed. It is recommended to receive a hepatitis-B vaccination. Because RTX is a chimeric anti-CD20 monoclonal antibody, patients may experience allergic reactions, including nausea, rash, itching, fever, chills, throat irritation, swelling of the tongue or throat (angioedema), headache, rhinitis, cough and bronchi spasticity, and tachycardia, with or without drug-related hypertension or hypotension. We will provide pre-medications to minimize the occurrence of these side effects. ECG, blood pressure, and transcutaneous oxygen saturation will be monitored during intravenous infusion therapy. If respiratory symptoms (dyspnoea, bronchospasm, or hypoxemia), hypotension, or other side effects occur during intravenous infusion, ECG and blood pressure monitoring will continue until 24 hours after the end of the infusion. RTX may increase the risk of respiratory infections, and reactivate hepatitis B, varicella zoster, pneumocystis carinii pneumonia, and other infections. Other adverse reactions include neutropenia, leukopenia, and persistent hypogammaglobulinemia.

The adverse reactions of sulphonamide include: allergic reactions, drug eruptions, photosensitivity, drug fever, and other serum sickness-like reactions; higher risks of haemolytic anaemia and haemoglobinuria in patients with glucose-6-phosphate dehydrogenase deficiency; crystalluria, haematuria, and casturia in the kidneys; gastrointestinal symptoms, such as nausea, vomiting, loss of appetite, diarrhoea; jaundice and liver dysfunction are mild symptoms which do not affect continued medication.

Risks of blood draw: This study requires phlebotomy, which is the same procedure as routine blood draw in hospitals without additional risks. A small number of people may experience temporary discomfort and/or bruising at the venipuncture point, which resolves spontaneously within a short period.

Other risks: There may also be some currently unforeseen risks, discomforts, drug interactions, or adverse reactions.

Principles for dealing with major adverse events: If the above adverse reactions caused by the drug are observed, the dose of the drug may need to be reduced or stopped, and symptomatic treatment will be initiated. If the adverse reactions subside, the therapeutic dose can be resumed according to the patient's condition. In this study, we will conduct a complete blood count, urine tests, and liver and kidney function tests during each visit, to achieve early detection and early treatment. We will try to minimize the impact of these reactions as much as possible on the premise of ensuring stability of the child’s condition.

6. What are the possible benefits of participating in the study?

There can be no certainty that your child will benefit from the study medication. Your child’s condition may improve. RTX may reduce relapse of nephrotic syndrome within one year. The
information that the study provides to the study sponsor may help to better treat children with nephrotic syndrome and improve treatment protocols for children.

7. Do I receive payment or compensation?

You will not receive any compensation for participating in this study.

8. Will the study cost me anything?

Participation in this research project will not add to the patient’s additional costs on regular monitoring.

9. What if my child is harmed in the study?

Please consult your child’s study doctor for further information. If your child suffers an injury or has an adverse event from prescribed medication, please contact the doctor and your child will be treated in time.

10. How will my child’s data be handled and used?

We will make every effort to protect your and your child's privacy to the extent permitted by law. Any public reporting of the results of this study will not disclose any personal information about you and your child. The data of this study may be consulted by the investigators, the Ethics Committee of the Children’s hospital of Fudan University, and the State Drug Administration.

Your child’s data, when forwarded to the study sponsor or other parties, will be represented by a code instead of your child’s name. This will ensure that your child’s identity is kept confidential. We call this encoded data. The documents linking the code with your child’s name will be kept at the study doctor’s site.

If any new information becomes available during the study which may affect your decision to continue your child’s participation, you will be notified.

11. What will happen if I do not wish to continue with the study?

Participation in this research project is entirely up to you and your child. You and your child may refuse to participate in this study, or withdraw from the study at any time during the study, without affecting your relationship with your doctor or affecting your child’s medical care.

The doctor may terminate the study if your child requires additional treatment, if he/she does not follow the study plan, if a trial-related injury occurs, or for other reasons.

12. Whom can I contact for further information?

If you have any questions or concerns about this study, you can consult the contact doctor: Dr. Liu Jialu, whose contact number is: 13816360839. If you have any questions about your child’s right to participate in this study, please consult the Ethics Committee of Children’s Hospital of Fudan University at 021-64931221 from 8.00 am to 11.30 am and 1.30 pm to 5.00 pm, Monday–Friday.
Informed Consent Form (Signature Page)

I have read and understood the information in this informed consent form. I have had the opportunity to ask questions and am satisfied with the answers to all of them. I have been given enough time and opportunity to ask for details about the study and to consider whether to participate in the study. I volunteered to have my child participate in this study. By signing this informed consent form, I do not waive any of my statutory rights.

I have been informed that I will receive a signed copy of this document.

