Published in final edited form as:

Pediatrics. 2008 December ; 122(Suppl 5): S240–S250. doi:10.1542/peds.2008-1285d.

Rationale and Design Issues of the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) Study

Ron Keren, MD, MPH^a, Myra A. Carpenter, PhD^b, Alejandro Hoberman, MD, MPH^c, Nader Shaikh, MD, MPH^c, Tej K. Matoo, MD^d, Russell W. Chesney, MD^e, Ranjiv Matthews, MD^f, Arlene C. Gerson, MD^g, Saul P. Greenfield, MD^h, Barbara Fivush, MD^g, Gordon A. McLurie, MD^h, H. Gil Rushton, MDⁱ, Douglas Canning, MD^j, Caleb P. Nelson, MD^k, Lawrence Greenbaum, MD, PhD^l, Timothy Bukowski, MD^m, William Primack, MDⁿ, Richard Sutherland, MD^m, James Hosking, PhD^{b,†}, Dawn Stewart, MS^b, Jack Elder, MD^o, Marva Moxey-Mims, MD^p, and Leroy Nyberg, MD^p

^aDepartment of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

^bDepartment of Biostatistics, University of North Carolina, Chapel Hill, North Carolina ^cDepartment of Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania ^dDepartment of Pediatrics, Wayne State University School of Medicine, Detroit, Michigan ^eDepartment of Pediatrics, Le Bonheur Children's Medical Center, Memphis, Tennessee ^fDepartment of Urology, Johns Hopkins School of Medicine, Baltimore, Maryland ^gDepartment of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland ^hDepartment of Urology, Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina ⁱDepartment of Urology, Children's National Medical Center, Washington, DC ^jDepartment of Urology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania ^kDepartment of Urology, Children's Hospital Boston, Boston, Massachusetts ^lDepartment of Pediatrics, Emory University School of Medicine, Atlanta, Georgia ^mDepartment of Urology, University of North Carolina, Chapel Hill, North Carolina ⁿDepartment of Pediatrics, University of North Carolina, Chapel Hill, North Carolina ^oDepartment of Urology, Rainbow Babies and Children's Hospital, Cleveland, Ohio ^pNational Institute of Diabetes and Digestive Kidney Disease, National Institutes of Health, Bethesda, Maryland

Abstract

OBJECTIVE—Our goal is to determine if antimicrobial prophylaxis with trimethoprim/sulfamethoxazole prevents recurrent urinary tract infections and renal scarring in children who are found to have vesicoureteral reflux after a first or second urinary tract infection.

DESIGN, PARTICIPANTS, AND METHODS—The Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) study is a double-blind, randomized, placebo-controlled trial. Six hundred children aged 2 to 72 months will be recruited from both primary and subspecialty care settings at clinical trial centers throughout North America. Children who are found to have grades I to IV vesicoureteral reflux after the index febrile or symptomatic urinary tract infection will be randomly assigned to receive daily doses of either trimethoprim/sulfamethoxazole or placebo for 2 years. Scheduled follow-up contacts include in-person study visits every 6 months and telephone

Copyright © 2008 by the American Academy of Pediatrics

Address correspondence to Ron Keren, MD, MPH, Children's Hospital of Philadelphia, 3535 Market St, Room 1524, Philadelphia, PA 19104. keren@email.chop.edu.

The authors have indicated they have no financial relationships relevant to this article to disclose.

[†]Deceased.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00405704).

interviews every 2 months. Biospecimens (urine and blood) and genetic specimens (blood) will be collected for future studies of the genetic and biochemical determinants of vesicoureteral reflux, recurrent urinary tract infection, renal insufficiency, and renal scarring.

RESULTS—The primary outcome is recurrence of urinary tract infection. Secondary outcomes include time to recurrent urinary tract infection, renal scarring (assessed by dimercaptosuccinic acid scan), treatment failure, renal function, resource utilization, and development of antimicrobial resistance in stool flora.

CONCLUSIONS—The RIVUR study will provide useful information to clinicians about the risks and benefits of prophylactic antibiotics for children who are diagnosed with vesicoureteral reflux after a first or second urinary tract infection. The data and specimens collected over the course of the study will allow researchers to better understand the pathophysiology of recurrent urinary tract infection and its sequelae.

Keywords

urinary tract infection; vesicoureteral reflux; antimicrobial prophylaxis; randomized; controlled trial; renal scarring

The randomized intervention for Children With Vesicoureteral Reflux (RIVUR) study is a multicenter, double-blind, randomized, placebo-controlled trial designed to evaluate the effectiveness of antimicrobial prophylaxis in children who are found to have vesicoureteral reflux (VUR) after a first or second urinary tract infection (UTI). The RIVUR study represents a collaboration of many clinical trial centers throughout North America, a central data-coordinating center at the University of North Carolina at Chapel Hill, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). In this article we describe the methodologic issues that were considered in designing the RIVUR study protocol and the rationale for the study design.

PARTICIPANTS, SETTING, AND PROTOCOL

The RIVUR study inclusion and exclusion criteria and study setting were specified to enroll children from study populations with a high prevalence of disease, to maximize generalizability of study results, and to ensure safety of the participants.

Participants

Children aged 2 to 72 months are eligible for enrollment in the RIVUR study. The age inclusion criterion for the RIVUR protocol was selected in an attempt to enroll children during the time at which they are most likely to have VUR and UTI. VUR is a condition that is present at birth and generally resolves or improves over time.¹⁻³ The timing of first UTI in children generally follows a bimodal distribution, with many infants presenting in the first year of life and a second wave of infections occurring between 2 and 4 years of age during the toilet-training years.^{4,5} After 6 years of age, new-onset UTIs in children are relatively infrequent and often associated with dysfunctional elimination^{6,7} or initiation of sexual intercourse. Despite the fact that girls are more likely to have UTIs than boys,^{4,5,8,9} we chose to include both genders to increase generalizability of study findings. The RIVUR study exclusion criteria (Table 1) were designed to exclude children with serious chronic diseases and to avoid the risks of prophylactic trimethoprim/sulfamethoxazole (TMP/SMZ) in certain children. We plan to enroll 600 children over a 2-year period and follow them for 2 years.

