The SCOUT Study: "Short Course Therapy for Urinary Tract Infections in Children"

Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance

Statistical Analysis Plan
Version 4.0

Sponsored by:

Division of Microbiology and Infectious Disease (DMID)
The National Institute of Allergy and Infectious Diseases

DMID Protocol Number: DMID 09-0103
DMID Funding Mechanism: Contract No. HHSN272200900022C

October 8, 2013
Revised: February 25, 2020

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Abbreviations

AE	Adverse Event
BDMC	Biostatistics and Data Management Core
CFU/mL	Colony Forming Units per milliliter
DSMB	Data and Safety Monitoring Board
ESBL	Extended Spectrum Beta Lactamases
ITT	Intention to Treat
NIH	National Institutes of Health
SCOUT	Short COurse Therapy for Urinary Tract Infections in Children
SAP	Statistical Analysis Plan
TMP-SMX	Trimethoprim-Sulfamethoxazole
TOC	Test of Cure
UTI	Urinary Tract Infection

1. Introduction

This statistical analysis plan (SAP) is based on the SCOUT study Protocol #09-0103 (Contract No. HHSN272200900022C) version 13.0, dated September 20, 2018. The SAP summarizes key aspects of the study to provide context of statistical methods for analyzing the data and the descriptive measures to be reported.

2. Project Overview

The SCOUT study is Phase II placebo-controlled randomized clinical trial. This section describes the design, objectives, outcomes, and treatments of this study as well as the study population and randomization. The definitions used for this study are also listed.

2.1 Project design

This is a multi-center, centrally randomized, double-blind, placebo-controlled non-inferiority clinical trial with children ages two months (at least 36 weeks gestational age birth for subjects < two years of age) to 10 years with a confirmed diagnosis of urinary tract infection (UTI). 724 children will be enrolled over a 4.5 year period and stratified based on presence of fever at the initial visit and by specific antibiotic therapy prescribed by the original treating clinical provider. At time of enrollment, children will be randomized to the standard course of antimicrobial therapy arm or the short course antimicrobial therapy arm. After the first 5 days of primary care physician initiated therapy, children who were randomized to the standard-of-care antimicrobial therapy arm continue on the same antibiotics for 5 more days and children who were randomized to the short-course antimicrobial therapy arm receive the placebo for 5 more days (for 10 days total).

2.2 Project objectives and outcomes

The primary, secondary, and sub-study objectives and outcomes of this study are as follows:

2.2.1 Primary objective

To determine if halting antimicrobial therapy in subjects who have exhibited clinical improvement 5 days after starting antibiotic therapy (short course therapy) have the same failure rate (symptomatic UTI) through test of cure (TOC) (visit Day 11-14) as subjects who continue to take antibiotics for an additional 5 days (standard course therapy).

2.2.2 Primary outcome

The primary efficacy outcome is symptomatic UTI as assessed at the TOC visit (Day 11-14).

2.2.3 Secondary objectives

a. To determine if short-course therapy compared to standard course therapy results in similar numbers of children experiencing a recurrent urinary tract infection (relapse and re-infection) at any time after TOC visit.

b. To determine if short-course therapy compared to standard course therapy results in similar numbers of children with asymptomatic bacteriuria at the TOC visit.

c. To determine if short-course therapy compared to standard course therapy results in similar numbers of children that become colonized with antimicrobial resistant *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) in the gastrointestinal tract as assessed through Day 24-30.

d. To determine if short-course therapy compared to standard course therapy results in similar numbers of children presenting with clinical symptoms that may be related to UTI prior to or at TOC visit.

e. To determine if short-course therapy compared to standard course therapy results in similar numbers of children with positive urine culture prior to or at TOC.

2.2.4 Secondary outcomes

The secondary outcome measures are:

a. Recurrent infection (includes a relapse UTI or a reinfection) at any time after the TOC visit (Day 11-14)

b. Asymptomatic bacteriuria at the TOC visit

c. Colonization with antimicrobial resistant E.coli and K. pneumoniae in the gastrointestinal tract as assessed through Day 24-30.

d. Presentation of clinical symptoms that may be related to UTI prior to or at the TOC visit

e. Positive urine culture prior to or at the TOC visit

2.2.5 Sub-study objectives

- To determine if E. coli and K. pneumoniae recovered from 2 or 3 stool cultures are more likely to be members of disease-associated subgroups within their respective species (E. coli phylogroups B2 and D, K. pneumoniae clusterKpI).
- To determine if treatment-susceptible strains recovered from cultures during treatment (culture #1 for 5-day arm; cultures #1 or #2, 10-day arm) are more likely to be members of disease-associated subgroups.
- To determine if treatment-resistant strains of either species are more likely than treatment susceptible strains to be recovered from cultures during treatment.

- To determine the overall prevalence of colonization with carbapenem-resistant Enterobacteriaceae (overall and for specific pathogens) in children after completion of the course of antibiotic therapy for UTI.
- To compare the overall biodiversity of the gut microbial community, as measured by culture-independent marker gene sequencing at each follow-up visit following short-course and standard-course antibiotic exposure.
- To compare the overall fraction of gut microbiome community represented by gammaproteobacteria measured by culture-independent marker gene sequencing at each follow-up visit following short-course and standard-course antibiotic exposure.
- To compare the average ecological similarity between microbial communities within and between treatment groups at each follow-up following short-course and standard-course antibiotic exposure.
- To describe the breadth of bacteria present in the stool of children receiving therapy for a urinary tract infection. These data will allow for comparison of aerobic bacteria composition in these children and present an opportunity to contrast them to similar data available from other pediatric patient populations.

2.2.6 Sub-study outcomes

The sub-study outcome measures are:

- Presence of E.coli and presence of K. pneumoniae
- Sub-types of E.coli (0=phylogroups A or B1, 1=phylogroups B2 or D), sub-types of K. pneumoniae
- Presence of treatment-susceptible E.coli, presence of treatment-susceptible K. pneumoniae
- Presence of treatment-resistant E.coli, presence of treatment- resistant K. pneumoniae

- Prevalence of colonization with carbapenem resistant Enterobactericiae in children after completion of the course of antibiotic therapy for UTI.
- Overall biodiversity of the gut microbial community, as measured by culture-independent marker gene sequencing.
- Overall fraction of gut microbiome community represented by gamma-proteobacteria measured by culture-independent marker gene sequencing.
- Average ecological similarity between microbial communities within and between treatment groups.
- Description of bacteria present on the aerobic stool cultures obtained at each of the three study timepoints.