Child’s Full Name (print):  _______________

Parent/guardian (print):  _______________  Relationship with patient:  _______________

Signature:  _______________  Contact number:  _______________

Date:  _______________

(Note: For children under the age of 8 years-old, who have a certain ability to understand and express, the legal representative and doctor are required to ask the child if he/she is willing to participate, after which his legal representative should sign the consent form. Children aged ≥8 years and adolescents will be required to provide their own signatures and consents along with the consents of their legal representatives.)

Researcher/person, taking the assent, declares:

I confirm that the details of this study, including the child’s rights and possible benefits and risks of participation, have been explained to the parent/guardian. A copy of this assent form has been provided.

Name of researcher/person taking the assent (print):  _______________

Signature:  _______________

Date:  _______________  Contact number:  _______________
Patient Information and Informed Consent Form
(minors ≥ 8 years old)

1. What is the purpose of the study?

Idiopathic nephrotic syndrome (INS) is one of the most common paediatric glomerular diseases. Although 80%–90% of children achieve complete remission after initial steroid therapy (steroid-sensitive nephrotic syndrome; SSNS); however, relapses are common after the reduction or discontinuation of corticosteroids. Half of these children will experience frequent relapses (FRNS) or become steroid-dependent (SDNS). They may experience serious side effects from further steroid treatment or other immunosuppressive drugs (including mycophenolate mofetil, calcineurin inhibitors, etc.). In addition, up to 15%–25% of childhood relapses persist into adulthood, and some may develop late-onset steroid resistance (SRNS) with a higher risk of progression to kidney failure and relapse after kidney transplantation. Long-term side effects of steroids and non-corticosteroid immunosuppressive medications are common and may include: poor growth, obesity, hypertension, cataracts, glaucoma, psychological disturbances, osteoporosis, nephrotoxicity, diabetes mellitus, dyslipidaemia, gonadal toxicity, and carcinogenicity, which significantly affect the prognosis and quality of life. In recent years, many high-quality clinical studies have shown that the use of anti-CD20 monoclonal antibody-rituximab (RTX) in FRNS/SDNS can effectively reduce relapse and promote better growth catch-up, even when steroids and other immunosuppressants are discontinued. The 2020 Kidney Disease Improving Global Outcome (KDIGO) guidelines are recommended to be used for children with FRNS/SDNS. Our centre is the first in China to report the efficacy and safety of RTX for treating FRNS/SDNS. The primary objective of our study is to assess whether RTX is effective and safe for children to maintain remission when initiated at the first episode of SSNS with the guideline-recommended corticosteroids. Exploratory endpoints include changes in immunologic factors, to be studied as predictors of response to RTX and relapse of INS.

2. What will happen in the study?

The follow-up period will be one year. In the beginning, your doctor will do a physical examination, collect urine, draw blood for tests, and ask your parent/guardian about your medical history. Additionally, a urinary ultrasound, electrocardiogram, cardiac ultrasound, and chest radiography will be performed along with an ophthalmological evaluation; the whole process takes...
about 1 hour. At each visit during the study, blood will be drawn once with a needle, approximately 20 mL, and your urine sample will be taken for testing. Before the doctor confirms that you can use rituximab, you need to undergo a physical examination, urine retention test, and blood test, and ask your parents/guardians about your condition. Blood will be drawn once with a needle, about 10 ml each time, and then take a sample of your urine for testing.

During the trial, you will need to go back to the hospital 8 times. Because of the need for a doctor's examination, you cannot eat breakfast and should not drink plenty of water on the morning of your visit to the hospital.

3. Is there anything in the research that makes me feel bad, scared, or uncomfortable?

During the study, you may experience some side effects. These side effects may cause nausea, vomiting, leg pain, rash, difficulty in breathing, etc. These conditions may not happen to every child. But if these side effects occur, you need to tell your doctor who will help you immediately.

During the test, the following situations may also be encountered:

• Questions the doctor or nurse asks may make you feel tired or embarrassed.
• When the blood is drawn for sampling, the needle will go into your arm and you may feel pain.
• You may get red spots, bruises, or feel soreness in your arms.
• An infection may occur in your arm where the needle was inserted.

You may also have other feelings, and you must tell your parents or your doctor if you feel unwell or take any other medication while participating in the study. You or your parents can call your doctor at any time.

4. Will participating in the research project help me?

By participating in this study, you will have regular follow-ups that will help monitor the progress of your own disease. You may or may not feel better with time, we cannot guarantee it. However, your participation may help children with the same disease as you, in the future.

5. Do I have to participate in this study?

It is your decision whether to participate in this study. If you choose not to take part in this
study, no one will blame you. Neither your doctor nor your parents can force you to participate in
the study if you do not agree. If you agree now and change your mind later, you can stop
participating in the research at any time. At any time during the study, if you wish to withdraw just
notify your doctor or your parent/legal representative. If you drop out of this study, you will be
asked to do some security checks before leaving the study centre. Even if you do not want to take
part in this study, your doctor will still take care of you.

