This supplement contains the following items:
1. Original protocol (Version 1.0), final protocol (Version 3.0), and summary of changes.
2. Statistical Analysis Plan (Version 1.0)

Strategies using Off-Patent antibiotics for Methicillin-Resistant *Staphylococcus aureus ("STOP MRSA") – A Phase IIB, multi-center, randomized, double-blind clinical trial*

DMID Protocol Number: 07-0040

DMID Funding Mechanism: HHSN272200700-32C

Pharmaceutical Support Provided by: N/A

Other Identifying Numbers:

IND Sponsor: DMID

Co-Principal Investigators: David A. Talan, MD & Gregory J. Moran, MD

DMID Protocol Champion: Christine Chiou, MD

DMID Medical Monitor: Shy Shorer, MD

DMID Clinical Affairs Specialist: Hyung Koo

DMID Regulatory Affairs Specialist: Emily Kough

Draft or Version Number: 1.0

Day Month Year
28 July 2008

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH E6; 62 Federal Register 25691 (1997)
- NIH Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Co Principal Investigators:

Signed: _____ Date: _____

Name: David A. Talan, MD
Title: Co-Principal Investigator

Signed: _____ Date: _____

Name: Gregory J. Moran, MD
Title: Co-Principal Investigator

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AIDS	Acquired Immunodeficiency Syndrome
BID	Twice daily
BUN	Blood Urea Nitrogen
CA-MRSA	Community-Acquired MRSA
CBC	Complete Blood Cell Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CLSI	Clinical and Laboratory Standards Institute
CRF	Case Report Form
CRO	Contract Research Organization
CTM	Clinical Trials Management
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DS	Double-Strength
DSMB	Data and Safety Monitoring Board
ECRF	Electronic Case Report Form
ED	Emergency Department
EFV	Extended Follow-Up Visit
EMMES	EMMES Corporation (Data Management Contractor)
EOT	End-of-Therapy Visit
FDA	Food and Drug Administration
FWA	Federalwide Assurance
G-6-PD	Glucose-6-Phosphate Dehydrogenase
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
I & D	Incision and Drainage
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IDES	Internet Data Entry System/AdvantageEDC
IDSA	Infectious Diseases Society of America
IEC	Independent or Institutional Ethics Committee

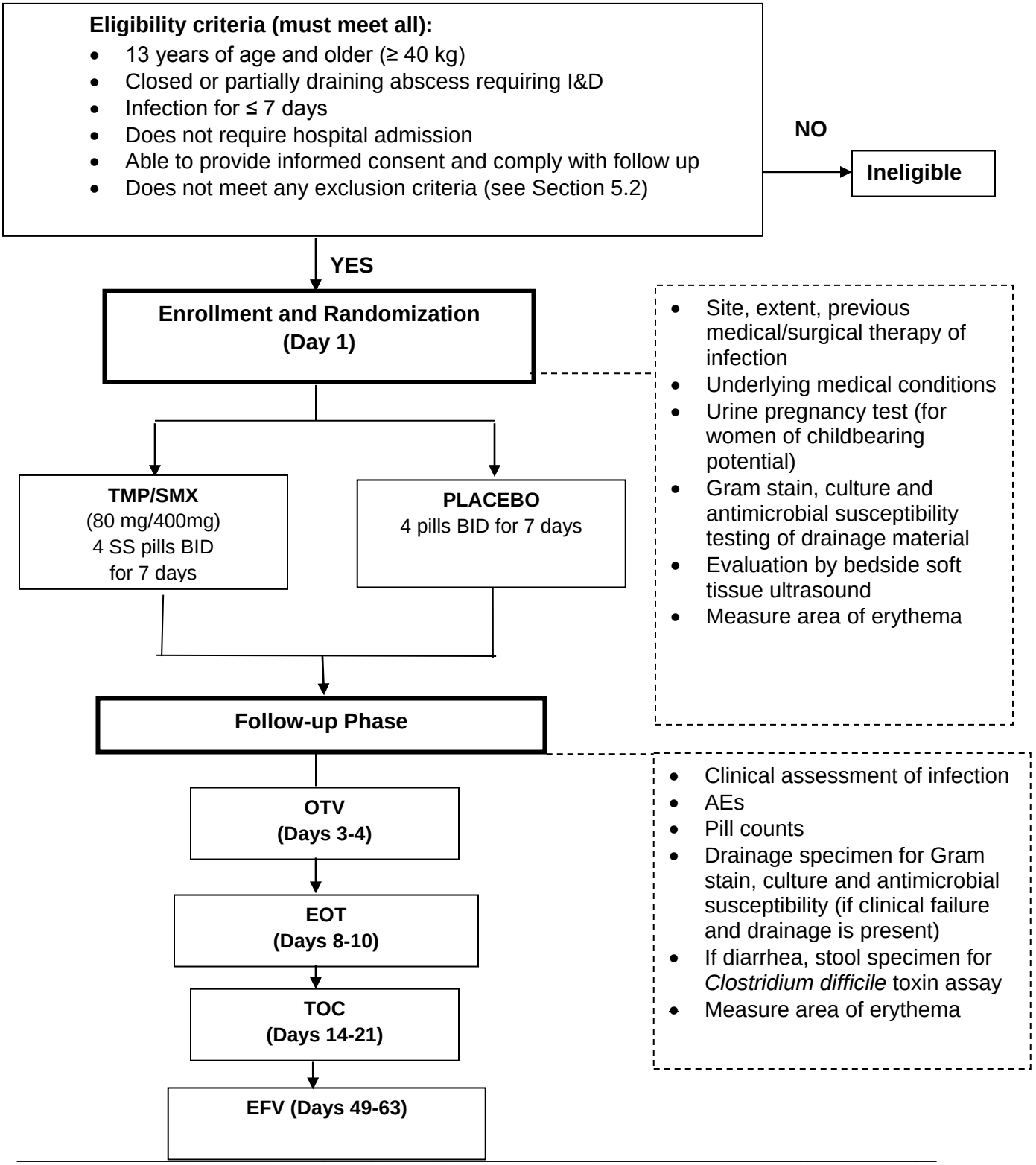
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MedDRA ®	Medical Dictionary for Regulatory Activities
MIC	Minimal Inhibitory Concentrations
mITT	Modified Intent-to-Treat
MOP	Manual of Procedures
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
N	Number (typically refers to subjects)
NCI	National Cancer Institute, NIH, DHHS
NDA	New Drug Application
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
OTV	On-Therapy Visit
PA	Clinician's Assistant
PatID	Subject ID
PDR	Clinician's Desk Reference
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PPD	PPD Development LP (Clinical Trial Management Contractor)
PVL	Panton-Valentine Leukocidin
QA	Quality Assurance
QC	Quality Control
QID	Four times daily
SAE	Serious Adverse Event/Serious Adverse Experience
S. aureus	*Staphylococcus aureus*
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SS	Single-strength
SSTI	Skin and Soft-Tissue Infection
TOC	Test-of-Cure Visit
TMP/SMX	Trimethoprim/Sulfamethoxazole
US	United States

PROTOCOL SUMMARY

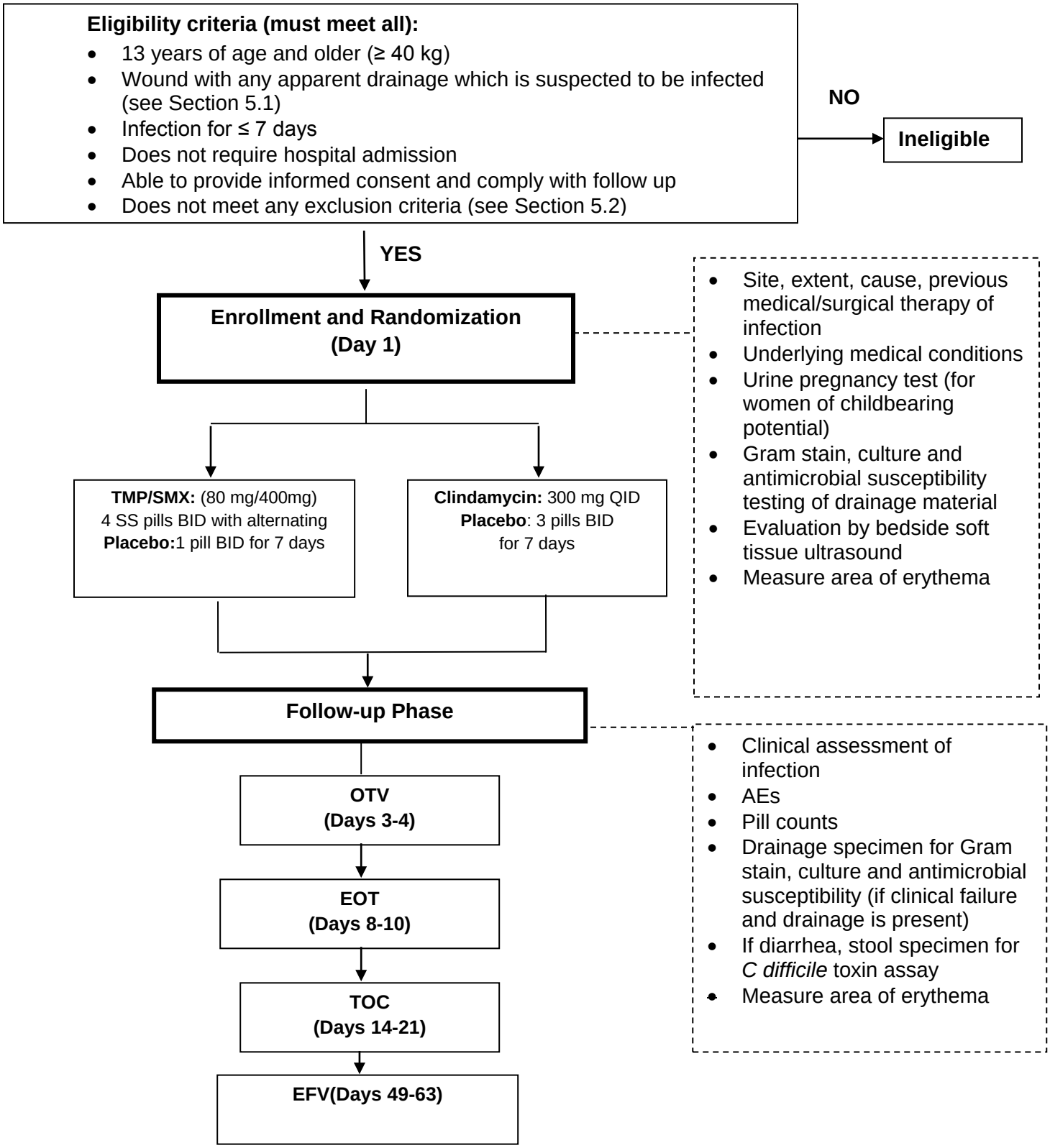
Title:	**Strategies using Off-Patent antibiotics for Methicillin-Resistant *Staphylococcus aureus* (*"STOP MRSA"*) – A Phase IIB, multi-center, randomized, double-blind clinical trial**
Phase:	IIB
Population:	1,590 subjects (male and female) 13 years of age and older with acute uncomplicated SSTIs
Informed consent	Required
Number of Sites:	5 large urban, academically-affiliated US EDs
Study Duration:	July 19, 2007 – July 18, 2012
Subject Participation Duration:	Subjects will be followed for approximately 9 weeks.
Description of Agent or Intervention:	Subjects will be stratified by the type of infection and then randomized (1:1) to one of two treatments for a total 7-day duration of treatment. The oral medications will be enclosed in a blister packet and labeled by the time of administration. A randomization scheme will maintain the blind and will be held by the EMMES statistician and accessible to a designated individual (e.g., pharmacist) at each site. Subjects with an abscess will either receive identical TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day) or 4 placebo pills twice per day. Subjects with an infected wound will either receive identical TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day, with alternating 1 identical placebo pill, twice per day), or clindamycin (300 mg, four times per day, with 3 placebo pills on alternating doses). Subjects with cellulitis will either receive identical cephalexin (500 mg, four times per day) and TMP/SMX (4 SS pills 80mg/400mg each, twice per day) or cephalexin (500 mg, four times per day) and 4 placebo pills twice per day.
Objectives:	The primary objectives for each type of SSTI studied are to compare

	the cure rates in the PP population: 1) for subjects with an acute uncomplicated cutaneous abscess receiving I&D, to determine whether the addition of TMP/SMX (4 SS pills, 80 mg/400 mg each, BID), an antibiotic with activity against CA-MRSA, is more clinically efficacious than I&D alone (4 placebo pills BID); 2) for subjects with an acute uncomplicated wound infection with any apparent drainage, to determine if clindamycin (300 mg, QID, with 3 placebo pills on alternating doses), an antibiotic with activity against CA-MRSA, MSSA, and streptococci is more clinically efficacious than TMP/SMX (4 SS pills, 80 mg/400 mg each, BID, with alternating 1 identical placebo pill, BID), an antibiotic with activity against CA-MRSA and MSSA; and 3) for subjects with acute uncomplicated cellulitis, to determine if cephalexin (500 mg, QID) and TMP/SMX (4 SS tables, 80mg/400mg each, BID), a regimen with activity against CA-MRSA, MSSA, and streptococci, is more clinically efficacious than cephalexin (500 mg, QID), an antibiotic with activity against MSSA and streptococci, and 4 placebo pills BID. The primary endpoint will be clinical cure at the TOC in the PP population (i.e., patients who meet enrollment criteria, have none of the exclusion criteria, complete 100% of the first 48 hours of antimicrobial therapy, and have physical follow-up at the TOC; subjects who have been determined to be a clinical failure at any time prior to TOC who took 100% of the first 48 hours of antimicrobial therapy but who do not have physical follow-up at the TOC will also be included in the PP population).
Description of Study Design:	This is a multi-center, randomized, double-blind clinical trial in which subjects will be stratified by the type of infection and then randomized to various 7-day oral antibiotic treatments, including placebo-controlled and comparative designs. The study population will include children 13 years of age and over and adults, who weigh ≥ 40 kg presenting to 5 large urban EDs. Therapy will start on the day of enrollment. Subjects will be evaluated upon enrollment, at 2-3 days after enrollment (OTV), at 1-3 days after the end-of-therapy (EOT), and at 7-14 days after the end-of-therapy (TOC), and at 6-8 weeks after the end-of-therapy (EFV).
Estimated Time to Complete Enrollment:	Subject enrollment will occur over 3 years (September, 2008 – August, 2011).

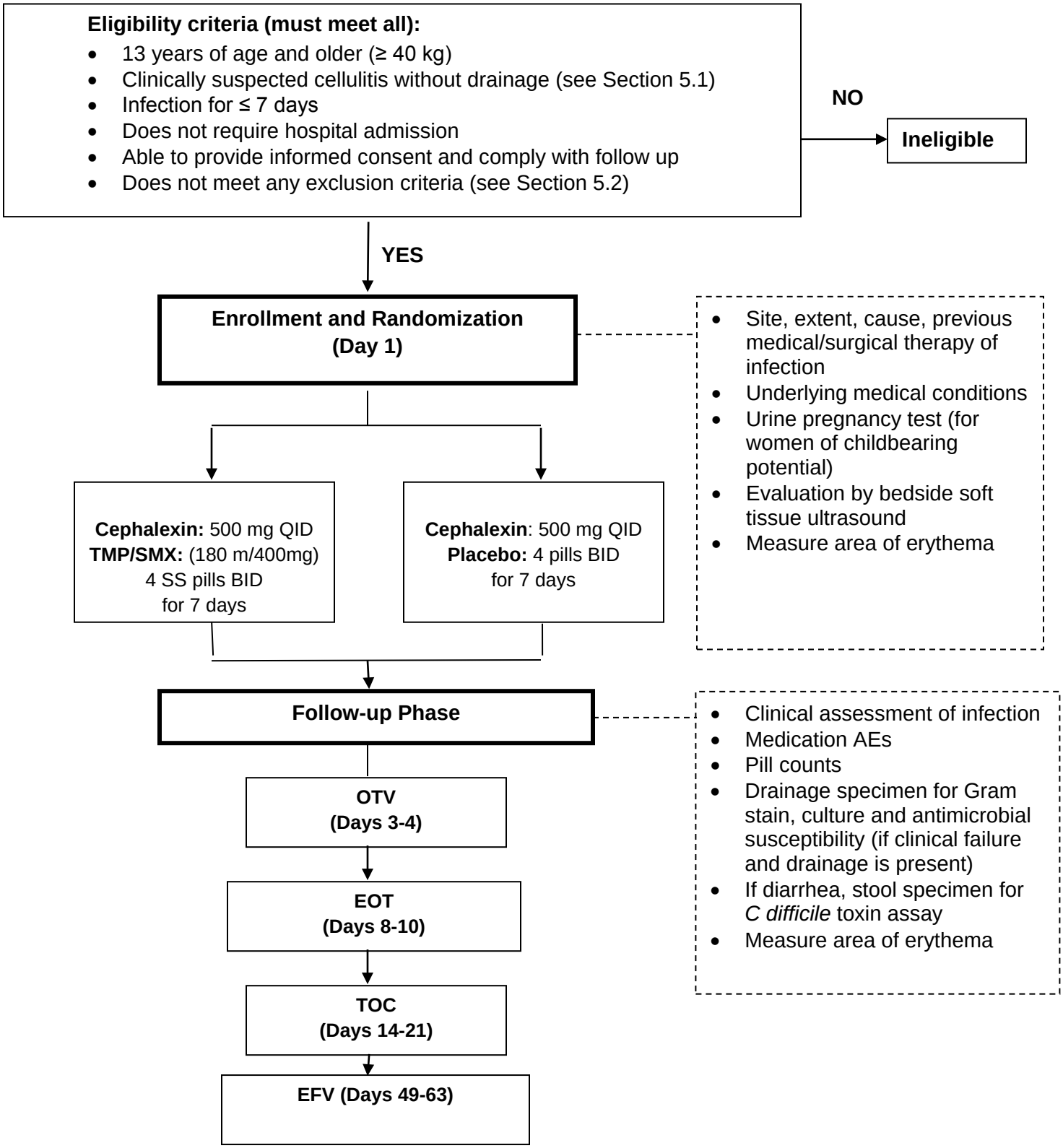
***Schematic of Study Design by Study Arm:**
TMP/SMX vs. Placebo for Outpatient Treatment of Subjects with an Acute Uncomplicated Cutaneous Abscess Requiring Incision and Drainage



TMP/SMX vs. Clindamycin for Outpatient Treatment of Subjects with an Acute Uncomplicated Wound Infection



Cephalexin and TMP/SMX vs. Cephalexin and Placebo for Outpatient Treatment of Subjects with Acute Uncomplicated Cellulitis



1. Key Roles

For questions regarding this protocol, contact Christine Chiou at cchiou@niaid.nih.gov.

Individuals:

Protocol Champion:
Christine Chiou, MD
Project Officer
Bacteriology and Mycology Branch, DMID, NIAID, NIH
6610 Rockledge Drive, Room 4064, MSC 6604
Bethesda, MD 20892-6604
Phone:301-496-7728
Fax:301-402-2508
Email: CChiou@niaid.nih.gov

Co-Principal Investigators:
David A. Talan, MD & Gregory J Moran, MD
Co-Principal Investigators
Olive View-UCLA Medical Center
14445 Olive View Drive, North Annex
Sylmar, CA 91342
Phone number: 818-364-3107
Fax number: 818-364-3268
Email: dtalan@ucla.edu, gmoran@ucla.edu

Medical Monitor:
Shy Shorer, MD
6610 Rockledge Drive, Rm 6051
Bethesda, MD 20817
Phone: 301-451-3025

Site Investigators/

Institutions:

1. Fredrick Abrahamian, DO
Olive View-UCLA Medical Center
Department of Emergency Medicine
14445 Olive View Drive, North Annex
Sylmar, CA 91342
Phone: 818-364-3112
Fax: 818-364-3268
Email: fmasjc@yahoo.com

2. David Karras, MD
Temple University School of Medicine/University Hospital
Department of Emergency Medicine
3401 Broad Street

Philadelphia, PA 19140
Phone: 215-707-5032
Fax: 215-707-3494
Email: david.karras@temple.edu

3. Frank LoVecchio, DO, MPH
Maricopa Medical Center
Department of Emergency Medicine Research
2601 E. Roosevelt St.
Phoenix, AZ 85008
Phone: 602-344-5058
Fax: 602-344-1208
Email: frank.lovecchio@bannerhealth.com

4. Richard E. Rothman, MD, PhD
Johns Hopkins University/JHMI
Department of Emergency Medicine
5801 Smith Avenue
Davis Building, Suite 3220
Baltimore, MD 21209
Phone: 410-735-6428
Fax: 410-735-6440
Email: rrothman@jhmi.edu

5. Mark Steele, M.D.
Truman Medical Center
Office of the Chief Medical Officer
2301 Holmes
Kansas City, MO 64108
Phone: 816-404-5300
Fax: 816-404-5305
Email: mark.steele@tmcmed.org

Other contacts:

William Mower, MD, PhD
Study Statistician
UCLA Emergency Department
924 Westwood Blvd., Suite 300
Los Angeles, CA 90024
Ph: (310) 794-0582
Fax: (310) 794-0599
wmower@ucla.edu

Anusha Krishnadasan, PhD

Project Director
14445 Olive View Drive, North Annex Bldg.
Sylmar, CA 91342
Phone: 818-364-3111
Fax: 818-364-3111
Email: stopmrsa@ucla.edu

PPD Development, LP
929 North Front Street
Wilmington, NC 28401-3331
Phone: 910 251 0081
Fax: 910 762 5820

EMMES Corporation
401 North Washington St.
Suite 700
Rockville, MD 20850
Phone: 301-251-1161
Fax: 301-251-1355
ca_mrsa@emmes.com

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

CA-MRSA has recently emerged as a cause of SSTI.[1,2,3,4,5] In August of 2004, Moran and colleagues studied 422 adults presenting to 11 US EDs with purulent SSTIs, including abscesses (81%), infected wounds (11%), and cellulitis (8%). This research was conducted through a network of EDs called *EMERGE*ncy ID NET. The network is supported by CDC and throughout the years has been involved and completed numerous infectious disease-related research projects. Fifty-nine percent (59%) of these subjects had infections caused by MRSA. Pulsed-field type USA 300 isolates accounted for 97% of MRSA isolates. SCC*mec* type IV and PVL toxin gene were detected in 98% of MRSA isolates. Of note, 27% of MRSA isolates met the epidemiologic definition of health care-associated MRSA, yet 98% of these strains had the genetic profile of CA-MRSA strains. The next most common pathogens were MSSA, which was isolated in 17% of infections, and streptococcal species, which were isolated in 7%. By type of SSTI, MRSA, MSSA, and streptococci were found in 63%, 11%, and 7% of abscesses, 61%, 13% and 10% of infected wounds, and 47%, 35%, and 18% of cellulitis cases, respectively.[1]

In this study, the in vitro susceptibilities of MRSA (99% with genetic/toxin characteristics of CA-MRSA) and MSSA to TMP/SMX, clindamycin, tetracycline, and cephalexin were as follows:

Antibiotic	**MRSA (n/total [%])**	**MSSA (n/total [%])**
TMP/SMX	217/217 (100%)	53/55 (96%)
Clindamycin	215/226 (95%)	60/63 (95%)
Tetracycline	207/226 (92%)	64/66 (97%)
Cephalexin	0/181 (0.0%)	58/64 (91%)

Despite the high prevalence of CA-MRSA in this study, penicillinase-resistant semisynthetic penicillins and first generation cephalosporins, which are inactive against MRSA, were prescribed to 64% of subjects. However, antibiotics not typically given prior to emergence of CA-MRSA were also used, including clindamycin in 18% and TMP/SMX in 16% of subjects. Among subjects with an abscess who received I&D, 77% were prescribed antibiotics.

In the current era of increasing CA-MRSA infections, the outpatient management of SSTIs has not been well studied. There are only a few recent clinical trials of intravenous antimicrobials

(e.g., vancomycin, linezolid, daptomycin, and dalbavancin) for treatment of SSTI that included subjects with MRSA infection, and in these studies CA-MRSA was not distinguished from health care-associated strains.[6,7,8] A few studies have been published on MRSA treatment with TMP/SMX and clindamycin for various infections, however these were done before the emergence of CA-MRSA.[9,10,11,12] There is one small study of clindamycin treatment of CA-MRSA infected infants and children[13], and another small, uncontrolled retrospective report of various treatments.[14] One recent clinical trial of uncomplicated SSTI comparing 2 oral cephalosporins without MRSA activity found cure rates of 95% for subjects with abscesses but only 71% for subjects with cellulitis.[15] No randomized, blinded trials of off-patent antibiotics for the treatment of CA-MRSA SSTI appear to exist in the published medical literature.

No off-patent antibiotic has a specific indication for MRSA SSTI (clindamycin has an indication for treatment of “susceptible” staphylococcal SSTIs). US FDA registration studies have been criticized because of their inclusion and consolidation of subjects with heterogeneous types of SSTIs.[16] The various types of common acute SSTI each present unique questions regarding their outpatient management in the era of CA-MRSA.

For abscesses, which are generally included in these clinical trials and which are now predominantly caused by CA-MRSA in many areas,[1,3] it is unclear whether or not treatment with antibiotics active against CA-MRSA are additionally efficacious compared to I&D alone. Previous investigations were mostly conducted before the emergence of CA-MRSA and were limited by non-randomized design, small numbers of enrolled subjects, vague outcome definitions, and/or treatment with an antibiotic not possessing appropriate in vitro activity (most recently, cephalexin for MRSA abscesses). Compared to subjects who underwent I&D and also received antibiotics, in general, these studies suggested high and similar cure rates of abscesses with I&D alone (i.e., without the addition of antibiotics).[15,17,18,19,20,21,22]

Various management recommendations for abscesses have been provided in recent authoritative publications from the IDSA,[23] The Sanford Guide® (2006),[24] and an expert panel convened by the CDC. [25] Whereas these sources acknowledge I&D as the primary treatment, they variously recommend addition of antibiotics based on the presence of fever and other signs of systemic illness, abscess size (e.g., > 5 cm)[22] or location, associated co-morbidities, extremes of age, and lack of response to I&D alone. Although consistent with common practice, we are not aware of prospectively validated data to support these recommendations. For large abscesses, The Sanford Guide® recommends TMP/SMX 2 double-strength pills twice per day for 5-10 days.[24]

Antibiotics are the primary treatment for patients with infected wounds with drainage, also called secondarily infected traumatic lesions (an FDA designated indication for topical mupirocin). Moran and colleagues also found CA-MRSA was the predominant pathogen among these infections.[1] MSSA and streptococci were the next most common pathogens. For post-traumatic infected extremity wounds, The Sanford Guide® recommends TMP/SMX 2 double-strength pills twice per day or clindamycin 300-450 mg 3 times per day.[22] Both clindamycin and TMP/SMX

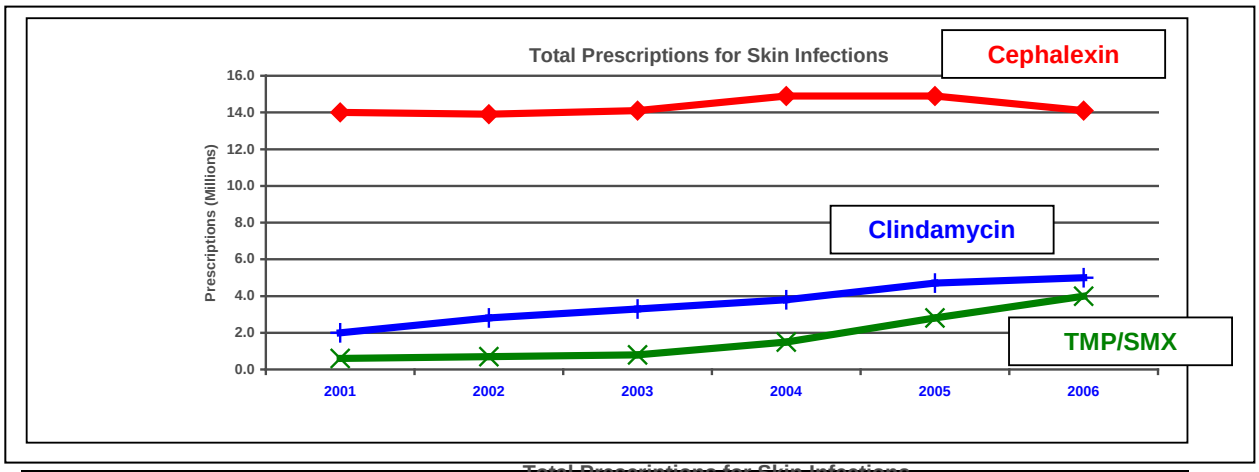
possess in vitro activity against CA-MRSA and MSSA, although in some areas of the US among CA-MRSA isolates defined by epidemiological criteria, in vitro resistance has been observed to these agents, and there have also been reports of both constitutive and inducible clindamycin resistance.[3,26,27,28] TMP/SMX is relatively inactive against streptococci compared to clindamycin. D'Oliveira and colleagues reported that approximately 78% of isolates had in vitro resistance to TMP/SMX.[29] Kaplan and colleagues reported no in vitro resistance of *S. pyogenes* to clindamycin.[30] Tricket and colleagues found that among subjects with streptococcal pharyngitis, only 70% of subjects treated with TMP/SMX had microbiological eradication compared to 88% of those who received penicillin.[31] Therefore, since clindamycin appears to have broader activity than TMP/SMX against the predominant Gram-positive pathogens, it may be more efficacious than TMP/SMX in the treatment of infected wounds.

Investigations into the etiology of cellulitis without drainage are limited by the lack of specimen availability. Studies using tissue biopsies and aspirate specimens and relying on conventional and non-conventional identification methods such as immunofluorescence and serologic testing suggest that streptococci are the predominant cause of cellulitis.[16,32,33,34,35,36,37,38,39,40] The most recent IDSA SSTI guidelines state "cellulitis that is diffuse or unassociated with a defined portal is most commonly caused by streptococcal species."[23] However, with the emergence of CA-MRSA, the role of this pathogen in these difficult-to-study infections is uncertain. Although cellulitis cases in the study by Moran and colleagues were uncommon, 47% of these cases that also had purulent drainage grew CA-MRSA, suggesting that this pathogen may have an etiologic role in cellulitis without drainage.[1] MSSA has also been noted as a pathogen in other studies.[32,33,34,35,36,37,38,39] For cellulitis, The Sanford Guide® recommends various antibiotics, none of which possess in vitro activity against CA-MRSA, including penicillin, dicloxacillin, or cefazolin.[24] Determining whether an antibiotic regimen with streptococcal and MSSA activity in addition to CA-MRSA activity (e.g., cephalexin and TMP/SMX) would be more efficacious than one without CA-MRSA activity (e.g., cephalexin alone) may help elucidate the pathogenic role of CA-MRSA in these infections.

This will be a clinical trial to evaluate oral off-patent antibiotics for outpatient treatment of patients with any of the 3 main types of acute uncomplicated SSTI, i.e., abscesses, infected wounds, and cellulitis. Upon enrollment, subjects will be stratified by type of infection, and then randomized to various treatments. Subjects with an acute uncomplicated cutaneous abscess receiving I&D will be treated with TMP/SMX or placebo to determine whether the addition of an antibiotic with activity against CA-MRSA is more clinically efficacious than I&D alone. Subjects with an acute wound infection will be treated with TMP/SMX or clindamycin to determine if clindamycin, an antibiotic with activity against CA-MRSA, MSSA, and streptococci is more clinically efficacious than TMP/SMX, an antibiotic with activity against CA-MRSA and MSSA. Subjects with acute cellulitis will be treated with cephalexin/TMP/SMX or cephalexin/placebo to determine if cephalexin/TMP/SMX is more clinically efficacious than cephalexin alone.

2.2 Rationale

The choices of antibiotics and comparisons were based on consideration of the most current and authoritative references regarding standards of treatment for SSTIs (i.e., the IDSA SSTI treatment guidelines, the CDC Expert Panel, and The Sanford Guide®). Further, comparisons were reviewed and endorsed by outside experts, including some involved in these publications. Moran and colleagues' recently published study of MRSA among ED patients with SSTI revealed that cephalexin, clindamycin, and TMP/SMX were among the most common antimicrobials used for treatment of SSTIs.[1] In addition, between 2001 through 2006, audit data of the three most frequently prescribed antibiotics for SSTI revealed continued use of cephalexin and increasing use of clindamycin and TMP/SMX.[41]



Prescriptions (Millions)	2001	2002	2003	2004	2005	2006
Cephalexin	14.0	13.9	14.1	14.9	14.9	14.1
Clindamycin	2.0	2.8	3.3	3.8	4.7	5.0
TMP/SMX	0.6	0.7	0.8	1.5	2.8	4.0

Currently, of all the off-patent antibiotic options, it appears that TMP/SMX has retained the most consistent activity against CA-MRSA. Since CA-MRSA is the predominant pathogen of cutaneous abscesses (and streptococci are rarely found), this antibiotic was selected to compare with placebo in those infections also treated with I&D. Many clinicians still appear to use cephalexin to treat SSTI, and we considered inclusion of this antibiotic as a treatment option for patients with infected wounds. However, consensus amongst various reviewers was that since cephalexin lacked MRSA activity, it posed an ethical/IRB conflict for the treatment of a type of SSTI frequently caused by this pathogen. However, for cellulitis, in which there exists a consensus that streptococci are the most important etiologic bacteria, cephalexin was considered a current practice standard and therefore a reasonable choice to compare with cephalexin plus TMP/SMX, an agent possessing CA-MRSA activity. Clindamycin was considered as a potential comparator to cephalexin. However, although 95% of CA-MRSA isolates from ED patients with SSTI demonstrated in vitro susceptibility to clindamycin in 2004,[1]

there have been increasing reports of clindamycin resistance among CA-MRSA isolates.[26] A survey of the 2006 antibiograms of the 5 investigative site EDs revealed an average MRSA susceptibility rate to clindamycin of 85% (range, 75% to 95% by site). CA-MRSA susceptibility to TMP/SMX appears to have remained more consistent than to clindamycin. Therefore, the combination of cephalexin/TMP/SMX would appear to be the better choice in order to evaluate and isolate the role of CA-MRSA in cellulitis than clindamycin. Also, for patients with an infected wound with drainage, TMP/SMX will be directly compared to clindamycin, and, as opposed to cellulitis, a culture specimen will be available in order to evaluate the effect of in vitro resistance of isolates to the treatment antibiotic if this should be observed.

Tetracycline class antibiotics were not chosen because of teratogenicity concerns. Rifampin was excluded based on rapid emergence of resistance of MRSA when this drug is used as monotherapy.[42] Rifampin was not proposed as a combination drug because no evidence exists of benefit from adding rifampin to another agent (e.g., TMP/SMX) for SSTI treatment.

Although one DS TMP/SMX would be expected to achieve serum levels above the MIC of CA-MRSA, concentrations in skin blister fluid are approximately 50% of serum and near *S. aureus* MIC breakpoints.[43] Therefore, in order to best test the efficacy of TMP/SMX, and to be consistent with current standard antibiotic recommendations, a regimen of 4 SS pills per day was elected.[22] (Note that SS pills were chosen instead of DS, because it was felt that the large size of over-encapsulated DS pills may decrease subject compliance in taking their study drug.) Similarly, for other antibiotic treatments, the higher end of the recommended dosage range was chosen.

The optimal duration of therapy for SSTI has not been clearly established. For most clinical trials the treatment duration is 7-10 days. One study of uncomplicated cellulitis reported that 5 days of levofloxacin was as clinically efficacious as 10 days, and another revealed that 85% of patients treated with dirithromycin for 5 days had clinical success.[44,45] Therefore, we have chosen 7 days as the duration of treatment for the 3 infection types. The study methods are consistent with FDA guidance to industry. [46]

The use of a research network of 5 geographically diverse sites will increase the chance that the study will be representative of antimicrobial susceptibility patterns throughout the US. All site hospitals are university-affiliated with strong research departments, and are currently affiliated with *EMERGE*ncy ID NET. All sites have the infrastructure and experience necessary to conduct multi-site research studies. They are equipped with a clinical pharmacy with several years of experience in storing and dispensing study drugs for clinical trial studies. Furthermore, they all possess on-site clinical microbiology laboratory facilities that are capable of conducting the necessary tests required for the proposed studies. All sites have a hospital information system that is accessible by investigators and study coordinators to collect laboratory results and other necessary data required for the proposed studies (although this system will have limited accessibility to investigators to maintain blinding of culture and susceptibility results for subject follow-up visits). Finally, all institutions have a team available on-site to troubleshoot and

provide information technology and network support for study personnel, delivering technology consulting, installations, migrations, upgrades, procurement and continuing support services.

Primary Hypotheses:

For subjects with an acute uncomplicated abscess receiving I&D, the clinical cure rate of subjects treated with TMP/SMX will be superior to that of subjects treated with placebo (i.e., the lower bound of the 95% CI around the difference in cure rates will be ≥7.5%) in the PP population at the TOC.

The clinical cure rate of subjects with an infected wound treated with clindamycin will be superior to that of subjects treated with TMP/SMX (i.e., the lower bound of the 95% CI around the difference in cure rates will be ≥ 10%) in the PP population at the TOC.

For subjects with acute uncomplicated cellulitis, the clinical cure rate of subjects treated with cephalexin and TMP/SMX will be superior to that of subjects treated with cephalexin alone (i.e., the lower bound of the 95% CI around the difference in cure rates will be ≥ 10%) in the PP population at the TOC visit.

2.3 Potential Risks and Benefits

The risks and benefits for subjects enrolled in this trial are appropriately balanced. All of the study interventions (e.g., I&D of abscess with or without antibiotics) are consistent with common clinical practice. The drugs under study (e.g., cephalexin, TMP/SMX, clindamycin) have been in use for many years and are currently the most common antibiotics used for SSTI, and clinicians are aware of their AE profile.

2.3.1 Potential Risks

The risks to subjects enrolled in the studies will be comparable to those encountered by similar patients receiving standard care. These risks include complications of I&D, and adverse reactions (AEs) to medications (see below).

Subjects will be carefully screened to ensure that they meet study inclusion criteria, and do not have any exclusion criteria that would put them at unnecessary risk from study participation. Subjects will be followed at prescribed follow-up visits, as indicated, and will have access 24-7 to on-call study coordinators, investigators, and emergency care if questions should arise and if there is any suspicion of worsening.

Subjects will be carefully screened for progression to invasive infection or other possible AEs at each study visit, and will be provided with information to contact the study team for any possible AE that occurs between visits. Subjects with findings suggestive of possible invasive infection (including osteomyelitis, septic arthritis, necrotizing fasciitis, bacteremia, pneumonia, endocarditis, or meningitis) will have the appropriate investigations performed. AEs will be

reported to the medical monitor as described in Section 9, and appropriate medical treatments will be provided at the study site institutions, all of which are prepared to provide comprehensive inpatient and outpatient care. Soft tissue ultrasound is non-invasive, enhances diagnostic accuracy, and is standard treatment in the participating site EDs, and therefore, poses no study-associated additional risk.

The study will be done in full compliance with 45 CFR 46 (Protection of Human Subjects). Procedures for managing PHI will be included in the written ICF. Numerous safeguards will be put in place to ensure the confidentiality and integrity of all data, addressing both the human and physical elements of protecting subject confidentiality. These include data management staff training in human subjects' protection and the ethical conduct of human research, systematic backup for the centralized database, use of encrypted data on durable media, and utilization of encryption and role-based access mechanisms for remote access in compliance with industry best practices and consistent with security and privacy requirements of site IRBs. Any paper documentation containing PHI, such as informed consent documents, will be stored securely by study staff. Consistent standards will be maintained as data passes between the study sites and the central site.

Depending on the stratification arm and randomization, a subject may receive TMP/SMX, cephalexin, clindamycin, and/or placebo. From the review of the most recent PDR (2007), the following precautions, interactions, and AEs are reported with these medications:

TMP/SMX

Precautions:

AIDS, folate or G-6-PD deficiency, history of allergy, and rash. (Note: development of rash at any point after enrollment will result in withdrawal of the subject from the study).

Interactions:

May potentiate oral anticoagulants, hypoglycemics, phenytoin, and methotrexate, may be potentiated by indomethacin, and may increase risk of thrombocytopenia with diuretics (esp. thiazides).

Adverse reactions:

GI upset, blood dyscrasias (e.g., megaloblastic anemia), hemolysis, hepatic or renal toxicity, crystalluria, pancreatitis, photosensitivity, drug fever, rash (may be serious, e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis), lupus-like syndrome, peripheral neuritis, depression, convulsions, and ataxia.

Cephalexin:

Precautions:

Penicillin or other allergy, severe renal dysfunction, and GI disease (especially colitis).

Interactions:

Potentiates metformin, and is potentiated by probenecid.

Adverse reactions:

GI disturbances, dizziness, fatigue, headache, hypersensitivity reactions, and itch; rare: blood dyscrasias and elevated liver enzymes.

Clindamycin:

Precautions:

Allergy, GI disease (especially colitis)

Interactions:

May potentiate neuromuscular blocking agents, and may antagonize erythromycin and antiperistaltic agents

Adverse reactions:

Pseudomembranous colitis, diarrhea, GI upset, rash, anaphylaxis, jaundice, renal dysfunction, blood dyscrasias, and polyarthritis.

Note: Package inserts or supplemental drug manual for all study drugs (TMP/SMX, clindamycin, and cephalexin) will be made available to all investigators as part of the IB.

Complications resulting from I&D are uncommon. To prevent contaminating surrounding skin and spread of the infection, the skin over the abscess will be cleansed with 7.5% Povidone iodine and allowed to dry. The clinician will attempt to keep the area as clean as possible and devoid of unnecessary contamination. Pain associated with the procedure is minimized by using local anesthetics. Bleeding associated with I&D is usually minimal and stops spontaneously or with local pressure. In most cases, some scarring will result at the site of the incision.

2.3.2 Known Potential Benefits

All of the study interventions (e.g., I&D of abscess with or without antibiotics) are standard, and all of the drugs under study are currently used for these conditions. The definitive treatment of choice for a soft-tissue abscess is I&D. This procedure allows for rapid decompression of

purulent collections, which in turn results in a significant improvement in symptoms and a rapid resolution of infection. Study participants will receive study drugs free of charge. An additional benefit is that subjects enrolled in the study will have much more intensive follow-up than would be routinely provided for ED patients in these facilities, and therefore, any complication or treatment failure may be addressed more promptly.

3 OBJECTIVES

3.1 Study Objectives

The primary objectives for each type of SSTI studied are to compare the cure rates in the PP population:

1) for subjects with an acute uncomplicated cutaneous abscess receiving I&D, to determine whether the addition of TMP/SMX (4 SS pills, 80 mg/400 mg each, BID), an antibiotic with activity against CA-MRSA, is more clinically efficacious than I&D alone (4 placebo pills BID);

2) for subjects with an acute uncomplicated wound infection with any apparent drainage, to determine if clindamycin (300 mg, QID, with 3 placebo pills on alternating doses), an antibiotic with activity against CA-MRSA, MSSA, and streptococci is more clinically efficacious than TMP/SMX (4 SS pills, 80 mg/400 mg each, BID, with alternating 1 identical placebo pill, BID), an antibiotic with activity against CA-MRSA and MSSA; and

3) for subjects with acute uncomplicated cellulitis, to determine if cephalexin (500 mg, QID) and TMP/SMX (4 SS tables, 80mg/400mg each, BID), a regimen with activity against CA-MRSA, MSSA, and streptococci, is more clinically efficacious than cephalexin (500 mg, QID), an antibiotic with activity against MSSA and streptococci, and 4 placebo pills BID.

Secondary objectives provide additional means of assessment for the clinical efficacy of the employed interventions and resolution of the infection and include describing microbiological cure, change in the dimension of erythema, composite cure, surgical procedures, invasive and recurrent infections, infections in household contacts, and time to normal activity and until analgesics are no longer used at various times in the PP/mITT populations.

Furthermore a secondary analysis of the ITT population (specifically, mITT, i.e., all subjects receiving at least one dose of the study drug) will also be conducted to assess any potential role of post-randomization drop-out on the findings of the PP analysis.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

Primary Outcome measures: Clinical cure at the TOC in the PP population.

Clinical Cure Definition at TOC:

- No failure on any previous visit (on or after the OTV; see below)

- Absence of fever, and
- Resolution *or* minimal presence of all the following signs and symptoms from baseline based on clinician assessment:
  - Erythema
  - Swelling
  - Tenderness

Primary Outcome population:

PP population - Subjects who meet enrollment criteria, have none of the exclusion criteria, complete 100% of the first 48 hours of antimicrobial therapy, and have physical follow-up at the TOC. Subjects who have been determined to be a clinical failure at any time prior to TOC who took 100% of the first 48 hours of antimicrobial therapy but who do not have physical follow-up at the TOC will also be included in the PP population.

3.2.2 Secondary Outcome Measures

Secondary outcome measures include: rates of change of the dimensions of erythema, composite (antibiotic/surgical) clinical cure, microbiological cure, surgical procedures, and invasive and recurrent infections. Furthermore, infections in household contacts, medication AEs, and time to normal activity and until analgesics are no longer used in the PP/mITT populations will be assessed by patient response at follow-up visits.

Secondary outcome definitions:

Composite clinical outcome:

Cure - resolution of all symptoms/signs of infection, or improvement to such an extent that no additional antibiotic therapy and/or surgical procedures are necessary.

Failure – lack of resolution of all signs and symptoms of infection to such an extent that further antibiotic therapy and/or surgical procedures are necessary.

Microbiological Outcome:

Cure (Presumed eradication) - not deemed a clinical failure through TOC

Failure – a clinical failure at any time up to or through TOC and further characterized as follows:

Persistence - persistent growth of a pre-therapy pathogen.

New infection - growth of a new pathogen and eradication of initial pathogen.

Super-infection - growth of a new pathogen in addition to persistent growth of pre-therapy pathogen.

Unclassified –

- no specimen present for culture, or
- growth of a pathogen in subsequent culture specimen of subjects with cellulitis.
- growth of a pathogen in subsequent culture specimen of subjects with abscess or infected wound for whom initial culture specimens were negative or were not obtained.

Indeterminate – not meeting any one of the above microbiologic outcome criteria.

Definitions for mITT population and analysis:

mITT population - Subjects who take at least one dose of study medication and have any follow-up evaluation, i.e., either a physical or telephone follow-up evaluation at the time of the TOC.

The only outcome of interest in the mITT analysis is the final assessment at the TOC. This assessment will be made using the following criteria:

Cure:

- Absence of fever, and
- Resolution *or* minimal presence of all the following signs and symptoms:
  - Erythema
  - Swelling
  - Tenderness

Failure:

- Presence of fever (attributable to the infection being studied), or
- More than the minimal presence of any of:
  - Erythema
  - Swelling
  - Tenderness, or
- Inability to obtain a definitive assessment (e.g., subjects who cannot be seen in person or contacted by telephone*).

*Subjects who can only be contacted by telephone at the TOC will be classified as failures in the mITT analysis if they report having fever or any of the above symptoms.

4 STUDY DESIGN

This is a multi-center, randomized, double-blind, phase IIB clinical trial to evaluate oral off-patent antibiotics for outpatient treatment of subjects with any of the 3 main types of acute SSTI, i.e., abscesses, infected wounds, and cellulitis, with the primary objective of determining optimal antibiotic treatment. Subject enrollment will occur over 3 years at 5 US EDs.

Subjects will be 13 years of age and older with acute uncomplicated infections who provide informed consent. The study will be double-blinded with subjects randomized to identical treatments with antibiotics and/or placebo for 7 days. Infection classification, wound care, and outcome assessment will be standardized prior to study initiation. Subjects will be evaluated after 2-3 days of treatment (OTV; Days 3-4), and at 1-3 days after end-of-therapy (EOT; Days 8-10), 7-14 days after end-of-therapy (TOC; Days 14-21), and 6-8 weeks after end-of-therapy (EFV; Days 49-63). Therefore, subjects will participate for approximately 9 weeks.

Upon enrollment, subjects will be stratified by type of infection, and then randomized to various oral treatments. In order to minimize the chance of misclassification of the type of infection, all subjects will be evaluated by bedside soft tissue ultrasound, which has been demonstrated to be effective at identifying occult abscesses.[47]

Subjects with an acute uncomplicated cutaneous abscess receiving I&D will be treated with TMP/SMX or placebo to determine whether the addition of an antibiotic with activity against CA-MRSA is more clinically efficacious than I&D alone. Subjects with an acute uncomplicated wound infection will be treated with TMP/SMX or clindamycin to determine if clindamycin, an antibiotic with activity against CA-MRSA, MSSA, and streptococci is more clinically efficacious than TMP/SMX, an antibiotic with activity against CA-MRSA and MSSA. Subjects with acute uncomplicated cellulitis will be treated with cephalexin and TMP/SMX or cephalexin and placebo to determine if a regimen with the addition of TMP/SMX, an antibiotic with activity against CA-MRSA , is more clinically efficacious than cephalexin alone, an antibiotic with activity against MSSA and streptococci but not CA-MRSA.

The primary outcome will be clinical cure at the TOC in the PP population (subjects who meet enrollment criteria, have none of the exclusion criteria, complete 100% of the first 48 hours of antimicrobial therapy, and have physical follow-up at the TOC; subjects who have been determined to be a clinical failure at any time prior to the TOC who took 100% of the first 48 hours of antimicrobial therapy but who do not have physical follow-up at the TOC will also be included in the PP population.

Secondary endpoints will include microbiological cure, change in the dimension of erythema, composite cure, surgical procedures, invasive and recurrent infections, infections in household

contacts, and time to normal activity and until analgesics are no longer used at various times in the PP/mITT populations.

Upon enrollment, information on the site, extent, cause, previous history of SSTI and relevant medical/surgical therapy, underlying medical conditions, and infections in household contacts will be obtained. The dimensions of erythema will be measured. Drainage material will be collected for Gram stain, culture, and antimicrobial susceptibility testing prior to antibiotic treatment by standard cotton swabs after I&D of abscesses or from open lesions (i.e., infected wounds with drainage).

All clinicians and study personnel participating in the study will receive standardized training (using training modules containing specific procedures as well as video demonstrations created by the main site) prior to study commencement to insure their knowledge of the definitions of abscess, infected wound, and cellulitis, use of ultrasound to evaluate the SSTI, wound assessment and measurement, and outcomes.

Follow-up evaluations will be in person but, if not possible, will be by telephone. Evaluations will include clinical assessment of the infection and medication AEs. The rate of resolution of the infection will also be followed by measuring the dimensions of erythema. For telephone evaluations, the subject will be asked if swelling, tenderness, and the dimensions of erythema has decreased, increased or stayed the same. At the TOC, the subject will be examined for fever, erythema, swelling, and tenderness in order to categorize their condition at the time as a cure or failure. Compliance will be judged by pill counts of blister packets. In addition, a digital thermometer will be provided to all enrolled subjects to monitor occurrence of fever between follow-up visits. This information will be recorded by the subject in the memory aids provided at enrollment. Subjects will also keep a record of days to return to normal activity and until analgesics are no longer used, and days of missed work. If the memory aid is lost, an attempt will be made to recreate it through subject interview by asking subjects to recall the answers.

Subjects will be screened carefully at entry and follow-up visits for possible invasive infection looking for findings such as vital sign abnormalities and toxicity (sepsis), abnormal cardiac murmur (endocarditis), a red, swollen joint (septic arthritis), respiratory symptoms, abnormal lung exam, and new chest X-ray infiltrate (pneumonia), necrotic bone or abnormal X-ray (osteomyelitis), and a SSTI with severe pain, swelling, vascular insufficiency and/or radiographic soft tissue gas (necrotizing fasciitis). Investigators will follow subjects with invasive disease and serious AEs until resolution (or deemed stable/chronic).

The only laboratory test required at the time of pre-enrollment is a urine pregnancy test, which will be conducted at the site hospital laboratory. A pregnancy test will be performed in all women of childbearing potential who have not been surgically sterilized. No other laboratory or radiographic evaluation is required by the study, unless it is deemed necessary by the investigator. Since the AEs of the study drugs are well known, baseline studies and serial

testing to identify asymptomatic abnormalities of renal, hepatic, and hematopoietic function will not be conducted unless, based on the judgment of the investigator, they are clinically indicated.

At enrollment, for subjects in the infected wound and abscess arms, drainage material, if present, will be submitted for Gram stain, culture, and susceptibility testing (drainage material will be obtained prior to antibiotic treatment by standard cotton swabs of drainage material after I&D or from open lesions). MRSA and MSSA isolates that exhibit erythromycin resistance and clindamycin susceptibility will be further tested for inducible resistance to clindamycin using the D-test. Culture and susceptibility results will not be readily available to study investigators, study staff, and clinicians involved in evaluating subjects at follow-up visits. Research-related microbiology results will be restricted so that they are not easily available in hospital information systems (e.g., with general laboratory results) and can only be accessed by the study coordinators with special approval of the site investigators.

Clinical Failure Definitions:

At the OTV, EOT, and any visit up to the TOC, only failure will be designated as an outcome. Any subject outcome designated as a failure at any time before and including the TOC, will be categorized as a failure for the PP analysis. Criteria for failure will mandate rescue antibiotics and will vary at the OTV, EOT, and TOC, and will become progressively more stringent as to the requirements for improvement.

Measures of improvement will be assessed at each visit, starting with the OTV, including serial change in the dimensions of erythema, time to return to normal activities, and no need for pain medications. The border of erythema will be marked with a pen at the initial visit, and used for comparison for subsequent assessments. Training as to standardized technique to mark and measure the dimensions of erythema will be given prior to the study.

At OTV:

Failure:

- Presence of fever (attributable to the infection being studied), or
- Increase in either the length or width of erythema > 25%, or
- Both of the following show worsening based on clinician assessment:
  - Swelling
  - Tenderness

Subjects who are determined to be failure at OTV will be taken off the study regimen and receive rescue antibiotics as described below. Failure will be designated as an outcome by these criteria no sooner than the OTV but at any time after the OTV.

At EOT:

Failure:

- Presence of fever (attributable to the infection being studied), or
- Increase or no improvement in either the length or width of erythema from baseline, or
- None of the following show improvement from baseline based on clinician assessment:
  - Swelling
  - Tenderness

Subjects who are determined to be failure at EOT will receive rescue antibiotics as below.

Note: By completion of the full duration of study drug, 7 days, it is expected that the dimensions of erythema will have decreased and swelling and tenderness will have improved (and that fever will not be present). Therefore, failure at the EOT includes subjects who have no improvement in the dimensions of erythema or swelling and tenderness whereas at the OTV (and up to the EOT), an increase of > 25% in either the length or width of erythema or worsening of both swelling and tenderness are required to be designated as a failure. Failure will be designated as an outcome by these criteria no sooner than the EOT but at any time after the EOT.

At TOC:

- Failure at any previous visit (on or after the OTV; see below for failure definitions)
- Presence of fever (attributable to the infection being studied), or
- More than the minimal presence of any of:
  - Erythema
  - Swelling
  - Tenderness

Subjects who are determined to be failure at TOC will receive rescue antibiotics as described below. By the TOC, 7-14 days after completion of the study drug, it is expected that erythema, swelling, and tenderness (due to infection) be completely resolved or minimally present (and that fever will not be present). Therefore, failure at the TOC includes subjects with more than minimal erythema, swelling, or tenderness whereas at EOT, an increase or no improvement in the dimensions of erythema, or no improvement in both swelling and tenderness is required to be designated as a failure.

Algorithms for rescue therapy for clinical failures:

At any point that the investigator determines that a subject is a clinical failure, the infection will be evaluated by soft tissue ultrasound in order to classify the type of infection present at the time of failed therapy (i.e., abscess, infected wound, or cellulitis), drainage material, if present will be submitted for Gram stain, culture, and susceptibility testing, and the following algorithms for rescue therapy will be used in order to minimize unblinding of the study drug assignment (see MOP).

Abscess:

The study coordinator will obtain culture and susceptibility data from the enrollment visit and notify the site PI or surrogate. If the subject does not require admission for IV antibiotics and the organism(s) is/are susceptible to an alternate agent such as cephalexin, clindamycin, or doxycycline, or there is no growth, then the treatment will not be unblinded and the clinician can choose one of these agents. If the subject does not require hospital admission for parenteral antibiotics and there is no suitable oral regimen other than TMP/SMX (e.g., MRSA resistant to clindamycin and doxycycline), then the clinician may request that the treatment be unblinded so that TMP/SMX could be used for those who were randomized to placebo. If the subject had been randomized to TMP/SMX and failed that regimen, then the clinician may opt to admit for parenteral vancomycin, or may treat with an oral agent such as linezolid.

If the subject requires IV antibiotics, and the organism(s) is/are susceptible to vancomycin or linezolid, then the clinician evaluating the subject will not be unblinded and may choose one of these agents. If the subject requires further I&D it will be performed in the ED or in the hospital, as deemed appropriate by the treating clinician.

Infected Wound:

The study coordinator will obtain culture and susceptibility data from the enrollment visit and notify the site PI or surrogate. If the subject does not require admission for IV antibiotics and if the organism(s) is/are susceptible to an agent that is not part of the study protocol (i.e., neither TMP/SMX nor clindamycin) such as cephalexin or doxycycline, or there is no growth, then the treatment will not be unblinded and the clinician can choose one of these agents. If the subject does not require hospital admission for parenteral antibiotics, there is no suitable non-study protocol oral regimen, and the pathogen is susceptible to one or both of the study drugs (e.g., MRSA resistant to clindamycin and doxycycline but susceptible to TMP/SMX), then the treating clinician may request that the treatment be unblinded so that one of the study drugs could be used for those who had been randomized to the other agent.

If the subject requires admission to the hospital for IV antibiotics and the organism(s) is/are susceptible to vancomycin or linezolid then the clinician evaluating the subject will not be unblinded and may choose one of these agents.

Cellulitis:

Subjects who are a treatment failure but believed to be suitable for outpatient treatment with oral medication will be treated with clindamycin or doxycycline. These agents were selected because they are not part of the study arm regimens, and are likely to be active against streptococci and most MRSA and MSSA. If the subject has allergies to clindamycin or doxycycline then the treatment assignment will be unblinded and if a subject was initially treated with cephalexin, they will be further treated with TMP/SMX. If the subject was initially treated

with TMP/SMX and cephalexin, they will be further treated with either oral linezolid or admitted to receive IV vancomycin.

If a subject requires admission for IV antibiotics, then the clinician will not be unblinded and the subject will be treated with either vancomycin or linezolid.

If a newly formed abscess is found upon ultrasound evaluation, I&D will be performed either in the ED or in the hospital, as deemed appropriate by the treating clinician. If there is drainage material available for culture at the time the subject is deemed a treatment failure, then cultures will be obtained and further treatment guided by those results.

At any time during the study period - if the subject experiences diarrhea, a stool specimen will be submitted for *C. difficile* toxin assay.

Data will be collected on source documents and eCRFs developed by the study investigators in conjunction with EMMES. All sites will be equipped with a computer with Internet access and Internet Explorer 5.5 or higher to access the IDES, created by EMMES. This system will allow site investigators to access study materials, ICFs, and eCRFs on a secured website, and enter data. Within 72 hours of enrollment and each follow-up visit, data will be entered by study coordinators onto EMMES' secure web-based data management system. Source documents and data entry will be checked for consistency, accuracy, and completeness by study coordinators and site investigators (see QM plan). Source documents will be kept in the study staff office in locked file cabinets. Upon completion of subject enrollment, data will be rechecked for accuracy and completeness by the study coordinators and site investigators, with the assistance of EMMES, and sent to the study statistician for final data analyses. Patient identifiers will be removed from all data sets after data cleaning.

Study drug management will be accomplished by Fisher Bioservices (the DMID Regulatory Support Contractor), the site pharmacies, and the study coordinators. Fisher Bioservices will package, label and distribute study drugs to all sites. The site pharmacies will store, manage, dispense study drugs to study participants, and destroy unused study drugs (upon written approval from DMID), with the assistance of the study coordinators. The EMMES system described above will be used to manage subject enrollment, randomization, and treatment allocations, and to track withdrawals.

During the trial, PPD will conduct periodic monitoring visits to all sites to ensure that the protocol and GCP are being followed, in compliance with federal regulatory requirements and DMID policies and procedures. The monitors will review source documents to confirm that the data recorded on eCRFs are accurate. They will also meet periodically with laboratory and pharmacy personnel to ensure QC for laboratory analyses and to ensure that the protocol is followed.

To assure that study participants are not exposed to unnecessary or unreasonable risks and that the study is being conducted according to high scientific and ethical standards, an

independent DSMB will be appointed to monitor the clinical trial as per DMID guidelines. To avoid any appearance of conflict of interest, DSMB members will not be involved in the study under review, have no vested interest in its outcome, have no ties to the study investigators, and have no financial ties to any commercial concerns likely to be affected by the study's outcome. This committee will be informed of each subject's group assignment (A vs B), but will be blinded with respect to which group received which study drug. The DSMB will have three responsibilities:

1) Overseeing identification, enrollment, and randomization procedures to detect any evidence of bias;

2) Monitoring AEs (including invasive infection) to determine if they occur disproportionately (see Section 9.5) in one treatment group per study arm; and

3) Tracking key clinical outcomes to determine if one treatment group does significantly better than the other.