2.3 Treatments

Short course therapy: prescribed antibiotic (Trimethoprim-Sulfamethoxazole (TMP-SMX), Amoxicillin-Clavulanate, Cefixime, Cefdinir or Cephalexin) for 5 days, followed by placebo for 5 days;
Standard therapy: prescribed antibiotic (TMP-SMX, Amoxicillin-Clavulanate, Cefixime, Cefdinir or Cephalexin) for 10 days.

2.4 Procedures

2.4.1 Study Population

Children: ages two months (at least 36 weeks gestational age at birth for subjects < two years of age) to 10 years with a confirmed diagnosis of a urinary tract infection (UTI) being treated by one of four antibiotics (TMP-SMX or Amoxicillin-Clavulanate or Cefixime or Cefdinir or Cephalexin). Only those subjects with documented clinical improvement (afebrile and asymptomatic) following four-five days of initial antibiotic therapy will be eligible.

2.4.2 Randomization and replacement

Children whose parents agree to participate in the study will be randomized to either (1) standard-of-care antimicrobial therapy (10 days of antibiotic therapy) or (2) short course antimicrobial therapy arm (five days of antibiotic therapy). We will stratify randomization within site based on (1) whether the UTI was originally associated with fever, and (2) the antibiotic prescribed at initiation of therapy. After treatment, the subjects will be followed for 38-44 days through follow-up phone calls and study visits. Subjects that withdraw or are withdrawn from the study prior to being evaluable for the primary outcome measure will be replaced. The study will continue until at least 652 subjects are evaluable for the primary outcome measure. At least 724 subjects will be enrolled in order to reach 652 evaluable subjects, but the total number that will be 'enrolled / consented' may exceed 724 if the study has not enrolled 652 evaluable for the primary endpoint.

2.5 Definitions

Day 1: The day when subject starts antibiotic treatment. The start of SCOUT-directed treatment is on Day 6, after five days of initial antibiotic treatment.
Fever/Febrile: A documented temperature of at least 100.4° F or 38° C, measured anywhere on the body (oral, axillary, tympanic, or rectal).
Afebrile: NO documented temperature greater than or equal to 100.4 °F or 38°C, measured anywhere on the body (oral, axillary, tympanic, or rectal) in the 24 hours prior to the enrollment visit.
Treatment failure: A subject will be categorized as a treatment failure, if he/she has a symptomatic UTI in period between Day 6 through the Day 11 – 14 Test of Cure (TOC) Visit:

I. The presence of at least one of the symptoms consistent with the diagnosis of UTI including:

- Symptoms for all children (ages two months to 10 years):
  - fever (a documented temperature of at least 100.4 °F OR 38°C measured anywhere on the body)
  - dysuria
- Additional symptoms for children > 2 years of age:
  - suprapubic, abdominal, or flank pain or tenderness OR
  - urinary urgency, frequency, or hesitancy (defined as an increase in these symptoms from pre-diagnosis conditions)
- Additional symptoms for children ≥ 2 months to 2 years of age:
  - poor feeding OR
  - vomiting

AND

II. Pyuria on urinalysis

- ≥10 WBC/mm^3 (uncentrifuged specimen) OR
- ≥5 WBC/hpf (centrifuged specimen), OR
- Leukocyte esterase ≥ trace on dipstick.

AND

III. Culture proven infection with a single uropathogen:

- ≥5 x 10^4 CFU/mL (catheterized or suprapubic aspiration urine specimen) OR
- ≥10^5 CFU/mL (clean void specimen).

NOTE: As per the above criteria, asymptomatic subjects (including subjects assessed as having asymptomatic bacteriuria) at the Day 11-14 TOC visit will NOT be considered a treatment failure for the primary outcome measure.

Recurrent Infection: A UTI that occurs anytime after the Day 11 – 14 Test of Cure Visit. This can include a relapse infection or reinfection.

Asymptomatic Bacteriuria: Asymptomatic Bacteriuria is defined in any SCOUT subject by:

(1) Absence of symptoms attributable to UTI including fever AND/OR the following:

- Symptoms for all children (ages two months to 10 years):
    - fever (a documented temperature of at least 100.4 °F OR 38°C measured anywhere on the body)
    - dysuria
- Additional symptoms for children > 2 years of age:
    - suprapubic, abdominal, or flank pain or tenderness OR
    - urinary urgency, frequency, or hesitancy (defined as an increase in these symptoms from pre-diagnosis conditions)
- Additional symptoms for children ≥ 2 months to 2 years of age:
    - poor feeding OR
    - vomiting

AND

(2) A positive urine culture

- 5×10^4 CFU/mL (catheterized or suprapubic aspiration urine specimen) OR
- $\geq 10^5$ CFU/mL (clean void specimen).

Antibiotic Resistance: Resistance against amoxicillin-clavulanate, TMP-SMX or evidence of ESBL production.

Multiple Drug Antibiotic Resistance: Resistance to two or more agents (this includes resistance against amoxicillin and amoxicillin-clavulanate).

K. pneumoniae **Multiple Drug Antibiotic Resistance**: Resistance to either two or more of the three agents (TMP-SMX, amoxicillin-clavulanate, cefixime, or cephalexin) that the SCOUT Study will test (excluding amoxicillin resistance).