5. **How will my privacy be protected if I participate in this study?**

We will make every effort to protect your privacy to the extent permitted by law. Any public
reporting of the results of this study will not disclose any personal information about you. The data
of this study may be consulted by the investigators, the Ethics Committee of the Children’s hospital
of Fudan University, and the State Drug Administration.

Your data, when forwarded to the study sponsor or other parties, will be represented by a code
instead of your child’s name. This will ensure that your identity is kept confidential. We call this
encoded data. The documents linking the code with your name will be kept at the study doctor’s site.
If any new information becomes available during the study which may affect your decision to
continue your participation, you will be notified.

6. **Who should I contact if I have questions?**

If you have any questions or concerns about this study, you can consult the contact doctor: Liu Jialu,
whose contact number is: 13816360839. If you have any questions about your right to participate in
this study, please consult the Ethics Committee of Children’s Hospital of Fudan University at 021-
64931221 from 8.00 am to 11.30 am and 1.30 pm to 5.00 pm Monday – Friday.
Informed Consent Form (Signature Page)

The doctor explained this information to me in detail, and I also asked the doctor about the words that I did not understand. I understand that participation in this study is voluntary. After consideration, I am willing to participate in this study and cooperate with the doctor's diagnosis, treatment, and follow-up. If there is any discomfort, I will promptly notify my parents/guardians or my doctors.

I understand that I can choose to stop participating in this study at any time and the doctors will still help me with other treatments.

Child’s Full Name (print): ___________________ Date of birth: ______

Signature: _______________________________ Date: ______________

Researcher/person, taking the assent, declares:

I confirm that the details of this study, including the child’s rights and possible benefits and risks of participation, have been explained to the child. A copy of this assent form has been provided.

Name of researcher/person taking the assent (print): ___________________

Signature: _______________________________

Date: _________________________________ Contact number: ____________
Patient Information and Informed Consent Form
(<8-year-old Minor Oral Notification Version)

Dear kids,

The foam in your urine and oedema are features of nephrotic syndrome, which is a very common kidney disease in children. Most children can be cured by taking steroids every day, but many of these children will get sick again within a year, and they will need to take medicine again, every day for several months. Long-term repeated use of medicine may cause weight gain, unhappiness, poor growth, and other side effects. There is a medicine called rituximab that can be used, with the help of doctors, to stop the need for other drugs earlier, and reduce the chance of getting sick again. This medicine was used for children who used to get repeatedly sick. Now, the doctor hopes to use this medicine earlier during treatment, so that you will not get sick again next year. If you get sick again, the doctors will help you get better also.

1. What do I need to do if I participate in the study?

If you try to use this medicine early, we will take care of you very carefully and do some tests on you, which is a routine clinical process. You can ask your parents and doctor to help you decide whether to participate in this study.

Your doctor will ask about your current treatments/drugs and may adjust some of them. You will need to come to the hospital with your mom, dad, or other family members to visit the doctor eight times during the study. If you want to participate in the study, we will also ask your parents for their approval.

2. Is there anything in the research that makes me feel bad, scared, or uncomfortable?

We hope the rituximab injection helps you feel better, but sometimes it can make you feel a little uncomfortable. Hence, if you feel sick, you have to tell your mom, dad, your doctor, or nurse. We will take good care of you so that your discomfort can get better quickly. During the test, you may experience uneasiness; for example, a blood draw, during which a doctor or nurse will use a needle to draw blood from your arm. It may become a little sore later. Your arm may develop a few red spots or bruises also.
3. Will participating in this research help me?

By participating in this study, you will have regular check-ups, and blood and urine tests that will help monitor the progress of your own disease. You may or may not get better with time, we cannot guarantee it. Your participation may help other children in the future with the same disease as you.

4. Is participation in this research voluntary?

No one will be offended whether you choose to participate or not. You may choose not to participate in this study, if you do not wish to. If you agree to take part in this study now and later do not want to, you can stop participating any time. Even if you do not want to participate in this study, your doctor will still take care of you.
知情同意书（监护人版）

尊敬的家长或法定监护人：

您的孩子将被邀请参加一项研究：利妥昔单抗减少激素敏感型肾病综合征患儿复发的疗效及安全性研究：单臂、开放、多中心临床研究。本知情同意书提供一些信息以帮助您和您的孩子决定是否参加此项研究。请您仔细阅读，如有任何疑问请向负责该项研究的研究者提出。