Setting

Five core clinical trial centers (Children's Hospital of Philadelphia [Philadelphia, PA], Children's Hospital of Pittsburgh [Pittsburgh, PA], Children's Hospital of Michigan [Detroit, MI], Johns Hopkins School of Medicine [Baltimore, MD], and Women and Children's Hospital of Buffalo [Buffalo, NY]) and an additional 14 satellite sites are enrolling or planning to enroll patients in the RIVUR protocol (see Table 2 for complete list of all participating sites). Extending recruitment to 19 centers increases the likelihood of meeting enrollment targets and enrolling a geographically, racially, and ethnically diverse patient population from which our results can be more readily generalized. Unlike previous VUR studies, which recruited children largely from subspecialty care practices, RIVUR study participants will be recruited from a variety of clinical settings, including the offices of primary care pediatricians, urologists, and nephrologists, as well as pediatric emergency departments and inpatient wards. Recruiting children with UTI from the primary care out-patient setting will greatly enhance the generalizability of study findings to that setting in which most pediatric UTIs are initially diagnosed and managed.

Protocol

The recruitment and follow-up plan for the protocol is outlined in Fig 1 and has been approved by the local institutional review boards at the clinical sites and the data-coordinating center. The protocol has also been approved by an independent data and safety monitoring board that will review safety and efficacy data periodically throughout the study. The trial also received permission to proceed from the Food and Drug Administration on the basis of Investigational New Drug Application 75739.

Children with febrile or symptomatic UTIs (F/S UTIs) will be identified in a variety of clinical settings. At some centers the study team will coordinate voiding cystourethrogram (VCUG) imaging to identify children with VUR who are eligible for the study. At other centers, children will be recruited after VUR is identified in the course of routine evaluation of a UTI. Children will need to have their VCUGs and renal ultrasounds completed within 16 weeks of the index UTI to be eligible for enrollment in the study. The trial will be described to parents of eligible children, and informed consent will be obtained. At the first visit, we will verify children's eligibility, randomly assign the study participants, and collect baseline data and specimens (blood, urine, and stool). Children will have a baseline dimercaptosuccinic acid (DMSA) scan within 16 weeks of the index UTI. Parents will receive a 6-month supply of study medication along with educational materials about UTI and VUR and a diary for recording intercurrent fever, symptoms, medication use, and medical care visits. Scheduled follow-up contacts include in-person study visits every 6 months and telephone interviews every 2 months. A complete blood count will be obtained at every study visit to monitor for signs of leukopenia caused by TMP/SMZ, and a DMSA scan will be performed at 12 months to detect any sub-clinical progression in renal scarring. The end-of-study visit will include additional data and specimen collection, a VCUG, and a final DMSA renal scan.

Table 3 summarizes observations and procedures that will occur during the trial. Parents will complete surveys to assess dysfunctional voiding symptoms,¹⁰ constipation,¹¹ and quality of life¹² at each study visit. The parents' diary will be reviewed at each study visit and each telephone contact to identify any interim UTIs not reported to the study team, other serious illnesses, or antibiotic courses. Measures of renal function obtained at baseline and at study exit will include a urinalysis, urine microalbumin/creatinine ratio, and serum creatinine, electrolytes, and cystatin C levels. Rectal swabs will be obtained at baseline and study exit to assess for resistant *Escherichia coli* in the stool.

Parents of enrolled children will receive educational materials (both printed and Web based) and ongoing counseling about early signs and symptoms of UTI to promote early diagnosis and treatment of UTI recurrences. Management of suspected and actual UTIs will be performed by the child's primary care provider with close involvement of the study investigators to ensure that the patients receive proper diagnosis and treatment and that the study team is able to collect all relevant data about recurrences (duration and severity of signs and symptoms, culture result, antibiotic susceptibilities, etc).

Treatment Assignment and Masking

Treatment-assignment tables for permuted block randomization, stratified according to recruitment site, were prepared by the data coordinating center by using SAS 9.1 (SAS Institute, Inc, Cary, NC). Randomization will occur through the study's Web-based data-management system at the time of the baseline visit. Immediately after entry of eligibility data, clinical site staff will enter a request to randomly assign a child. This request will trigger verification of eligibility on the basis of entered data, and children who meet all eligibility requirements will immediately be randomly assigned.

A placebo was developed that is nearly identical in color, odor, taste, and consistency to TMP/SMZ. Placebo and medication were bottled in identical 500-mL amber high-density polyethylene containers with child-proof caps. Each study-medication bottle has a unique code on its label. After randomization, clinical site staff members will only be informed of which bottle code to distribute. The linkage between this unique code and whether it is assigned to active or placebo medication is only known to a small number of individuals at the data coordinating center and the study medication-bottling facility. In the event that a child's clinical care necessitates unmasking, the use of unique bottle codes in conjunction with permuted block assignment ensures that only the target participant will be unmasked. Emergency unmasking is expected to be rare in this trial.

DEFINITIONS: UTI AND VUR

UTI

We will restrict enrollment to children who experience a first or second UTI to assemble an inception cohort of children with a low likelihood of previous UTI-associated renal scarring. Children with a history of 2 previous UTIs are eligible for enrollment only if their VUR was diagnosed after the second UTI. Children who were diagnosed with VUR or received prolonged antimicrobial prophylaxis between the first and second UTI will be excluded.

Our criteria for defining UTI are more stringent than might be used in clinical practice (Table 3); thus, some children with true UTI may not be eligible for enrollment. By requiring evidence of pyuria and excluding children diagnosed by bag urine collection, those with <50 000 colony-forming units per mL, and those with >1 isolated organism, the sensitivity of our diagnostic criteria may suffer, but specificity will be improved, thus increasing the probability that the children enrolled have true UTI and not asymptomatic bacteriuria or contaminated urine specimens.

