B. Braun Medical Inc.

HC-G-H-1601

A Phase 4, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Safety of 1 g of Cefazolin in Pediatric Subjects With a Weight of at Least 25 kg but Less Than 60 kg Scheduled for Surgery and the Safety of 2 g of Cefazolin in Pediatric Subjects with a Weight of at Least 60 kg Scheduled for Surgery

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Final Statistical Analysis Plan

Version 1.0

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List of Abbreviations

AE	adverse event
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
FDA	Food and Drug Administration
IV	intravenous
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
PT	preferred term
SAE	serious adverse event
SOC	system organ class
USP	United States Pharmacopeia
WHO	World Health Organization

1. Introduction

Cefazolin for Injection United States Pharmacopeia (USP) and Dextrose Injection USP is a sterile, nonpyrogenic, single-use, packaged combination of Cefazolin Sodium USP (lyophilized) and sterile iso-osmotic diluent (i.e., Dextrose Injection USP) in the DUPLEX® sterile container and are supplied as a lyophilized form equivalent to either 1 g or 2 g of cefazolin.

Currently, cefazolin is a standard of care for perioperative infection prophylaxis in pediatric patients and is administered in a wide variety of surgical procedures. Older children and adolescents may benefit from the availability of a fixed-dose system for the prophylactic administration of cefazolin.

This study is a post-marketing requirement established by the Food and Drug Administration (FDA) as part of the Pediatric Research Equity Act to evaluate the safety of cefazolin in children aged 10 to 17 years (inclusive) receiving weight-based 1 g or 2 g of cefazolin intravenously over 30 minutes delivered via the DUPLEX drug delivery system for surgical prophylaxis.

This document outlines the statistical methods to be implemented during the analysis of data collected within the scope of B. Braun Medical Inc., protocol HC-G-H-1601 version 2.0 (A Phase 4, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Safety of 1 g of Cefazolin in Pediatric Subjects With a Weight of at Least 25 kg but Less than 60 kg Scheduled for Surgery and the Safety of 2 g of Cefazolin in Pediatric Subjects With a Weight of at Least 60 kg Scheduled for Surgery), dated 24 March 2017. The purpose of this plan is to provide specific guidelines for which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR). The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses performed subsequent to database lock will be considered post-hoc and exploratory. Post-hoc analyses will be identified in the CSR.

2. Objectives

The primary objective of this study is to evaluate the safety of a single 30-minute infusion of a weight-based dose of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery.

The secondary objective of this study is to determine the cefazolin plasma concentrations following a single 30-minute infusion of a weight-based dose of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 4, open-label, single-dose, parallel-group, multicenter, safety study of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery. This study will be conducted at approximately 5 study sites (to a maximum of 15 sites) in the United States.

Approximately 110 subjects will be enrolled and assigned to 1 of the 2 dose groups in a 1:1 ratio (55 subjects in each group). Subjects with a weight of at least 25 kg but less than 60 kg will receive a single dose of 1-g cefazolin. Subjects with a weight of at least 60 kg will receive a single dose of 2-g cefazolin. Dose groups will not be balanced by age or gender. Additional subjects may be enrolled if necessary to ensure at least 50 evaluable subjects with complete safety data per dose group complete the study.

The study consists of a Screening Period of up to 30 days, a Treatment Period on Day 1 (day of surgery), and a Follow-up Period including a visit on Day 8 (±1 day). The maximal study duration for an individual subject will be 39 days. Safety will be assessed by monitoring adverse events (AEs), physical examination, vital signs, electrocardiographs (ECGs), and clinical laboratory tests. In addition, 4 pharmacokinetic (PK) samples will be obtained in a subset of approximately 40 subjects to determine the cefazolin plasma concentrations in this population. A minimum of ten of these 40 subjects are planned to be in the 10 to 13-year-old age bracket.

The schedule of study procedures is presented in Appendix 12.1.

3.2. Study Endpoints

The primary endpoints are:

- Type and incidence of AEs
- Physical examination
- Vital signs (systolic and diastolic blood pressure, pulse, respiratory rate, and oral body temperature)
- ECGs
- Clinical laboratory tests (hematology and clinical chemistry)

The PK endpoint is:

- PK plasma concentrations of cefazolin

The PK analysis will be detailed in a separate document.

3.3. Treatments

A peripheral venous catheter will be placed for all subjects before the start of the study drug administration for the intravenous (IV) infusion of the cefazolin and dextrose solution. Subjects with a weight of at least 25 kg but less than 60 kg will receive 1-g cefazolin. Subjects with a weight of at least 60 kg will receive 2-g cefazolin. After reconstitution, the solution will be administered over 30 minutes through an infusion line by using an infusion pump on Day 1 (day of surgery) for surgery prophylaxis. The study drug administration will begin 0.5 to 1 hour prior to the start of surgery and following institution guidelines.

3.4. Dose Adjustment/Modifications

If surgery is unexpectedly extended beyond the 3-hour limit, additional doses of study drug are permitted according to institutional guidelines. For subjects who consent to participate in PK sampling, best efforts will be made to obtain the 3-hour and possibly the 4-hour PK samples prior to administration of the additional dose of study drug. PK sample collection will not continue after administration of an additional dose of study drug. In this case, subjects from whom a 3-hour PK sample is obtained prior to administration of the additional dose are considered PK completers.

4. General Statistical Considerations

Statistical analysis of the Safety and PK sets will be performed using SAS® software (SAS Institute Inc., Cary, North Carolina) version 9.3 or later. Descriptive statistics will be presented for all safety parameters. Continuous variables will be summarized by treatment group using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages.

No inferential statistical analysis will be performed.

Baseline will be defined as the values obtained at Screening.

All data collected during the study will be analyzed and reported unless stated otherwise. No algorithm for missing data imputation will be employed.

If there are repeated measurements at a time point, the original scheduled measurement at that time point will be used in the summary tables. If the original scheduled measurement at that time point is missing, the next available repeated measurement will be used in the summary tables.

Unscheduled results will not be included in the summary tables except for determining Baseline, but will be presented in data listings.

4.1. Sample Size

Approximately 110 subjects (males and females) will be enrolled in this study. This sample size was determined based on the requirement of the FDA as part of the Pediatric Research Equity Act to evaluate the safety of a single dose of cefazolin for surgical prophylaxis in 100 pediatric subjects using the dose equivalent to 2-g cefazolin exposure in adults.

Additional subjects may be enrolled if necessary to ensure at least 50 evaluable subjects with complete safety data per dose group complete the study.

Approximately 40 subjects (males and females across both dose groups) will be enrolled in the PK subgroup. This sample size was determined using model-based simulations designed to explore both the number of subjects needed and the optimal times at which to obtain PK samples from those subjects. The previously-developed population PK model (Trang et al 2014) was employed using permutations introduced empirically to approximate potential PK differences in children enrolled in this study. Specifically, the previous population PK analysis found that pediatric surgical patients had, on average, 32% slower cefazolin clearance than healthy adult volunteers. The model-based simulations assessed how many subjects would be required to adequately capture the "true" difference in clearance between pediatric surgical subjects and healthy adults if the underlying difference was either greater than previous observation (i.e., a 50% decrease in clearance) or less than the previous observation (25%, 10%, or 0% difference). A range of sample sizes and PK sampling schemes were evaluated. Note that optimal sampling schemes were first identified using a multiple linear regression approach and then verified using the model-based simulations.

The results of the model-based simulation analyses indicated that a sample size of 40 subjects, each of which provides 4 blood samples for cefazolin assay at times of 0.5 to 1.0 hours, 2.0 hours, 3.0 hours, and 4.0 hours after the start of the cefazolin infusion, would be expected to provide adequate power to detect the true difference in clearance between pediatric surgical subjects and healthy adult volunteers.

A minimum of 10 of the 40 PK subjects are planned to be in the 10- to 13-year-old age bracket to ensure adequate representation of that age bracket in the refined population PK model.

Additional subjects maybe enrolled if necessary to ensure complete PK data from at least 40 subjects.

4.2. Randomization, Stratification, and Blinding

This is an open-label, non-randomized study.

4.3. Analysis Sets

4.3.1. Safety

The safety analysis set will consist of all subjects who received any study drug. All analyses using the safety analysis set will group subjects according to treatment actually received. This analysis set will be used for the primary analysis.