To assist the DSMB in its work, the EMMES statistician will monitor the progress of the study. The EMMES statistician will report to the DSMB on a regularly scheduled basis to be determined by the DSMB (see DSMB charter).

The following sample sizes are estimated to be necessary to evaluate each SSTI subgroup. For subjects with an abscess receiving I&D, to determine if the clinical cure rate for subjects treated with TMP/SMX is superior to that of subjects treated with placebo (i.e., $\geq$97.5% vs. 90%), it is necessary to enroll 502 evaluable subjects (590 subjects assuming 15% attrition). For subjects with an infected wound, to determine if the clinical cure rate for subjects treated with clindamycin is superior to that of subjects treated with TMP/SMX (i.e., >95% vs. 85%), it is necessary to enroll 426 evaluable subjects (500 subjects assuming 15%attrition). For subjects with cellulitis, to determine if the clinical cure rate for subjects treated with cephalexin and TMP/SMX is superior to that of subjects treated with cephalexin alone (i.e., >95% vs. 85%), it is necessary to enroll 426 evaluable subjects (500 subjects assuming 15%attrition). These enrollment goals approximate 1 subject per week for each infection type at each site, an achievable rate considering that approximately 10 subjects per week were enrolled at each site in the previous SSTI study by Moran and colleagues and the enrollment criteria are more inclusive in the present study.[1]

Interim analyses will be performed by the DSMB, with the assistance of the EMMES statistician, when 50% of subjects are enrolled and again when 75% of subjects have been enrolled per study arm. Interim analyses of safety information will involve the examination of the incidence, severity and type of AEs reported during the study (See Section 11.3). The DSMB and EMMES statistician will also monitor the progress of the study in order to ensure that sites are meeting target subject enrollment rates.

4.1 Sub-studies (if applicable)

Not Applicable.

5 STUDY ENROLLMENT AND WITHDRAWAL

The study's aim is to enroll a total of 1,590 subjects 13 years of age and older from US urban, academically-affiliated EDs (note that at the Kansas City, MO site, only subjects 18 years of age and older will be enrolled). It is anticipated that most subjects will have good baseline health, but subjects with most chronic medical conditions will not be excluded, other than those described in the exclusion criteria (see Section 5.2).

Women and minorities will be included in the study population. The study site EDs serve populations in which diverse racial and ethnic groups are well represented. The racial breakdown of subjects in our previous study of SSTI through the *EMERGE*ncy ID NET was: white non-Hispanic (28%), black non-Hispanic (44%), Hispanic (26%), other (2%). Patients who are institutionalized or prisoners will be excluded from enrollment. Women of childbearing potential will not be excluded, but will have a negative pregnancy test documented prior to enrollment because of concern about possible teratogenic effects of study medications.

Women of childbearing potential will be instructed to use adequate contraception, defined as hormonal contraception, intrauterine device, barrier methods (condom or vaginal diaphragm) with spermicide, or abstinence while taking the study drug. The pre-study pregnancy test (urine or serum pregnancy test) must be negative. Women who have been surgically sterilized or are at least two years postmenopausal may be enrolled and do not have to use birth control. Women whose method of birth control is hormonal are required to use additional barrier methods during therapy.

Children 13 years of age and older who weigh ≥ 40 kg will be included in the study population. Children less than 13 will be excluded because of difficulty providing blinded study medications in all pediatric dosing ranges. An estimated 10-15% of subjects are expected to be between the ages of 13 and 17 years, and, therefore, approximately 150-200 children are expected to be enrolled.

While the demographic diversity of the ED population that includes many at-risk persons is a strength of the program's representativeness, many ED patients have a relative lack of financial and social support resources to facilitate follow-up evaluations. All proposed EDs have experience with managing follow-up of these patients in clinical trials. It is anticipated that each of the 5 sites will be supported with a full-time study coordinator and on-call coverage to achieve 24 hours/7 days a week enrollment and adequate subject follow-up. To further facilitate follow-up, subjects will be provided reasonable funds for transportation to follow-up evaluations in accordance with local IRB guidelines and with prior approval.

ED staff and clinic doctors will be educated about the study objectives and procedures prior to subject enrollment. Posters will be placed in the ED doctors work room area indicating study

enrollment criteria. Treating clinicians will determine whether a patient meets the following eligibility criteria:

- Patients ages 13 years and over;
- Patients with an uncomplicated SSTI, i.e, abscess, infected wound, or cellulitis without drainage; and
- Patients that will be treated as outpatients.

If a patient is eligible for the study based on information regarding inclusion and exclusion criteria that is collected as part of standard medical care (and not obtained only for study purposes), then the clinician, following confirmation with the patients that they are interested to hear about the study, will contact the on-call study coordinator/investigator who will approach the subject and initiate the informed consent process (Section 14.3). After consent is obtained, the study coordinator/investigator will verify that the subject still meets all inclusion and exclusion criteria (including study-related criteria) prior to enrollment (assignment of a study ID) and randomization to a treatment regimen. Screen failures (i.e., consented subjects who do not meet inclusion or exclusion criteria) will be recorded in the regulatory binder.

5.1 Subject Inclusion Criteria

Subjects must meet all of the inclusion criteria in order to be eligible to participate in the study.

1) Adult or child 13 years of age and older (who weighs ≥ 40 kg);

2) Have a SSTI with all three local findings of erythema (> 2 cm across the lesion or from a discrete wound edge), tenderness, and swelling. Fever, leukocytosis, and lymphangitis will be noted, but are not enrollment criteria. SSTI with these local findings will be further categorized and defined as one of:

a. Abscess - a fluctuant and/or indurated lesion, or findings of a fluid-filled cavity on soft tissue ultrasound evaluation that, when opened reveals purulent material, receiving I&D and having a minimum diameter (along any axis) of at least 2 cm (measured from the borders of induration, if a fluctuant lesion, or borders of the abscess cavity on ultrasound, if not fluctuant)

b. Infected Wound - a wound (defined as any apparent break in the skin) with any apparent drainage limited in depth to only involving skin and subcutaneous tissue, including sutured cutaneous wounds not involving intra-peritoneal surgery, and

c. Cellulitis - an area of erythema without the presence of a wound with drainage or abscess;

Cellulitis associated with an abscess will be categorized as an abscess. Cellulitis associated with an infected wound will be classified as an infected wound. Patients with cellulitis and an abscess less than 2 cm will be excluded.

3) Have the infected lesion for 7 days or less duration;

4) Are to receive outpatient treatment;

5) Express willingness and ability to be contacted and return for re-evaluation according to the study protocol;

6) Provide written informed consent (and for subjects ages 13-17, consent from their guardian and assent);

7) Negative pregnancy test for subjects who are women of childbearing potential.

5.2 Subject Exclusion Criteria

Subjects must not have any exclusion criteria:

1) Severe allergy or reaction to study drug or drugs similar to the study drug relevant to whichever study arm the subject would be assigned to (e.g., patients with severe or life-threatening penicillin allergies, allergy to any cephalosporin, clindamycin, or sulfonamides, or any other drug containing sulfur such as thiazides, furosemide, and oral sulfonylureas);

2) Concomitant treatment with coumadin, phenytoin, or methotrexate, or suspected G-6-PD or folic acid deficiency;

3) Expected inability to swallow or absorb the study drug (assessed by patient history);

4) Pregnancy, nursing, or expectation of becoming pregnant during the treatment period;

5) Perirectal (within 5 cm of anus), perineal non-skin lesions. (i.e., mucosal), or paronychial location of infection. Scrotal and labial abscesses will not be excluded.

6) An infection due to a mammalian bite;

7) Treatment with a study drug relevant to their infection type, or another systemic antibiotic in the previous 48 hours unless associated with treatment failure which is defined as a patient who has been on prior (non study drug) antibiotics for at least 72 hours and failed.

8) Expected concurrent treatment with a topical antibiotic or another systemic antibiotic;

9) Immunodeficiency (e.g., absolute neutrophil count <500/mm^3, chronic immunosuppressive drugs, active chemotherapy, or known AIDS or AIDS-defining illness within the last year; assessed by patient history);

10) Burn or active chronic skin condition (e.g., including rash or eczema) related to the SSTI;

11) Infection related to percutaneous prosthetic device (e.g., intravenous line), excepting sutures associated with qualifying infected wounds which will be removed upon enrollment;

12) Infection for which prior cultures reveal in vitro resistance of a pathogen to a study drug in the previous month;

13) Known or suspected osteomyelitis or septic arthritis;

14) Infection related to diabetic foot, decubitus, or ischemic ulcer;

15) Known severe renal insufficiency (creatinine clearance < 50 mL/min) calculated by measurement of serum creatinine if patient provides this history or based on past studies);

16) Prior enrollment in this study within 12 weeks;

17) Another active infection or more than one active SSTI site;

18) Presence of an abscess that has completely drained, either spontaneously or by a healthcare provider prior to enrollment;

19) An infected wound or cellulitis that has been surgically explored and does not reveal an abscess;

20) Currently incarcerated in a detention facility;

21) For patients with an infected wound, history of *C. difficile* infection, pseudomembranous colitis, or active diarrhea;

22) For patients with an infected wound, severe liver disease based on patient history;

23) An IV drug user in the last month with current presence of fever;

24) Current residence in a nursing home or other long term care facility;

25) Use of other investigational drug or vaccine;

26) For patients with an abscess, cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis is reasonable including patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair, history of

previous infective endocarditis, congenital heart disease (excluding mitral valve prolapse), and history of cardiac transplantation recipients who develop cardiac valvulopathy.

5.3 Treatment Assignment Procedures

This is a Phase IIB randomized, double-blinded study with 3 study arms. All eligible subjects will be stratified by the type of infection and then randomized to various 7-day treatments using a centralized randomization system in the ratio of 1:1.

- Subjects with an acute uncomplicated cutaneous abscess will be randomized to receive either TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day) or 4 placebo pills (twice per day).

- Subjects with an acute uncomplicated wound infection will be randomized to receive TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day, with alternating 1 identical placebo pill, twice per day) or clindamycin (300 mg, four times per day, with 3 placebo pills on alternating doses).

- Subjects with acute uncomplicated cellulitis will be randomized to receive cephalexin (500 mg, four times per day) and TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day) or cephalexin (500 mg, four times per day) and placebo (4 pills, twice per day).

The randomization schedule is generated, secured, distributed, and stored by EMMES in accordance with key parameters specified by their statistician. The system will be accessible on-line to the study coordinators. The subject is expected to begin study treatment on the day of randomization.

5.3.1 Randomization Procedures

Enrollment will be done online using the enrollment module created by EMMES (i.e., Internet Data Entry System (IDES)). The randomization code will be prepared by statisticians at EMMES and included in the enrollment module for the trial, stratified by type of infection. The randomization code will link to the treatment assignment. IDES will assign each subject a randomization code after demographic and eligibility data have been entered into the system. A designated individual (e.g., pharmacist) at each site will be provided with a code list for emergency unblinding purposes, which will be kept in a secure place.

Instructions for use of the enrollment module are included in the IDES User's Guide. Manual back-up procedures and instructions are provided for use in the event that the site temporarily loses access to the internet or the online enrollment system is unavailable.

Screening records will be kept to document the reason why an individual was screened but failed trial entry criteria.

The subjects, the site study personnel, data entry personnel at the sites, and laboratory personnel will be blinded to treatment assignment. The DSMB may receive data in aggregate and presented by treatment group, but without the treatment group (or dose level) identified.

The DSMB may be unblinded to individual study treatment assignments, as needed, to adequately assess safety issues.

The site investigator and study coordinators will not be provided with the code list to break the blind. Under normal study circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. The blind should be broken only when the specific conditions listed in section 5.3.2 have been met.

5.3.2 Masking Procedures

The treatment arms will be masked to both the subject and the study staff and maintained according to standard practices. Fisher BioServices will package all study drugs and ensure they are already masked according to applicable regulatory requirements.
Culture and susceptibility results will not be available to clinicians involved in evaluating subjects at follow-up visits. Research-related microbiology results will be restricted so that they are not easily available in hospital information systems (e.g., with general laboratory results) and can only be accessed with special approval of the study coordinator/site investigators. The blind will not be broken if microbiological testing shows resistance to one of the antibiotics being studied (see Section 4). If a site is discontinued, subjects enrolled will continue with care and be followed and the blind will not be broken.

In general, for cases requiring emergency treatment, the treating clinician will contact the investigator/study coordinator-on-call, who will contact the designated individual with the code list for emergency unblinding purposes to break the blind. The medical monitor will be informed as soon as possible. Individual code breaks by the investigator/study coordinator-on-call will result in withdrawal of the subject from the study. For cases not requiring emergency treatment, the investigator will contact the medical monitor and state the reason(s) for unblinding. If the medical monitor approves unblinding, the investigator/study coordinator on call will contact the designated individual with the code list for emergency unblinding purposes to break the blind. In either case, the date, time, and reason for the unblinding will be documented in the appropriate section of the source document and eCRF.

The blind will be broken only if the following situations develop:

1) Specific emergency treatment (e.g., subject is experiencing Grade 3 or 4 AEs related to the study drug) would be dictated by knowing the treatment status of the subject.

2) At any point that the treating clinician determines that a subject is a clinical failure and there is no suitable alternative treatment available based on culture and susceptibility results such that the clinician requires knowledge of prior treatment assignment to provide appropriate and safe rescue therapy (see Section 4).

3) Subjects who become pregnant during treatment. If their study treatment included TMP/SMX, the subject will be informed to discontinue this medication immediately.

4) At any point, if the subject develops a concomitant infection that requires therapy with antibacterial agents and the clinician believes knowledge of treatment assignment for assigning therapy is necessary.

5) In the event that the study is discontinued, subjects who are already enrolled in the study and have not completed all protocol procedures will be notified and asked to return to the ED for re-evaluation. The blind will be broken and the treating clinician will make a decision of appropriate continued therapy for the subject according to standard of care. If a site is discontinued, subjects enrolled will continue with care and be followed and the blind will not be broken.

5.3.3 Reasons for Withdrawal

A study subject will be withdrawn (but continue follow-up) for the following reasons:

- Any clinical AE of a certain nature (e.g., development of a possible allergic rash at any point after enrollment), or sufficient severity (e.g., severe diarrhea), laboratory abnormality (if obtained, e.g. elevated bilirubin confirming suspected jaundice), concurrent illness, or other medical condition or situation occurs such that based on the determination of the treating clinician continued treatment with the study drug would not be in the best interest of the subject.
- Withdrawal by the PI for noncompliance with the protocol or when the PI deems it necessary or in the subject's best interest. (See also the informed consent form)
- Development of any exclusion criteria.
- Subjects are free to withdraw from participating in the study at any time upon request.

5.3.4 Handling of Withdrawals

If the subject is taken off of study medication due to adverse reaction (e.g., rash), then it is not necessary to routinely unblind the treatment. Subjects with SAEs related to the relevant study drug and who require emergency treatment will have the study medication unblinded so that treating clinicians will know what they had received. For subjects with less severe AEs, the study medication will be unblinded only if the clinician believes it would be important to immediately know the assigned treatment e.g,, because treatment of the adverse event requires it, or if subject has contraindications to alternative treatments that were not part of the study regimens. Otherwise, the subject's treatment will remain blinded until after evaluation at the TOC, at which point a letter will be mailed to the subject from the site pharmacist to inform the subject as to which treatment they received that is suspected of having caused the AE. The investigator will not be informed of the treatment assignment.

Abscess:

If the subject is taken off study medication due to an adverse reaction (e.g., rash), then the clinician can determine whether the subject requires further antimicrobial therapy at the time of study withdrawal. If the subject is not felt to require further treatment, then the study drug will be stopped, no further antibiotic will be prescribed, and the subject will continue follow-up visits as usual. Those subjects who are eligible to be included in the PP analysis (i.e., received 100% of at least the first 48 hours of treatment) can still be included in that analysis. Subjects who are felt to require further antibiotic treatment will be treated with clindamycin to complete 7 days. This agent was selected because it is not part of the study regimen, and is likely to be active against the likely pathogens. These subjects will not be evaluable in the PP analysis, but all will be included in the mITT analysis. We believe it is reasonable to allow subjects in the abscess arm to have treatment stopped without requiring further antibiotic treatment because half of them will be randomized to placebo, and we expect that many subjects with an abscess will be improved by the time study drug is stopped.

Infected Wound:

If the subject is taken off study medication due to an adverse reaction (e.g., rash), then the subject will be treated with doxycycline to complete 7 days. This agent was selected because it is not part of the study regimen, and is likely to be active against the likely pathogens. If there is a contraindication to doxycycline, then the investigator can request that the treatment be unblinded to choose the alternate study regimen. Subjects treated with antibiotics other than the assigned study regimen will not be evaluable in the PP analysis, but all will be included in the mITT analysis.

Cellulitis:

If the subject is taken off study medication due to an adverse reaction (e.g., rash), then the subject will be treated with clindamycin to complete 7 days. This agent was selected because it is not part of the study regimen, and is likely to be active against the likely pathogens. Subjects treated with antibiotics other than the assigned study regimen will not be evaluable in the PP analysis, but all will be included in the mITT analysis.

Subjects will be screened for worsening of infection including progression to invasive infection and other possible AEs at each study visit, and will be provided with information to contact the study team for any possible AE that occurs between visits. Subjects with findings suggestive of possible invasive infection (including osteomyelitis, septic arthritis, necrotizing fasciitis, bacteremia, pneumonia, endocarditis, or meningitis) will undergo appropriate medical investigations. AEs will be reported to the medical monitor, and appropriate medical treatments will be provided at the study site institutions, all of which are prepared to provide comprehensive inpatient and outpatient care.

If a subject elects to withdraw from the study, they will be asked about the reason for withdrawal (particularly AEs) and requested to continue scheduled evaluations, complete the EFV and will be given appropriate care under medical supervision. If the subject experiences and requests to be withdrawn from the study due to an AE, they will be given appropriate medical treatment until the symptoms of any AE resolve or the subject's condition becomes stable. If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations will be performed and no additional data collected. The investigators may retain and continue to use data collected before such withdrawal of consent.

Participants who discontinue the study early will not be replaced.

5.3.5 Termination of Study

The medical monitor is responsible for ongoing monitoring of reports of SAEs submitted by the sites in real time to ensure GCP and to quickly identify safety concerns. The investigators will prepare regular reports concerning SAEs (not segregated by treatment group) for submission to the Co-PIs, DMID, and the DSMB. Such reports will be submitted on a regular basis, to be determined by the DSMB (e.g., real time, monthly, or quarterly). In the event of unexpected SAEs or an unduly high rate of SAEs, the medical monitor will promptly contact the Co-PIs and the DSMB. The DSMB may convene a meeting or teleconference to consider the concerns and plan appropriate action. The final authority to continue or terminate the study is vested with DMID. If the study is halted, ORA will notify the FDA.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

Package inserts or the supplemental drug manual for all study drugs (TMP/SMX, clindamycin, and cephalexin) will be made available to all investigators as part of the IB.

6.1.1 Acquisition

All study drugs will be acquired through Fisher BioServices, i.e., they will purchase all study drugs from an FDA approved manufacturer. Fisher Bioservices will perform the encapsulation, packaging and labeling of study drug according to applicable regulatory requirements. Study drug will be shipped by Fisher Bioservices to the sites (e.g., pharmacies), where they will be stored in a location specific to this study, until dispensed to an enrolled subject.

6.1.2 Formulation, Packaging, and Labeling

All study drugs, including TMP/SMX, clindamycin, cephalexin, and placebo will be administered as capsules in pre-labeled, pre-numbered blister packs. Labeling of study supplies will be in compliance with applicable regulatory requirements. Fisher Bioservices will formulate all capsules (ensuring appropriate blinding), package capsules in blister packs, and label packs appropriately to indicate which capsules should be taken and when. Labels will be affixed to the packs so the study coordinator can write in the subject's name, date of birth, randomization number and the patID, and attach a label with the study coordinators and site investigators name and contact phone number.

- For the abscess arm, TMP/SMX or placebo will be provided in a blister pack with 56 identical capsules for treatment for 7 days.
- For the infected wound arm, TMP/SMX/placebo or clindamycin/placebo will be provided in a blister pack with 70 identical capsules for treatment for 7 days.
- For the acute cellulitis arm, cephalexin and TMP/SMX or cephalexin and placebo will be provided in a blister pack with 84 identical capsules for treatment for 7 days.

6.1.3 Product Storage and Stability

All study drugs will be kept in a non-refrigerated locked facility, stored at cool ambient temperatures (59-86 °F or 15-30 °C), away from direct sunlight and moisture, and accessible

only to authorized study personnel. All drug supplies will be stored in accordance with the manufacturers' instructions. Study drugs will be stored separately from normal hospital/practice stocks. Until dispensed to the subjects, the study medication will be stored in a securely locked area and only accessible to authorized study personnel.

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

All study drugs will be encapsulated with the appropriate dosing and then packaged in non-specific blister packs that are pre-labeled by consecutive days (1-7) indicating when each dose/capsule should be taken. Study drugs will be assigned to subjects with the help of a web tele-randomization system provided by EMMES.

Fisher Bioservices will perform the labeling of study supplies according to applicable regulatory requirements. They will provide the investigators with sufficient amounts of the study medication. The investigators will administer/dispense the study medication only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the study medication that is assigned to him/her. All dispensing will be documented in the eCRF and other study drug record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Once enrolled, subjects will be stratified by infection type and treated with the appropriate oral treatment.

- Subjects with an acute uncomplicated cutaneous abscess will receive either TMP/SMX (4 SS pills, 80 mg/160 mg each, twice per day) or 4 placebo pills (twice per day). Subjects will be encouraged to take these treatments approximately every 12 hours.

Daily Dosing Scheme (12 hours between doses):

	Dose 1	Dose 2
Treatment group	4 SS TMP/SMX	4 SS TMP/SMX
Placebo group	4 Placebo pills	4 Placebo pills

- Subjects with an acute wound infection will receive TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day, with alternating 1 identical placebo pill, twice per day) or clindamycin (300 mg, four times per day, with 3 placebo pills on alternating doses). Subjects will be encouraged to take these treatments approximately every 6 hours.

Daily Dosing Scheme (6 hours between doses):

	Dose 1	Dose 2	Dose 3	Dose 4
Treatment A	4 SS TMP/SMX	1 Placebo pill	4 SS TMP/SMX	1 Placebo Pill
Treatment B	1 300mg Clindamycin pill 3 placebo pills	1 300mg Clindamycin pill	1 300mg Clindamycin pill 3 placebo pills	1 300mg Clindamycin pill

- Subjects with acute cellulitis will receive cephalexin (500 mg, four times per day) and TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day) or cephalexin (500 mg, four times per day) and 4 placebo pills (twice per day). Subjects will be encouraged to take these treatments approximately every 6 hours.

Daily Dosing Scheme (6 hours between doses):

	Dose 1	Dose 2	Dose 3	Dose 4
Treatment A	1 500mg cephalexin pill 4 SS TMP/SMX	1 500 mg cephalexin pill	1 500 mg cephalexin pill 4 SS TMP/SMX	1 500 mg cephalexin pill
Treatment B	1 500mg cephalexin pill 4 Placebo pills	1 500mg cephalexin pill	1 500mg cephalexin pill 4 Placebo pills	1 500mg cephalexin pill

Subjects will receive the first dose of study drug in the ED. Subjects are expected to continue study medication for 7 days.

6.3 Modification of Study Intervention/Investigational Product for a Participant

See Section 5.3.2

6.4 Accountability Procedures for the Study Intervention/Investigational Product(s)

The investigator will ensure that deliveries of study products from Fisher Bioservices are correctly received by a member of the study staff (e.g., a study coordinator or pharmacist), that all receipts are recorded in writing and that the products are stored in a secure area under recommended storage conditions. The staff member who receives the study products will acknowledge receipt of the products to Fisher Bioservices. It is the responsibility of the investigator to ensure that the integrity of the study product not be jeopardized prior to dispensing. Each individual subject pack will be dispensed as provided by Fisher Bioservices with no further repackaging done at the site.

The study coordinators will maintain adequate records documenting receipt, use, loss or other disposition of the study product. EMMES will supply drug accountability forms. The individual who dispensed the drug will sign the forms. Fisher Bioservices will determine the frequency and amount of study drug shipped to each site. No study drugs will be shipped until the IND is active, and copies of site IRB approvals are sent to Fisher Bioservices. The investigator is responsible for the onsite drug accountability, including inventory tracking (receipt and dispensing).

At the end of the trial, DMID will provide instructions as to the disposition of any unused study drug. Unused study drugs will be recorded by the investigator and verified through monitoring prior to destruction on site.

6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

The investigator will maintain records documenting all trial medication administered to each subject for the entire study period. Subjects will be asked to complete a memory aid and bring their blister packs at the OTV and EOT. The memory aid will be used to record daily study medication taken, concomitant medications (e.g., pain medication), days to normal activity, and temperature (using thermometer provided). The study coordinator/investigator will document any missed doses of study medication by counting any pills remaining in blister packs and provide counseling per study sites' routine procedures to promote compliance with study medication. Blister packs will be collected from the subjects at the EOT if in person (Section 7.3).

6.6 Concomitant Medications/Treatments

Any medication that the subject takes other than the study drugs specified in the protocol is considered concomitant medication. All concomitant medications will be recorded in the subject's medical record and on the eCRFs from enrollment through the EFV. Subjects will be provided with a list of medications to avoid while taking the study drugs. If the subject takes an unapproved medication this will be recorded in a source document and the eCRF, and the subject will be advised to discontinue the unapproved medication.

At the Screening/Baseline visit, a patient will be excluded from the study if he/she is on a concomitant treatment with topical/systemic antibiotics, coumadin, phenytoin, or methotrexate. A patient will also be excluded from the study if he/she was treated with another systemic antibiotic in the previous 48 hours unless associated with treatment failure of the SSTI (Section 5.2).

7 STUDY SCHEDULE

Subjects will be evaluated upon enrollment, at 2-3 days after enrollment (OTV; Days 3-4), at 1-3 days after the end-of-therapy (EOT; Days 8-10), and at 7-14 days after the end-of-therapy (TOC; Days 14-21), and at 6-8 weeks after the end-of-therapy (EFV; Days 49-63).

Subjects will be carefully screened at entry and follow-up visits for possible invasive infection looking for findings such as vital sign abnormalities and toxicity (sepsis), abnormal cardiac murmur (endocarditis), a red, swollen joint (septic arthritis), respiratory symptoms, abnormal lung exam, and new chest X-ray infiltrate (pneumonia), necrotic bone or abnormal X-ray (osteomyelitis), and a SSTI with severe pain, swelling, vascular insufficiency and/or radiographic soft tissue gas (necrotizing fasciitis). If at any point after consent and enrollment the investigator determines that a subject is a clinical failure (see Section 3.2.1), the algorithm for assigning rescue therapy described in Section 4 will be used in order to modify therapy. Investigators will follow subjects with invasive disease and serious medication AEs until resolution.

7.1 Screening Visit

Screening and enrollment/baseline visit will be performed at the same visit.

The following screening procedures will be performed prior to enrollment (assignment of study ID) and randomization:

- Obtain written informed consent (must be signed prior to the initiation of any study related activities)
- Verify conformance with inclusion and exclusion criteria. Note that written informed consent will be obtained prior to assessment for conformance with inclusion and exclusion criteria that are strictly study-related and not collected during standard medical practice.
- Evaluate by bedside soft tissue ultrasound to verify infection type and size
- Obtain urine pregnancy test for all women of childbearing potential who have not been surgically sterilized

7.2 Enrollment/Baseline Visit

- Inquire about history of skin infections in household members (e.g., similar skin infection in a family member)

- Record concomitant medications and pre-existing conditions
- Record results of history and physical examination (e.g., vital signs (blood pressure, pulse, respiratory rate, and body temperature*)* medication allergies, previous or concurrent treatments, pre-existing medical conditions, etc.; see Section 8.1).
- Record signs and symptoms of infection (e.g., fever, swelling, tenderness)
- Assess the wound and describe the infection site (e.g., location, size, extent, cause)
- Measure and mark the dimensions of erythema
- For abscess or infected wound: obtain drainage material for Gram stain, culture, and antimicrobial susceptibility testing prior to antibiotic treatment. The drainage material may be collected by standard cotton swabs of drainage material after I&D or from open lesions
- For abscess: measure and record the length of incision made for I&D
- Provide memory aid and thermometer and educate subject as to its use
- Start study medication

7.3 Follow-up

Follow-up evaluations will be in person but, if not possible, will be by telephone. They will occur 2-3 days after enrollment (OTV; Days 3-4), at 1-3 days after the end-of-therapy (EOT; Days 8-10), and at 7-14 days after the end-of-therapy (TOC; Days 14-21).

- Clinical assessment of the infection
- Measure the dimensions of erythema
- Collect information on AEs
- Medication compliance will be judged by pill counts of blister packets (at OTV and EOT)
- Record information on subject memory aid onto a source document
- At EOT, collect unused study medication if in person
- If diarrhea is present and visit is in-person, send stool specimen for *C. difficile* toxin assay

- If subject is a clinical failure, evaluate by soft tissue ultrasound and follow algorithm for rescue treatment (Section 4)

- If subject is a clinical failure, drainage material is present, and the visit is in person, obtain drainage material for Gram stain, culture and antimicrobial susceptibility testing

- If subject suspects she became pregnant since last visit, perform pregnancy test

Subjects will be encouraged to return to the ED for all follow-up visits. However, if any of the above follow-up visits are conducted by telephone, the study coordinator or investigator will obtain the following information using a standardized telephone script and record it on a source document. The subject will be asked 1) to assess their infection (e.g., presence of fever, change in the dimensions of erythema, and degree of tenderness, swelling, and drainage); 2) if they experienced any AEs; 3) the number of pills they took each day; 4) information recorded on their memory aid (e.g., days to normal activity, etc.); and 5) if they took any other medication. They will also be asked to return to the ED for their next visit (if applicable). If contact with subject occurs after Day 7, they will be asked to come back to the ED to return any unused study medication. If they cannot return to the ED, a prepaid envelope will be sent to them to mail unused study medication to the study coordinator.

Outcome will not be assessed over the phone. If the subject is considered to be a possible failure due to their telephone responses, they will be asked to return to the ED immediately for clinician evaluation. It will be noted in the eCRF that the information was collected by telephone interview. During data analysis, data collected by telephone will be compared to data collected by in-person evaluation to detect any potential bias or important differences. Note that the TOC must be in-person for a subject to be included in the PP analysis.

7.4 Final Study Visit

Final study visit will be in person but, if not possible, will be by telephone at 6-8 weeks after the end-of-therapy (EFV; Days 49-63).

- Clinical assessment of the infection

- Collect information on AEs

- If present and in person, obtain drainage material for Gram stain, culture and antimicrobial susceptibility testing.

- If diarrhea is present, send stool specimen for *C. difficile* toxin assay

If this visit is conducted by telephone, the same procedures described in Section 7.3 will be employed.

7.5 Early Termination Visit

The reasons for early termination will be noted in the eCRF. If possible, subject will continue follow up through EFV. If subject participation is terminated due to an AE, then subjects will be followed until their symptoms resolve or are deemed stable/chronic. If the subject is unable to be evaluated in person, they will be contacted by telephone to obtain relevant information.

7.6 Unscheduled Visit

Unscheduled visits will be recorded in the eCRF, including the date and reason for the visit. If the reason for the visit is because subject is unsure of follow-up dates, they will be evaluated by a clinician and re-educated about the follow-up schedule by the study coordinator. If the reason for the unscheduled visit is due to the subject experiencing worsening symptoms, the blind will not be broken and subject will receive rescue therapy as described in Section 4. If the subject is experiencing any Grade 1 or Grade 2 AEs, the blind will not be broken and subject will receive rescue therapy as described in Section 5.3.4. If the subject experiences any SAE related to the study drugs or interventions and requires emergency therapy, the blind will be broken and the subject withdrawn from the study. The site investigator will make sure the subject receives appropriate care and follow-up according to standard of care until their symptoms resolve or are deemed stable/chronic. The investigator will also contact the medical monitor and will state the relationship of the SAE to the study drug. The date, time, and reason for the unblinding will be documented in the appropriate section of the eCRF.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

- Demographics

  - Demographics will include the subject's gender, date of birth, and racial/ethnic origin (and will be entered on the eCRF).

- Medical/Surgical History

  - A medical and surgical history will be present in the source documents. The medical history should include a thorough review of body systems, including but not limited to cardiovascular disease, metabolic disease, peripheral vascular disease, allergies, and drug reactions. The review will include all medical and surgical history that is significant in relation to the current infection, including medication allergies and reactions.

- Concomitant Medications/Concomitant Antibiotics/Non-Drug Treatments/Procedures

  - All previous antibiotics (systemic or topical within 7 days prior to study entry) and current antibiotics will be recorded. Additionally all medications taken during the study will be recorded. At all visits, any changes in the concomitant medications since the last visit will be recorded in the eCRF and source documentation. Concomitant medications include prescription medications and nonprescription medications. Documentation of concomitant medications will include the agent, the reason for taking the medication, and actual or estimated start and stop dates, or if the medication is ongoing. Particular attention will be made regarding the receipt of any exclusionary or prohibited medications.

  - All medical or surgical procedures (e.g., I&D and/or debridement) that are related to the current infection under study or significant to the health of the subject, performed within the last 7 days prior to study entry and during the study period will be recorded. The information will include the name of the procedure, reason for the procedure and the start and end dates of procedure or if the procedure is ongoing. In addition, if a surgical procedure led to the infection under study, it will be recorded and information included as above even if it was performed greater than 7 days prior to study entry.

  - Presence of symptoms and use of analgesic medications as recorded in subject memory aids.

- Pre-existing conditions.

- Physical examination: A complete physical examination will be performed at the Screening/Baseline visit.

- Vital signs: Temperature, respiratory rate, heart rate (pulse) and resting blood pressure (after 5 minute rest) will be recorded at all visits while on study. Weight will be obtained at the Screening/Baseline visit only.

- Signs and symptoms of infection: Type of drainage or exudates, erythema, swelling, and tenderness to palpation or pain at site will be recorded at each visit.

- Infection site/wound assessment: The following assessments will be collected:

  - Anatomic location at screening/baseline visit.

  - If applicable at all visits, measurements of infection site/wound will include the dimensions of erythema. For abscess arm: depth of the infection site will be measured and then characterized as limited to skin/subcutaneous tissue or involving deep fascia/muscle. For infected wound arm: depth of infection site will be characterized as limited to skin, involving subcutaneous tissue, or involving deep fascia/muscle.

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

All clinical laboratory evaluations will be performed locally at each site's laboratory, which all meet Federal safety regulations and guidelines as defined by College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) licensing. Bacteriology performed by the local lab includes isolation, susceptibility, and Gram staining of the infection site/wound culture. Before starting the study, the investigator will supply DMID with a list of the normal ranges, units of measurement, and current laboratory certification. The investigator will supply DMID with all updates to reference ranges and laboratory certification occurring during the study.

The following laboratory tests will be performed at the specified protocol visits (see Appendix A).

- Infection site/wound culture: Gram stain and culture (aerobic and anaerobic) of drainage material from the infection site will be performed at the Screening/Baseline visit. The infection site/wound culture should be repeated only if 1) the subject is deemed a clinical failure, drainage material is available and evaluation is in-person at

the OTV, EOT or TOC; or 2) if the subject develops an infection and there is drainage material available and evaluation is in person at EFV.

Acceptable methods for specimen collection include:

Abscess

- Deep swab of the abscess cavity after performing the I&D

Infected wound

- Deep swab of the wound cavity

- If applicable, pregnancy test will be done in all women of childbearing potential who have not been surgically sterilized prior to study intervention and results must be available prior to administration of study product.

- At any time after the initial dose of study medication, if the subject experiences diarrhea, a stool specimen will be sent for *C. difficile* toxin assay (Toxins A and B). Patients with persistent diarrhea will be retested if the initial assay is negative.

Since the AEs of the study drugs are well known, baseline studies and serial testing to identify asymptomatic abnormalities of renal, hepatic, and hematopoietic function will not be conducted unless, based on the judgment of the investigator, they are clinically indicated.

8.2.2 Special Assays or Procedures

Investigators will receive standardized training in ultrasound methods prior to study initiation. Prior to ultrasound evaluation, lesions with open wounds will have specimens taken of any drainage for culture and susceptibility testing. The involved skin will be wiped free of debris and cleaned with 70% isopropyl alcohol. Ultrasound gel will then be applied to the skin. The underlying involved soft tissue will then be scanned using a high-frequency, high-resolution (5-10 MHz) transducer probe, which, if there is drainage material, will be covered with ultrasound gel and placed in a clean protective sheath. A presumed abscess based on soft tissue ultrasound will be defined as the finding of a defined fluid pocket. Subjects with this finding on ultrasound, and those subjects without these findings for whom the clinician suspects the presence of an abscess based on physical examination, will have incision and exploration. Findings of a subcutaneous collection of purulent material on direct examination by incision and exploration will define the existence of an abscess. Following the procedure, the ultrasound probe will be cleaned with a dry towel and disinfected.

I&D is a commonly performed ED procedure to drain cutaneous abscesses. The procedure is described in standard emergency medicine textbooks.[48,49] In order to establish a uniform

approach, all investigators will receive standardized training on proper technique to drain abscesses.

The initial step in performing an I&D will be to prepare the site for incision and remove any dirt or debris. The skin over the abscess will be cleaned with 70% isopropyl alcohol and allowed to dry. Although this procedure is not considered sterile, the clinician will attempt to keep the area as clean as possible and devoid of unnecessary contamination.

The area will then be anesthetized with preservative-free 1%-2% lidocaine. Injection of lidocaine within the abscess cavity has been shown not to alter microbiologic data.[50] After 2-5 minutes, after the onset of anesthesia, using a #11 scalpel, a straight incision will be made over the area of maximal fluctuance or over the central area of the ultrasound-located cavity. The length of the incision will depend on the size of the abscess. However, the incision will be made large enough to promote adequate drainage. The minimum incision will be ¼ of the greatest length of fluctuance, but no less than 1 cm. After obtaining culture material and the initial decompression of purulent material, the abscess cavity will be probed thoroughly using a curved/straight hemostat or the operator's gloved finger. This action will further release any pockets of purulent material. The operator will then rotate the hemostat or finger around the entire abscess cavity to explore and remove any remaining loculations and adhesions. All necrotic and devitalized tissue will be debrided.

The abscess cavity will then be irrigated with sterile saline to remove all loosened purulent and necrotic material. The abscess cavity will be loosely packed using plain gauze. One to 2-cm of the packing material will extend outside of the wound in order to make sure the incision site will remain open and allow for continued drainage. The last step will include dressing the area using absorbent 4x4 gauze to cover the wound. All subjects will receive standardized instructional sheet on how to care for their wounds.

Standardized susceptibility testing will be conducted by the site laboratory on *S. aureus* and other pathogens. All laboratories use methods for antimicrobial susceptibility testing that are FDA-approved and conform to Clinical and Laboratory Standards Institute (CLSI) standards and all test for susceptibility to the following antimicrobial agents: methicillin/oxacillin, tetracycline, erythromycin, TMP/SMX, and clindamycin (including inducible resistance), vancomycin, rifampin, and levofloxacin and/or moxifloxacin. All laboratories participate in annual audits or other QA programs.

8.2.3 Specimen Preparation, Handling, and Shipping

Wound culture specimens will be collected and labeled as a research specimen and with the subject's unique patID (assigned by the EMMES system) by the investigator or study

coordinator. After culture and susceptibility testing at the site laboratory, cultures will be stored in the site laboratory freezers at -70°C.

All MRSA isolates will be saved and those from subjects with treatment failure, isolates with unusual antimicrobial susceptibility results (such as resistance or reduced susceptibility to vancomycin, linezolid, or daptomycin), and a random sample (10%) of isolates from remaining subjects at each site will be sent from the site laboratories to the CDC laboratories for further molecular biology testing on a semi-annual basis after subject enrollment begins. Isolates will be characterized at CDC by pulsed field gel electrophoresis, SCC*mec* typing, and detection of toxin genes. All isolates sent to CDC will be de-identified and only labeled with the subject's patID or a barcode.

We will employ the EMMES Global Trace System to track wound culture specimens from the site laboratories to the CDC laboratories. After molecular biology testing of isolates, DMID will be contacted by the Co-PIs for instruction on further handling of the study specimens. Specimens will not be destroyed at the site or CDC laboratories without written permission from DMID.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Safety will be evaluated by the collection and analysis of data on AEs, clinical laboratory tests, physical examination, vital signs, and concomitant medications. The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events (AEs)

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for “SAE” will be captured on the appropriate source document and eCRF. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, DO, PA, or Nurse Practitioner), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened will be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it will be recorded as an AE.

All AEs will be graded for severity and relationship to study product. Adverse reactions to the drugs examined in this study are listed in Section 2.3.1.

Severity of AEs: All AEs will be assessed by the clinician using a protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify intensity.

- None (Grade 0): No AE reported.
- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe (Grade 3): Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening (Grade 4): Any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death. It does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Products: The clinician's assessment of an AE's relationship to test article is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs will have their relationship to study product assessed using the terms "associated" or "not associated." In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used:

- Associated – The event is temporally related to the administration of the study product and no other etiology more likely explains the event.
- Not Associated – The event is temporally independent of study product and/or the event is more likely explained by another etiology.

9.2.2 Serious Adverse Events (SAE)

An SAE is defined as an AE that meets one of the following conditions:

- Death during the period of protocol-defined surveillance.
- Life-threatening event (defined as a subject at immediate risk of death at the time of the event).
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol-defined surveillance.

- Results in a persistent or significant disability/incapacity.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, or women who become pregnant while on study medication and have a child with a congenital anomaly or birth defect.

All SAEs will be:

- Recorded on the appropriate SAE source document.
- Reviewed and evaluated by a study clinician.
- Followed until satisfactory resolution or until the Co-PIs or investigator deems the event to be chronic or the subject to be stable.

9.2.3 Procedures to be Followed in the Event of Abnormal Clinical Findings or Abnormal Laboratory Test Values

Abnormal assessments (e.g., vital signs, etc.) and abnormal laboratory findings (e.g., clinical chemistry, hematology), if obtained, will be recorded as AEs or SAEs if they meet the definition of an AE as defined in Section 9.2.1, or SAE defined in Section 9.2.3. Abnormal laboratory findings (if obtained) or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

9.3 Reporting Procedures

AEs including local and systemic reactions not meeting the criteria for “SAEs” should be captured on the appropriate source document and eCRF. Information to be collected includes event description, time of onset, investigator assessment of severity, relationship to study product, time of resolution of the event, seriousness, and outcome. All AEs occurring during the study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study it should be recorded as an AE.

Withdrawal due to AE will be distinguished from withdrawal due to other reasons, according to the definition of AE noted earlier, and recorded on the appropriate AE source document and eCRF page. When a subject withdraws due to a SAE, the AE will be reported in accordance with the reporting requirements defined below.

9.3.1 Serious Adverse Events

Any AE considered serious by the Co-PIs or investigators of which meets the aforementioned criteria will be submitted on an SAE form to PPD, NIAID's pharmacovigilance contractor, at the following address:

Medical Affairs/Pharmacovigilance
PPD, Inc
3151 South 17th Street
Wilmington, NC 28412
SAE Fax line: 888-488-9697

Questions about SAE reporting can be referred to the SAE Hotline (available 24 hours a day/7 days a week) at 800-201-8725.

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and sent by fax within 24 hours of site awareness.
- SAEs other than death and immediately life-threatening events, regardless of relationship, will be reported via fax by the site within 72 hours of becoming aware of the event.

Other supporting documentation of the event may be requested by PPD and should be provided as soon as possible.

All SAEs will be followed until satisfactory resolution or until the Co-PIs or investigator deems the event to be chronic or the subject to be stable.

9.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the investigator, DMID, the IND sponsor, will report events that are both serious and unexpected and that are associated with study product(s) to the FDA within the required timelines as specified in 21 CFR Part 312.32: fatal and life-threatening events within 7 calendar days (by phone or fax) and all other SAEs in writing within 15 calendar days. All serious events designed as "not associated" to study product(s), will be reported to the FDA at least annually in a summary format.

9.3.3 Reporting of Pregnancy

Pregnancies occurring during this study will be reported by the investigational staff within one working day of their knowledge of the event using the Pregnancy Notification Form (provided by EMMES). Subjects who become pregnant during the treatment period of the study will be promptly withdrawn. The blind will be broken and if the study drug is TMP/SMX, the subject will be informed to discontinue the medication immediately and appropriate care will be provided (e.g., obstetrics follow-up). If the subject becomes pregnant after completing therapy they will continue participation in the study through all follow-up visits.

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to the medical monitor on the subject's condition. All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

9.5 Halting Rules

The DMID medical monitor will monitor reports of SAEs submitted by the study sites in real time to ensure GCP and to quickly identify safety concerns. If rates of drug-related SAEs are unexpectedly high (i.e., for each study arm, more than four such events per each 12 month study period), the medical monitor will promptly conduct a safety review involving the DSMB to determine if suspension of enrollment is warranted.

Any arm of the study may be halted if the DSMB determines that there is overwhelming evidence of harm or benefit associated with one of the selected treatments in that arm. If there is evidence of benefit at interim analyses, FDA concurrence for termination of the study will be sought.

An arm may also be terminated if, on the basis of the interim analyses, the EMMES statistician determines that there is overwhelming evidence to support the acceptance or rejection of the primary hypothesis for that arm (see Section 11.3.1). The entire study can be halted if, and only if all three arms are halted.

9.6 Safety Oversight (DSMB)

An ISM will be appointed at each site to provide independent safety review for selected AEs or SAEs immediately after they occur and follow for resolution. The ISM will be a clinician with relevant expertise who is not associated with the study. The ISM will report directly to the medical monitor and/or the DSMB.

Safety oversight will be under the direction of a DSMB. The DSMB will meet regularly (to be determined by the DSMB) to assess safety and efficacy data on each arm of the study, with the assistance of the EMMES statistician. If halting rules are initiated, more frequent meetings may be held. The DMSB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will advise DMID of its findings.

10 CLINICAL MONITORING

10.1 Site Monitoring Plan

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DMID SOPs. PPD will conduct site monitoring visits as detailed in the monitoring plan or in the MOP.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, ICFs, medical and laboratory reports, and protocol compliance. PPD study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Our study contains three separate sub-trials that will evaluate treatment on three independent populations. These sub-trials will examine treatments for the following conditions: 1) acute uncomplicated abscess; 2) acute uncomplicated wound infections; 3) acute uncomplicated cellulitis. Each sub-trial involves a specific independent hypothesis that will be assessed on an independent population.

1 – Hypothesis for acute uncomplicated abscesses: For patients with an acute uncomplicated abscess, we hypothesize that the clinical cure rate of patients treated with TMP/SMX will be superior to that of patients treated with placebo in the PP population at the TOC.

2 – Hypothesis for acute uncomplicated wound infections: For patients with an infected wound, we hypothesize that the clinical cure rate of patients treated with clindamycin will be superior to that of patients treated with TMP/SMX in the PP population at the TOC.

3 – Hypothesis for acute uncomplicated cellulitis: For patients with acute uncomplicated cellulitis, we hypothesize that the clinical cure rate of patients treated with cephalexin and TMP/SMX will be superior to that of patients treated with cephalexin and placebo in the PP population at the TOC.

11.2 Sample Size Considerations

The primary outcome variable for all study sub-trials is clinical cure (or failure) at the TOC.

Sample size calculations for all three study sub-trials were conducted using the following equations described by Fleiss. [51]

Fleiss method:

Equations:

$$n = \frac{n'}{4}\left(1+\sqrt{1+\frac{4}{n'\left|P_2-P_1\right|}}\right)^2$$

Where $$n' = \frac{\left(z_{\alpha}\sqrt{2\left(\frac{P_1+P_2}{2}\right)\left(\frac{Q_1+Q_2}{2}\right)} - z_{1-\beta}\sqrt{P_1Q_1+P_2Q_2} \right)^2}{(P_2-P_1)^2}$$

P_1 = Probability of cure using initial treatment strategy
P_2 = Probability of cure using alternative treatment strategy
$Q_1 = 1 - P_1$
$Q_2 = 1 - P_2$

Notes: i -Total sample size is given by N = 2*n*

ii - Our estimates employ a statistical significance level of $\alpha = 0.05$ (this is adjusted to a nominal value of 0.044 to reflect alpha spending in our proposed interim analyses), and a power of 90% ($\beta = 0.10$).

Abscess study sub-trial

To determine whether TMP/SMX with drainage is superior to drainage alone in treating a subject with an acute uncomplicated cutaneous abscess. It is assumed that there will be a cure rate of 90% with I&D alone and a cure rate of 97.5% or more with TMP/SMX to be a sufficient difference for clinicians to justify antibiotic use.[17,18,19,20,21,22]

The following null and alternative hypotheses were used where CR is the clinical cure rate:

H_0: $CR_{(TMP/SMX)} - CR_{(I\&D)} = 0.0\%$
H_1: $CR_{(TMP/SMX)} - CR_{(I\&D)} = 7.5\%$;
where $CR_{(I\&D)} = 90.0\%$ and $CR_{(TMP/SMX)} = 97.5\%$

For $\alpha = 0.044$, $\beta = 0.10$, and assumed cure of 90% for simple drainage ($P_1 = 0.90$): Testing for 7.5% improvement with TMP/SMX ($P_2 = 0.975$) would require a sample containing N = 502 patients (251 per sub-trial). Assuming a 85% evaluability rate, 590 patients would need to be enrolled to ensure an adequate sample size.

$$N_{Abscess} = 590$$

Infected wound study sub-trial

To determine whether clindamycin is superior to TMP/SMX in treating subjects with infected wounds. It is estimated that the clinical cure rate of subjects with infected wounds is 85%. A cure rate of 95% or more is the reasonable threshold for clinicians to justify its preferred use.

The following null and alternative hypotheses were used where CR is the clinical cure rate:

H_0: CR $_{(clindamycin)}$ – CR $_{(TMP/SMX)}$ = 0.0%
H_1: CR $_{(clindamycin)}$ – CR $_{(TMP/SMX)}$ = 10%;
where CR $_{(TMP/SMX)}$ = 85.0% and CR $_{(clindamycin)}$ = 95.0%

For α = 0.044, β = 0.10, and an assumed cure of 85% for TMP/SMX treatment (P_1 = 0.85): Testing for 10% improvement with clindamycin (P_2 = 0.95) would require a sample containing 426 patients (213 per sub-trial). Assuming a 85% evaluability rate, 500 patients need to be enrolled to complete the study.

$$N_{Infected\ wound} = 500$$

Cellulitis study sub-trial

To determine whether cephalexin and TMP/SMX is superior to cephalexin and placebo in treating subjects with acute uncomplicated cellulitis. It is estimated that the clinical cure rate of subjects with acute cellulitis is approximately 85%.[52,53,54,55,56,57,58,59,60] A cure rate of 95% or more is the reasonable threshold for clinicians to justify its preferred use.

The following null and alternative hypotheses were used where CR is the clinical cure rate:

H_0: CR $_{(TMP/SMX/cephalexin)}$ – CR $_{(cephalexin)}$ = 0.0%
H_1: CR $_{(TMP/SMX/cephalexin)}$ – CR $_{(cephalexin)}$ = 10%;
where CR $_{(cephalexin)}$ = 85.0% and CR $_{(TMP/SMX/cephalexin)}$ = 95.0%

For α = 0.044, β = 0.10 and assumed cure of 85% for treatment with cephalexin alone (P_2 = 0.95): Testing for 10% improvement with cephalexin and TMP/SMX (P_2 = 0.95) would require a sample containing N = 426 patients (213 per sub-trial). Assuming a 85% evaluability rate, 500 patients would need to be enrolled to ensure an adequate sample size.

$$N_{Cellulitis} = 500$$

A detailed summary of our sample size explorations, including estimates for differing cure rates and levels of attrition, is presented in Appendix B.

Our prior SSTI study that included a more limited population of adults with purulent lesions enrolled on average about 10 subjects/week/site. For this clinical trial, approximately1 evaluable subject per type of SSTI, per site, per week, will have to be enrolled, which, for each of the 3 types of SSTI, would amount to about 52 subjects/site/year, 156 subjects/site over 3 years, and 780 total enrolled subjects/SSTI type for all 5 sites. This illustrates the ability to enroll more subjects than are necessary to achieve the required study sample size (1,406 subjects), since 780 subjects/SSTI type would amount to 2,340 eligible subjects. In the unexpected instance

that we are unable to meet enrollment goals at 90% power, we also present an alternative approach in Appendix B using a less stringent power of 80% ($\beta = 0.20$) which will also yield an acceptable sample size to achieve our study goals.

Subjects who withdraw from the study because of AEs (see section 5.3.3-4), and who have been judged as clinical failures prior to their withdrawal, will be classified as clinical failures. All other subjects who withdraw from the study prior to final classification will be included in the mITT population, but will be classified as failures. Cases will be classified as clinical cures only when they meet the explicit criteria described in section 3.2.1.

Cases involving protocol violations will be handled on a case-by-case basis. Site investigators will first make an assessment of the severity of the violation. Any cases that involve violations that could threaten the study validity (e.g., administering open antibiotics prior to randomization) will be excluded from the study population. Cases that involve violations that do not threaten study validity (e.g., failure to procure a culture specimen) may be included in the study population, provided there are not other reasons that mandate withdrawal. The decision to include or exclude a specific case will be made prior to unblinding of the study antibiotic assignment. Cases that are excluded from the study on the basis of protocol violations will not be counted in the PP analysis, regardless of their outcome status at the time of the violation, but will be included in the mITT population. If subjects miss doses of study drug, data will be collected and recorded on the amount of drug taken. Secondary analysis will be conducted to examine potential differences between various thresholds of compliance.

The sample size estimates provide a sufficient number of cases to definitively test the primary hypotheses on all three study sub-trials. These numbers are too small to provide conclusive statistical assessments of the secondary outcomes. However, the enrollment estimates are likely to reveal trends in secondary outcomes, and these trends may serve as primary hypotheses for future investigations.

11.3 Planned Interim Analyses (if applicable)

To ensure trial integrity, study investigators and staff will not be allowed access to data or reports containing data (including aggregate response data) that could jeopardize trial integrity. Interim analyses will be performed by the DSMB and/or EMMES statistician.

Interim analyses are scheduled to occur after each sub-trial of the study has achieved 50% and 75% of its anticipated enrollments. These interim analyses are designed to assess efficacy and futility, and evaluate all other endpoints, including safety data, and provide guidance in determining whether there is overwhelming evidence that might justify early termination of any of the three sub-trials, or the study as a whole (in the unlikely event that termination is appropriate for all three sub-trials).

The interim analyses are also designed to provide the investigators with information to enhance sample size estimation and ensure that each sub-trial will attain sufficient power to produce meaningful results. In particular, after the completion of each interim analysis, study investigators will be provided with the cure rates observed in the control populations.

The following analytic recommendations are designed to help inform and guide the interim analyses.

Clinical Outcome Classifications for Interim Analyses

All interim analyses will be based on PP outcomes, and patients will be classified based on assessments at the TOC. In the interim analysis for a given sub-trial of the study, the numerator for p_1 will consist of all patients who received control treatment, as PP for that sub-trial, and were judged to be cured at the TOC. The denominator will consist of patients who received control treatment, as PP for that sub-trial, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all patients who received experimental treatment, as PP for that sub-trial, and were judged to be cured at the TOC. The denominator will consist of patients who received experimental treatment, as PP for that sub-trial, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator.

Assessment for Efficacy

The interim efficacy analyses will consist of statistical evaluations of the primary study outcomes (differences in cure rates between treatment and control populations), using adjusted α error rates. Based on a Lan-DeMets alpha spending function with an O'Brien-Flemming boundry, the first interim analysis will occur after an individual sub-trial accrues 50% of its anticipated enrollment, and will employ an $\alpha = 0.0015$.[61] The second interim analysis will occur after the sub-trial has accrued 75% of its anticipated enrollment and will employ an $\alpha = 0.0091$. This will yield an $\alpha = 0.044$ for use in conducting the final analyses.

The primary statistical outcomes of interest in the interim analyses are the observed difference in the proportion of cures between patients receiving experimental therapies and those receiving the control therapies.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between patients receiving the experimental therapy and those receiving the control therapy.

p_2 = Proportion of cures among patients receiving the experimental therapy.

p_1 = Proportion of cures among patients receiving the control therapy.

The observed differences in cure rates themselves do not provide sufficient information to evaluate any of our hypotheses. A complete evaluation requires knowledge of the confidence interval surrounding each of the observed differences. The upper and lower bounds for these confidence intervals are given by the following equations from Fleiss:

$$\Delta_L = (p_2 - p_1) - z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} - \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

$$\Delta_U = (p_2 - p_1) + z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} + \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

Where:

Δ_L = Lower confidence interval for the difference in proportions

Δ_U = Upper confidence interval for the difference in proportions

p_1 = Proportion of cures among patients receiving control therapy

p_2 = Proportion of cures among patients receiving experimental therapy

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

n_1 = Total number of patients receiving control therapy

n_2 = Total number of patients receiving experimental therapy

The interpretation of interim observations for each sub-trial will be based on which one of six potential configurations these bounds assume in relationship to the clinically significant difference in cure rates defined for that sub-trial. The clinically significant difference in cure rate is 7.5% for the abscess sub-trial, 10% for the infected wound sub-trial, and 10% for the cellulitis sub-trial.

The interpretations of possible outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: The experimental treatment produces lower cure rates than the control treatment. This observation would be consistent with futility of the experimental treatment (use of TMP/SMX) in the abscess and cellulitis sub-trials of the study, and should trigger a recommendation for early termination of the corresponding sub-trial. In contrast, this outcome would suggest superiority of TMP/SMX over clindamycin in treating infected wounds, and should trigger a recommendation to continue the trial to assess magnitude of effect in this sub-trial.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces cure rates similar to the control treatment. In all three sub-trials of the study this observation should trigger a futility analysis (as described below) to determine whether there is sufficient evidence to recommend terminating the study on the basis of futility.

Case III: Lower bound is less than zero, and upper bound is greater than the predefined clinically significant cure rate.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered at current enrollment levels and no conclusion is possible. In all three sub-trials of the study this observation should trigger a recommendation to continue enrollments without interruption.

Case IV: Lower bound is greater than zero, while the upper bound is less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than the control treatment, but the observed difference is not clinically significant. In all three sub-trials of the study this observation should trigger a recommendation to continue enrollments to assess magnitude of effect.

Case V: Lower bound is greater than zero, but less than the predefined clinically significant cure rate, while the upper bound is greater than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than control treatment, but the study is unable to assess whether this difference is clinically significant. In all three sub-trials of the study this observation should trigger a recommendation to continue enrollments to assess magnitude of effect, and ultimately assess efficacy.

Case VI: Lower and upper bound both exceed the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than the control treatment, and this difference is clinically important. This observation would be consistent with superiority of the experimental treatment in all three sub-trials of the study, and should trigger a recommendation for early termination of the involved sub-trial on the basis of demonstrated efficacy.

Assessment for Futility

Futility analyses will be conducted whenever the computed lower confidence bound in an interim analysis is less than zero, while the upper bound is greater than zero, but less than the clinically significant cure rate.

The futility analysis will be based on predicted intervals (PI) obtained by calculating the confidence intervals that might be expected at future time points should the study be allowed to continue. Four methods will be used to extrapolate future data: 1) observed trends continue; 2) future data conforms to the alternative hypothesis; 3) future data conforms to the null hypothesis; and 4) future data follows best-case (all experimental treatments produce cures, whole all control treatments result in failures) or worse-case (all experimental treatments produce failures, whole all control treatments result in cures) scenarios.

The interpretation of the three possible outcomes of interest that may arise from these prediction intervals are as follows:

Case I: Upper prediction interval is less than zero.

Interpretation: The experimental treatment is expected to result in lower cure rates than the control treatment. This observation would be consistent with futility of the experimental treatment (use of TMP/SMX) in the abscess and cellulitis sub-trials of the study, and should trigger a recommendation for early termination of the corresponding sub-trial. In contrast, this outcome would suggest superiority of TMP/SMX over clindamycin in treating infected wounds, and should trigger a recommendation to continue the trial to assess magnitude of effect in this sub-trial.

Case II: Lower prediction bound is less than zero, while the upper bound is greater than zero, but less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment will produce cure rates similar to the control treatment, evidence from current data is conclusive and further enrollments are unnecessary. This observation should trigger a recommendation for early termination on the basis of futility.

Case III: Lower prediction bound is greater than zero.

Interpretation: The experimental treatment is expected to produce higher cure rates than control treatment, but the study may not be able to assess whether this difference is clinically significant. In all three sub-trials of the study this observation should trigger a recommendation to continue enrollments to assess magnitude of effect, and ultimately assess efficacy.

In the event that an interim analysis produces evidence of efficacy or futility, the results of the analyses will be presented to the DSMB and NIH Project Officer, who will proceed with termination of the corresponding sub-trial of the study after obtaining FDA concurrence with the findings, if necessary. The decision to terminate any sub-trial of the study for safety reasons will

involve both the DMID and DSMB. The Co-PIs may suspend patient enrollment pending this decision.

11.3.1 Safety Review

The occurrence of AEs will be monitored and summarized quarterly during subject enrollment.