2.6 Clinical evaluations

Subjects will be seen by a clinician for three study visits:

1. Enrollment visit (Day 2-6)
2. Test of Cure visit (Day 11-14)
3. Outcome assessment visit (Day 24-30)

Subjects enrolled prior to Day 5 of their prescribed medication will be verified as afebrile and with no worsening of conditions on Day 5 or prior to receiving the first dose of SCOUT therapy on Day 6. In addition, subjects will be contacted by phone at the end of the study period on the Follow-up Phone Call (Day 38 - 44). Clinical evaluations at each visit will be as follows:

***Day 2-6 (any time after initiation of antibiotic treatment but prior to starting the sixth day of study treatment)*:**

To confirm eligibility including clinical improvement (afebrile and asymptomatic) a pain assessment will be performed checking for any suprapubic, abdominal, or flank pain or tenderness. If a study RN receives a report of a UTI symptom at a study visit, he/she will inform the parent/guardian that the child should be seen by a clinician licensed to diagnose and treat the UTI. If this occurs at the enrollment visit, the child will be excluded from the study and will be referred back to the PCP who initially treated the child.

Confirmation is obtained by study staff that the subject remains afebrile with no worsening of symptoms on Day 5-6 (prior to taking the first dose of SCOUT therapy on Day 6) for subjects enrolled prior to Day 5. Any volunteer that develops a fever or worsening of symptoms will be withdrawn from the study and considered an entry failure.

Day 11 -14 Test of Cure Post Treatment Visit (one – four days after completing the study product:

The child will be clinically assessed for the presence of UTI symptoms and a urine specimen will be collected for test of cure. If a study RN receives a report of a UTI

symptom at the Test of Cure visit, he/she will inform the parent/guardian that the child should be seen by a clinician licensed to diagnose and treat the UTI. The RN will document the symptom on the appropriate case report form and will contact a study physician to arrange follow-up visit.

Day 24 - 30 Outcome Assessment Visit (14-20 days following study product completion):

The child will be clinically assessed for the presence of UTI symptoms. If a urine specimen could not be collected at the Day 11 – 14 TOC Visit for asymptomatic subjects, another attempt to collect a urine sample at this visit will be made. If a study RN receives a report of a UTI symptom at the Outcome Assessment visit, he/she will inform the parent/guardian that the child should be seen by a clinician licensed to diagnose and treat the UTI. The RN will document the symptom on the appropriate case report form and will contact a study physician to arrange follow-up visit.

***Day 38 - 44 Follow-up Phone Call* (*28-34 days after completing the study product*):**

Subjects will be asked regarding presence or absence of UTI symptoms, if they sought medical care for possible recurrence of UTI, and to report any inter-current illnesses.

3. Statistical Considerations

3.1 Statistical design

This is a prospective, stratified, randomized, double-blind, placebo-controlled non-inferiority clinical trial with standard-of-care antimicrobial therapy as arm 1 and short-course antimicrobial therapy placebo-controlled as arm 2.

Primary objective

To determine if halting antimicrobial therapy in children who have exhibited clinical improvement 5 days after starting antibiotic therapy (short course therapy) have the same failure rate (symptomatic UTI) through TOC (visit Day 11-14) as subjects who continue to take antibiotics for an additional 5 days (standard course therapy).

Secondary objectives

a. To determine if short-course therapy compared to standard course therapy results in similar numbers of children experiencing a recurrent infection (relapse and reinfection) at any time after the TOC visit (Day 11-14).

b. To determine if short-course therapy compared to standard course therapy results in similar numbers of children with asymptomatic bacteriuria at the TOC visit.

c. To determine if short-course therapy compared to standard course therapy results in similar numbers of children that become colonized with antimicrobial resistant *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) in the gastrointestinal tractas assessed through outcome assessment visit (Day 24-30).

d. To determine if short-course therapy compared to standard course therapy results in similar numbers of subjects presenting with clinical symptoms that may be related to UTI prior to or at the TOC visit.

e. To determine if short-course therapy compared to standard course therapy results in similar numbers of children with positive urine cultures prior to or at the TOC visit.

Sub-study objectives

- To determine if E. coli and K. pneumoniae recovered from 2 or 3 stool cultures are more likely to be members of disease-associated subgroups within their respective species (E. coli phylogroups B2 and D, K. pneumoniae clusterKpI)

- To determine if treatment-susceptible strains recovered from cultures during treatment (culture #1 for 5-day arm; cultures #1 or #2, 10-day arm) are more likely to be members of disease-associated subgroups;
- To determine if treatment-resistant strains of either species are more likely than treatment susceptible strains to be recovered from cultures during treatment.
- To determine the overall prevalence of colonization with carbapenem-resistant Enterobacteriaceae (overall and for specific pathogens) in ambulatory children after completion of treatment for UTI.
- To compare the overall biodiversity of the gut microbial community, as measured by culture-independent marker gene sequencing at each follow-up visit following short-course and standard-course antibiotic exposure.
- To compare the overall fraction of gut microbiome community represented by gammaproteobacteria measured by culture-independent marker gene sequencing at each follow-up visit following short-course and standard-course antibiotic exposure.
- To compare the average ecological similarity between microbial communities within and between treatment groups at each follow-up following short-course and standard-course antibiotic exposure.
- To describe the breadth of bacteria present in the stool of children receiving therapy for a urinary tract infection. These data will allow for comparison of aerobic bacteria stool composition in these children and present an opportunity to contrast them to similar data available from other pediatric patient populations.

3.2 Sample size determination and power calculations

The primary aim of this study is to determine whether short-course antimicrobial therapy (five days) is non-inferior to standard-of care antimicrobial therapy (10

days) for the treatment of UTI in children with respect to reinfection of UTI through TOC visit Day 11-14. The treatment failure rate under the standard of care, R_0, is expected to be 5%. This estimate is based on data from previously published studies [1, 2]. The power and sample size calculations are based on the assumption that recurrence under the short-course therapy, R_{SC}, will range from 5% to 9%.

In the non-inferiority test, on which power and sample size are based, the null hypothesis that short-course therapy is inferior to standard-of-care therapy is tested against the alternative that short-course therapy is non-inferior. That is, H_0: $R_{SC} > R_0 + \delta$ is tested against H_a: $R_{SC} \leq R_0 + \delta$, where δ is the "interval of equivalence," the range in which the treatment failure rates of the two therapies would be considered clinically equivalent. We believe that an interval of equivalence of 5% would be clinically acceptable; a success rate of 95% for the standard-of-care therapy group when compared to 90% for the short-course therapy group. For all power and sample size calculations, the significance level (chance of incorrectly rejecting the null hypothesis) is $\alpha = 0.05$.