4.3.2. Pharmacokinetic

The PK analysis set will consist of all subjects from whom at least one measurable concentration PK sample is obtained.

5. Subject Disposition

5.1. Disposition

Subject disposition will be summarized for the safety analysis set and presented by treatment. The summary table includes the number and percentage of subjects who completed the study, subjects who discontinued from the study, subjects in the safety analysis set, and subjects in the PK set. All percentages will be based on the number of subjects in the safety analysis set.

The reasons for study discontinuation will also be summarized in this table. The reason for study discontinuation may include any of the following: protocol violation, noncompliance with the protocol, serious AE (SAE), intolerable AE, lost to follow-up, pregnancy, subject withdrew consent, legally authorized representative (LAR) withdrew consent, or investigator decision.

Subject disposition data will be presented in a listing. Subject informed consent and assent data will be presented in a listing.

Admission criteria deviations will be presented in a listing.

Subjects excluded from any analysis population will be presented in a listing.

5.2. Protocol Deviations

Protocol deviations are defined in the Study Deviation Rules document. All protocol deviations will be recorded in a clinical trial management system and reviewed. Any deviations deemed CSR reportable after review will be presented in a data listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

A summary of demographics and baseline information will be presented by treatment and overall. This summary will be presented for both the safety analysis set and the PK analysis set. The demographic characteristics consist of age (years), sex, race, and ethnicity. The baseline characteristics consist of baseline height (cm) and baseline weight (kg).

A subject's age in years will be calculated using the date of the informed consent and date of birth. Age (years), baseline height (cm), and baseline weight (kg). The number and percentage of subjects by age category (>=10 to <=13, >13 to <=17), sex (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino), will also be reported. Percentages will be based on the total number of subjects in the analysis set.

Subject demographic and baseline characteristics will be presented in a listing.

6.2. Medical History

A complete medical history will be taken at the Screening visit. Medical history will be updated prior to surgery on Day 1 of the study. Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and presented in a listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

The use of any medication (e.g., prescription, herbal, over-the-counter medication[s] or dietary supplements) known to interact with cefazolin within 5 days prior to the study drug administration until completion of the follow-up visit is prohibited. Concomitant use of probenecid is also prohibited for this period. Any concomitant medications taken during conduct of the study (from Screening through completion of follow-up) will be recorded in the case report form (CRF), as well as any changes in concomitant medications. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. All medications will be coded according to the World Health Organization drug dictionary (WHODrug version 01DEC2016).

Prior and concomitant medications will be presented in a listing.

7.2. Medical or Surgical Treatment Procedures

The occurrence of any medical or surgical treatment procedure (aside from the primary surgery associated with cefazolin treatment) during the conduct of the study (from Screening through completion of follow-up) will be recorded in the CRF. All procedures will be coded according to the MedDRA dictionary, version 19.1. Medical and surgical procedures will be presented in a listing.

7.3. Surgery

Details of the surgery associated with cefazolin treatment will be collected in the CRF. Surgery data will be presented in a listing.

7.4. Study Treatments

Dosing details, including location of infusion catheter, whether any interruption of the infusion occurred with relevant dates and times, and volume of dose administered will be recorded in the CRF for the planned dose as well as any supplemental doses. This data will be presented in a listing.

8. Safety Analysis

8.1. Adverse Events

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug. In addition to subject observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, vital sign changes) or identified from review of other documents that are relevant to subject safety will be documented on the AE page in the CRF.

An AE is treatment emergent if it is not present before exposure to study drug or the event worsens in either intensity or frequency after exposure to study drug. Only treatment-emergent AEs that were not present at Screening or described in medical history will be reported in the CRF and included in summary tables and listings.

In all summary tables, system organ class (SOC) is displayed in descending order of frequency for “Total”, then alphabetically. Preferred term (PT) is displayed in descending order of frequency for “Total”, then alphabetically within SOC. Percentages will be based upon the number of subjects in the safety analysis set overall and within each treatment. At each level of subject summarization, a subject with 2 or more AEs will be counted only once in that level using the most severe event (for the severity table) or the most related event (for the relationship to study drug table).

The MedDRA version 19.1 will be used to code all AEs.

All analyses of AEs will be conducted using the safety analysis set.

8.1.1. Incidence of Adverse Events

Summaries of the number and percentage of subjects with at least one AE will be provided by treatment group and overall. AEs will be presented by SOC and PT. At each level of subject summarization, a subject is counted once if the subject reported one or more events.

All AEs will be presented in a listing.

8.1.2. Relationship of Adverse Events to Study Drug

A summary of AEs by relationship to study drug will be presented in a table by incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are “Unrelated”, “Possible”, “Probable”, and “Definite”. In the AE relationship table, if a subject reports multiple occurrences of the same AE, only the most closely related occurrence will be presented. If a subject has the relationship missing for all occurrences of the same AE, then the relationship will be presented in the summary tables as “Missing”. AEs that are missing a relationship will be presented in the data listing with a missing relationship.

8.1.3. Severity of Adverse Event

A summary of AEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are “Mild,” “Moderate,” and “Severe.” In the AE severity table, if a subject reported multiple occurrences of the same AE, the subject will be counted only once for the most severe occurrence. AEs that are missing severity will be presented in tables as “Missing” and will be presented in the data listing with a missing severity.

8.1.4. Serious Adverse Events

The seriousness of an AE should be assessed by the Investigator independently from the severity of the AE. An SAE is an event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the

subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The SAEs will be listed.

8.1.5. Adverse Events Leading to Early Discontinuation

All AEs leading to study discontinuation will be listed. An AE will be considered to have led to study discontinuation if the AE's identifier is listed on a subject's study completion form and that subject has given "Serious AE" or "Intolerable AE" as the primary reason for discontinuation.

8.2. Clinical Laboratory Evaluations

Laboratory tests except for screening procedures will be performed by the central laboratory. Screening laboratory tests should be performed within 30 days of Day 1 and can be the same tests as assessed for surgical clearance. Screening laboratory tests will be performed at local laboratories. Aliquots of the serum and plasma collected at Screening will be sent to the central laboratory for replicate analysis and will serve as the baseline laboratory values. Blood samples for clinical laboratory assessments (hematology and chemistry) will be collected at Screening, Presurgery, Postsurgyre, and Follow-up. Urine samples for pregnancy testing will be collected at Screening and Presurgery.

All summaries will be based on SI units. In the event that the aliquots provide to the central lab cannot be used to determine the baseline lab values, local lab values will be entered into the CRF. These values will be converted to the same units as the central lab values.

The following laboratory analyses will be performed:

Hematology	Clinical Chemistry
• Hemoglobin • Hematocrit • Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration • Platelets • Red blood cell • White blood cell with differential count	• Alanine aminotransferase • Albumin • Alkaline phosphatase • Aspartate aminotransferase • Blood urea nitrogen • Serum creatinine • Total bilirubin • Sodium • Potassium • Chloride • Bicarbonate • Glucose • Uric acid • Calcium • Phosphate • Total protein • Creatine phosphokinase • Lactic acid dehydrogenase

Baseline is defined in section 4.

Summary tables presenting observed values and changes from baseline will be presented for hematology and clinical chemistry results with numeric values by treatment and overall for subjects in the safety analysis set.

All clinical laboratory test results (including urine pregnancy) will be presented in the data listings sorted by subject, laboratory test, and sample collection date/time. For hematology and clinical chemistry, values that are outside of the normal reference range will be flagged in the listings.

8.3. Vital Sign Measurements

Vital signs (including blood pressure [systolic and diastolic], pulse, body temperature, and respiratory rate) will be measured and assessed at Screening, Day 1, and at the follow up visit on Day 8 (±1 day). Pre-surgery vital sign measurements should be obtained within approximately 30 minutes before the start of study drug administration. Time points for vital sign measurements on Day 1 are pre-surgery, 15 minutes [±5 minutes], 0.5 to 1.0 hour, and 3.0 hours [±15minutes] after the start of the study drug infusion, and after surgery.

A summary table presenting observed values and changes from baseline will be presented for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (ºC), pulse (beats/minute), and respiration (breaths/minute), by treatment and overall for subjects in the safety analysis set.