Any sub-trial of the study may be halted if the DSMB and DMID determine that there is overwhelming evidence of harm or benefit associated with one of the selected treatments in that sub-trial and obtains FDA concurrence with the findings of the interim analysis. An sub-trial may also be terminated if, on the basis of the interim analyses, the DSMB determines that there is overwhelming evidence to support the acceptance or rejection of the primary hypothesis for that sub-trial. The entire study can be halted if, and only if all three sub-trials are halted.

11.3.2 Immunogenicity or Efficacy Review

Not applicable

11.4 Final Analysis Plan

Final analyses will be conducted by the study statistician with the assistance of EMMES.

Primary analysis

General Principles

Our final analyses will evaluate the hypotheses that drive each of the three distinct sub-trials of the study. We will use a similar statistical approach in each of the different sub-trials. Our primary statistical outcome is the observed difference in the proportion of cures between patients receiving the experimental therapy and those receiving the control therapy.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between patients receiving the experimental therapy and those receiving the control therapy.

p_2 = Proportion of cures among patients receiving the experimental therapy.

p_1 = Proportion of cures among patients receiving the control therapy.

The observed differences in cure rates do not provide sufficient information to evaluate any of our hypotheses. A complete evaluation requires knowledge of the confidence interval surrounding each of the observed differences. The upper and lower bounds for these confidence intervals are given by the following equations from Fleiss:

$$\Delta_L = (p_2 - p_1) - z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} - \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

$$\Delta_U = (p_2 - p_1) + z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} + \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

Where:

Δ_L = Lower confidence interval for the difference in proportions

Δ_U = Upper confidence interval for the difference in proportions

p_1 = Proportion of cures among patients receiving control therapy

p_2 = Proportion of cures among patients receiving experimental therapy

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

n_1 = Total number of patients receiving control therapy

n_2 = Total number of patients receiving experimental therapy

Our interpretation of the final outcome for each sub-trial will be based on which one of six potential configurations these bounds assume in relationship to the clinically significant cure rate we have defined for that sub-trial. The interpretation of possible outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: The experimental treatment produces lower cure rates than the control treatment.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces cure rates similar to the control treatment.

Case III: Lower bound is less than zero, and upper bound is greater than the predefined clinically significant cure rate.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, while the upper bound is less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than the control treatment, but the observed difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than the predefined clinically significant cure rate, while the upper bound is greater than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than control treatment, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than the control treatment, and this difference is clinically important.

The specific application of this approach is detailed for the individual sub-trials of the study as described below.

Treatment of Uncomplicated Abscesses

For the first sub-trial of the study, involving patients with an acute uncomplicated abscess, we will determine whether the clinical cure rate of patients treated with TMP/SMX is superior to that of patients treated with placebo. Our primary statistical measure will be the difference in the proportion of cures between patients receiving TMP/SMX and those receiving placebo.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between patients receiving TMP/SMX and those receiving placebo.

p_2 = Proportion of cures among patients receiving TMP/SMX.

p_1 = Proportion of cures among patients receiving placebo.

To evaluate our hypothesis, we will consider the confidence interval surrounding our observed difference in cure rates. The upper and lower bounds for this confidence interval are given by the following equations from Fleiss:

$$\Delta_L = (p_2 - p_1) - z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} - \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

$$\Delta_U = (p_2 - p_1) + z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} + \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

Where:

Δ_L = Lower confidence interval for the difference in proportions

Δ_U = Upper confidence interval for the difference in proportions

p_1 = Proportion of cures among patients receiving placebo

p_2 = Proportion of cures among patients receiving TMP/SMX

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

n_1 = Total number of patients receiving placebo

n_2 = Total number of patients receiving TMP/SMX

The interpretation of our final outcome will be based on which one of six potential configurations these bound assume in relationship to our clinically significant cure rate of 7.5%. These outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: Treatment with TMP/SMX produces lower cure rates than treatment with placebo.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than 7.5%.

Interpretation: Treatment with TMP/SMX produces cure rates similar to placebo.

Case III: Lower bound is less than zero, and upper bound is greater than 7.5%.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, but less than 7.5%, while the upper bound is less than 7.5%.

Interpretation: Treatment with TMP/SMX produces higher cure rates than treatment with placebo, but difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than 7.5%, while the upper bound is greater than 7.5%.

Interpretation: Treatment with TMP/SMX produces higher cure rates than treatment with placebo, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed 7.5%.

Interpretation: Treatment with TMP/SMX produces higher cure rates than treatment with placebo, and the difference is clinically important.

Clinical Outcome Classifications for the Treatment of Uncomplicated Abscesses

For the PP analysis, patients will be classified based on assessments at the TOC. The numerator for p_1 will consist of all patients who received placebo as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received placebo as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all patients who received TMP/SMX as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received TMP/SMX as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator.

For the mITT analysis, patients will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received a placebo on their initial visit and were classified as cured on final outcome. The denominator will include all patients who received placebo on their initial visit, including those with definite outcome assignments, those lost to follow-up, and any others with missing or unassigned outcomes. The numerator for p_2 will include only those individuals who received TMP/SMX on their initial visit and who were classified as cured on final outcome. The denominator will include all patients who received TMP/SMX on their initial visit, including those with definite outcome assignments, those lost to follow-up, and any others with missing or unassigned outcomes.

Treatment of Infected Wounds

For the next sub-trial of the study, involving patients with infected wounds, we will determine whether the clinical cure rate of patients treated with clindamycin is superior to that of patients treated with TMP/SMX. Our primary statistical measure will be the difference in the proportion of cures between patients receiving clindamycin and those receiving TMP/SMX.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between patients receiving clindamycin and those receiving TMP/SMX.

p_2 = Proportion of cures among patients receiving clindamycin.

p_1 = Proportion of cures among patients receiving TMP/SMX.

To evaluate our hypothesis, we will consider the confidence interval surrounding our observed difference in cure rates. The upper and lower bounds for this confidence interval are given by the following equations from Fleiss:

$$\Delta_L = (p_2 - p_1) - z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} - \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

$$\Delta_U = (p_2 - p_1) + z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} + \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

Where:

Δ_L = Lower confidence interval for the difference in proportions

Δ_U = Upper confidence interval for the difference in proportions

p_1 = Proportion of cures among patients receiving TMP/SMX

p_2 = Proportion of cures among patients receiving clindamycin

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

n_1 = Total number of patients receiving TMP/SMX

n_2 = Total number of patients receiving clindamycin

The interpretation of our final outcome will be based on which one of six potential configurations these bound assume in relationship to our clinically significant cure rate of 10%. These outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: Treatment with clindamycin produces lower cure rates than treatment with TMP/SMX.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than 10%.

Interpretation: Treatment with clindamycin produces cure rates similar to treatment with TMP/SMX.

Case III: Lower bound is less than zero, and upper bound is greater than 10%.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, but less than 10%, while the upper bound is less than 10%.

Interpretation: Treatment with clindamycin produces higher cure rates than treatment with TMP/SMX, but difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than 10%, while the upper bound is greater than 10%.

Interpretation: Treatment with clindamycin produces higher cure rates than treatment with TMP/SMX, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed 10%.

Interpretation: Treatment with clindamycin produces higher cure rates than treatment with TMP/SMX, and the difference is clinically important.

Clinical Outcome Classifications for the Treatment of Infected Wounds

For the PP analysis, patients will be classified based on assessments at the TOC. The numerator for p_1 will consist of all patients who received TMP/SMX as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received TMP/SMX as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all patients who received clindamycin as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received clindamycin as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other with unassigned outcomes will not be counted in the denominator.

For the mITT analysis, patients will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received TMP/SMX on their initial visit and were classified as cured on final outcome. The denominator will include all patients who received TMP/SMX on their initial visit, including those with definite diagnostic assignments,

those lost to follow-up, and any others with missing or unassigned outcomes. The numerator for p_2 will include only those individuals who received clindamycin on their initial visit and who were classified as cured on final diagnosis. The denominator will include all patients who received clindamycin on their initial visit, including those with definite diagnostic assignments, those lost to follow-up, and any others with missing or unassigned outcomes.

Treatment of Cellulitis

For the next sub-trial of the study, involving patients with cellulitis, we will determine whether the clinical cure rate of patients treated with TMP/SMX and cephalexin is superior to that of patients treated with cephalexin alone. Our primary statistical measure will be the difference in the proportion of cures between patients receiving TMP/SMX and cephalexin, and those receiving cephalexin alone.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between patients receiving TMP/SMX and cephalexin, and those receiving cephalexin alone.

p_2 = Proportion of cures among patients receiving TMP/SMX and cephalexin.

p_1 = Proportion of cures among patients receiving cephalexin alone.

To evaluate our hypothesis, we will consider the confidence interval surrounding our observed difference in cure rates. The upper and lower bounds for this confidence interval are given by the following equations from Fleiss:

$$\Delta_L = (p_2 - p_1) - z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} - \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

$$\Delta_U = (p_2 - p_1) + z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} + \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

Where:

Δ_L = Lower confidence interval for the difference in proportions

Δ_U = Upper confidence interval for the difference in proportions

p_1 = Proportion of cures among patients receiving cephalexin alone

p_2 = Proportion of cures among patients receiving TMP/SMX and cephalexin

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

n_1 = Total number of patients receiving cephalexin alone

n_2 = Total number of patients receiving TMP/SMX and cephalexin

The interpretation of our final outcome will be based on which one of six potential configurations these bound assume in relationship to our clinically significant cure rate of 10%. These outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: Treatment with TMP/SMX and cephalexin produces lower cure rates than treatment with cephalexin alone.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces cure rates similar to treatment with cephalexin alone.

Case III: Lower bound is less than zero, and upper bound is greater than 10%.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, but less than 10%, while the upper bound is less than 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces higher cure rates than treatment with cephalexin alone, but difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than 10%, while the upper bound is greater than 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces higher cure rates than treatment with cephalexin alone, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces higher cure rates than treatment with cephalexin alone, and the difference is clinically important.

<u>Clinical Outcome Classifications for the Treatment of Cellulitis</u>

For the PP analysis, patients will be classified based on assessments at the TOC. The numerator for p_1 will consist of all patients who received only cephalexin as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received only cephalexin as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all patients who received both cephalexin and TMP/SMX as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received both cephalexin and TMP/SMX as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator.

For the mITT analysis, patients will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received only cephalexin on their initial visit and were classified as cured on final outcome. The denominator will include all patients who received only cephalexin on their initial visit, including those with definite outcome assignments, those lost to follow-up, and any others with missing or unassigned outcomes. The numerator for p_2 will include only those individuals who received both cephalexin and TMP/SMX on their initial visit and who were classified as cured on final outcome. The denominator will include all patients who received both cephalexin and TMP/SMX on their initial visit, including those with definite outcome assignments, those lost to follow-up, and any others with missing or unassigned outcomes.

Secondary Analyses

We anticipate that non-compliance and attrition among study participants will produce significant bias in assessing treatment efficacy using mITT methodology. In particular our primary mITT analyses is based on worst-case assumptions of outcomes, and posits that patients lost to follow-up will most negatively effect patient assigned to experimental treatment groups. This approach provides conservative outcomes that underestimate treatment efficacy. Consequently we plan to conduct sensitivity analyses to ascertain the potential scope and implications of these biases.

Our proposed sensitivity analyses include examining cure rates while varying our assumptions regarding outcomes among patients lost to attrition. In particular, we plan to use imputation to calculate “best guess” cure rates among patients lost to attrition, and use this information to calculate best estimate of the overall cure rates for the treatment and control groups. We will also plan to examine the most optimistic treatment efficacy by assigning outcomes to un-evaluable patients that most favor treatment effects.

We also plan to examine antimicrobial resistance rates among the cultured specimens. These rates will be described in terms of point statistics and dispersions, and will be specified in terms of proportion of specific organism isolates susceptible to a given antibiotic. This information will be used to assign expected microbiological cure rates to the associated individual patients.

These expected cure rates will then be compared to actual observed cure rates at various stages of treatment (OTV, EOT, TOC). The expected versus observed cure information will be summarized as raw counts in a four-fold table for treatment stage.

As part of our secondary analyses, we also plan to calculate point estimates and 95% confidence intervals for the proportion of patients who are compliant in taking 80% or more of the doses of the prescribed antibiotics. We will use these populations to calculate adjust "compliant" cure rates of the various regimens, and compare these "compliant" cure rates with the cure rates on the control populations to assess the maximum potential benefit of the experimental agents.

Outcome populations:

PP population - Subjects who meet enrollment criteria, have none of the exclusion criteria, complete at least 100% of the first 48 hours of antimicrobial therapy, and have physical follow-up at the TOC. Subjects who have been determined to be a clinical failure at any time prior to the TOC who took at least 100% of the first 48 hours of antimicrobial therapy but who do not have physical follow-up at the TOC will also be included in the PP population

mITT population - Subjects who take at least one dose of study medication and have any follow-up evaluation.

The primary efficacy endpoint of the study is the clinical response to study medication at the TOC in the PP population. A subject will be considered evaluable for the PP population if the subject:

- ⇒ Has met all study entry criteria;
- ⇒ Has not met any one of the exclusion criteria;
- ⇒ Has received 100% of the first 48 hours of study medication;
- ⇒ Has returned for clinical evaluation at the TOC;
- ⇒ Has not used any of the prohibited concomitant medications;
- ⇒ Has been determined to be a clinical failure at any time prior to TOC and took 100% of the first 48 hours of antimicrobial therapy but who did not have physical follow-up at the TOC.

Any subject who was originally considered eligible for and is entered into this study, and is subsequently found to be at variance with any of the study inclusion/exclusion criteria (Sections 5.1 and 5.2), will be ineligible for PP population analysis, due to a protocol violation. Subjects will only be excluded from the PP population from the time that the protocol violation occurs. For example, a subject who returns for the follow-up visit outside the protocol specified time interval would be excluded from analyses at follow-up, but not from analyses at end of therapy. All decisions on eligibility for inclusion into the PP population will be made prior to data evaluation.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

EMMES will assist the Co-PIs in creating source documents for the study prior to subject enrollment, including source documents to record information on screening (i.e., meeting inclusion and exclusion criteria), enrollment (demographics, patient history, pre-existing conditions, etc.), all follow-up visits, memory aid data, pregnancy notification, laboratory and medical record data, AEs, and all information entered on the eCRFs (section 15.2).

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Following written SOPs, PPD will verify that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Reports will be submitted to DMID on monitoring activities. The investigational sites will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by PPD, and inspection by local and regulatory authorities.

EMMES will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

A QM plan will be created and approved by DMID. It will include information, such as 1) how data will be evaluated for compliance with the protocol and for accuracy in relation to source documents; 2) the documents to be reviewed (e.g., eCRFs, clinic notes, product accountability), who is responsible, and the frequency for reviews; and 3) methods of training for staff. This QM Plan will be reviewed for effectiveness annually and revised when indicated. New or revised QM Plans will be sent to DMID for review and approval.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997); 21 CFR 50.

14.2 Institutional Review Board

Each participating institution will provide for the review and approval of this protocol and the associated ICFs and recruitment material by an appropriate independent ethics committee (IEC) or IRB registered with the OHRP. Any amendments to the protocol or consent materials will also be approved before they are placed into use. Only institutions holding a current US FWA issued by OHRP are participating in this study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator or study coordinator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the ICF prior to any procedures being done specifically for the study. The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the ICF will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that they will still be able to receive medical care at the facility if they decline to participate in this study.

Each participating site will be provided with a model ICF for subject participation. The consent form will be separate from the protocol document. Each institution will place the ICF in its own

template. Each site may add but not remove anything from the model consent form. The IRB approved consents will be provided to DMID.

14.3.1 Informed Consent/Assent Process (in Case of a Minor)

This study includes subjects ages 13 to 17, who may be enrolled in the trial only with the consent of the subject's legally authorized representative. Such subjects will be informed about the trial to the extent compatible with the subject's understanding. If capable, the subject will assent and sign and personally date the written consent form. A separate IRB-approved assent form, describing (in simplified terms) the details of the study intervention/product, study procedures, and risks will be used. Assent by the subject and the consent by the legal guardian will be obtained. Assent forms will not substitute for the consent form signed by the subject's legally authorized representative.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

Women and minorities will be included in the study population. The study site EDs serve populations in which diverse racial and ethnic groups are well represented. The racial breakdown of subjects in the previous study of SSTI through the ***EMERGE*ncy ID Net** by Moran and colleagues[1] was: white non-Hispanic (28%), black non-Hispanic (44%), Hispanic (26%), other (2%). Women of childbearing potential will not be excluded, but will have a negative pregnancy test documented prior to enrollment because of concern about possible teratogenic effects of study medications. Children less than 13 (or < 40 Kg) will be excluded because of difficulty providing blinded study medications in all pediatric dosing ranges.

Prisoners will be excluded from the study population.

14.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the DMID and their other clinical research support contractors. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The DMID or authorized representatives of PPD may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records

(office, clinic, or hospital) and pharmacy records for the subjects in this study. All clinical study sites will permit access to such records.

14.6 Study Discontinuation

In the event that the study is discontinued, subjects that are already enrolled in the study and have not completed all protocol procedures will be notified and asked to return to the ED for re-evaluation. The blind will be broken and the treating clinician will make a decision of appropriate continued therapy for the subject according to standard of care.

14.7 Future Use of Stored Specimens

Wound culture specimens will be stored at the site laboratories, and a subset shipped to the CDC laboratories (see Section 8.2.3) for further testing. All patient identifiers will be removed and specimens will be labeled only with a barcode label provided by EMMES that links to the subject's patID before shipment to the CDC. After all laboratory testing for this study is completed, DMID will be contacted by the Co-PIs for instruction on further handling of the study specimens.

15 DATA HANDLING AND RECORD KEEPING

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Forms for use as source documents will be derived from the eCRFs and provided by EMMES to the sites to record and maintain data for each subject enrolled in the study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry will be crossed out with a single line, and the change should be initialed and dated. Research staff will not erase, overwrite, or use correction fluid or tape on the original. Data reported in the eCRF should be consistent with the source documents or the discrepancies should be documented.

DMID will provide guidance to investigators on making corrections to the source documents and eCRFs.

Additional details are provided in the study-specific Data Management Plan, which will be reviewed and approved by DMID.

15.1 Data Management Responsibilities

All source documents and laboratory reports (after subject follow-up is completed) will be reviewed by the study coordinators who will ensure that they are accurate and complete. AEs will be graded, assessed for severity and causality, and reviewed by the investigator.

Data collection is the responsibility of the study staff at the site under the supervision of the site investigator. During the study, the site investigator will maintain complete and accurate documentation for the study.

EMMES will serve as the Statistical and Data Coordinating Center for this study and will provide support for data management, quality review, analysis, and reporting of the study data.

15.2 Data Capture Methods

Clinical data (including AEs, concomitant medications, and outcomes) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant IDES provided by EMMES. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Source documents will be created by EMMES and the main study staff for data collection.

15.3 Types of Data

Data for this study will include clinical data, laboratory information (bacteriologic), and outcome measures (e.g., cure rates, infection type).

15.4 Timing/Reports

During enrollment, data will be monitored by the EMMES statistician on a regular basis. Any immediate problems or issues will be discussed with the study investigators during their monthly conference calls. Reports will be prepared and submitted to DMID and DSMB. A Final Report will be due for the final year of the study. Outcome measure data will be collected and entered into the IDES system and monitored by EMMES.

15.5 Study Records Retention

Study documents will be retained for a minimum of 2 years after the FDA acknowledgement of IND inactivation date of the study. These documents will be retained for a longer period, if required by local regulations. No records will be destroyed without the written consent of DMID, until these documents are no longer needed. It is the responsibility of DMID to inform the investigator when these documents no longer need to be retained.

15.6 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol, GCP, or MOPs requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.

5.1 Quality Assurance and Quality Control, section 5.1.1.

5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations will be promptly reported to DMID.

All deviations from the protocol will be addressed in study subject source documents. A completed copy of the DMID Protocol Deviation Form will be maintained in the regulatory file, as

well as in the subject's source document. Protocol deviations will be sent to the local IRB/IEC per their guidelines. The site investigator/study staff will be responsible for knowing and adhering to their IRB/IEC requirements.

16 PUBLICATION POLICY

Following completion of the study, the primary investigators in association with site investigators are expected to publish the results of this research in a scientific journal. The ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov,[62] which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of DMID to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before subject enrollment.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from this policy.

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SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Procedures		Screening (Day 1)	Baseline/Enrollment (Day 1)	Follow-Up Schedule: OT Visit (Days 3-4)	EOT Visit (Days 8-10)	TOC visit (Days 14-21)	EF Visit (Days 49-63)	Unscheduled Visit	Premature Discontinuation
Signed Consent Form		X							
Assessment of Eligibility Criteria		X							
Review of Medical History		X	X						
Review of Concomitant Medications		X	X	X	X	X	X	X	X
Administered and provided with study drug			X						
Physical Examination	Complete	X							
	Symptom-Directed			(X)	(X)	(X)	(X)	(X)	(X)
	Vital Signs		X	X	X	X	X	X	X
Assessment of Adverse Events				X	X	X	X	X	X
Clinical Laboratory	Chemistry		(X)	(X)	(X)	(X)	(X)	(X)	(X)
	Hematology		(X)	(X)	(X)	(X)	(X)	(X)	(X)
	Urine pregnancy test	X		(X)	(X)	(X)	(X)	(X)	(X)
Gram stain, culture (aerobic & anaerobic), and susceptibility testing of purulent material			X*	(X)	(X)	(X)	(X)	(X)	(X)
Medication check				X	X			(X)	(X)
Memory aid check				X	X	X		(X)	(X)

			Follow-Up Schedule					
Procedures	Screening (Day 1)	Baseline/Enrollment (Day 1)	OT Visit (Days 3-4)	EOT Visit (Days 8-10)	TOC visit (Days 14-21)	EF Visit (Days 49-63)	Unscheduled Visit	Premature Discontinuation
C. diff toxin assay of stool specimen			(X)	(X)	(X)	(X)	(X)	(X)

X - Required
(X) - As deemed indicated by site investigator
* Required for abscess and infected wound arms, but not for cellulitis

At baseline, all procedures will be done before study interventions.

APPENDIX B : SAMPLE SIZE CALCULATIONS AT 80% POWER (β = 0.20)

Abscess Sub-trial:

Sample estimates under this constraint indicate the need for a population of at least 318 cases (159 subjects each in the treatment and control groups). Table 1 provides sample estimates for the different scenarios associated with this choice.

Table 1.

α = 0.045 (one-tailed α = 0.09); Power = 80%

	Attrition					
Cure rates	*None*	*5%*	*10%*	*15%*	*20%*	*25%*
92.5% vs 100%	214	224	236	250	266	284
90.0% vs 97.5%	**318**	334	352	374	396	424
87.5% vs 95.0%	416	436	462	488	520	554
85.0% vs 92.5%	508	534	564	596	634	676
82.5% vs 90.0%	594	624	660	698	742	792

Under realistic scenarios, with 15% attrition, the analysis could be completed with approximately 374 cases.

Cellulitis Sub-trial:

Sample estimates under this constraint indicate the need for a population of at least 270 cases (135 subjects each in the treatment and control groups). Table 2 provides sample estimates for the different scenarios associated with this choice.

Table 2.

α = 0.045 (one-tailed α = 0.09); Power = 80%

	Attrition					
Cure rates	*None*	*5%*	*10%*	*15%*	*20%*	*25%*
90.0% vs 100%	158	166	174	184	196	210
87.5% vs 97.5%	216	226	240	254	270	288
85.0% vs 95.0%	**270**	284	300	316	336	360
82.5% vs 92.5%	320	336	354	376	400	426
80.0% vs 90.0%	366	384	406	430	456	488

Under realistic scenarios, with 15% attrition, the dual analyses could be completed with approximately 316 cases.

Infected Wound Sub-trial:

Sample estimates under this constraint indicate the need for a population of at least 330 cases (165 subjects in each of the treatment and control groups). Table 3 provides sample estimates for the different scenarios associated with this choice.

Table 3.

α = 0.045; Power = 80%	Attrition					
Cure rates	*None*	*5%*	*10%*	*15%*	*20%*	*25%*
90.0% vs 100%	190	200	210	222	236	252
87.5% vs 97.5%	262	274	290	308	326	348
85.0% vs 95.0%	**330**	346	366	388	412	440
82.5% vs 92.5%	392	412	434	460	490	522
80.0% vs 90.0%	450	472	500	528	562	600

Under realistic scenarios, with 15% attrition, these analyses could be completed with approximately 460 cases.

Strategies using Off-Patent antibiotics for Methicillin-Resistant *Staphylococcus aureus ("STOP MRSA") – A Phase IIB, multi-center, randomized, double-blind clinical trial*

DMID Protocol Number: 07-0040

DMID Funding Mechanism: HHSN272200700-32C

Pharmaceutical Support Provided by: N/A

Other Identifying Numbers:

IND Sponsor: DMID

Lead Co-Principal Investigators: David A. Talan, MD & Gregory J. Moran, MD

DMID Protocol Champion: Christine Chiou, MD

DMID Medical Monitor: Luigi S. Girardi, MD

DMID Clinical Affairs Specialist: Hyung Koo

Draft or Version Number: 3.0

Day Month Year
2 December 2010

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH E6; 62 Federal Register 25691 (1997)
- NIH Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Lead Co-Principal Investigators:

Signed: _____ Date: _____

Name: David A. Talan, MD
Title: Lead Co-Principal Investigator

Signed: _____ Date: _____

Name: Gregory J. Moran, MD
Title: Lead Co-Principal Investigator

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AIDS	Acquired Immunodeficiency Syndrome
BID	Twice daily
BUN	Blood Urea Nitrogen
CA-MRSA	Community-Acquired MRSA
CBC	Complete Blood Cell Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CLSI	Clinical and Laboratory Standards Institute
CRF	Case Report Form
CRO	Contract Research Organization
CROMS	Clinical Research Operations and Management Support
CTM	Clinical Trials Management
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DS	Double-Strength
DSMB	Data and Safety Monitoring Board
ECRF	Electronic Case Report Form
ED	Emergency Department
EFV	Extended Follow-Up Visit
EMMES	EMMES Corporation (Data Management Contractor)
EOT	End-of-Therapy Visit
FDA	Food and Drug Administration
FWA	Federalwide Assurance
G-6-PD	Glucose-6-Phosphate Dehydrogenase
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
I & D	Incision and Drainage
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IDES	Internet Data Entry System/AdvantageEDC
IDSA	Infectious Diseases Society of America
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application

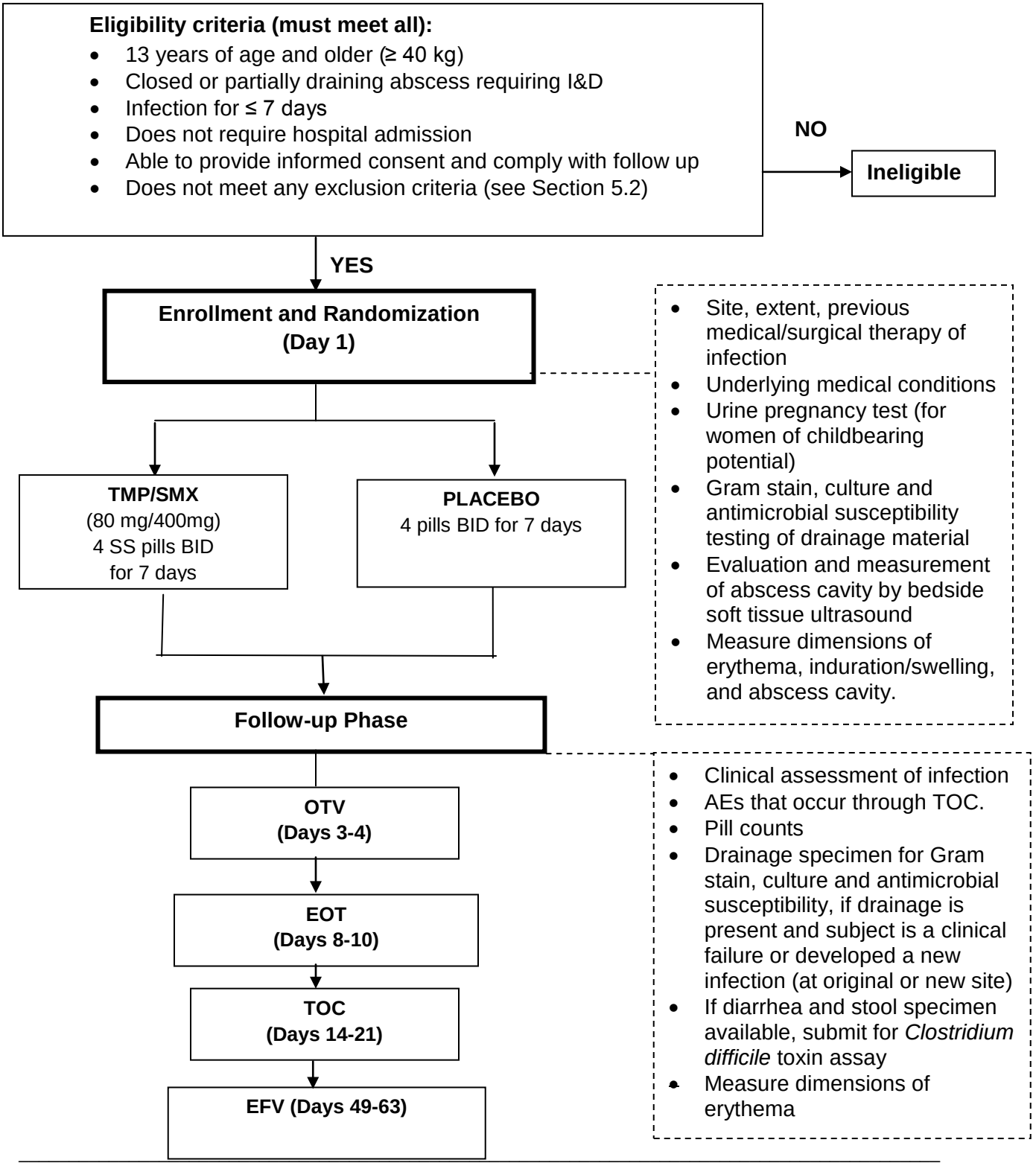
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MedDRA ®	Medical Dictionary for Regulatory Activities
MIC	Minimal Inhibitory Concentrations
mITT	Modified Intent-to-Treat
MOP	Manual of Procedures
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
N	Number (typically refers to subjects)
NCI	National Cancer Institute, NIH, DHHS
NDA	New Drug Application
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
OTV	On-Therapy Visit
PA	Clinician's Assistant
PatID	Subject ID
PDR	Clinician's Desk Reference
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PPD	PPD Development LP (former Clinical Trial Management Contractor)
PVL	Panton-Valentine Leukocidin
QA	Quality Assurance
QC	Quality Control
QID	Four times daily
SAE	Serious Adverse Event/Serious Adverse Experience
S. aureus	*Staphylococcus aureus*
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SS	Single-strength
SSTI	Skin and Soft-Tissue Infection
TOC	Test-of-Cure Visit
TMP/SMX	Trimethoprim/Sulfamethoxazole
US	United States

PROTOCOL SUMMARY

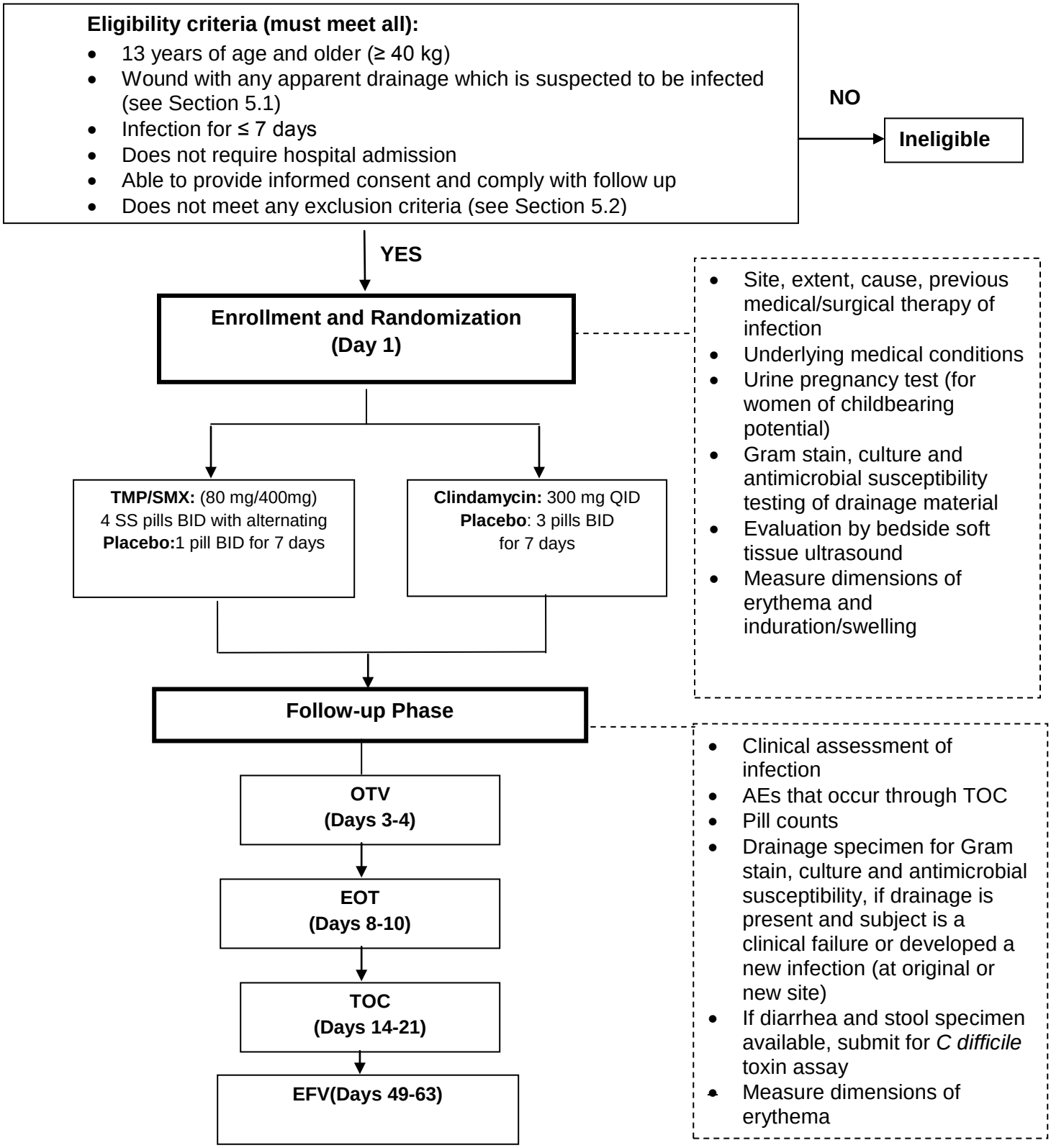
Title:	**Strategies using Off-Patent antibiotics for Methicillin-Resistant *Staphylococcus aureus* (*"STOP MRSA"*) – A Phase IIB, multi-center, randomized, double-blind clinical trial**
Phase:	IIB
Population:	At least 2,235 subjects (male and female) 13 years of age and older with acute uncomplicated SSTIs
Informed consent	Required
Number of Sites:	5 large urban, academically-affiliated US EDs
Study Duration:	July 19, 2007 – July 18, 2013
Subject Participation Duration:	Subjects will be followed for approximately 9 weeks.
Description of Agent or Intervention:	Subjects will be stratified by the type of infection and then randomized (1:1) to one of two treatments for a total 7-day duration of treatment. The oral medications will be enclosed in a blister packet and labeled by the time of administration. A randomization scheme will maintain the blind and will be held by the EMMES statistician and accessible to a designated individual (e.g., pharmacist) at each site. Subjects with an abscess will either receive identical TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day) or 4 placebo pills twice per day. Subjects with an infected wound will either receive identical TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day, with alternating 1 identical placebo pill, twice per day), or clindamycin (300 mg, four times per day, with 3 placebo pills on alternating doses). Subjects with cellulitis will either receive identical cephalexin (500 mg, four times per day) and TMP/SMX (4 SS pills 80mg/400mg each, twice per day) or cephalexin (500 mg, four times per day) and 4 placebo pills twice per day.
Objectives:	The primary objectives for each type of SSTI studied are to compare

	the cure rates in the PP population: 1) for subjects with an acute uncomplicated cutaneous abscess receiving I&D, to determine whether the addition of TMP/SMX (4 SS pills, 80 mg/400 mg each, BID), an antibiotic with activity against CA-MRSA, is more clinically efficacious than I&D alone (4 placebo pills BID); 2) for subjects with an acute uncomplicated wound infection with any apparent drainage, to determine if clindamycin (300 mg, QID, with 3 placebo pills on alternating doses), an antibiotic with activity against CA-MRSA, MSSA, and streptococci is more clinically efficacious than TMP/SMX (4 SS pills, 80 mg/400 mg each, BID, with alternating 1 identical placebo pill, BID), an antibiotic with activity against CA-MRSA and MSSA; and 3) for subjects with acute uncomplicated cellulitis, to determine if cephalexin (500 mg, QID) and TMP/SMX (4 SS tables, 80mg/400mg each, BID), a regimen with activity against CA-MRSA, MSSA, and streptococci, is more clinically efficacious than cephalexin (500 mg, QID), an antibiotic with activity against MSSA and streptococci, and 4 placebo pills BID. The primary endpoint will be clinical cure at the TOC in the PP population (i.e., patients who meet enrollment criteria, have none of the exclusion criteria, complete 75% of the first 5 days of antimicrobial therapy, and have physical follow-up at the TOC; subjects who have been determined to be a clinical failure at any time prior to TOC who took 75% of the first 48 hours of antimicrobial therapy but who do not have physical follow-up at the TOC will also be included in the PP population).
Description of Study Design:	This is a multi-center, randomized, double-blind clinical trial in which subjects will be stratified by the type of infection and then randomized to various 7-day oral antibiotic treatments, including placebo-controlled and comparative designs. The study population will include children 13 years of age and over and adults, who weigh ≥ 40 kg presenting to 5 large urban EDs. Therapy will start on the day of enrollment. Subjects will be evaluated upon enrollment, at 2-3 days after enrollment (OTV), at 1-3 days after the end-of-therapy (EOT), and at 7-14 days after the end-of-therapy (TOC), and at 6-8 weeks after the end-of-therapy (EFV).
Estimated Time to Complete Enrollment:	Subject enrollment will occur over 3 ½ years (April, 2009 – November, 2012).

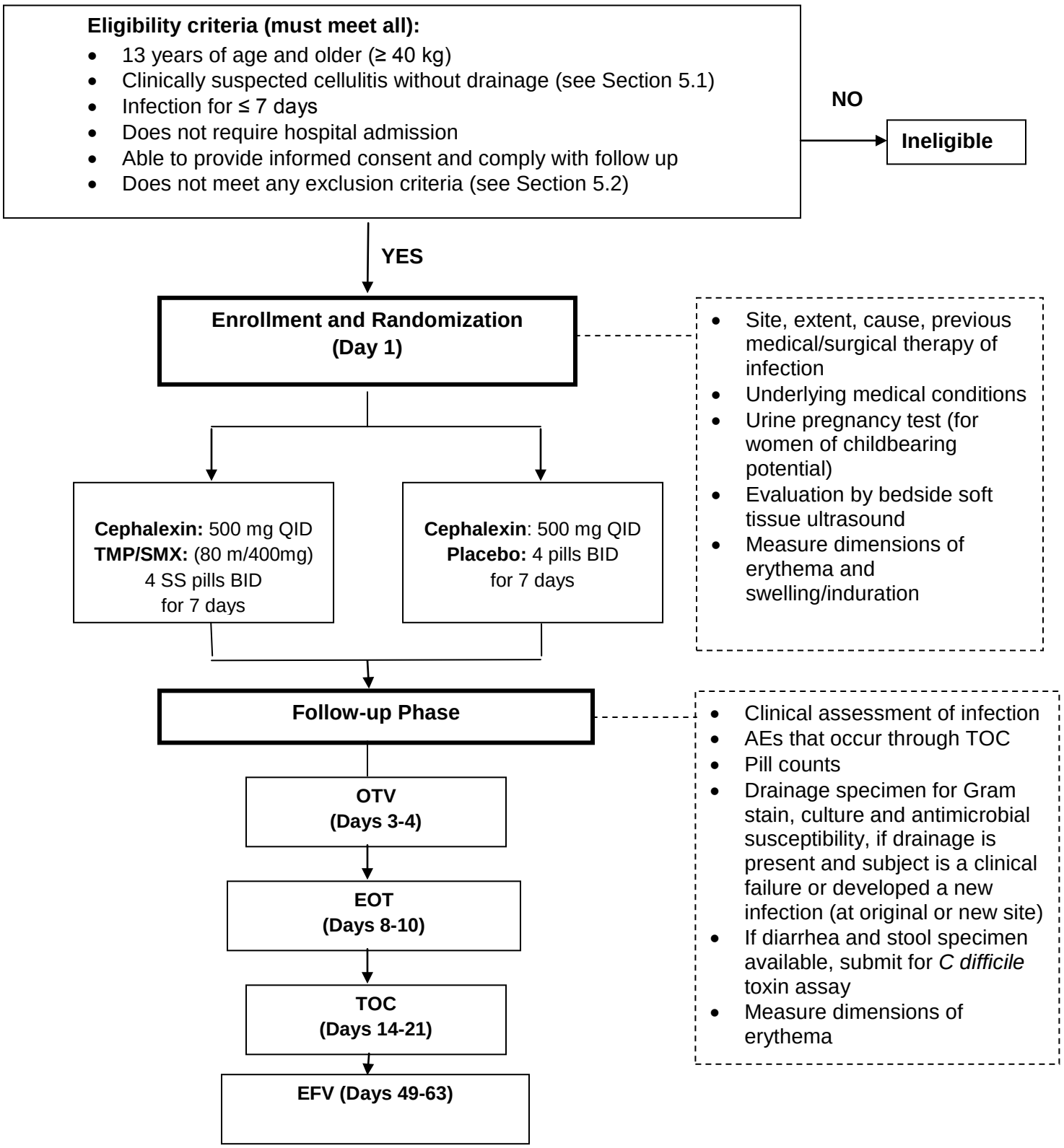
***Schematic of Study Design by Study Sub-trial:**
TMP/SMX vs. Placebo for Outpatient Treatment of Subjects with an Acute Uncomplicated Cutaneous Abscess Requiring Incision and Drainage



TMP/SMX vs. Clindamycin for Outpatient Treatment of Subjects with an Acute Uncomplicated Wound Infection



Cephalexin and TMP/SMX vs. Cephalexin and Placebo for Outpatient Treatment of Subjects with Acute Uncomplicated Cellulitis



1. Key Roles

For questions regarding this protocol, contact Christine Chiou at cchiou@niaid.nih.gov.

Individuals:

Protocol Champion:
Christine Chiou, MD
Project Officer
Bacteriology and Mycology Branch, DMID, NIAID, NIH
6610 Rockledge Drive, Room 4064, MSC 6604
Bethesda, MD 20892-6604
Phone:301-496-7728
Fax:301-402-2508
Email: CChiou@niaid.nih.gov

Lead Co-Principal Investigators:
David A. Talan, MD & Gregory J Moran, MD
Olive View-UCLA Medical Center
14445 Olive View Drive, North Annex
Sylmar, CA 91342
Phone number: 818-364-3107
Fax number: 818-364-3268
Email: dtalan@ucla.edu, gmoran@ucla.edu

Medical Monitor:
Luigi S. (Gino) Girardi, MD
Medical Officer
NIH/NIAID/DMID/OCRA
6610 Rockledge Drive, Room 4506
Bethesda, MD 20892-6603
Direct phone: 301-443-7707
Fax: 301-480-0728
Email: girardils@mail.nih.gov

Site Investigators/

Institutions:

1. Fredrick Abrahamian, DO
Olive View-UCLA Medical Center
Department of Emergency Medicine
14445 Olive View Drive, North Annex
Sylmar, CA 91342
Phone: 818-364-3112
Fax: 818-364-3268
Email: fmasjc@yahoo.com

2. David Karras, MD

Temple University School of Medicine/University Hospital
Department of Emergency Medicine
3401 Broad Street
Philadelphia, PA 19140
Phone: 215-707-5032
Fax: 215-707-3494
Email: david.karras@temple.edu

3. Frank LoVecchio, DO, MPH
Maricopa Medical Center
Department of Emergency Medicine Research
2601 E. Roosevelt St.
Phoenix, AZ 85008
Phone: 602-344-5058
Fax: 602-344-1208
Email: frank.lovecchio@bannerhealth.com

4. Richard E. Rothman, MD, PhD
Johns Hopkins University/JHMI
Department of Emergency Medicine
5801 Smith Avenue
Davis Building, Suite 3220
Baltimore, MD 21209
Phone: 410-735-6428
Fax: 410-735-6440
Email: rrothman@jhmi.edu

5. Mark Steele, M.D.
Truman Medical Center
Office of the Chief Medical Officer
2301 Holmes
Kansas City, MO 64108
Phone: 816-404-5300
Fax: 816-404-5305
Email: mark.steele@tmcmed.org

Other contacts:

William Mower, MD, PhD
Study Statistician
UCLA Emergency Department
924 Westwood Blvd., Suite 300
Los Angeles, CA 90024
Ph: (310) 794-0582
Fax: (310) 794-0599

wmower@ucla.edu

Anusha Krishnadasan, PhD
Project Director
14445 Olive View Drive, North Annex Bldg.
Sylmar, CA 91342
Phone: 818-364-3111
Fax: 818-364-3111
Email: stopmrsa@ucla.edu

DMID-CROMS Essential Regulatory Documents Group (ERDG)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817
E-mail: ERDG@dmidcroms.com
Fax: 301-897-7482
Web: www.dmidcroms.com

EMMES Corporation
401 North Washington St.
Suite 700
Rockville, MD 20850
Phone: 301-251-1161
Fax: 301-251-1355
ca_mrsa@emmes.com

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

CA-MRSA has recently emerged as a cause of SSTI.[1,2,3,4,5] In August of 2004, Moran and colleagues studied 422 adults presenting to 11 US EDs with purulent SSTIs, including abscesses (81%), infected wounds (11%), and cellulitis (8%).[1] This research was conducted through a network of EDs called *EMERGE*ncy ID NET. The network is supported by CDC and throughout the years has been involved and completed numerous infectious disease-related research projects. Fifty-nine percent (59%) of these subjects had infections caused by MRSA. Pulsed-field type USA 300 isolates accounted for 97% of MRSA isolates. SCC*mec* type IV and PVL toxin gene were detected in 98% of MRSA isolates. Of note, 27% of MRSA isolates met the epidemiologic definition of health care-associated MRSA, yet 98% of these strains had the genetic profile of CA-MRSA strains. The next most common pathogens were MSSA, which was isolated in 17% of infections, and streptococcal species, which were isolated in 7%. By type of SSTI, MRSA, MSSA, and streptococci were found in 63%, 11%, and 7% of abscesses, 61%, 13% and 10% of infected wounds, and 47%, 35%, and 18% of cellulitis cases, respectively.[1]

In this study, the in vitro susceptibilities of MRSA (99% with genetic/toxin characteristics of CA-MRSA) and MSSA to TMP/SMX, clindamycin, tetracycline, and cephalexin were as follows:

Antibiotic	**MRSA (n/total [%])**	**MSSA (n/total [%])**
TMP/SMX	217/217 (100%)	53/55 (96%)
Clindamycin	215/226 (95%)	60/63 (95%)
Tetracycline	207/226 (92%)	64/66 (97%)
Cephalexin	0/181 (0.0%)	58/64 (91%)

Despite the high prevalence of CA-MRSA in this study, penicillinase-resistant semisynthetic penicillins and first generation cephalosporins, which are inactive against MRSA, were prescribed to 64% of subjects. However, antibiotics not typically given prior to emergence of CA-MRSA were also used, including clindamycin in 18% and TMP/SMX in 16% of subjects. Among subjects with an abscess who received I&D, 77% were prescribed antibiotics.

In the current era of increasing CA-MRSA infections, the outpatient management of SSTIs has not been well studied. There are only a few recent clinical trials of intravenous antimicrobials

(e.g., vancomycin, linezolid, daptomycin, and dalbavancin) for treatment of SSTI that included subjects with MRSA infection, and in these studies CA-MRSA was not distinguished from health care-associated strains.[6,7,8] A few studies have been published on MRSA treatment with TMP/SMX and clindamycin for various infections, however these were done before the emergence of CA-MRSA.[9,10,11,12] There is one small study of clindamycin treatment of CA-MRSA infected infants and children[13], and another small, uncontrolled retrospective report of various treatments.[14] One recent clinical trial of uncomplicated SSTI comparing 2 oral cephalosporins without MRSA activity found cure rates of 95% for subjects with abscesses but only 71% for subjects with cellulitis.[15] No randomized, blinded trials of off-patent antibiotics for the treatment of CA-MRSA SSTI appear to exist in the published medical literature.

No off-patent antibiotic has a specific indication for MRSA SSTI (clindamycin has an indication for treatment of “susceptible” staphylococcal SSTIs). US FDA registration studies have been criticized because of their inclusion and consolidation of subjects with heterogeneous types of SSTIs.[16] The various types of common acute SSTI each present unique questions regarding their outpatient management in the era of CA-MRSA.

For abscesses, which are generally included in these clinical trials and which are now predominantly caused by CA-MRSA in many areas,[1,3] it is unclear whether or not treatment with antibiotics active against CA-MRSA are additionally efficacious compared to I&D alone. Previous investigations were mostly conducted before the emergence of CA-MRSA and were limited by non-randomized design, small numbers of enrolled subjects, vague outcome definitions, and/or treatment with an antibiotic not possessing appropriate in vitro activity (most recently, cephalexin for MRSA abscesses). Compared to subjects who underwent I&D and also received antibiotics, in general, these studies suggested high and similar cure rates of abscesses with I&D alone (i.e., without the addition of antibiotics).[15,17,18,19,20,21,22]

Various management recommendations for abscesses have been provided in recent authoritative publications from the IDSA,[23] The Sanford Guide® (2006),[24] and an expert panel convened by the CDC. [25] Whereas these sources acknowledge I&D as the primary treatment, they variously recommend addition of antibiotics based on the presence of fever and other signs of systemic illness, abscess size (e.g., > 5 cm)[22] or location, associated co-morbidities, extremes of age, and lack of response to I&D alone. Although consistent with common practice, we are not aware of prospectively validated data to support these recommendations. For large abscesses, The Sanford Guide® recommends TMP/SMX 2 double-strength pills twice per day for 5-10 days.[24]

Antibiotics are the primary treatment for patients with infected wounds with drainage, also called secondarily infected traumatic lesions (an FDA designated indication for topical mupirocin). Moran and colleagues also found CA-MRSA was the predominant pathogen among these infections.[1] MSSA and streptococci were the next most common pathogens. For post-traumatic infected extremity wounds, The Sanford Guide® recommends TMP/SMX 2 double-strength pills twice per day or clindamycin 300-450 mg 3 times per day.[22] Both clindamycin and TMP/SMX

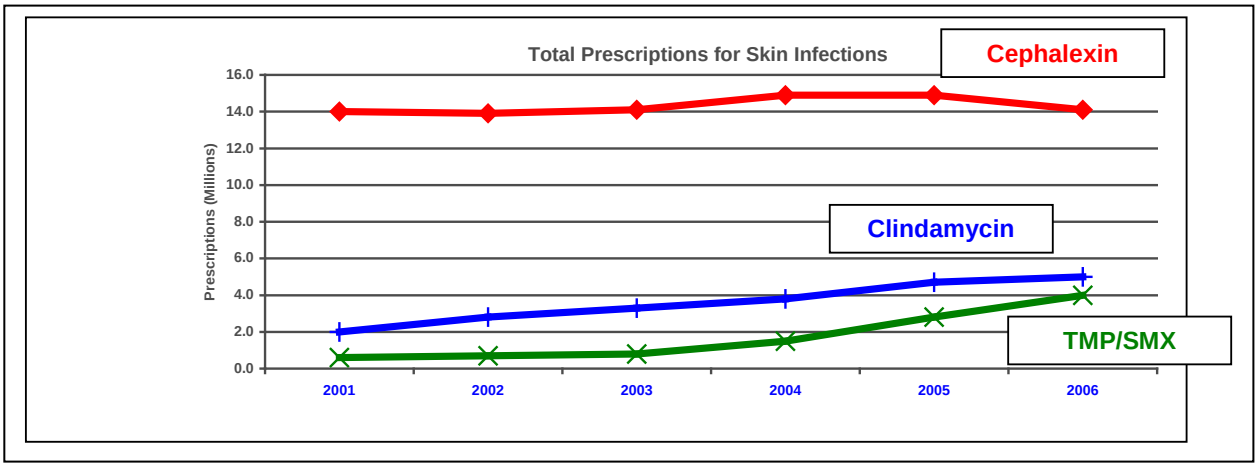
possess in vitro activity against CA-MRSA and MSSA, although in some areas of the US among CA-MRSA isolates defined by epidemiological criteria, in vitro resistance has been observed to these agents, and there have also been reports of both constitutive and inducible clindamycin resistance.[3,26,27,28] TMP/SMX is relatively inactive against streptococci compared to clindamycin. D'Oliveira and colleagues reported that approximately 78% of isolates had in vitro resistance to TMP/SMX.[29] Kaplan and colleagues reported no in vitro resistance of *S. pyogenes* to clindamycin.[30] Tricket and colleagues found that among subjects with streptococcal pharyngitis, only 70% of subjects treated with TMP/SMX had microbiological eradication compared to 88% of those who received penicillin.[31] Therefore, since clindamycin appears to have broader activity than TMP/SMX against the predominant Gram-positive pathogens, it may be more efficacious than TMP/SMX in the treatment of infected wounds.

Investigations into the etiology of cellulitis without drainage are limited by the lack of specimen availability. Studies using tissue biopsies and aspirate specimens and relying on conventional and non-conventional identification methods such as immunofluorescence and serologic testing suggest that streptococci are the predominant cause of cellulitis.[16,32,33,34,35,36,37,38,39,40] The most recent IDSA SSTI guidelines state "cellulitis that is diffuse or unassociated with a defined portal is most commonly caused by streptococcal species."[23] However, with the emergence of CA-MRSA, the role of this pathogen in these difficult-to-study infections is uncertain. Although cellulitis cases in the study by Moran and colleagues were uncommon, 47% of these cases that also had purulent drainage grew CA-MRSA, suggesting that this pathogen may have an etiologic role in cellulitis without drainage.[1] MSSA has also been noted as a pathogen in other studies.[32,33,34,35,36,37,38,39] For cellulitis, The Sanford Guide® recommends various antibiotics, none of which possess in vitro activity against CA-MRSA, including penicillin, dicloxacillin, or cefazolin.[24] Determining whether an antibiotic regimen with streptococcal and MSSA activity in addition to CA-MRSA activity (e.g., cephalexin and TMP/SMX) would be more efficacious than one without CA-MRSA activity (e.g., cephalexin alone) may help elucidate the pathogenic role of CA-MRSA in these infections.

This will be a clinical trial to evaluate oral off-patent antibiotics for outpatient treatment of patients with any of the 3 main types of acute uncomplicated SSTI, i.e., abscesses, infected wounds, and cellulitis. Upon enrollment, subjects will be stratified by type of infection, and then randomized to various treatments. Subjects with an acute uncomplicated cutaneous abscess receiving I&D will be treated with TMP/SMX or placebo to determine whether the addition of an antibiotic with activity against CA-MRSA is more clinically efficacious than I&D alone. Subjects with an acute wound infection will be treated with TMP/SMX or clindamycin to determine if clindamycin, an antibiotic with activity against CA-MRSA, MSSA, and streptococci is more clinically efficacious than TMP/SMX, an antibiotic with activity against CA-MRSA and MSSA. Subjects with acute cellulitis will be treated with cephalexin/TMP/SMX or cephalexin/placebo to determine if cephalexin/TMP/SMX is more clinically efficacious than cephalexin alone.

2.2 Rationale

The choices of antibiotics and comparisons were based on consideration of the most current and authoritative references regarding standards of treatment for SSTIs (i.e., the IDSA SSTI treatment guidelines, the CDC Expert Panel, and The Sanford Guide®). Further, comparisons were reviewed and endorsed by outside experts, including some involved in these publications. Moran and colleagues' recently published study of MRSA among ED patients with SSTI revealed that cephalexin, clindamycin, and TMP/SMX were among the most common antimicrobials used for treatment of SSTIs.[1] In addition, between 2001 through 2006, audit data of the three most frequently prescribed antibiotics for SSTI revealed continued use of cephalexin and increasing use of clindamycin and TMP/SMX.[41]



Prescriptions (Millions)	2001	2002	2003	2004	2005	2006
Cephalexin	14.0	13.9	14.1	14.9	14.9	14.1
Clindamycin	2.0	2.8	3.3	3.8	4.7	5.0
TMP/SMX	0.6	0.7	0.8	1.5	2.8	4.0

Currently, of all the off-patent antibiotic options, it appears that TMP/SMX has retained the most consistent activity against CA-MRSA. Since CA-MRSA is the predominant pathogen of cutaneous abscesses (and streptococci are rarely found), this antibiotic was selected to compare with placebo in those infections also treated with I&D. Many clinicians still appear to use cephalexin to treat SSTI, and we considered inclusion of this antibiotic as a treatment option for patients with infected wounds. However, consensus amongst various reviewers was that since cephalexin lacked MRSA activity, it posed an ethical/IRB conflict for the treatment of a type of SSTI frequently caused by this pathogen. However, for cellulitis, in which there exists a consensus that streptococci are the most important etiologic bacteria, cephalexin was considered a current practice standard and therefore a reasonable choice to compare with cephalexin plus TMP/SMX, an agent possessing CA-MRSA activity. Clindamycin was considered as a potential comparator to cephalexin. However, although 95% of CA-MRSA isolates from ED patients with SSTI demonstrated in vitro susceptibility to clindamycin in 2004,[1]

there have been increasing reports of clindamycin resistance among CA-MRSA isolates.[26] A survey of the 2006 antibiograms of the 5 investigative site EDs revealed an average MRSA susceptibility rate to clindamycin of 85% (range, 75% to 95% by site). CA-MRSA susceptibility to TMP/SMX appears to have remained more consistent than to clindamycin. Therefore, the combination of cephalexin/TMP/SMX would appear to be the better choice in order to evaluate and isolate the role of CA-MRSA in cellulitis than clindamycin. Also, for patients with an infected wound with drainage, TMP/SMX will be directly compared to clindamycin, and, as opposed to cellulitis, a culture specimen will be available in order to evaluate the effect of in vitro resistance of isolates to the treatment antibiotic if this should be observed.

Tetracycline class antibiotics were not chosen because of teratogenicity concerns. Rifampin was excluded based on rapid emergence of resistance of MRSA when this drug is used as monotherapy.[42] Rifampin was not proposed as a combination drug because no evidence exists of benefit from adding rifampin to another agent (e.g., TMP/SMX) for SSTI treatment.

Although one DS TMP/SMX would be expected to achieve serum levels above the MIC of CA-MRSA, concentrations in skin blister fluid are approximately 50% of serum and near *S. aureus* MIC breakpoints.[43] Therefore, in order to best test the efficacy of TMP/SMX, and to be consistent with current standard antibiotic recommendations, a regimen of 4 SS pills per day was elected.[22] (Note that SS pills were chosen instead of DS, because it was felt that the large size of over-encapsulated DS pills may decrease subject compliance in taking their study drug.) Similarly, for other antibiotic treatments, the higher end of the recommended dosage range was chosen.

The optimal duration of therapy for SSTI has not been clearly established. For most clinical trials the treatment duration is 7-10 days. One study of uncomplicated cellulitis reported that 5 days of levofloxacin was as clinically efficacious as 10 days, and another revealed that 85% of patients treated with dirithromycin for 5 days had clinical success.[44,45] Therefore, we have chosen 7 days as the duration of treatment for the 3 infection types. The study methods are consistent with FDA guidance to industry. [46]

The use of a research network of 5 geographically diverse sites will increase the chance that the study will be representative of antimicrobial susceptibility patterns throughout the US. All site hospitals are university-affiliated with strong research departments, and are currently affiliated with *EMERGE*ncy ID NET. All sites have the infrastructure and experience necessary to conduct multi-site research studies. They are equipped with a clinical pharmacy with several years of experience in storing and dispensing study drugs for clinical trial studies. Furthermore, they all possess on-site clinical microbiology laboratory facilities that are capable of conducting the necessary tests required for the proposed studies. All sites have a hospital information system that is accessible by investigators and study coordinators to collect laboratory results and other necessary data required for the proposed studies (although this system will have limited accessibility to investigators to maintain blinding of culture and susceptibility results for subject follow-up visits). Finally, all institutions have a team available on-site to troubleshoot and

provide information technology and network support for study personnel, delivering technology consulting, installations, migrations, upgrades, procurement and continuing support services.

Primary Hypotheses:

For subjects with an acute uncomplicated abscess receiving I&D, the clinical cure rate of subjects treated with TMP/SMX will be superior to that of subjects treated with placebo (i.e., the lower bound of the 95% CI around the difference in cure rates will be ≥7.5%) in the PP population at the TOC.

The clinical cure rate of subjects with an infected wound treated with clindamycin will be superior to that of subjects treated with TMP/SMX (i.e., the lower bound of the 95% CI around the difference in cure rates will be ≥ 10%) in the PP population at the TOC.