Table 1 gives the power for testing the non-inferiority hypothesis with a sample size of 300 evaluable subjects per arm and with equivalence intervals (i.e., δ) ranging from 2% to 5%. With 300 subjects per arm, there would be 87% power with $R_{SC} = 5\%$ and $\delta = 5\%$. The power decreases as either the equivalence interval decreases or as R_{SC} increases; in other words, as the recurrence rates of the two regimens become more similar, large sample sizes are required to discriminate between them.

Table 2 gives the sample sizes required to obtain 80% power with the same parameters for R_{SC} and δ. A sample size of 235 per arm is sufficient for 80% power with $R_{SC} = 5\%$ and $\delta = 5\%$, while larger sample sizes are required for larger values of R_{SC} or smaller values of δ. Finally, Table 3 gives the sample sizes required to obtain 90% power; a sample size of 326 subjects per arm would be required for 90% power with $R_{SC} = 5\%$ and $\delta = 5\%$.

Table 1: Power (%) for comparing standard and shortened treatment for UTI

Interval of equivalence	Recurrence rate under shortened treatment				
	5%	6%	7%	8%	9%
2%	30	13	–	–	–
3%	51	28	12	–	–
4%	72	48	27	12	–
5%	**87**	69	46	25	12

Notes: Values for power in the table are given in percent and were calculated for comparing rates of recurrence between standard and shortened treatment for UTI, with sample sizes of 300 per arm and an assumed significance level of 0.05. The assumed recurrence rate for standard treatment is 5%. As an example, if the actual recurrence rate for shortened treatment is 6%, there is 28% power for finding non-inferiority with an equivalence interval of 3%. However, the power increases to 69% with an equivalence interval of 5%.

Table 2: Sample sizes for 80% power for non-inferiority of shortened vs. standard UTI antibiotic regimen

Interval of equivalence	Recurrence rate under shortened treatment				
	5%	6%	7%	8%	9%
2%	1,469	6,424	–	–	–
3%	653	1,606	6,962	–	–
4%	368	714	1,741	7,488	–
5%	**235**	402	774	1,872	8,001

This table gives sample sizes PER ARM for achieving 80% power for testing non-inferiority under the given values for recurrence rates and equivalence intervals. The significance level is assumed to be 0.05. The assumed recurrence rate for standard treatment is 5%. As an example, 653 study participants per arm (1,306 total) would be required for 80% power if the recurrence rate for the standard of care and shorted regimens were both 5%, with an equivalence interval of 3%.

Table 3: Sample sizes for 90% power for non-inferiority of shortened vs. standard UTI antibiotic regimen

Interval of equivalence	Recurrence rate under shortened treatment				
	5%	6%	7%	8%	9%
2%	2,034	8,898	–	–	–
3%	904	2,225	9,643	–	–
4%	509	989	2,411	10,371	–
5%	**326**	557	1,072	2,593	11,082

This table gives sample sizes PER ARM for achieving 90% power for testing non-inferiority under the given values for recurrence rates and equivalence intervals. The significance level is assumed to be 0.05. The assumed recurrence rate for standard treatment is 5%. As an example, 509 study participants per arm (1,018 total) would be required for 90% power if the recurrence rate for the standard of care and shortened regimens were both 5%, with an equivalence interval of 4%.

Based on these calculations, we propose a sample size of 326 per arm. However, this value must be adjusted upwards to offset loss to follow-up. It is expected that loss to follow-up will be minimal in this study. Because the study is of short duration, we are hopeful that we will be able to follow virtually all subjects to study completion. However, some study participants will not return for the follow-up visits to determine the primary endpoint. Furthermore, some percentage may need to disrupt or discontinue study treatment, or may not have the endpoint determined due to problems with specimens or laboratory processing. Altogether, these factors may reduce the sample size by as much as 10%. Thus we propose to increase the sample by approximately 11% to offset this sample size reduction, resulting in the final proposed sample size of 362 study participants per arm.

4. Statistical Analyses

The methods for the planned statistical interim analysis including the timing of the interim analysis, the scope of the interim analysis (a description of which endpoints will be analyzed), and the methods or statistical tests that will be used in the interim

analysis are described. The general description of the planned final analysis is provided.

4.1 Interim Analysis

After half of the subjects (373 subjects) have enrolled, an interim analysis for the primary endpoint of treatment failure rate will be performed. This efficacy analysis will test the null hypothesis that the treatment failure rate under short-course therapy is less than or equal to that of standard-of-care therapy; the alternative hypothesis is that the failure rate under short-course therapy is greater than using standard-of-care therapy. This test will be one-sided test of hypothesis of equal treatment failure rates between the short-course therapy and standard-of-care therapy with α=0.05. We will calculate the difference in treatment failure rates between short-course therapy and standard-of-care therapy, and a one-sided 95% lower confidence limit using normal approximation for large samples. If the lower confidence limit exceeds zero, we will conclude that short-course therapy has a significantly higher failure rate than standard-of-care therapy. Since the interim analysis is for superiority of standard-of-care therapy and the final efficacy analysis is for non-inferiority of short-course therapy, there is no impact of the interim analysis on the Type I error of the final efficacy analysis and thus no adjustments to the significance level are required.

In addition, conditional power estimates may be calculated. The conditional power analysis is a re-assessment of the power given the results of the study to date. If the recurrence rate for short course therapy is smaller than expected relative to standard therapy, then there would be high conditional power; if the recurrence rate for short course therapy is greater than expected relative to standard therapy, then there would be lower power than initially expected. The need for this analysis will be

decided in conjunction with the DSMB, along with other data to be presented to the DSMB.

4.2 Final analyses

The data analysis will consists of several parts. First, descriptive and baseline characteristics will be generated for outcome measures for the purpose of describing the study population and comparing the two study arms at baseline. Second, the primary and secondary analyses will be conducted. Finally, primary and secondary outcome measures will be compared between various subgroups of the study participants to assess potential interactions with treatment effects. Details are provided below.