All vital sign data (both observed and change from baseline) will be presented in a listing.

8.4. Physical Examination

A complete physical examination will be performed at Screening. The complete physical examination includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, and respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems).

A brief physical examination will be performed both before and after dosing on Day 1 and at the follow up visit.

Abnormal physical examination findings will be listed.

8.5. Electrocardiograph

Electrocardiographs will be performed at Screening and post-surgery. Clinical review and assessment of cardiac rhythm, conduction, waveform morphology and ECG interval duration will be performed at the study site, as close as possible to the time an ECG was obtained, by the investigator or his/her designee.

A summary table presenting observed values and changes from baseline will be presented for ECG data, including heart rate (bpm), PR Interval (msec), QRS Duration (msec), QT Interval (msec), and QTcF Interval (msec), by treatment and overall for subjects in the safety analysis set. Changes from baseline to each scheduled post-baseline visit will be presented.

All ECG data (both observed and change from baseline) will be presented in a listing.

8.6. Other Safety Data

The site of study drug infusion will be evaluated for signs of infusion-related reactions on Day 1 at 15 minutes, 0.5-1.0 hours, and 3.0 hours (± 15 minutes), and at the follow-up visit on Day 8 (±1 day). Any reaction observed will be recorded in the CRF as an AE.

A summary table presenting observed values will be presented. All infusion site assessment data will be presented in a listing.

9. Pharmacokinetics

Four PK blood collections will be obtained in a subset of approximately 40 subjects to determine the cefazolin plasma concentrations in this population. Pharmacokinetic samples will be obtained at 0.5 to 1.0 hours, 2.0 hours (± 15 minutes), 3.0 hours (± 15 minutes), and 4.0 hours (± 15 minutes) after the start of the study drug infusion.

If the surgery is unexpectedly extended beyond the 3-hour limit and an additional dose of study drug will be administered best efforts will be made to obtain the 3-hour and possibly the 4-hour PK samples prior to administration of the additional dose of study drug. Pharmacokinetic sample collection will not continue after the administration of an additional dose of study drug. In the cases of an additional dose of study drug, subjects from whom a 3-hour PK sample is obtained prior to administration of the additional dose are considered PK completers.

Cefazolin plasma concentrations will be listed by subject and scheduled time point/interval. Concentrations will also be summarized by treatment and age bracket for each schedule time point/interval using descriptive statistics (n, mean, SD, % coefficient of variation, median, minimum, and maximum).

Mean cefazolin plasma concentrations versus scheduled time point/interval will be presented on linear and semi-logarithmic plots. Individual cefazolin plasma concentrations versus actual time point will be presented on linear and semi-logarithmic plots.

Cefazolin plasma concentrations will be used for population PK modeling. Details of the population PK model will be contained in a separate document.

10. Interim Analysis

No interim analysis will be conducted in this study.

11. References

Trang M, Forrest A, Rubino C. Population PK Analysis for Cefazolin Using Data from HC-G-H-1202: Implications for Dosing in Children, Report from Institute for Clinical Pharmacodynamics for B. Braun Medical Inc. 2014. 72 p.

12. Appendices

12.1. Schedule of Study Procedures

Study Phase	**Screening Period**	**Treatment Period (Day of Surgery)**							**Follow-up Period**
Procedure	**Screening[1]**	**Pre-surgery**	**Surgery**					**Post-surgery[2]**	**Safety Follow-up Visit[3]**
Study Day	**Up to 30 Days Before Study Drug Administration**	**1**						**1 or 2**	**8 (±1)**
Time point after start of infusion			**15 min (±5 min)**	**0.5 h – 1.0 h**	**2.0 h (±15 min)**	**3.0 h (±15 min)**	**4.0 h (±15 min)**		
Informed consent for study participation	X								
Informed consent for pharmacokinetic (PK) participation	X								
Inclusion/exclusion criteria	X								
Subject identification number assignment	X								
Demographics	X								
Height (without shoes)	X								
Weight[4]	X	X							
Medical history	X								
Medication history	X								

Study Phase	**Screening Period**	**Treatment Period (Day of Surgery)**							**Follow-up Period**
Procedure	**Screening[1]**	**Pre-surgery**	**Surgery**					**Post-surgery[2]**	**Safety Follow-up Visit[3]**
Study Day	**Up to 30 Days Before Study Drug Administration**	**1**						**1 or 2**	**8 (±1)**
Time point after start of infusion			**15 min (±5 min)**	**0.5 h – 1.0 h**	**2.0 h (±15 min)**	**3.0 h (±15 min)**	**4.0 h (±15 min)**		
Updated medical history for eligibility		X							
Physical examination[5]	X	X						X	X
Vital signs[6, 7]	X	X[7]	X	X		X		X	X
Electrocardiograph (ECG)[6]	X							X	
Clinical Laboratory tests (blood)[8]	X[9]	X						X	X
Pregnancy test[10]	X	X							
Study drug infusion site assessment			X	X		X		X	X
Pharmacokinetic blood collection[11]				X	X	X	X		
Concomitant medications	Continuous								
Adverse event monitoring	Continuous								
Study drug administration[12]		X							

[1] If Screening visit occurs on Day 1 (day of surgery), all Screening visit assessments must be properly completed.

[2] Postsurgery assessments will be performed at 24 hours after surgery or discharge from the study site, whichever comes first.

[3] Safety Follow-up visit will be performed for subjects who complete the study or terminate prematurely after receiving study drug, whenever possible.

[4] Weight will be measured with indoor clothing and without shoes.

[5] Details of physical examination are outlined in Section 6.2.2 of the protocol. The complete physical examination includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, and respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems). A brief physical examination will be performed both before and after dosing on Day 1 and at the Safety Follow-up visit.

[6] Vital signs (including blood pressure [systolic and diastolic], pulse, body temperature, and respiratory rate) and ECGs should be taken with subjects in supine position after resting for 5 minutes. Details of vital sign measurements are outlined in Section 6.2.3 of the protocol. Details of ECGs are outlined in Section 6.2.4 of the protocol. Vital signs and ECG obtained at Screening will be considered as Baseline.

[7] Predose vital sign measurements should be obtained within approximately 30 minutes before the start of study drug administration.

[8] Clinical laboratory tests will include hematology and clinical chemistry. Details of laboratory tests are outlined in Section 6.4 of the protocol. Laboratory tests except for screening procedures will be performed by the central laboratory.

[9] Screening laboratory tests should be performed within 30 days of Day 1 and can be the same tests as those assessed for surgical clearance. Screening laboratory tests will be performed at local laboratories.

[10] Urine pregnancy tests will be performed for all females of childbearing potential at Screening and be repeated on Day 1. If positive, pregnancy will be confirmed with serum test. If pregnancy is confirmed, the subject will not be enrolled or if already enrolled and not yet dosed the subject will be dropped. If a pregnant subject is administered study drug in error, the subject will be followed through the completion or termination of the pregnancy. All pregnancy tests will be performed at local laboratories.

[11] Pharmacokinetic blood samples will be obtained at the designated time points after the start of the study drug infusion. NOTE: The catheter that is used for study drug infusion and the arm it is inserted in cannot be used for collection of the PK samples. Pharmacokinetic samples must be taken from the opposite arm of the study drug infusion.

[12] Study drug will be administered over 30 minutes as an infusion starting 0.5 to 1 hour before surgery begins and following institutional guidelines. The start time of the study drug infusion and the start time of the anesthesia induction will be recorded in the CRF. Subjects with a weight of at least 25 kg but less than 60 kg will receive 1-g cefazolin. Subjects with a weight of at least 60 kg will receive 2-g cefazolin. If the surgery is extended unexpectedly beyond the 3-hour limit, additional doses of study drug are permitted according to institutional guidelines.