The steering committee debated whether to restrict enrollment to children with febrile UTI and exclude afebrile children who only have urinary symptoms (dysuria, frequency, urgency). One reason to study only children with febrile UTIs is that UTI associated with fever is more likely to represent pyelonephritis, which, unlike isolated cystitis or urethritis, can result in renal scarring and the associated sequelae that prophylactic antibiotics are intended to prevent. However, for several reasons, the committee decided to include children who had UTIs associated with either fever or symptoms referable to the urinary tract. First, several studies have demonstrated that the presence of fever does not accurately discriminate between

pyelonephritis and cystitis in children with UTI.¹³⁻¹⁵ Second, the absence of fever (and pyelonephritis) with the index UTI does not mean that subsequent UTIs will be afebrile or restricted to the lower urinary tract. Thus, prophylactic antibiotics may confer a benefit to children diagnosed with an afebrile UTI who are at increased risk of developing a second UTI that could involve fever and pyelonephritis. Finally, the consensus of the committee was that clinicians do not always distinguish between febrile and afebrile UTIs in making decisions about subsequent evaluation and management. Similarly, the American Urological Association's practice guideline on management of VUR also does not distinguish between febrile and afebrile UTI in its recommendations for imaging and treatment.¹⁶ Therefore, from a practical perspective, we thought clinicians would be interested in the effectiveness of prophylactic antibiotics for children who present with either febrile or afebrile but symptomatic UTI. Given what we know about the epidemiology and clinical presentation of UTIs, we anticipate that the majority of enrolled children younger than 2 years will present with febrile UTIs and few symptoms referable to the urinary tract, whereas children 2 to 6 years of age will more commonly present with afebrile UTIs and more symptoms referable to the urinary tract. Unlike previous studies of interventions for VUR,^{17,18} the RIVUR study provides explicit and specific inclusion criteria that will permit subgroup analyses (eg, difference in outcomes among children with febrile versus nonfebrile index UTI) and enhance interpretability and generalizability of the results.

VUR

The steering committee considered a variety of VUR grades (Fig 2) in developing the inclusion criteria. The choices included restricting participants to (1) those with higher-grade VUR (III–V) who are known to have the highest risk of developing renal scars¹⁹⁻²¹ and, thus, may benefit the most from prophylactic antibiotics; (2) those with low-grade VUR (I–III) who account for the majority of children with VUR who are affected by current guideline recommendations concerning prophylaxis; and (3) all grades of VUR except grade V to avoid withholding potentially beneficial therapy from children with a very high risk of recurrent UTI and renal scarring. These choices reflected the tension commonly encountered in designing clinical trials between targeting children with the greatest chance of benefiting from an intervention, maximizing the generalizability of the findings by including children with the highest prevalence of disease, and excluding children for whom there may not be equipoise regarding the risks and benefits of a placebo-controlled trial. The steering committee decided on the third option, excluding only children with grade V VUR, who the committee members did not feel comfortable potentially randomly assigning to placebo, but including all other grades of VUR to enhance generalizability.

INTERVENTION

Children will be randomly assigned to receive daily doses of either TMP/SMZ or placebo for 2 years. The choice of TMP/SMZ as the active drug was based on the high prevalence of sensitivity of *E coli* to TMP/SMZ at the clinical trial sites, its acceptability by physicians at the clinical trial sites, and its favorable safety profile. Nitrofurantoin was considered as an alternative prophylactic agent but was not chosen because of common complaints of nausea and vomiting in children who take it on a daily basis. TMP/SMZ is contraindicated in children with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Although rare, severe reactions including Stevens-Johnson syndrome may occur in some children. The steering committee considered having a “back-up” prophylactic antibiotic (and placebo) produced to use in these situations, but the cost was prohibitively high and not justified given the relatively low prevalence of G6PD deficiency and occurrence of Stevens-Johnson syndrome. The dose of prophylactic TMP/SMZ cited in previous trials and drug references ranges from 2 to 5 mg/kg of TMP administered once daily. Because study-drug refills will be provided every 6 months,

we chose to prescribe the TMP/SMZ (or corresponding volume of placebo) at a dose of 3 mg/kg per day to avoid under-dosing of TMP/SMZ at the end of the 6-month interval as the child gains weight.

OUTCOMES AND HYPOTHESES

Recurrent UTI

We will evaluate multiple outcomes for this study (Table 4). The primary outcome is the development of recurrent F/S UTI during the 2-year follow-up period. A recurrent F/S UTI will be defined as an infection >14 days after the end of appropriate treatment of the index UTI, after a negative urine culture, or infection with a new organism. We will also measure the time to first recurrent F/S UTI, which will allow us to include patient data in situations in which there is censoring (loss to follow-up or no UTI during the study period) and also to determine if prophylactic antibiotics prolong the time to recurrent F/S UTI.

Our primary hypothesis is that the proportion of children with a recurrence of F/S UTI will be lower among those in the antimicrobial prophylaxis group than in the placebo group.

We also hypothesize that the time to first recurrence of F/S UTI will be shorter in the placebo group than in the antimicrobial prophylaxis group.

Renal Scarring

A secondary outcome of interest is the development of renal scarring. All children will have a baseline DMSA scan within 2 weeks after random assignment, and no more than 16 weeks after the index UTI, to determine the presence of cortical defects. For most participants, we will determine the incidence and extent of renal scarring with a DMSA scan obtained 24 months after the index UTI. For children who are deemed “treatment failures” (see below), we will use the outcome scan to assess the scarring end point at an earlier time point. For these children, we will obtain the outcome scan ~4 months after the recurrence of UTI that leads to classification as treatment failure and study-treatment discontinuation. For children who meet treatment-failure criteria on the basis of the interim 12-month scan, this scan may provide the basis of the outcome assessment.