本项研究由复旦大学附属儿科医院徐虹教授及其团队牵头在全国多家医院开展的一项有关儿童肾病综合征的临床研究。

1、本项研究的研究背景和研究目的是什么？

原发性肾病综合征是儿童最常见的肾小球疾病。虽然初始糖皮质激素治疗后 80%~90% 的患儿可获完全缓解（激素敏感肾病综合征，SSNS），但绝大多数在起病后 1 年内于激素减量和/或停药后复发，这其中约 50%表现为频复发/激素依赖（FRNS/SDNS），导致感染等风险明显增加且激素及免疫抑制剂治疗（包括霉酚酸酯、钙调神经磷酸酶抑制剂等）。此外，高达 15% ~25%的儿童期复发可延续至成年期，部分可能会出现迟发激素耐药（SRNS），进展为尿毒症和肾移植后复发的风险较高。由于病情反复、治疗迁延可出现生长发育延迟、肥胖、高血压、白内障或青光眼、行为改变、骨质疏松、糖耐量异常等激素副作用，以及肾毒性、高血糖、血脂异常、性腺毒性、致癌性等免疫抑制剂的副作用，严重影响预后和生活质量。近年来已有的多项高质量临床研究显示，使用抗 CD20 单克隆抗体--利妥昔单抗（RTX）注射液在停用激素和其他免疫抑制剂情况下也可有效降低复发率，同时有效促进更好的生长追赶。2020 年改善全球肾脏病预后组织和国内指南均推荐应用于 FRNS/SDNS 患儿。本中心率先在国内使用 RTX 治疗儿童 FRNS/SDNS 有效且安全。我们的研究目的是希望初始激素诱导缓解后早期应用 RTX 减少疾病复发，尽可能减少激素等其他免疫抑制剂应用，为制定减少初发 SSNS 的复发有效且安全的治疗奠定基础。

2、该研究是怎样进行的？

您的孩子参加并完成本研究大约需要 1 年时间。该研究将在 8 个研究中心进行，将会有 44 例患者入组本项研究，是竞争入组。

参加研究后，将会按以下流程进行：

筛选访视

签署本知情同意书之后研究开始，首先进行筛选访视。筛选访视的目的是为了查明您的孩子是否符合参加本项研究的各项要求。

筛选访视需要做的是：1、常规入组前检查；人口学信息、病史采集、体格检查、生命
体征（血压、心率）、身高、体重。2. 实验室检查：血常规+\( \text{C} \) 反应蛋白、尿常规、尿沉渣、
尿蛋白/肌酐、24 小时尿蛋白（大于 3 岁）、尿微量蛋白、血肌酐、尿素氮、白蛋白、谷丙转
氨酶、谷草转氨酶、胆固醇、甘油三酯、电解质（钠钾氯钙磷）、血气分析、EBV/CMV DNA
和抗体、HBsAg、HBsAb、HBeAg、HbcAb、HCV、梅毒、HIV、结核、抗核抗体、CD 系
列、免疫球蛋白、应用激素前血标本。3. 眼科、泌尿系统超声、心电图、心脏超声、胸部
X 线片。

肾病综合征常规激素标准疗程治疗，如 4 周内达到完全缓解，诊断为激素敏感型肾病综
合征。研究医生将会确定您的孩子是否有资格继续参加研究。利妥昔单抗用药前再次进行病
史采集，体格检查，生命体征（血压、心率），身高，体重，尿常规、尿沉渣，尿蛋白/肌酐，
血常规+\( \text{C} \) 反应蛋白，肝肾功能、CD 系列、免疫球蛋白、应用利妥昔单抗前血标本。从利妥
昔单抗用药第一天使用甲氧苄啶-磺胺甲嘧啶 3 月，以预防感染。

如果您的孩子不能继续参加研究，研究医生也会向您解释原因，并与您讨论其他治疗方
案。

随访访视

本研究中，您的孩子将完成以下几项检查和步骤或评估：

在入组用药后第 1 月，进行病史采集，体格检查，生命体征（血压、心率），身高，体
重，尿常规、尿沉渣，尿蛋白/肌酐，血常规+\( \text{C} \) 反应蛋白，肝肾功能、CD 系列、免疫球蛋白
、血和尿标本留取。

在入组用药后第 3 月，进行病史采集，体格检查，生命体征（血压、心率），身高，体
重，尿常规、尿沉渣，尿蛋白/肌酐，血常规+\( \text{C} \) 反应蛋白，肝肾功能、CD 系列、免疫球蛋白
、血和尿标本留取。眼科评估。

在入组用药后第 4.5 月，进行病史采集，体格检查，生命体征（血压、心率），身高，体
重，尿常规、尿沉渣，尿蛋白/肌酐，血常规+\( \text{C} \) 反应蛋白，肝肾功能、CD 系列、免疫球蛋白
、血和尿标本留取。

在入组用药后第 6 月，进行病史采集，体格检查，生命体征（血压、心率），身高，体
重，尿常规、尿沉渣，尿蛋白/肌酐，血常规+\( \text{C} \) 反应蛋白，肝肾功能、CD 系列、免疫球蛋白
、血和尿标本留取。