12.2. Table, Listing, and Figure Shell Table of Contents

Tables

Listings

Figures

Table 14.1.1
Subject Disposition
Safety Analysis Set

	Treatment A (N=xx) n (%)	Treatment B (N=xx) n (%)	Total (N=xx) n (%)
Total Number of Subjects			
Completed	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary Reason for Discontinuation			
Protocol violation	xx (xx.x)	xx (xx.x)	xx (xx.x)
Noncompliance with the protocol	xx (xx.x)	xx (xx.x)	xx (xx.x)
Serious AE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Intolerable AE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject withdrew consent	xx (xx.x)	xx (xx.x)	xx (xx.x)
LAR withdrew consent [1]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator decision	xx (xx.x)	xx (xx.x)	xx (xx.x)
Analysis Sets			
Safety [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)
PK [3]	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Percentages are based on the number of subjects in the safety analysis set.
[1] LAR = Legally Authorized Representative.
[2] Safety analysis set includes all subjects who received any study drug.
[3] Pharmacokinetic (PK) analysis set includes all subjects from whom at least one measurable concentration PK sample is obtained.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.1 and Listing 16.2.3

Table 14.1.2.1
Demographic and Baseline Characteristics
Safety Analysis Set

	Treatment A (N=xx)	Treatment B (N=xx)	Total (N=xx)
Age (years)			
n	xx	xx	xx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Age categories, n (%)			
>=10 to <=13 years	xx (xx.x)	xx (xx.x)	xx (xx.x)
>13 to <=17 years	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sex, n (%)			
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race, n (%)			
White	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African American	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)
American Indian or Alaska Native	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)
Multi-racial	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity, n (%)			
Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note to programmer: Summarize subjects who report two or more races as "Multi-racial". If there are no such subject, remove "Multi-racial" category. Continue with Height (cm) and Weight (kg)

Note: Percentages are based on the number of subjects in the safety analysis set.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.4.1

Table 14.1.2.2
Demographic and Baseline Characteristics
Pharmacokinetic Analysis Set

Use the same Table shell as for Table 14.1.2.1, but display for the PK analysis set.
Source Data: Listing 16.2.4.1

Table 14.2.1.1
Summary of Plasma Concentrations of Cefazolin by Treatment and Age
Pharmacokinetic Analysis Set

Scheduled Time Point	Statistics	Treatment A >=10 to <=13 years old	Treatment A >13 to <=17 years old	Treatment A All Ages	Treatment B >=10 to <=13 years old	Treatment B >13 to <=17 years old	Treatment B All Ages
0.5-1.0 HR	n	xx	xx	xx	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
	CV%	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Max	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Note to Programmer: Sort by Scheduled Time Point. Plasma samples for PK assessments of Cefazolin will be collected from all subjects at the following time points: between 0.5-1 hr, 2, 3, and 4 hr relative to start of study drug infusion. Concentrations that are BLQ will be treated as 0. Mean BLQ concentrations will be presented as 0, SD and CV will be presented as NA.

Note: Concentrations that were BLQ were treated as zero for descriptive statistics. NA = Not applicable.
Sample collection times are from the start of infusion.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.6.1.

Table 14.3.1.1
Overall Summary of Adverse Events
Safety Analysis Set

	Treatment A (N=xx) n (%)	Treatment B (N=xx) n (%)	Total (N=xx) n (%)
Any AE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Treatment-Related AE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Moderate AE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Treatment-Related Moderate AE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Severe AE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Treatment-Related Severe AE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any SAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Treatment-Related SAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any AE Leading to Early Discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Death	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: A treatment-related AE is defined as any AE with a relationship designated as 'Possible', 'Probable', or 'Definite' by the investigator. At each level of subject summarization, a subject is counted once if the subject reported one or more events. n represents the number of subjects at each level of summarization. Percentages are based on the number of subjects in the safety analysis set within each treatment and overall.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.7.1, Listing 16.2.7.2 and Listing 16.2.7.3

Table 14.3.1.2
Adverse Events
Safety Analysis Set

System Organ Class Preferred Term	Treatment A (N=xx) n (%)	Treatment B (N=xx) n (%)	Total (N=xx) n (%)
All AE	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			

Note to Programmer: System organ class is displayed in descending order of frequency for "Total" then alphabetically. Preferred term is displayed in descending order of frequency for "Total" then alphabetically within system organ class. If there are no AEs, then display "No adverse events were reported."

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events. n represents the number of subjects at each level of summarization. Percentages are based on the number of subjects in the safety analysis set within each treatment and overall. Adverse events were coded using MedDRA version 19.1.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.7.1

Table 14.3.1.3
Adverse Events by Relationship to Study Drug
Safety Analysis Set

System Organ Class Preferred Term Relationship	Treatment A (N=xx) n (%)	Treatment B (N=xx) n (%)	Total (N=xx) n (%)
All AEs	xx (xx.x)	xx (xx.x)	xx (xx.x)
UNRELATED	xx (xx.x)	xx (xx.x)	xx (xx.x)
POSSIBLE	xx (xx.x)	xx (xx.x)	xx (xx.x)
PROBABLE	xx (xx.x)	xx (xx.x)	xx (xx.x)
DEFINITE	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
UNRELATED	xx (xx.x)	xx (xx.x)	xx (xx.x)
POSSIBLE	xx (xx.x)	xx (xx.x)	xx (xx.x)
PROBABLE	xx (xx.x)	xx (xx.x)	xx (xx.x)
DEFINITE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			

Note to programmer: System organ class is displayed in descending order of frequency for "Total" then alphabetically. Preferred term is displayed in descending order of frequency for "Total" then alphabetically within system organ class. If there are no AEs, then display "No adverse events were reported."

Note: At each level of subject summarization, a subject is counted once for the most related event. n represents the number of subjects at each level of summarization. Percentages are based on the number of subjects in the Safety analysis set within each treatment and overall. Adverse events were coded using MedDRA version 19.1.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.7.1

Table 14.3.1.4
Adverse Events by Severity
Safety Analysis Set

System Organ Class Preferred Term Relationship	Treatment A (N=xx) n (%)	Treatment B (N=xx) n (%)	Total (N=xx) n (%)
All AEs	xx (xx.x)	xx (xx.x)	xx (xx.x)
MILD	xx (xx.x)	xx (xx.x)	xx (xx.x)
MODERATE	xx (xx.x)	xx (xx.x)	xx (xx.x)
SEVERE	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
MILD	xx (xx.x)	xx (xx.x)	xx (xx.x)
MODERATE	xx (xx.x)	xx (xx.x)	xx (xx.x)
SEVERE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			

Note to programmer: System organ class is displayed in descending order of frequency for "Total" then alphabetically. Preferred term is displayed in descending order of frequency for "Total" then alphabetically within system organ class. If there are no AEs, then display "No adverse events were reported."

Note: At each level of subject summarization, a subject is counted once for the most severe event. n represents the number of subjects at each level of summarization. Percentages are based on the number of subjects in the Safety analysis set within each treatment and overall. Adverse events were coded using MedDRA version 19.1.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.7.1

Table 14.3.4.1
Summary and Change from Baseline in Hematology
Safety Analysis Set

Parameter (Unit): XXXXXXXXXXX (XXXX)

Visit	Actual Value						Change from Baseline					
Treatment	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Baseline												
Treatment A (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx						
Treatment B (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx						
Total (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx						
Postsurgery												
Treatment A (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx	xx	xx.x	xx.xx	xx.x	xx	xx
Treatment B (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx	xx	xx.x	xx.xx	xx.x	xx	xx
Total (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx	xx	xx.x	xx.xx	xx.x	xx	xx
…												

Note to programmer: The post-baseline visits are: Postsurgery, and Follow-up. Start a new page for each parameter.

Note: Baseline is defined as the screening visit; Postsurgery is defined as 24 hours after surgery or at discharge from the study site, whichever comes first.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.8.1

Table 14.3.4.2
Summary and Change from Baseline in Clinical Chemistry
Safety Analysis Set

Use the same Table shell as for Table 14.3.4.1, but display Clinical Chemistry parameters.
Source Data: Listing 16.2.8.2

Table 14.3.5
Summary and Change from Baseline in Vital Sign Measurements
Safety Analysis Set

Parameter (Unit): XXXXXXXXXXX (XXXX)

Visit/Timepoint	Actual Value						Change from Baseline					
Treatment	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Baseline												
Treatment A (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx						
Treatment B (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx						
Total (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx						
Day 1/Pre-dose												
Treatment A (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx	xx	xx.x	xx.xx	xx.x	xx	xx
Treatment B (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx	xx	xx.x	xx.xx	xx.x	xx	xx
Total (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx	xx	xx.x	xx.xx	xx.x	xx	xx
…												

Note to programmer: The post-baseline visit/timepoints are: Day 1/Pre-dose, Day 1/15 min, Day 1/.5hr-1.0hr, 3.0hr, Postsurgery, and Follow-up. Start a new page for each parameter.