4.2.1 Descriptive analyses

Standard descriptive statistics will be used to describe subjects' baseline characteristics and study outcome measures overall and within each treatment group. Summary statistics such as means, standard deviations, medians, and ranges will be produced for continues variables. Frequency counts and percentage will be generated for describing variables that are dichotomous or polytomous in nature. The balance of baseline measures between short-course therapy group and standard-of-care therapy group will be compared using two-sample *t*-tests for normally distributed data or, the Mann-Whitney test for non-normally distributed data and using chi-square tests for categorical variables (*Table 1 and 2 in Section 7.1*).

4.2.2 Primary/Efficacy analysis

The primary endpoint of this study is the proportion of children experiencing treatment failure (symptomatic UTI) at the TOC visit (Day 11-14).

The primary analysis will follow intent-to-treat (ITT) principles, with subjects analyzed according to randomized treatment assignment (*Table 3 in Section 7.1*). In addition, a "per-protocol" analysis will be performed; the per-protocol analysis would include only subjects who were adherent to their assigned study regimen and completed more than 80% of the prescribed dose (*Table 4 in Section 7.1*). All subjects taking at least one dose of study treatment between Day 6 and Day 10 who have been evaluated for treatment success at TOC visit or have failed before TOC will be included in the ITT analysis (See Table 4 below).

The primary analysis will be a non-inferiority test comparing the proportion of children with symptomatic UTIs at the TOC visit between two treatment arms to evaluate whether the difference is within the 5% equivalence interval. This test will be conducted by calculating the one-sided 95% upper confidence limit for the difference in symptomatic UTI (treatment failure) rates between the short-course and standard-of-care therapies. If this limit is less than or equal to the equivalence interval (0.05), then we will conclude that short course therapy is not inferior to standard therapy. Subjects with asymptomatic bacteriuria or who are asymptomatic with a positive culture including pyuria will NOT be considered treatment failures for the primary outcome measure.

Table 4: SCOUT Study Medication Dosage Adherence

Antibiotic Drug	Antibiotic Dosage	80% of Expected Doses
Trimethoprim-Sulfamethoxazole (TMP-SMX)	8 mg/kg/day of Trimethoprim in 2 divided doses, Max 160mg BID Trimethoprim	Eight doses
Amoxicillin-Clavulanate	45 mg/kg/day in 2 divided doses, Max 875 mg Q12H	Eight doses
Cefixime	8 mg/kg/day in 1 dose, Max 400 mg	Four doses
Cephalexin	50mg/kg/day in 3 divided doses	Twelve Doses

4.2.3 Secondary analysis

The secondary endpoints include:

a. The proportion of children experiencing a recurrent urinary tract infection at any time after the TOC visit.

b. The proportion of children with asymptomatic bacteriuria at the TOC visit.

c. The proportion of children that develop the gastrointestinal colonization of antimicrobial resistant *Escherichia coli* (*E. Coli*) and *Klebsiella pneumoniae* (*K. Pneumoniae*) assessed through Outcome Assessment visit (Day 24-30).

d. The proportion of children presenting with clinical symptoms that may be related to UTI prior to or at the TOC visit.

e. The proportion of children with positive urine culture prior to or at TOC visit.

The secondary analysis for recurrent infection (Table 5 in Section 7.1), asymptomatic bacteriuria (Table 6 in Section 7.1), presenting with clinical symptoms (Table 7 in Section 7.1), and positive urine culture (Table 8 in Section 7.1) (Endpoints a, b, d and e), will include conventional tests to evaluate whether the proportions between two treatment arms are equal. These tests will be conducted by calculating the two-sided 95% confidence limit for the difference between the short-course and standard-of-care therapies. Analyses will be performed on per-protocol population, with appropriate exclusions of treatment failures. Details of these exclusions are shown in Section 5.1.

The secondary analysis for proportion of children that become colonized with antibiotic-resistant *E. coli* and *Klebsiella pneumoniae* assessed through Outcome Assessment visit (Day 24-30) (Endpoint c) will consist of two-sample tests for differences between proportions, using a chi-square test at significance level of 0.05 (*Table 9 in Section 7.1*). We hypothesize that children with short-course therapy will be less likely to become colonized with emergent antibiotic-resistant E. coli and K.

pneumoniae. These analyses will examine whether antibiotic resistance after enrollment emerges differently between the short course and standard of care arms. First, a summary of antibiotic resistance present at enrollment, TOC and Outcome Assessment among the per-protocol population excluding treatment failures with a sample at TOC (Population 4) will be presented (*Table 9 in Section 7.1*).

Emergent antibiotic resistance will be defined as follows:

Among Population 4 (per-protocol population excluding treatment failures without TOC sample), define an indicator for emergent antibiotic resistance at TOC and Outcome Assessment. A child would have emergent antibiotic resistance if they

1. Had no antibiotic-resistant E.coli or K.pneumoniae at enrollment but one or both are now present. OR
2. Had either antibiotic-resistant E.coli or K.pneumoniae at enrollment but now the other antibiotic-resistant organism is present OR
3. Had antibiotic-resistant E.coli and/or K.pneumoniae at enrollment, but have now developed resistance to new antibiotics in either organism.

Emergent antibiotic resistance will be examined by treatment arm in Table 10. We also want to show which antibiotics the organism showed resistance (ceftazidime, amoxicillin-clavulanate, TMP-SMX, or ampicillin). Prior to unblinding, patterns of multiple resistance will be summarized and if there are a few very common patterns they will also be included in this table (*Table 11 in Section 7.1*).

Longitudinal models such as mixed-effects logistic regression models and logistic regression models with generalized estimating equation (GEE) will be explored to analyze the repeated outcome of emergent antibiotic resistance.