在入组用药后第 9 月，进行病史采集，体格检查，生命体征（血压、心率），身高，体
重，尿常规、尿沉渣，尿蛋白/肌酐，血常规+\( \text{C} \) 反应蛋白，肝肾功能、CD 系列、免疫球蛋白
、血和尿标本留取。

在入组用药后第 12 月，进行病史采集，体格检查，生命体征（血压、心率），身高，体
重，尿常规，尿沉渣，尿蛋白/肌酐，血常规+C 反应蛋白，肝肾功能，CD 系列，免疫球蛋白，血和尿标本留取。

如复发进行病史采集，体格检查，生命体征（血压、心率），身高，体重，血常规+C 反应蛋白，尿常规，尿沉渣，尿蛋白/肌酐，24 小时尿蛋白（大于 3 岁）、尿微量蛋白、血肌酐、尿素氮、白蛋白、谷丙转氨酶、谷草转氨酶、胆固醇、甘油三酯、电解质（钠钾氯钙磷）、血气分析，EBV/CMV DNA 和抗体、HBsAg、HBsAb、HBeAg、HbcAb、HCV、梅毒、HIV、结核、抗核抗体、CD 系列，免疫球蛋白，血和尿标本。3、眼科、泌尿系统超声，心电图，胸部 X 线片，心脏超声。

需要按照规定的时间表随访。每次随访都到访身高体重血压，采集尿液样本和血液样本。在进行治疗后每日尿蛋白试纸监测晨尿尿蛋白情况。如发生蛋白尿复发时及时与临床研究者联系，给予一定的复发方案治疗。每次随访和复发时均进行体格检查，采集尿液样本和血液样本。

进行每次取血量在 10-20ml 左右，与临床常规治疗相似。由于本试验需要检测晨尿和肝肾功能，请您的孩子在就诊前请勿饮食和大量饮水。

3、我的孩子是否有其他的治疗选择？

除了参加本研究外，该疾病的治疗方案还有：密切关注孩子尿蛋白情况，如果 1 年内有 1 次或多次复发，激素诱导转阴后，根据情况完善肾活检等检查应用其他免疫抑制剂。

4、研究中我的孩子需要做些什么？

提供有关自身病史和当前身体状况的真实信息；告诉研究医生您的孩子在本次研究期间所出现的任何不适和治疗，告诉研究医生您的孩子在最近是否曾参与其他研究，或目前正参与其他研究。

5、我的孩子参加此研究会有什么风险和不良反应？

本试验所用药物均为已在国内上市的正规药物，亦为临床常规治疗的药物，其不良反应与目前临床常规治疗中相似。具体如下：

糖皮质激素（强的松、强的松龙或甲强龙等）的不良反应包括：（1）体液及电解质紊乱；钠潴留，某些敏感患者的充血性心力衰竭，高血压，体液潴留，钾离子丧失，低钾性碱中毒；（2）肌肉骨骼系统：类固醇性肌病，肌无力，骨质疏松，无菌性坏死，压缩性椎骨骨折，病理性骨折，腱断裂，特别是跟腱；（3）胃肠道：可能穿孔或出血的消化道溃疡，消化道出血，胰腺炎，肠穿孔；（4）皮肤及皮下软组织：伤口愈合不良，瘢点和瘢痕，皮肤脆薄，痤疮；（5）代谢：因蛋白质分解造成负氮平衡；（6）神经系统：颅内压升高，假性脑肿瘤，精神错乱；（7）内分泌：月经失调，引发柯兴氏症，抑制垂体－肾上腺皮质轴，糖耐量降低，引发潜在的糖尿病，增加糖尿病患者对胰岛素和口服降糖药的需求，抑制儿童生长；（8）过敏反应：血管水肿；（9）眼：长期使用糖皮质激素可引发后房囊下白内障，青光
眼和可能损伤视神经，并增加眼部继发真菌或病毒感染的机会，为防止角膜穿孔，糖皮质激素慎用于眼部单纯疱疹及眼部症状的带状疱疹患者，眼内压增高，眼球突出；（10）心血管：心肌梗死后的心肌断裂，高剂量引起心动过速；（11）免疫系统：掩盖感染，潜在感染发作，机会性感染，过敏反应（包括严重的过敏反应），可能抑制皮试反应。

利妥昔单抗是免疫抑制剂，如果有感染时使用可能会有危险，我们会进行临床筛选是否存在重大或隐匿感染，建议必要时完善乙肝疫苗接种，仔细的体格检查，试验前后生命体征的变化（记录呼吸、心率和血压），血、尿常规，肝肾功能，免疫功能，感染指标，心电图，超声，胸部X 线。由于是合并型抗体，可能有部分人会有过敏表现，多表现为恶心、皮疹、瘙痒、发热、寒战、咽喉刺激、舌或喉部肿胀（血管性水肿）、头痛、鼻炎、咳嗽和支气管痉挛、心动过速，伴或不伴有关于药物治疗相关的高血压或低血压。我们会根据之前的经验提前用药，尽可能减少这些副作用的发生。静滴治疗期间心电、血压、经皮氧饱和度监测；如静滴期间出现呼吸系统症状（呼吸困难、支气管痉挛、低氧血症）或低血压等副作用时，心电、血压监护持续至静滴结束后 24 小时。增加呼吸道感染，乙肝病毒再激活，水痘带状疱疹，卡氏肺孢子虫肺炎等感染风险，其他不良反应包括中性粒细胞减少症、白细胞减少症、持续性低丙种球蛋白血症等。