Note: Baseline is defined as the screening visit.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.9.1

Table 14.3.6
Summary and Change from Baseline in Electrocardiograms
Safety Analysis Set

Parameter (Unit): XXXXXXXXXXX (XXXX)

Visit	Actual Value						Change from Baseline					
Treatment	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Baseline												
Treatment A (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx						
Treatment B (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx						
Total (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx						
Postsurgery												
Treatment A (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx	xx	xx.x	xx.xx	xx.x	xx	xx
Treatment B (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx	xx	xx.x	xx.xx	xx.x	xx	xx
Total (N=xx)	xx	xx.x	xx.xx	xx.x	xx	xx	xx	xx.x	xx.xx	xx.x	xx	xx
…												

Note to programmer: The post-baseline visits are: Postsurgery and Follow-up. Start a new page for each parameter.

Note: Baseline is defined as the screening visit.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.9.2

Table 14.3.7
Summary of Infusion Site Assessments
Safety Analysis Set

Visit/Timepoint Assessment Response	Treatment A (N=xx) n (%)	Treatment B (N=xx) n (%)	Total (N=xx) n (%)
Day 1/15 min			
Pain			
YES	xx (xx.x)	xx (xx.x)	xx (xx.x)
NO	xx (xx.x)	xx (xx.x)	xx (xx.x)
NOT DONE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Erythema/Redness			
YES	xx (xx.x)	xx (xx.x)	xx (xx.x)
NO	xx (xx.x)	xx (xx.x)	xx (xx.x)
NOT DONE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Induration/Swelling			
YES	xx (xx.x)	xx (xx.x)	xx (xx.x)
NO	xx (xx.x)	xx (xx.x)	xx (xx.x)
NOT DONE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Localized Warmth			
YES	xx (xx.x)	xx (xx.x)	xx (xx.x)
NO	xx (xx.x)	xx (xx.x)	xx (xx.x)
NOT DONE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other			
YES	xx (xx.x)	xx (xx.x)	xx (xx.x)
NO	xx (xx.x)	xx (xx.x)	xx (xx.x)
NOT DONE	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			

Note to programmer: The visit/timepoints are: Day 1/15 min, Day 1/.5hr-1.0hr, 3.0hr, Postsurgery, and Follow-up. Present the Assessments in the order shown (Pain, Erythema/Redness, Induration/Swelling, Localized Warmth, and Other).

Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.9.4

Listing 16.2.1.1
Subject Disposition

Treatment: A

Subject	Date of Dose	Date (Day) of Final Contact	Completed Study?	Discontinuation	
				Date (Day)	Reason
xxxxxxx	DDMMMYYYY	DDMMMYYYY (xx)	Yes		
xxxxxxx	DDMMMYYYY	DDMMMYYYY (xx)	No	DDMMMYYYY (xx)	xxxxxxxxxxxx
xxxxxxx	DDMMMYYYY	DDMMMYYYY (xx)	No	DDMMMYYYY (xx)	Adverse Event: xxxxx

Note to Programmer: Sort by treatment and subject. If discontinuation occurred due to AE, append the corresponding AE term. Start a new page for each treatment.

Note: Day corresponds to study day. Day 1 is date of surgery.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.1.2
Informed Consent and Assent

Treatment: A

Subject	Informed Consent Date	HIPAA Auth. Date	Assent Required?/ Assent Date	Pharmacokinetic (PK) Blood Collection: Did subject consent to participate in PK sampling?	Pharmacokinetic (PK) Blood Collection: PK Informed Consent Date	Pharmacokinetic (PK) Blood Collection: PK Assent Required?/ PK Assent Date
xxxxxxx	DDMMMYYYY	DDMMMYYYY	Yes/ DDMMMYYYY	Yes	DDMMMYYYY	No
xxxxxxx	DDMMMYYYY	DDMMMYYYY	Yes/ DDMMMYYYY	Yes	DDMMMYYYY	Yes/ DDMMMYYYY
xxxxxxx	DDMMMYYYY	DDMMMYYYY	No	No		

Note to Programmer: Sort by treatment and subject. If discontinuation occurred due to AE, append the corresponding AE term. Start a new page for each treatment.

Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.2.1
Admission Criteria Deviations

Treatment: x

Subject	Protocol Date – Version	Criteria Type	Criteria Number	Comment
xxxxxxx	DDMMMYYYY - xxxxxxx	Inclusion	xx	
xxxxxxx	DDMMMYYYY - xxxxxxx	Exclusion	xx	
…				

Note to Programmer: Sort by treatment and subject. Start a new page for each treatment. If there are no admission criteria deviations, then display "No admission criteria deviations were reported."

Deviated criteria:
Inclusion xx: xxxxxxxxxxxxxxxxxxxx
Exclusion xx: xxxxxxxxxxxxxx
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.2.2
Protocol Deviations

Treatment: x

Subject	Date (Day) [1] of Deviation	Deviation Type	Description
xxxxxxx	DDMMMYYYY (xx)	xxxxxxxxx	xxxxxxxxxxxxxxxx
xxxxxxx	DDMMMYYYY (xx)	xxxxxxxxxx	xxxxxxxxxxxxxxx

…

Note to Programmer: Sort by treatment and subject. Start a new page for each treatment. If there are no protocol deviations, then display "No protocol deviations were reported."

[1] Day corresponds to study day. Day 1 is date of surgery.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.3
Subjects Excluded from Analysis Sets

Treatment: x

Subject	Excluded from Safety [1]/ Reason for Exclusion	Excluded from Pharmacokinetic [2]/ Reason for Exclusion
xxxxxxx	No	Yes/ xxxxxxxxxxxxxx
xxxxxxx	No	No
xxxxxxx	Yes/ xxxxxxxxxxxxxxxxx	Yes/ xxxxxxxxxxxxxx

Note to Programmer: Sort by treatment and subject. Start a new page for each treatment.

[1] Safety analysis set includes all subjects who received any study drug.
[2] Pharmacokinetic (PK) analysis set includes all subjects from whom at least one measurable concentration PK sample is obtained.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.4.1
Demographic and Baseline Characteristics

Treatment: A

Subject	Date of Birth	Age (years) [1]	Sex	Race	Eth. [2]	Screening Height (cm)	Screening Weight (kg)
xxxxxxx	DDMMMYYYY	xx	Male	xxxxxxxxxxxxx	H	xxx.x	xxx.x
xxxxxxx	DDMMMYYYY	xx	Female	xxxxxxxxx	N	xxx.x	xx.x
xxxxxxx	DDMMMYYYY	xx	xxxxxx	xxxxxxxxxx	X	xxx.x	xxx.x

Note to Programmer: Sort by treatment and subject. Start a new page for each treatment.

[1] Age in years is the integer part of (Date of Informed Consent – Date of Birth)/365.25.
[2] Ethnicity: H = Hispanic or Latino, N = Not Hispanic or Latino.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.4.2
Medical History

Treatment: x

Subject	Body System	Condition/Diagnosis	System Organ Class [1]/ Preferred Term [1]	Start/Stop Date
xxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxx	xxxxxxxxxxxxxxxx/ xxxxxxxxxxx	DDMMMYYYY/ DDMMMYYYY
xxxxxxx	xxxxxxxxxxxx	xxxxxxxxxx	xxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxxx	DDMMMYYYY/ Ongoing

…

Note to Programmer: Sort by treatment, subject, condition/diagnosis, and start/stop date. Start a new page for each treatment. Display "Ongoing" in place of Stop Date if the condition is ongoing. If there are no medical histories, then display "No medical histories were reported."