For subjects with acute uncomplicated cellulitis, the clinical cure rate of subjects treated with cephalexin and TMP/SMX will be superior to that of subjects treated with cephalexin alone (i.e., the lower bound of the 95% CI around the difference in cure rates will be ≥ 10%) in the PP population at the TOC visit.

2.3 Potential Risks and Benefits

The risks and benefits for subjects enrolled in this trial are appropriately balanced. All of the study interventions are consistent with common clinical practice. The drugs under study (e.g., cephalexin, TMP/SMX, clindamycin) have been in use for many years and are currently the most common antibiotics used for SSTI, and clinicians are aware of their AE profile.

2.3.1 Potential Risks

The risks to subjects enrolled in the studies will be comparable to those encountered by similar patients receiving standard care. These risks include complications of I&D (i.e., standard care for abscesses), and adverse reactions (AEs) to medications (see below).

Subjects will be carefully screened to ensure that they meet study inclusion criteria, and do not have any exclusion criteria that would put them at unnecessary risk from study participation. Subjects will be followed at prescribed follow-up visits, as indicated, and will have access 24-7 to on-call study coordinators, investigators, and emergency care if questions should arise and if there is any suspicion of worsening.

Subjects will be carefully screened for progression to invasive infection or other possible SAEs at each study visit, and will be provided with information to contact the study team for any possible AE that occurs between visits. Subjects with findings suggestive of possible invasive infection (including osteomyelitis, septic arthritis, necrotizing fasciitis, bacteremia, pneumonia, endocarditis, or meningitis) will have the appropriate investigations performed. SAEs will be reported to the medical monitor as described in Section 9, and appropriate medical treatments

will be provided at the study site institutions, all of which are prepared to provide comprehensive inpatient and outpatient care. Soft tissue ultrasound is non-invasive, enhances diagnostic accuracy, and is standard treatment in the participating site EDs, and therefore, poses no study-associated additional risk.

The study will be done in full compliance with 45 CFR 46 (Protection of Human Subjects) and the Privacy Act. Procedures for managing PHI will be included in the written ICF. Numerous safeguards will be put in place to ensure the confidentiality and integrity of all data, addressing both the human and physical elements of protecting subject confidentiality. These include data management staff training in human subjects' protection and the ethical conduct of human research, systematic backup for the centralized database, use of encrypted data on durable media, and utilization of encryption and role-based access mechanisms for remote access in compliance with industry best practices and consistent with security and privacy requirements of site IRBs. Any paper documentation containing PHI, such as informed consent documents, will be stored securely by study staff. Consistent standards will be maintained as data passes between the study sites and the central site.

Depending on the stratification sub-trial and randomization, a subject may receive TMP/SMX, cephalexin, clindamycin, and/or placebo. From the review of the most recent PDR (2007), the following precautions, interactions, and AEs are reported with these medications:

TMP/SMX

Precautions:

AIDS, folate or G-6-PD deficiency, history of allergy, and rash. (Note: development of rash at any point while on study drug will result in discontinuation of study drug).

Interactions:

May potentiate oral anticoagulants, hypoglycemics, phenytoin, digoxin,and methotrexate, may be potentiated by indomethacin, and may increase risk of thrombocytopenia with diuretics (esp. thiazides).

Adverse reactions:

GI upset, blood dyscrasias (e.g., megaloblastic anemia), hemolysis, hepatic or renal toxicity, crystalluria, pancreatitis, photosensitivity, drug fever, rash (may be serious, e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis), lupus-like syndrome, peripheral neuritis, depression, convulsions, and ataxia.

Cephalexin:

Precautions:

Penicillin or other allergy, severe renal dysfunction, and GI disease (especially colitis).

Interactions:

Potentiates metformin, and is potentiated by probenecid.

Adverse reactions:

GI disturbances, dizziness, fatigue, headache, hypersensitivity reactions, and itch; rare: blood dyscrasias and elevated liver enzymes.

Clindamycin:

Precautions:

Allergy, GI disease (especially colitis)

Interactions:

May potentiate neuromuscular blocking agents, and may antagonize erythromycin and antiperistaltic agents

Adverse reactions:

Pseudomembranous colitis, diarrhea, GI upset, rash, anaphylaxis, jaundice, renal dysfunction, blood dyscrasias, and polyarthritis.

Note: Package inserts or supplemental drug manual for all study drugs (TMP/SMX, clindamycin, and cephalexin) will be made available to all investigators as part of the IB.

Complications resulting from I&D are uncommon. To prevent contaminating surrounding skin and spread of the infection, the skin over the abscess will be cleansed with a topical antiseptic solution, e.g., betadine and/or 70% isopropyl alcohol, and allowed to dry. The clinician will attempt to keep the area as clean as possible and devoid of unnecessary contamination. Pain associated with the procedure is minimized by using local anesthetics. Bleeding associated with I&D is usually minimal and stops spontaneously or with local pressure. In most cases, some scarring will result at the site of the incision.

2.3.2 Known Potential Benefits

All of the study interventions are standard, and all of the drugs under study are currently used for these conditions. The definitive treatment of choice for a soft-tissue abscess is I&D. This procedure allows for rapid decompression of purulent collections, which in turn results in a significant improvement in symptoms and a rapid resolution of infection. Study participants will

receive study drugs free of charge. An additional benefit is that subjects enrolled in the study will have much more intensive follow-up than would be routinely provided for ED patients in these facilities, and therefore, any complication or treatment failure may be addressed more promptly.

3 OBJECTIVES

3.1 Study Objectives

The primary objectives for each type of SSTI studied are to compare the cure rates in the PP population:

1) for subjects with an acute uncomplicated cutaneous abscess receiving I&D, to determine whether the addition of TMP/SMX (4 SS pills, 80 mg/400 mg each, BID), an antibiotic with activity against CA-MRSA, is more clinically efficacious than I&D alone (4 placebo pills BID);

2) for subjects with an acute uncomplicated wound infection with any apparent drainage, to determine if clindamycin (300 mg, QID, with 3 placebo pills on alternating doses), an antibiotic with activity against CA-MRSA, MSSA, and streptococci is more clinically efficacious than TMP/SMX (4 SS pills, 80 mg/400 mg each, BID, with alternating 1 identical placebo pill, BID), an antibiotic with activity against CA-MRSA and MSSA; and

3) for subjects with acute uncomplicated cellulitis, to determine if cephalexin (500 mg, QID) and TMP/SMX (4 SS tables, 80mg/400mg each, BID), a regimen with activity against CA-MRSA, MSSA, and streptococci, is more clinically efficacious than cephalexin (500 mg, QID), an antibiotic with activity against MSSA and streptococci, and 4 placebo pills BID.

Secondary objectives provide additional means of assessment for the clinical efficacy of the employed interventions and resolution of the infection and include describing microbiological cure, change in the dimension of erythema, composite cure, surgical procedures, invasive and recurrent infections, infections in household contacts, and time to normal activity and until analgesics are no longer used at various times in the PP/mITT populations.

Furthermore a secondary analysis of the ITT population (specifically, mITT, i.e., all subjects receiving at least one dose of the study drug) will also be conducted to assess any potential role of post-randomization drop-out on the findings of the PP analysis.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

Primary Outcome measures: Clinical cure at the TOC in the PP population.

Clinical Cure Definition at TOC:

- No failure on any previous visit

- Absence of fever, and
- Resolution *or* minimal presence of all the following signs and symptoms from baseline based on clinician assessment:
  - Erythema
  - Swelling
  - Tenderness

Primary Outcome population:

PP population - Subjects who meet enrollment criteria, have none of the exclusion criteria, complete 75% of the first 5 days of antimicrobial therapy, and have physical follow-up at the TOC. Subjects who have been determined to be a clinical failure at any time prior to TOC who took 75% of the first 48 hours of antimicrobial therapy but who do not have physical follow-up at the TOC will also be included in the PP population.

3.2.2 Secondary Outcome Measures

Secondary outcome measures include: rates of change of the dimensions of erythema, composite (antibiotic/surgical) clinical cure, microbiological cure, surgical procedures, and invasive and recurrent infections. Furthermore, infections in household contacts, medication AEs, and time to normal activity and until analgesics are no longer used in the PP/mITT populations will be assessed by patient response at follow-up visits.

Secondary outcome definitions:

Composite clinical outcome:

Cure - resolution of all symptoms/signs of infection, or improvement to such an extent that no additional antibiotic therapy and/or surgical procedures are necessary.

Failure – lack of resolution of all signs and symptoms of infection to such an extent that further antibiotic therapy and/or surgical procedures are necessary.

Microbiological Outcome:

Cure (Presumed eradication) - not deemed a clinical failure through TOC

Failure – a clinical failure at any time up to or through TOC and further characterized as follows:

Persistence - persistent growth of a pre-therapy pathogen.

New infection - growth of a new pathogen and eradication of initial pathogen.

Super-infection - growth of a new pathogen in addition to persistent growth of pre-therapy pathogen.

Unclassified –

- no specimen present for culture, or
- growth of a pathogen in subsequent culture specimen of subjects with cellulitis.
- growth of a pathogen in subsequent culture specimen of subjects with abscess or infected wound for whom initial culture specimens were negative or were not obtained.

Indeterminate – not meeting any one of the above microbiologic outcome criteria.

Definitions for mITT population and analysis:

mITT population - Subjects who take at least one dose of study medication

The outcome of interest in the mITT analysis is the assessment at the TOC. The following definitions for cure and failure will be used.

Cure: No change in antibiotic therapy due to persistence or worsening of infection (based on study clinician assessment, the subject's assessment, or assessment by another outside clinician) prior to or through TOC.

Failure: Subject had a change in antibiotic therapy due to persistence or worsening of infection (based on study clinician assessment, the subject's assessment, or assessment by another outside clinician) at any time up to or through TOC.

4 STUDY DESIGN

This is a multi-center, randomized, double-blind, phase IIB clinical trial to evaluate oral off-patent antibiotics for outpatient treatment of subjects with any of the 3 main types of acute SSTI, i.e., abscesses, infected wounds, and cellulitis, with the primary objective of determining optimal antibiotic treatment. Subject enrollment will occur over 3 ½ years at 5 US EDs.

Subjects will be 13 years of age and older with acute uncomplicated infections who provide informed consent. The study will be double-blinded with subjects randomized to identical treatments with antibiotics and/or placebo for 7 days. Infection classification, wound care, and outcome assessment will be standardized prior to study initiation. Subjects will be evaluated after 2-3 days of treatment (OTV; Days 3-4), and at 1-3 days after end-of-therapy (EOT; Days 8-10), 7-14 days after end-of-therapy (TOC; Days 14-21), and 6-8 weeks after end-of-therapy (EFV; Days 49-63). Therefore, subjects will participate for approximately 9 weeks.

Upon enrollment, subjects will be stratified by type of infection, and then randomized to various oral treatments. In order to minimize the chance of misclassification of the type of infection, all subjects will be evaluated by bedside soft tissue ultrasound, which has been demonstrated to be effective at identifying occult abscesses.[47]

Subjects with an acute uncomplicated cutaneous abscess receiving I&D will be treated with TMP/SMX or placebo to determine whether the addition of an antibiotic with activity against CA-MRSA is more clinically efficacious than I&D alone. Subjects with an acute uncomplicated wound infection will be treated with TMP/SMX or clindamycin to determine if clindamycin, an antibiotic with activity against CA-MRSA, MSSA, and streptococci is more clinically efficacious than TMP/SMX, an antibiotic with activity against CA-MRSA and MSSA. Subjects with acute uncomplicated cellulitis will be treated with cephalexin and TMP/SMX or cephalexin and placebo to determine if a regimen with the addition of TMP/SMX, an antibiotic with activity against CA-MRSA, is more clinically efficacious than cephalexin alone, an antibiotic with activity against MSSA and streptococci but not CA-MRSA.

The primary outcome will be clinical cure at the TOC in the PP population (subjects who meet enrollment criteria, have none of the exclusion criteria, complete 75% of the first 5 days of antimicrobial therapy, and have physical follow-up at the TOC; subjects who have been determined to be a clinical failure at any time prior to the TOC who took 75% of the first 48 hours of antimicrobial therapy but who do not have physical follow-up at the TOC will also be included in the PP population).

Secondary endpoints will include microbiological cure, change in the dimension of erythema, composite cure, surgical procedures, invasive and recurrent infections, infections in household

contacts, and time to normal activity and until analgesics are no longer used at various times in the PP/mITT populations.

Upon enrollment, information on the site, extent, cause, previous history of SSTI and relevant medical/surgical therapy, underlying medical conditions, and infections in household contacts will be obtained. The dimensions of erythema will be measured. Drainage material will be collected for Gram stain, culture, and antimicrobial susceptibility testing prior to antibiotic treatment by standard cotton swabs after I&D of abscesses or from open lesions (i.e., infected wounds with drainage).

All clinicians and study personnel participating in the study will receive standardized training (using training modules containing specific procedures as well as video demonstrations created by the main site) prior to study commencement to insure their knowledge of the definitions of abscess, infected wound, and cellulitis, use of ultrasound to evaluate the SSTI, wound assessment and measurement, and outcomes.

Follow-up evaluations will be in person but, if not possible, will be by telephone. Evaluations will include clinical assessment of the infection and medication AEs up through TOC. The rate of resolution of the infection will also be followed by measuring the dimensions of erythema. For telephone evaluations, the subject will be asked if swelling/induration, tenderness, and the dimensions of erythema has decreased, increased or stayed the same. At the TOC, the subject will be examined for fever, erythema, swelling, and tenderness in order to categorize their condition at the time as a cure or failure. Compliance will be judged by pill counts of blister packets. If blister packs are lost or unavailable, the memory aid will be used to record study medication compliance. If neither blister pack nor memory aid are available, study medication compliance will be obtained by subject interview. In addition, a digital thermometer will be provided to all enrolled subjects to monitor occurrence of fever between follow-up visits. This information can be recorded by the subject in the memory aids provided at enrollment. Subjects will also keep a record of days to return to normal activity and until analgesics are no longer used, and days of missed work. If the memory aid is lost or incomplete, an attempt will be made to recreate it or fill in missing information through subject interview by asking subjects to recall the answers.

Subjects will be screened carefully at entry and follow-up visits for possible invasive infection looking for findings such as vital sign abnormalities and toxicity (sepsis), abnormal cardiac murmur (endocarditis), a red, swollen joint (septic arthritis), respiratory symptoms, abnormal lung exam, and new chest X-ray infiltrate (pneumonia), necrotic bone or abnormal X-ray (osteomyelitis), and a SSTI with severe pain, swelling, vascular insufficiency and/or radiographic soft tissue gas (necrotizing fasciitis). Investigators will follow subjects with invasive disease and SAEs until resolution (or deemed stable/chronic).

The only laboratory test required at the time of pre-enrollment is a urine pregnancy test, which will be conducted at the site hospital laboratory or in the ED. A pregnancy test will be performed

in all women of childbearing potential who have not been surgically sterilized. No other laboratory or radiographic evaluation is required by the study, unless it is deemed necessary by the investigator. Since the AEs of the study drugs are well known, baseline studies and serial testing to identify asymptomatic abnormalities of renal, hepatic, and hematopoietic function will not be conducted unless, based on the judgment of the investigator, they are clinically indicated.

At enrollment, for subjects in the infected wound and abscess sub-trials, drainage material, if present, will be submitted for Gram stain, culture, and susceptibility testing (drainage material will be obtained prior to antibiotic treatment by standard cotton swabs of drainage material after I&D or from open lesions). MRSA and MSSA isolates that exhibit erythromycin resistance and clindamycin susceptibility will be further tested for inducible resistance to clindamycin using the D-test. Culture and susceptibility results will not be readily available to study investigators, study staff, and clinicians involved in evaluating subjects at follow-up visits. Research-related microbiology results will be restricted so that they are not easily available in hospital information systems (e.g., with general laboratory results) and can only be accessed by the study coordinators in case emergency unblinding of microbiology results is necessary with special approval of the site investigator or after subjects have completed the study protocol. During follow-up, if a subject is a clinical failure, develops a recurrent infection at the original site, or a new infection at another site and there is drainage available, a wound culture specimen will be obtained and submitted for culture and susceptibility testing.

Clinical Failure Definitions:

At any visit up to the TOC, only failure will be designated as an outcome. Any subject outcome designated as a failure at any time before and including the TOC will be categorized as a failure for the PP analysis. Criteria for failure will mandate rescue therapy and will vary at the OTV, EOT, and TOC, and will become progressively more stringent as to the requirements for improvement.

Measures of improvement will be assessed at each visit, starting with the OTV, including serial change in the dimensions of erythema, time to return to normal activities, and no need for pain medications. The border of erythema will be marked with a pen at the initial visit, and used for comparison for subsequent assessments. Training as to standardized technique to mark and measure the dimensions of erythema will be given prior to the study.

At OTV:

Failure:

- Presence of fever (attributable to the infection being studied), or
- Increase in either the length or width of erythema > 25%, or
- Both of the following show worsening based on clinician assessment:
  - Swelling

- Tenderness

Subjects who are determined to be failure at OTV will be taken off the study regimen and may receive rescue therapy as described below. Failure will be designated as an outcome by these criteria between the enrollment visit and EOT.

At EOT:

Failure:

- Presence of fever (attributable to the infection being studied), or
- Increase or no improvement in either the length or width of erythema from baseline, or
- None of the following show improvement from baseline based on clinician assessment:
  - Swelling
  - Tenderness

Subjects who are determined to be a failure at EOT may receive rescue therapy as below.

Note: By completion of the full duration of study drug, 7 days, it is expected that the dimensions of erythema will have decreased and swelling and tenderness will have improved (and that fever will not be present). Therefore, failure at the EOT includes subjects who have no improvement in the dimensions of erythema or swelling and tenderness whereas at the OTV (and up to the EOT), an increase of > 25% in either the length or width of erythema or worsening of both swelling and tenderness are required to be designated as a failure. Failure will be designated as an outcome by these criteria no sooner than the EOT but at any time after the EOT and up to TOC.

At TOC:

- Failure at any previous visit
- Presence of fever (attributable to the infection being studied), or
- More than the minimal presence of any of:
  - Erythema
  - Swelling
  - Tenderness

Subjects who are determined to be failures at TOC may receive rescue therapy as described below. By the TOC, 7-14 days after completion of the study drug, it is expected that erythema, swelling, and tenderness (due to infection) be completely resolved or minimally present (and that fever will not be present). Therefore, failure at the TOC includes subjects with more than minimal erythema, swelling, or tenderness whereas at EOT, an increase or no improvement in the dimensions of erythema, or no improvement in both swelling and tenderness is required to be designated as a failure.

Algorithms for rescue therapy for clinical failures:

The following algorithms are recommendations/guidelines and treatment decisions are ultimately left up to the treating clinician.

At any point that the investigator determines that a subject is a clinical failure, the infection will be evaluated by soft tissue ultrasound in order to classify the type of infection present at the time of failed therapy (i.e., abscess, infected wound, or cellulitis), drainage material, if present will be submitted for Gram stain, culture, and susceptibility testing, and the following algorithms for rescue therapy may be used in order to minimize unblinding of the study drug assignment (see MOP).

Abscess:

The study coordinator will obtain culture and susceptibility data from the enrollment visit and notify the site PI or surrogate. If the subject does not require admission for IV antibiotics and the organism(s) is/are susceptible to an alternate agent such as cephalexin, clindamycin, or doxycycline, or there is no growth, then the treatment will not be unblinded and the clinician can choose one of these agents. If the subject does not require hospital admission for parenteral antibiotics and there is no suitable oral regimen other than TMP/SMX (e.g., MRSA resistant to clindamycin and doxycycline), then the clinician may request that the treatment be unblinded so that TMP/SMX could be used for those who were randomized to placebo. If the subject had been randomized to TMP/SMX and failed that regimen, then the clinician may opt to admit for parenteral vancomycin, or may treat with an oral agent such as linezolid.

If the subject requires IV antibiotics, and the organism(s) is/are susceptible to vancomycin or linezolid, then the clinician evaluating the subject will not be unblinded and may choose one of these agents. If the subject requires further I&D it will be performed in the ED or in the hospital, as deemed appropriate by the treating clinician.

Infected Wound:

The study coordinator will obtain culture and susceptibility data from the enrollment visit and notify the site PI or surrogate. If the subject does not require admission for IV antibiotics and if the organism(s) is/are susceptible to an agent that is not part of the study protocol (i.e., neither TMP/SMX nor clindamycin) such as cephalexin or doxycycline, or there is no growth, then the treatment will not be unblinded and the clinician can choose one of these agents. If the subject does not require hospital admission for parenteral antibiotics, there is no suitable non-study protocol oral regimen, and the pathogen is susceptible to one or both of the study drugs (e.g., MRSA resistant to clindamycin and doxycycline but susceptible to TMP/SMX), then the treating clinician may request that the treatment be unblinded so that one of the study drugs could be used for those who had been randomized to the other agent.

If the subject requires admission to the hospital for IV antibiotics and the organism(s) is/are susceptible to vancomycin or linezolid then the clinician evaluating the subject will not be unblinded and may choose one of these agents.

Cellulitis:

Subjects who are a treatment failure but believed to be suitable for outpatient treatment with oral medication may be treated with clindamycin or doxycycline. These agents were selected because they are not part of the study sub-trial regimens, and are likely to be active against streptococci and most MRSA and MSSA. If the subject has allergies to clindamycin or doxycycline then the treatment assignment will be unblinded and if a subject was initially treated with cephalexin, they may be further treated with TMP/SMX. If the subject was initially treated with TMP/SMX and cephalexin, they may be further treated with either oral linezolid or admitted to receive IV vancomycin.

If a subject requires admission for IV antibiotics, then the clinician will not be unblinded and the subject will be treated with either vancomycin or linezolid.

Note that subjects in the cellulitis sub-trial may develop an abscess during follow-up, and thus require I&D and wound culture. If a newly formed abscess is found upon ultrasound evaluation, I&D will be performed either in the ED or in the hospital, as deemed appropriate by the treating clinician. If there is drainage material available for culture at the time the subject is deemed a treatment failure, then cultures will be obtained and further treatment guided by those results.

At any time during the study period if the subject experiences diarrhea and is able to provide a stool specimen, the specimen will be submitted for a *C. difficile* toxin assay.

Data will be collected on source documents and eCRFs developed by the study investigators in conjunction with EMMES. All sites will be equipped with a computer with Internet access and Internet Explorer 5.5 or higher to access the IDES, created by EMMES. This system will allow site investigators to access study materials, ICFs, and eCRFs on a secured website, and enter data. Within 72 hours of enrollment and each follow-up visit, data will be entered by study coordinators onto EMMES' secure web-based data management system. Source documents and data entry will be checked for consistency, accuracy, and completeness by study coordinators and site investigators (see QM plan). Source documents will be kept in the study staff office in locked file cabinets. Upon completion of subject enrollment, data will be rechecked for accuracy and completeness by the study coordinators and site investigators, with the assistance of EMMES, and sent to the study statistician for final data analyses. Patient identifiers will be removed from all data sets after data cleaning.

Study drug management will be accomplished by Fisher Bioservices (the DMID Regulatory Support Contractor), the site pharmacies, site investigators, and the study coordinators. Fisher Bioservices will package, label and distribute study drugs to all sites. The site pharmacies will store, manage, dispense study drugs to study participants, and destroy unused study drugs

(upon written approval from DMID), with the assistance of the study coordinators. Once the study drug reaches the site, study drug management is the responsibility of the site investigator. The EMMES system described above will be used to manage subject enrollment, randomization, and treatment allocations, and to track withdrawals.

During the trial, CROMS will conduct periodic monitoring visits to all sites to ensure that the protocol and GCP are being followed, in compliance with federal regulatory requirements and DMID policies and procedures. The monitors will review source documents to confirm that the data recorded on eCRFs are accurate. They will also meet periodically with laboratory and pharmacy personnel to ensure QC for laboratory analyses and to ensure that the protocol is followed.

To assure that study participants are not exposed to unnecessary or unreasonable risks and that the study is being conducted according to high scientific and ethical standards, an independent DSMB will be appointed to monitor the clinical trial as per DMID guidelines. To avoid any appearance of conflict of interest, DSMB members will not be involved in the study under review, have no vested interest in its outcome, have no ties to the study investigators, and have no financial ties to any commercial concerns likely to be affected by the study's outcome. This committee will be informed of each subject's group assignment (A vs B), but will be blinded with respect to which group received which study drug. The DSMB will have three responsibilities:

1) Overseeing identification, enrollment, and randomization procedures to detect any evidence of bias;

2) Monitoring AEs (including invasive infection) to determine if they occur disproportionately (see Section 9.5) in one treatment group per study sub-trial; and

3) Tracking key clinical outcomes to determine if one treatment group does significantly better than the other.

To assist the DSMB in its work, the EMMES statistician will monitor the progress of the study. The EMMES statistician will report to the DSMB on a regularly scheduled basis to be determined by the DSMB (see DSMB charter).

The following sample sizes are estimated to be necessary to evaluate each SSTI subgroup. For subjects with an abscess receiving I&D, to determine if the clinical cure rate for subjects treated with TMP/SMX is superior to that of subjects treated with placebo, it is necessary to enroll at least 1074 evaluable subjects (at least 1265 subjects assuming 15% attrition; Note: The sample size for the abscess sub-trial was re-estimated in October, 2010 based on results of the 75% enrollment interim analysis conducted by the DSMB and EMMES statistician per Section 11.3). For subjects with an infected wound, to determine if the clinical cure rate for subjects treated with clindamycin is superior to that of subjects treated with TMP/SMX (i.e., >95% vs. 85%), it is necessary to enroll at least 426 evaluable subjects (at least 500 subjects assuming 15%

attrition). For subjects with cellulitis, to determine if the clinical cure rate for subjects treated with cephalexin and TMP/SMX is superior to that of subjects treated with cephalexin alone (i.e., >95% vs. 85%), it is necessary to enroll at least 426 evaluable subjects (at least 500 subjects assuming 15% attrition). These enrollment goals approximate 4 subjects per month for each infection type at each site, an achievable rate considering that approximately 10 subjects per week were enrolled at each site in the previous SSTI study by Moran and colleagues and the enrollment criteria are more inclusive in the present study.[1]

Interim analyses will be performed by the EMMES statistician and presented to the DSMB, when 50% of subjects are enrolled and again when 75% of subjects have been enrolled per study sub-trial. Interim analyses of safety information will involve the examination of the incidence, severity and type of AEs reported during the study (See Section 11.3). The DSMB and EMMES statistician will also monitor the progress of the study in order to ensure that sites are meeting target subject enrollment rates.

4.1 Sub-studies (if applicable)

Not Applicable.

5 STUDY ENROLLMENT AND WITHDRAWAL

The study's aim is to enroll at least 2,235 subjects 13 years of age and older from US urban, academically-affiliated EDs (note that at the Kansas City, MO site, only subjects 18 years of age and older will be enrolled). It is anticipated that most subjects will have good baseline health, but subjects with most chronic medical conditions will not be excluded, other than those described in the exclusion criteria (see Section 5.2).

Women and minorities will be included in the study population; however our Baltimore, MD site will not be enrolling Spanish-speaking patients (which only comprise about 2% of their patient population) due to logistical difficulties in obtaining a translator for consent procedures. The study site EDs serve populations in which diverse racial and ethnic groups are well represented. The racial breakdown of subjects in our previous study of SSTI through the *EMERGE*ncy ID NET was: white non-Hispanic (28%), black non-Hispanic (44%), Hispanic (26%), other (2%). Patients who are institutionalized or prisoners will be excluded from enrollment. Women of childbearing potential will not be excluded, but will have a negative pregnancy test documented prior to enrollment because of concern about possible teratogenic effects of study medications.

Women of childbearing potential will be instructed to use adequate contraception, defined as hormonal contraception, intrauterine device, barrier methods (condom or vaginal diaphragm) with spermicide, or abstinence while taking the study drug. The pre-study pregnancy test (urine or serum pregnancy test) must be negative. Women who have been surgically sterilized or are at least two years postmenopausal may be enrolled and do not have to use birth control. Women whose method of birth control is hormonal are instructed to use additional barrier methods during therapy.

Children 13 years of age and older who weigh ≥ 40 kg will be included in the study population. Children less than 13 will be excluded because of difficulty providing blinded study medications in all pediatric dosing ranges. An estimated 5% of subjects are expected to be between the ages of 13 and 17 years, and, therefore, approximately 100 children are expected to be enrolled.

While the demographic diversity of the ED population that includes many at-risk persons is a strength of the program's representativeness, many ED patients have a relative lack of financial and social support resources to facilitate follow-up evaluations. All proposed EDs have experience with managing follow-up of these patients in clinical trials. It is anticipated that each of the 5 sites will be supported with a full-time study coordinator and on-call coverage to achieve 24 hours/7 days a week enrollment and adequate subject follow-up. To further facilitate follow-up, subjects will be provided reasonable funds for transportation to follow-up evaluations in accordance with local IRB guidelines and with prior approval.

ED staff and clinic doctors will be educated about the study objectives and procedures prior to subject enrollment. Posters will be placed in the ED doctors work room area indicating study enrollment criteria. Treating clinicians will determine whether a patient meets the following eligibility criteria:

- Patients ages 13 years and over;
- Patients with an uncomplicated SSTI, i.e., abscess, infected wound, or cellulitis without drainage; and
- Patients that will be treated as outpatients at baseline/enrollment.

If a patient is eligible for the study based on information regarding inclusion and exclusion criteria that is collected as part of standard medical care (and not obtained only for study purposes), then the clinician, following confirmation with the patients that they are interested to hear about the study, will contact the on-call study coordinator/investigator who will approach the subject and initiate the informed consent process (Section 14.3). After consent by the subject or the subject's legally authorized representative with assent from the minors is obtained, the study coordinator/investigator will verify that the subject still meets all inclusion and exclusion criteria (including study-related criteria) prior to enrollment (assignment of a study ID) and randomization to a treatment regimen. Limited information on screen failures (i.e., consented subjects who do not meet inclusion or exclusion criteria) will be collected and entered in the data entry system.

5.1 Subject Inclusion Criteria

Subjects must meet all of the inclusion criteria in order to be eligible to participate in the study.

1) Adult or child 13 years of age and older (who weighs ≥ 40 kg);

2) Have a SSTI with all three local findings of erythema (> 2 cm across the lesion or from a discrete wound edge), tenderness, and swelling/induration. Fever, leukocytosis, and lymphangitis will be noted, but are not enrollment criteria. SSTI with these local findings will be further categorized and defined as one of:

a. Abscess - a fluctuant and/or indurated lesion, or findings of a fluid-filled cavity on soft tissue ultrasound evaluation that, when opened reveals purulent material, receiving I&D (considered standard care for abscess) and having a minimum diameter (along any axis) of at least 2 cm (measured from the borders of induration, if a fluctuant lesion, or borders of the abscess cavity on ultrasound, if not fluctuant).

Note: Although I&D of an abscess is considered standard care (i.e., patients will receive I&D whether or not they are enrolled in the study), the procedure may be performed after enrollment into the study so that prior measurements of the area of erythema and swelling/induration can be obtained unless it is an occult abscess in which the I&D will be

performed prior to enrollment to verify infection type and ensure correct classification of the subject.

b. Infected Wound - a wound (defined as any apparent break in the skin) with any apparent drainage limited in depth to only involving skin and subcutaneous tissue, including sutured cutaneous wounds not involving intra-abdominal surgeries contaminated with bacterial or bowel contents (e.g., colon surgery and empyema drainage), and

c. Cellulitis - an area of erythema without the presence of a wound with drainage or abscess;

Cellulitis associated with an abscess will be categorized as an abscess. Cellulitis associated with an infected wound will be classified as an infected wound. Patients with cellulitis and an abscess less than 2 cm will be excluded. Infected wound associated with an abscess that may require I&D, will be classified as an infected wound.

3) Have the infected lesion for 7 days or less duration;

4) Are to receive outpatient treatment at enrollment/baseline;

5) Express willingness and ability to be contacted and return for re-evaluation according to the study protocol;

6) Provide written informed consent (and for subjects ages 13-17, consent from their guardian and assent);

7) Negative pregnancy test for subjects who are women of childbearing potential.

5.2 Subject Exclusion Criteria

Subjects must not have any exclusion criteria:

1) Severe allergy or reaction to study drug or drugs similar to the study drug relevant to whichever study sub-trial the subject would be assigned to (e.g., patients with severe or life-threatening penicillin allergies, allergy to any cephalosporin, clindamycin, or sulfonamides, or any other drug containing sulfur such as thiazides, furosemide, and oral sulfonylureas);

2) Concomitant treatment (i.e., while on study drug therapy) with coumadin, phenytoin, or methotrexate, or suspected G-6-PD or folic acid deficiency;

3) Expected inability to swallow or absorb the study drug (assessed by patient history);

4) Pregnancy, nursing, or expectation of becoming pregnant while on study drug;

5) Perirectal (within 5 cm of anus), perineal non-skin lesions (i.e., mucosal), or paronychial location of infection. Scrotal and labial abscesses will not be excluded.

6) An infection due to a mammalian bite;

7) Treatment with a study drug relevant to their infection type, or another systemic antibiotic in the previous 48 hours (i.e., before screening/baseline) unless associated with treatment failure which is defined as a patient who has been on prior (non study drug) antibiotics for at least 72 hours and failed.

8) Expected concurrent treatment with a topical antibiotic or another systemic antibiotic up to TOC (note: if patient was using a topical antibiotic previously, they can still be enrolled if they agree to stop using it);

9) Immunodeficiency [e.g., absolute neutrophil count <500/mm^3, chronic immunosuppressive drugs, active chemotherapy, or known AIDS (CD4 count <200 or AIDS-defining illness within the last year) assessed by patient history]. Note: patients who had prior AIDS-defining illness or CD4 count <200 in the past may be enrolled if most recent CD4 count >200;

10) Burn or active chronic skin condition (e.g., including rash or eczema) related to the SSTI at screening/baseline;

11) Infection related to currently indwelling device (e.g., intravenous line), excepting sutures associated with qualifying infected wounds which will be removed upon enrollment;

12) Infection for which prior cultures reveal in vitro resistance of a pathogen to a study drug in the previous month prior to screening/baseline;

13) Known or suspected osteomyelitis or septic arthritis;

14) Infection related to diabetic foot, decubitus, or ischemic ulcer;

15) Known severe renal insufficiency (creatinine clearance < 50 mL/min) calculated by measurement of serum creatinine if patient provides this history or based on past studies at baseline/enrollment;

16) Prior enrollment in this study within 12 weeks;

17) Another active infection of another organ system (e.g., pneumonia) or more than one active (i.e., currently on antibiotic treatment and/or requiring I&D) SSTI site (e.g., a site noncontiguous with the infection under study). Note: Minor folliculitis at secondary site is not an exclusion;

18) Presence of an abscess that has completely drained, either spontaneously or by a healthcare provider prior to enrollment. Note: This exclusion refers to the primary infection site;

19) An infected wound or cellulitis that has been surgically explored (>1 cm incision) and does not reveal an abscess. Cellulitis that has been needled, minimally incised (≤ 1 cm) or punch biopsied and no purulent drainage found can still be enrolled;

20) Currently incarcerated in a detention facility or in police custody (note: patients wearing a monitoring device can be enrolled) at baseline/screening;

21) For patients with an infected wound, history of *C. difficile* infection, pseudomembranous colitis, or active diarrhea at baseline/screening;

22) For patients with an infected wound, severe liver disease based on patient history;

23) An IV drug user in the last month with current presence of fever;

24) Current residence in a nursing home or other long term care facility at baseline/screening;

25) Expected use of other investigational drug or vaccine while on study drug;

26) For patients with an abscess, cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis is reasonable, including patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair, history of previous infective endocarditis, congenital heart disease (excluding mitral valve prolapse), and history of cardiac transplantation recipients who develop cardiac valvulopathy;

27) Presence of an organic foreign body, e.g., wood (note: subjects with embedded non-organic materials, e.g., metal or glass, that can be completely removed can still be enrolled if physician is certain there is no foreign body left).

5.3 Treatment Assignment Procedures

This is a Phase IIB randomized, double-blinded study with 3 study sub-trials. All eligible subjects will be stratified by the type of infection and then randomized to various 7-day treatments using a centralized randomization system in the ratio of 1:1.

- Subjects with an acute uncomplicated cutaneous abscess will be randomized to receive either TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day) or 4 placebo pills (twice per day).

- Subjects with an acute uncomplicated wound infection will be randomized to receive TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day, with alternating 1 identical placebo pill, twice per day) or clindamycin (300 mg, four times per day, with 3 placebo pills on alternating doses).

- Subjects with acute uncomplicated cellulitis will be randomized to receive cephalexin (500 mg, four times per day) and TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day) or cephalexin (500 mg, four times per day) and placebo (4 pills, twice per day).

The randomization schedule is generated, secured, distributed, and stored by EMMES in accordance with key parameters specified by their statistician. The system will be accessible on-line to the study coordinators. The subject is expected to begin study treatment on the day of randomization.

5.3.1 Randomization Procedures

Enrollment will be done online using the enrollment module created by EMMES (i.e., Internet Data Entry System (IDES)). The randomization code will be prepared by statisticians at EMMES and included in the enrollment module for the trial, stratified by type of infection. The randomization code will link to the treatment assignment. IDES will assign each subject a randomization code after demographic and eligibility data have been entered into the system. A designated individual (e.g., pharmacist) at each site will be provided with a code list for emergency unblinding purposes, which will be kept in a secure place.

Instructions for use of the enrollment module are included in the IDES User's Guide. Manual back-up procedures and instructions are provided for use in the event that the site temporarily loses access to the internet or the online enrollment system is unavailable.

Screening records will be kept to document the reason why an individual was screened but failed trial entry criteria.

The subjects, the site study personnel, data entry personnel at the sites, and laboratory personnel will be blinded to treatment assignment. The DSMB may receive data in aggregate and presented by treatment group, but without the treatment group (or dose level) identified. The DSMB may be unblinded to individual study treatment assignments, as needed, to adequately assess safety issues.

The site investigator and study coordinators will not be provided with the code list to break the blind. Under normal study circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. The blind should be broken only when the specific conditions listed in section 5.3.2 have been met.

5.3.2 Masking Procedures

The treatment sub-trials will be masked to both the subject and the study staff and maintained according to standard practices. Fisher BioServices will package all study drugs and ensure they are already masked according to applicable regulatory requirements.

Culture and susceptibility results will not be available to clinicians involved in evaluating subjects at follow-up visits. Research-related microbiology results will be restricted so that they are not easily available in hospital information systems (e.g., with general laboratory results) and can

only be accessed with special approval of the study coordinator/site investigators. The treatment blind will not be broken if microbiological testing shows resistance to one of the antibiotics being studied (see Section 4). If a site is discontinued, subjects enrolled will continue with care and be followed and the blind will not be broken.

In general, for cases requiring emergency treatment, the treating clinician will contact the investigator/study coordinator-on-call, who will contact the designated individual with the code list for emergency unblinding purposes to break the treatment blind. The medical monitor will be informed as soon as possible. Individual code breaks by the investigator/study coordinator-on-call will result in withdrawal of the subject from the study. For cases not requiring emergency treatment, the investigator will contact the medical monitor and state the reason(s) for unblinding treatment. If the medical monitor approves unblinding treatment, the investigator/study coordinator on call will contact the designated individual with the code list for emergency unblinding purposes to break the blind. In either case, the date, time, and reason for the unblinding treatment will be documented in the appropriate section of the source document and eCRF.

The blind of treatment regimen will be broken only if the following situations develop:

1) Specific emergency treatment (e.g., subject is experiencing Grade 3 or 4 AEs related to the study drug) would be dictated by knowing the treatment status of the subject.

2) At any point that the treating clinician determines that a subject is a clinical failure and there is no suitable alternative treatment available based on culture and susceptibility results such that the clinician requires knowledge of prior treatment assignment to provide appropriate and safe rescue therapy (see Section 4).

3) Subjects who become pregnant during study drug treatment. If their study treatment included TMP/SMX, the subject will be informed to discontinue this medication immediately.

4) At any point, if the subject develops a concomitant infection that requires therapy with antibacterial agents and the clinician believes knowledge of treatment assignment for assigning therapy is necessary.

5) In the event that the study is discontinued, subjects who are already enrolled in the study and have not completed all protocol procedures will be notified and asked to return to the ED for re-evaluation. The blind will be broken and the treating clinician will make a decision of appropriate continued therapy for the subject according to standard of care. If a site is discontinued, subjects enrolled will continue with care and be followed and the blind will not be broken.

5.3.3 Reasons for Withdrawal

A study subject will be withdrawn for the following reasons:

- Withdrawal by the site PI for noncompliance with the protocol or when the site PI deems it necessary or in the subject's best interest. (See also the informed consent form)
- Development of relevant exclusion criteria. Note: some exclusion criteria are only relevant at baseline/enrollment and/or while the subject is on study drug therapy, and not during the entire period of follow-up (see Section 5.2).
- Subjects are free to withdraw from participating in the study at any time upon request.
- Subjects who are lost to follow-up, not including subjects who were lost to follow-up after the TOC visit and only missed the EFV visit or early clinical failures (prior to TOC).

5.3.4 Handling of Withdrawals

If the site PI withdraws a subject due to noncompliance with the protocol or because they deem it necessary or in the subject's best interest, no further evaluations will be performed and no additional data collected. If the subject experienced an AE up to and including TOC or an SAE (at any time during subject follow-up) prior to withdrawal by the site PI, they will be followed until the AE/SAE resolves or is deemed stable/chronic (see section 9.4).

If the subject experiences and requests to be withdrawn from the study due to an AE, they will be given appropriate medical treatment until the symptoms of the AE resolve or the subject's condition becomes stable, but will not continue with scheduled study follow-ups. If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations will be performed and no additional data collected. The investigators may retain and continue to use data collected before such withdrawal of consent.

Study coordinators will attempt to contact subjects, who do not show up or cannot be contacted for follow-up visits, up until the last day of EFV (i.e., Day 63). If no contact is established with subjects up to the last date of the EFV window, the subject will be considered lost to follow-up on the date of last contact with the subject.

Participants who discontinue the study early will not be replaced.

5.3.5 Termination of Study

The medical monitor is responsible for ongoing monitoring of reports of SAEs submitted by the sites in real time to ensure GCP and to quickly identify safety concerns. The investigators will prepare regular reports concerning SAEs (not segregated by treatment group) for submission to the Co-PIs, DMID, and the DSMB. Such reports will be submitted on a regular basis, to be determined by the DSMB (e.g., real time, monthly, or quarterly). In the event of unexpected

SAEs or an unduly high rate of SAEs, the medical monitor will promptly contact the Co-PIs and the DSMB. The DSMB may convene a meeting or teleconference to consider the concerns and plan appropriate action. The final authority to continue or terminate the study is vested with DMID. If the study is halted, ORA will notify the FDA.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

Package inserts or the supplemental drug manual for all study drugs (TMP/SMX, clindamycin, and cephalexin) will be made available to all investigators as part of the IB.

6.1.1 Acquisition

All study drugs will be acquired through Fisher BioServices, i.e., they will purchase all study drugs from an FDA approved manufacturer. Fisher Clinical Services will perform the encapsulation, packaging and labeling of study drug according to applicable regulatory requirements. Study drug will be shipped by Fisher BioServices to the sites (e.g., pharmacies), where they will be stored in a location specific to this study, until dispensed to an enrolled subject.

6.1.2 Formulation, Packaging, and Labeling

All study drugs, including TMP/SMX, clindamycin, cephalexin, and placebo will be administered as capsules in pre-labeled, pre-numbered blister packs. Labeling of study supplies will be in compliance with applicable regulatory requirements. Fisher Bioservices will formulate all capsules including placebo (ensuring appropriate blinding), package capsules in blister packs, and label packs appropriately to indicate which capsules should be taken and when. Labels will be affixed to the packs so the study coordinator can write in the subject's name, date of birth, and the patID, and attach a label with the study coordinators and site investigators name and contact phone number.

For the cutaneous abscess sub-trial, TMP/SMX or placebo will be provided in a kit containing 64 identical capsules. Each kit will consist of two blister cards containing 32 capsules each for a total of 64 capsules arranged in rows labeled with icons to indicate the morning and evening doses and columns labeled as study day 1 through 8. The clinician or study coordinator will remove the dose(s) in day one and/or in day eight not needed to complete a full seven day regimen depending on the start time of dose one (morning or evening).

For the acute wound infection sub-trial TMP/SMX/placebo or clindamycin/placebo will be provided in a kit with 80 identical capsules. Each kit will consist of two blister cards containing 40 capsules each for a total of 80 capsules arranged in rows labeled with icons to indicate the breakfast, lunch, dinner and bedtime doses and columns labeled as study day 1 through 8. The clinician or study coordinator will remove the dose(s) in day one and in day eight not needed to

complete a full seven day regimen depending on the start time of dose one (breakfast, lunch, dinner or bedtime).

For the acute cellulitis sub-trial, cephalexin and TMP/SMX or cephalexin and placebo will be provided in a kit with 96 identical capsules. Each kit will consist of two blister cards containing 48 capsules each for a total of 96 capsules arranged in rows labeled with icons to indicate the breakfast, lunch, dinner and bedtime doses and columns labeled as study day 1 through 8. The clinician or study coordinator will remove the dose(s) in day one and in day eight not needed to complete a full seven day regimen depending on the start time of dose one (breakfast, lunch, dinner or bedtime).

6.1.3 Product Storage and Stability

All study drugs will be kept in a non-refrigerated locked facility, stored at cool ambient temperatures (59-86 °F or 15-30 °C), away from direct sunlight and moisture, and accessible only to authorized study personnel. All drug supplies will be stored in accordance with the manufacturers' instructions. Study drugs will be stored separately from normal hospital/practice stocks. Until dispensed to the subjects, the study medication will be stored in a securely locked area and only accessible to authorized study personnel.

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

All study drugs will be encapsulated with the appropriate dosing and then packaged in non-specific blister packs that are pre-labeled by consecutive days (1-8) indicating when each dose/capsule should be taken. Study drugs will be assigned to subjects with the help of a web tele-randomization system provided by EMMES.

Fisher Clinical Services will perform the labeling of study supplies according to applicable regulatory requirements. Fisher BioServices will provide the investigators with sufficient amounts of the study medication. The investigators will administer/dispense the study medication only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the study medication that is assigned to him/her. All dispensing will be documented in the eCRF and other study drug record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Once enrolled, subjects will be stratified by infection type and treated with the appropriate oral treatment.

- Subjects with an acute uncomplicated cutaneous abscess will receive either TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day) or 4 placebo pills (twice per day). Subjects will be encouraged to take these treatments approximately every 12 hours.

Daily Dosing Scheme (12 hours between doses):

	Dose 1	Dose 2
Treatment group	4 SS TMP/SMX	4 SS TMP/SMX
Placebo group	4 Placebo pills	4 Placebo pills

- Subjects with an acute wound infection will receive TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day, with 1 alternating identical placebo pill, twice per day) or clindamycin (300 mg, four times per day, with 3 placebo pills on alternating doses). Subjects will be encouraged to take these treatments approximately every 6 hours.

Daily Dosing Scheme (6 hours between doses):

	Dose 1	Dose 2	Dose 3	Dose 4
Treatment A	4 SS TMP/SMX	1 Placebo pill	4 SS TMP/SMX	1 Placebo Pill
Treatment B	1 300mg Clindamycin pill 3 placebo pills	1 300mg Clindamycin pill	1 300mg Clindamycin pill 3 placebo pills	1 300mg Clindamycin pill

- Subjects with acute cellulitis will receive cephalexin (500 mg, four times per day) and TMP/SMX (4 SS pills, 80 mg/400 mg each, twice per day) or cephalexin (500 mg, four times per day) and 4 placebo pills (twice per day). Subjects will be encouraged to take these treatments approximately every 6 hours.

Daily Dosing Scheme (6 hours between doses):

	Dose 1	Dose 2	Dose 3	Dose 4
Treatment A	1 500mg cephalexin pill	1 500 mg cephalexin pill	1 500 mg cephalexin pill	1 500 mg cephalexin pill

	4 SS TMP/SMX		4 SS TMP/SMX	
Treatment B	1 500mg cephalexin pill 4 Placebo pills	1 500mg cephalexin pill	1 500mg cephalexin pill 4 Placebo pills	1 500mg cephalexin pill

Subjects will receive the first dose of study drug in the ED. Subjects are expected to continue study medication for 7 days.

6.3 Modification of Study Intervention/Investigational Product for a Participant

No modifications will be made to the study drug. If a subject experiences an allergic reaction to the study drug, they will be taken off of the study drug. If they experience an AE, no modifications will be made to the study drug. If the clinician decides it is necessary to stop study drug treatment due to an AE, then the algorithm in Section 9.4 may be followed.

6.4 Accountability Procedures for the Study Intervention/Investigational Product(s)

The investigator will ensure that deliveries of study products from Fisher BioServices are correctly received by a member of the study staff (e.g., a study coordinator or pharmacist), that all receipts are recorded in writing and that the products are stored in a secure area under recommended storage conditions. The staff member who receives the study products will acknowledge receipt of the products to Fisher BioServices. It is the responsibility of the investigator to ensure that the integrity of the study product not be jeopardized prior to dispensing. Each individual subject pack will be dispensed as provided by Fisher BioServices with no further repackaging done at the site, except to remove the unnecessary doses to ensure the subject only receives 7 complete days of study drug (see section 6.1.2).
The study coordinators or pharmacist will maintain adequate records documenting receipt, use, loss or other disposition of the study product. EMMES will supply drug accountability forms. The individual who dispensed the drug will sign the forms. Fisher Bioservices will determine the frequency and amount of study drug shipped to each site. No study drugs will be shipped until the IND is active, and copies of site IRB approvals are sent to:

DMID-CROMS Essential Regulatory Documents Group (ERDG)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817
E-mail: ERDG@dmidcroms.com, Fax: 301-897-7482.

The investigator is responsible for the onsite drug accountability, including inventory tracking (receipt and dispensing).

At the end of the trial, DMID will provide instructions as to the disposition of any unused study drug. Unused study drugs will be recorded by the investigator and verified through monitoring prior to destruction on site.

Blister packs that are collected from study subjects can be destroyed on site (following their site pharmacy procedures for disposing of used/empty blister packs) only after CROMS study monitors have completed their drug accountability review and initialed the relevant entries on the Study Product Accountability Form.

6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

The investigator will maintain records documenting all trial medication administered to each subject for the entire study period. Subjects will be asked to complete a memory aid and bring their blister packs at the OTV and EOT. The memory aid will be used to record daily study medication taken, concomitant medications (e.g., pain medication), days to normal activity, and temperature (using thermometer provided). The study coordinator/investigator will document any missed doses of study medication by counting any pills remaining in blister packs and provide counseling per study sites' routine procedures to promote compliance with study medication. Blister packs will be collected from the subjects at the EOT if in person (Section 7.3) or at subsequent in person follow-up visits. If the subject is not seen in person, then they will be contacted and given instructions to mail their blister packs to the site.

If blister packs are lost or unavailable, the memory aid will be used to record study medication compliance. The information on the memory aid will be recorded on a source document, but the memory aid will not be collected from the subject. If neither blister pack nor memory aid are available, study medication compliance will be obtained by subject interview. The study coordinator/investigator will record how study drug compliance information was obtained.

6.6 Concomitant Medications/Treatments

Any medication that the subject takes other than the study drugs specified in the protocol is considered concomitant medication. All concomitant medications will be recorded in the subject's medical record and on the eCRFs from enrollment through the EFV. Subjects will be provided with a list of medications to avoid while taking the study drugs. If the subject takes an unapproved medication (e.g., *blood thinners (coumadin), phenytoin (Dilantin®), methotrexate)* this will be recorded in a source document and the eCRF, and the subject will be advised to discontinue the unapproved medication.

At the Screening/Baseline visit, a patient will be excluded from the study if he/she is on a concomitant treatment with topical/systemic antibiotics, coumadin, phenytoin, or methotrexate. A patient will also be excluded from the study if he/she was treated with another systemic antibiotic in the previous 48 hours unless associated with treatment failure of the SSTI (Section 5.2).

7 STUDY SCHEDULE

Subjects will be evaluated upon enrollment, at 2-3 days after enrollment (OTV; Days 3-4), at 1-3 days after the end-of-therapy (EOT; Days 8-10), and at 7-14 days after the end-of-therapy (TOC; Days 14-21), and at 6-8 weeks after the end-of-therapy (EFV; Days 49-63).

Subjects will be carefully screened at entry and follow-up visits for possible invasive infection looking for findings such as vital sign abnormalities and toxicity (sepsis), abnormal cardiac murmur (endocarditis), a red, swollen joint (septic arthritis), respiratory symptoms, abnormal lung exam, and new chest X-ray infiltrate (pneumonia), necrotic bone or abnormal X-ray (osteomyelitis), and a SSTI with severe pain, swelling, vascular insufficiency and/or radiographic soft tissue gas (necrotizing fasciitis). If at any point after consent and enrollment the investigator determines that a subject is a clinical failure (see Section 3.2.1), the algorithm for assigning rescue therapy described in Section 4 can be used in order to modify therapy, with the concurrence of the treating clinician. Investigators will follow subjects with invasive disease and SAEs until resolution.

7.1 Screening Visit

Screening and enrollment/baseline visit will be performed at the same visit.

The following screening procedures will be performed prior to enrollment (assignment of study ID) and randomization:

- Obtain written informed consent (must be signed prior to the initiation of any study related activities) from the participant or the participant's legally authorized representative with assent from the minors (ages 13-17)
- Verify conformance with inclusion and exclusion criteria. Note that written informed consent (and assent if necessary) will be obtained prior to assessment for conformance with inclusion and exclusion criteria that are strictly study-related and not collected during standard medical practice
- Evaluate by bedside soft tissue ultrasound to verify infection type and size
- Obtain urine pregnancy test for all women of childbearing potential who have not been surgically sterilized

7.2 Enrollment/Baseline Visit

- Inquire about history of skin infections in household members (e.g., similar skin infection in a family member). This information will be obtained from subject response.
- Record concomitant medications and pre-existing conditions
- Record results of history and physical examination (e.g., vital signs (blood pressure, pulse, respiratory rate, and body temperature) medication allergies, previous or concurrent treatments, pre-existing medical conditions, etc.; see Section 8.1)
- Record signs and symptoms of infection (e.g., fever, swelling, tenderness)
- Assess the wound and describe the infection site (e.g., location, size, extent, cause)
- Measure and mark the dimensions of erythema
- For abscess or infected wound: obtain drainage material for Gram stain, culture, and antimicrobial susceptibility testing prior to antibiotic treatment. The drainage material may be collected by standard cotton swabs of drainage material after I&D or from open lesions
- For abscess: measure and record the length of incision made for I&D. Note: Although I&D of an abscess is considered standard care (i.e., patients will receive I&D whether or not they are enrolled in the study), the procedure may be performed after enrollment into the study so that prior measurements of the area of erythema and swelling/induration can be obtained
- Provide memory aid and thermometer and educate subject as to its use
- Start study medication

7.3 Follow-up

Follow-up evaluations will be in person but, if not possible, will be by telephone. They will occur 2-3 days after enrollment (OTV; Days 3-4), at 1-3 days after the end-of-therapy (EOT; Days 8-10), and at 7-14 days after the end-of-therapy (TOC; Days 14-21).

- Clinical assessment of the infection if in person
- Measure the dimensions of erythema if in person
- Collect information on AEs

- Medication compliance will be judged by pill counts of blister packets (at OTV and EOT), but if blister packs are not available, study coordinators will review the subject's memory aid, or rely on subject recall. The source of how medication compliance was obtained (i.e., blister pack count, memory aid or subject recall) will be recorded on the source document

- Record information on subject memory aid onto a source document. If the memory aid is not available (e.g., subject forgets memory aid, or phone visit), this information will be obtained by subject recall

- At EOT, collect unused study medication if in person

- If diarrhea is present and visit is in-person, and stool specimen is available, submit for *C. difficile* toxin assay

- If subject is a clinical failure, evaluate by soft tissue ultrasound and follow algorithm for rescue therapy with treating clinician concurrence (Section 4)

- If drainage material is present and subject is a clinical failure, or subject experiences a recurrent skin infection at the original site, or a new skin infection at a different site, and the visit is in person, obtain drainage material for Gram stain, culture and antimicrobial susceptibility testing

- If subject suspects she became pregnant since last visit, perform pregnancy test

Subjects will be encouraged to return to the ED for all follow-up visits. However, if any of the above follow-up visits are conducted by telephone, the study coordinator or investigator will obtain the following information and record it on a source document. The subject will be asked 1) to assess their infection (e.g., presence of fever, change in the dimensions of erythema, and degree of tenderness, swelling, and drainage); 2) if they experienced any AEs; 3) the number of pills they took each day; 4) information recorded on their memory aid (e.g., days to normal activity, etc.); and 5) if they took any other medication (including other antibiotics). They will also be asked to return to the ED for their next visit (if applicable). If contact with subject occurs after Day 7, they will be asked to come back to the ED to return any unused study medication. If they cannot return to the ED, a prepaid envelope will be sent to them to mail unused study medication to the study coordinator.

Outcome for PP analysis will not be assessed over the phone. If the subject is considered to be a possible failure due to their telephone responses, they will be asked to return to the ED immediately for clinician evaluation. It will be noted in the eCRF that the information was collected by telephone interview. During data analysis, data collected by telephone will be compared to data collected by in-person evaluation to detect any potential bias or important differences. Note that the TOC must be in-person for a subject to be included in the PP analysis.

7.4 Final Study Visit

Final study visit will be in person but, if not possible, will be by telephone at 6-8 weeks after the end-of-therapy (EFV; Days 49-63).

- Clinical assessment of the infection if in person
- Collect information on SAEs or new or recurrent skin infections.
- If present and in person, obtain drainage material for Gram stain, culture and antimicrobial susceptibility testing.
- If diarrhea is present and stool specimen is available, send stool specimen for *C. difficile* toxin assay

If this visit is conducted by telephone, the same procedures described in Section 7.3 will be employed.

7.5 Early Termination Visit

The reasons for early termination will be noted in the eCRF. If possible, subject will continue follow up through EFV. If subject participation is terminated due to an AE that occurs up through the TOC, then subjects will be followed until their symptoms resolve or are deemed stable/chronic. If the subject is unable to be evaluated in person, they will be contacted by telephone to obtain relevant information.

7.6 Unscheduled Visit

Unscheduled visits related to their initial skin infection will be recorded in the eCRF, including the date and reason for the visit. If the subject presents to the ED for a complaint unrelated to their initial skin infection, any AEs that occurred up through the TOC will be recorded, but no other information will be collected. After the TOC, only SAEs and recurrent skin infections in the same site or new skin infections in another site will be recorded.

If the reason for the visit is because subject is unsure of follow-up dates, they will be evaluated by a clinician and re-educated about the follow-up schedule by the study coordinator. If the reason for the unscheduled visit is due to the subject experiencing worsening symptoms of their infection, the blind will not be broken and subject may receive rescue therapy as described in Section 4. If the subject is experiencing any Grade 1 or Grade 2 AEs, the blind will not be broken and subject may receive rescue therapy as described in Section 9.4.

If the subject experiences any SAE related to the study drugs or interventions and requires emergency therapy, the blind will be broken and the subject withdrawn from the study. The site investigator will make sure the subject receives appropriate care and follow-up according to standard care until their symptoms resolve or are deemed stable/chronic. The investigator or study coordinator will also contact the medical monitor and will state the relationship of the SAE to the study drug. The date, time, and reason for the unblinding will be documented in the appropriate section of the eCRF.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

- Demographics

  - Demographics will include the subject's gender, date of birth, and racial/ethnic origin (and will be entered on the eCRF).

- Medical/Surgical History

  - A medical and surgical history will be present in the source documents. The medical history should include a thorough review of body systems, including but not limited to cardiovascular disease, metabolic disease, peripheral vascular disease, allergies, and drug reactions. The review will include all medical and surgical history that is significant in relation to the current infection, including medication allergies and reactions.

- Concomitant Medications/Concomitant Antibiotics/Non-Drug Treatments/Procedures

  - All previous antibiotics (systemic or topical within 7 days prior to study entry) and current antibiotics will be recorded. Additionally all medications taken during the study will be recorded. At all visits, any changes in the concomitant medications since the last visit will be recorded in the eCRF and source documentation. Concomitant medications include prescription medications and nonprescription medications. Documentation of concomitant medications will include the agent, the reason for taking the medication, and actual or estimated start and stop dates, or if the medication is ongoing. Particular attention will be made regarding the receipt of any exclusionary or prohibited medications.

  - All medical or surgical procedures (e.g., I&D and/or debridement) that are related to the current infection under study or significant to the health of the subject, performed within the last 7 days prior to study entry and during the study period, except for the initial I&D of an abscess for subjects in the abscess or infected wound sub-trials, will be recorded. The information will include the name of the procedure, reason for the procedure and the start and end dates of procedure or if the procedure is ongoing. In addition, if a surgical procedure led to the infection under study, it will be recorded and information included as above even if it was performed greater than 7 days prior to study entry.

  - Presence of symptoms and use of analgesic medications as recorded in subject memory aids.

- Pre-existing conditions.

- Physical examination: A complete physical examination will be performed at the Screening/Baseline visit.