In some cases, subjects who experienced treatment failure will not be evaluable for the secondary objectives. Specifically:

- *Recurrent infection*: Subjects with treatment failures will not be evaluable for recurrent infection.
- *Asymptomatic bacteriuria*: subjects with treatment failure will be evaluable (all will be negative for asymptomatic bacteriuria – by definition, treatment failures are symptomatic so cannot be considered to have asymptomatic bacteriuria).
- *Colonization*: Generally, subjects with treatment failure will not be evaluable for colonization. However, one exception would be that if the child completes the Test of Cure visit but is a treatment failure, we collect a stool specimen at that visit and thus will have a specimen to evaluate for colonization with resistant bacteria.
- *Clinical symptoms*: subjects with treatment failure will be evaluable (all will be positive for clinical symptoms).
- *Positive Cultures*: subjects with treatment failure will be evaluable (all will have positive cultures).

4.2.4 Sub-study analyses

Sub-study endpoints include:

1. The proportion of patients with E. coli detected and the proportion of patients with K. pneumoniae detected within each treatment arm.

2. The proportions of sub-type 0 (phylogroups A or B1) or sub-type 1 (phylogroups B2 or D) among patients with E. coli detected and among patients with K. pneumoniae detected within each treatment arm.

3. The proportions of patients with treatment-susceptible E. coli among patients with E.coli detected and the proportions of patients with treatment-susceptible K.

pneumoniae among patients with K. pneumoniae detected within each treatment arm.

4. The proportion of treatment-resistant E. coli among the patients with E.coli detected and the proportion of treatment-resistant K. pneumoniae among the patients with K. pneumonia detected within each arm.

5. The proportion of colonization with carbapenem resistant Enterobactericiae in children after completion of the course of antibiotic therapy for UTI within each treatment arm.

6. Overall biodiversity of the gut microbial community, as measured by culture-independent marker gene sequencing.

7. Overall fraction of gut microbiome community represented by gammaproteobacteria measured by culture-independent marker gene sequencing.

8. Average ecological similarity between microbial communities within and between treatment groups.

The analysis plan for the sub-studies are designed and executed outside of the SCOUT protocol by the Principal Investigators. The analysis for the sub-study is not discussed further in this SAP.

4.2.5 Sub-population analyses

Treatment effects for the primary and secondary endpoints will be estimated as differences between proportions and compared for subpopulations defined by age (defined initially as less than 3 years old, 3 to 6 years old, and 7 to 10 years old), febrile or non-febrile UTI, type of originally prescribed antibiotic, and site. First, proportions will be tabulated as two-sample comparisons and chi-square tests for treatment differences in the endpoints within subgroups will be calculated (*Table 12-*

17 in Section 7.1). Factors where significant differences are observed will be further assessed using logistic regression analysis (*Table 18-23 in Section 7.1*). Goodness of fit test will be reported for model checking. Treatment-by-subpopulation interactions will be tested using likelihood ratio tests. The power of these comparisons is expected to be low for both primary and secondary endpoints. The study is only likely to detect marked differences in treatment effects in these subpopulations. These analyses will use only the per-protocol population with appropriate exclusions (see Section 5.1). Because these analyses are exploratory, significance level at 0.05 will be used.

4.2.6 Safety Analysis

Safety will be evaluated by the collection and analysis of data on (S)AEs. All (S)AEs will be reported, regardless of their relationship to study product (*Table 24 in Section 7.1*). The number of subjects with adverse events and the number of adverse events will be reported by body system and by treatment arm (*Table 24A-B in Section 7.1*). (S)AEs results (the number of subjects with adverse event and the number of adverse events) will be compared by treatment arm, with statistical tests for differences in proportion of subjects with serious adverse events between study arms. These analyses will use the ITT population and two-sided tests with significance level of 0.05 (*Table 25A in Section 7.1*).

Missing Data: Initially we will assess the extent and pattern of missing data using frequencies and cross-tabulations. If data are missing for only a few cases (5% or less), then data analysis will be conducted only on study participants with complete data. However, when such a strategy would result in loss of data from a substantial proportion of participants (i.e., 20%) or would lead to biased or inaccurate results, then sensitivity analysis or some form of imputation will be performed. The form of

imputation used will depend on the nature of the data that are missing. If data are missing for primary endpoint (treatment failure), frequencies for missing data by center, patient characteristic (clinical and demographic), and medication used will be examined. If there are significant associations of missingness with any of these characteristics, we would consider intent-to treat analysis with imputation methods such as regression technique, hot-deck, or best/worst case (for binary outcomes) and choose the one that would be most appropriate for type of missing data pattern (missing at random). If there is partial follow-up, that partial data might allow us to do an imputation. The imputation will be employed if there is a clear evidence of bias due to missing data. Sensitivity analyses will be performed to assess how sensitive results are to reasonable changes in the assumptions that are made for missing data.

To be considered evaluable a child must meet (a) below and one of (b) , (c) or (d):

(a) have taken study medication, AND;

(b) complete the Test of Cure visit, OR;

(c) have prior evidence of a treatment failure;

(d) answered YES to OS #3 (The Off Study CRF Question #3 is "Was a Test of Cure visit completed (or an interim visit if the subject was symptomatic prior to Test of Cure)?").

5. Planned Outputs

5.1 Tables

- **Definition of populations**

- **Population 1**: All subjects taking at least one dose of study treatment between Day 6 and Day 10 who have been evaluated for treatment success at TOC or have failed prior to TOC (ITT population)
- **Population 2:** The enrolled subjects who were adherent to their assigned study regimen and completed more than 80% of the prescribed dose between Day 6 and Day 10 (per-protocol population)
- **Population 3:** Subjects in population 2 who did not experience a treatment failure.
- **Population 4:** Subjects in population 2 who have a stool sample at TOC visit. Some treatment failures will not have a sample collected at TOC because they failed prior to TOC. Treatment failures without the sample at TOC would be excluded from population 4.

- **Definition for a subject having primary endpoint**

The primary endpoint of this study is the proportion of children experiencing treatment failure (symptomatic UTI) at the TOC visit (Day 11-14).

- **Data handling**

- Treat blanks and "." as missing unless specified otherwise.

6. References

1. Keren R, Chan E. A meta-analysis of randomized, controlled trials comparing short- and long-course antibiotic therapy for urinary tract infections in children. Pediatrics. May 2002; 109(5):E70-70.