[1] From MedDRA version 19.1.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.4.3
Prior and Concomitant Medications

Treatment: x

Subject	Med ID	Preferred Drug Name [1]/ Drug Name	Type [2]	Dose	Unit	Start/Stop Date (Day) [3]/ Time	Route/ Frequency	Indication (AE ID)
xxxxxxx	xxx	xxxxxxxxxxxxx/ xxxxxxxxxxxx	PC	xxxx	xxxxxxx	DDMMMYYYY (xx)/ HH:MM/ Ongoing	xxxxxxx/ xxxxxxxxxx	xxxxxxxxx
	xxx	xxxxxxxxxxxxx/ xxxxxxxxxxxx	P	xx.x	xxxxxx	DDMMMYYYY (xx)/ HH:MM/ DDMMMYYYY (xx)/ HH:MM	xxxxxxx/ xxxxxxxxxx	xxxxxxxxxxx
	xxx	xxxxxxxxxxxxx/ xxxxxxxxxxxx	C	xxxx	xxxxxx	DDMMMYYYY (xx)/ HH:MM/ DDMMMYYYY (xx)/ HH:MM	xxxxxxx/ xxxxxxxxxx	xxxxxxxxx (xxxx)

…

Note to Programmer: Sort by treatment, subject, preferred drug name, and date/time started. Start a new page for each treatment. Display "Ongoing" in place of Stop Date/Time if the medication is ongoing. If there are no prior or concomitant medications, then display "No prior or concomitant medications were reported."

[1] From WHODrug version 01DEC2016.
[2] P = Prior, C = Concomitant.
[3] Day corresponds to study day. Day 1 is date of surgery.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.4.4
Medical or Surgical Treatment Procedures

Treatment: x

Subject	System Organ Class [1]/ Preferred Term [1]/ Procedure	Reason [AE ID]	Start/Stop Date (Day) [2]
xxxxxxx	xxxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxx/ xxxxxxxxxx	xxxxxxxxxxx [xxxxxxxx]	DDMMMYYYY (xx)/ DDMMMYYYY (xx)
xxxxxxx	xxxxxxxxxxxxx/ xxxxxxxxxxxxx/ xxxxxxxxxxxxxxx	Other: XXXXXXXX	DDMMMYYYY (xx)/ Ongoing

…

Note to Programmer: Sort by treatment, subject, procedure, and start/stop date. If procedure is ongoing then display "Ongoing" in the place of Stop Date. If the procedure was for an AE, please attach the corresponding AE ID to Reason. Start a new page for each treatment.
If there are no medical or surgical treatment procedures, then display "No medical or surgical treatment procedures were reported."

[1] From MedDRA, version 19.1.
[2] Day corresponds to study day. Day 1 is date of surgery.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.4.5
Surgery

Treatment: x

Subject	Procedure	Start/Stop Date/Time	Anesthesia Start Date/Time	Comment
xxxxxxx	xxxxxxxxxxxxxxxxxxx	DDMMMYYYY/HH:MM/ DDMMMYYYY/HH:MM	DDMMMYYYY/HH:MM	xxxxxxxxxxx
xxxxxxx	xxxxxxxxxxxxx	DDMMMYYYY/HH:MM/ DDMMMYYYY/HH:MM	DDMMMYYYY/HH:MM	

…

Note to Programmer: Sort by treatment, subject, procedure, and start/stop date. Start a new page for each treatment.

Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.5
Study Drug Administration

Treatment: x

Subject	Catheter Location [1]	Lot Number/ Reconstitution Date/Time	Dose Start/Stop Date/Time	Volume (mL)	Interrupt/ Restart Date/Time	Comment
xxxxxxx	RIGHT HAND	xxxxxxxx/ DDMMMYYYY/HH:MM	DDMMMYYYY/HH:MM/ DDMMMYYYY/HH:MM	xx	DDMMMYYYY/HH:MM/ DISCONTINUED	xxxxxxxxxx
xxxxxxx	LEFT FOREARM	xxxxxxxx/ DDMMMYYYY/HH:MM	DDMMMYYYY/HH:MM/ DDMMMYYYY/HH:MM	xx	DDMMMYYYY/HH:MM/ DDMMMYYYY/HH:MM	xxxxxxx
xxxxxxx	RIGHT HAND	xxxxxxxx/ DDMMMYYYY/HH:MM	DDMMMYYYY/HH:MM/ DDMMMYYYY/HH:MM	xx	NOT INTERRUPTED	
	LEFT LEG S	xxxxxxxx/ DDMMMYYYY/HH:MM	DDMMMYYYY/HH:MM/ DDMMMYYYY/HH:MM	xx	NOT INTERRUPTED	xxxxxxxxx

…

Note to programmer: Sort by treatment, subject, and start date/time. If study drug was not interrupted, display "NOT INTERRUPTED" in Interrupt/Restart Date/Time column. If drug was discontinued without restart, display 'DISCONTINUED' for Restart Date/Time. If record represents a supplemental infusion, display 'S' after Catheter Location.

[1] S = Supplemental infusion.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.6.1
Individual Plasma Concentrations of Cefazolin
Pharmacokinetic Analysis Set

Treatment: A

Subject/ Age (yr)/ Weight (kg)	Scheduled Time	Sample Collection Date/Time	Deviation from Scheduled Time (minutes)	Cefazolin Concentration (unit)	Comment
xxxxxxx/xx/xx	0.5-1.0 HR	DDMONYYYY/HH:MM	.	xx.xx	xxxxxxxxxxxx
	2 HR	DDMONYYYY/HH:MM	x	xx.xx	
	3 HR	DDMONYYYY/HH:MM	x	xx.xx	
	4 HR	DDMONYYYY/HH:MM	x	xx.xx	
xxxxxxx/xx/xx	0.5-1.0 HR	DDMONYYYY/HH:MM	.	xx.xx	xxxxxxxxxxxx
	2 HR	DDMONYYYY/HH:MM	x	xx.xx	
	3 HR	DDMONYYYY/HH:MM	x	xx.xx	
	4 HR	DDMONYYYY/HH:MM	x	xx.xx	
xxxxxxx/xx/xx	0.5-1.0 HR	DDMONYYYY/HH:MM	.	xx.xx	xxxxxxxxxxxx
	2 HR	DDMONYYYY/HH:MM	x	xx.xx	
	3 HR	DDMONYYYY/HH:MM	x	xx.xx	
	4 HR	DDMONYYYY/HH:MM	x	xx.xx	

Note: The lower limit of quantification is x.xx ng/mL for cefazolin. NS = no sample.
Sample collection times are from the start of infusion.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: CRF data and concentration data.

Note to Programmer: Sort by Subject and Schedule Time. Repeat for Treatment B. Plasma samples for PK assessments of Cefazolin will be collected from all subjects at the following time points: between 0.5-1 hr, 2, 3, and 4 hr relative to start of study drug infusion.

Listing 16.2.7.1
Adverse Events

Treatment: A

Subject	AE ID	System Organ Class/ Preferred Term/ Adverse Event	Start/Stop Date (Day) [1]/ Time	Frequency/ Severity/ Relationship	Action/ Outcome/ Serious	Treatment Required
xxxxxxx	xx	XXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXXX/ XXXXXXXXXXXXXXX	DDMMMYYYY (xx)/ HH:MM DDMMMYYYY (xx)/ HH:MM	XXXXXXXXXX/ XXXXXXXXXX/ XXXXXXXXX	XXXXXXXXX/ XXXXXXXX/ XX	XXXXXXX
xxxxxxx	xx	XXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXX	DDMMMYYYY (xx)/ HH:MM Ongoing	XXXXXXXXXX/ XXXXXXXXXX/ XXXXXXXXX	XXXXXXXXX/ XXXXXXXX/ XX	XXXXXXX

…

Note to Programmer: Sort by treatment, subject, and AE ID. Start a new page for each treatment. Display "Ongoing" in place of Stop Date/Time if the AE is ongoing.
If there are no AEs, then display 'No adverse events were reported.'