- Vital signs: Temperature, respiratory rate, heart rate (pulse) and resting blood pressure (after 5 minute rest) will be recorded at all in-person visits while on study. Weight will be obtained at the Screening/Baseline visit only.

- Signs and symptoms of infection: Type of drainage or exudates, erythema, swelling, and tenderness to palpation or pain at site will be recorded at each visit.

- Infection site/wound assessment: The following assessments will be collected:

  - Anatomic location at screening/baseline visit.

  - If applicable at all in-person visits, measurements of infection site/wound will include the dimensions of erythema. For abscess sub-trial: depth of the infection site will be measured and then characterized as limited to skin/subcutaneous tissue or involving deep fascia/muscle. For infected wound sub-trial: depth of infection site will be characterized as limited to skin, involving subcutaneous tissue, or involving deep fascia/muscle.

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

All clinical laboratory evaluations will be performed locally at each site's laboratory, which all meet Federal safety regulations and guidelines as defined by College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) licensing. Bacteriology performed by the local lab includes isolation, susceptibility, and Gram staining of the infection site/wound culture. Before starting the study, the investigator will supply DMID with a list of the normal ranges, units of measurement, and current laboratory certification. The investigator will supply DMID with all updates to reference ranges and laboratory certification occurring during the study.

The following laboratory tests will be performed at the specified protocol visits (see Appendix A).

- Infection site/wound culture: Gram stain and culture (aerobic) of drainage material from the infection site will be performed at the Screening/Baseline visit. The infection

site/wound culture should be repeated if drainage material is available and the subject is a clinical failure, or develops a new skin infection at another site or a recurrent skin infection at the original site and evaluation is in-person. Wound cultures will be obtained from subjects in the abscess and infected wound sub-trials at enrollment.

Acceptable methods for specimen collection include:

Abscess

- Deep swab of the abscess cavity after performing the I&D

Infected wound

- Deep swab of the wound cavity

- If applicable, pregnancy test will be done in all women of childbearing potential who have not been surgically sterilized prior to study intervention and results must be available prior to administration of study product.

- At any time after the initial dose of study medication, if the subject experiences diarrhea and has a stool specimen available at the time of the visit, the stool specimen will be sent for *C. difficile* toxin assay (Toxins A and B). Patients with persistent diarrhea will be retested if the initial assay is negative.

Since the AEs of the study drugs are well known, baseline studies and serial testing to identify asymptomatic abnormalities of renal, hepatic, and hematopoietic function will not be conducted unless, based on the judgment of the investigator, they are clinically indicated.

8.2.2 Special Assays or Procedures

Investigators will receive standardized training of wound measurement using ultrasound prior to study initiation. Prior to ultrasound evaluation, lesions with open wounds will have specimens taken of any drainage for culture and susceptibility testing. The involved skin will be wiped free of debris and cleaned. Ultrasound gel will then be applied to the skin. The underlying involved soft tissue will then be scanned using a high-frequency, high-resolution (5-10 MHz) transducer probe, which, if there is drainage material, will be covered with ultrasound gel and placed in a clean protective sheath. A presumed abscess based on soft tissue ultrasound will be defined as the finding of a defined fluid pocket. Subjects with this finding on ultrasound, and those subjects without these findings for whom the clinician suspects the presence of an abscess based on physical examination, will have incision and exploration. Findings of a subcutaneous collection of purulent material on direct examination by incision and exploration will define the existence of

an abscess. Following the procedure, the ultrasound probe will be cleaned with a dry towel and disinfected.

I&D is a commonly performed ED procedure to drain cutaneous abscesses. The procedure is described in standard emergency medicine textbooks.[48,49] In order to establish a uniform approach, all investigators will receive standardized training on proper technique to drain abscesses.

The initial step in performing an I&D will be to prepare the site for incision and remove any dirt or debris. The skin over the abscess will be cleaned with a topical antiseptic solution, e.g., betadine and/or 70% isopropyl alcohol, and allowed to dry. Although this procedure is not considered sterile, the clinician will attempt to keep the area as clean as possible and devoid of unnecessary contamination.

The area will then be anesthetized with preservative-free 1%-2% lidocaine (with or without epinephrine). Injection of lidocaine within the abscess cavity has been shown not to alter microbiologic data.[50] After 2-5 minutes, after the onset of anesthesia, using a #11 scalpel, a straight incision will be made over the area of maximal fluctuance or over the central area of the ultrasound-located cavity. The length of the incision will depend on the size of the abscess. However, the incision will be made large enough to promote adequate drainage. The minimum incision will be ¼ of the greatest length of fluctuance, but no less than 1 cm. After obtaining culture material and the initial decompression of purulent material, the abscess cavity will be probed thoroughly using a curved/straight hemostat or the clinician's gloved finger. This action will further release any pockets of purulent material. The clinician will then rotate the hemostat or finger around the entire abscess cavity to explore and remove any remaining loculations and adhesions. All necrotic and devitalized tissue will be debrided.

The abscess cavity will then be irrigated with sterile saline to remove all loosened purulent and necrotic material. The abscess cavity will be loosely packed using plain gauze. One to 2-cm of the packing material will extend outside of the wound in order to make sure the incision site will remain open and allow for continued drainage. The last step will include dressing the area using absorbent 4x4 gauze to cover the wound. All subjects will receive a standardized instructional sheet on how to care for their wounds.

Standardized susceptibility testing will be conducted by the site laboratory on *S. aureus* and other pathogens. All laboratories use methods for antimicrobial susceptibility testing that are FDA-approved and conform to Clinical and Laboratory Standards Institute (CLSI) standards and all test for susceptibility to the following antimicrobial agents: methicillin/oxacillin, tetracycline, erythromycin, TMP/SMX, and clindamycin (including inducible resistance), vancomycin, rifampin, and levofloxacin and/or moxifloxacin. MRSA and MSSA isolates that exhibit erythromycin resistance and clindamycin susceptibility will be further tested for inducible resistance to clindamycin using the D-test. All laboratories participate in annual audits or other QA programs.

Subjects with isolates that exhibit vancomycin resistance or intermediate susceptibility will not have their treatment or culture results unblinded (unless they are clinical failures) or be withdrawn from the study. The responsibility of reporting unusual susceptibility patterns to the local public health department or infection control department will be left up to the laboratory staff, as required.

8.2.3 Specimen Preparation, Handling, and Shipping

Wound culture specimens will be collected and labeled as a research specimen and with the subject's unique patID (assigned by the EMMES system) by the investigator or study coordinator. After culture and susceptibility testing at the site laboratory, cultures will be stored in the site laboratory freezers at -70°C (except at the OV-UCLA site, which initially hold cultures in the site laboratory, but then will periodically ship their isolates to an off-site laboratory for storage).

All MRSA isolates will be saved and those from subjects with treatment failure, isolates with unusual antimicrobial susceptibility results (such as resistance or reduced susceptibility to vancomycin, linezolid, or daptomycin), and a random sample (10%) of isolates from remaining subjects at each site will be sent from the site laboratories to the CDC laboratories for further molecular biology testing on a semi-annual basis after subject enrollment begins. Isolates will be characterized at CDC by pulsed field gel electrophoresis, SCC*mec* typing, and detection of toxin genes. All isolates sent to CDC will be de-identified and only labeled with a barcode label provided by EMMES.

We will employ the EMMES Global Trace System to track wound culture specimens from the site laboratories to the off-site laboratory for OV-UCLA, and to the CDC laboratories. After molecular biology testing of isolates, DMID will be contacted by the Co-PIs for instruction on further handling of the study specimens. Specimens will not be destroyed at the site or CDC laboratories without written permission from DMID.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Safety will be evaluated by the collection and analysis of data on AEs, clinical laboratory tests, physical examination, vital signs, and concomitant medications. The investigator is responsible for reporting all AEs that are observed or reported up through the TOC, regardless of their relationship to study product.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events (AEs)

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for “SAE” will be captured on the appropriate source document and eCRF. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, DO, PA, or Nurse Practitioner), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs that occur up through the TOC and all SAEs will be followed to adequate resolution. After TOC, only recurrent skin infections and new skin infections should be reported as AEs.

Any medical condition that is present at the time that the patient is screened will be considered as baseline and not reported as an AE. However, if it deteriorates at any time up through the TOC, it will be recorded as an AE.

All AEs will be graded for severity and relationship to study product. Adverse reactions to the drugs examined in this study are listed in Section 2.3.1.

Severity of AEs: All AEs will be assessed by the clinician using a protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify intensity.

- None (Grade 0): No AE reported.
- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe (Grade 3): Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening (Grade 4): Any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death. It does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Products: The clinician's assessment of an AE's relationship to test article is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs will have their relationship to study product assessed using the terms "associated" or "not associated." In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used:

- Associated – The event is temporally related to the administration of the study product and no other etiology more likely explains the event.
- Not Associated – The event is temporally independent of study product and/or the event is more likely explained by another etiology.

9.2.2 Serious Adverse Events (SAE)

An SAE is defined as an AE that meets one of the following conditions:

- Death during the period of protocol-defined surveillance.
- Life-threatening event (defined as a subject at immediate risk of death at the time of the event).
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol-defined surveillance.

- Results in a persistent or significant disability/incapacity.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, or women who become pregnant while on study medication and have a child with a congenital anomaly or birth defect.

All SAEs will be:

- Recorded on the appropriate SAE source document.
- Reviewed and evaluated by a study clinician.
- Followed until satisfactory resolution or until the Co-PIs or investigator deems the event to be chronic or the subject to be stable.

9.2.3 Procedures to be Followed in the Event of Abnormal Clinical Findings or Abnormal Laboratory Test Values

Abnormal assessments (e.g., vital signs, etc.) and abnormal laboratory findings (e.g., clinical chemistry, hematology), if obtained, will be recorded as AEs (up through the TOC) or SAEs if they meet the definition of an AE as defined in Section 9.2.1, or SAE defined in Section 9.2.2. Abnormal laboratory findings (if obtained) or other abnormal assessments that are detected through the TOC or are present at baseline and significantly worsen up through the TOC will be reported as AEs or SAEs.

9.3 Reporting Procedures

AEs including local and systemic reactions not meeting the criteria for “SAEs” should be captured on the appropriate source document and eCRF. Information to be collected includes event description, time of onset, investigator assessment of severity, relationship to study product, time of resolution of the event, seriousness, and outcome. All AEs occurring during the study will be documented appropriately regardless of relationship. All AEs that occur up through the TOC and SAEs will be followed to adequate resolution.

For AEs that occur through the TOC, the date of resolution (or when the event is deemed stable/chronic) will be noted on the Adverse Event source document.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates through the TOC it should be recorded as an AE.

Withdrawal due to an AE will be distinguished from withdrawal due to other reasons, according to the definition of AE noted earlier, and recorded on the appropriate AE source document and eCRF page. When a subject withdraws due to a SAE, it will be reported in accordance with the reporting requirements defined below.

9.3.1 Serious Adverse Events

Any AE considered serious by the Co-PIs or investigators of which meets the aforementioned criteria will be submitted on an SAE form to CROMS, DMID's pharmacovigilance contractor that replaced PPD, Inc in July, 2010, at the following fax number: 1-800-275-7619 (US) or 1-301-897-1710

Questions about SAE reporting can be referred to the SAE Hotline (available 24 hours a day/7 days a week) at 1-800-537-9979 (US) or 1-301-897-1709

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and sent by fax within 24 hours of site awareness.
- SAEs other than death and immediately life-threatening events, regardless of relationship, will be reported via fax by the site within 72 hours of becoming aware of the event.

Other supporting documentation of the event may be requested by CROMS and should be provided as soon as possible.

The completed SAE form must also be emailed or faxed to the project director within one week of sending the SAE report to CROMS. The project director will email the form to all sites to ensure that SAEs that occur at all study sites are reported in accordance with each local site IRB requirements.

All SAEs should also be reported by the study staff to the site (primary or secondary) ISM within 24 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until study investigator deems the event to be chronic or the subject to be stable. At this time, resolution or stability of the event will be reported by noting this in the AE source document and eCRF. If SAE is not resolved by EFV, follow-up may occur by phone, unless physical follow-up is deemed necessary by the site investigator.

9.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the investigator, DMID, the IND sponsor, will report events that are both serious and unexpected and that are associated with study product(s) to the FDA within the required timelines as specified in 21 CFR Part 312.32: fatal and life-threatening events within 7 calendar days (by phone or fax) and all other SAEs in writing within 15 calendar days. All serious events designed as "not associated" to study product(s), will be reported to the FDA at least annually in a summary format.

9.3.3 Reporting of Pregnancy

Pregnancies occurring during this study will be reported by the investigational staff within one working day of their knowledge of the event using the Pregnancy Notification Form (provided by EMMES). Subjects who become pregnant during the treatment period of the study will be promptly withdrawn. The blind will be broken and if the study drug is TMP/SMX, the subject will be informed to discontinue the medication immediately and appropriate care will be provided (e.g., obstetrics follow-up). If the subject becomes pregnant after completing therapy they will continue participation in the study through all follow-up visits.

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to the medical monitor on the subject's condition. All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts. All AEs that occur through the TOC and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE source document and eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If an AE or SAE is not resolved by EFV, follow-up may be conducted by phone, unless the site investigator believes physical follow-up is necessary.

If the subject is taken off of study medication due to adverse reaction (e.g., rash), then it is not necessary to routinely unblind the treatment. Subjects with SAEs related to the relevant study drug and who require emergency treatment will have the study medication unblinded so that treating clinicians will know what they had received. For subjects with less severe AEs, the study medication will be unblinded only if the clinician believes it would be important to

immediately know the assigned treatment e.g., because treatment of the adverse event requires it, or if subject has contraindications to alternative treatments that were not part of the recommended study regimens. Otherwise, the subject's treatment will remain blinded until after evaluation at the TOC, at which point a letter will be mailed to the subject from the site pharmacist to inform the subject as to which treatment they received that is suspected of having caused the AE. The investigator will not be informed of the treatment assignment.

The following are recommendations of alternate therapy to maintain blinding of treatment, but patient care decisions are left up to the treating clinician.

Abscess:

If the subject is taken off study medication due to an adverse reaction (e.g., rash), then the clinician can determine whether the subject requires further antimicrobial therapy. If the subject is not felt to require further treatment, then the study drug will be stopped, no further antibiotic will be prescribed, and the subject will continue follow-up visits as usual. Those subjects who are eligible to be included in the PP analysis (i.e., received 75% of the first 5 days of treatment) can still be included in that analysis. Subjects who are felt to require further antibiotic treatment can be treated with clindamycin to complete 7 days. This agent was selected because it is not part of the study regimen, and is likely to be active against the likely pathogens. These subjects will not be evaluable in the PP analysis, but all will be included in the mITT analysis. We believe it is reasonable to allow subjects in the abscess sub-trial to have treatment stopped without requiring further antibiotic treatment because half of them will be randomized to placebo, and we expect that many subjects with an abscess will be improved by the time study drug is stopped.

Infected Wound:

If the subject is taken off study medication due to an adverse reaction (e.g., rash), then the subject can be treated with doxycycline to complete 7 days. This agent was selected because it is not part of the study regimen, and is likely to be active against the likely pathogens. If there is a contraindication to doxycycline, then the investigator can request that the treatment be unblinded to choose the alternate study regimen. Subjects treated with antibiotics other than the assigned study regimen will not be evaluable in the PP analysis, but all will be included in the mITT analysis.

Cellulitis:

If the subject is taken off study medication due to an adverse reaction (e.g., rash), then the subject can be treated with clindamycin to complete 7 days. This agent was selected because it is not part of the study regimen, and is likely to be active against the likely pathogens. Subjects treated with antibiotics other than the assigned study regimen will not be evaluable in the PP analysis, but all will be included in the mITT analysis.

9.5 Halting Rules

The DMID medical monitor will monitor reports of SAEs submitted by the study sites in real time to ensure GCP and to quickly identify safety concerns. If rates of drug-related SAEs are unexpectedly high (i.e., for each study sub-trial, more than four such events per each 12 month study period), the medical monitor will promptly conduct a safety review involving the DSMB to determine if suspension of enrollment is warranted.

Interim analyses will be conducted by the EMMES statistician and presented to the DSMB.

Any sub-trial of the study may be halted if the DSMB determines that there is overwhelming evidence of harm or benefit associated with one of the selected treatments in that sub-trial. If there is evidence of benefit at interim analyses, FDA concurrence for termination of the study will be sought.

A sub-trial may also be terminated if, on the basis of the interim analyses, there is overwhelming evidence to support the acceptance or rejection of the primary hypothesis for that sub-trial (see Section 11.3.1). The entire study can be halted if, and only if all three sub-trials are halted.

9.6 Safety Oversight (DSMB)

An ISM will be appointed at each site to provide independent safety review for SAEs immediately after they occur. The ISM will be a clinician with relevant expertise who is not associated with the study. The ISM will send their report to the project director who will forward information to the medical monitor, project officer, and Safety Oversight Committee. If the medical monitor and/or DSMB require(s) further clarification from the ISM regarding a particular SAE, they may contact them directly.

Safety oversight will be under the direction of a DSMB. The DSMB will meet regularly (to be determined by the DSMB) to assess safety and efficacy data on each sub-trial of the study, with the assistance of the EMMES statistician. If halting rules are initiated, more frequent meetings may be held. The DMSB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will advise DMID of its findings.

10 CLINICAL MONITORING

10.1 Site Monitoring Plan

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DMID SOPs. CROMS (the new DMID clinical monitoring subcontractor that replaced PPD in July, 2010) will conduct site monitoring visits as detailed in the monitoring plan or in the MOP.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, ICFs, medical and laboratory reports, and protocol compliance. CROMS study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Our study contains three separate sub-trials that will evaluate treatment on three independent populations. These sub-trials will examine treatments for the following conditions: 1) acute uncomplicated abscess; 2) acute uncomplicated wound infections; 3) acute uncomplicated cellulitis. Each sub-trial involves a specific independent hypothesis that will be assessed on an independent population.

1 – Hypothesis for acute uncomplicated abscesses: For patients with an acute uncomplicated abscess, we hypothesize that the clinical cure rate of patients treated with TMP/SMX will be superior to that of patients treated with placebo in the PP population at the TOC.

2 – Hypothesis for acute uncomplicated wound infections: For patients with an infected wound, we hypothesize that the clinical cure rate of patients treated with clindamycin will be superior to that of patients treated with TMP/SMX in the PP population at the TOC.

3 – Hypothesis for acute uncomplicated cellulitis: For patients with acute uncomplicated cellulitis, we hypothesize that the clinical cure rate of patients treated with cephalexin and TMP/SMX will be superior to that of patients treated with cephalexin and placebo in the PP population at the TOC.

11.2 Sample Size Considerations

The primary outcome variable for all study sub-trials is clinical cure (or failure) at the TOC.

Sample size calculations for all three study sub-trials were conducted using the following equations described by Fleiss. [51]

Fleiss method:

Equations:

$$n = \frac{n'}{4}\left(1+\sqrt{1+\frac{4}{n'\left|P_2-P_1\right|}}\right)^2$$

Where $$n' = \frac{\left(z_{\alpha}\sqrt{2\left(\frac{P_1+P_2}{2}\right)\left(\frac{Q_1+Q_2}{2}\right)} - z_{1-\beta}\sqrt{P_1Q_1+P_2Q_2} \right)^2}{(P_2-P_1)^2}$$

P_1 = Probability of cure using initial treatment strategy
P_2 = Probability of cure using alternative treatment strategy
$Q_1 = 1 - P_1$
$Q_2 = 1 - P_2$

Notes: i -Total sample size is given by N = 2*n*

ii - Our estimates employ a statistical significance level of $\alpha = 0.05$ (this is adjusted to a nominal value of 0.044 to reflect alpha spending in our proposed interim analyses), and a power of 90% ($\beta = 0.10$).

Abscess study sub-trial

To determine whether TMP/SMX with drainage is superior to drainage alone in treating a subject with an acute uncomplicated cutaneous abscess. It is assumed that there will be a cure rate of 90% with I&D alone and a cure rate of 97.5% or more with TMP/SMX to be a sufficient difference for clinicians to justify antibiotic use.[17,18,19,20,21,22]

The following null and alternative hypotheses were used where CR is the clinical cure rate:

H_0: $CR_{(TMP/SMX)} - CR_{(I\&D)} = 0.0\%$
H_1: $CR_{(TMP/SMX)} - CR_{(I\&D)} = 7.5\%$;
where $CR_{(I\&D)} = 90.0\%$ and $CR_{(TMP/SMX)} = 97.5\%$

For $\alpha = 0.044$, $\beta = 0.10$, and assumed cure of 90% for simple drainage ($P_1 = 0.90$): Testing for 7.5% improvement with TMP/SMX ($P_2 = 0.975$) would require a sample containing N = 502 patients (251 per treatment arm). Assuming an 85% evaluability rate, 590 patients would need to be enrolled to ensure an adequate sample size.

$$N_{Abscess} = 590$$

This original estimated sample size estimate was revised in October, 2010 based on the results of interim analyses conducted by the DSMB and EMMES. The new sample size estimate calculated by EMMES statisticians for the abscess sub-trial is 1074. Assuming an 85% evaluability rate, at least 1265 subjects will need to be enrolled. Study investigators were not given information on how these sample size estimates were calculated to maintain the blind of the study.

Infected wound study sub-trial

To determine whether clindamycin is superior to TMP/SMX in treating subjects with infected wounds. It is estimated that the clinical cure rate of subjects with infected wounds is 85%. A cure rate of 95% or more is the reasonable threshold for clinicians to justify its preferred use.

The following null and alternative hypotheses were used where CR is the clinical cure rate:

H_0: $CR_{(clindamycin)} - CR_{(TMP/SMX)} = 0.0\%$
H_1: $CR_{(clindamycin)} - CR_{(TMP/SMX)} = 10\%$;
where $CR_{(TMP/SMX)} = 85.0\%$ and $CR_{(clindamycin)} = 95.0\%$

For $\alpha = 0.044$, $\beta = 0.10$, and an assumed cure of 85% for TMP/SMX treatment ($P_1 = 0.85$): Testing for 10% improvement with clindamycin ($P_2 = 0.95$) would require a sample containing at least 426 patients (213 per treatment arm). Assuming an 85% evaluability rate, at least 500 patients need to be enrolled to complete the study.

$$N_{Infected\ wound} = 500$$

Cellulitis study sub-trial

To determine whether cephalexin and TMP/SMX is superior to cephalexin and placebo in treating subjects with acute uncomplicated cellulitis. It is estimated that the clinical cure rate of subjects with acute cellulitis is approximately 85%.[52,53,54,55,56,57,58,59,60] A cure rate of 95% or more is the reasonable threshold for clinicians to justify its preferred use.

The following null and alternative hypotheses were used where CR is the clinical cure rate:

H_0: $CR_{(TMP/SMX/cephalexin)} - CR_{(cephalexin)} = 0.0\%$
H_1: $CR_{(TMP/SMX/cephalexin)} - CR_{(cephalexin)} = 10\%$;
where $CR_{(cephalexin)} = 85.0\%$ and $CR_{(TMP/SMX/cephalexin)} = 95.0\%$

For $\alpha = 0.044$, $\beta = 0.10$ and assumed cure of 85% for treatment with cephalexin alone ($P_2 = 0.95$): Testing for 10% improvement with cephalexin and TMP/SMX ($P_2 = 0.95$) would require a sample containing at least 426 patients (213 per treatment arm). Assuming an 85% evaluability rate, at least 500 patients would need to be enrolled to ensure an adequate sample size.

$$N_{Cellulitis} = 500$$

A detailed summary of our sample size explorations, including estimates for differing cure rates and levels of attrition, is presented in Appendix B. All sample sizes provided above are

estimates and can be increased or decreased based on interim analysis conducted by EMMES and the DSMB (see Section 11.3 under 'Assessment for Efficacy').

Our prior SSTI study that included a more limited population of adults with purulent lesions enrolled on average about 10 subjects/week/site. For this clinical trial, approximately 3-4 evaluable subject per type of SSTI, per site, per month, will have to be enrolled, which, for each of the 3 types of SSTI, would amount to about 48 subjects/site/year, 144 subjects/site over 3 years, and estimated 720 total enrolled subjects per sub-trial at all 5 sites. In the unexpected instance that we are unable to meet enrollment goals at 90% power, we also present an alternative approach in Appendix B using a less stringent power of 80% ($\beta = 0.20$) which will also yield an acceptable sample size to achieve our study goals.

All subjects who withdraw from the study prior to final classification will be included in the mITT population, but will be classified as failures. Cases will be classified as clinical cures only when they meet the explicit criteria described in section 3.2.1.

Cases involving protocol violations will be handled on a case-by-case basis. Site investigators will first make an assessment of the severity of the violation. Any cases that involve violations that could threaten the study validity (e.g., administering open antibiotics prior to randomization) will be excluded from the study population. Cases that involve violations that do not threaten study validity (e.g., failure to procure a culture specimen) may be included in the study population, provided there are not other reasons that mandate withdrawal. The decision to include or exclude a specific case will be made prior to unblinding of the study antibiotic assignment. Cases that are excluded from the study on the basis of protocol violations will not be counted in the PP analysis, regardless of their outcome status at the time of the violation, but will be included in the mITT population. If subjects miss doses of study drug, data will be collected and recorded on the amount of drug taken. Secondary analysis will be conducted to examine potential differences between various thresholds of compliance.

The sample size estimates provide a sufficient number of cases to definitively test the primary hypotheses on all three study sub-trials. These numbers are too small to provide conclusive statistical assessments of the secondary outcomes. However, the enrollment estimates are likely to reveal trends in secondary outcomes, and these trends may serve as primary hypotheses for future investigations.

11.3 Planned Interim Analyses (if applicable)

To ensure trial integrity, study investigators and staff will not be allowed access to data or reports containing data (including aggregate response data) that could jeopardize trial integrity. Interim analyses will be performed by the EMMES statistician.

Interim analyses are scheduled to occur after each sub-trial of the study has achieved 50% and 75% of its anticipated enrollments. These interim analyses are designed to assess efficacy and

futility, and evaluate all other endpoints, including safety data, and provide guidance in determining whether there is overwhelming evidence that might justify early termination of any of the three sub-trials, or the study as a whole (in the unlikely event that termination is appropriate for all three sub-trials).

The interim analyses are also designed to provide the investigators with information to enhance sample size estimation and ensure that each sub-trial will attain sufficient power to produce meaningful results.

The following analytic recommendations are designed to help inform and guide the interim analyses.

Clinical Outcome Classifications for Interim Analyses

All interim analyses will be based on PP outcomes, and patients will be classified based on assessments at the TOC. In the interim analysis for a given sub-trial of the study, the numerator for p_1 will consist of all patients who received control treatment, as PP for that sub-trial, and were judged to be cured at the TOC. The denominator will consist of patients who received control treatment, as PP for that sub-trial, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all patients who received experimental treatment, as PP for that sub-trial, and were judged to be cured at the TOC. The denominator will consist of patients who received experimental treatment, as PP for that sub-trial, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator.

Assessment for Efficacy

The interim efficacy analyses will consist of statistical evaluations of the primary study outcomes (differences in cure rates between treatment and control populations), using adjusted α error rates. Based on a Lan-DeMets alpha spending function with an O'Brien-Flemming boundry, the first interim analysis will occur after an individual sub-trial accrues 50% of its anticipated enrollment, and will employ an $\alpha = 0.0015$.[61] The second interim analysis will occur after the sub-trial has accrued 75% of its anticipated enrollment and will employ an $\alpha = 0.0091$. This will yield an $\alpha = 0.044$ for use in conducting the final analyses.

The primary statistical outcomes of interest in the interim analyses are the observed difference in the proportion of cures between patients receiving experimental therapies and those receiving the control therapies.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between patients receiving the experimental therapy and those receiving the control therapy.

p_2 = Proportion of cures among patients receiving the experimental therapy.

p_1 = Proportion of cures among patients receiving the control therapy.

The observed differences in cure rates themselves do not provide sufficient information to evaluate any of our hypotheses. A complete evaluation requires knowledge of the confidence interval surrounding each of the observed differences. The upper and lower bounds for these confidence intervals are given by the following equations from Fleiss:

$$\Delta_L = (p_2 - p_1) - z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} - \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

$$\Delta_U = (p_2 - p_1) + z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} + \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

Where:

Δ_L = Lower confidence interval for the difference in proportions

Δ_U = Upper confidence interval for the difference in proportions

p_1 = Proportion of cures among patients receiving control therapy

p_2 = Proportion of cures among patients receiving experimental therapy

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

n_1 = Total number of patients receiving control therapy

n_2 = Total number of patients receiving experimental therapy

The interpretation of interim observations for each sub-trial will be based on which one of six potential configurations these bounds assume in relationship to the clinically significant difference in cure rates defined for that sub-trial. The clinically significant difference in cure rate is 7.5% for the abscess sub-trial, 10% for the infected wound sub-trial, and 10% for the cellulitis sub-trial.

The interpretations of possible outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: The experimental treatment produces lower cure rates than the control treatment. This observation would be consistent with futility of the experimental treatment (use of TMP/SMX) in the abscess and cellulitis sub-trials of the study, and should trigger a recommendation for early termination of the corresponding sub-trial. In contrast, this outcome would suggest superiority of TMP/SMX over clindamycin in treating infected wounds, and should trigger a recommendation to continue the trial to assess magnitude of effect in this sub-trial.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces cure rates similar to the control treatment. In all three sub-trials of the study this observation should trigger a futility analysis (as described below) to determine whether there is sufficient evidence to recommend terminating the study on the basis of futility.

Case III: Lower bound is less than zero, and upper bound is greater than the predefined clinically significant cure rate.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered at current enrollment levels and no conclusion is possible. In all three sub-trials of the study this observation should trigger a recommendation to continue enrollments without interruption.

Case IV: Lower bound is greater than zero, while the upper bound is less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than the control treatment, but the observed difference is not clinically significant. In all three sub-trials of the study this observation should trigger a recommendation to continue enrollments to assess magnitude of effect.

Case V: Lower bound is greater than zero, but less than the predefined clinically significant cure rate, while the upper bound is greater than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than control treatment, but the study is unable to assess whether this difference is clinically significant. In all three sub-trials of the study this observation should trigger a recommendation to continue enrollments to assess magnitude of effect, and ultimately assess efficacy.

Case VI: Lower and upper bound both exceed the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than the control treatment, and this difference is clinically important. This observation would be consistent with superiority of the experimental treatment in all three sub-trials of the

study, and should trigger a recommendation for early termination of the involved sub-trial on the basis of demonstrated efficacy.

Assessment for Futility

Futility analyses will be conducted whenever the computed lower confidence bound in an interim analysis is less than zero, while the upper bound is greater than zero, but less than the clinically significant cure rate.

The futility analysis will be based on predicted intervals (PI) obtained by calculating the confidence intervals that might be expected at future time points should the study be allowed to continue. Four methods will be used to extrapolate future data: 1) observed trends continue; 2) future data conforms to the alternative hypothesis; 3) future data conforms to the null hypothesis; and 4) future data follows best-case (all experimental treatments produce cures, while all control treatments result in failures) or worse-case (all experimental treatments produce failures, while all control treatments result in cures) scenarios.

The interpretation of the three possible outcomes of interest that may arise from these prediction intervals are as follows:

Case I: Upper prediction interval is less than zero.

Interpretation: The experimental treatment is expected to result in lower cure rates than the control treatment. This observation would be consistent with futility of the experimental treatment (use of TMP/SMX) in the abscess and cellulitis sub-trials of the study, and should trigger a recommendation for early termination of the corresponding sub-trial. In contrast, this outcome would suggest superiority of TMP/SMX over clindamycin in treating infected wounds, and should trigger a recommendation to continue the trial to assess magnitude of effect in this sub-trial.

Case II: Lower prediction bound is less than zero, while the upper bound is greater than zero, but less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment will produce cure rates similar to the control treatment, evidence from current data is conclusive and further enrollments are unnecessary. This observation should trigger a recommendation for early termination on the basis of futility.

Case III: Lower prediction bound is greater than zero.

Interpretation: The experimental treatment is expected to produce higher cure rates than control treatment, but the study may not be able to assess whether this difference is clinically significant. In all three sub-trials of the study this observation should trigger a recommendation to continue enrollments to assess magnitude of effect, and ultimately assess efficacy.

In the event that an interim analysis produces evidence of efficacy or futility, the results of the analyses will be presented to the DSMB and NIH Project Officer, who will proceed with termination of the corresponding sub-trial of the study. DMID will notify the FDA of the findings if

necessary per DMID guidelines. The decision to terminate any sub-trial of the study for safety reasons will involve both the DMID and DSMB. The Co-PIs may suspend patient enrollment pending this decision.

11.3.1 Safety Review

The occurrence of AEs will be monitored and summarized quarterly during subject enrollment.

Any sub-trial of the study may be halted if the DSMB and DMID determine that there is overwhelming evidence of harm or benefit associated with one of the selected treatments in that sub-trial. DMID will notify the FDA of the findings if necessary. A sub-trial may also be terminated if, on the basis of the interim analyses, the DSMB determines that there is overwhelming evidence to support the acceptance or rejection of the primary hypothesis for that sub-trial. The entire study can be halted if, and only if all three sub-trials are halted.

11.3.2 Immunogenicity or Efficacy Review

Not applicable

11.4 Final Analysis Plan

Final analyses will be conducted by the study statistician with the assistance of EMMES.

Primary analysis

General Principles

Our final analyses will evaluate the hypotheses that drive each of the three distinct sub-trials of the study. We will use a similar statistical approach in each of the different sub-trials. Our primary statistical outcome is the observed difference in the proportion of cures between patients receiving the experimental therapy and those receiving the control therapy.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between patients receiving the experimental therapy and those receiving the control therapy.

p_2 = Proportion of cures among patients receiving the experimental therapy.

p_1 = Proportion of cures among patients receiving the control therapy.

The observed differences in cure rates do not provide sufficient information to evaluate any of our hypotheses. A complete evaluation requires knowledge of the confidence interval surrounding each of the observed differences. The upper and lower bounds for these confidence intervals are given by the following equations from Fleiss:

$$\Delta_L = (p_2 - p_1) - z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} - \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

$$\Delta_U = (p_2 - p_1) + z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} + \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

Where:

Δ_L = Lower confidence interval for the difference in proportions

Δ_U = Upper confidence interval for the difference in proportions

p_1 = Proportion of cures among patients receiving control therapy

p_2 = Proportion of cures among patients receiving experimental therapy

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

n_1 = Total number of patients receiving control therapy

n_2 = Total number of patients receiving experimental therapy

Our interpretation of the final outcome for each sub-trial will be based on which one of six potential configurations these bounds assume in relationship to the clinically significant cure rate we have defined for that sub-trial. The interpretation of possible outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: The experimental treatment produces lower cure rates than the control treatment.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces cure rates similar to the control treatment.

Case III: Lower bound is less than zero, and upper bound is greater than the predefined clinically significant cure rate.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, while the upper bound is less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than the control treatment, but the observed difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than the predefined clinically significant cure rate, while the upper bound is greater than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than control treatment, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than the control treatment, and this difference is clinically important.

The specific application of this approach is detailed for the individual sub-trials of the study as described below.

Treatment of Uncomplicated Abscesses

For the first sub-trial of the study, involving patients with an acute uncomplicated abscess, we will determine whether the clinical cure rate of patients treated with TMP/SMX is superior to that of patients treated with placebo. Our primary statistical measure will be the difference in the proportion of cures between patients receiving TMP/SMX and those receiving placebo.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between patients receiving TMP/SMX and those receiving placebo.

p_2 = Proportion of cures among patients receiving TMP/SMX.

p_1 = Proportion of cures among patients receiving placebo.

To evaluate our hypothesis, we will consider the confidence interval surrounding our observed difference in cure rates. The upper and lower bounds for this confidence interval are given by the following equations from Fleiss:

$$\Delta_L = (p_2 - p_1) - z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} - \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

$$\Delta_U = (p_2 - p_1) + z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} + \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

Where:

Δ_L = Lower confidence interval for the difference in proportions

Δ_U = Upper confidence interval for the difference in proportions

p_1 = Proportion of cures among patients receiving placebo

p_2 = Proportion of cures among patients receiving TMP/SMX

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

n_1 = Total number of patients receiving placebo

n_2 = Total number of patients receiving TMP/SMX

The interpretation of our final outcome will be based on which one of six potential configurations these bound assume in relationship to our clinically significant cure rate of 7.5%. These outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: Treatment with TMP/SMX produces lower cure rates than treatment with placebo.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than 7.5%.

Interpretation: Treatment with TMP/SMX produces cure rates similar to placebo.

Case III: Lower bound is less than zero, and upper bound is greater than 7.5%.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, but less than 7.5%, while the upper bound is less than 7.5%.

Interpretation: Treatment with TMP/SMX produces higher cure rates than treatment with placebo, but difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than 7.5%, while the upper bound is greater than 7.5%.

Interpretation: Treatment with TMP/SMX produces higher cure rates than treatment with placebo, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed 7.5%.

Interpretation: Treatment with TMP/SMX produces higher cure rates than treatment with placebo, and the difference is clinically important.

Clinical Outcome Classifications for the Treatment of Uncomplicated Abscesses

For the PP analysis, patients will be classified based on assessments at the TOC. The numerator for p_1 will consist of all patients who received placebo as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received placebo as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all patients who received TMP/SMX as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received TMP/SMX as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator.

For the mITT analysis, patients will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received a placebo on their initial visit and were classified as cured on final outcome. The denominator will include all patients who received placebo on their initial visit, including those with definite outcome assignments, those lost to follow-up, and any others with missing or unassigned outcomes. The numerator for p_2 will include only those individuals who received TMP/SMX on their initial visit and who were classified as cured on final outcome. The denominator will include all patients who received TMP/SMX on their initial visit, including those with definite outcome assignments, those lost to follow-up, and any others with missing or unassigned outcomes.

Treatment of Infected Wounds

For the next sub-trial of the study, involving patients with infected wounds, we will determine whether the clinical cure rate of patients treated with clindamycin is superior to that of patients treated with TMP/SMX. Our primary statistical measure will be the difference in the proportion of cures between patients receiving clindamycin and those receiving TMP/SMX.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between patients receiving clindamycin and those receiving TMP/SMX.

p_2 = Proportion of cures among patients receiving clindamycin.

p_1 = Proportion of cures among patients receiving TMP/SMX.

To evaluate our hypothesis, we will consider the confidence interval surrounding our observed difference in cure rates. The upper and lower bounds for this confidence interval are given by the following equations from Fleiss:

$$\Delta_L = (p_2 - p_1) - z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} - \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

$$\Delta_U = (p_2 - p_1) + z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} + \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

Where:

Δ_L = Lower confidence interval for the difference in proportions

Δ_U = Upper confidence interval for the difference in proportions

p_1 = Proportion of cures among patients receiving TMP/SMX

p_2 = Proportion of cures among patients receiving clindamycin

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

n_1 = Total number of patients receiving TMP/SMX

n_2 = Total number of patients receiving clindamycin

The interpretation of our final outcome will be based on which one of six potential configurations these bound assume in relationship to our clinically significant cure rate of 10%. These outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: Treatment with clindamycin produces lower cure rates than treatment with TMP/SMX.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than 10%.

Interpretation: Treatment with clindamycin produces cure rates similar to treatment with TMP/SMX.

Case III: Lower bound is less than zero, and upper bound is greater than 10%.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, but less than 10%, while the upper bound is less than 10%.

Interpretation: Treatment with clindamycin produces higher cure rates than treatment with TMP/SMX, but difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than 10%, while the upper bound is greater than 10%.

Interpretation: Treatment with clindamycin produces higher cure rates than treatment with TMP/SMX, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed 10%.

Interpretation: Treatment with clindamycin produces higher cure rates than treatment with TMP/SMX, and the difference is clinically important.

Clinical Outcome Classifications for the Treatment of Infected Wounds

For the PP analysis, patients will be classified based on assessments at the TOC. The numerator for p_1 will consist of all patients who received TMP/SMX as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received TMP/SMX as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all patients who received clindamycin as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received clindamycin as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other with unassigned outcomes will not be counted in the denominator.

For the mITT analysis, patients will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received TMP/SMX on their initial visit and were classified as cured on final outcome. The denominator will include all patients who received TMP/SMX on their initial visit, including those with definite diagnostic assignments,

those lost to follow-up, and any others with missing or unassigned outcomes. The numerator for p_2 will include only those individuals who received clindamycin on their initial visit and who were classified as cured on final diagnosis. The denominator will include all patients who received clindamycin on their initial visit, including those with definite diagnostic assignments, those lost to follow-up, and any others with missing or unassigned outcomes.

Treatment of Cellulitis

For the next sub-trial of the study, involving patients with cellulitis, we will determine whether the clinical cure rate of patients treated with TMP/SMX and cephalexin is superior to that of patients treated with cephalexin alone. Our primary statistical measure will be the difference in the proportion of cures between patients receiving TMP/SMX and cephalexin, and those receiving cephalexin alone.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between patients receiving TMP/SMX and cephalexin, and those receiving cephalexin alone.

p_2 = Proportion of cures among patients receiving TMP/SMX and cephalexin.

p_1 = Proportion of cures among patients receiving cephalexin alone.

To evaluate our hypothesis, we will consider the confidence interval surrounding our observed difference in cure rates. The upper and lower bounds for this confidence interval are given by the following equations from Fleiss:

$$\Delta_L = (p_2 - p_1) - z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} - \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

$$\Delta_U = (p_2 - p_1) + z_{\alpha/2}\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} + \frac{1}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$$

Where:

Δ_L = Lower confidence interval for the difference in proportions

Δ_U = Upper confidence interval for the difference in proportions

p_1 = Proportion of cures among patients receiving cephalexin alone

p_2 = Proportion of cures among patients receiving TMP/SMX and cephalexin

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

n_1 = Total number of patients receiving cephalexin alone

n_2 = Total number of patients receiving TMP/SMX and cephalexin

The interpretation of our final outcome will be based on which one of six potential configurations these bound assume in relationship to our clinically significant cure rate of 10%. These outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: Treatment with TMP/SMX and cephalexin produces lower cure rates than treatment with cephalexin alone.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces cure rates similar to treatment with cephalexin alone.

Case III: Lower bound is less than zero, and upper bound is greater than 10%.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, but less than 10%, while the upper bound is less than 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces higher cure rates than treatment with cephalexin alone, but difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than 10%, while the upper bound is greater than 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces higher cure rates than treatment with cephalexin alone, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces higher cure rates than treatment with cephalexin alone, and the difference is clinically important.

<u>Clinical Outcome Classifications for the Treatment of Cellulitis</u>

For the PP analysis, patients will be classified based on assessments at the TOC. The numerator for p_1 will consist of all patients who received only cephalexin as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received only cephalexin as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all patients who received both cephalexin and TMP/SMX as PP, and were judged to be cured at the TOC. The denominator will consist of patients who received both cephalexin and TMP/SMX as PP, and were assigned any clinical diagnosis at the TOC. Patients with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator.

For the mITT analysis, patients will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received only cephalexin on their initial visit and were classified as cured on final outcome. The denominator will include all patients who received only cephalexin on their initial visit, including those with definite outcome assignments, those lost to follow-up, and any others with missing or unassigned outcomes. The numerator for p_2 will include only those individuals who received both cephalexin and TMP/SMX on their initial visit and who were classified as cured on final outcome. The denominator will include all patients who received both cephalexin and TMP/SMX on their initial visit, including those with definite outcome assignments, those lost to follow-up, and any others with missing or unassigned outcomes.

Secondary Analyses

We anticipate that non-compliance and attrition among study participants will produce significant bias in assessing treatment efficacy using mITT methodology. In particular our primary mITT analyses is based on worst-case assumptions of outcomes, and posits that patients lost to follow-up will most negatively effect patient assigned to experimental treatment groups. This approach provides conservative outcomes that underestimate treatment efficacy. Consequently we plan to conduct sensitivity analyses to ascertain the potential scope and implications of these biases.

Our proposed sensitivity analyses include examining cure rates while varying our assumptions regarding outcomes among patients lost to attrition. In particular, we plan to use imputation to calculate “best guess” cure rates among patients lost to attrition, and use this information to calculate best estimate of the overall cure rates for the treatment and control groups. We will also plan to examine the most optimistic treatment efficacy by assigning outcomes to un-evaluable patients that most favor treatment effects.

We also plan to examine antimicrobial resistance rates among the cultured specimens. These rates will be described in terms of point statistics and dispersions, and will be specified in terms of proportion of specific organism isolates susceptible to a given antibiotic. This information will be used to assign expected microbiological cure rates to the associated individual patients.

These expected cure rates will then be compared to actual observed cure rates at various stages of treatment (OTV, EOT, TOC). The expected versus observed cure information will be summarized as raw counts in a four-fold table for treatment stage.

As part of our secondary analyses, we also plan to calculate point estimates and 95% confidence intervals for the proportion of patients who are compliant in taking 80% or more of the doses of the prescribed antibiotics. We will use these populations to calculate adjusted "compliant" cure rates of the various regimens, and compare these "compliant" cure rates with the cure rates on the control populations to assess the maximum potential benefit of the experimental agents.

Outcome populations:

PP population - Subjects who meet enrollment criteria, have none of the exclusion criteria, complete at least 75% of the first 5 days of antimicrobial therapy, and have physical follow-up at the TOC. Subjects who have been determined to be a clinical failure at any time prior to the TOC who took at least 75% of the first 48 hours of antimicrobial therapy but who do not have physical follow-up at the TOC will also be included in the PP population

mITT population - Subjects who take at least one dose of study medication and have any follow-up evaluation.

The primary efficacy endpoint of the study is the clinical response to study medication at the TOC in the PP population. A subject will be considered evaluable for the PP population if the subject:

- ⇒ Has met all study entry criteria;
- ⇒ Has not met any of the relevant exclusion criteria. Note: some exclusion criteria are only relevant at baseline/enrollment and/or while the subject is on study drug therapy, and not during the entire period of follow-up (see Section 5.2);
- ⇒ Has received 75% of the first 5 days of study medication;
- ⇒ Has returned for clinical evaluation at the TOC;
- ⇒ Has not used any of the prohibited concomitant medications while on study drug therapy;
- ⇒ Has been determined to be a clinical failure at any time prior to TOC and took 75% of the first 48 hours of antimicrobial therapy.

Any subject who was originally considered eligible for and is entered into this study, and is subsequently found to be at variance with any of the relevant study inclusion/exclusion criteria (Sections 5.1 and 5.2), will be ineligible for PP population analysis, due to a protocol violation. Subjects will only be excluded from the PP population from the time that the protocol violation occurs. For example, a subject who returns for the TOC outside the protocol specified time

interval would be excluded from analyses at TOC, but not from analyses at EOT. All decisions on eligibility for inclusion into the PP population will be made prior to data evaluation.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

EMMES will assist the Co-PIs in creating source documents for the study prior to subject enrollment, including source documents to record information on screening (i.e., meeting inclusion and exclusion criteria), enrollment (demographics, patient history, pre-existing conditions, etc.), all follow-up visits, memory aid data, pregnancy notification, laboratory and medical record data, AEs, and all information entered on the eCRFs (section 15.2).

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Following written SOPs, CROMS will verify that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Reports will be submitted to DMID on monitoring activities. The investigational sites will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by CROMS, and inspection by local and regulatory authorities.

EMMES will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

A QM plan will be created by the main study site and approved by DMID. The approved QM plan will be disseminated and implemented at all study sites. It will include information, such as 1) how data will be evaluated for compliance with the protocol and for accuracy in relation to source documents; 2) the documents to be reviewed (e.g., eCRFs, clinic notes, product accountability), who is responsible, and the frequency for reviews; and 3) methods of training for staff. This QM Plan will be reviewed for effectiveness annually and revised when indicated. New or revised QM Plans will be sent to DMID for review and approval.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997); 21 CFR 50.

14.2 Institutional Review Board

Each participating institution will provide for the review and approval of this protocol and the associated ICFs and recruitment material by an appropriate independent ethics committee (IEC) or IRB registered with the OHRP. Any amendments to the protocol or consent materials will also be approved before they are placed into use. Only institutions holding a current US FWA issued by OHRP are participating in this study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Consent and assent forms will be IRB-approved and the subject will be given sufficient time to read and review the document and discuss with their family member, friend or legal representative. If they require assistance to reach their family member, friend or legal representative, such as the use of a telephone, that will be facilitated. After this, they will be specifically asked if they have any questions or concerns, which will be addressed, or would like more time to consider their participation, which will also be provided. The investigator or study coordinator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the ICF prior to any procedures being done specifically for the study**.** The subjects may withdraw consent at any time throughout the course of the trial. A copy of the ICF will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that they will still be able to receive medical care at the facility if they decline to participate in this study.

Each participating site will be provided with a model ICF for subject participation. The consent form will be separate from the protocol document. Each institution will place the ICF in its own template. Each site may add but not remove anything from the model consent form. The IRB approved consents will be provided to DMID.

14.3.1 Informed Consent/Assent Process (in Case of a Minor)

This study includes subjects ages 13 to 17, who may be enrolled in the trial only with the consent of the subject's legally authorized representative. Such subjects will be informed about the trial to the extent compatible with the subject's understanding. If capable, the subject will assent and sign and personally date the written consent form. A separate IRB-approved assent form, describing (in simplified terms) the details of the study intervention/product, study procedures, and risks will be used. Assent by the subject and the consent by the legal guardian will be obtained. Assent forms will not substitute for the consent form signed by the subject's legally authorized representative.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

Women and minorities will be included in the study population. The study site EDs serve populations in which diverse racial and ethnic groups are well represented. The racial breakdown of subjects in the previous study of SSTI through the ***EMERGE*ncy ID Net** by Moran and colleagues[1] was: white non-Hispanic (28%), black non-Hispanic (44%), Hispanic (26%), other (2%). Women of childbearing potential will not be excluded, but will have a negative pregnancy test documented prior to enrollment because of concern about possible teratogenic effects of study medications. Children less than 13 (or < 40 Kg) will be excluded because of difficulty providing blinded study medications in all pediatric dosing ranges.

Prisoners will be excluded from the study population at screening/baseline. If a subject is imprisoned temporarily during study follow-up but has been released and is available for assessments at follow-up visits, they will not be withdrawn from the study.

14.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the DMID and their other clinical research support contractors. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The DMID or authorized representatives of CROMS may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. All clinical study sites will permit access to such records.

14.6 Study Discontinuation

In the event that the study is discontinued, subjects that are already enrolled in the study and have not completed all protocol procedures will be notified and asked to return to the ED for re-evaluation. The blind will be broken and the treating clinician will make a decision of appropriate continued therapy for the subject according to standard of care.

14.7 Future Use of Stored Specimens

Wound culture specimens will be stored at the site laboratories or an off-site laboratory (OV-UCLA), and a subset shipped to the CDC laboratories (see Section 8.2.3) for further testing. All patient identifiers will be removed and specimens will be labeled only with a barcode label provided by EMMES that links to the subject's patID before shipment to the CDC. CDC laboratories will not have access to the study database, and will therefore not be able to link the isolate to the subject's study data, including their patID. Specimens not shipped to the CDC will remain at the site laboratories or off-site laboratory in freezers at -70°C. After all laboratory testing for this study is completed, DMID will be contacted by the Co-PIs for instruction on further handling of the study specimens.

15 DATA HANDLING AND RECORD KEEPING

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Forms for use as source documents will be derived from the eCRFs and provided by EMMES to the sites to record and maintain data for each subject enrolled in the study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry will be crossed out with a single line, and the change should be initialed and dated. Research staff will not erase, overwrite, or use correction fluid or tape on the original. Data reported in the eCRF should be consistent with the source documents or the discrepancies should be documented.

DMID will provide guidance to investigators on making corrections to the source documents and eCRFs.

Additional details are provided in the study-specific Data Management Plan, which will be reviewed and approved by DMID.

15.1 Data Management Responsibilities

All source documents and laboratory reports (after subject follow-up is completed) will be reviewed by the study coordinators who will ensure that they are accurate and complete. AEs will be graded, assessed for severity and causality, and reviewed by the investigator.

Data collection is the responsibility of the study staff at the site under the supervision of the site investigator. During the study, the site investigator will maintain complete and accurate documentation for the study.

EMMES will serve as the Statistical and Data Coordinating Center for this study and will provide support for data management, quality review, analysis, and reporting of the study data.

15.2 Data Capture Methods

Clinical data (including AEs, concomitant medications, and outcomes) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant IDES provided by EMMES. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Source documents will be created by EMMES and the main study staff for data collection.

15.3 Types of Data

Data for this study will include clinical data, laboratory information (bacteriologic), and outcome measures (e.g., cure rates, infection type).

15.4 Timing/Reports

During enrollment, data will be monitored by the EMMES statistician on a regular basis. Any immediate problems or issues will be discussed with the study investigators during their monthly conference calls. Reports will be prepared and submitted to DMID and DSMB. A Final Report will be due for the final year of the study. Outcome measure data will be collected and entered into the IDES system and monitored by EMMES.

15.5 Study Records Retention

Study documents should be retained for a minimum of 2 years after study completion. No study records will be destroyed without the written consent of DMID, until these documents are no longer needed. It is the responsibility of DMID to inform the investigator when these documents no longer need to be retained. Sites should request DMID approval prior to destroying any study records.

15.6 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol, GCP, or MOPs requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.

5.1 Quality Assurance and Quality Control, section 5.1.1.

5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations will be promptly reported to DMID.

All deviations from the protocol will be addressed in study subject source documents. A completed copy of the DMID Protocol Deviation Form will be maintained in the regulatory file, as

well as in the subject's source document. Protocol deviations will be sent to the local IRB/IEC per their guidelines. The site investigator/study staff will be responsible for knowing and adhering to their IRB/IEC requirements.

16 PUBLICATION POLICY

Following completion of the study, the primary investigators in association with site investigators are expected to publish the results of this research in a scientific journal. The ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov,[62] which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of DMID to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before subject enrollment.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from this policy.

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SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

			Follow-Up Schedule					
Procedures	Screening (Day 1)	Baseline/Enrollment (Day 1)	OT Visit (Days 3-4)	EOT Visit (Days 8-10)	TOC visit (Days 14-21)	EF Visit (Days 49-63)	Unscheduled Visit	Premature Discontinuation
Signed Consent Form	X							
Assessment of Eligibility Criteria	X							
Review of Medical History	X	X						
Review of Concomitant Medications	X	X	X	X	X	X	X	X
Administered and provided with study drug		X						
Physical Examination – Complete		X						
Physical Examination – Symptom-Directed			(X)	(X)	(X)	(X)	(X)	(X)
Physical Examination – Vital Signs		X	X†	X†	X†	X†	X†	X†
Assessment of Adverse Events			X	X	X	X**	X**	X
Clinical Laboratory – Chemistry		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Clinical Laboratory – Hematology		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Clinical Laboratory – Urine pregnancy test	X		(X)	(X)	(X)	(X)	(X)	(X)
Gram stain, culture (aerobic & anaerobic), and susceptibility testing of purulent material		X*	(X)	(X)	(X)	(X)	(X)	(X)
Medication check			X†	X†			(X)	(X)
Memory aid check			X†	X†	X†		(X)	(X)

			Follow-Up Schedule					
Procedures	Screening (Day 1)	Baseline/Enrollment (Day 1)	OT Visit (Days 3-4)	EOT Visit (Days 8-10)	TOC visit (Days 14-21)	EF Visit (Days 49-63)	Unscheduled Visit	Premature Discontinuation
C. diff toxin assay of stool specimen			(X)	(X)	(X)	(X)	(X)	(X)

X - Required
(X) - As deemed indicated by site investigator
† - Required if visit is conducted in-person. If visit is conducted over the phone, as much information as possible can be collected by subject recall (e.g., medication compliance and memory aid information).
* Required for abscess and infected wound sub-trials, but not for cellulitis
** After TOC, only AEs that are new or recurrent skin infections are recorded.
At baseline, all procedures will be done before study interventions.

APPENDIX B : SAMPLE SIZE CALCULATIONS AT 80% POWER (β = 0.20)

Abscess Sub-trial:

Sample estimates under this constraint indicate the need for a population of at least 318 cases (159 subjects each in the treatment and control groups). Table 1 provides sample estimates for the different scenarios associated with this choice.

Table 1.

α = 0.045 (one-tailed α = 0.09); Power = 80%

	Attrition					
Cure rates	*None*	*5%*	*10%*	*15%*	*20%*	*25%*
92.5% vs 100%	214	224	236	250	266	284
90.0% vs 97.5%	**318**	334	352	374	396	424
87.5% vs 95.0%	416	436	462	488	520	554
85.0% vs 92.5%	508	534	564	596	634	676
82.5% vs 90.0%	594	624	660	698	742	792

Under realistic scenarios, with 15% attrition, the analysis could be completed with approximately 374 cases.

Cellulitis Sub-trial:

Sample estimates under this constraint indicate the need for a population of at least 270 cases (135 subjects each in the treatment and control groups). Table 2 provides sample estimates for the different scenarios associated with this choice.

Table 2.

α = 0.045 (one-tailed α = 0.09); Power = 80%

	Attrition					
Cure rates	*None*	*5%*	*10%*	*15%*	*20%*	*25%*
90.0% vs 100%	158	166	174	184	196	210
87.5% vs 97.5%	216	226	240	254	270	288
85.0% vs 95.0%	**270**	284	300	316	336	360
82.5% vs 92.5%	320	336	354	376	400	426
80.0% vs 90.0%	366	384	406	430	456	488

Under realistic scenarios, with 15% attrition, the dual analyses could be completed with approximately 316 cases.

Infected Wound Sub-trial:

Sample estimates under this constraint indicate the need for a population of at least 330 cases (165 subjects in each of the treatment and control groups). Table 3 provides sample estimates for the different scenarios associated with this choice.

Table 3.

α = 0.045; Power = 80%	Attrition					
Cure rates	*None*	*5%*	*10%*	*15%*	*20%*	*25%*
90.0% vs 100%	190	200	210	222	236	252
87.5% vs 97.5%	262	274	290	308	326	348
85.0% vs 95.0%	**330**	346	366	388	412	440
82.5% vs 92.5%	392	412	434	460	490	522
80.0% vs 90.0%	450	472	500	528	562	600

Under realistic scenarios, with 15% attrition, these analyses could be completed with approximately 460 cases.

Protocol Title: Strategies using Off-Patent Antibiotics for Methicillin-Resistant *Staphylococcus aureus* ("STOP MRSA")- A phase IIB, multi-center, randomized, double-blind clinical trial

DMID Protocol #07-0040
Amendment 1/ Version 2.0 of Protocol/ Version 3.0 of ICFs for Abscess, Cellulitis and Infected Wound Sub-trials.

The following changes/revisions were made to the Protocol and ICFs based on:

1) ORA comments from Emily Kough dated 7/10/2008
2) FDA comments dated 10/29/2008
3) CE committee comments received in an email from Dr. Chiou 9/22/2008
4) Issues that arose during PPD Site Initiation Visits that needed clarification/revision
5) Clarifications requested by DSMB during Organizational Meeting on 10/20/2008
6) Other clarifications and procedure changes that have been made since study enrollment began by main study staff.
7) Responses to comments from the initial protocol amendment submission from DMID (ORA and OCRA) dated August 7, 2009.

The revisions were made in tracked changes mode to the protocol and are described below by Protocol Section. Tracked and clean versions of the Protocol Version 2.0 and ICFs Version 3.0 templates are also attached (note: no changes were made to the assent form). Note that some of the very minor revisions were not specifically noted below, but are visible in the tracked version of the protocol.

General:

1. The titles of David A. Talan and Gregory J. Moran were changed from "Co-Prinicipal Investigators" to "***Lead*** Co-Principal Investigators" and throughout the protocol as necessary per DMID guidelines.
2. As requested by one of the DSMB members, the 3 infection type groups (abscess, cellulitis, and infected wound) are now referred to as "***sub-trials***" instead of "arms" throughout the protocol.

Protocol Summary:

1. In Objectives: Revision in this section and throughout the protocol as necessary, in response to FDA comment #2.

"The primary endpoint will be clinical cure at the TOC in the PP population (i.e., patients who meet enrollment criteria, have none of the exclusion criteria, complete ***75% of the first 5 days*** of antimicrobial therapy, and have physical follow-up at the TOC; subjects who have been determined to be a clinical failure at any time prior to

TOC who took ***75% of the first 48 hours*** of antimicrobial therapy but who do not have physical follow-up at the TOC will also be included in the PP population)."

2. In Estimated time to Complete Enrollment, changed the months to:

"Subject enrollment will occur over 3 years (***April, 2009 – April, 2012***)."

Schematic of Study Designs:

Abscess Sub-trial - clarified procedures at enrollment as follows:

- "Evaluation ***and measurement of abscess cavity*** by bedside soft tissue ultrasound
- "Measure ***dimensions*** of erythema, ***induration/swelling, and abscess cavity***"

Infected Wound Sub-trial – clarified procedures at enrollment as follows:

- Measure ***dimensions*** of erythema ***and induration/swelling***

Cellulitis Sub-trial – clarified procedures at enrollment as follows:

- Measure ***dimensions*** of erythema ***and induration/swelling***

Correction of dosage of TMP/SMX from "***180***mg/400mg" to "***80***mg/400mg"

For all three sub-trials, clarified procedures at follow-up as follows:

- "Measure ***dimensions*** of erythema"

Note: Revisions have been made through the protocol to reflect the following changes"

- Follow-up of AEs "***that occur through TOC***"
- Drainage specimen for Gram stain, culture and antimicrobial susceptibility, ***"if drainage is present and subject is a clinical failure or developed a new infection (at original or new site)"***
- If diarrhea "***and"*** stool specimen ***"available, submit for"*** *Clostridium difficile* toxin assay.