复方磺胺甲噁唑的不良反应包括：过敏反应，药疹较为常见，也可表现为光敏反应，药物热等血清病样反应；葡萄糖-6-磷酸脱氢酶缺乏者用药后易发生溶血性贫血及血红蛋白尿，肾脏可发生结晶尿、血尿和管型尿，恶心、呕吐、食欲减退、腹泻等胃肠道症状，可发生黄疸、肝功能减退，一般症状轻微，不影响继续用药。

抽血的风险：本研究需要进行静脉采血，此采血过程与医院的常规采血过程相同，不会带来额外的风险。少数人针刺点可能有短暂的不适和/或青紫，短时间内可自行消退。

其他风险：还可能存在一些目前无法预知的风险，不适、药物相互作用或不良反应。

主要不良事件的处理原则：一旦发现由以上药物引起的不良反应者，根据患者异常指标情况调整用药，减低药物剂量，并对症治疗，同时疏导患者心理情绪；若不良反应不消减或较严重时，停用以上药物的使用。若不良反应消减后，可根据患者病情，恢复治疗剂量。同时，在本研究中，我们对每次访问的孩子进行血常规、肝肾功能的检查，做到及早发现，及早治疗；此外，在孩子用药期间，我们对孩子的病情进行具体分析后调整用药，在保证孩子病情稳定的前提下，尽可能的减少药物对孩子的效果。

6. 这项研究对我的孩子有什么好处？

可能会治愈疾病或减缓疾病的发展，可能会减少 1 年内复发的可能。但是我们不能对此做出保证。血液、尿液标本及病史采集及检测将有助于对疾病做出诊断，为受试者的治疗提供必要的建议，或为疾病的研究提供有益的信息。

7. 参加该研究会不会得到报酬?

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您不会因参加本试验或本研究而获得任何酬劳。

8、参加该研究，我需要支付哪些费用？

参加本研究项目不会增加您额外支出，常规的定期监测。

9、如果我的孩子在参加研究期间受到伤害该怎么办？

若您的孩子在参加研究期间发生伤害或用药治疗期间发生不良事件，请与您的研究医生联系，您的孩子将得到及时治疗。

10、是否会对孩子信息进行保密？

我们将在法律允许的范围内，尽一切努力保护您和您孩子的个人隐私，任何有关本项研究结果的公开报告不会披露您和您的孩子任何的个人信息。本研究的病例资料可能被研究者、复旦大学附属儿科医院伦理委员会、国家药品监督管理局查阅。

您孩子的所有研究相关的文件将使用代码来区分，因此本研究的所有报告和论文都不会以任何方式标识出您孩子的身份。所有数据与您和您孩子隐私信息的关联编码由研究者所在单位（部门）的安全地方保管。

研究期间，任何与您孩子健康有关的有意义的新进展或新医疗信息，我们将及时联系您，如建议您孩子进行些检查来确定这些新信息等。任何可能影响您选择是否继续让您的孩子参加研究的所有新信息，我也会及时告知您。

11、我的孩子必须参加此研究吗？

是否参加研究完全取决于您和您孩子的自愿。您和您的孩子可以拒绝参加此项研究，或在研究过程中的任何时候退出本研究，这都不会影响您和医生间的关系，都不会影响对您孩子的医疗或有其他方面利益的损失。

如果您您的孩子需要其他治疗，或者您的孩子没有遵守研究计划，或者发生了与试验相关的损伤或者有任何其他原因，研究医师可以终止您的孩子继续参与本项研究。

12、如果我有问题，我应该联系谁？

如果你对本研究有任何疑问或者顾虑，可向负责本研究的联络医生；刘佳璐咨询，联系电话：13816360839。如果你对参与本研究的权利有任何疑问，请向复旦大学附属儿科医院伦理委员会咨询，联系电话：021-64931221，工作时间：工作日 8:00-11:30,13:30-17:00。
知情同意书（签字页）

我已阅读并理解本知情同意书中的信息。我已有机会提出问题，并且对所有问题的答复感到满意。我已被给予足够的时间和机会询问关于研究的细节内容并考虑是否参加研究。我自愿让我的孩子参加本项研究。签署本知情同意书不代表我会放弃我的任何法定权利。