Permanent scarring will be distinguished from transient changes seen in DMSA scans performed shortly after a UTI in 2 ways. First, the central readers will distinguish scarring from acute pyelonephritis (APN) on the basis of decreased uptake of tracer associated with loss of contours or cortical thinning. Second, the readers will have access to all the DMSA scans so that decreased uptake seen in earlier studies that disappears on later studies can be attributed to APN and not permanent scarring. If a child does not have a follow-up (outcome) scan, then that child will have missing data for the outcome of renal scarring.

To quantify the extent of renal scarring, we will divide each kidney into 12 segments and apply a 5-level grading system (Fig 3). We will define severe scarring as the presence of grades 3 or 4 scarring on at least 1 kidney. We hypothesize that the proportion of children with (1) any renal scarring and (2) severe scarring identified on the outcome DMSA scan will be lower among those in the antimicrobial prophylaxis group than in the placebo group.

The DMSA-scan protocol has been standardized across clinical trial centers. Children will be injected with a dose of 5 mCi of Technetium-99m-dimercaptosuccinic acid per 1.73 m² body surface area (minimum dose: 1 mCi). High-resolution magnified images of the kidney will be obtained, including posterior and both right and left posterior oblique projections, by using a γ -camera computer system equipped with a high-resolution parallel collimator between 2 and 4 hours after injection. Right-to-left relative function will be calculated by the ratio of right

kidney to left kidney counts obtained from the posterior views after background correction. The results will be described quantitatively as the percentage uptake in the right kidney versus left kidney. Absolute uptakes will not be obtained. Using criteria established by Majd and coworkers,^{22,23} defects will be classified as APN or preexistent renal scarring. These evaluations will be made by 2 reference nuclear medicine investigators on the Imaging Studies Reading and Classification Committee.

Treatment Failure

We derived a composite outcome of treatment failure from the frequency and rate of F/S UTI reoccurrence or identification of new or worsening renal scarring. Treatment failure is defined as follows:

1. In any participant:

- occurrence of 2 recurrent FUTIs or a total of 4 recurrent F/S UTIs within the study period or
- interim 12-month scan that shows new or worsening scarring at a site different from the index APN or worsening scarring evidenced by extension of a preexistent scar seen on the baseline DMSA scan (note that the interim scan may serve as the outcome DMSA scan in these participants)

or

2. In children with baseline scarring grade 3 or higher:

- children whose initial DMSA scan shows grade 3 or higher scarring in either kidney will have a repeat DMSA performed at the time of any recurrent F UTI; if additional renal segment involvement is observed (APN or scar) compared with the baseline scan, then the child will be categorized as a treatment failure and have an outcome DMSA scan at ~4 months after the F UTI.

We designed this treatment-failure outcome as a safety measure to minimize the risk of severe renal scarring. For children with severe renal scarring diagnosed on the baseline DMSA scan, we added an extra level of safety by requiring repeat DMSA scans for any recurrent UTIs to identify new areas of pyelonephritis or scarring. All treatment failures will be discontinued from study medication or placebo and referred to local urologists for further evaluation and treatment but will continue to be followed for the full 2 years after enrollment. We hypothesize that the proportion of children classified as treatment failures will be lower among those in the antimicrobial prophylaxis group than in the placebo group.

Antimicrobial Resistance

In addition to determining the potential benefits of prophylactic antibiotics (prevention of UTIs and renal scarring), we will also consider their risks. Continuous exposure to antimicrobial prophylaxis is predicted to alter the microbial flora in the urine and stool of treated children and result in recurrent infections with resistant organisms.²⁴ We hypothesize that (1) the proportion of children who develop stool *E coli* resistant to TMP/SMZ will be greater in the antimicrobial prophylaxis group than in the placebo group and (2) the proportion of children with recurrent F/S UTI caused by TMP/SMZ-resistant organisms will be greater in the antimicrobial prophylaxis group than in the placebo group. Ancillary studies have been initiated to evaluate the impact of other antibiotic usage and environmental exposures (eg, day care) on stool *E coli* resistance and to determine the impact of TMP/SMZ prophylaxis on *Streptococcus pneumoniae* and *Staphylococcus aureus* carriage and resistance.

Resource Utilization

Finally, we will collect information about resource utilization during scheduled telephone calls and intermittent chart review. We will record the number of study visits (scheduled and unscheduled), visits to the emergency department or primary care physician, imaging studies, laboratory tests (urine/blood), days of missed work caused by urinary tract-related visits, days on which alternate day care arrangements were made, antibiotics used for UTIs or other conditions, and hospitalizations.

COVARIATES

In addition to obtaining extensive data on demographic and clinical characteristics of the children and their presenting UTI signs and symptoms, we plan to collect information on several important covariates that may either confound or modify the effect of prophylactic antibiotics on recurrent UTI and renal scarring.

Dysfunctional Voiding

Dysfunctional voiding refers to overactivity of the bladder and/or pelvic floor muscles during the voiding phase of the micturition cycle. It is relatively common in the pediatric population (prevalence of ~15%)²⁵ and is often underdiagnosed and undertreated by primary care physicians.²⁶ Approximately 40% of toilet-trained children with their first UTI^{7,27,28} and 80% of children with recurrent UTI⁶ report symptoms of dysfunctional voiding. In a study of 141 girls >3 years of age with recurrent (≥ 3) UTIs, 108 (77%) had dysfunctional voiding symptoms.⁶ Dysfunctional voiding also is a risk factor for persistence of VUR^{29,31} and renal scarring.^{27,28} Dysfunctional voiding is best assessed through urodynamic studies, but these tests are invasive and uncomfortable for most children. Noninvasive studies to identify contracted pelvic floor muscles with voiding include uroflowmetry, surface electrode electromyography, and measurement of ultra-sound postvoid residual volume. The dysfunctional voiding scoring system (DVSS), developed and validated by Farhat et al,^{10,32} is a noninvasive questionnaire for identifying symptoms of voiding dysfunction and monitoring compliance with therapy.³³