Section 2:

Section 2.3.1:

1. Clarification that I&D is considered standard care for abscesses.

These risks include complications of I&D (***i.e., standard care for abscesses***), and adverse reactions (AEs) to medications

2. Privacy Act was referenced in response to comment by CE committee.

The study will be done in full compliance with 45 CFR 46 (Protection of Human Subjects) and ***the Privacy Act***.

3. Addition: added "***digoxin***" to list of drug interactions

4. Clarification/Revision:

To prevent contaminating surrounding skin and spread of the infection, the skin over the abscess will be cleansed with ***a topical antiseptic solution, e.g., betadine and/or 70% isopropyl alcohol***, and allowed to dry.

Section 2.3.2:

1. Deletion: "(e.g., I&D of abscess with or without antibiotics)" to clarify again that I&D is not a study-related procedure/intervention, but standard care.

"All of the study interventions are standard, and all of the drugs under study are currently used for these conditions."

Section 3:

1. Revised outcome definitions for mITT population:

The outcome of interest in the mITT analysis is the assessment at the TOC. The following definitions for cure and failure will be used.

Cure: No change in antibiotic therapy due to persistence or worsening of infection (based on study clinician assessment, the subject's assessment, or assessment by another outside clinician) prior to or through TOC.

Failure: Subject had a change in antibiotic therapy due to persistence or worsening of infection (based on study clinician assessment, the subject's assessment, or assessment by another outside clinician) at any time up to or through TOC.

Section 4:

1. Addition: "***If blister packs are lost or unavailable, the memory aid will be used to record study medication compliance. If neither blister pack nor memory aid are available, study medication compliance will be obtained by subject interview***."

2. Clarification: "Research-related microbiology results will be restricted so that they are not easily available in hospital information systems (e.g., with general laboratory results) and can only be accessed by the study coordinators ***in case emergency unblinding of microbiology results is necessary*** with special approval of the site investigators"

3. Addition: ***"During follow-up, if subject is a clinical failure, develops a recurrent infection at the original site, or a new infection at another site and there is drainage available, a wound culture specimen will be obtained and submitted for culture and susceptibility testing."***

4. Clinical failure definitions: Changes have been made to this section to allow subjects to be deemed failures even prior to OTV.

5. Addition to clarify that the algorithms for rescue therapy are recommendations. Similar changes relevant to this clarification have been made throughout the protocol.

   "The following algorithms are recommendations/guidelines and treatment decisions are ultimately left up to the treating clinician."

6. Clarification in response to comment from ORA about whether it was necessary to include information about "bacterial specimens" on ICF for cellulitis.

   "Note that subjects in the cellulitis arm may develop an abscess during follow-up, and thus require an I&D and wound culture."

7. Clarification regarding subjects who experience diarrhea to only require C diff toxin assay if stool specimen is available at the time of the visit.

   "At any time during the study period if the subject experiences diarrhea ***and is able to provide a stool specimen,*** it will be submitted for a *C. difficile* toxin assay."

8. Clarification of the role of the site investigators in study drug management:

   "Once the study drug reaches the site, study drug management is the responsibility of the site investigator."

9. Clarification requested by DSMB: "Interim analyses will be performed by the EMMES statistician ***and presented to the DSMB,*** when 50% of subjects are enrolled and again when 75% of subjects have been enrolled per study arm."

Section 5:

1. Revision stating that one of our site hospitals will not be enrolling Spanish-speaking patients. Since this site does not typically see Spanish-speakers (only about 2% of their patient population), they do not have a translator or staff on site that can translate for the consent process. Therefore, we are excluding Spanish-speaking patients from this site only. We added the following:

"however our Baltimore, MD site will not be enrolling Spanish-speaking patients (which only comprises about 2% of their patient population) due to logistical difficulties in obtaining a translator for consent procedures."

2. Revision: "Women whose method of birth control is hormonal are ***instructed*** to use additional barrier methods during therapy."

3. Clarification in response to CE committee's comments:

"After consent by the ***subject or the subject's legally authorized representative with assent from the minors*** is obtained…"

4. Clarification: "***Limited information on*** screen failures (i.e., consented subjects who do not meet inclusion or exclusion criteria) ***will be collected and entered in the data entry system***."

Section 5.1

1. Clarification in response to ORA comments :

"Abscess - a fluctuant and/or indurated lesion, or findings of a fluid-filled cavity on soft tissue ultrasound evaluation that, when opened reveals purulent material, receiving I&D (***considered standard care for abscess***) and having a minimum diameter (along any axis) of at least 2 cm (measured from the borders of induration, if a fluctuant lesion, or borders of the abscess cavity on ultrasound, if not fluctuant).

Note: Although I&D of an abscess is considered standard care (i.e., patients will receive I&D whether or not they are enrolled in the study), the procedure may be performed after enrollment into the study so that prior measurements of the area of erythema and swelling/induration can be obtained unless it is an occult abscess in which the I&D may be performed prior to enrollment to verify infection type and ensure correct classification of the subject."

2. Clarification of infected wound definition:

"Infected Wound - a wound (defined as any apparent break in the skin) with any apparent drainage limited in depth to only involving skin and subcutaneous tissue, including sutured cutaneous wounds ***not involving intra-abdominal surgeries contaminated with bacterial or bowel contents (e.g., colon surgery and empyema drainage),"***

3. Clarification/Addition: ***"Infected wound associated with an abscess that may require I&D, will be classified as an infected wound."***

Section 5.2

1. General Note: Several of the exclusion criteria were clarified. One of the clarifications involves several of the criteria and relates to specifying when the particular criteria are relevant, e.g., while on study drug, or at enrollment/baseline. Please see protocol for the other clarifications.

2. The following exclusion was added:

27) "Presence of an organic foreign body, e.g., wood (note: subjects with embedded non-organic materials, e.g., metal or glass, that can be completely removed can still be enrolled if physician is certain there is no foreign body left"

Sections 5.3.3 & 5.3.4

1. Clarification: The blind of treatment regimen will be broken only….3) Subjects who become pregnant during "***study drug***" treatment.

2. After recent phone meeting with EMMES (our data management subcontractor), we were informed that our definition of "withdrawal" was partially incorrect. Thus, appropriate changes were made to this section to correct this. Also, the entire section on rescue therapy for AEs was moved from here to section 9.4.

3. Addition/Clarification: ***"If the site PI withdraws a subject due to noncompliance with the protocol or because they deem it necessary or in the subject's best interest, no further evaluations will be performed and no additional data collected. If the subject experienced an AE up to and including TOC or an SAE (at any time during subject follow-up) prior to withdrawal by the site PI, they will be followed until the AE/SAE resolves or is deemed stable/chronic (see section 9.4)."***

4. Addition/Clarification: If the subject experiences and requests to be withdrawn…, ***"but will not continue with scheduled study follow-ups"***

5. Addition/Clarification: ***"Study coordinators will attempt to contact subjects, who do not show up or cannot be contacted for follow-up visits, up until the last day of EFV (i.e., Day 63). If no contact is established with subjects up to the last date of the EFV window, the subject will be considered lost to follow-up on the date of last contact with the subject."***

<u>Section 6</u>

Section 6.1.2

More specific details about the blister packs, including the number of capsules and arrangement and removal of extra doses from blister packs were added to this section.

Section 6.2

1. Correction of typo:
"Subjects with an acute uncomplicated cutaneous abscess will receive either TMP/SMX (4 SS pills, 80 mg/***400*** mg each, twice per day) or 4 placebo pills (twice per day). Subjects will be encouraged to take these treatments approximately every 12 hours."

Section 6.3

Addition: ***"No modifications will be made to the study drug. If a subject experiences an allergic reaction to the study drug, they will be taken off of the study drug. If they experience an AE, no modifications will be made to the study drug. If the clinician decides it is necessary to stop study drug treatment due to an AE, then the algorithm in Section 9.4 may be followed."***

Section 6.4

1. Procedures were added for what do with used/returned blister packs.

"Blister packs that are collected from study subjects can be destroyed on site (following their site pharmacy procedures for disposing of used/empty blister packs) only after PPD study monitors have completed their drug accountability review and initialed the relevant entries on the Study Product Accountability Form."

Section 6.5

1. Clarification regarding collection of blister packs.

Blister packs will be collected from the subjects at the EOT if in person (Section 7.3) "***or at subsequent in person follow-up visits. If the subject is not seen in person, then they will be contacted and given instructions to mail their blister packs to the site."***

2. Procedures were added for what to do if blister packs are lost of unavailable.

"If blister packs are lost or unavailable, the memory aid will be used to record study medication compliance. The information on the memory aid will be recorded on a source document, but the memory aid will not be collected from the subject. If neither blister pack nor memory aid are available, study medication compliance will be obtained by subject interview. The study coordinator/investigator will record how study drug compliance information was obtained."

Section 6.6

1. List of unapproved medications were added to this section in response to FDA comment #4.

"If the subject takes an unapproved medication ***(e.g., blood thinners (coumadin), phenytoin (Dilantin®), methotrexate)*** this will be recorded in a source document and the eCRF, and the subject will be advised to discontinue the unapproved medication."

Section 7

Section 7.1

1. Clarification in response to CE committee's comments regarding assent.

a. Obtain written informed consent (must be signed prior to the initiation of any study related activities) ***from the participant or the participant's legally authorized representative with assent from the minors (ages 13-17).***
b. Verify conformance with inclusion and exclusion criteria. Note that written informed consent ***(and assent if necessary)*** will be obtained prior to assessment for conformance with inclusion and exclusion criteria that are strictly study-related and not collected during standard medical practice.

Section 7.2

1. Clarification:

Inquire about history of skin infections in household members (e.g., similar skin infection in a family member). ***This information will be obtained from subject response.***

2. Clarification in response to ORA comment regarding I&D procedure:

For abscess: measure and record the length of incision made for I&D. ***Note: Although I&D of an abscess is considered standard care (i.e., patients will receive I&D whether or not they are enrolled in the study), the procedure may be performed after enrollment into the study so that prior measurements of the area of erythema and swelling/induration can be obtained.***

Section 7.3

1. Clarification that some follow-up assessments are only relevant when the visit is in person.
2. Clarification about how to assess medication blister packs, if blister packs are not available.

Medication compliance will be judged by pill counts of blister packets (at OTV and EOT), "***but if blister packs are not available, study coordinators will review the subject's memory aid, or rely on subject recall. The source of how medication compliance was obtained (i.e., blister pack count, memory aid or subject recall) will be recorded on the source document."***

3. Clarification about how to assess memory aid information if memory aid is not available.

If the memory aid is not available (e.g., subject forgets memory aid, or phone visit), this information will be obtained by subject recall

4. Clarification that drainage material for culture and susceptibility testing will be obtained from subjects who have recurrent skin infections or new skin infections.

If drainage material is present and subject is a clinical failure, or subject experiences a recurrent skin infection at the original site, or a new skin infection at a different site, and the visit is in person, obtain drainage material for Gram stain, culture and antimicrobial susceptibility testing

5. Deleted: ***"using a standardized telephone script"***

Section 7.6

1. Clarification of when unscheduled visits should be recorded

"Unscheduled ***visits related to their initial skin infection*** will be recorded in the eCRF, including the date and reason for the visit. ***If the subject presents to the ED for a complaint unrelated to their initial skin infection, any AEs that occurred up through the TOC will be recorded, but no other information will be collected. After the TOC, only SAEs and recurrent skin infections in the same site or new skin infections in another site will be recorded."***

<u>Section 8</u>

Section 8.2.1

1. Deleted ***"anaerobic"*** cultures.

2. Clarification regarding when wound cultures should be obtained.

"The infection site/wound culture should be repeated if drainage material is available and the subject is a clinical failure, or develops a new skin infection at another site or a recurrent skin infection at the original site and evaluation is in-person. Wound cultures will be obtained from subjects in the abscess and infected wound sub-trials at enrollment."

Section 8.2.2

1. The sentence "Investigators will receive standardized training in ultrasound methods prior to study initiation." was revised to:

"Investigators will receive standardized training in wound measurement using ultrasound prior to study initiation."

2. The following clarifications were added:

"The skin over the abscess will be cleaned with ***a topical antiseptic solution, e.g., betadine and/or*** 70% isopropyl alcohol, and allowed to dry."

"The area will then be anesthetized with preservative-free 1%-2% lidocaine (***with or without epinephrine***)."

3. The following clarification was added in response to FDA comment #3 of Micro section.

"MRSA and MSSA isolates that exhibit erythromycin resistance and clindamycin susceptibility will be further tested for inducible resistance to clindamycin using the D-test."

4. The following clarification was added in response to an issue arising at the Truman Site Initiation visit:

"Subjects with isolates that exhibit vancomycin resistance or intermediate susceptibility will not have their treatment or culture results unblinded (unless they are clinical failures) or be withdrawn from the study. The responsibility of reporting unusual susceptibility patterns to the local public health department or infection control department will be left up to the laboratory staff, as required."

Section 8.2.3

1. Clarifications were made to specify that culture isolates will be refrigerated at the OV-UCLA site and shipped to an off-site laboratory for storage.

2. The following revision was made:

"All isolates sent to CDC will be de-identified and only labeled with ***a barcode label provided by EMMES***."

Section 9

Section 9.2.1

1. Clarification/revision regarding follow-up of AEs:

All AEs that ***occur up through the TOC*** and all SAEs will be followed to adequate resolution. ***After TOC, only recurrent skin infections and new skin infections should be reported as AEs.***

Section 9.3.1

1. Addition regarding SAE reporting to site IRBs and ISMs and follow-up of SAEs:

"The completed SAE form must also be emailed or faxed to the project director within one week of sending the SAE report to PPD. The project director will email the form to all sites to ensure that SAEs that occur at all study sites are reported in accordance with each local site IRB requirements.

All SAEs should also be reported by the study staff to the site (primary or secondary) ISM within 24 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until study investigator deems the event to be chronic or the subject to be stable. At this time, resolution or stability of the event will be reported by noting this in the AE source document and eCRF. If SAE is not resolved by EFV, follow-up may occur by phone, unless physical follow-up is deemed necessary by the site investigator."

Section 9.4

1. Clarification regarding follow up of AEs and SAEs.

"If an AE or SAE is not resolved by EFV, follow-up may be conducted by phone, unless the site investigator believes physical follow-up is necessary."

Section 9.5

1. The following clarifications were made in response to DSMB organizational meeting comment.

"Interim analyses will be conducted by the EMMES statistician and presented to the DSMB."

Deleted "the EMMES statistician determines that"

Section 9.6

1. The following clarification was made in response to DSMB organizational meeting comment regarding role of ISM.

Deleted ***" selected AEs or"***

2. Clarification/revision to clarify ISM reporting procedures:

"The ISM will send their report to the project director who will forward information to the medical monitor, project officer, and Safety Oversight Committee. If the medical monitor and/or DSMB require(s) further clarification from the ISM regarding a particular SAE, they may contact them directly."

Section 11

Section 11.3

1. The following clarification was made in response to DSMB organizational meeting comment regarding who performs interim analyses.

Deleted ***"DSMB and/or"***

2. The following sentence was deleted in response to comments from Angelita Ray and Shy Shorer at OV-UCLA Site Initiation Visit.

Deleted ***"In particular, after the completion of each interim analysis, study investigators will be provided with the cure rates observed in the control populations."***

3. The following revision was made:

Deleted: "and obtains FDA concurrence with the findings" and added ***"DMID will notify the FDA of the findings if necessary."***

Section 11.3.1

Deleted: "and obtains FDA concurrence with the findings of the interim analysis" and added ***"DMID will notify the FDA of the findings if necessary.***"

Section 14

Section 14.3

1. The following text was added for clarification in response to ORA comments:

"Consent ***and assent forms*** will be IRB-approved and the subject will be given sufficient time to read and review the document and discuss with their family member, friend or legal representative. ***If they require assistance to reach their family member, friend or legal representative, such as the use of a telephone, that***

will be facilitated. After this, they will be specifically asked if they have any questions or concerns, which will be addressed, or would like more time to consider their participation, which will also be provided."

Section 14.4

1. Clarification/Addition:

"Prisoners will be excluded from the study population ***at screening/baseline***. ***If a subject is imprisoned temporarily during study follow-up but has been released and is available for assessments at follow-up visits, they will not be withdrawn from the study***."

Section 14.7

1. The following text was added for clarification in response to ORA comments:

"CDC laboratories will not have access to the study database, and will therefore not be able to link the isolate to the subject's study data, including their patID. Specimens not shipped to the CDC will remain at the site laboratories in freezers at -70°C."

<u>Section 15</u>

Section 15.5

1. The following text was deleted and added in response to comments from Shy Shorer and Angelita Ray at Site Initiation visits.

Deleted: "Study documents will be retained for a minimum of 2 years after study completion."

Added: "Sites should request DMID approval prior to destroying any study records"

<u>ICFs and Assent Forms</u>

The following additions were made to each of the three ICFs

1. In Follow-up: ***"If you develop another skin infection in the same place or different place from your current infection, the doctor may collect a culture swab specimen if there is pus present."***
2. In Risks: ***"If you develop another abscess in the same place or different place from your current infection, the doctor may perform another I&D."***

List of Major Changes to STOP MRSA Study Protocol (Version 3.0).

1. The medical monitor of the study was changed from Shy Shorer, MD to Luigi Girardi, MD.

2. The study duration was extended from July, 2012 to July, 2013 and subject enrollment was extended from 3 years to 3 ½ years.

3. The clinical monitoring group for the study was changed from PPD, Inc to CROMS group. Any reference to the clinical monitoring contracting group were also changed to CROMS throughout the protocol.

4. The original estimated sample size estimate for the abscess sub-trial was revised in October, 2010 based on the results of interim analyses conducted by the DSMB and EMMES. The new sample size estimate calculated by EMMES statisticians for the abscess sub-trial is 1074. Assuming an 85% evaluability rate, at least 1265 subjects will need to be enrolled. Study investigators were not given information on how these sample size estimates were calculated to maintain the blind of the study, but the explanation given by the DSMB was that the cure rate in the placebo group is lower than our original assumed cure rate. Changes were made throughout the protocol to reflect this change in sample size and language was added to allow for further changes (increases or decreases) in sample sizes for all three sub-trials based on results of further interim analyses (Section 11.1).

5. Minor clarifications were made throughout the protocol, but none of these were changes to study procedures. Version numbers and dates were also updated.

STATISTICAL ANALYSIS PLAN

for

DMID Protocol 07-0040

Strategies using Off-Patent antibiotics for Methicillin-Resistant *Staphylococcus aureus (“STOP MRSA”)* – A Phase IIB, multi-center, randomized, double-blind clinical trial

Version 1.0; February 28, 2013

Prepared and distributed by:
The EMMES Corporation

arch 29, 2011

Strategies using Off-Patent antibiotics for Methicillin-Resistant *Staphylococcus aureus* (“*STOP MRSA*”) – A Phase IIB, multi-center, randomized, double-blind clinical trial

Statistical Analysis Plan

Trial Number code:	DMID Protocol: 07-0040
Development Phase:	Phase IIB
Products:	Abscess sub-trial: TMP/SMX or placebo Infected Wound sub-trial: TMP/SMX Clindamycin Cellulitis sub-trial: Cephalexin with TMP/SMX or Cephalexin alone
Form/Route:	Pill/Oral
Sponsor:	Division of Microbiology and Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Principal Investigator:	David Talan, MD and Gregory Moran, MD Olive View-UCLA Medical Center
Clinical/Medical Monitor:	Georgia Latham, MD Office of Clinical Research Affairs Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Disease National Institutes of Health 6610 Rockledge Drive, Room 4506 Bethesda, MD 20892-6603
Biostatistician:	Nancy Browning, PhD and Bill Mower, MD, PhD
Clinical Trial Initiation Date:	April 13, 2009
Clinical Trial Completion Date:	July, 2013
Date of the Analysis Plan:	February 28, 2013
Version Number:	Version 1.0

This study was performed in compliance with Good Clinical Practice

TABLE OF CONTENTS

List of Abbreviations	
AE	Adverse Events
BID	Twice daily
CA-MRSA	Community-Acquired Methicillin-Resistant *Staphylococcus aureus*
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
EFV	Extended Follow-up Visit
EMMES	EMMES Corporation (Data Management Contractor)
EOT	End of Therapy Visit
FDAGEEP	FDA Guidance Early Endpoint Population
I & D	Incision and Drainage
IDES	Internet Data Entry System/AdvantageEDC
IQR	Interquartile Range
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
OmITT	Original Modified Intent-to-Treat
OTV	On-therapy Visit
PP	Per Protocol
QID	Four times daily
RmITT	Revised Modified Intent-to-Treat
SAE	Serious adverse event
SS	Single-strength
SSTI	Skin and Soft-Tissue Infection
TMP/SMX	Trimethoprim/Sulfamethoxazole
TOC	Test-of-Cure Visit

1 INTRODUCTION

This is a multi-center, randomized, double-blind clinical trial in which subjects will be stratified by the type of infection and then randomized to various 7-day oral antibiotic treatments, including placebo-controlled and comparative designs. The study population will include children 13 years of age and over and adults, who weigh ≥ 40 kg presenting to 5 large urban Emergency Departments (EDs). Therapy will start on the day of enrollment. Subjects will be evaluated upon enrollment, at 2-3 days after enrollment (On-therapy visit (OTV)), at 1-3 days after the end-of-therapy (EOT), and at 7-14 days after the end-of-therapy (Test-of-cure visit (TOC)), and at 6-8 weeks after the end-of-therapy (Extended Follow-up Visit (EFV)). The objective of this study is to determine the optimal generic antibiotic therapy for treatment of skin and soft tissue infections (SSTI) caused by community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA) and other pathogens.

2 STUDY OBJECTIVES

The primary objectives for each type of skin and SSTI studied are to compare the cure rates in the per protocol (PP) population:

1.) for subjects with an acute uncomplicated cutaneous abscess receiving incision and drainage (I&D), to determine whether the addition of Trimethoprim/Sulfamethoxazole (TMP/SMX) (4 single-strength (SS) pills, 80 mg/400 mg each, BID), an antibiotic with activity against CA-MRSA, is more clinically efficacious than I&D alone (4 placebo pills BID);

2.) for subjects with an acute uncomplicated wound infection with any apparent drainage, to determine if clindamycin (300 mg, QID, with 3 placebo pills on alternating doses), an antibiotic with activity against CA-MRSA, methicillin-susceptible *Staphylococcus aureus* (MSSA), and streptococci is more clinically efficacious than TMP/SMX (4 SS pills, 80 mg/400 mg each, BID, with alternating 1 identical placebo pill, BID), an antibiotic with activity against CA-MRSA and MSSA; and

3.) for subjects with acute uncomplicated cellulitis, to determine if cephalexin (500 mg, QID) and TMP/SMX (4 SS tablets, 80mg/400mg each, BID), a regimen with activity against CA-MRSA, MSSA, and streptococci, is more clinically efficacious than cephalexin (500 mg, QID), an antibiotic with activity against MSSA and streptococci, and 4 placebo pills BID.

Secondary objectives provide additional means of assessment for the clinical efficacy of the employed interventions and resolution of the infection and include describing microbiological cure, change in the dimension of erythema, composite cure, surgical procedures, invasive and recurrent infections, infections in household contacts, and time to normal activity and until analgesics are no longer used at various times in the PP, original modified Intent-to-Treat (OmITT), and revised modified intent-to-treat (RmITT) populations.

2.1 Study Outcome Measures

2.1.1 Primary Outcome Measures

The Primary outcome measure is clinical cure at the TOC visit in the per protocol population.

2.1.2 Secondary Outcome Measures

The Secondary outcome measures include: rates of change of the dimensions of erythema, composite (antibiotic/surgical) clinical cure, microbiological cure, surgical procedures, and invasive and recurrent infections. Furthermore, infections in household contacts, medication AEs, and time to normal activity and until analgesics are no longer used in the PP/mITT populations will be assessed by subject response at follow-up visits.

3 STUDY DESIGN

3.1 General Design and Plan

This is a multi-center, randomized, double-blind, phase IIB clinical trial to evaluate oral off-patent antibiotics for outpatient treatment of subjects with any of the 3 main types of acute SSTI, i.e., abscesses, infected wounds, and cellulitis, with the primary objective of determining optimal antibiotic treatment. Subject enrollment will occur over 3 ½ years at 5 US EDs.

Subjects will be 13 years of age and older with acute uncomplicated infections who provide informed consent. The study will be double-blinded with subjects randomized to identical treatments with antibiotics and/or placebo for 7 days. Infection classification, wound care, and outcome assessment will be standardized prior to study initiation. Subjects will be evaluated after 2-3 days of treatment (OTV; Days 3-4), and at 1-3 days after end-of-therapy (EOT; Days 8-10), 7-14 days after end-of-therapy (TOC; Days 14-21), and 6-8 weeks after end-of-therapy (EFV; Days 49-63). Therefore, subjects will participate for approximately 9 weeks.

Upon enrollment, subjects will be stratified by type of infection, and then randomized to various oral treatments. In order to minimize the chance of misclassification of the type of infection, all subjects will be evaluated by bedside soft tissue ultrasound, which has been demonstrated to be effective at identifying occult abscesses.

Subjects with an acute uncomplicated cutaneous abscess receiving I&D will be treated with TMP/SMX or placebo to determine whether the addition of an antibiotic with activity against CA-MRSA is more clinically efficacious than I&D alone. Subjects with an acute uncomplicated wound infection will be treated with TMP/SMX or clindamycin to determine if clindamycin, an antibiotic with activity against CA-MRSA, MSSA, and streptococci is more clinically efficacious than TMP/SMX, an antibiotic with activity against CA-MRSA and MSSA. Subjects with acute uncomplicated cellulitis will be treated with cephalexin and TMP/SMX or cephalexin and placebo to determine if a regimen with the addition of TMP/SMX, an antibiotic with activity against CA-MRSA, is more clinically efficacious than cephalexin alone, an antibiotic with activity against MSSA and streptococci but not CA-MRSA.

The primary outcome will be clinical cure at the TOC in the PP population (subjects who meet enrollment criteria, have none of the exclusion criteria, complete 75% of the first 5 days of antimicrobial therapy, and have physical follow-up at the TOC; subjects who have been determined to be a clinical failure at any time prior to the TOC who took 75%

of the first 48 hours of antimicrobial therapy but who do not have physical follow-up at the TOC will also be included in the PP population).

Secondary endpoints will include microbiological cure, change in the dimension of erythema, composite cure, surgical procedures, invasive and recurrent infections, infections in household contacts, and time to normal activity and until analgesics are no longer used at various times in the PP/mITT populations.

Upon enrollment, information on the site, extent, cause, previous history of SSTI and relevant medical/surgical therapy, underlying medical conditions, and infections in household contacts will be obtained. The dimensions of erythema will be measured. Drainage material will be collected for Gram stain, culture, and antimicrobial susceptibility testing prior to antibiotic treatment by standard cotton swabs after I&D of abscesses or from open lesions (i.e., infected wounds with drainage).

All clinicians and study personnel participating in the study will receive standardized training (using training modules containing specific procedures as well as video demonstrations created by the main site) prior to study commencement to insure their knowledge of the definitions of abscess, infected wound, and cellulitis, use of ultrasound to evaluate the SSTI, wound assessment and measurement, and outcomes.

Follow-up evaluations will be in person but, if not possible, will be by telephone. Evaluations will include clinical assessment of the infection and medication AEs up through TOC. The rate of resolution of the infection will also be followed by measuring the dimensions of erythema. For telephone evaluations, the subject will be asked if swelling/induration, tenderness, and the dimensions of erythema has decreased, increased or stayed the same. At the TOC, the subject will be examined for fever, erythema, swelling, and tenderness in order to categorize their condition at the time as a cure or failure. Compliance will be judged by pill counts of blister packets. If blister packs are lost or unavailable, the memory aid will be used to record study medication compliance. If neither blister pack nor memory aid are available, study medication compliance will be obtained by subject interview. In addition, a digital thermometer will be provided to all enrolled subjects to monitor occurrence of fever between follow-up visits. This information can be recorded by the subject in the memory aids provided at enrollment. Subjects will also keep a record of days to return to normal activity and until analgesics are no longer used, and days of missed work. If the memory aid is lost or incomplete, an attempt will be made to recreate it or fill in missing information through subject interview by asking subjects to recall the answers.

Subjects will be screened carefully at entry and follow-up visits for possible invasive infection looking for findings such as vital sign abnormalities and toxicity (sepsis), abnormal cardiac murmur (endocarditis), a red, swollen joint (septic arthritis), respiratory

symptoms, abnormal lung exam, and new chest X-ray infiltrate (pneumonia), necrotic bone or abnormal X-ray (osteomyelitis), and a SSTI with severe pain, swelling, vascular insufficiency and/or radiographic soft tissue gas (necrotizing fasciitis). Investigators will follow subjects with invasive disease and serious adverse events (SAEs) until resolution (or deemed stable/chronic).

The only laboratory test required at the time of pre-enrollment is a urine pregnancy test, which will be conducted at the site hospital laboratory or in the ED. A pregnancy test will be performed in all women of childbearing potential who have not been surgically sterilized. No other laboratory or radiographic evaluation is required by the study, unless it is deemed necessary by the investigator. Since the AEs of the study drugs are well known, baseline studies and serial testing to identify asymptomatic abnormalities of renal, hepatic, and hematopoietic function will not be conducted unless, based on the judgment of the investigator, they are clinically indicated.

At enrollment, for subjects in the infected wound and abscess sub-trials, drainage material, if present, will be submitted for Gram stain, culture, and susceptibility testing (drainage material will be obtained prior to antibiotic treatment by standard cotton swabs of drainage material after I&D or from open lesions). MRSA and MSSA isolates that exhibit erythromycin resistance and clindamycin susceptibility will be further tested for inducible resistance to clindamycin using the D-test. Culture and susceptibility results will not be readily available to study investigators, study staff, and clinicians involved in evaluating subjects at follow-up visits. Research-related microbiology results will be restricted so that they are not easily available in hospital information systems (e.g., with general laboratory results) and can only be accessed by the study coordinators in case emergency unblinding of microbiology results is necessary with special approval of the site investigator or after subjects have completed the study protocol. During follow-up, if a subject is a clinical failure, develops a recurrent infection at the original site, or a new infection at another site and there is drainage available, a wound culture specimen will be obtained and submitted for culture and susceptibility testing.

3.2 Sample Size

The primary outcome variable for all study sub-trials is clinical cure (or failure) at the TOC.

Sample size calculations for all three study sub-trials were conducted using the following equations described by Fleiss.

Fleiss method:

Equations:

$$n = \frac{n'}{4}\left(1+\sqrt{1+\frac{4}{n'|P_2-P_1|}}\right)^2$$

Where

$$n' = \frac{\left(z_\alpha\sqrt{2\left(\frac{P_1+P_2}{2}\right)\left(\frac{Q_1+Q_2}{2}\right)}-z_{1-\beta}\sqrt{P_1Q_1+P_2Q_2}\right)^2}{(P_2-P_1)^2}$$

P_1 = Probability of cure using initial treatment strategy
P_2 = Probability of cure using alternative treatment strategy
$Q_1 = 1 - P_1$
$Q_2 = 1 - P_2$

Notes: i -Total sample size is given by N = 2*n*

ii - Our estimates employ a statistical significance level of α = 0.05 (this is adjusted to a nominal value of 0.044 to reflect alpha spending in our proposed interim analyses), and a power of 90% (β = 0.10).

Abscess study sub-trial

To determine whether TMP/SMX with drainage is superior to drainage alone in treating a subject with an acute uncomplicated cutaneous abscess. It is assumed that there will be a cure rate of 90% with I&D alone and a cure rate of 97.5% or more with TMP/SMX to be a sufficient difference for clinicians to justify antibiotic use.

The following null and alternative hypotheses were used where CR is the clinical cure rate:

H_0: $CR_{(TMP/SMX)} - CR_{(I\&D)} = 0.0\%$
H_1: $CR_{(TMP/SMX)} - CR_{(I\&D)} = 7.5\%$;
where $CR_{(I\&D)} = 90.0\%$ and $CR_{(TMP/SMX)} = 97.5\%$

For α = 0.044, β = 0.10, and assumed cure of 90% for simple drainage ($P_1 = 0.90$): Testing for 7.5% improvement with TMP/SMX ($P_2 = 0.975$) would require a sample containing N = 502 subjects (251 per treatment arm). Assuming an 85% evaluability rate, 590 subjects would need to be enrolled to ensure an adequate sample size.

$N_{Abscess} = 590$

This original estimated sample size estimate was revised in October, 2010 based on the results of interim analyses conducted by the Data and Safety Monitoring Board (DSMB) and EMMES. The new sample size estimate calculated by EMMES statisticians for the abscess sub-trial is 1074. Assuming an 85% evaluability rate, at least 1265 subjects will need to be enrolled. Study investigators were not given

information on how these sample size estimates were calculated to maintain the blind of the study.

Infected wound study sub-trial

To determine whether clindamycin is superior to TMP/SMX in treating subjects with infected wounds. It is estimated that the clinical cure rate of subjects with infected wounds is 85%. A cure rate of 95% or more is the reasonable threshold for clinicians to justify its preferred use.

The following null and alternative hypotheses were used where CR is the clinical cure rate:

H_0: $CR_{(clindamycin)} - CR_{(TMP/SMX)} = 0.0\%$
H_1: $CR_{(clindamycin)} - CR_{(TMP/SMX)} = 10\%$;
where $CR_{(TMP/SMX)} = 85.0\%$ and $CR_{(clindamycin)} = 95.0\%$

For $\alpha = 0.044$, $\beta = 0.10$, and an assumed cure of 85% for TMP/SMX treatment ($P_1 = 0.85$): Testing for 10% improvement with clindamycin ($P_2 = 0.95$) would require a sample containing at least 426 subjects (213 per treatment arm). Assuming an 85% evaluability rate, at least 500 subjects need to be enrolled to complete the study.

$N_{Infected\ wound} = 500$

Cellulitis study sub-trial

To determine whether cephalexin and TMP/SMX is superior to cephalexin and placebo in treating subjects with acute uncomplicated cellulitis. It is estimated that the clinical cure rate of subjects with acute cellulitis is approximately 85%. A cure rate of 95% or more is the reasonable threshold for clinicians to justify its preferred use.

The following null and alternative hypotheses were used where CR is the clinical cure rate:

H_0: $CR_{(TMP/SMX/cephalexin)} - CR_{(cephalexin)} = 0.0\%$
H_1: $CR_{(TMP/SMX/cephalexin)} - CR_{(cephalexin)} = 10\%$;
where $CR_{(cephalexin)} = 85.0\%$ and $CR_{(TMP/SMX/cephalexin)} = 95.0\%$

For $\alpha = 0.044$, $\beta = 0.10$ and assumed cure of 85% for treatment with cephalexin alone ($P_2 = 0.95$): Testing for 10% improvement with cephalexin and TMP/SMX ($P_2 = 0.95$) would require a sample containing at least 426 subjects (213 per treatment arm). Assuming an 85% evaluability rate, at least 500 subjects would need to be enrolled to ensure an adequate sample size.

$N_{Cellulitis} = 500$

A detailed summary of our sample size explorations, including estimates for differing cure rates and levels of attrition, is presented in Appendix B of the study protocol. All sample sizes provided above are estimates and can be increased or decreased based on interim analysis conducted by EMMES and the DSMB (see Section 11.3 of the Protocol under 'Assessment for Efficacy' subsection).

Our prior SSTI study that included a more limited population of adults with purulent lesions enrolled on average 10 subjects/week/site. For this clinical trial, approximately 3-4 evaluable subject per type of SSTI, per site, per month, will have to be enrolled, which, for each of the 3 types of SSTI, would amount to about 48 subjects/site/year, 144 subjects/site over 3 years, and estimated 720 total enrolled subjects per sub-trial at all 5 sites. In the unexpected instance that we are unable to meet enrollment goals at 90% power, we also present an alternative approach in Appendix B of the study protocol using a less stringent power of 80% ($\beta = 0.20$) which will also yield an acceptable sample size to achieve our study goals.

Cases involving protocol violations will be handled on a case-by-case basis. Site investigators will first make an assessment of the severity of the violation. Any cases that involve violations that could threaten the study validity (e.g., administering open antibiotics prior to randomization) will be excluded from the study population. Cases that involve violations that do not threaten study validity (e.g., failure to procure a culture specimen) may be included in the study population, provided there are not other reasons that mandate withdrawal. The decision to include or exclude a specific case will be made prior to unblinding of the study antibiotic assignment. Cases that are excluded from the study on the basis of protocol violations will not be counted in the PP or OmITT analyses, regardless of their outcome status at the time of the violation, but will be included in the RmITT population. If subjects miss doses of study drug, data will be collected and recorded on the amount of drug taken. Secondary analysis will be conducted to examine potential differences between various thresholds of compliance.

The sample size estimates provide a sufficient number of cases to definitively test the primary hypotheses on all three study sub-trials. These numbers are too small to provide conclusive statistical assessments of the secondary outcomes. However, the enrollment estimates are likely to reveal trends in secondary outcomes, and these trends may serve as primary hypotheses for future investigations.

3.3 Randomization and Blinding

Enrollment will be done online using the enrollment module created by EMMES (i.e., Internet Data Entry System (IDES)). The randomization is stratified by type of infection. The randomization code will link to the treatment assignment. IDES will assign each subject a randomization code after demographic and eligibility data have been entered

into the system. A designated individual (e.g., pharmacist) at each site will be provided with a code list for emergency unblinding purposes, which will be kept in a secure place.

The subjects, the site study personnel, data entry personnel at the sites, and laboratory personnel will be blinded to treatment assignment. The DSMB may receive data in aggregate and presented by treatment group, but without the treatment group (or dose level) identified. The DSMB may be unblinded to individual study treatment assignments, as needed, to adequately assess safety issues.

The site investigator and study coordinators will not be provided with the code list to break the blind. Under normal study circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. The blind should be broken only when the specific conditions listed in Protocol section 5.3.2 have been met.

The treatment sub-trials will be masked to both the subject and the study staff and maintained according to standard practices. Fisher BioServices will package all study drugs and ensure they are already masked according to applicable regulatory requirements.

Culture and susceptibility results will not be available to clinicians involved in evaluating subjects at follow-up visits. Research-related microbiology results will be restricted so that they are not easily available in hospital information systems (e.g., with general laboratory results) and can only be accessed with special approval of the study coordinator/site investigators. The treatment blind will not be broken if microbiological testing shows resistance to one of the antibiotics being studied (see Protocol Section 4). If a site is discontinued, subjects enrolled will continue with care and be followed and the blind will not be broken.

3.4 Study Assessments

SCHEDULE OF EVENTS

Procedures		Screening (Day 1)	Follow-Up Schedule: Baseline/Enrollment (Day 1)	OT Visit (Days 3-4)	EOT Visit (Days 8-10)	TOC Visit (Days 14-21)	EF Visit (Days 49-63)	Unscheduled Visit	Premature Discontinuation
Signed Consent Form		X							
Assessment of Eligibility Criteria		X							
Review of Medical History		X	X						
Review of Concomitant Medications		X	X	X	X	X	X	X	X
Administered and provided with study drug			X						
Physical Examinations	Complete		X						
	Symptom-Directed			(X)	(X)	(X)	(X)	(X)	(X)
	Vital Signs		X	X†	X†	X†	X†	X†	X†
Assessment of Adverse Events				X	X	X	X**	X**	X
Clinical Laboratory	Chemistry		(X)	(X)	(X)	(X)	(X)	(X)	(X)
	Hematology		(X)	(X)	(X)	(X)	(X)	(X)	(X)
	Urine Pregnancy Test	X		(X)	(X)	(X)	(X)	(X)	(X)
Gram stain, culture (aerobic & anaerobic), and susceptibility testing of purulent material			X*	(X)	(X)	(X)	(X)	(X)	(X)
Medication Check				X†	X†			(X)	(X)
Memory Aid Check				X†	X†	X†		(X)	(X)
C. diff toxin assay of stool specimen				(X)	(X)	(X)	(X)	(X)	(X)

X – Required

(X) – As deemed indicated by site investigator

† - Required if visit is conducted in-person. If visit is conducted over the phone, as much information as possible can be collected by subject recall (e.g., medication compliance and memory aid information).

*Required for abscess and infected wound sub-trials, but not for cellulitis

** After TOC, only AEs that are new or recurrent skin infections are recorded

At baseline, all procedures will be done before study interventions.

4 STUDY POPULATIONS

4.1 Inclusion Criteria

1. Adult or child 13 years of age and older (who weighs ≥ 40 kg);
2. Have a SSTI with all three local findings of erythema (> 2 cm across the lesion or from a discrete wound edge), tenderness, and swelling/induration. Fever, leukocytosis, and lymphangitis will be noted, but are not enrollment criteria. SSTI with these local findings will be further categorized and defined as one of:
    a. Abscess - a fluctuant and/or indurated lesion, or findings of a fluid-filled cavity on soft tissue ultrasound evaluation that, when opened reveals purulent material, receiving I&D (considered standard care for abscess) and having a minimum diameter (along any axis) of at least 2 cm (measured from the borders of induration, if a fluctuant lesion, or borders of the abscess cavity on ultrasound, if not fluctuant).

        Note: Although I&D of an abscess is considered standard care (i.e., subjects will receive I&D whether or not they are enrolled in the study), the procedure may be performed after enrollment into the study so that prior measurements of the area of erythema and swelling/induration can be obtained unless it is an occult abscess in which the I&D will be performed prior to enrollment to verify infection type and ensure correct classification of the subject.

    b. Infected Wound - a wound (defined as any apparent break in the skin) with any apparent drainage limited in depth to only involving skin and subcutaneous tissue, including sutured cutaneous wounds not involving intra-abdominal surgeries contaminated with bacterial or bowel contents (e.g., colon surgery and empyema drainage), and

    c. Cellulitis - an area of erythema without the presence of a wound with drainage or abscess;

    Note: Cellulitis associated with an abscess will be categorized as an abscess. Cellulitis associated with an infected wound will be classified as an infected wound. Subjects with cellulitis and an abscess less than 2 cm will be excluded. Infected wound associated with an abscess that may require I&D, will be classified as an infected wound.
3. Have the infected lesion for 7 days or less duration;
4. Are to receive outpatient treatment at enrollment/baseline;

5. Express willingness and ability to be contacted and return for re-evaluation according to the study protocol;
6. Provide written informed consent (and for subjects ages 13-17, consent from their guardian and assent);
7. Negative pregnancy test for subjects who are women of childbearing potential.

4.2 Exclusion Criteria

1. Severe allergy or reaction to study drug or drugs similar to the study drug relevant to whichever study sub-trial the subject would be assigned to (e.g., subjects with severe or life-threatening penicillin allergies, allergy to any cephalosporin, clindamycin, or sulfonamides, or any other drug containing sulfur such as thiazides, furosemide, and oral sulfonylureas);
2. Concomitant treatment (i.e., while on study drug therapy) with coumadin, phenytoin, or methotrexate, or suspected G-6-PD or folic acid deficiency;
3. Expected inability to swallow or absorb the study drug (assessed by subject history);
4. Pregnancy, nursing, or expectation of becoming pregnant while on study drug;
5. Perirectal (within 5 cm of anus), perineal non-skin lesions (i.e., mucosal), or paronychial location of infection. Scrotal and labial abscesses will not be excluded.
6. An infection due to a mammalian bite;
7. Treatment with a study drug relevant to their infection type, or another systemic antibiotic in the previous 48 hours (i.e., before screening/baseline) unless associated with treatment failure which is defined as a subject who has been on prior (non study drug) antibiotics for at least 72 hours and failed.
8. Expected concurrent treatment with a topical antibiotic or another systemic antibiotic up to TOC (note: if subject was using a topical antibiotic previously, they can still be enrolled if they agree to stop using it);
9. Immunodeficiency [e.g., absolute neutrophil count $<500/mm^3$, chronic immunosuppressive drugs, active chemotherapy, or known AIDS (CD4 count <200 or AIDS-defining illness within the last year) assessed by subject history]. Note: subjects who had prior AIDS-defining illness or CD4 count <200 in the past may be enrolled if most recent CD4 count >200;
10. Burn or active chronic skin condition (e.g., including rash or eczema) related to the SSTI at screening/baseline;

11. Infection related to currently indwelling device (e.g., intravenous line), excepting sutures associated with qualifying infected wounds which will be removed upon enrollment;
12. Infection for which prior cultures reveal in vitro resistance of a pathogen to a study drug in the previous month prior to screening/baseline;
13. Known or suspected osteomyelitis or septic arthritis;
14. Infection related to diabetic foot, decubitus, or ischemic ulcer;
15. Known severe renal insufficiency (creatinine clearance < 50 mL/min) calculated by measurement of serum creatinine if subject provides this history or based on past studies at baseline/enrollment;
16. Prior enrollment in this study within 12 weeks;
17. Another active infection of another organ system (e.g., pneumonia) or more than one active (i.e., currently on antibiotic treatment and/or requiring I&D) SSTI site (e.g., a site noncontiguous with the infection under study). Note: Minor folliculitis at secondary site is not an exclusion;
18. Presence of an abscess that has completely drained, either spontaneously or by a healthcare provider prior to enrollment. Note: This exclusion refers to the primary infection site;
19. An infected wound or cellulitis that has been surgically explored (>1 cm incision) and does not reveal an abscess. Cellulitis that has been needled, minimally incised (≤ 1 cm) or punch biopsied and no purulent drainage found can still be enrolled;
20. Currently incarcerated in a detention facility or in police custody (note: subjects wearing a monitoring device can be enrolled) at baseline/screening;
21. For subjects with an infected wound, history of *C. difficile* infection, pseudomembranous colitis, or active diarrhea at baseline/screening;
22. For subjects with an infected wound, severe liver disease based on subject history;
23. An IV drug user in the last month with current presence of fever;
24. Current residence in a nursing home or other long term care facility at baseline/screening;
25. Expected use of other investigational drug or vaccine while on study drug;
26. For subjects with an abscess, cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis is reasonable, including subjects with prosthetic cardiac valve or prosthetic

material used for cardiac valve repair, history of previous infective endocarditis, congenital heart disease (excluding mitral valve prolapse), and history of cardiac transplantation recipients who develop cardiac valvulopathy;

27. Presence of an organic foreign body, e.g., wood (note: subjects with embedded non-organic materials, e.g., metal or glass, that can be completely removed can still be enrolled if physician is certain there is no foreign body left).

4.3 Subject Disposition

The disposition of the subjects from screening to each sub-study will be presented as shown in Figure 1. In addition, the completion status and reasons for early discontinuation from the study will be summarized. A subject could be discontinued from the study after enrollment into the study for several reasons including the following: their condition worsened, the physician found the subject met an exclusion criterion, and the subject withdrew voluntary. The following reasons for discontinuing early are being collected during the study:

- Adverse Event,
- Death,
- Lost to follow-up,
- Voluntary withdrawal by subject,
- Withdrawal by investigator,
- Termination of site or study by sponsor,
- Subject was randomized but not treated,
- Any other reason not specified above.

Table 9 summarizes the completion and discontinuation reasons for the study.

4.4 Definition of Populations for Analysis

4.4.1 Per Protocol (PP) Population

The PP Population will include all subjects who meet enrollment criteria, have none of the exclusion criteria, complete at least 75% of the first 5 days of antimicrobial therapy, and have physical follow-up at the TOC. Subjects who have been determined to be a clinical failure at any time prior to the TOC but may or may not have physical follow-up at the TOC and who took at least 75% of the first 48 hours of antimicrobial therapy will also be included in the PP population.

4.4.2 Original Modified Intent-to-Treat Population (OmITT)

The OmITT population will consist of subjects who take at least one dose of study medication and have an assessment at the TOC. The following definitions for cure and failure will be used:

Cure: No change in antibiotic therapy due to persistence or worsening of infection (based on study clinician assessment, the subject's assessment, or assessment by another outside clinician) prior to or through TOC.

Failure: Subject had a change in antibiotic therapy due to persistence or worsening of infection (based on study clinician assessment, the subject's assessment, or assessment by another outside clinician) at any time up to or through TOC. All subjects who withdraw from the study, are lost to follow-up prior to final classification or have missing or unassigned outcomes, will also be included in the OmITT population, but will be classified as failures.

4.4.3 Revised Modified Intent-to-Treat Population (RmITT)

The RmITT population will consist of subjects who take at least one dose of study medication and have any follow-up evaluation, i.e., either a physical or telephone follow-up evaluation at any time during the study. The RmITT population was added on recommendation from the Data Safety Monitoring Board (DSMB).

4.4.4 Population for Safety Evaluations

The population for safety evaluations comprises all subjects who were randomized, received study product and did not return 100% of doses. The treatment group used in safety analyses is that of all subjects who consumed at least one dose of study medication.

4.4.5 Population for Protocol Deviation Evaluations

The population for protocol deviations evaluation includes all subjects that were enrolled and randomized into the study.

4.4.6 Definition of Sub-group Population in Different Analyses

The following subgroups will be analyzed for the abscess and infected wound sub-trials:

- Clinical Cures versus Clinical Failures
- Large Abscess versus Small Abscess
- MRSA versus Non-MRSA
- MSSA versus Non-MSSA
- Strep versus Non-Strep.

Clinical cures versus clinical failures: Clinical cure and clinical failures are defined in Section 8.1 below.

Large Abscess versus Small Abscess: A large abscess will be defined and analyzed in 3 separate ways:

Baseline measurement of > 5cm on either length or width of swelling/induration (external measure).

Baseline measurement of > 5 cm on length, width, or depth of abscess cavity measured by probe.

Baseline measurement of > 5 cm on length, width or depth of abscess cavity measured by ultrasound.

If an abscess is not classified as a large abscess by the above criteria, then it will be classified as a small abscess.

MRSA versus Non-MRSA: The MRSA subgroup consists of subjects that grew MRSA on at least one culture (including those with multiple organisms). The Non-MRSA subgroup consists of those subjects who did not grow MRSA on any culture, including those subjects with no organism growth. Note: These populations may include subjects with MSSA and other non-MRSA pathogens.

MSSA versus Non-MSSA: The MSSA subgroup consists of subjects that grew MSSA on at least one culture (including those with multiple organisms). The Non-MSSA subgroup consists of those subjects who did not grow MSSA on any culture, including those subjects with no organism growth. Note: These populations may include subjects with MRSA and other non-MSSA pathogens.

Strep versus Non-Strep: The Strep subgroup consists of subjects that grew any species or strain of Streptococcus on at least one culture (including those with multiple organisms). The Non-Strep subgroup consists of those subjects who did not grow any species or strain of Streptococcus on any culture, including those subjects with no organism growth. Note: These populations may include subjects with MRSA, MSSA and other non-MRSA and non-MSSA pathogens.

4.4.7 FDA Guidance Early Endpoint Population

The FDA guidance early endpoint population (FDAGEEP) will consist of subjects who take at least one dose of study medication and complete the follow-up evaluation at the On-therapy visit. The FDA endpoint population was added to provide outcome assessments similar to current FDA guidance for evaluating SSTI studies.

5 STATISTICAL CONSIDERATIONS

5.1 General/Introduction

The design of this clinical trial is consistent with guidelines of the Center for Drug Evaluation and Research July 1998 FDA Draft Guidance for Industry entitled, "Uncomplicated and Complicated Skin and Skin Structure Infection- Developing Antimicrobial Drugs for Treatment." Elements are also consistent with document E9 (Statistical Principles for Clinical Trials) and the CONSORT statement (http://www.consort-statement.org/). Clinical trial results will be presented in a flowchart consistent with the Flow Diagram of the CONSORT statement (http://www.consort-statement.org/).

5.2 Pooling of Sites

Five sites are planned for the study with similar enrollment at each site. There is no plan at present to pool any of the sites.

5.3 Sample Size Considerations

Sample size discussion can be found in Section 3.2 - Sample Size.

5.4 Study Hypotheses

This study contains three separate sub-trials that will evaluate treatment on three independent populations. These sub-trials will examine treatments for the following conditions: 1) acute uncomplicated abscess; 2) acute uncomplicated wound infections; 3) acute uncomplicated cellulitis. Each sub-trial involves a specific independent hypothesis that will be assessed on an independent population.

5.4.1 Abscess Sub-trial

For subjects with acute uncomplicated abscess, the hypothesis is that the clinical cure rate of subjects treated with TMP/SMX will be superior to that of subjects treated with placebo in the Per Protocol population at the Test of Cure (TOC) visit.

5.4.2 Infected Wound Sub-trial

For subjects with an infected wound, the hypothesis is that the clinical cure rate of subjects treated with clindamycin will be superior to that of subjects treated with TMP/SMX in the Per Protocol population at the TOC.

5.4.3 Cellulitis Sub-trial

For subjects with acute uncomplicated cellulitis, the hypothesis is that the clinical cure rate of subjects treated with cephalexin and TMP/SMX will be superior to that of subjects treated with cephalexin and placebo in the Per Protocol population at the TOC.

5.5 Interim Analyses

Interim analyses were performed by the EMMES statistician. Study investigators and staff were not allowed access to data or reports containing data that could jeopardize trial integrity.

Interim analyses were scheduled to occur after each sub-trial of the study achieved 50% and 75% of its anticipated enrollments. These interim analyses were designed to assess efficacy and futility, and evaluated all other endpoints, including safety data, and provided guidance in determining whether there was overwhelming evidence that would justify early termination of any of the three sub-trials, or the study as a whole. In addition, the interim analyses provided the investigators with information to enhance sample size estimation and ensured that each sub-trial would attain sufficient power to produce meaningful results. The sample size of the Abscess sub-trial was adjusted following the 75% interim analysis and the enrollment target for the abscess sub-trial was increased from 590 to 1265. No additional interim analyses were performed after the sample size increase.

All interim efficacy analyses were based on the Per Protocol outcomes and subjects were classified based on assessments at the TOC.

5.6 Time-Points/Definitions for Analysis

The primary efficacy variable was clinical cure at the TOC visit in the Per Protocol population.

5.7 Methods for Handling Missing Data

No imputation will be performed in this study.

5.8 Statistical Analytical Issues

There are no current statistical issues that are not explained in other sections.

6 EVALUATION OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1 Demographics and Baseline Characteristics

6.1.1 Demographics Data

Demographic data will be summarized using counts and percentages for categorical variables such as gender and race. For continuous variables, such as age, the mean, standard deviation, median, minimum, maximum, and number of subjects will be presented. The following demographic data will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol populations:

- Gender - categorical
- Race - categorical
- Ethnicity - categorical
- Age - continuous
- Age Group - categorical

In addition, subgroup analyses of clinical cures versus clinical failures will be performed for all sub-trials. A subgroup analysis of large versus small abscess will also be performed for the Abscess and Infected Wound sub-trials.

A mock-up of this table is presented in Table 1.

6.1.2 Baseline Characteristics

Baseline Characteristics of oral temperature, vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate) and weight will be summarized by mean, standard deviation, median, minimum, maximum, and number of subjects. The following baseline characteristic data will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol populations:

- Temperature (C)
- Vital Signs
- Weight (kg)

A mock-up of this table is presented in Table 2.

6.1.3 Baseline Data as Entry Criteria

Baseline Infection Site Characteristics will be summarized for each sub-trial for the OmITT, RmITT, FDAGEEP, and Per Protocol Populations. Categorical variables will be summarized using counts and percentages and continuous variables will be

summarized using mean, standard deviation, median, minimum, maximum, lower quartile, upper quartile, interquartile range and number of subjects.

For the Abscess and Infected Wound sub-trials a summary of the different species identified in the baseline infection site culture will be presented as shown in Table 3. In addition, a bar chart will be presented summarizing the number of subjects by the susceptibility of each infection site culture as shown in Figure 2.

Abscess Sub-trial: For the Abscess sub-trial, the following infection site data will be summarized as shown in Table 4a:

- Location of Infection Site
- Purulent Drainage Present
- Length, Width, Depth and Volume of Abscess Cavity Ultrasound Measurements in cm - Interquartile Range (IQR).
- Maximal Depth of Abscess Cavity split between skin and subcutaneous and those involving deep fascia in cm - IQR.
- Length, Width, Depth and Volume of Abscess Cavity with I & D probe Measurements in cm - IQR.
- Area of Erythema in cm - median and IQR.
- Area of Swelling/Induration in cm - median and IQR.
- Presence of Fever at Baseline where fever is defined as > 100.4 F or > 38 C.

The area of erythema is calculated using the formula for an ellipse (1/4pi*length*width) and subtracting area of probe measurements of abscess cavity (using length and width measurements of abscess cavity) from area of erythema (using length and width) measurements of erythema. The area of swelling/induration is calculated using the formula for an ellipse (1/4pi*length*width) and subtracting area of probe measurements of abscess cavity (using length and width measurements of abscess cavity) from area of swelling/induration (using length and width) measurements of swelling/induration.

Infected Wound Sub-trial: For the Infected Wound sub-trial, the following infection site data will be summarized as shown in Table 4b:

- Location of Infection Site
- Purulent Drainage Present
- Wound Type
- Length of Wound in cm - median and IQR.
- Previous Surgical Procedure which Lead to Infection.
- Foreign Body/Material Retained
- Abscess Present

- If Abscess Present was I&D performed
- Length, Width, Depth and Volume of Abscess Cavity Ultrasound Measurements in cm - Interquartile Range (IQR).
- Length, Width, Depth and Volume of Abscess Cavity with I & D probe Measurements in cm - IQR.
- Presence of Fever at Baseline where fever is defined as > 100.4 F or > 38 C.

Cellulitis Sub-trial: For the Cellulitis sub-trial, the following infection site data will be summarized as shown in Table 4c:

- Location of Infection Site
- Purulent Drainage Present
- Area of Erythema in cm - median and IQR.
- Area of Swelling/Induration in cm - median and IQR.
- Presence of Fever at Baseline where fever is defined as > 100.4 F or > 38 C.

See definition under Abscess Sub-trial for area of erythema and area of swelling/induration.

6.2 Medical History and Prior Conditions

Medical History and Prior Conditions data will be summarized using counts and percentages for categorical variables and median and interquartile range (IQR) for continuous variables. The following medical history information will be summarized as presented in Table 5:

- Co-morbidities
- Close Household contact with someone with similar skin infection in last month.
- Fever in the last week
- Number of days of SSTI symptoms - median and IQR.
- Previously treated for this infection with antibiotics.
- General Functional Impairment
- Level of Functional Impairment.

Medical History information will be summarized for all sub-trials for the OmITT, RmITT, FDAGEEP, and the Per Protocol Populations. For all three sub-trials, the subgroups of clinical cures versus clinical failures will be analyzed (replace treatment group) in the Per Protocol Population. For Abscess and Infected Wound Sub-trial, the subgroups of large abscess versus small abscess will be analyzed (replace treatment group) in the Per Protocol Population.

6.3 Prior Therapies and Medications

Prior antibiotic therapy will be summarized for subjects who were taking antibiotics at baseline/enrollment and failed previous treatment or for subjects who took antibiotics in the past month prior to enrollment. Counts and percentages will be used to summarize the number of subjects who fall into each of the above categories plus each individual antibiotic therapy for all sub-trials for the OmITT, RmITT, FDAGEEP, and the Per Protocol Populations. A mock-up of the table is presented in Table 6.

7 EVALUATION OF TREATMENT COMPLIANCE AND EXPOSURE

7.1 Study Visit Compliance

Study visit compliance will be summarized for each visit: Enrolled (Day 1), On Therapy visit (Days 3-4 Post Enrollment), End of Therapy visit (Days 8-10 Post Enrollment), Test of Cure visit (Days 14-21 Post Enrollment), and Extended Follow-up visit (Days 39-63 Post Enrollment). Visit compliance will be categorized as completed, missed visit or not done, or not completed due to early termination. For the interim analyses two additional categories will be summarized: expected and data pending. A mock-up of these tables is presented in Table 7.

7.2 Compliance to Study Drug

Study medication compliance will be summarized overall. Compliance will be calculated by taking the total number of daily doses to be taken (dependent on sub-trial and study medication) and dividing by the number of days a subject is in the treatment period. A subject will be categorized as being fully compliant - took 100% of the doses, or not fully compliant - took less than 100% of the doses or more than 100% of the doses. Subjects who are not fully compliant will be further classified into the following categories: 0-25%, 26%-50%, 51% - 75%, 76%-99%, 100% or more doses taken, or unknown. A mock-up of this table is presented in Table 8. In addition to counts of subjects and percentages, a pie graph will be created for each sub-trial and site as specified in Figure 3.

7.3 Protocol Deviations

Non-subject specific and subject specific protocol deviations will be summarized for each sub-trial. Table 10 presents a mock-up of the listing of non-subject specific protocol deviations. Counts of all subject specific protocol deviations will be summarized for the following categories as presented in Table 11: Blinding Policy/Procedure, Eligibility/Enrollment, Follow-up Visit Schedule, Product Administration/Dosing, Product Administration/Dosing Schedule, and Protocol Procedures/Assessments. In addition to individual categories, the total number of deviations and the total number of subjects enrolled will be summarized.