Note: Adverse events were coded by system organ class and preferred term using MedDRA Version 19.1.
[1] Day corresponds to study day. Day 1 is date of surgery.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.7.2
Serious Adverse Events

Treatment: A

Subject	AE ID	System Organ Class/ Preferred Term/ Adverse Event	Start/Stop Date (Day) [1]/ Time	Frequency/ Severity/ Relationship	Action/ Outcome/ Category [2]	Treatment Required
xxxxxxx	xx	XXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXXX/ XXXXXXXXXXXXXXX	DDMMMYYYY (xx)/ HH:MM DDMMMYYYY (xx)/ HH:MM	XXXXXXXXXX/ XXXXXXXXXX/ XXXXXXXXX	XXXXXXXXX/ XXXXXXXX/ XX	XXXXXXX
xxxxxxx	xx	XXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXX/ XXXXXXXXXXXXXXX	DDMMMYYYY (xx)/ HH:MM Ongoing	XXXXXXXXXX/ XXXXXXXXXX/ XXXXXXXXX	XXXXXXXXX/ XXXXXXXX/ XX	XXXXXXX

…

Note to Programmer: Sort by treatment, subject, and AE ID. Start a new page for each treatment. Display "Ongoing" in place of Stop Date/Time if the AE is ongoing.
If there are no AEs, then display 'No adverse events were reported.'

Note: Adverse events were coded by system organ class and preferred term using MedDRA Version 19.1.
[1] Day corresponds to study day. Day 1 is date of surgery.
[2] 1=Death, 2=Life Threatening, 3=Persistent or significant incapacity, 4=Congenital anomaly or birth defect, 5=Hospitalization, 6=Prolonged Hospitalization, 7=Other important medical events
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.7.3
Adverse Events Leading to Early Discontinuation

Use the same Listing shell as Listing 16.2.7.1, but display only AEs given on the study completion page when the primary reason for discontinuation was either Serious AE or Intolerable AE.

Listing 16.2.8.1
Hematology Laboratory Test Results

Treatment: x

Subject	Lab Test (Unit)	Visit [1]	Collection Date (Day) [2]/ Time	Result	Reference Range	Abnormal Flag	Comment
xxxxxxx	xxxxxxxxxxxx (xxxxx)	SCREENING	DDMONYYYY (xx)/ HH:MM	xxx.x	xxx.x - xxx.x	LOW	xxxxxxxxxx
		SCREENING, R	DDMONYYYY (xx)/ HH:MM	xxx.x	xxx.x - xxx.x		xxxxxxxx
		ENROLLMENT	DDMONYYYY (xx)/ HH:MM	xxx.x	xxx.x - xxx.x	xxxx	
		POSTSURGERY	DDMONYYYY (xx)/ HH:MM	xxx.x	xxx.x - xxx.x		
		…					
	…						
…							

Note to Programmer: Sort by treatment, subject, lab test, and collection date/time. Start a new page for each treatment.

[1] R = Repeat.
[2] Day corresponds to study day. Day 1 is date of surgery.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.8.2
Clinical Chemistry Laboratory Test Results

Use the same Listing shell as Listing 16.2.8.1, but display clinical chemistry results.

Listing 16.2.8.3
Pregnancy Test Results

Treatment: x

Subject	Was Urine Pregnancy Performed?	Visit	Collection Date (Day) [1]/ Time	Result	Serum Test Result [2]
xxxxxxx	Yes	SCREENING	DDMONYYYY (xx)/ HH:MM	Negative	
		ENROLLMENT	DDMONYYYY (xx)/ HH:MM	Positive	Positive

…

Note to Programmer: Sort by treatment, subject, and collection date/time. Start a new page for each treatment. Only include females of childbearing potential.

[1] Day corresponds to study day. Day 1 is date of surgery.
[2] If urine test is positive, then a serum test is done for confirmation.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.9.1
Vital Sign Measurements

Treatment: x

Subject	Visit/ Timepoint	Collection Date (Day) [1]/ Time	Body Position	Actual Value: Sys BP	Actual Value: Dia BP	Actual Value: Pulse	Actual Value: Resp	Actual Value: Temp	Change from Baseline [2]: Sys BP	Change from Baseline [2]: Dia BP	Change from Baseline [2]: Pulse	Change from Baseline [2]: Resp	Change from Baseline [2]: Temp
xxxxxxx	SCREENING	DDMONYYYY (xx)/ HH:MM	SITTING	xxx	xx	xx	xx	xx.x					
	DAY 1/ PREDOSE	DDMONYYYY (xx)/ HH:MM	xxxxxx	xxx	xx	xx	xx	xx.x	xxx	xx	xx	xx	xx.x
	DAY 1/ 15 min	DDMONYYYY (xx)/ HH:MM	xxxxxx	xxx	xx	xx	xx	xx.x	xxx	xx	xx	xx	xx.x
…													

Note to programmer: The post-baseline visits are: Day 1/Pre-dose, Day 1/15 min, Day 1/.5hr-1.0hr, 3.0hr, Postsurgery, and Follow-up. Start a new page for each treatment.

Note: Sys BP = Systolic Blood Pressure in mmHg; Dia BP = Diastolic Blood Pressure in mmHg; Pulse = Pulse in beats/min; Resp = Respiratory Rate in breaths/min; Temp = Temperature in degrees C.
[1] Day corresponds to study day. Day 1 is date of surgery.
[2] Baseline is defined as the screening visit.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.9.2
Electrocardiograms

Treatment: x

Subject	Visit	Collection Date (Day)[1]/ Time	Actual Value HR	PR	QRS	QT	QTCF	Interpretation	Change from Baseline [2] HR	PR	QRS	QT	QTcF
xxxxxxx	SCREENING	DDMONYYYY (xx)/ HH:MM	xxx	xx	xx	xxx	xxx	Normal					
	POSTSURGERY	DDMONYYYY (xx)/ HH:MM	xxx	xx	xx	xxx	xxx	xxxxxxxx	xxx	xx	xx	xx	xx
	FOLLOW=UP	DDMONYYYY (xx)/ HH:MM	xxx	xx	xx	xxx	xxx	xxxxxxxx	xxx	xx	xx	xx	xx
…													

Note to programmer: The post-baseline visits are: Postsurgery and Follow-up. Start a new page for each treatment.

Note: HR = Heart rate in beats/min; PR = PR interval in msec; QRS = QRS duration in msec; QT = QT interval in msec; QTcF = QTcF interval in msec.
[1] Day corresponds to study day. Day 1 is date of surgery.
[2] Baseline is defined as the screening visit.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.9.3
Abnormal Physical Examination Findings

Treatment: x

Subject	Visit	Date (Day) [1]	Assessment	Findings
xxxxxxx	SCREENING	DDMONYYYY (xx)	GENERAL APPEARANCE	
			DERMATOLOGIC	xxxxxxxxxxxxxxxx
			HEEN	
			…	
	POSTSURGERY	DDMONYYYY (xx)	OVERALL	
	…			
…				

Note to Programmer: Sort by treatment, subject, date, and assessment (in the order as they appear in CRF with 'OVERALL' sorted last). Start a new page for each treatment. Include only those physical examinations with determined to be abnormal

[1] Day corresponds to study day. Day 1 is date of surgery.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

Listing 16.2.9.4
Infusion Site Assessments

Treatment: x

Subject	Visit/Timepoint	Date (Day) [1]/Time	Assessment	Result	Comment
xxxxxxx	SCREENING	DDMONYYYY (xx)/ HH:MM	PAIN	YES	Xxxxxxxx
			ERYTHEMA/REDNESS	NOT DONE	xxxxxxxxxxxxxxx
			INDURATION/SWELLING	NO	
			LOCALIZED WARMTH	NO	
			OTHER: xxxxxxx	NO	
	DAY 1/15 MIN	DDMONYYYY (xx)/ HH:MM	PAIN	YES	Xxxxxxxx
	…				
…					