The steering committee discussed the utility of invasive and noninvasive urodynamic studies to assess dys-functional voiding as part of the trial but decided against it because (1) they would not be informative for children younger than 2 years old, whom we anticipate will make up the majority of study participants, and (2) for the minority of children older than 2 years, the tests would add considerable cost, inconvenience, and potential dis-incentive to recruitment. The RIVUR study will use only the DVSS to assess dysfunctional voiding symptoms. A score of >6 in female and >9 in male children ≥ 3 years of age will be considered evidence of dysfunctional voiding.¹⁰

Constipation

The presence of constipation will be assessed by using definitions published by the Paris Consensus on Childhood Constipation Terminology (PACCT) Group.¹¹ According to the PACCT Group, chronic constipation in the toilet-trained child is defined as the occurrence of ≥ 2 of the following during the previous 8 days:

- frequency of bowel movement <3 per week;
- more than 1 episode of fecal incontinence per week;
- large stools in the rectum or palpable on abdominal examination;
- passing of large stools that may obstruct the toilet;

- display of retentive posturing and withholding behaviors; and
- painful defecation.

Adherence

The effectiveness of prophylactic antibiotics is likely to be related to the consistency with which the child receives them. Previous studies have documented poor adherence to daily prophylactic antibiotic regimens for VUR,³⁴⁻³⁶ but none have measured the impact of adherence on the effectiveness of prophylaxis. Recognizing the importance of adherence as a potential effect modifier, the steering committee sought to measure it as accurately as possible. Medication Event Monitoring System (MEMS) caps are considered the gold standard for measuring adherence in clinical trials.³⁷⁻³⁹ The MEMS cap is a medication bottle cap with an embedded microchip to record bottle openings and has been used for adult studies to measure the dispensing of pills or tablets from bottles. However, the RIVUR trial involves liquid medicine and placebo, and the MEMS cap has not been used to measure adherence with a liquid medicine for a 2-year study period. To test its feasibility as a tool for measuring adherence in the RIVUR study, a pilot study was performed. Unfortunately, during the pilot study the crystals in the liquid TMP/SMZ caused the plunger in the MEMS cap to jam, preventing it from accurately counting the number of times that the bottle was opened. For this reason, the RIVUR trial steering committee decided to forego the use of MEMS caps for measurement of adherence.

Instead, the trial will rely on 2 separate measures of adherence. First, parents will be asked to bring their study-medicine bottles to each study visit so that the bottle can be weighed to calculate the volume of medicine that was dispensed in the previous 6 months. Also, every 2 months (by telephone call and semiannual in-person study visits) research staff will ask parents about the frequency with which they administered the study medicine in the previous week and previous 2 months.

STATISTICAL METHODS

Power Analysis

Power calculations were based on a simple comparison of the difference in proportion of events between treatment groups. Table 5 presents estimates of the study power for a range of plausible event rates and treatment effects. The calculations assume that the event rate in the placebo group will be either 20% or 25%. The event rate in adherent children in the active treatment group is assumed to be 10%. All calculations assume a type I error rate of $\alpha = .05$ (2-sided).

In estimating the effect of nonadherence, including drop-out, we assumed that children in the treated group who drop out or are noncompliant have the same rate of F/SUTIs as those in the placebo group (ie, no treatment effect). Because many of those children will receive some active therapy for some period of time, this is a somewhat conservative assumption. To adjust for these effects, the observed event rate in the treated group was estimated as a blend of the unadjusted event rates for the 2 groups (Table 6). Thus, for example, if the event rate in the placebo group is 20%, the nonadjusted event rate in the treated group is 10%, and nonadherence/attrition rate is 15%, the adjusted event rate in the treated group will be $(0.10 \times 0.85) + (0.20 \times 0.15) = 0.115$.

These analyses suggest that we will have adequate power to detect a clinically significant treatment effect over a wide range of assumptions about the placebo event and nonadherence/attrition rates.

Statistical Analysis Plan

A detailed statistical analysis plan has been developed. The primary efficacy analysis will be a Cochran-Mantel-Haenszel test stratified according to clinical site on an intention-to-treat data set; an unstratified analysis will also be performed. Secondary analyses for the primary end point will use logistic regression to adjust for severity of VUR at baseline and other prognostic variables. Subgroup analyses will be performed to estimate treatment effects according to age, gender, baseline severity of VUR, and other covariates by using logistic regression models. Also, additional safety and tolerability analyses are planned. Interim efficacy analyses will be performed on the basis of a schedule approved by the data and safety monitoring board. The overall type I error rate will be controlled by using a Lan-DeMets spending function. Conditional power will also be estimated at the time of interim efficacy analyses.⁴⁰⁻⁴²

The primary analysis of the dichotomous secondary outcomes (treatment failure, renal scarring, and antimicrobial resistance) will also be a Cochran-Mantel-Haenszel test stratified according to clinical site and using the intention-to-treat principle. Additional analyses adjusting for covariates will use logistic regression. The primary analysis of time to recurrent F/S UTI will use a stratified log-rank test.

Repositories and Ancillary Studies

Biospecimens (urine and blood) and genetic specimens (blood) from participants for whom appropriate consent has been obtained will be collected, processed, and submitted to the National Institute of Diabetes and Digestive and Kidney Diseases specimen and genetics repositories at baseline and after the 24-month visit. These specimens will serve as material for ancillary studies to understand the genetic and biochemical basis for VUR, recurrent UTI, renal insufficiency, and renal scarring. An ancillary study committee has been formed and drafted a policy for ancillary studies using repository specimens and/or data collected during the RIVUR study.

CONCLUSIONS

The RIVUR study will provide useful information to clinicians about the risks and benefits of prophylactic antibiotics for children who have had a first or second UTI and are found to have VUR. The data and specimens collected over the course of the study will allow researchers to better understand the pathophysiology of recurrent UTI and its sequelae.