8 EVALUATION OF EFFICACY PARAMETERS

8.1 Definitions of Outcomes

8.1.1 Clinical Cure at TOC in the PP Population

Clinical cure at TOC in the PP Population was defined as:

- No failure on any previous visit up through the TOC,
- Absence of fever, and
- Resolution or minimal presence of all the following signs and symptoms from baseline based on clinician assessment:
    - Erythema
    - Swelling
    - Tenderness

8.1.2 Clinical Failure Definitions in the PP Population

At the on therapy visit (OTV), end of therapy (EOT) and any visit up to the test of cure visit (TOC), only failure will be designated as an outcome. Any subject outcome designated as a failure at any time before and including the TOC, will be categorized as a failure for the PP analysis. Measures of improvement will be assessed at each visit, starting with the OTV, including serial change in the dimensions of erythema, time to return to normal activities, and no need for pain medications.

<u>Failure at OTV:</u>

- Presence of fever (attributable to the infection being studied), or
- Increase in either the length or width of erythema > 25%, or
- Both of the following show worsening based on clinician assessment:
    - Swelling
    - Tenderness

Failure will be designated as an outcome by these criteria between the enrollment visit and EOT.

<u>Failure at EOT:</u>

- Presence of fever (attributable to the infection being studied), or
- Increase or no improvement in either the length or width of erythema from baseline, or
- None of the following show improvement from baseline based on clinician assessment:

- Swelling
- Tenderness

Failure at the EOT includes subjects who have no improvement in the dimensions of erythema or swelling or tenderness whereas at the OTV (and up to the EOT), an increase of > 25% in either the length or width of erythema or worsening of both swelling and tenderness are required to be designated as a failure. Failure will be designated as an outcome by these criteria no sooner than the EOT but at any time after the EOT up to the TOC.

Failure at TOC:

- Failure at any previous visit (on or after the OTV)
- Presence of fever (attributable to the infection being studied), or
- More than the minimal presence of any of the following:
  - Erythema
  - Swelling
  - Tenderness

Failure at the TOC includes subjects with more than minimal erythema, swelling, or tenderness whereas at EOT, an increase or no improvement in the dimensions of erythema, or no improvement in both swelling or tenderness is required to be designated as a failure.

8.1.3 Clinical Cure Definitions in the OmITT

The definition of a clinical cure in the original mITT population will be any subject who takes at least one dose of study medication and receives no change in antibiotic therapy due to persistence or worsening of infection (based on study clinician assessment, the subject's assessment, or assessment by another outside clinician) prior to or through TOC.

Subjects will be classified as failures in the OmITT analysis if they had a change in antibiotic therapy due to persistence or worsening of infection (based on study clinician assessment, the subject's assessment, or assessment by another outside clinician) at any time up to or through TOC. All subjects who withdraw from the study, are lost to follow-up prior to final classification or have missing or unassigned outcomes will also be included in the OmITT population, but will be classified as failures.

8.1.4 Clinical Cure Definitions in the RmITT

The DSMB recommended that the definition of the mITT population be revised to be less restrictive and include subjects with any follow-up information after the initial visit. For the RmITT population, classification of a clinical cure will be based on findings from

the last recorded follow-up visit. Subjects who have at least one follow-up visit and are not deemed clinical failures prior to or on the last recorded follow-up visit, will be regarded as clinical cures. A subject will need to be deemed a clinical failure to be classified as a clinical failure.

Clinical cure in the RmITT population is defined as:

- No failure on any previous visit up through the last recorded visit,
- Absence of fever, and
- Resolution or minimal presence of all the following signs and symptoms from baseline based on clinician assessment:
    - Erythema
    - Swelling
    - Tenderness

Failure in the RmITT population at non-TOC follow-up visits:

- Presence of fever (attributable to the infection being studied), or
- Increase or no improvement in either the length or width of erythema from baseline, or
- None of the following show improvement from baseline based on clinician assessment:
    - Swelling
    - Tenderness

Failure at the EOT includes subjects who have no improvement in the dimensions of erythema or swelling or tenderness whereas at the OTV (and up to the EOT), an increase of > 25% in either the length or width of erythema or worsening of both swelling and tenderness are required to be designated as a failure. Failure will be designated as an outcome by these criteria no sooner than the EOT but at any time after the EOT up to the TOC.

Failure in the RmITT population at TOC:

- Failure at any previous visit (on or after the OTV)
- Presence of fever (attributable to the infection being studied), or
- More than the minimal presence of any of the following:
    - Erythema
    - Swelling
    - Tenderness

Failure at the TOC includes subjects with more than minimal erythema, swelling, or tenderness whereas at EOT, an increase or no improvement in the dimensions of erythema, or no improvement in both swelling or tenderness is required to be designated as a failure.

8.1.5 Composite Clinical Outcome

Cure – resolution of all symptoms/signs of infection, or improvement to such an extent that no additional antibiotic therapy and/or surgical procedures are necessary.

Failure – lack of resolution of all signs and symptoms of infection to such an extent that further antibiotic therapy and/or surgical procedures are necessary.

8.1.6 Microbiological Outcome

Cure (Presumed eradication) – not deemed a clinical failure through TOC

Failure – a clinical failure at any time up to or through TOC and further characterized as follows:

Persistence – persistent growth of a pre-therapy pathogen.

New infection – growth of a new pathogen and eradication of initial pathogen.

Super-infection – growth of a new pathogen in addition to persistent growth of pre-therapy pathogen.

Unclassified –

- no specimen present for culture, or
- growth of a pathogen in subsequent culture specimen of subjects with cellulitis
- growth of a pathogen in subsequent culture specimen of subjects with abscess or infected wound for whom initial culture specimens were negative or were not obtained.

Indeterminate – not meeting any one of the above microbiologic outcome criteria.

8.1.7 FDA Guidance Early Endpoint Assessment

Cure (Clinical response) – At the On-therapy visit (OTV)

- Cessation (no change or decrease) in the length, width and area of erythema from baseline/enrollment, and

- No worsening seen in swelling/induration, and
- Absence of fever (i.e., Temperature < 37.7°C)

Failure (Clinical failure) - At the On-therapy visit (OTV)

- Death, or
- Continued fever (i.e., temperature greater than or equal to 37.7°C), or
- Increase in the size (length, width, and area) of erythema from baseline, and/or
- Worsening seen in swelling/induration, or
- administration of rescue antibacterial drug therapy at OTV, or administration of non-trial antibacterial drug therapy for treatment of SSTI before the OTV.

8.2 Analysis of Primary, Secondary and Other Efficacy Parameters

The final analyses will evaluate the hypotheses that drive each of the three distinct sub-trials of the study. A similar statistical approach will be used in each of the different sub-trials.

For the PP analysis, subjects will be classified based on assessments at the TOC. The numerator in each treatment group for the analysis will be all subjects who were a clinical cure at the TOC. The denominator will consist of all subjects who received treatment and were assigned any clinical diagnosis at the TOC. Subjects with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator.

For the OmITT analysis, subjects will be grouped by their initial assignment at randomization. The numerator will include those subjects who received study drug on their initial visit and were classified as cured on final outcome. The denominator will include all subjects who received study drug at the initial visit, and were assigned any clinical diagnosis at the TOC (using OmITT definitions for cure and failure in 8.1.3). All subjects who withdraw from the study, are lost to follow-up prior to final classification, or have missing or unassigned outcomes will also be included in the OmITT population, but will be classified as failures.

For the RmITT analysis, subjects will be grouped by their initial assignment at randomization. The numerator will include those subjects who received study drug on their initial visit and were classified as a clinical cure as defined in Section 8.1.4. The denominator will include all subjects who received study drug at the initial visit and had at least one follow-up visit after the initial visit.

For the FDAGEEP analysis, subjects will be classified based on assessments at the OTV. The numerator in each treatment group for the analysis will be all subjects who were a clinical cure (clinical response) at the OTV. The denominator will consist of all subjects who received treatment and were assigned any clinical diagnosis at the OTV. Subjects with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator.

Mock-ups of the primary and secondary efficacy tables for clinical cures are shown in Tables 12A - 12E.

8.2.1 Primary Analysis

The primary statistical outcome is the observed difference in the proportion of cures between subjects receiving the experimental therapy and those receiving the control therapy.

$$\Delta = p_2 - p_1$$

Where:

Δ = Difference in the proportion of cures between subjects receiving the experimental therapy and those receiving the control therapy.

p_2 = Proportion of cures among subjects receiving the experimental therapy.

p_1 = Proportion of cures among subjects receiving the control therapy.

The upper and lower confidence bounds will be calculated by using confidence intervals with a continuity correction. The interpretations of possible outcomes are as follows:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: The experimental treatment produces lower cure rates than the control treatment.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces cure rates similar to the control treatment.

Case III: Lower bound is less than zero, and upper bound is greater than the predefined clinically significant cure rate.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, while the upper bound is less than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than the control treatment, but the observed difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than the predefined clinically significant cure rate, while the upper bound is greater than the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than control treatment, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed the predefined clinically significant cure rate.

Interpretation: The experimental treatment produces higher cure rates than the control treatment, and this difference is clinically important.

8.2.1.1 Abscess Sub-trial

For the abscess sub-trial, the analysis will determine whether the clinical cure rates of subjects treated with TMP/SMX is superior to that of subjects treated with placebo. The primary statistical measure will be the difference in the proportion of cures between subjects receiving TMP/SMX and those receiving placebo.

To evaluate the hypothesis, the confidence interval surrounding the observed difference in cure rates will be evaluated. The interpretation of the final outcome will be based on the following six cases:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: Treatment with TMP/SMX produces lower cure rates than treatment with placebo.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than 7.5%.

Interpretation: The TMP/SMX produces cure rates similar to placebo.

Case III: Lower bound is less than zero, and upper bound is greater than 7.5%.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, but less than 7.5%, while the upper bound is less than 7.5%.

Interpretation: Treatment with TMP/SMX produces higher cure rates than treatment with placebo, but the observed difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than 7.5%, while the upper bound is greater than 7.5%.

Interpretation: Treatment with TMP/SMX produces higher cure rates than treatment with placebo, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed 7.5%.

Interpretation: Treatment with TMP/SMX produces higher cure rates than treatment with placebo, and the difference is clinically important.

8.2.1.2 Infected Wound Sub-trial

For the infected wound sub-trial, the analysis will determine whether the clinical cure rates of subjects treated with clindamycin is superior to that of subjects treated with TMP/SMX. The primary statistical measure will be the difference in the proportion of cures between subjects receiving clindamycin and those receiving TMP/SMX.

To evaluate the hypothesis, the confidence interval surrounding the observed difference in cure rates will be evaluated. The interpretation of the final outcome will be based on the following six cases:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: Treatment with clindamycin produces lower cure rates than treatment with TMP/SMX.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than 10%.

Interpretation: The clindamycin produces cure rates similar to TMP/SMX.

Case III: Lower bound is less than zero, and upper bound is greater than 10%.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, but less than 10%, while the upper bound is less than 10%.

Interpretation: Treatment with clindamycin produces higher cure rates than treatment with TMP/SMX, but the observed difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than 10%, while the upper bound is greater than 10%.

Interpretation: Treatment with clindamycin produces higher cure rates than treatment with TMP/SMX, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed 10%.

Interpretation: Treatment with clindamycin produces higher cure rates than treatment with TMP/SMX, and the difference is clinically important.

8.2.1.3 Cellulitis Sub-trial

For the cellulitis sub-trial, the analysis will determine whether the clinical cure rates of subjects treated with TMP/SMX and cephalexin is superior to that of subjects treated with cephalexin alone. The primary statistical measure will be the difference in the proportion of cures between subjects receiving TMP/SMX and cephalexin and those receiving cephalexin alone.

To evaluate the hypothesis, the confidence interval surrounding the observed difference in cure rates will be evaluated. The interpretation of the final outcome will be based on the following six cases:

Case I: Upper and lower confidence bounds are both less than zero.

Interpretation: Treatment with TMP/SMX and cephalexin produces lower cure rates than treatment with cephalexin alone.

Case II: Lower bound is less than zero, while the upper bound is greater than zero, but less than 10%.

Interpretation: The TMP/SMX and cephalexin produces cure rates similar to cephalexin alone.

Case III: Lower bound is less than zero, and upper bound is greater than 10%.

Interpretation: Confidence interval is too wide for interpretation. Study is underpowered and no conclusion is possible.

Case IV: Lower bound is greater than zero, but less than 10%, while the upper bound is less than 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces higher cure rates than treatment with cephalexin alone, but the observed difference is not clinically significant.

Case V: Lower bound is greater than zero, but less than 10%, while the upper bound is greater than 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces higher cure rates than treatment with cephalexin alone, but the study is unable to assess whether this difference is clinically significant.

Case VI: Lower and upper bound both exceed 10%.

Interpretation: Treatment with TMP/SMX and cephalexin produces higher cure rates than treatment with cephalexin alone, and the difference is clinically important.

8.2.2 Secondary Analyses

It is anticipated that non-compliance and attrition among subjects will produce significant bias in assessing treatment efficacy using classical ITT methodology. We will employ modified ITT analyses and sensitivity analyses to ascertain the potential scope and implications of these biases.

The original modified ITT (OmITT) and revised mITT (RmITT) analyses are described in section 8.1.3 and 8.1.4. The proposed sensitivity analyses include examining cure rates while varying the assumptions regarding outcomes among subjects lost to attrition. In particular, we plan to calculate the "best" and “worst” case overall cure rates for the treatment and control groups. In addition, we will summarize those subjects who had a 50% - 75% compliance rate using the definition of cure from the PP population, but modifying the compliance rate to 50% - 75%.

8.3 Method of Analysis for Efficacy Parameters

8.3.1 Clinical Outcome Classifications for the Treatment of Uncomplicated Abscesses

8.3.1.1 Original Clinical Outcomes

For the Per-Protocol (PP) analysis, subjects will be classified based on assessments at the TOC. The numerator for p_1 will consist of all subjects who received placebo as PP, and were judged to be cured at the TOC. The denominator will consist of subjects who received placebo as PP, and were assigned any clinical diagnosis at the TOC. Subjects with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all subjects who received TMP/SMX as PP, and were judged to be cured at the TOC. The denominator will consist of subjects who received TMP/SMX as PP, and were assigned any clinical diagnosis at the TOC. Subjects with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator.

For the OmITT analysis, subjects will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received a placebo on their initial visit and were classified as cured on final outcome (received no change in antibiotic therapy due to persistence or worsening of infection prior to or through TOC - see section 8.1.3). The denominator will include all subjects who received placebo on their initial visit and received either cure or failure classification by the TOC, this population will include all subjects who have definite OmITT outcome assignments, and only subjects who have definite OmITT outcome assignments as described in section 8.1.3. The numerator for p_2 will include only those individuals who received TMP/SMX on their initial visit and who were classified as cured on final outcome (received no change in antibiotic therapy due to persistence or worsening of infection prior to or through TOC - see section 8.1.3). The denominator will include all subjects who received TMP/SMX on their initial visit and received either cure or failure classification by the TOC, this population will include all subjects who have definite OmITT outcome assignments, and only subjects who have definite OmITT outcome assignments as described in section 8.1.3.

For the RmITT analysis, subjects will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received a placebo on their initial visit and were classified as cure according to Section 8.1.4. The denominator will include all subjects who received placebo on their initial visit and had at least one follow-up assessment after the initial visit. The numerator for p_2 will include only those individuals who received TMP/SMX on their initial visit and who were classified as cured according to Section 8.1.4. The denominator will include all subjects

who received TMP/SMX on their initial visit and had at least one follow-up assessment after the initial visit (as described in section 8.1.4).

For the FDAGEEP analysis, subjects will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received a placebo on their initial visit and were classified as cure (clinical response) according to Section 8.1.7. The denominator will include all subjects who received placebo on their initial visit and completed follow-up assessments at the OTV. The numerator for p_2 will include only those individuals who received TMP/SMX on their initial visit and who were classified as cured (clinical response) according to Section 8.1.7. The denominator will include all subjects who received TMP/SMX on their initial visit and completed follow-up assessments at the OTV (as described in section 8.1.7).

Analytic summary for the OmITT, RmITT, and FDAGEEP populations will mirror the PP results using the appropriate population.

8.3.1.2 Best-Case Outcomes

For the Per-Protocol (PP) assessments, this analysis assigns outcomes to all subjects, including those that did not complete the study "per protocol." Subjects who complete the study "per protocol" will retain the same outcome as they received in the final PP analysis. Subjects who were not included in the PP population will be assigned a "clinical cure" outcome if they were randomized to receive experimental therapy (TMP/SMX), and "clinical failure" if they were randomized to receive standard therapy (placebo).

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to TMP/SMX, C_{BE} is the ratio of cures to all enrolled subjects and is equal to the sum of TMP/SMX subjects judged to be cured on the PP evaluation, and all TMP/SMX subjects not in the PP population, divided by the total number of enrolled TMP/SMX subjects.

  $C_{BE} = (NC_{EPP} + NC_{ENPP})/(NC_{EPP} + NC_{ENPP} + NF_{EPP})$

  Where:
  C_{BE} = Best experimental cure rate
  NC_{EPP} = Number of cures assigned to TMP/SMX subjects in the PP population
  NC_{ENPP} = Number of cures assigned to TMP/SMX subjects not in the PP population = Number of subjects who did not complete "per protocol" evaluation.
  NF_{EPP} = Number of failures assigned to TMP/SMX subjects in the

PP population.

- Standard cure rate C_{WS}: Among subjects assigned to placebo, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of placebo subjects judged to be cured in the PP population, divided by the total number of enrolled placebo subjects.

  $C_{WS} = (NC_{SPP})/(NC_{SPP} + NF_{SNPP} + NF_{SPP})$

  Where:
  C_{WS} = Standard cure rate (actually the worst standard cure rate)
  NC_{SPP} = Number of cures assigned to placebo subjects in the PP population
  NF_{SNPP} = Number of failures assigned to placebo subjects not in the PP population = Number of placebo subjects who did not complete "per protocol" evaluation.

  NF_{SPP} = Number of failures assigned to placebo subjects in the PP population.

- The primary outcome is the difference in cure rates between TMP/SMX and Placebo treatment groups and the 95% confidence interval.

  $Delta_{BestPP} = C_{BE} - C_{WS}$

For the OmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the OmITT population. Subjects in the OmITT population will retain the same outcome as they received in the final OmITT analysis. Subjects not in the OmITT population will be assigned a "clinical cure" outcome if they were randomized to receive TMP/SMX and a "clinical failure" outcome if they were randomized to receive placebo.

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to TMP/SMX, C_{BE} is the ratio of cures to all enrolled subjects and is equal to the sum of TMP/SMX subjects judged to be cured in the OmITT population, and all TMP/SMX subjects not in the OmITT population, divided by the total number of enrolled subjects.

  $C_{BE} = (NC_{EOMITT} + NC_{ENOMITT})/(NC_{EOMITT} + NC_{ENOMITT} + NF_{EOMITT})$

  Where:
  C_{BE} = Best experimental cure rate
  NC_{EOMITT} = Number of cures assigned to TMP/SMX subjects in the OmITT population
  $NC_{ENOMIiTT}$ = Number of cures assigned to TMP/SMX subjects not in

the OmITT population = Number of enrolled subjects who did not receive an OmITT outcome classification.
NF_{EOMITT} = Number of failures assigned to TMP/SMX subjects in the OmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to placebo, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of placebo subjects judged to be cured in the OmITT population, divided by the total number of enrolled placebo subjects.

  $C_{WS} = (NC_{SOMITT})/(NC_{SOMITT} + NF_{SNOMITT} + NF_{OMITT})$

  Where:
  C_{WS} = Standard cure rate (actually the worst standard cure rate)
  NC_{SOMITT} = Number of cures assigned to placebo subjects in the OmITT population
  $NF_{SNOMITT}$ = Number of failures assigned to placebo subjects not in the OmITT population = Number of enrolled subjects who did not receive an OmITT outcome classification.

  NF_{OMITT} = Number of failures assigned to placebo subjects in the OmITT population.

- The primary outcome is the difference in cure rates between TMP/SMX and Placebo treatment groups and the 95% confidence interval.

  $Delta_{BestOMITT} = C_{BE} - C_{WS}$

For the RmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the RmITT population. Subjects in the RmITT population will retain the same outcome as they received in the final RmITT analysis. Subjects not in the RmITT population will be assigned a "clinical cure" outcome if they were randomized to receive TMP/SMX and a "clinical failure" outcome if they were randomized to receive placebo.

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to TMP/SMX, C_{BE} is the ratio of cures to all enrolled subjects and is equal to the sum of TMP/SMX subjects judged to be cured in the RmITT population, and all TMP/SMX subjects not in the RmITT population, divided by the total number of enrolled subjects.

  $C_{BE} = (NC_{ERMITT} + NC_{ENRMITT})/(NC_{ERMITT} + NC_{ENRMITT} + NF_{ERMITT})$

  Where:
  C_{BE} = Best experimental cure rate

NC_{ERMITT} = Number of cures assigned to TMP/SMX subjects in the RmITT population
$NC_{ENRMITT}$ = Number of cures assigned to TMP/SMX subjects not in the RmITT population = Number of enrolled subjects who did not receive RmITT outcome classification.
$NF_{ERMITTPP}$ = Number of failures assigned to TMP/SMX subjects in the RmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to placebo, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of placebo subjects judged to be cured in the RmITT population, divided by the total number of enrolled placebo subjects.

  $C_{WS} = (NC_{SRMITT})/(NC_{SRMITT} + NF_{SNRMITT} + NF_{SRMITT})$

  Where:
  C_{WS} = Standard cure rate (actually the worst standard cure rate)
  NC_{SRMITT} = Number of cures assigned to placebo subjects in the RmITT population
  $NF_{SNRMITT}$ = Number of failures assigned to placebo subjects not in the RmITT population = Number of enrolled subjects who did not receive RmITT outcome classification.

  NF_{SRMITT} = Number of failures assigned to placebo subjects in the RmITT population.

- The primary outcome is the difference in cure rates between TMP/SMX and Placebo treatment groups and the 95% confidence interval.

  $Delta_{BestRMITT} = C_{BE} - C_{WS}$

For the FDAGEEP assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the FDAGEEP population. Subjects in the FDAGEEP population will retain the same outcome as they received in the final FDAGEEP analysis. Subjects not in the FDAGEEP population will be assigned a "clinical cure" (clinical response) outcome if they were randomized to receive TMP/SMX and a "clinical failure" outcome if they were randomized to receive placebo.

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to TMP/SMX, C_{BE} is the ratio of cures to all enrolled subjects and is equal to the sum of TMP/SMX subjects judged to be cured (clinical response) in the FDAGEEP population, and all TMP/SMX subjects not in the FDAGEEP population, divided by the total number of enrolled subjects.

$C_{BE} = (NC_{EFDAGEEP} + NC_{ENFDAGEEP})/(NC_{EFDAGEEP} + NC_{ENFDAGEEP} + NF_{EFDAGEEP})$

Where:
C_{BE} = Best experimental cure rate
$NC_{EFDAGEEP}$ = Number of cures (clinical responses) assigned to TMP/SMX subjects in the FDAGEEP population
$NC_{ENFDAGEEP}$ = Number of cures (clinical responses) assigned to TMP/SMX subjects not in the FDAGEEP population = Number of enrolled patients who did not receive FDAGEEP outcome classification.
$NF_{ERFDAGEEP}$ = Number of failures assigned to TMP/SMX subjects in the FDAGEEP population.

- Standard cure rate C_{WS}: Among subjects assigned to placebo, C_{WS} is the ratio of cures (clinical responses) to all enrolled subjects, and is equal to the number of placebo subjects judged to be cured in the FDAGEEP population, divided by the total number of enrolled placebo subjects.

  $C_{WS} = (NC_{SRFDAGEEP})/(NC_{SFDAGEEP} + NF_{SNFDAGEEP} + NF_{SFDAGEEP})$

  Where:
  C_{WS} = Standard cure rate (actually the worse standard cure rate)
  $NC_{SFDAGEEP}$ = Number of cures (clinical responses) assigned to placebo subjects in the FDAGEEP population
  $NF_{SNFDAGEEP}$ = Number of failures assigned to placebo subjects not in the FDAGEEP population = Number of enrolled patients who did not receive FDAGEEP outcome classification.

  $NF_{SFDAGEEP}$ = Number of failures assigned to placebo subjects in the FDAGEEP population.

- The primary outcome is the difference in cure rates between TMP/SMX and Placebo treatment groups and the 95% confidence interval.

  $Delta_{BestFDAGEEP} = C_{BE} - C_{WS}$

The contents of the analytic summary will mirror the analytic summary for the PP population.

8.3.1.3 Worst-Case Outcomes

For the Per-Protocol (PP) assessments, this analysis assigns outcomes to all subjects, including those that did not complete the study "per protocol." Subjects who complete the study "per protocol" will retain the same outcome as they received in the final PP analysis. Subjects who were not included in the "Per Protocol" population will be

assigned a "clinical failure" outcome if they were randomized to receive TMP/SMX, and "clinical cure" if they were randomized to receive placebo.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to TMP/SMX, C_{WE} is the ratio of cures to all enrolled subjects and is equal to the sum of subjects judged to be cured on the PP evaluation, divided by the total number of enrolled subjects.

  $CW_E = (NC_{EPP})/(NC_{EPP} + NF_{ENPP} + NF_{EPP})$

  Where:
  C_{WE} = Worst experimental cure rate
  NC_{EPP} = Number of cures assigned to TMP/SMX subjects in the PP population
  NF_{ENPP} = Number of failures assigned to TMP/SMX subjects not in the PP population = Number of subjects who did not complete "per protocol" evaluation.
  NF_{EPP} = Number of failures assigned to TMP/SMX subjects in the PP population.

- Standard cure rate C_{BS}: Among subjects assigned to placebo, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of subjects judged to be cured in the PP population, as well as all subjects who were not failures on the PP population, divided by the total number of enrolled placebo subjects.

  $C_{BS} = (NC_{SPP} + NC_{SNPP})/(NC_{SPP} + NC_{SNPP} + NF_{SPP})$

  Where:
  CB_S = Standard cure rate (actually the best standard cure rate)
  NC_{SPP} = Number of cures assigned to placebo subjects in the PP population
  NC_{SNPP} = Number of cures assigned to placebo subjects not in the PP population = Number of placebo subjects who did not complete "per protocol" evaluation.

  NF_{SPP} = Number of failures assigned to placebo subjects in the PP population.

- The primary outcome is the difference in cure rates between TMP/SMX and Placebo treatment groups and the 95% confidence interval.

  $Delta_{WorstPP} = C_{WE} - C_{BS}$

For the OmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the OmITT population. Subjects in the OmITT population will retain the same outcome as they received in the final OmITT analysis. Subjects not in the OmITT population will be assigned a "clinical failure" outcome if they were randomized to receive TMP/SMX and a "clinical cure" outcome if they were randomized to receive placebo.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to TMP/SMX, C_{WE} is the ratio of cures to all enrolled subjects and is equal to the number of TMP/SMX subjects judged to be cured in the OmITT population, divided by the total number of enrolled subjects.

  $C_{WE} = (NC_{EOMITT})/(NC_{EOMITT} + NF_{ENOMITT} + NF_{EOMITT})$

  Where:
  CW_E = Worst experimental cure rate
  NC_{EOMITT} = Number of cures assigned to TMP/SMX subjects in the OmITT population
  $NF_{ENOMITT}$ = Number of failures assigned to TMP/SMX subjects not in the OmITT population = Number of enrolled subjects who did not receive OmITT outcome classification.
  NF_{EOMITT} = Number of failures assigned to TMP/SMX subjects in the OmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to placebo, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the sum of placebo subjects judged to be cured in the OmITT population, and all placebo subjects not in the OmITT population, divided by the total number of enrolled placebo subjects.

  $C_{WS} = (NC_{SOMITT} + NC_{SNOMITT})/(NC_{SOMITT} + NC_{SNOMITT} + NF_{SOMITT})$

  Where:
  C_{WS} = Worst standard cure rate
  NC_{SOMITT} = Number of cures assigned to placebo subjects in the OmITT population
  $NC_{SNOMITT}$ = Number of cures assigned to placebo subjects not in the OmITT population = Number of enrolled subjects who did not receive OmITT outcome classification.

  NF_{SOMITT} = Number of failures assigned to placebo subjects in the OmITT population.

- The primary outcome is the difference in cure rates between TMP/SMX and Placebo treatment groups and the 95% confidence interval.

  $Delta_{BestOMITT} = C_{BE} - C_{WS}$

For the RmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the RmITT population. Subjects in the RmITT population will retain the same outcome as they received in the final RmITT analysis. Subjects not in the RmITT population will be assigned a "clinical failure" outcome if they were randomized to receive TMP/SMX and a "clinical cure" outcome if they were randomized to receive placebo.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to TMP/SMX, C_{WE} is the ratio of cures to all enrolled subjects and is equal to the number of TMP/SMX subjects judged to be cured in the RmITT population, divided by the total number of enrolled subjects.

  $C_{WE} = (NC_{ERMITT})/(NC_{ERMITT} + NF_{ENRMITT} + NF_{ERMITT})$

  Where:
  CW_E = Worst experimental cure rate
  NC_{EPP} = Number of cures assigned to TMP/SMX subjects in the RmITT population
  $NF_{ENRMITT}$ = Number of failures assigned to TMP/SMX subjects not in the RmITT population = Number of enrolled subjects who did not receive RmITT outcome classification.
  NF_{ERMITT} = Number of failures assigned to TMP/SMX subjects in the RmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to placebo, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the sum of placebo subjects judged to be cured in the RmITT population, and all placebo subjects not in the RmITT population, divided by the total number of enrolled placebo subjects.

  $C_{WS} = (NC_{SRMITT} + NC_{SNRMITT})/(NC_{SRMITT} + NC_{SNRMITT} + NF_{SRMITT})$

  Where:
  C_{WS} = Worst standard cure rate
  NC_{SRMITT} = Number of cures assigned to placebo subjects in the RmITT population
  $NC_{SNRMITT}$ = Number of cures assigned to placebo subjects not in the RmITT population = Number of enrolled subjects who did not receive RmITT outcome classification.

NF_{SRMITT} = Number of failures assigned to placebo subjects in the RmITT population.

- The primary outcome is the difference in cure rates between TMP/SMX and Placebo treatment groups and the 95% confidence interval.

  $Delta_{BestRMITT} = C_{BE} - C_{WS}$

For the FDAGEEP assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the FDAGEEP population. Subjects in the FDAGEEP population will retain the same outcome as they received in the final FDAGEEP analysis. Subjects not in the FDAGEEP population will be assigned a "clinical failure" outcome if they were randomized to receive TMP/SMX and a "clinical cure" (clinical response) outcome if they were randomized to receive placebo.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to TMP/SMX, C_{WE} is the ratio of cures (clinical responses) to all enrolled subjects and is equal to the number of TMP/SMX subjects judged to be cured in the FDAGEEP population, divided by the total number of enrolled subjects.

  $C_{WE} = (NC_{EFDAGEEP})/(NC_{EFDAGEEP} + NF_{ENFDAGEEP} + NF_{EFDAGEEP})$

  Where:
  C_{WE} = Worse experimental cure rate
  $NC_{EFDAGEEP}$ = Number of cures assigned to TMP/SMX subjects in the FDAGEEP population
  $NF_{ENFDAGEEP}$ = Number of failures assigned to TMP/SMX subjects not in the FDAGEEP population = Number of enrolled patients who did not receive FDAGEEP outcome classification.
  $NF_{EFDAGEEP}$ = Number of failures assigned to TMP/SMX subjects in the FDAGEEP population.

- Standard cure rate C_{WS}: Among subjects assigned to placebo, C_{WS} is the ratio of cures (clinical responses) to all enrolled subjects, and is equal to the sum of placebo subjects judged to be cured in the FDAGEEP population, and all placebo subjects not in the FDAGEEP population, divided by the total number of enrolled placebo subjects.

  $C_{WS} = (NC_{SFDAGEEP} + NC_{SNFDAGEEP})/(NC_{SFDAGEEP} + NC_{SNFDAGEEP} + NF_{SFDAGEEP})$

  Where:
  C_{WS} = Worse standard cure rate

$NC_{SFDAGEEP}$ = Number of cures assigned to placebo subjects in the FDAGEEP population
$NC_{SNFDAGEEP}$ = Number of cures assigned to placebo subjects not in the FDAGEEP population = Number of enrolled patients who did not receive FDAGEEP outcome classification.

$NF_{SFDAGEEP}$ = Number of failures assigned to placebo subjects in the FDAGEEP population.

- The primary outcome is the difference in cure rates between TMP/SMX and Placebo treatment groups and the 95% confidence interval.

  $Delta_{WorseFDAGEEP} = C_{WE} - C_{WS}$

The contents of the analytic summary will mirror the analytic summary for the PP population.

8.3.2 Clinical Outcome Classifications for the Treatment of Infected Wounds

8.3.2.1 Original Clinical Outcomes

For the PP analysis, subjects will be classified based on assessments at the TOC. The numerator for p_1 will consist of all subjects who received TMP/SMX as PP, and were judged to be cured at the TOC. The denominator will consist of subjects who received TMP/SMX as PP, and were assigned any clinical diagnosis at the TOC. Subjects with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all subjects who received clindamycin as PP, and were judged to be cured at the TOC. The denominator will consist of subjects who received clindamycin as PP, and were assigned any clinical diagnosis at the TOC. Subjects with other outcomes, including those lost to follow-up, those with protocol violations and those with any other with unassigned outcomes will not be counted in the denominator.

For the OmITT analysis, subjects will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received TMP/SMX on their initial visit and were classified as cured on final outcome (received no change in antibiotic therapy due to persistence or worsening of infection prior to or through TOC - see section 8.1.3). The denominator will include all subjects who received TMP/SMX on their initial visit and received either cure or failure classification by the TOC, this population will include all subjects who have definite OmITT outcome assignments, and only subjects who have definite OmITT outcome assignments as described in section 8.1.3. The numerator for p_2 will include only those individuals who received clindamycin on their initial visit and who were classified as cured on final diagnosis (received no change in antibiotic therapy due to persistence or worsening of infection prior to or through TOC - see section 8.1.3). The denominator will include all

subjects who received clindamycin on their initial visit and received either cure or failure classification by the TOC, this population will include all subjects who have definite OmITT outcome assignments, and only subjects who have definite OmITT outcome assignments as described in section 8.1.3.

For the RmITT analysis, subjects will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received TMP/SMX on their initial visit and were classified as cure according to Section 8.1.4. The denominator will include all subjects who received TMP/SMX on their initial visit and had at least one follow-up assessment after the initial visit. The numerator for p2 will include only those individuals who received clindamycin on their initial visit and who were classified as cured according to Section 8.1.4. The denominator will include all subjects who received clindamycin on their initial visit and had at least one follow-up assessment after the initial visit (as described in section 8.1.4).

For the FDAGEEP analysis, subjects will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received TMP/SMX on their initial visit and were classified as cure (clinical response) according to Section 8.1.7. The denominator will include all subjects who received TMP/SMX on their initial visit and completed follow-up assessments at the on therapy visit. The numerator for p_2 will include only those individuals who received clindamycin on their initial visit and who were classified as cured (clinical response) according to Section 8.1.7. The denominator will include all subjects who received clindamycin on their initial visit and completed follow-up assessments at the on therapy visit (as described in section 8.1.7).

Analytic summary for the OmITT, RmITT, and FDAGEEP populations will mirror the PP results using the appropriate population.

8.3.2.2 Best-Case Outcomes

For the Per-Protocol (PP) assessments, this analysis assigns outcomes to all subjects, including those that did not complete the study "per protocol." Subjects who complete the study "per protocol" will retain the same outcome as they received in the final PP analysis. Subjects who were not included in the PP population will be assigned a "clinical cure" outcome if they were randomized to receive experimental therapy (clindamycin), and "clinical failure" if they were randomized to receive standard therapy (TMP/SMX).

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to clindamycin, C_{BE} is the ratio of cures to all enrolled subjects and is equal to the sum of

clindamycin subjects judged to be cured on the PP evaluation, and all clindamycin subjects not in the PP population, divided by the total number of enrolled clindamycin subjects.

$C_{BE} = (NC_{EPP} + NC_{ENPP})/(NC_{EPP} + NC_{ENPP} + NF_{EPP})$

Where:
C_{BE} = Best experimental cure rate
NC_{EPP} = Number of cures assigned to clindamycin subjects in the PP population
NC_{ENPP} = Number of cures assigned to clindamycin subjects not in the PP population = Number of subjects who did not complete "per protocol" evaluation.
NF_{EPP} = Number of failures assigned to clindamycin subjects in the PP population.

- Standard cure rate C_{WS}: Among subjects assigned to TMP/SMX, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of TMP/SMX subjects judged to be cured in the PP population, divided by the total number of enrolled TMP/SMX subjects.

  $C_{WS} = (NC_{SPP})/(NC_{SPP} + NF_{SNPP} + NF_{SPP})$

  Where:
  C_{WS} = Worst standard cure rate
  NC_{SPP} = Number of cures assigned to TMP/SMX subjects in the PP population
  NF_{SNPP} = Number of failures assigned to TMP/SMX subjects not in the PP population = Number of TMP/SMX subjects who did not complete "per protocol" evaluation.

  NF_{SPP} = Number of failures assigned to TMP/SMX subjects in the PP population.

- The primary outcome is the difference in cure rates between clindamycin and TMP/SMX treatment groups and the 95% confidence interval.

  $Delta_{BestPP} = C_{BE} - C_{WS}$

For the OmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the OmITT population. Subjects in the OmITT population will retain the same outcome as they received in the final OmITT analysis. Subjects not in the OmITT population will be assigned a "clinical cure" outcome if they were randomized to receive clindamycin and a "clinical failure" outcome if they were randomized to receive TMP/SMX.

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to clindamycin, C_{BE} is the ratio of cures to all enrolled subjects and is equal to the sum of clindamycin subjects judged to be cured in the OmITT population, and all clindamycin subjects not in the OmITT population, divided by the total number of enrolled subjects.

  $C_{BE} = (NC_{EOMITT} + NC_{ENOMITT})/(NC_{EOMITT} + NC_{ENOMITT} + NF_{EOMITT})$

  Where:
  C_{BE} = Best experimental cure rate
  NC_{EOMITT} = Number of cures assigned to clindamycin subjects in the OmITT population
  $NC_{ENOMITT}$ = Number of cures assigned to clindamycin subjects not in the OmITT population = Number of clindamycin subjects who did not receive OmITT outcome classification.
  NF_{EOMITT} = Number of failures assigned to clindamycin subjects in the OmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to TMP/SMX, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of TMP/SMX subjects judged to be cured in the OmITT population, divided by the total number of enrolled TMP/SMX subjects.

  $C_{WS} = (NC_{SOMITT})/(NC_{SOMITT} + NF_{SNOMITT} + NF_{SOMITT})$

  Where:
  C_{WS} = Standard cure rate (actually the worst standard cure rate)
  NC_{SOMITT} = Number of cures assigned to TMP/SMX subjects in the OmITT population
  $NF_{SNOMITT}$ = Number of failures assigned to TMP/SMX subjects not in the OmITT population = Number of TMP/SMX subjects who did not receive OmITT outcome classification.

  NF_{SOMITT} = Number of failures assigned to TMP/SMX subjects in the OmITT population.

- The primary outcome is the difference in cure rates between clindamycin and TMP/SMX treatment groups and the 95% confidence interval.

  $Delta_{BestOMITT} = C_{BE} - C_{WS}$

For the RmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the RmITT population. Subjects in the RmITT population will retain the same outcome as they received in the final RmITT analysis. Subjects not

in the RmITT population will be assigned a "clinical cure" outcome if they were randomized to receive clindamycin and a "clinical failure" outcome if they were randomized to receive TMP/SMX.

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to clindamycin, C_{BE} is the ratio of cures to all enrolled subjects and is equal to the sum of clindamycin subjects judged to be cured in the RmITT population, and all clindamycin subjects not in the RmITT population, divided by the total number of enrolled subjects.

  $C_{BE} = (NC_{ERMITT} + NC_{ENRMITT})/(NC_{ERMITT} + NC_{ENRMITT} + NF_{ERMITT})$

  Where:
  C_{BE} = Best experimental cure rate
  NC_{ERMITT} = Number of cures assigned to clindamycin subjects in the RmITT population
  $NC_{ENRMITT}$ = Number of cures assigned to clindamycin subjects not in the RmITT population Number of clindamycin subjects who did not receive RmITT outcome classification.
  NF_{ERMITT} = Number of failures assigned to clindamycin subjects in the RmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to TMP/SMX, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of TMP/SMX subjects judged to be cured in the RmITT population, divided by the total number of enrolled TMP/SMX subjects.

  $C_{WS} = (NC_{SRMITT})/(NC_{SRMITT} + NF_{SNRMITT} + NF_{SRMITT})$

  Where:
  C_{WS} = Standard cure rate (actually the worst standard cure rate)
  NC_{SRMITT} = Number of cures assigned to TMP/SMX subjects in the RmITT population
  $NF_{SNRMITT}$ = Number of failures assigned to TMP/SMX subjects not in the RmITT population = Number of TMP/SMX subjects who did not receive RmITT outcome classification.

  NF_{SRMITT} = Number of failures assigned to TMP/SMX subjects in the RmITT population.

- The primary outcome is the difference in cure rates between clindamycin and TMP/SMX treatment groups and the 95% confidence interval.

  $Delta_{BestRMITT} = C_{BE} - C_{WS}$

For the FDAGEEP assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the FDAGEEP population. Subjects in the FDAGEEP population will retain the same outcome as they received in the final FDAGEEP analysis. Subjects not in the FDAGEEP population will be assigned a "clinical cure" (clinical response) outcome if they were randomized to receive clindamycin and a "clinical failure" outcome if they were randomized to receive TMP/SMX.

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to clindamycin, C_{BE} is the ratio of cures (clinical responses) to all enrolled subjects and is equal to the sum of clindamycin subjects judged to be cured in the FDAGEEP population, and all clindamycin subjects not in the FDAGEEP population, divided by the total number of enrolled subjects.

  $C_{BE} = (NC_{EFDAGEEP} + NC_{ENFDAGEEP})/(NC_{EFDAGEEP} + NC_{ENFDAGEEP} + NF_{EFDAGEEP})$

  Where:
  C_{BE} = Best experimental cure rate
  $NC_{EFDAGEEP}$ = Number of cures (clinical responses) assigned to clindamycin subjects in the FDAGEEP population
  $NC_{ENFDAGEEP}$ = Number of cures assigned to clindamycin subjects not in the FDAGEEP population Number of clindamycin subjects who did not receive FDAGEEP outcome classification.
  $NF_{EFDAGEEP}$ = Number of failures assigned to clindamycin subjects in the FDAGEEP population.

- Standard cure rate C_{WS}: Among subjects assigned to TMP/SMX, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of TMP/SMX subjects judged to be cured (clinical responses) in the FDAGEEP population, divided by the total number of enrolled TMP/SMX subjects.

  $C_{WS} = (NC_{SFDAGEEP})/(NC_{SFDAGEEP} + NF_{SNFDAGEEP} + NF_{SFDAGEEP})$

  Where:
  C_{WS} = Standard cure rate (actually the worse standard cure rate)
  $NC_{SFDAGEEP}$ = Number of cures assigned to TMP/SMX subjects in the FDAGEEP population
  $NF_{SNFDAGEEP}$ = Number of failures assigned to TMP/SMX subjects not in the FDAGEEP population = Number of TMP/SMX subjects who did not receive FDAGEEP outcome classification.

$NF_{SFDAGEEP}$ = Number of failures assigned to TMP/SMX subjects in the FDAGEEP population.

- The primary outcome is the difference in cure rates between clindamycin and TMP/SMX treatment groups and the 95% confidence interval.

  $Delta_{BestFDAGEEP} = C_{BE} - C_{WS}$

The contents of the analytic summary will mirror the analytic summary for the PP population.

8.3.2.3 Worst-Case Outcomes

For the Per-Protocol (PP) assessments, this analysis assigns outcomes to all subjects, including those that did not complete the study "per protocol." Subjects who complete the study "per protocol" will retain the same outcome as they received in the final PP analysis. Subjects who were not included in the "Per Protocol" population will be assigned a "clinical failure" outcome if they were randomized to receive clindamycin, and "clinical cure" if they were randomized to receive TMP/SMX.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to clindamycin, C_{WE} is the ratio of cures to all enrolled subjects and is equal to the sum of subjects judged to be cured on the PP evaluation, divided by the total number of enrolled subjects.

  $$CW_E = (NC_{EPP})/(NC_{EPP} + NF_{ENPP} + NF_{EPP})$$

  Where:
  C_{WE} = Worst experimental cure rate
  NC_{EPP} = Number of cures assigned to clindamycin subjects in the PP population
  NF_{ENPP} = Number of failures assigned to clindamycin subjects not in the PP population = Number of subjects who did not complete "per protocol" evaluation.
  NF_{EPP} = Number of failures assigned to clindamycin subjects in the PP population.

- Standard cure rate C_{BS}: Among subjects assigned to TMP/SMX, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of subjects judged to be cured in the PP population, as well as all subjects who were not failures on the PP population, divided by the total number of enrolled TMP/SMX subjects.

  $$C_{BS} = (NC_{SPP} + NC_{SNPP})/(NC_{SPP} + NC_{SNPP} + NF_{SPP})$$

Where:
CB_S = Standard cure rate (actually the best standard cure rate)
NC_{SPP} = Number of cures assigned to TMP/SMX subjects in the PP population
NC_{SNPP} = Number of cures assigned to TMP/SMX subjects not in the PP population = Number of TMP/SMX subjects who did not complete "per protocol" evaluation.

NF_{SPP} = Number of failures assigned to TMP/SMX subjects in the PP population.

- The primary outcome is the difference in cure rates between clindamycin and TMP/SMX treatment groups and the 95% confidence interval.

  $Delta_{WorstPP} = C_{WE} - C_{BS}$

For the OmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the OmITT population. Subjects in the OmITT population will retain the same outcome as they received in the final OmITT analysis. Subjects not in the OmITT population will be assigned a "clinical failure" outcome if they were randomized to receive clindamycin and a "clinical cure" outcome if they were randomized to receive TMP/SMX.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to clindamycin, C_{WE} is the ratio of cures to all enrolled subjects and is equal to the number of clindamycin subjects judged to be cured in the OmITT population, divided by the total number of enrolled subjects.

  $C_{WE} = (NC_{EOMITT})/(NC_{EOMITT} + NF_{ENOMITT} + NF_{EOMITT})$

  Where:
  CW_E = Best experimental cure rate
  NC_{EOMITT} = Number of cures assigned to clindamycin subjects in the OmITT population
  $NF_{ENOMITT}$ = Number of failures assigned to clindamycin subjects not in the OmITT population = Number of clindamycin subjects who did not receive OmITT outcome classification
  NF_{EOMITT} = Number of failures assigned to clindamycin subjects in the OmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to TMP/SMX, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the sum of TMP/SMX subjects judged to be cured in the OmITT population, and all TMP/SMX subjects not in the OmITT population, divided by the total number of enrolled TMP/SMX subjects.

$C_{WS} = (NC_{SOMITT} + NC_{SNOMITT})/(NC_{SOMITT} + NC_{SNOMITT} + NF_{SOMITT})$

Where:
C_{WS} = Standard cure rate (actually the worst standard cure rate)
NC_{SOMITT} = Number of cures assigned to TMP/SMX subjects in the OmITT population
$NC_{SNOMITT}$ = Number of cures assigned to TMP/SMX subjects not in the OmITT population = Number of TMP/SMX subjects who did not receive OmITT outcome classification

NF_{SOMITT} = Number of failures assigned to TMP/SMX subjects in the OmITT population.

- The primary outcome is the difference in cure rates between clindamycin and TMP/SMX treatment groups and the 95% confidence interval.

  $Delta_{BestOMITT} = C_{BE} - C_{WS}$

For the RmITT analysis, this analysis assigns outcomes to all enrolled subjects, including those not included in the RmITT population. Subjects in the RmITT population will retain the same outcome as they received in the final RmITT analysis. Subjects not in the RmITT population will be assigned a "clinical failure" outcome if they were randomized to receive clindamycin and a "clinical cure" outcome if they were randomized to receive TMP/SMX.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to clindamycin, C_{WE} is the ratio of cures to all enrolled subjects and is equal to the number of clindamycin subjects judged to be cured in the RmITT population, divided by the total number of enrolled subjects.

  $C_{WE} = (NC_{ERMITT})/(NC_{ERMITT} + NF_{ENRMITT} + NF_{ERMITT})$

  Where:
  CW_E = Best experimental cure rate
  NC_{ERMITT} = Number of cures assigned to clindamycin subjects in the RmITT population
  $NF_{ENRMITT}$ = Number of failures assigned to clindamycin subjects not in the RmITT population = Number of clindamycin subject who did not receive RmITT outcome classifications
  NF_{ERMITT} = Number of failures assigned to clindamycin subjects in the RmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to TMP/SMX, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the

sum of TMP/SMX subjects judged to be cured in the RmITT population, and all TMP/SMX subjects not in the RmITT population, divided by the total number of enrolled TMP/SMX subjects.

$C_{WS} = (NC_{SRMITT} + NC_{SNRMITT})/(NC_{SRMITT} + NC_{SNRMITT} + NF_{SRMITT})$

Where:
C_{WS} = Standard cure rate (actually the worst standard cure rate)
NC_{SRMITT} = Number of cures assigned to TMP/SMX subjects in the RmITT population
$NC_{SNRMITT}$ = Number of cures assigned to TMP/SMX subjects not in the RmITT population = Number of TMP/SMX subjects who did not receive RmITT outcome classification

NF_{SRMITT} = Number of failures assigned to TMP/SMX subjects in the RmITT population.

- The primary outcome is the difference in cure rates between clindamycin and TMP/SMX treatment groups and the 95% confidence interval.

  $Delta_{BestRMITT} = C_{BE} - C_{WS}$

For the FDAGEEP analysis, this analysis assigns outcomes to all enrolled subjects, including those not included in the FDAGEEP population. Subjects in the FDAGEEP population will retain the same outcome as they received in the final FDAGEEP analysis. Subjects not in the FDAGEEP population will be assigned a "clinical failure" outcome if they were randomized to receive clindamycin and a "clinical cure" (clinical response) outcome if they were randomized to receive TMP/SMX.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to clindamycin, C_{WE} is the ratio of cures (clinical responses) to all enrolled subjects and is equal to the number of clindamycin subjects judged to be cured in the FDAGEEP population, divided by the total number of enrolled subjects.

  $C_{WE} = (NC_{EFDAGEEP})/(NC_{EFDAGEEP} + NF_{ENFDAGEEP} + NF_{EFDAGEEP})$

  Where:
  C_{WE} = Best experimental cure rate
  $NC_{EFDAGEEP}$ = Number of cures assigned to clindamycin subjects in the FDAGEEP population
  $NF_{ENFDAGEEP}$ = Number of failures assigned to clindamycin subjects not in the FDAGEEP population = Number of clindamycin subject who did not receive FDAGEEP outcome classifications
  $NF_{EFDAGEEP}$ = Number of failures assigned to clindamycin subjects

in the FDAGEEP population.

- Standard cure rate C_{WS}: Among subjects assigned to TMP/SMX, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the sum of TMP/SMX subjects judged to be cured in the FDAGEEP population, and all TMP/SMX subjects not in the FDAGEEP population, divided by the total number of enrolled TMP/SMX subjects.

  $C_{WS} = (NC_{SRFDAGEEP} + NC_{SNFDAGEEP})/(NC_{SFDAGEEP} + NC_{SNFDAGEEP} + NF_{SFDAGEEP})$

  Where:
  C_{WS} = Standard cure rate (actually the worse standard cure rate)
  $NC_{SFDAGEEP}$ = Number of cures assigned to TMP/SMX subjects in the FDAGEEP population
  $NC_{SNFDAGEEP}$ = Number of cures assigned to TMP/SMX subjects not in the FDAGEEP population = Number of TMP/SMX subjects who did not receive FDAGEEP outcome classification

  $NF_{SFDAGEEP}$ = Number of failures assigned to TMP/SMX subjects in the FDAGEEP population.

- The primary outcome is the difference in cure rates between clindamycin and TMP/SMX treatment groups and the 95% confidence interval.

  $Delta_{WorseFDAGEEP} = C_{WE} - C_{WS}$

The contents of the analytic summary will mirror the analytic summary for the PP population.

8.3.3 Clinical Outcome Classifications for the Treatment of Cellulitis

8.3.3.1 Original Clinical Outcomes

For the PP analysis, subjects will be classified based on assessments at the TOC. The numerator for p_1 will consist of all subjects who received cephalexin and placebo as PP, and were judged to be cured at the TOC. The denominator will consist of subjects who received cephalexin only as PP, and were assigned any clinical diagnosis at the TOC. Subjects with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator. The numerator for p_2 will consist of all subjects who received both cephalexin and TMP/SMX as PP, and were judged to be cured at the TOC. The denominator will consist of subjects who received both cephalexin and TMP/SMX as PP, and were assigned any clinical diagnosis at the TOC. Subjects with other outcomes, including those lost to follow-up, those with protocol violations and those with any other unassigned outcome will not be counted in the denominator.

For the OmITT analysis, subjects will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received only cephalexin on their initial visit and were classified as cured on final outcome (received no change in antibiotic therapy due to persistence or worsening of infection prior to or through TOC - see section 8.1.3). The denominator will include all subjects who received only cephalexin on their initial visit and received either cure or failure classification by the TOC. This population will include all subjects who have definite OmITT outcome assignments, and only subjects who have definite OmITT outcome assignments as described in section 4.4.2. The numerator for p_2 will include only those individuals who received both cephalexin and TMP/SMX on their initial visit and who were classified as cured on final outcome (received no change in antibiotic therapy due to persistence or worsening of infection prior to or through TOC - see section 8.1.3). The denominator will include all subjects who received both cephalexin and TMP/SMX on their initial visit and received either cure or failure classification by the TOC. This population will include all subjects who have definite OmITT outcome assignments, and only subjects who have definite OmITT outcome assignments as described in section 8.1.3.

For the RmITT analysis, subjects will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received only cephalexin on their initial visit and were classified as cure according to Section 8.1.4. The denominator will include all subjects who received only cephalexin on their initial visit and had at least one follow-up assessment after the initial visit. The numerator for p_2 will include only those individuals who received both cephalexin and TMP/SMX on their initial visit and who were classified as cured according to Section 8.1.4. The denominator will include all subjects who received both cephalexin and TMP/SMX on their initial visit and had at least one follow-up assessment after the initial visit (as described in section 8.1.4).

For the FDAGEEP analysis, subjects will be grouped by their initial assignment at randomization. The numerator for p_1 will include only those individuals who received only cephalexin on their initial visit and were classified as cure (clinical response) according to Section 8.1.7. The denominator will include all subjects who received only cephalexin on their initial visit and had at least one follow-up assessment after the initial visit. The numerator for p_2 will include only those individuals who received both cephalexin and TMP/SMX on their initial visit and who were classified as cured (clinical response) according to Section 8.1.7. The denominator will include all subjects who received both cephalexin and TMP/SMX on their initial visit and completed follow-up assessments at the on therapy visit (as described in section 8.1.7).

Analytic summary for the OmITT, RmITT, and FDAGEEP populations will mirror the PP results using the appropriate population.

8.3.3.2 Best-Case Outcomes

For the Per-Protocol (PP) assessments, this analysis assigns outcomes to all subjects, including those that did not complete the study "per protocol." Subjects who complete the study "per protocol" will retain the same outcome as they received in the final PP analysis. Subjects who were not included in the PP population will be assigned a "clinical cure" outcome if they were randomized to receive experimental therapy (cephalexin+TMP/SMX), and "clinical failure" if they were randomized to receive standard therapy (only cephalexin).

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to cephalexin+TMP/SMX, C_{BE} is the ratio of cures to all enrolled subjects and is equal to the sum of cephalexin+TMP/SMX subjects judged to be cured on the PP evaluation, and all cephalexin+TMP/SMX subjects not in the PP population, divided by the total number of enrolled cephalexin+TMP/SMX subjects.

  $C_{BE} = (NC_{EPP} + NC_{ENPP})/(NC_{EPP} + NC_{ENPP} + NF_{EPP})$

  Where:
  C_{BE} = Best experimental cure rate
  NC_{EPP} = Number of cures assigned to cephalexin+TMP/SMX subjects in the PP population
  NC_{ENPP} = Number of cures assigned to cephalexin+TMP/SMX subjects not in the PP population = Number of cephalexin+TMP/SMX subjects who did not complete "per protocol" evaluation.
  NF_{EPP} = Number of failures assigned to cephalexin+TMP/SMX subjects in the PP population.

- Standard cure rate C_{WS}: Among subjects assigned to cephalexin only, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of only cephalexin subjects judged to be cured in the PP population, divided by the total number of enrolled cephalexin only subjects.

  $C_{WS} = (NC_{SPP})/(NC_{SPP} + NF_{SNPP} + NF_{SPP})$

  Where:
  C_{WS} = Standard cure rate (actually the worst standard cure rate)

NC_{SPP} = Number of cures assigned to cephalexin only subjects in the PP population
NF_{SNPP} = Number of failures assigned to cephalexin only subjects not in the PP population = Number of cephalexin only subjects who did not complete "per protocol" evaluation.

NF_{SPP} = Number of failures assigned to cephalexin only subjects in the PP population.

- The primary outcome is the difference in cure rates between cephalexin+TMP/SMX and cephalexin only treatment groups and the 95% confidence interval.

  $Delta_{BestPP} = C_{BE} - C_{WS}$

For the OmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the OmITT population. Subjects in the OmITT population will retain the same outcome as they received in the final OmITT analysis. Subjects not in the OmITT population will be assigned a "clinical cure" outcome if they were randomized to receive cephalexin+TMP/SMX and a "clinical failure" outcome if they were randomized to receive cephalexin only.

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to cephalexin+TMP/SMX, C_{BE} is the ratio of cures to all enrolled subjects and is equal to the sum of cephalexin+TMP/SMX subjects judged to be cured in the OmITT population, and all cephalexin+TMP/SMX subjects not in the OmITT population, divided by the total number of enrolled subjects.

  $$C_{BE} = (NC_{EOMITT} + NC_{ENOMITT})/(NC_{EOMITT} + NC_{ENOMITT} + NF_{EOMITT})$$

  Where:
  C_{BE} = Best experimental cure rate
  NC_{EOMITT} = Number of cures assigned to cephalexin+TMP/SMX subjects in the OmITT population
  $NC_{ENOMITT}$ = Number of cures assigned to cephalexin+TMP/SMX subjects not in the OmITT population + Number of cephalexin+TMP/SMX subject who did not receive OmITT outcome classification.
  NF_{EOMITT} = Number of failures assigned to cephalexin+TMP/SMX subjects in the OmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to cephalexin only, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of cephalexin only subjects judged to be cured in the

OmITT population, divided by the total number of enrolled cephalexin only subjects.

$C_{WS} = (NC_{SOMITT})/(NC_{SOMITT} + NF_{SNOMITT} + NF_{SOMITT})$

Where:
C_{WS} = Standard cure rate (actually the worst standard cure rate)
NC_{SOMITT} = Number of cures assigned to cephalexin only subjects in the OmITT population
$NF_{SNOMITT}$ = Number of failures assigned to cephalexin only subjects not in the OmITT population = Number of cephalexin only subjects who did not receive OmITT outcome classification.

NF_{SOMITT} = Number of failures assigned to cephalexin only subjects in the OmITT population.

- The primary outcome is the difference in cure rates between cephalexin+TMP/SMX and cephalexin only treatment groups and the 95% confidence interval.

$Delta_{BestOMITT} = C_{BE} - C_{WS}$

For the RmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the RmITT population. Subjects in the RmITT population will retain the same outcome as they received in the final RmITT analysis. Subjects not in the RmITT population will be assigned a "clinical cure" outcome if they were randomized to receive cephalexin+TMP/SMX and a "clinical failure" outcome if they were randomized to receive cephalexin only.

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to cephalexin+TMP/SMX, C_{BE} is the ratio of cures to all enrolled subjects and is equal to the sum of cephalexin+TMP/SMX subjects judged to be cured in the RmITT population, and all cephalexin+TMP/SMX subjects not in the RmITT population, divided by the total number of enrolled subjects.

$C_{BE} = (NC_{ERMITT} + NC_{ENRMITT})/(NC_{ERMITT} + NC_{ENRMITT} + NF_{ERMITT})$

Where:
C_{BE} = Best experimental cure rate
NC_{ERMITT} = Number of cures assigned to cephalexin+TMP/SMX subjects in the RmITT population
$NC_{ENRMITT}$ = Number of cures assigned to cephalexin+TMP/SMX subjects not in the RmITT population = Number of cephalexin+TMP/SMX subjects who did not receive RmITT

outcome classification
NF_{ERMITT} = Number of failures assigned to cephalexin+TMP/SMX subjects in the RmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to cephalexin only, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of cephalexin only subjects judged to be cured in the RmITT population, divided by the total number of enrolled cephalexin only subjects.