2. Hoberman A, Wald ER, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. Pediatrics. Jul 1999; 104(1 Pt 1):79-86.

7. Appendices

7.1 SAP Table shells

Table 1. Randomization review

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)
Presence of fever		
Yes		
No		
Antibiotic Type		
TMP-SMX		
Amoxicillin-Clavulanate		
Cefixime		
Cefdinir		
Cephalexin		

Note: Chi-square tests for frequencies across two treatment groups

1. P=0.xxxx for Presence of fever versus No fever
2. P=0.xxxx for Antibiotic Type

Table 2. Demographic and baseline data

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	p-value
Age, Mean ± SD			
2 months -35 months			
3 – 6 years			
7 – 10 years			
Gender			
Male			
Female			
Race/ethnicity			
White			
Black/African American			
Asian			
Native Hawaiian/Other Pacific Islander			
American Indian/Alaska Native			
Multi-Racial			
Other			
Hispanic			
Yes			
No			

Table 2 Specifications

- Repeat the analysis on population 1 (ITT population) and 2 (per-protocol population) separately as Table 2a and 2b.
- Table 2 was designed to show the frequencies and column percentage of subjects within each category unless was specified as to show means and standard deviation. Some categorical variables may need to be created based on numeric values.

Table 3. Comparison of the proportion of subjects with symptomatic UTIs prior to or at the TOC visit for ITT population (Population 1) (Primary analysis)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	Difference of proportion and one-sided 95% confidence limit
Treatment Failure			

SAS note: Using RISKDIFF ALPHA=0.10 in the TABLE STATEMENT of PROC FREQ procedures to calculate the difference of proportion and one sided 95% CI

Table 4. Comparison of the proportion of subjects with symptomatic UTIs prior to or at the TOC visit for per protocol population (Population 2) (Primary analysis)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	Difference of proportion and one-sided 95% confidence limit
Treatment Failure			

Table 5. Comparison of the proportion of subjects with a recurrent infection at any time after the TOC visit for per protocol population (Population 3) (Secondary analysis, Endpoint a)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	Difference of proportion and two-sided 95% confidence limit
Recurrent Infection			

Table 6. Comparison of the proportion of subjects with asymptomatic bacteriuria at the TOC visit for per protocol population (Population 2) (Secondary analysis, Endpoint b)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	Difference of proportion and two-sided 95% confidence limit
Asymptomatic Bacteriuria			

Table 7. Comparison of the proportion of subjects with clinical symptoms that may be related to a UTI prior to or at the TOC visit for per protocol population (Population 2) (Secondary analysis, Endpoint d)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	Difference of proportion and two-sided 95% confidence limit
Clinical Symptoms			

Table 8. Comparison of the proportion of subjects with positive urine cultures prior to or at the TOC visit for per protocol population (Population 2) (Secondary analysis, Endpoint e)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	Difference of proportion and two-sided 95% confidence limit
Positive Urine Cultures			

Table 9: Comparison of the proportion of children that develop the gastrointestinal colonization of antimicrobial resistant E. coli and K. pneumoniae through Outcome assessment visit (Day 24-30) for per protocol population (Population 2) (Secondary analysis, Endpoint c)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	*p*-value for Chi-square test
Enrollment visit (Day 2-6)			
Any antibiotic-resistant E. coli Any antibiotic-resistant K. pneumoniae Any antibiotic resistance Both antibiotic-resistant E. coli and antibiotic-resistant K. pneumoniae Multiple antibiotic-resistant E. coli Multiple antibiotic-resistant K. pneumoniae			
TOC visit (Day 11-14)			
Any antibiotic-resistant E. coli Any antibiotic-resistant K. pneumoniae Any antibiotic resistance Both antibiotic-resistant E. coli and antibiotic-resistant K. pneumoniae Multiple antibiotic resistance to E. coli Multiple antibiotic resistance to K. pneumoniae			
Outcome assessment visit (Day 24-30)			
Any antibiotic-resistant E. coli Any antibiotic-resistant K. pneumoniae Any antibiotic resistance Both antibiotic-resistant E. coli and antibiotic-resistant K. pneumoniae Multiple antibiotic resistance to E. coli Multiple antibiotic resistance to K. pneumoniae			

Table 10: Comparison of the proportion of children that develop emergent gastrointestinal colonization of antimicrobial resistant E. coli or K.pneumoniae through outcome assessment visit (day 24-30) for per protocol population (Population 4) (Secondary analysis c)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	p-value for Chi-square test
TOC visit (Day 11-14)			
Outcome assessment visit (Day 24-30)			

Table 11: Comparison of the proportion of children that develop emergent gastrointestinal colonization of antimicrobial resistant E. coli or K.pneumoniae by resistant agent through outcome assessment visit (day 24-30) for per protocol population (Population 4) (Secondary analysis c)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	p-value for Chi-square test
TOC visit (Day 11-14) Emergent Resistance to TMP-SMX Emergent Resistance to Amoxicillin-clavulanate Emergent Resistance to Ceftazi-dime Emergent Resitance to Ampicillin			
Outcome assessment visit (Day 24-30) Emergent Resistance to TMP-SMX Emergent Resistance to Amoxicillin-clavulanate Emergent Resistance to Ceftazi-dime Emergent Resitance to Ampicillin			

Table 12. Comparison of the proportion of subjects with symptomatic UTIs prior to or at the TOC visit for subpopulations (Population 2) (Primary endpoint)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	p-value for Chi-square test
Age Group			
2 month – 35 months			
3 – 6 years			
7-10 years			
Febrile			
Febrile UTI			
Non-Febrile UTI			
Antibiotic Type			
TMP-SMX			
Amoxicillin-Clavulanate			
Cefixime			
Cefdinir			
Cephalexin			
Site			
CHOP			
PITT			

Table 13. Comparison of the proportion of subjects with a recurrent infection at any time after the TOC visit for subpopulations (Population 3) (Secondary endpoint a)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	p-value for Chi-square test
Age Group			
2 month – 35 months			
3 – 6 years			
7-10 years			
Febrile			
Febrile UTI			
Non-Febrile UTI			
Antibiotic Type			
TMP-SMX			
Amoxicillin-Clavulanate			
Cefixime			
Cefdinir			
Cephalexin			
Site			
CHOP			
PITT			