Acknowledgments

This research was supported by grant U01DK074059 from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services.

This article honors the memory of Dr James D. Hosking, a superb clinical trials biostatistician and systems designer. As an integral member of the RIVUR Steering Committee, his experience and expertise were critical to the development of this protocol.

Abbreviations

RIVUR	Randomized Intervention for Children With Vesicoureteral Reflux
VUR	vesicoureteral reflux
UTI	urinary tract infection
TMP/SMZ	trimethoprim/sulfamethoxazole
F/S UTI	febrile or symptomatic UTI

VCUG	voiding cystourethrogram
DMSA	dimercaptosuccinic acid
G6PD	glucose-6-phosphate dehydrogenase
APN	acute pyelonephritis
DVSS	dysfunctional voiding scoring system
PACCT	Paris Consensus on Childhood Constipation Terminology
MEMS	Medication Event Monitoring System

REFERENCES

1. Schwab CW Jr, Wu HY, Selman H, Smith GH, Snyder HM 3rd, Canning DA. Spontaneous resolution of vesicoureteral reflux: a 15-year perspective. *J Urol* 2002;168(6):2594–2599. [PubMed: 12441993]
2. Smellie JM, Jodal U, Lax H, Möbius TT, Hirche H, Olbing H. Outcome at 10 years of severe vesicoureteric reflux managed medically: report of the International Reflux Study in Children. *J Pediatr* 2001;139(5):656–663. [PubMed: 11713442]
3. Greenfield SP, Ng M, Wan J. Resolution rates of low grade vesicoureteral reflux stratified by patient age at presentation. *J Urol* 1997;157(4):1410–1413. [PubMed: 9120966]
4. Conway PH, Cnaan A, Zaoutis T, Henry BV, Grundmeier RW, Keren R. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. *JAMA* 2007;298(2):179–186. [PubMed: 17622599]
5. Kwok WY, de Kwaadsteniet MC, Harmsen M, van Suijlekom-Smit LW, Schellevis FG, van der Wouden JC. Incidence rates and management of urinary tract infections among children in Dutch general practice: results from a nation-wide registration study. *BMC Pediatr* 2006;6:10. [PubMed: 16584577]
6. Mazzola BL, von Vigier RO, Marchand S, Tonz M, Bianchetti MG. Behavioral and functional abnormalities linked with recurrent urinary tract infections in girls. *J Nephrol* 2003;16(1):133–138. [PubMed: 12649544]
7. Wan J, Kaplinsky R, Greenfield S. Toilet habits of children evaluated for urinary tract infection. *J Urol* 1995;154(2 pt 2):797–799. [PubMed: 7609183]
8. Hoberman A, Chao HP, Keller DM, Hickey R, Davis HW, Ellis D. Prevalence of urinary tract infection in febrile infants. *J Pediatr* 1993;123(1):17–23. [PubMed: 8320616]
9. Shaw KN, Gorelick M, McGowan KL, Yakscoe NM, Schwartz JS. Prevalence of urinary tract infection in febrile young children in the emergency department. *Pediatrics* 1998;102(2) Available at: www.pediatrics.org/cgi/content/full/102/2/e16.
10. Farhat W, Bagli DJ, Capolicchio G, et al. The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. *J Urol* 2000;164(3 pt 2):1011–1015. [PubMed: 10958730]
11. Benninga M, Candy DC, Catto-Smith AG, et al. The Paris Consensus on Childhood Constipation Terminology (PACCT) Group. *J Pediatr Gastroenterol Nutr* 2005;40(3):273–275. [PubMed: 15735478]
12. Stein RE, Jessop DJ. Functional status II(R): a measure of child health status. *Med Care* 1990;28(11):1041–1055. [PubMed: 2250491]
13. Rosenberg AR, Rossleigh MA, Brydon MP, Bass SJ, Leighton DM, Farnsworth RH. Evaluation of acute urinary tract infection in children by dimercaptosuccinic acid scintigraphy: a prospective study. *J Urol* 1992;148(5 pt 2):1746–1749. [PubMed: 1331546]
14. Tappin DM, Murphy AV, Mocan H, et al. A prospective study of children with first acute symptomatic *E. coli* urinary tract infection: early 99mtechnetium dimercaptosuccinic acid scan appearances. *Acta Paediatr Scand* 1989;78(6):923–929. [PubMed: 2557721]
15. Verboven M, Ingels M, Delree M, Piepsz A. 99mTc-DMSA scintigraphy in acute urinary tract infection in children. *Pediatr Radiol* 1990;20(7):540–542. [PubMed: 2170901]