我已被告知，我将会收到一份已签署的本文件副本。

受试患儿姓名（正楷）： ___________________

法定监护人姓名（正楷）： ___________________

法定监护人签名： ________________ 与患儿关系： ________________

签名日期： ________________  联系电话： ___________________

（注：8岁以下儿童，并且有一定的理解及表达能力，需要其法定代理人及医生询问孩子本人是否愿意参加，同时由他的法定代理人在同意书上签字；8岁以上儿童、青少年，获得其法定代理人签字同意的同时，还需本人签字同意。）

知情同意获取人声明：

我确认已向受试者监护人解释本项研究的详细情况，包括其权利以及可能的受益和风险，并给其一份签署过的知情同意书副本。

知情同意获取人姓名（正楷）__________________

知情同意获取人签名__________________

签名日期__________________  联系电话__________________
知情同意书（≥8 岁未成年人书面告知版）

我们邀请你参加的是一项临床研究，研究的名称是：《利妥昔单抗减少激素敏感型肾病综合征患儿复发的疗效及安全性研究：单臂、开放、多中心临床研究》，做这个临床研究是为了可以防止或减少你再次生病。下面会介绍下这个研究，待你充分了解后再决定是否要参加。如果你对下面的内容有疑问或不懂的地方，可以问你的研究医生，研究医生会给你仔细的讲解，直到你理解为止。

1、本项研究的研究背景和研究目的是什么

原发性肾病综合征是儿童最常见的肾小球疾病。虽然初始糖皮质激素治疗后 80%~90%的患儿可获完全缓解（激素敏感肾病综合征，SSNS），但绝大部分在起病后 1 年内于激素减量和/或停药后复发，这其中约 50%表现为频复发/激素依赖（FRNS/SDNS），导致感染等风险明显增加且激素免疫抑制剂治疗（包括霉酚酸酯、钙调神经磷酸酶抑制剂等）。此外，高达 15%~25%的儿童期复发可延续至成年期，部分可能会出现迟发激素耐药（SRNS），进展为尿毒症和移植后复发的风险较高。由于病情反复、治疗迁延可出现生长发育延迟、肥胖、高血压、白内障或青光眼、行为改变、骨质疏松、性腺毒性等相关的副作用，以及肾毒性、高血糖、血脂异常、相关免疫抑制剂的副作用，严重影响预后和生活质量。近年来已有的多项高质量临床研究显示，使用抗 CD20 单克隆抗体—利妥昔单抗（RTX）注射液在停用激素和其他免疫抑制剂情况下也可有效降低复发率，同时有效促进更好的生长追赶。2020 年改善全球肾脏病预后组织和国内指南中均推荐应用于 FRNS/SDNS 患儿。本中心率先在国内使用 RTX 治疗儿童 FRNS/SDNS 有效且安全。我们的研究目的是希望初始激素诱导缓解后早期应用 RTX 减少疾病复发，尽可能减少激素等其他免疫抑制剂应用，评估治疗前后相关免疫因子变化，为制定减少初发 SSNS 的复发有效且安全的治疗奠定基础。

2、如果我参加本研究会碰到什么？

参加并完成本研究大约需要 1 年时间。

在试验的最初的时候，医生会为你做体检检查、留尿、抽血进行化验，向你的家长/监护人询问病情，还有需要做眼科、泌尿系统超声、心电图、心脏超声、胸部 X 线片检查，整个过程大概 1 小时左右。研究过程中，将用针头抽取血液 1 次，大概 20 毫升，随后将留取你的尿样用于检查。医生确认可以利用皮质药物前还需要为你做体检检查、留尿、抽血进行化验，向你的家长/监护人询问病情，将用针头抽取血液 1 次，每次大概 10 毫升，随后将留取你的尿样用于检查。
在试验期间的还有 8 次需要到医院就诊。医生会为你做基本的体格检查，抽血进行化验，向你的家长/监护人询问病情。研究过程中，将用针头抽取血液 1 次，每次大概 10 毫升，随后将留取你的尿样用于检查。

因为医生检查的需要，所以你在回医院看病的当天早晨，不能吃早饭和大量的饮水。

3、研究中会有让我感到难受、害怕或不适的事情吗？

研究过程中，你可能会经历一些副作用，这些副作用可能会导致恶心、呕吐、腹泻、长皮疹、呼吸困难等，这些情况不一定每个小朋友都会出现。但是出现的话，需要马上告诉医生，医生会帮助你的。

试验过程中还可能会遇到这样的情况：

- 医生或护士问的问题可能会使你感到疲倦或尴尬。
- 抽取血样时，针头会插进你的胳膊，这时你会感到疼痛。
- 你的胳膊上可能会出现红斑或青肿，或者感到酸痛。
- 你的胳膊上进针的地方可能发生感染。