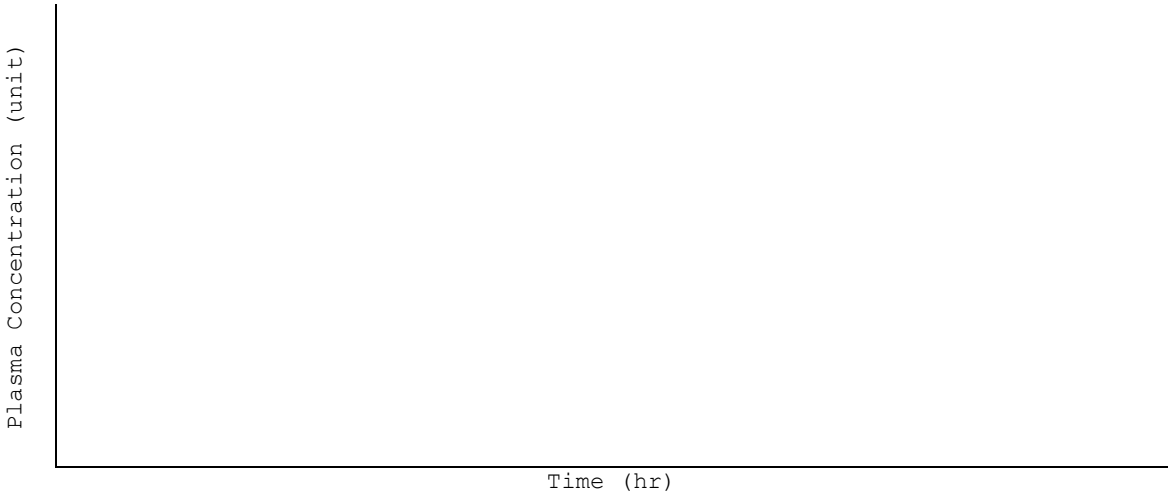
Note to Programmer: Sort by treatment, subject, date/time, and assessment (in the order PAIN, ERYTHEMA/REDNESS, INDURATION/SWELLING, LOCALIZED WARMTH, OTHER). If OTHER, SPECIFY value is present,display "OTHER: xxxx" where "xxxx" is the value specified; otherwise display "OTHER". Start a new page for each treatment.

[1] Day corresponds to study day. Day 1 is date of surgery.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.

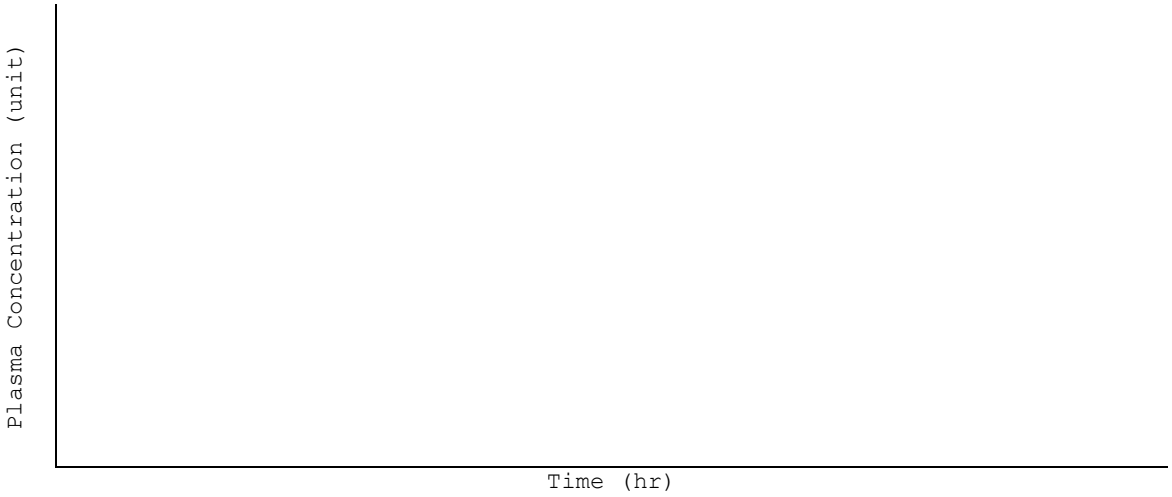
Figure 14.2.1
Mean (+/-SD) Plasma Concentrations of Cefazolin versus Time
Pharmacokinetic Analysis Set

Age Bracket: >=10 to <=13 years old

Linear Scale



Semi-Logarithmic Scale

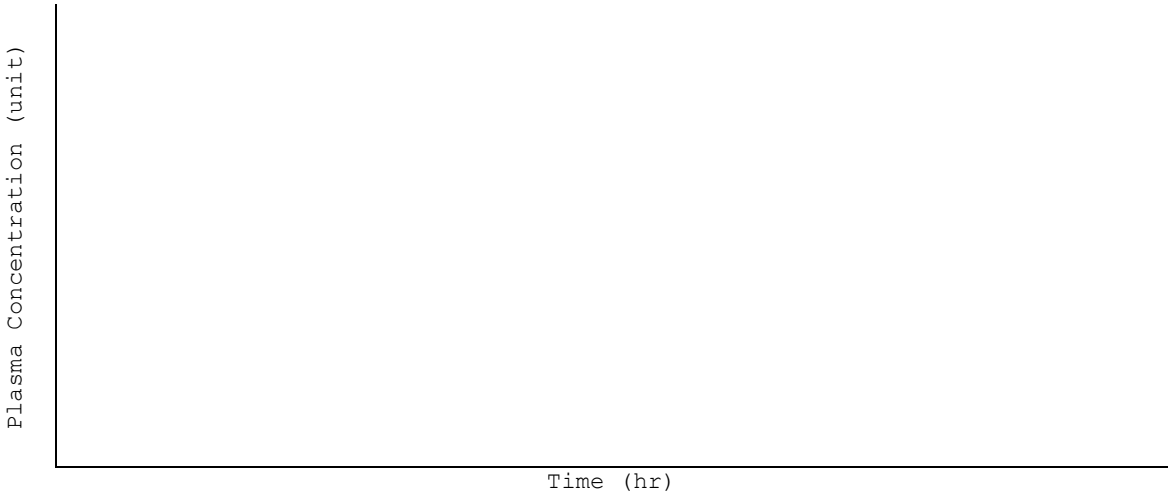


Note to programmer: Show both treatments on the same plot. Show treatments in legend. Repeat for age bracket >13 to ≤17 years old and All Ages. Use the mid-point for the interval 0.5-1.0 hr for the x-axis coordinate.

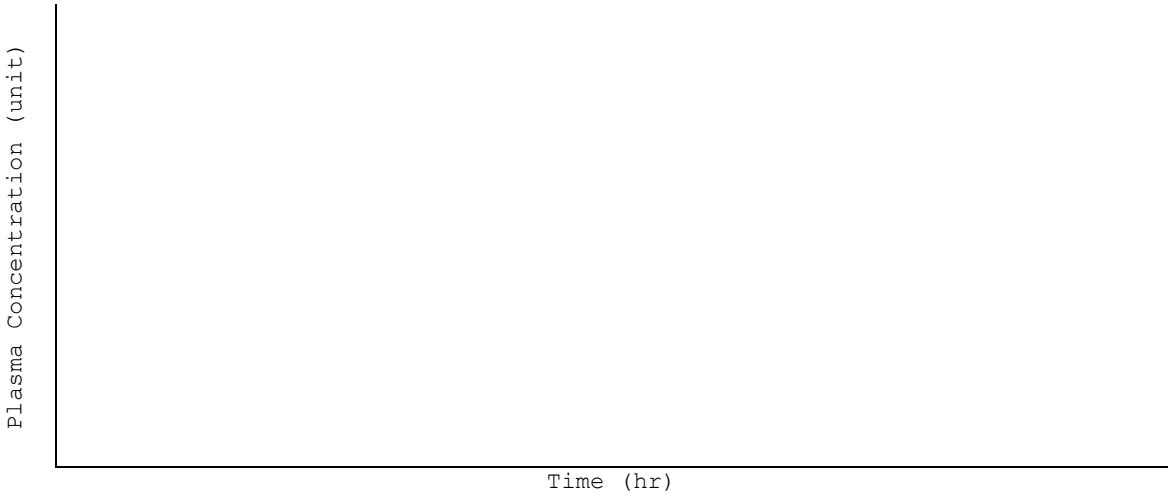
Note: Concentrations that were BLQ were treated as zero for descriptive statistics.
Sample collection times are from the start of infusion.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Table 14.2.1.1

Figure 14.2.2
Individual Plasma Concentrations of Cefazolin versus Time
Pharmacokinetic Analysis Set
Subject: xxxx
Age Bracket: xxxx

Linear Scale



Semi-Logarithmic Scale



Note to programmer: Show treatments in legend, same designations as F14.2.1.1.1. Set the y-axis scale uniform for each dose level.

Sample collection times are from the start of infusion.
Treatment A: 1g cefazolin for pediatric surgical subjects weighing >= 25 kg but < 60 kg;
Treatment B: 2g cefazolin for pediatric surgical subjects weighing >= 60 kg.
Source Data: Listing 16.2.6.1