16. Elder JS, Peters CA, Arant BS Jr, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J Urol* 1997;157(5):1846–1851. [PubMed: 9112544]
17. Weiss R, Tamminen-Möbius T, Koskimies O, et al. Characteristics at entry of children with severe primary vesicoureteral reflux recruited for a multicenter, international therapeutic trial comparing medical and surgical management. The International Reflux Study in Children. *J Urol* 1992;148(5 pt 2):1644–1649. [PubMed: 1433580]
18. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. Birmingham Reflux Study Group. *Br Med J (Clin Res Ed)* 1987;295(6592):237–241.
19. Hoberman A, Wald ER, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics* 1999;104(1 pt 1):79–86. [PubMed: 10390264]
20. Rushton HG, Majd M, Jantusch B, Wiedermann BL, Belman AB. Renal scarring following reflux and nonreflux pyelonephritis in children: evaluation with 99mtechnetium-dimercaptosuccinic acid scintigraphy. *J Urol* 1992;147(5):1327–1332. [PubMed: 1314912]
21. Jakobsson B, Berg U, Svensson L. Renal scarring after acute pyelonephritis. *Arch Dis Child* 1994;70(2):111–115. [PubMed: 8129430]
22. Andrich MP, Majd M. Diagnostic imaging in the evaluation of the first urinary tract infection in infants and young children. *Pediatrics* 1992;90(3):436–441. [PubMed: 1518703]
23. Rushton HG, Majd M, Chandra R, Yim D. Evaluation of 99mtechnetium-dimercapto-succinic acid renal scans in experimental acute pyelonephritis in piglets. *J Urol* 1988;140(5 pt 2):1169–1174. [PubMed: 2846898]
24. Lutter SA, Currie ML, Mitz LB, Greenbaum LA. Antibiotic resistance patterns in children hospitalized for urinary tract infections. *Arch Pediatr Adolesc Med* 2005;159(10):924–928. [PubMed: 16203936]
25. Hellström A, Hanson E, Hansson S, Hjalmas K, Jodal U. Association between urinary symptoms at 7 years old and previous urinary tract infection. *Arch Dis Child* 1991;66(2):232–234. [PubMed: 2001110]
26. Shaikh N, Hoberman A, Wise B, et al. Dysfunctional elimination syndrome: is it related to urinary tract infection or vesicoureteral reflux diagnosed early in life? *Pediatrics* 2003;112(5):1134–1137. [PubMed: 14595058]
27. Naseer SR, Steinhardt GF. New renal scars in children with urinary tract infections, vesicoureteral reflux and voiding dysfunction: a prospective evaluation. *J Urol* 1997;158(2):566–568. [PubMed: 9224361]
28. Snodgrass W. Relationship of voiding dysfunction to urinary tract infection and vesicoureteral reflux in children. *Urology* 1991;38(4):341–344. [PubMed: 1755143]
29. Koff SA, Wagner TT, Jayanthi VR. The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. *J Urol* 1998;160(3 pt 2):1019–1022. [PubMed: 9719268]
30. Seruca H. Vesicoureteral reflux and voiding dysfunction: a prospective study. *J Urol* 1989;142(2 pt 2):494–498. discussion 501. [PubMed: 2746764]
31. van Gool JD, Hjalmas K, Tamminen-Möbius T, Olbing H. Historical clues to the complex of dysfunctional voiding, urinary tract infection and vesicoureteral reflux. The International Reflux Study in Children. *J Urol* 1992;148(5 pt 2):1699–1702. [PubMed: 1433591]
32. Farhat W, McLorie GA, O'Reilly S, Khoury A, Bagli DJ. Reliability of the pediatric dysfunctional voiding symptom score in monitoring response to behavioral modification. *Can J Urol* 2001;8(6):1401–1405. [PubMed: 11788017]
33. Upadhyay J, Bolduc S, Bagli DJ, McLorie GA, Khoury AE, Farhat W. Use of the dysfunctional voiding symptom score to predict resolution of vesicoureteral reflux in children with voiding dysfunction. *J Urol* 2003;169(5):1842–1846. discussion 1846; author reply 1846. [PubMed: 12686859]
34. Greenfield SP, Wan J. Vesicoureteral reflux: practical aspects of evaluation and management. *Pediatr Nephrol* 1996;10(6):789–794. [PubMed: 8971908]

35. Wan J, Greenfield SP, Talley M, Ng M. An analysis of social and economic factors associated with followup of patients with vesicoureteral reflux. *J Urol* 1996;156(2 pt 2):668–672. [PubMed: 8683756]
36. Cohen AL, Rivara FP, Davis R, Christakis DA. Compliance with guidelines for the medical care of first urinary tract infections in infants: a population-based study. *Pediatrics* 2005;115(6):1474–1478. [PubMed: 15930206]
37. Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: a summary of the literature. *Med Care* 2004;42(7):649–652. [PubMed: 15213489]
38. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med* 2001;134(10):968–977. [PubMed: 11352698]
39. Vrijens B, Urquhart J. Patient adherence to prescribed antimicrobial drug dosing regimens. *J Antimicrob Chemother* 2005;55(5):616–627. [PubMed: 15772145]
40. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med* 1994;13(13–14):1341–1352. discussion 1353–1356. [PubMed: 7973215]
41. Halperin M, Lan KK, Ware JH, Johnson NJ, DeMets DL. An aid to data monitoring in long-term clinical trials. *Control Clin Trials* 1982;3(4):311–323. [PubMed: 7160189]
42. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35(3):549–556. [PubMed: 497341]

FIGURE 1.
Flow diagram for recruitment and follow-up.

FIGURE 2.
International Reflux Study VUR grading scheme.

FIGURE 3.

Grading system for characterizing the extent of renal scarring: 0, no kidney segments affected; 1, 1 to 2 kidney segments affected; 2, 3 to 4 kidney segments affected; 3, >4 kidney segments affected; 4, global atrophy characterized by a diffusely scarred and shrunken kidney.

TABLE 1

Inclusion and Exclusion Criteria for the RIVUR Trial

Inclusion Criteria	Exclusion Criteria
Age at randomization: at least 2 mo but <6 y of age; note that children as young as 1 mo may be screened for the study	UTI diagnosis >112 d before randomization
Diagnosed first or second _{F/S} UTI within 112 d before randomization	For children <6 mo of age at randomization, gestational age <34 wk
Presence of grade I to IV VUR on the basis of radiographic VCUG performed within 112 d of diagnosis of index UTI	Comorbid urologic anomalies ^a
Appropriately treated index _{F/S} UTI	Known sulfa allergy, G6PD deficiency, or other conditions that are contraindications for use of TMP/SMZ History of other renal injury/disease Unable to complete the study protocol Congenital or acquired immunodeficiency Underlying anomalies or chronic diseases that could potentially interfere with response to therapy such as chronic gastrointestinal conditions (ie, malabsorption, inflammatory bowel disease), liver or kidney failure, or malignancy Complex cardiac disease Syndromes associated with VUR or bladder dysfunction Index UTI not treated successfully

^aHydronephrosis, Society for Fetal Urology (SFU) grade 4, ureterocele, urethral valve, solitary kidney, profoundly decreased renal size unilaterally on ultrasound, multicystic dysplastic kidney, neurogenic bladder, pelvic kidney or fused kidney.