Table 14. Comparison of the proportion of subjects with asymptomatic bacteriuria at the TOC visit for subpopulation (Population 2) (Secondary endpoint b)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	p-value for Chi-square test
Age Group			
2 month – 35 months			
3 – 6 years			
7-10 years			
Febrile			
Febrile UTI			
Non-Febrile UTI			
Antibiotic Type			
TMP-SMX			
Amoxicillin-Clavulanate			
Cefixime			
Cefdinir			
Cephalexin			
Site			
CHOP			
PITT			

Table 15. Comparison of the proportion of subjects with clinical symptoms that may be related to a UTI prior to or at the TOC visit for subpopulation (Population 2) (Secondary endpoint d)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	p-value for Chi-square test
Age Group			
2 month – 35 months			
3 – 6 years			
7-10 years			
Febrile			
Febrile UTI			
Non-Febrile UTI			
Antibiotic Type			
TMP-SMX			
Amoxicillin-Clavulanate			
Cefixime			
Cefdinir			
Cephalexin			
Site			
CHOP			
PITT			

Table 16. Comparison of the proportion of subjects with positive urine cultures prior to or at the TOC visit for subpopulation (Population 2) (Secondary endpoint e)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	p-value for Chi-square test
Age Group 2 month – 35 months 3 – 6 years 7-10 years			
Febrile Febrile UTI Non-Febrile UTI			
Antibiotic Type TMP-SMX Amoxicillin-Clavulanate Cefixime Cefdinir Cephalexin			
Site CHOP PITT			

Table 17. Comparison of Risk of emergent colonization with antimicrobial resistant E. coli or K. pneumoniae in Gastrointestinal Tract for Subpopulations (Population 4) (Secondary endpoint c)

	Arm 1: Standard Course Total= xxx N (%)		Arm 2: Short Course Total= xxx N (%)		p-value 1	p-value 2
	TOC visit	Outcome visit	TOC visit	Outcome visit		
Age Group 2 – 35 months 3 – 6 years 7-10 years						
Febrile Febrile UTI Non-Febrile UTI						
Antibiotic Type TMP-SMX Amoxicillin-Clavulanate Cefixime Cefdinir Cephalexin						
Site CHOP PITT						

p-value 1 and p-value 2 will reported from Chi-square test comparing the proportions between sub-populations and treatment arms at TOC visit, and Outcome assessment visit, respectively.

Table 18. Multivariable Logistic Regression Analysis for Treatment failure (Symptomatic UTI at TOC visit) (Population 1) (Primary endpoint)

	Odds ratio	95% CI	*p*-value
Arm 1 Standard Course(reference) Arm 2 Short Course			
Covariates			

Interaction Term			

CI: Confidence Interval

SAS tips: SCALE=NONE in the MODEL statement of the PROC LOGISTIC procedure to generate deviance and Pearson chi-square for goodness of fit test.

Table 19. Multivariable Logistic Regression Analysis for Recurrent Infection at any time after the TOC visit (Population 3) (Secondary endpoint a)

	Odds ratio	95% CI	*p*-value
Arm 1 Standard Course(reference) Arm 2 Short Course			
Covariates			

Interaction Term			

SAS tips: SCALE=NONE in the MODEL statement of the PROC LOGISTIC procedure to generate deviance and Pearson chi-square for goodness of fit test.

Table 20. Multivariable Logistic Regression Analysis for Asymptomatic Bacteriuria at the TOC visit (Population 2) (Secondary endpoint b)

	Odds ratio	95% CI	*p*-value
Arm 1 Standard Course(reference) Arm 2 Short Course			
Covariates			

Interaction Term			

Table 21. Multivariable Logistic Regression Analysis for Symptoms that may be related to a UTI prior to or at the TOC visit (Population 2) (Secondary endpoint d)

	Odds ratio	95% CI	*p*-value
Arm 1 Standard Course(reference) Arm 2 Short Course			
Covariates			

Interaction Term			

Table 22. Multivariable Logistic Regression Analysis for positive urine cultures prior to or at the TOC visit (Population 2) (Secondary endpoint e)

	Odds ratio	95% CI	*p*-value
Arm 1 Standard Course(reference) Arm 2 Short Course			
Covariates			

Interaction Term			

Table 23. Multivariable Logistic Regression Analysis for Risk of emergent colonization with any antimicrobial resistant E. coli or K. pneumoniae in Gastrointestinal Tract (Population 4) (Secondary endpoint c)

	Odds ratio	95% CI	*p*-value
Arm 1 Standard Course(reference) Arm 2 Short Course			
Covariates			

Interaction Term			

Table 23 specifications: Repeat the analysis at enrollment visit, TOC visit, and outcome assessment visit separately as Table 26a, Table 26b, and Table 26c.

Table 24. Detailed listing for all adverse events possibly/probably related to study drug

Study Arm	Subject ID	Adverse event description	Onset date	Severity	Duration	Relationship to medication	Outcome

Table 24A. Adverse events possibly/probably related to study drug by body system and treatment arm (number of subjects)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	
Total number of subject with adverse events			
Body as whole			

Table 24B. Adverse events possibly/probably related to study drug by body system and treatment arm (number of adverse events)

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	
Total number of adverse events			
Body as whole			

Table 25. Adverse events possibly/probably related to study drug by treatment arm

	Arm 1: Standard Course Total= xxx N (%)	Arm 2: Short Course Total= xxx N (%)	*p*-value
Total number of subjects with AEs			
Total number of Adverse events			
Number of AEs per patient			
0			
1			
2			
3+			
Severity of AE			
Mild			
Moderate			
Severe			
Serious adverse events			
Yes			
No			
Relationship to medication			
Related			
Not related			
Outcome			
Recovered/Resolved			
Unchanged			
Ongoing			
Yes			
No			

Specifications

- Restrict the analysis to population 1 separately by number of subjects with adverse event(s) (Table 24A) and number of adverse events (Table 24B).

The test for independence of AE among two arms can be obtained using Chi-square test (or Fisher test if any cell expected count is less than 5).

7.2 Consort diagram

Figure 1: Consort Diagram