你可能还会有其他感觉，参与研究的过程中，如果你感到不适或服用任何药物时，必须告知你的父母或医生，你或你的父母可在任何时候给医生打电话。

4、参与研究对我有帮助吗？

参加本研究，将定期对你进行检查和血液尿液检测，将有助于对你本身疾病的进展进行监测。你可能变得更好，也可能不好，我们无法保证。你的参加，也许可以帮助到患有和你相同疾病的孩子。

5、我必须参与这个研究吗？

是否参加这个研究由你决定。如果你选择不参加本研究，没有人会责怪你。如果你不同意，你的医生或父母也不能强迫你参与研究。如果你现在同意，之后改变了主意，你可以随时停止参与研究。任何时候你想退出研究，只要告诉你的医生或者你的父母/法定代表人就可以了。如果你放弃了本研究，在离开研究中心之前，你将被要求做一些安全检查。即使你不想参加这个研究，你的医生仍会照顾你。

6、如果参加此项研究，我的隐私将受到怎样的保护？
我们将在法律允许的范围内，尽一切努力保护你的个人隐私。你所有研究相关的文件将使用代码来区分，任何有关本项研究结果的公开报告不会披露你的个人信息。

所有数据与隐私信息的关联编码由研究者所在单位（部门）的安全地方保管，保存地点为浙江大学医学院附属儿童医院。研究数据将保留5年。

研究期间，任何与你健康有关的有意义的新进展或新医疗信息，我们将及时联系你和你的父母/监护人，如建议你进行些检查来确定这些新信息等。

7、 如果我有疑问，我应该联系谁？

如果你对本研究有任何疑问或者顾虑，可向负责本研究的医生：刘佳璐咨询，联系电话是：13816360839。如果你对参与本研究的权利有任何疑问，请向复旦大学附属儿科医院伦理委员会咨询，联系电话是：021-64931221，工作时间：工作日 8:00-11:30,13:30-17:00。
知情同意书（签字页）

医生已经将这份资料向我做出了详细的说明，不明白的字和词语我也问过了医生。我理解参加本项研究是自愿的。经过考虑后，我愿意参加这项研究，并且配合医生的诊疗、随访，如果有不舒服的情况，会及时通知父母/监护人或者医生。

我明白我任何时候都可以停止这项研究，医生还会帮助我进行其他的治疗。

受试者患儿姓名正楷：__________ 出生日期：_____ 年 __月 __日
受试者患儿签名：__________ 日期：_____ 年 __月 __日

医生声明

我确认已向患者解释了本试验的详细情况，包括其权力以及可能的受益和风险，并给其一份签署过的知情同意书副本。

知情同意谈话医生（研究者）签字：__________
签字日期：_____年_____月_____日  联系电话：__________
知情同意书（<8 岁未成年人口头告知版）

小朋友你好：
你生病出现尿中泡沫多，水肿这些是肾病综合征，是小朋友中很常见的肾脏疾病。大部分小朋友每天吃激素这个药可以治好，但是很多小朋友 1 年内会再生病，又需要每天吃药几个月，长期反复吃药可能会有些长胖，不开心，长不高等等副作用。有个叫利妥昔单抗的针可以帮助医生早些停用这些药，减少再次生病，这个药之前用在反复生这病的小朋友，现在医生希望提早用这个针，让你这一年不再生病，如果再次生病也希望这个针可以帮到你。

1、如果参加研究，需要做些什么？
如果你尝试早些用这个药，我们将很小心的照顾你，并对你进行一些检查，这个就是临床研究。你可以让你的爸爸妈妈和医生来帮你决定是不是参加这个研究。
医生将会问你现在使用的治疗/药物，并且可能会调整其中一些治疗/药物。你需要和你的爸爸或妈妈或其他家人一起来医院拜访医生 8 次。如果你想参加这个研究，我们还会问你爸爸或妈妈是否同意。

2、研究中会有让我感到难受、害怕或不适的事情吗？
我们希望利妥昔单抗注射液可以帮你感觉更好，但是有时候利妥昔单抗注射液也可能会让你会感到一些不适，所以如果你觉得生病了，你要告诉你的爸爸或妈妈，或者告诉你医生或护士。
我们会很好的照顾你，让你不舒服的感觉能够很快好转。试验过程中可能会遇到这样的情况：（比如抽血，医生或护士会用针来抽你（胳膊）的血。可能会有点疼。你的胳膊可能会出现红点或青肿。）

3、参与本研究会对我有帮助吗？
参加本研究，将定期对你进行检查和血液尿液检测，将有助于对你本身疾病的进展进行监测。你可能变得更好，也可能不好，我们无法保证。你的参加，也许可以帮助到患有你相同疾病的其他小朋友。

4、参与本项研究是自愿的吗？
不管你选择参加还是不参加，没有人会生气。如果你不愿意，你可以不参与本研究。如果你现在同意参加本研究，之后又不想参加，你仍然可以停止参与本研究。即使你不想参加这个研究，你的医生仍会照顾你。