TABLE 2

RIVUR Clinical Trial Centers

Hospital	City, State, Country	Recruitment Sites ^a
Children's Hospital of Philadelphia	Philadelphia, PA	PCP, ED, UP, IS
Children's Hospital of Pittsburgh	Pittsburgh, PA	PCP, ED, UP, IS
Johns Hopkins School of Medicine	Baltimore, MD	PCP, UP, NP, IS
Children's Hospital of Michigan	Detroit, MI	IS
Women and Children's Hospital of Buffalo	Buffalo, NY	PCP, ED, UP, IS
Children's Hospital Boston	Boston, MA	PCP, ED, UP, NP
Children's Hospital of Columbus	Columbus, OH	PCP, ED
Children's Mercy Hospital	Kansas City, MO	UP, NP, IS
Texas Children's Hospital	Houston, TX	UP, NP
University of Alabama at Birmingham	Birmingham, AL	PCP, UP, NP
Children's National Medical Center	Washington, DC	PCP, ED, UP, NP, IS
University of Oklahoma	Oklahoma City, OK	UP
Cincinnati Children's Hospital	Cincinnati, OH	PCP, UP, IS
Alfred I. du Pont Hospital for Children	Wilmington, DE	PCP, UP, IS
Penn State Hershey Medical Center	Hershey, PA	PCP, ED, UP, NP, IS
Children's Memorial Hospital	Chicago, IL	PCP, ED, UP, NP, IS
Wake Forest University Baptist Medical Center	Winston-Salem, NC	PCP, ED, UP, NP, IS
University of Wisconsin Children's Hospital	Madison, WI	PCP, ED, UP, NP, IS
Akron Children's Hospital	Akron, OH	PCP, ED, UP, NP, IS

^aPCP indicates primary care practice; ED, emergency department; UP, urology practice; NP, nephrology practice; IS, inpatient service.

TABLE 3

Summary of Observations and Procedures

Study Month	-2-to 0-mo Visit (Screening)	0-mo Visit (Random Assignment/ Baseline)	6-mo Visit (Follow-up)	12-mo Visit (Follow-up)	18-mo Visit (Follow-up)	24-mo Exit Visit (Follow-up)	Every 2 mo (Telephone Follow-up)
Ultrasound	X ^a						
Contrast VCUG	X ^a					X	
Informed consent	X						
DMSA scan	X ^b			X		X ^c	
Detailed medical history	X						
Interim history		X	X	X	X	X	
Physical examination	X	X	X	X	X	X	
Questionnaires							
DVSS and PACCT Group criteria (age ≥ 3 y)		X		X		X	
Parent diary ^d		X	X	X	X	X	
Quality-of-life assessment		X		X		X	
Randomization		X					
Study-medication dispensation		X	X	X	X		
Study medication		X	X	X	X	X	
Accountability							
Urine tests							
Urinalysis		X				X	
Culture		X ^e				X ^e	
Microalbumin/creatinine		X				X	
Urine for central repository		X				X	
Blood tests							
CBC with differential		X	X	X	X	X	
Creatinine, electrolytes		X				X	
Cystatin C		X				X	
Blood for central Repository		X				X	

Study Month	-2-to 0-mo Visit (Screening)	0-mo Visit (Random Assignment/ Baseline)	6-mo Visit (Follow-up)	12-mo Visit (Follow-up)	18-mo Visit (Follow-up)	24-mo Exit Visit (Follow-up)	Every 2 mo (Telephone Follow-up)
Rectal swabs ^f		X					X
Telephone Follow-up							X

CBC indicates complete blood count.

^a Screening ultrasound and VCUG may occur any time within 16 weeks after the index UTI.

^b Screening DMSA may occur any time within 16 weeks after the index UTI.

^c Twenty-four-month DMSA scan may not occur if a study outcome scan has already been obtained.

^d Paper or Web-based data collection.

^e If urinalysis results are positive, culture is obtained.

^f Rectal swabs will also be collected when participants meet treatment-failure criteria.

TABLE 4

Definition of UTI

Febrile UTI (FUTI)	Symptomatic Nonfebrile UTI (SUTI)
I. Fever Documented temperature of at least 100.4°F or 38°C, measured anywhere on the body either at home or at doctor's office and II. Pyuria on urinalysis ≥10 WBCs per mm ³ (uncentrifuged specimen) or ≥5 WBCs per hpf (centrifuged specimen) or Trace or more leukocyte esterase on dipstick and III. Culture-proven infection with a single organism ≥5 × 10 ⁴ CFU per mL (catheterized or suprapubic aspiration urine specimen) or ≥10 ⁵ CFU per mL (clean voided specimen)	I. Symptoms Suprapubic, abdominal, or flank pain or tenderness, or urinary urgency, frequency, or hesitancy, or dysuria, or foul-smelling urine, or in infants ≤4 mo old, failure to thrive, dehydration, or hypothermia and II. Pyuria on urinalysis ≥10 WBCs per mm ³ (uncentrifuged specimen) or ≥5 WBCs per hpf (centrifuged specimen) or Trace or more leukocyte esterase on dipstick and III. Culture-proven infection with a single organism ≥5 × 10 ⁴ CFU per mL (catheterized or suprapubic aspiration urine specimen) or ≥10 ⁵ CFU per mL (clean voided specimen)

WBC indicates white blood cell; hpf, high-powered field; CFU, colony-forming units.

TABLE 5

Estimated Power

Placebo Event Rate	Nonadherence/Attrition Rate		
	5%	10%	15%
20%	0.87	0.83	0.78
25%	0.99	0.98	0.97

The estimated study power for the primary hypothesis, given the assumptions and adjustments shown in Table 5, is shown.

TABLE 6

Event Rate in Treated Group, Adjusted for Nonadherence/Attrition

Placebo Event Rate	Nonadherence/Attrition Rate		
	5%	10%	15%
20%	0.105	0.11	0.115
25%	0.108	0.115	0.122