  $C_{WS} = (NC_{SRMITT})/(NC_{SRMITT} + NF_{SNRMITT} + NF_{SRMITT})$

  Where:
  C_{WS} = Standard cure rate (actually the worst standard cure rate)
  NC_{SRMITT} = Number of cures assigned to cephalexin only subjects in the RmITT population
  $NF_{SNRMITT}$ = Number of failures assigned to cephalexin only subjects not in the RmITT population = Number of cephalexin only subjects who did not receive RmITT outcome classification.

  NF_{SRMITT} = Number of failures assigned to cephalexin only subjects in the RmITT population.

- The primary outcome is the difference in cure rates between cephalexin+TMP/SMX and cephalexin only treatment groups and the 95% confidence interval.

  $Delta_{BestRMITT} = C_{BE} - C_{WS}$

For the FDAGEEP assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the FDAGEEP population. Subjects in the FDAGEEP population will retain the same outcome as they received in the final FDAGEEP analysis. Subjects not in the FDAGEEP population will be assigned a "clinical cure" (clinical response) outcome if they were randomized to receive cephalexin+TMP/SMX and a "clinical failure" outcome if they were randomized to receive cephalexin only.

Cure rates:

- Experimental cure rate C_{BE}: Among subjects randomized to cephalexin+TMP/SMX, C_{BE} is the ratio of cures (clinical responses) to all enrolled subjects and is equal to the sum of cephalexin+TMP/SMX subjects judged to be cured (clinical response) in the FDAGEEP population, and all cephalexin+TMP/SMX subjects not in the FDAGEEP population, divided by the total number of enrolled subjects.

  $C_{BE} = (NC_{EFDAGEEP} + NC_{ENFDAGEEP})/(NC_{EFDAGEEP} + NC_{ENFDAGEEP} +$

NF_{ERMITT})

Where:
C_{BE} = Best experimental cure rate
$NC_{EFDAGEEP}$ = Number of cures (clinical responses) assigned to cephalexin+TMP/SMX subjects in the FDAGEEP population
$NC_{ENFDAGEEP}$ = Number of cures (clinical responses) assigned to cephalexin+TMP/SMX subjects not in the FDAGEEP population = Number of cephalexin+TMP/SMX subjects who did not receive FDAGEEP outcome classification
$NF_{EFDAGEEP}$ = Number of failures assigned to cephalexin+TMP/SMX subjects in the FDAGEEP population.

- Standard cure rate C_{WS}: Among subjects assigned to cephalexin only, C_{WS} is the ratio of cures (clinical responses) to all enrolled subjects, and is equal to the number of cephalexin only subjects judged to be cured (clinical response) in the FDAGEEP population, divided by the total number of enrolled cephalexin only subjects.

  $C_{WS} = (NC_{SFDAGEEP})/(NC_{SFDAGEEP} + NF_{SNFDAGEEP} + NF_{SFDAGEEP})$

  Where:
  C_{WS} = Standard cure rate (actually the worse standard cure rate)
  $NC_{SFDAGEEP}$ = Number of cures (clinical responses) assigned to cephalexin only subjects in the FDAGEEP population
  $NF_{SNFDAGEEP}$ = Number of failures assigned to cephalexin only subjects not in the FDAGEEP population = Number of cephalexin only subjects who did not receive FDAGEEP outcome classification.

  $NF_{SFDAGEEP}$ = Number of failures assigned to cephalexin only subjects in the FDAGEEP population.

- The primary outcome is the difference in cure rates between cephalexin+TMP/SMX and cephalexin only treatment groups and the 95% confidence interval.

  $Delta_{BestFDAGEEP} = C_{BE} - C_{WS}$

The contents of the analytic summary will mirror the analytic summary for the PP population.

8.3.3.3 Worst-Case Outcomes

For the Per-Protocol (PP) assessments, this analysis assigns outcomes to all subjects, including those that did not complete the study "per protocol." Subjects who complete the study "per protocol" will retain the same outcome as they received in the final PP analysis. Subjects who were not included in the "Per Protocol" population will be

assigned a "clinical failure" outcome if they were randomized to receive cephalexin+TMP/SMX, and "clinical cure" if they were randomized to receive only cephalexin.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to cephalexin+TMP/SMX, C_{WE} is the ratio of cures to all enrolled subjects and is equal to the sum of subjects judged to be cured on the PP evaluation, divided by the total number of enrolled subjects.

  $CW_E = (NC_{EPP})/(NC_{EPP} + NF_{ENPP} + NF_{EPP})$

  Where:
  C_{WE} = Worst experimental cure rate
  NC_{EPP} = Number of cures assigned to cephalexin+TMP/SMX subjects in the PP population
  NF_{ENPP} = Number of failures assigned to cephalexin+TMP/SMX subjects not in the PP population = Number of subjects who did not complete "per protocol" evaluation.
  NF_{EPP} = Number of failures assigned to cephalexin+TMP/SMX subjects in the PP population.

- Standard cure rate C_{BS}: Among subjects assigned to cephalexin only, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the number of subjects judged to be cured in the PP population, as well as all subjects who were not failures on the PP population, divided by the total number of enrolled cephalexin only subjects.

  $C_{BS} = (NC_{SPP} + NC_{SNPP})/(NC_{SPP} + NC_{SNPP} + NF_{SPP})$

  Where:
  CB_S = Best case standard cure rate
  NC_{SPP} = Number of cures assigned to cephalexin only subjects in the PP population
  NC_{SNPP} = Number of cures assigned to cephalexin only subjects not in the PP population = Number of cephalexin only subjects who did not complete "per protocol" evaluation.

  NF_{SPP} = Number of failures assigned to cephalexin only subjects in the PP population.

- The primary outcome is the difference in cure rates between cephalexin+TMP/SMX and cephalexin only treatment groups and the 95% confidence interval.

  $Delta_{WorstPP} = C_{WE} - C_{BS}$

For the OmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the OmITT population. Subjects in the OmITT population will retain the same outcome as they received in the final OmITT analysis. Subjects not in the OmITT population will be assigned a "clinical failure" outcome if they were randomized to receive cephalexin+TMP/SMX and a "clinical cure" outcome if they were randomized to receive only cephalexin.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to cephalexin+TMP/SMX, C_{WE} is the ratio of cures to all enrolled subjects and is equal to the number of cephalexin+TMP/SMX subjects judged to be cured in the OmITT population, divided by the total number of enrolled subjects.

  $C_{WE} = (NC_{EOMITT})/(NC_{EOMITT} + NF_{ENOMITT} + NF_{EOMITT})$

  Where:
  CW_E = Worst case experimental cure rate
  NC_{EOMITT} = Number of cures assigned to cephalexin+TMP/SMX subjects in the OmITT population
  $NF_{ENOMITT}$ = Number of failures assigned to cephalexin+TMP/SMX subjects not in the OmITT population = Number of cephalexin+TMP/SMX subjects who did not receive OmITT outcome classification.
  NF_{EOMITT} = Number of failures assigned to cephalexin+TMP/SMX subjects in the OmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to cephalexin only, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the sum of cephalexin only subjects judged to be cured in the OmITT population, and all cephalexin only subjects not in the OmITT population, divided by the total number of enrolled cephalexin only subjects.

  $C_{WS} = (NC_{SOMITT} + NC_{SNOMITT})/(NC_{SOMITT} + NC_{SNOMITT} + NF_{SOMITT})$

  Where:
  C_{WS} = Worst case standard cure rate
  NC_{SOMITT} = Number of cures assigned to cephalexin only subjects in the OmITT population
  $NC_{SNOMITT}$ = Number of cures assigned to cephalexin only subjects not in the OmITT population = Number of cephalexin only subjects who did not receive OmITT outcome classification

NF_{SOMITT} = Number of failures assigned to cephalexin only subjects in the OmITT population.

- The primary outcome is the difference in cure rates between cephalexin+TMP/SMX and cephalexin only treatment groups and the 95% confidence interval.

  $Delta_{BestOMITT} = C_{BE} - C_{WS}$

For the RmITT assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the RmITT population. Subjects in the RmITT population will retain the same outcome as they received in the final RmITT analysis. Subjects not in the RmITT population will be assigned a "clinical failure" outcome if they were randomized to receive cephalexin+TMP/SMX and a "clinical cure" outcome if they were randomized to receive only cephalexin.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to cephalexin+TMP/SMX, C_{WE} is the ratio of cures to all enrolled subjects and is equal to the number of cephalexin+TMP/SMX subjects judged to be cured in the RmITT population, divided by the total number of enrolled subjects.

  $C_{WE} = (NC_{ERMITT})/(NC_{ERMITT} + NF_{ENRMITT} + NF_{ERMITT})$

  Where:
  CW_E = Worst case experimental cure rate
  NC_{EPP} = Number of cures assigned to cephalexin+TMP/SMX subjects in the RmITT population
  NF_{ENPP} = Number of failures assigned to cephalexin+TMP/SMX subjects not in the RmITT population
  NF_{EPP} = Number of failures assigned to cephalexin+TMP/SMX subjects in the RmITT population.

- Standard cure rate C_{WS}: Among subjects assigned to cephalexin only, C_{WS} is the ratio of cures to all enrolled subjects, and is equal to the sum of cephalexin only subjects judged to be cured in the RmITT population, and all cephalexin only subjects not in the RmITT population, divided by the total number of enrolled cephalexin only subjects.

  $C_{WS} = (NC_{SRMITT} + NC_{SNRMITT})/(NC_{SRMITT} + NC_{SNRMITT} + NF_{SRMITT})$

  Where:
  C_{WS} = Worst case standard cure rate

NC_{SRMITT} = Number of cures assigned to cephalexin only subjects in the RmITT population
$NC_{SNRMITT}$ = Number of cures assigned to cephalexin only subjects not in the RmITT population = Number of cephalexin only subjects who did not receive RmITT outcome classification

NF_{SRMITT} = Number of failures assigned to cephalexin only subjects in the RmITT population.

- The primary outcome is the difference in cure rates between cephalexin+TMP/SMX and cephalexin only treatment groups and the 95% confidence interval.

  $Delta_{BestRMITT} = C_{BE} - C_{WS}$

For the FDAGEEP assessments, this analysis assigns outcomes to all enrolled subjects, including those not included in the FDAGEEP population. Subjects in the FDAGEEP population will retain the same outcome as they received in the final FDAGEEP analysis. Subjects not in the FDAGEEP population will be assigned a "clinical failure" outcome if they were randomized to receive cephalexin+TMP/SMX and a "clinical cure" (clinical response) outcome if they were randomized to receive only cephalexin.

Cure rates:

- Experimental cure rate C_{WE}: Among subjects randomized to cephalexin+TMP/SMX, C_{WE} is the ratio of cures (clinical responses) to all enrolled subjects and is equal to the number of cephalexin+TMP/SMX subjects judged to be cured (clinical response) in the FDAGEEP population, divided by the total number of enrolled subjects.

  $C_{WE} = (NC_{EFDAGEEP})/(NC_{EFDAGEEP} + NF_{ENFDAGEEP} + NF_{EFDAGEEP})$

  Where:
  C_{WE} = Worse case experimental cure rate
  $NC_{EFDAGEEP}$ = Number of cures (clinical responses) assigned to cephalexin+TMP/SMX subjects in the FDAGEEP population
  $NF_{ENFDAGEEP}$ = Number of failures assigned to cephalexin+TMP/SMX subjects not in the FDAGEEP population
  $NF_{EFDAGEEP}$ = Number of failures assigned to cephalexin+TMP/SMX subjects in the FDAGEEP population.

- Standard cure rate C_{WS}: Among subjects assigned to cephalexin only, C_{WS} is the ratio of cures (clinical responses) to all enrolled subjects, and is equal to the sum of cephalexin only subjects judged to be cured (clinical response) in the FDAGEEP population, and all cephalexin only subjects not in the FDAGEEP population, divided by

the total number of enrolled cephalexin only subjects.

$C_{WS} = (NC_{SFDAGEEP} + NC_{SNFDAGEEP})/(NC_{SFDAGEEP} + NC_{SNFDAGEEP} + NF_{SRMITT})$

Where:
C_{WS} = Worse case standard cure rate
$NC_{SFDAGEEP}$ = Number of cures (clinical responses) assigned to cephalexin only subjects in the FDAGEEP population
$NC_{SNFDAGEEP}$ = Number of cures (clinical responses) assigned to cephalexin only subjects not in the FDAGEEP population = Number of cephalexin only subjects who did not receive FDAGEEP outcome classification

$NF_{SFDAGEEP}$ = Number of failures assigned to cephalexin only subjects in the FDAGEEP population.

- The primary outcome is the difference in cure rates between cephalexin+TMP/SMX and cephalexin only treatment groups and the 95% confidence interval.

  $Delta_{WorseFDAGEEP} = C_{WE} - C_{WS}$

The contents of the analytic summary will mirror the analytic summary for the PP population.

8.4 Secondary Endpoints

8.4.1 Change in Dimension of Erythema

A secondary analysis will include the change in the dimension of erythema. The assumption is that the areas of erythema, induration and abscess cavity size are elliptical in shape with area given by the formula for an ellipse (A = 1/4*pi*height *width). The change in area is given by the difference in area between successive measurements (Change = original - subsequent), and the proportional change in area is given by the ratio of the change in area divided by the original area (% Change = Change/original).

The change in area of erythema will be calculated for each subject from the initial visit /Baseline(Visit 1) to the OTV (Visit 2), the EOT (Visit 3) and the TOC (Visit 4). The percent change will be summarized in 5% intervals (i.e. No Change, >0-5%, >5%-10%, >10%-15%, etc.) and summarized by treatment group. The erythema tables will be summarized for all sub-trials and for the per protocol, OmITT, RmITT, and FDAGEEP populations. A mock-up of the table is presented in Table 13.

A graph of the change in erythema over time will be created by plotting the area of erythema at each visit for all sub-trials and for the per protocol, OmITT, RmITT, and FDAGEEP, populations. Figure 4 presents the graph of erythema over time.

8.4.2 Follow-up Visit Infection Site Characteristics

The presence of swelling/induration and presence of tenderness will be summarized at the OTV (Visit 2), EOT (Visit 3) and TOC (Visit 4) compared to Baseline (Visit 1). The numerator will be the number of subjects with the presence of the indicated characteristic in the treatment group being summarized. The denominator will be the number of subjects in the treatment group at Baseline (Visit 1). The difference in proportions will be presented along with the 95% CI. The follow-up visit infection site characteristics will be summarized for all sub-trials and for the per protocol, OmITT, RmITT, and FDAGEEP populations. A mock-up of the table is presented in Table 14.

8.4.3 Follow-up Infection Characteristics

The proportion of subjects with specific infection characteristics through the TOC (Visit 4) and through the EFV (Visit 5) will be summarized by treatment group. The numerator will be the number of subjects with the specified characteristic in the specific treatment group. The denominator will be the number of subjects in the population and specified treatment group being summarized. The following infection characteristics will be summarized as shown in Table 15:

- Admission to hospital after baseline through TOC.
- Development of similar infection in household through TOC and through EFV.
- Surgical procedures performed after baseline (I & D) through TOC and through EFV.
- Taking another antibiotic because of persistent or worsening infection after baseline through TOC and through EFV.
- Recurrent infection at original infection site through TOC and through EFV.
- New skin infection at a different location through TOC and through EFV.
- Development of invasive infection through TOC and through EFV.

The infection characteristics will be summarized for all sub-trials and for the per protocol, OmITT, RmITT, and FDAGEEP populations.

8.4.4 Quality of Life Measures

Quality of life measures were collected on memory aid diaries which were suppose to be filled out by subjects for the first 14 days after enrollment. The diary collected information on fever, missed time from school or work, missed time from normal activities, other medications taken, and whether the packing material was changed for

abscess subjects. A fever is defined as a temperature greater than 38.0 degrees C or 100.4 degrees F. If a subject did not report a temperature but reported that they felt like they had a fever, then they will be counted as having a fever on that day.

An overall summary table that counts the number of days a subject had fever, number of days that a subject missed work or school, number of days a subject missed normal activities, number of days a subject took medication and, for the abscess sub-trial, the number of days a subject changed his packing material will be presented as mocked-up in Table 16.

The last day a subject reported missing normal activities or missing work or school will be defined as the last day a subject missed normal activities or work or school. The last day a subject missed normal activities or work or school will be summarized by study day as presented in Table 17 by treatment and overall.

A summary of whether a subject had fever during the first 14 study days will be presented as shown in Table 18. The number of respondents on each day will be the number of subjects who reported a temperature on the memory aid diary for that study day. The number of subjects who had fever will be the number of subjects who reported a temperature greater than 38.0 degrees C or 100.4 degrees F. If a subject did not report a temperature they will not be counted on this table for that day.

An additional table will be presented that will summarize the last day that a subject reported a fever. The memory aid diaries will be reviewed and the last day that a subject reported a temperature that was defined as a fever (> 38.0 degrees C or 100.4 degrees F) will be noted as the last day of fever for the subject. The last day a subject reported a fever will be summarized for each of the 14 study days that temperature was collected and presented as shown in Table 19.

The Quality of life measures will be summarized for all sub-trials and for the enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations. In addition, they will be summarized two ways based on culture results for each therapy. The first will be culture results of MRSA versus all others (including "no growth" and contaminants), and the second, MRSA or MSSA versus all others (including "no growth" or contaminants).

8.4.5 Other Endpoints

The use of analgesics during the first 14 days of the study is of interest. Analgesic use will be determined from medications reported on the concomitant medication case report form. The number of subjects who used analgesics during the first 14 days of the study will be summarized by treatment group for all sub-trials for the per protocol, OmITT, RmITT, and FDAGEEP populations as shown in Table 20.

An additional table will be presented that will summarize the last day that a subject used analgesics during the first 14 days of the study as presented in Table 21. The last day will be defined as the last reported day during the first 14 study days on which a subject reported using an analgesic. The last day of analgesic use will be summarized for all sub-trials for the per protocol, OmITT, RmITT, and FDAGEEP populations.

A summary of the failure characteristics for subjects classified as clinical failures will be presented by treatment group for all sub-trials and for the per protocol, OmITT, RmITT, and FDAGEEP populations. Failure characteristics include occult abscess found on ultrasound, presence of purulent drainage, development of invasive infection, and rescue therapy received. Individual rescue therapies will be summarized separately, if appropriate, and modified for each sub-trial. A mock-up of this table is presented in Table 22.

9 EVALUATION OF SAFETY PARAMETERS

9.1 Adverse Events

Adverse events will be coded to a Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 15.0 or higher terms. Verbatim description and the MedDRA System Organ Class and Preferred Term for all adverse events will be contained in the subject data listings. A separate listing sorted by MedDRA System Organ Class and Preferred Term will include all verbatim descriptions associated with the Preferred Terms.

Data for adverse events will be analyzed using the treatment-emergent signs and symptoms philosophy. Treatment emergent signs and symptoms are defined as adverse events where:

- onset occurs during exposure to study medication or within 7 days after the last dose of study medication, having been absent prior to receiving study medication, or
- onset reoccurs during exposure to study medication or within 7 days after the last dose of study medication, having been present but stopping prior to receiving study medication, or
- worsening in severity occurs during exposure to study medication relative to the pre-treatment state, when the adverse event is continuous.

All reported adverse events (regardless of treatment-emergent or not) will be included in a by-subject adverse event listing. Only treatment-emergent adverse events will be included in summary tables. The number of subjects (incidence) of treatment-emergent adverse events will be presented as well as the frequency of all adverse events reported.

Summary tables of adverse events will include the following:

- Summary of all adverse events
- Summary of adverse events by severity and relationship
- Summary of related adverse events
- Summary of serious adverse events
- Summary of serious adverse events by severity and relationship
- A listing of any on-study pregnancies.
- A listing of serious adverse events

Mock-up tables of the adverse event tables are presented in Tables 23 - 29.

9.2 Clinical Gram Stain and Microbiologic Data

9.2.1 Antimicrobial Susceptibility

Gram stain and Microbiologic data, including primary pathogen, secondary pathogens and multiple pathogens (MRSA, MSSA, Strep, Coagulase negative Staph, etc), and antimicrobial susceptibility will be summarized by treatment for each sub-trial.

The susceptibility testing to the following antimicrobials were to be conducted for all MRSA and MSSA pathogens and for any other pathogen specified by the clinician:

- Oxacillin
- Tetracycine
- Erythromycin
- TMP/SMX
- Clindamycin
- Vancomycin
- Rifampin
- Moxifloxacin
- Levofloxacin
- Linezolid
- Cefazolin
- Cefoxitin
- Penicillin

Summary tables of susceptibility will be presented by individual organisms as well as by cases for each treatment group for the enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations. The following organisms: MRSA, MSSA, or any species of Streptococcus will be summarized separately for each antimicrobial tested and results will be presented as susceptible, resistant, indeterminate, or not tested. The numerator will be the number of organisms in each category and the denominator will be the number of organisms isolated. Mock-ups of the tables by organism are presented in Tables 30.1 - 30.3.

In addition, cases will be summarized for the following groups:

- MRSA only is isolated, no other organism is isolated
- MSSA only is isolated, no other organism is isolated
- Streptococcus species is isolated, no other organism is isolated
- MRSA and MSSA are both isolated, no other organisms are isolated.
- MRSA and any Streptococcus species are isolated, no other organisms are isolated.
- MSSA and any Streptococcus species are isolated, no other organisms are isolated.

- All organisms.

For cases, if all isolates summarized on the table are susceptible to an antimicrobial or if at least one isolate is susceptible and all others are not tested, then the case will be counted as susceptible. If at least one isolate is resistant to an antimicrobial, then the case will be counted as resistant to that antimicrobial. If at least one isolate is indeterminate and at least one of the other isolates are not resistant, then the case will be counted as indeterminate. If all isolates are not tested, then the case will be counted as not tested. The numerator will be the number of cases in that category and the denominator will be the total number of cases. Mock-ups of the tables by cases are presented in Tables 31.1 - 31.7.

9.2.2 Expected Cure Rates

Antimicrobial resistance rates among the cultured specimens will be examined. These rates will be specified in terms of proportion of specific organism isolates susceptible to a given antibiotic. This information will be used to assign expected microbiological cure rates to the associated individual subjects. These expected cure rates will then be compared to actual observed cure rates at various stages of treatment (OTV, EOT, TOC). The expected versus observed cure information will be summarized as raw counts by treatment.

For the abscess sub-trial, subjects who received TMP/SMX and have all isolates susceptible to TMP/SMX, will be counted as an expected cure.

For the infected wound sub-trial, subjects who received clindamycin and had all isolates susceptible to clindamycin will be counted as an expected cure and those subjects who received TMP/SMX and have all isolates that are susceptible to TMP/SMX will be counted as an expected cure.

For the cellulitis sub-trial, subjects who received TMP/SMX + cephalexin and had all isolates susceptible to TMP/SMX or all isolates susceptible to cefazolin will be counted as an expected cure and those subjects who received cephalexin only and had all isolates susceptible to cefazolin will be counted as an expected cure.

A summary table comparing the expected cure rates with the observed cure rates will be presented as shown in Table 32. The number and percent of subjects in each treatment that were observed as a cure and compared to those expected to be cured will be summarized.

9.3 *C. difficile* Infection

Subjects that experienced diarrhea and were able to provide a stool specimen were tested for presence of *C. difficile* infection. The results of the test (presence/absence)

will be summarized for each visit by treatment and overall for each sub-trial for the safety population. A mock-up of the table is shown in Table 33.

9.4 Concomitant Medications

The use of prior and concomitant medications taken during the study will be recorded on the CRFs. No listings are planned at this time.

9.5 Vital Signs and Physical Examinations

Vital sign measurements included systolic blood pressure, diastolic blood pressure, pulse, respiratory rate and temperature. Vital signs were assessed at each clinical site visit. All vital signs summary tables will be presented for subjects in the Safety population.

For each treatment group, descriptive summary statistics (mean, standard deviation, median, minimum and maximum) of vital sign parameters at each visit will be calculated along with the change from screening. A mock-up of the table is shown in Table 34.

Physical Examinations were also collected at each clinical site visit.

10 TABLES AND FIGURES

10.1 Demographics and Baseline Characteristic

Figure 1:
Disposition of Study Subjects – All Screened Subjects

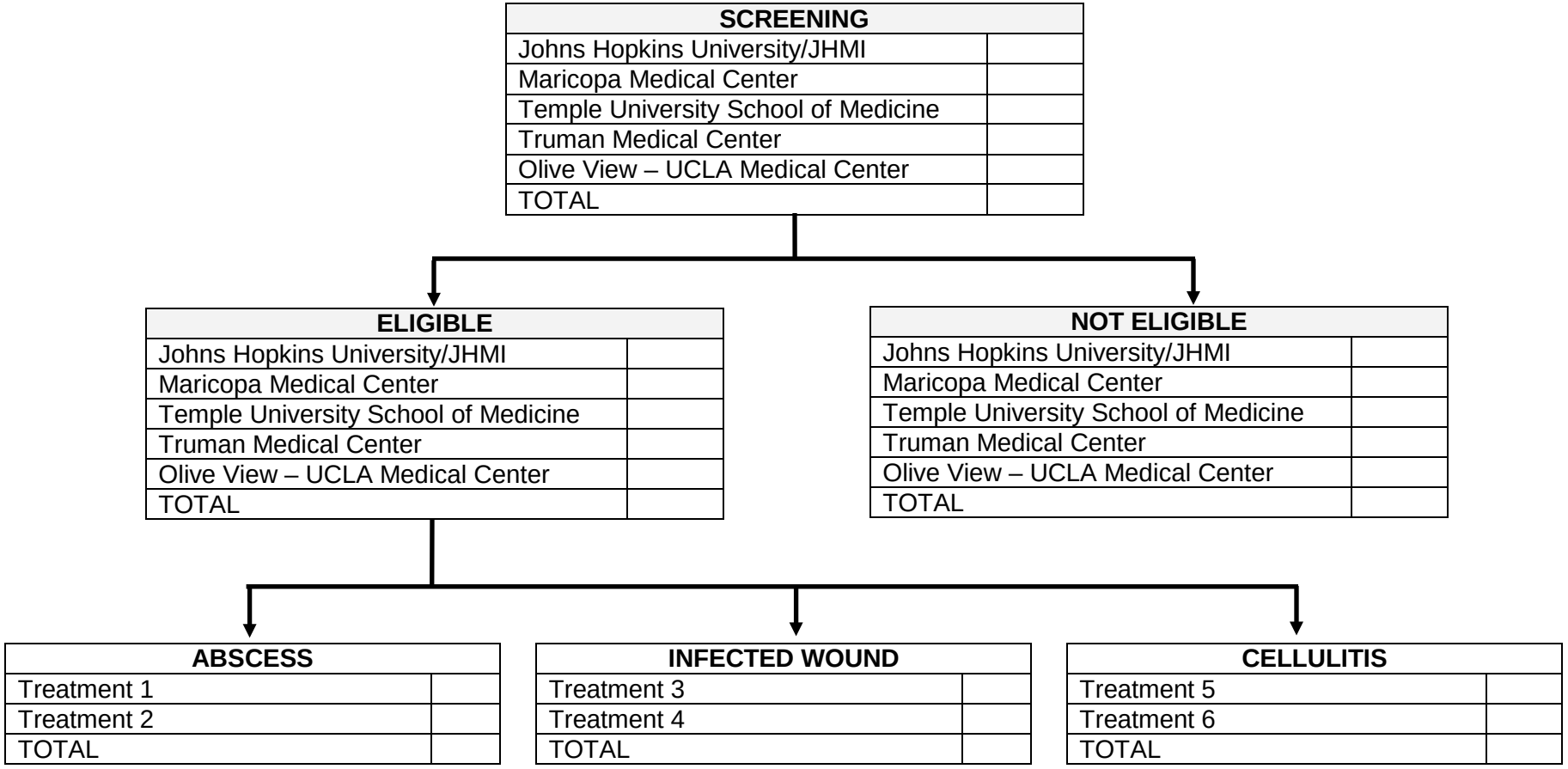

Table 1:
Demographics: Gender, Ethnicity, Race and Age

Sub-trial *Population/Subgroup*			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
Gender - n (%)			
Male			
Female			
Ethnicity - n(%)			
Non-Hispanic or Non-Latino			
Hispanic or Latino			
Race - n(%)			
American Indian/Alaskan Native			
Asian			
Hawaiian/Pacific Islander			
Black/African American			
White			
Multi-Racial			
Other/Unknown			
Age - n(%)			
Mean (SD)			
Median			
Min, Max			
<1 Years - n(%)			
1-8 Years - n(%)			
9-17 Years - n(%)			
>=18 - n(%)			

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis by treatment group and overall. In addition, it will be summarized for the OmITT RmITT, FDAGEEP, and Per Protocol Populations.

For all three Sub-trials, the following subgroups will be analyzed (replace treatment group):

- *Clinical Cures Versus Clinical Failures in the Per Protocol Population*

For Abscess and Infected Wound Sub-trial, the following subgroups will be analyzed:

- *Large Abscess versus Small Abscess in the Per Protocol Population*

Table 2:
Baseline Characteristics: Oral Temperature, Vital Signs and Weight

Sub-trial Population			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
Temperature (C)			
n			
Mean (SD)			
Median			
(Min, Max)			
Systolic Blood Pressure (mm Hg)			
n			
Mean (SD)			
Median			
(Min, Max)			
Diastolic Blood Pressure (mm Hg)			
n			
Mean (SD)			
Median			
(Min, Max)			
Pulse (beats per minute)			
n			
Mean (SD)			
Median			
(Min, Max)			
Respiratory Rate (breaths per minute)			
n			
Mean (SD)			
Median			
(Min, Max)			
Weight (kg)			
n			
Mean (SD)			
Median			
(Min, Max)			

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol Populations.

Table 3
Summary of Infection Site Culture by Species at Baseline

Sub-trial Population			
	Therapy		
Primary Infection Site Species	**T1 (N)**	**T2 (N)**	**All Therapies (N)**
Staphylococcus species			
MRSA			
MSSA			
Coagulase-negative staphylococcus			
Streptococcus species			
Group A streptococcus			
Group B streptococcus			
S. pyogenes			
Beta-hemolytic group C streptococcus			
Beta-hemolytic group F streptococcus			
Non-group A and B beta-hemolytic streptococcus			
Viridans group streptococcus			
Alpha-hemolytic streptococcus			
Other Species			
Diphtheroid bacilli			
Enterobacter species			
Enterococcus species			
Escherichia coli			
Haemophilus species			
Klebsiella species			
Lactobacillus species			
Proteus mirabilis			
Bacterial growth NOS			
Other			
Culture Obtained but No Growth			
Culture Obtained but No Results			
No Culture Obtained			

Programming Notes: This table will be created for Abscess and Infected Wound Sub-trial. In addition, it will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol Populations.

Figure 2:
Summary of Infection Site Culture and Susceptibility

This will be a bar chart with species along the x-axis and number of subjects along the y-axis.

This figure will be created for the Abscess and the Infected Wound Sub-trials for the OmITT, RmITT, FDAGEEP, and the Per Protocol Populations.

Table 4A:
Summary of Baseline Infection Site Characteristics

Abscess Sub-trial Population			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
Location of Infection Site, n (%)			
Head/Neck			
Trunk/Abdomen/Back			
Groin/Buttocks			
Upper Extremity			
Lower Extremity			
Ultrasound Measurements (cm)			
Length of Abscess Cavity			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Width of Abscess Cavity			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Depth of Abscess Cavity			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Ultrasound Measurements (cm) Continued			
Volume of Abscess Cavity*			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			

Table 4A
Summary of Baseline Infection Site Characteristics
Continued

Abscess Sub-trial Population			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
Abscess Cavity Measurement with I&D (cm)			
Length of Abscess Cavity			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Width of Abscess Cavity			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Depth of Abscess Cavity			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Volume of Abscess Cavity*			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Maximal Depth of Abscess Cavity, n (%)			
Limited to Skin/Subcutaneous			
Involves Deep Fascia			
Erythema Maximal Dimensions (cm)			
Length			
n			
Mean (SD)			

Table 4A
Summary of Baseline Infection Site Characteristics
Continued

Abscess Sub-trial Population			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
Median			
(Min, Max)			
q1-q3 (IQR)			
Width			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Area**			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Induration/Swelling Maximal Dimensions(cm)			
Length			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Induration/Swelling Maximal Dimensions(cm)			
Width			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Area***			
n			

Table 4A
Summary of Baseline Infection Site Characteristics
Continued

Abscess Sub-trial Population			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Presence of Fever**** at Baseline, n (%)			

Note:

*Volume of abscess (cm^3) = Length x Width X Depth.
** Area of Erythema is calculated using formula for an ellipse (1/4*π*length*width) minus area of probe measurements from area of erythema.
*** Area of Swelling/Induration is calculated using formula for an ellipse (1/4*π*length*width) minus area of probe measurements from area of swelling/induration.
****Fever at baseline is defined as > 100.4 F or > 38 C.

Programming Notes: Table 3A will be created for the Abscess Sub-trial by treatment group and overall. In addition, it will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol Populations.
Sub-groups that will be analyzed (replacing treatment group):

- *Clinical Cures Versus Clinical Failures in the Per Protocol Population*
- *Large Abscess versus Small Abscess in the Per Protocol Population*
- *MRSA versus Non-MRSA subjects in the Per Protocol Population*

Table 4B:
Summary of Baseline Infection Site Characteristics

Infected Wound Sub-trial Population			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
Location of Infection Site, n (%)			
Head/Neck			
Trunk/Abdomen/Back			
Groin/Buttocks			
Upper Extremity			
Lower Extremity			
Purulent Drainage Present, n (%)			
Wound Type, n (%)			
Ulcer			
Complex/Stellate Irr lac			
Linear Lac			
Abrasion			
Other			
Length of Wound (cm)			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Wound Depth, n (%)			
Limited to Skin			
Involves Subcutaneous			
Involves Deep Fascia			
Previous Surgical Procedure Led to Infection?			
Foreign Body/Material Retained			
Abscess Present?			
If Abscess Present, was I&D Performed?			
Abscess Cavity Measurement with I&D (cm)			
Ultrasound Measurements (cm)			
Length of Abscess Cavity			

Table 4B
Summary of Baseline Infection Site Characteristics
Continued

Infected Wound Sub-trial Population			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Width of Abscess Cavity			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Depth of Abscess Cavity			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Volume of Abscess Cavity*			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Abscess Cavity Measurement with I&D (cm)			
Length of Abscess Cavity			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Width of Abscess Cavity			

Table 4B
Summary of Baseline Infection Site Characteristics
Continued

Infected Wound Sub-trial Population			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Abscess Cavity Measurement with I&D (cm)			
Depth of Abscess Cavity			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Volume of Abscess Cavity*			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Presence of Fever* at Baseline, n (%)			

Note: *Fever at baseline is defined as > 100.4 F or > 38.0 C.

Programming Notes: This table will be created for the Infected Wound Sub-trial by treatment group and overall. In addition, it will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol Populations.
Sub-groups that will be analyzed (replacing treatment group):

- *Clinical Cures Versus Clinical Failures in the Per Protocol Population*
- *Large Abscess versus Small Abscess in the Per Protocol Population*
- *MRSA versus Non-MRSA subjects in the Per Protocol Population*

Table 4C:
Summary of Baseline Infection Site Characteristics

Cellulitis Sub-trial Population			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
Location of Infection Site, n (%)			
Head/Neck			
Trunk/Abdomen/Back			
Groin/Buttocks			
Upper Extremity			
Lower Extremity			
Purulent Drainage Present, n (%)			
Erythema Maximal Dimensions (cm)			
Length			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Width			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Area*			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Swelling/Induration Maximal Dimensions (cm)			
Length			
n			
Mean (SD)			
Median			

Table 4C
Summary of Baseline Infection Site Characteristics
Continued

Cellulitis Sub-trial Population			
	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
(Min, Max)			
q1-q3 (IQR)			
Width			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Area**			
n			
Mean (SD)			
Median			
(Min, Max)			
q1-q3 (IQR)			
Presence of Fever*** at Baseline, n (%)			

Note:

* Area of Erythema is calculated using formula for an ellipse (1/4*π*length*width) minus area of probe measurements from area of erythema.
** Area of Swelling/Induration is calculated using formula for an ellipse (1/4*π*length*width) minus area of probe measurements from area of swelling/induration.
*** Fever at baseline is defined as > 100.4 F or > 38 C.

Programming Notes: This table will be created for the Abscess Sub-trial by treatment group and overall. In addition, it will be summarized for the OmITT, RmITT, FDAGEEP, and the Per Protocol Populations.
Sub-groups that will be analyzed (replacing treatment group):

- *Clinical Cures Versus Clinical Failures in the Per Protocol Population*
- *Large Abscess versus Small Abscess in the Per Protocol Population*
- *MRSA versus Non-MRSA subjects in the Per Protocol Population*

Table 5:
Summary of Pre-Existing Conditions/Medical History

Sub-trial Population			
	Therapy		
Medical History Factors	**T1 (N=xxx) n (%)**	**T2 (N=xxx) n (%)**	**All Therapies (N=xxx) n (%)**
Co-morbidities			
History of Prior MRSA Infection			
Diabetes			
Eczema or Other Chronic Skin Infection			
Chronic Edema			
COPD			
CHF			
HIV+			
Cancer			
Other			
Close household contact with someone with similar skin infection in last month?			
Fever in the last week?			
Number of days SSTI symptoms (median, IQR)?			
Previously treated for this infection with antibiotics?			
General Function Impairment			
Can do all ADL			
Can do some ADL			
Cannot do any ADL			
Level of Functional Impairment of Affected SSTI Area			
Full Use			
Partial Use			
No Use			
Not Applicable			
SSTI Related to Intravenous Drug Use			
Any Serious Allergies			

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis by treatment group and overall. In addition, it will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol Populations.

Table 5
Summary of Pre-Existing Conditions/Medical History
Continued

For all three Sub-trials, the following subgroups will be analyzed(replace treatment group):

- *Clinical Cures Versus Clinical Failures in the Per Protocol Population*

For Abscess and Infected Wound Sub-trial, the following subgroups will be analyzed:

- *Large Abscess versus Small Abscess in the Per Protocol Population*
- *MRSA versus Non-MRSA subjects in the Per Protocol Population*

Table 6:
Summary of Prior Antibiotic Therapy

Sub-trial Population			
	Therapy		
Prior Antibiotic Therapy	**T1 (N=xxx) n (%)**	**T2 (N=xxx) n (%)**	**All Therapies (N=xxx) n (%)**
Subjects with Prior Antibiotic Therapy at Baseline			
Failed Previous Treatment			
Antibiotic Treatment 1			
Antibiotic Treatment 2			
.....			
Stopped 1 Month Prior to Baseline			
Antibiotic Treatment 1			
Antibiotic Treatment 2			
.....			

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis by treatment group and overall. In addition, it will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol Populations.

10.2 Study Compliance

Table 7:
Summary of Study Visit Compliance

Enrolled

	Therapy		
Enrollment	**T1 (N)**	**T2 (N)**	**All Therapies (N)**

On Therapy Visit (Days 3-4 Post Enrollment)

	Therapy		
On Therapy Visit	**T1 (N)**	**T2 (N)**	**All Therapies (N)**
Completed			
Expected			
Missed Visit, Lost or Not Done			
Data Pending*			
Total			

End of Therapy Visit (Days 8-10 Post Enrollment)

	Therapy		
End of Therapy Visit	**T1 (N)**	**T2 (N)**	**All Therapies (N)**
Completed			
Expected			
Missed Visit, Lost or Not Done			
Data Pending*			
Total			

Note**:** * At the end of the study all pending data should be received so Data Pending and Expected rows will be removed at the end of the study.

Table 7
Summary of Study Visit Compliance
Continued

Test of Cure Visit (Days 14-21 Post Enrollment)

	Therapy		
Test of Cure Visit	**T1 (N)**	**T2 (N)**	**All Therapies (N)**
Completed			
Expected			
Missed Visit, Lost or Not Done			
Data Pending*			
Total			

Extended Follow-up Visit (Days 49-63 Post Enrollment)

	Therapy		
Extended Follow-up Visit	**T1 (N)**	**T2 (N)**	**All Therapies (N)**
Completed			
Expected			
Missed Visit, Lost or Not Done			
Data Pending*			
Total			

Note**:** * At the end of the study all pending data should be received so Data Pending and Expected rows will be removed at the end of the study.

Figure 3:
Graph of Compliance with Study Medication

This will be a pie chart by site and treatment group, of the number of subjects falling into each compliance category: 0-25% doses taken; 26-50% of doses taken; 51-75% of doses taken; 76-99% of doses taken; fully compliant; and Unknown.

Table 8:
Compliance with Study Medication

	Therapy		
	T1 (N=xxx)	**T2 (N=xxx)**	**All Therapies (N=xxx)**
Fully Compliant			
Not Fully Compliant			
0-25% Doses Taken			
26%-50% Doses Taken			
51%-75% Doses Taken			
76%-99% Doses Taken			
100% or More Doses Taken			
Unknown			
Total			

Table 9:
Reasons for Early Termination

	T1 (N=xxx) n (%)	T2 (N=xxx) n (%)	All Therapies (N=xxx) n (%)
Completed Study			
Discontinued Study Early			
Reasons for Early Discontinuation			
Adverse Event			
Death			
Lost to Follow-up			
Voluntary Withdrawal by Subject			
Withdrawal by Investigator			
Termination of Site by Sponsor			
Randomized but not Treated			
Other			

Table 10:
Listing of Non-Subject Specific Protocol Deviations

Site	Deviation Description	Reason for Deviation	Deviation Category	Deviation Resulted in AE	Deviation Resulted in Termination	Affected Product Stability	Reported to IRB

Table 11:
Summary of Protocol Deviations – All Subjects

	Therapy		
	T1 (N=xxx)	**T2 (N=xxx)**	**All Therapies (N=xxx)**
Blinding Policy/Procedure			
Eligibility/Enrollment			
Follow-up Visit Schedule			
Product Administration/Dosing			
Product Administration/Dosing Schedule			
Protocol Procedure/Assessment			
Total # of Deviations			
Total # Enrolled			

10.3 Efficacy

- Summary of Treatment Outcome at the TOC Visit
- Analysis of Observed Cure Rates – Per Protocol Population
- Analysis of Observed Cure Rates – RmITT Population
- Analysis of Observed Cure Rates – OmITT Population
- Analysis of Observed Cure Rates – FDAGEEP Population
- Analysis of Best Case Cure Rates - PP, RmITT, OmITT, and FDAGEEP Population
- Analysis of Worst Case Cure Rates - PP, RmITT, OmITT, and FDAGEEP Population
- Sensitivity Analysis to Assess Implications of Bias due to Visit Non-Compliance and Adjusted Cure Rates Based on Treatment Compliance

Table 12A:
Analysis of Primary and Secondary Outcomes Between Treatment Groups, Per Protocol Population

Sub-trial			
Proportion of	**T2 (P2) (N=)**	**T1 (P1) (N=)**	**Difference (P2 - P1) (95% CI)**
Original Definition			
Clinical Cures [1]	xx	xx	xx.x (xx.x - xx.x)
Clinical Failures [1]	xx	xx	
Best Case Scenario [2]			
Clinical Cures	xx	xx	xx.x (xx.x - xx.x)
Clinical Failures	xx	xx	
Worst Case Scenario [2]			
Clinical Cures	xx	xx	xx.x (xx.x - xx.x)
Clinical Failures	xx	xx	
Other Cure Definitions			
Composite Clinical Cure [3]	xx	xx	xx.x (xx.x - xx.x)
Microbiologic Cure [4]	xx	xx	xx.x (xx.x - xx.x)
MRSA positive infection site culture	xx	xx	xx.x (xx.x - xx.x)

Note:

N = the number of subjects in the per protocol population and specified treatment group.
P2 = n/N - where n = the number of subjects in the T2 treatment group with the specified characteristic.
P1 = n/N - where n = the number of subjects in the T1 treatment group with the specified characteristic.
[1] Clinical Cures and Failures are defined in Section 8.1.1 and Section 8.1.2, respectively, of the Statistical Analysis Plan (SAP).
[2] Best Case and Worst Case Clinical Cures and Failures are defined in Section 8.3 of the SAP.
[3] Clinical Cures and Failures are defined in Section 8.1.4 of the SAP.
[4] Composite Clinical Cure is defined in Section 8.1.5 of the SAP.
[5] Microbiologic Cure is defined in Section 8.1.6 of the SAP.

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis.*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
    - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
    - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
    - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone.*

Sub-groups that will be analyzed (replacing treatment group):

- *Clinical Cures Versus Clinical Failures in the Per Protocol Population*
- *Large Abscess versus Small Abscess in the Per Protocol Population*
- *MRSA versus Non-MRSA subjects in the Per Protocol Population*

Table 12B:
Analysis of Secondary Outcomes Between Treatment Groups,
Original Modified Intent-to-Treat Population

Sub-trial			
Proportion of	**T2 (P2) (N=)**	**T1 (P1) (N=)**	**Difference (P2 - P1) (95% CI)**
Original Definition			
Clinical Cures [1]	xx	xx	xx.x (xx.x - xx.x)
Clinical Failures [1]	xx	xx	
Best Case Scenario [2]			
Clinical Cures	xx	xx	xx.x (xx.x - xx.x)
Clinical Failures	xx	xx	
Worst Case Scenario [2]			
Clinical Cures	xx	xx	xx.x (xx.x - xx.x)
Clinical Failures	xx	xx	
Other Cure Definitions			
Composite Clinical Cure [3]	xx	xx	xx.x (xx.x - xx.x)
Microbiologic Cure [4]	xx	xx	xx.x (xx.x - xx.x)
MRSA positive infection site culture	xx	xx	xx.x (xx.x - xx.x)

Note:

N = the number of subjects in the OmITT population and specified treatment group.
P2 = n/N - where n = the number of subjects in the T2 treatment group with the specified characteristic.
P1 = n/N - where n = the number of subjects in the T1 treatment group with the specified characteristic.
[1] Clinical Cures and Failures are defined in Section 8.1.3 of the Statistical Analysis Plan (SAP).
[2] Best Case and Worst Case Clinical Cures and Failures are defined in Section 8.3 of the SAP.
[3] Clinical Cures and Failures are defined in Section 8.1.4 of the SAP.
[4] Composite Clinical Cure is defined in Section 8.1.5 of the SAP.
[5] Microbiologic Cure is defined in Section 8.1.6 of the SAP.

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis.*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
    - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
    - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
    - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone.*

Sub-groups that will be analyzed (replacing treatment group):

- *Clinical Cures Versus Clinical Failures in the OmITT Population*
- *Large Abscess versus Small Abscess in the OmITT Population*
  MRSA versus Non-MRSA subjects in the OmITT Population

Table 12C:
Analysis of Secondary Outcomes Between Treatment Groups, Revised Modified Intent-to-Treat Population

Sub-trial			
Proportion of	**T2 (P2) (N=)**	**T1 (P1) (N=)**	**Difference (P2 - P1) (95% CI)**
Original Definition			
Clinical Cures [1]	xx	Xx	xx.x (xx.x - xx.x)
Clinical Failures [1]	xx	Xx	
Best Case Scenario [2]			
Clinical Cures	xx	Xx	xx.x (xx.x - xx.x)
Clinical Failures	xx	Xx	
Worst Case Scenario [2]			
Clinical Cures	xx	Xx	xx.x (xx.x - xx.x)
Clinical Failures	xx	Xx	
Other Cure Definitions			
Composite Clinical Cure [3]	xx	Xx	xx.x (xx.x - xx.x)
Microbiologic Cure [4]	xx	Xx	xx.x (xx.x - xx.x)
MRSA positive infection site culture	xx	Xx	xx.x (xx.x - xx.x)

Note:

N = the number of subjects in the RmITT population and specified treatment group.
P2 = n/N - where n = the number of subjects in the T2 treatment group with the specified characteristic.
P1 = n/N - where n = the number of subjects in the T1 treatment group with the specified characteristic.
[1] Clinical Cures and Failures are defined in Section 8.1.4 of the Statistical Analysis Plan (SAP).
[2] Best Case and Worst Case Clinical Cures and Failures are defined in Section 8.3 of the SAP.
[3] Clinical Cures and Failures are defined in Section 8.1.4 of the SAP.
[4] Composite Clinical Cure is defined in Section 8.1.5 of the SAP.
[5] Microbiologic Cure is defined in Section 8.1.6 of the SAP.

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis.*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
    - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
    - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
    - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone.*

Sub-groups that will be analyzed (replacing treatment group):

- *Clinical Cures Versus Clinical Failures in the RmITT Population*
- *Large Abscess versus Small Abscess in the RmITT Population*
  MRSA versus Non-MRSA subjects in the RmITT Population

Table 12D:
Analysis of Secondary Outcomes Between Treatment Groups,
FDA Guidance Early Endpoint Population

Sub-trial			
Proportion of	**T2 (P2) (N=)**	**T1 (P1) (N=)**	**Difference (P2 - P1) (95% CI)**
Original Definition			
Clinical Cures [1]	xx	Xx	xx.x (xx.x - xx.x)
Clinical Failures [1]	xx	Xx	
Best Case Scenario [2]			
Clinical Cures	xx	Xx	xx.x (xx.x - xx.x)
Clinical Failures	xx	Xx	
Worst Case Scenario [2]			
Clinical Cures	xx	Xx	xx.x (xx.x - xx.x)
Clinical Failures	xx	Xx	
Other Cure Definitions			
Composite Clinical Cure [3]	xx	Xx	xx.x (xx.x - xx.x)
Microbiologic Cure [4]	xx	Xx	xx.x (xx.x - xx.x)
MRSA positive infection site culture	xx	Xx	xx.x (xx.x - xx.x)

Note:

N = the number of subjects in the FDAGEEP population and specified treatment group.
P2 = n/N - where n = the number of subjects in the T2 treatment group with the specified characteristic.
P1 = n/N - where n = the number of subjects in the T1 treatment group with the specified characteristic.
[1] Clinical Cures and Failures are defined in Section 8.1.7 of the Statistical Analysis Plan (SAP).
[2] Best Case and Worst Case Clinical Cures and Failures are defined in Section 8.3 of the SAP.
[3] Clinical Cures and Failures are defined in Section 8.1.7 of the SAP.
[4] Composite Clinical Cure is defined in Section 8.1.5 of the SAP.
[5] Microbiologic Cure is defined in Section 8.1.6 of the SAP.

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis.*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
    - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
    - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
    - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone.*

Sub-groups that will be analyzed (replacing treatment group):

- *Clinical Cures Versus Clinical Failures in the FDAGEEP Population*
- *Large Abscess versus Small Abscess in the FDAGEEP Population*
  MRSA versus Non-MRSA subjects in the FDAGEEP Population

Table 12E:
Sensitivity Analysis Adjusting Cure Rates for Compliance Rate, Subjects with a 50 - 75% Compliance Rate at the TOC Visit

Sub-trial			
Proportion of	**T2 (P2) (N=)**	**T1 (P1) (N=)**	**Difference (P2 - P1) (95% CI)**
Clinical Cures [1]	xx	Xx	xx.x (xx.x - xx.x)
Clinical Failures [1]	xx	Xx	

Note:

N = the number of subjects with a 50-75% Compliance rate at the TOC visit in the specified treatment group.
P2 = n/N - where n = the number of subjects in the T2 treatment group with the specified characteristic.
P1 = n/N - where n = the number of subjects in the T1 treatment group with the specified characteristic.
[1] Clinical Cures and Failures are defined in Section 8.1.3 of the Statistical Analysis Plan (SAP).

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis.*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
  - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
  - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
  - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone.*

Table 13:
Secondary Analysis of Follow-up Visit Erythema

Sub-trial *Population*			
	T2 (N=)	**T1 (N=)**	**Mean Difference (95% CI)**
Change in Area of Erythema *			
On-Therapy Visit - Baseline			
n	xx	xx	
Mean Change (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x)
Percent Change, n (%) **			
No Change***	xx (xx.x)	xx (xx.x)	
>0% - 5%	xx (xx.x)	xx (xx.x)	
>5% - 10%	xx (xx.x)	xx (xx.x)	
>10% - 15%	xx (xx.x)	xx (xx.x)	
>15% - 20%	xx (xx.x)	xx (xx.x)	
.....			
End of Therapy Visit - Baseline			
n	xx	xx	
Mean Change (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x)
Percent Change, n (%) **			
No Change***	xx (xx.x)	xx (xx.x)	
>0% - 5%	xx (xx.x)	xx (xx.x)	
.....			
Continue for Test of Cure Visit			

Note:

n = the number of subjects with measurements at each visit for each treatment group.
* Area of erythema is calculated by 1/4 x pi x Length x Width. Change in Area is calculated as Baseline - Visit.
** Percent Change is calculated as (Change in Area)/(Baseline Area) x 100%.
*** No Change is any subjects whose % Change <= 0.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol Populations. The Per Protocol Population will be listed first and is the primary analysis
Replace T1 and T2 in the headers with the actual name of the Treatments:
For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo
For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX
For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone

Sub-groups that will be analyzed (replacing treatment group):

- *Clinical Cures Versus Clinical Failures in the Per Protocol Population*
- *Large Abscess versus Small Abscess in the Per Protocol Population*
- *MRSA versus Non-MRSA subjects in the Per Protocol Population*

Figure 4:
Graph of Change in Area of Erythema over Time

This will be a line graph with the mean area of erythema plotted at each visit for each treatment group. The upper quartile and lower quartile will be plotted also with a bar connecting them to each other and the mean. This graph will be plotted for all sub-trails and for the per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 14:
Secondary Analysis of Follow-up Visit Infection Site Characteristics

Sub-trial Population			
	T2 (P2) (N=xxx)	**T1 (P1) (N=xxx)**	**Difference (95% CI)**
Presence of Swelling/Induration*, (P)			
On-Therapy Visit	xx.x	xx.x	xx.x (xx.x - xx.x)
End of Therapy Visit	xx.x	xx.x	xx.x (xx.x - xx.x)
Test of Cure Visit	xx.x	xx.x	xx.x (xx.x - xx.x)
Presence of Tenderness*, (P)			
On-Therapy Visit	xx.x	xx.x	xx.x (xx.x - xx.x)
End of Therapy Visit	xx.x	xx.x	xx.x (xx.x - xx.x)
Test of Cure Visit	xx.x	xx.x	xx.x (xx.x - xx.x)

Note:

N = the number of subjects with information at the specified visits and Visit 1 for the population specified.
P = n/N - where n is the number of subjects with the characteristic present
* The proportion of subjects with presence of the indicated characteristic will be compared by using the same algorithms as the primary analysis.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol Populations. The Per Protocol Population will be listed first and is the primary analysis
Replace T1 and T2 in the headers with the actual name of the Treatments:
For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo
For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX
For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone

Table 15:
Secondary Analysis of Follow-up Infection Characteristics

Sub-trial Population			
	T2 (P2) (N=xxx)	**T1 (P1) (N=xxx)**	**Difference (95% CI)**
Admission to hospital after baseline through TOC	xx	Xx	xx.x (xx.x - xx.x)
Development of similar infection in household			
through TOC	xx	Xx	xx.x (xx.x - xx.x)
through EFV	xx	Xx	xx.x (xx.x - xx.x)
Surgical procedures performed after baseline (I&D)			
through TOC	xx	Xx	xx.x (xx.x - xx.x)
through EFV	xx	Xx	xx.x (xx.x - xx.x)
Taking another antibiotic because of persistent or worsening infection after baseline			
through TOC	xx	Xx	xx.x (xx.x - xx.x)
through EFV	xx	Xx	xx.x (xx.x - xx.x)
Recurrent infection at original infection site			
through TOC	xx	Xx	xx.x (xx.x - xx.x)
through EFV	xx	Xx	xx.x (xx.x - xx.x)
New skin infection at different location			
through TOC	xx	Xx	xx.x (xx.x - xx.x)
through EFV	xx	Xx	xx.x (xx.x - xx.x)
Development of Invasive Infection			
through TOC	xx	Xx	xx.x (xx.x - xx.x)
through EFV	xx	Xx	xx.x (xx.x - xx.x)

Note:

N = the number of subjects in the population and specified treatment group.
P2 = n/N - where n = the number of subjects in the T2 treatment group with the specified characteristic.
P1 = n/N - where n = the number of subjects in the T1 treatment group with the specified characteristic.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the mITT, RmITT, FDAGEEP, and Per Protocol Populations. The Per Protocol Population will be listed first and is the primary analysis
Replace T1 and T2 in the headers with the actual name of the Treatments:
For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo
For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX
For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone

Table 16:
Days Reported for Quality of Life Measures

Sub-trial *Population*		
	T1 **(N)**	**T2** **(N)**
Days of Fever		
n	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
(Min, Max)	(xx, xx)	(xx, xx)
Days missed from work or school		
n	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
(Min, Max)	(xx, xx)	(xx, xx)
Days missed from normal activities		
n	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
(Min, Max)	(xx, xx)	(xx, xx)
Days using Study Medications		
n	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
(Min, Max)	(xx, xx)	(xx, xx)
Days changed Packing Material*		
n	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
(Min, Max)	(xx, xx)	(xx, xx)

* Days changed packing material is only summarized for the Abscess sub-trial.

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the Enrolled, OmITT, RmITT, FDAGEEP, and Per Protocol Populations. The Per Protocol Population will be listed first and is the primary analysis*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
  - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
  - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
  - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone*
- *Sub-groups that will be analyzed (replacing treatment group):*
  - *MRSA vs. Non-MRSA (including no growth and contaminants for the Per Protocol Population.*
  - *MRSA and MSSA vs. all others (including no growth and contaminants for the Per Protocol Population.*

Table 17:
Summary of Last Day Subject Recorded Missed Normal Activities or Missed Days of School or Work by Study Day

Sub-trial Population			
	T1	T2	All Therapies
Number of Respondents	xxx	xxx	xxx
Study Days			
1	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)
5	xx (xx.x)	xx (xx.x)	xx (xx.x)
6	xx (xx.x)	xx (xx.x)	xx (xx.x)
7	xx (xx.x)	xx (xx.x)	xx (xx.x)
8	xx (xx.x)	xx (xx.x)	xx (xx.x)
9	xx (xx.x)	xx (xx.x)	xx (xx.x)
10	xx (xx.x)	xx (xx.x)	xx (xx.x)
11	xx (xx.x)	xx (xx.x)	xx (xx.x)
12	xx (xx.x)	xx (xx.x)	xx (xx.x)
13	xx (xx.x)	xx (xx.x)	xx (xx.x)
14	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note:
The denominator for percentages is the number of respondents. The numerator is the number of subjects who reported their last day of missed normal activities or missed day of school or work on the study day being summarized.

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the Enrolled, OmITT, RmITT, FDAGEEP, and Per Protocol Populations. The Per Protocol Population will be listed first and is the primary analysis*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
  - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
  - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
  - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone*
- *Sub-groups that will be analyzed (replacing treatment group):*
  - *MRSA vs. Non-MRSA (including no growth and contaminants for the Per Protocol Population.*
  - *MRSA and MSSA vs. all others (including no growth and contaminants for the Per Protocol Population.*

Table 18:
Summary of Fever by Study Day

Sub-trial *Population*				
	T1		**T2**	
	Number Respondents	**Have Fever n (%)**	**Number Respondents**	**Have Fever n (%)**
Study Days				
1	xxx	xx (xx.x)	xxx	xx (xx.x)
2	xxx	xx (xx.x)	xxx	xx (xx.x)
3	xxx	xx (xx.x)	xxx	xx (xx.x)
4	xxx	xx (xx.x)	xxx	xx (xx.x)
5	xxx	xx (xx.x)	xxx	xx (xx.x)
6	xxx	xx (xx.x)	xxx	xx (xx.x)
7	xxx	xx (xx.x)	xxx	xx (xx.x)
8	xxx	xx (xx.x)	xxx	xx (xx.x)
9	xxx	xx (xx.x)	xxx	xx (xx.x)
10	xxx	xx (xx.x)	xxx	xx (xx.x)
11	xxx	xx (xx.x)	xxx	xx (xx.x)
12	xxx	xx (xx.x)	xxx	xx (xx.x)
13	xxx	xx (xx.x)	xxx	xx (xx.x)
14	xxx	xx (xx.x)	xxx	xx (xx.x)

Note: Fever is defined as a recorded temperature > 38.0 degrees C or 100.4 degrees F.

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the Enrolled, OmITT, RmITT, FDAGEEP, and Per Protocol Populations. The Per Protocol Population will be listed first and is the primary analysis*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
  - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
  - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
  - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone*
- *Sub-groups that will be analyzed (replacing treatment group):*
  - *MRSA vs. Non-MRSA (including no growth and contaminants for the Per Protocol Population.*
  - *MRSA and MSSA vs. all others (including no growth and contaminants for the Per Protocol Population.*

Table 19:
Summary of Last Day of Recorded Fever by Study Day

Sub-trial Population			
	T1	T2	All Therapies
Number of Respondents	xxx	xxx	xxx
Study Days			
1	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)
5	xx (xx.x)	xx (xx.x)	xx (xx.x)
6	xx (xx.x)	xx (xx.x)	xx (xx.x)
7	xx (xx.x)	xx (xx.x)	xx (xx.x)
8	xx (xx.x)	xx (xx.x)	xx (xx.x)
9	xx (xx.x)	xx (xx.x)	xx (xx.x)
10	xx (xx.x)	xx (xx.x)	xx (xx.x)
11	xx (xx.x)	xx (xx.x)	xx (xx.x)
12	xx (xx.x)	xx (xx.x)	xx (xx.x)
13	xx (xx.x)	xx (xx.x)	xx (xx.x)
14	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Fever is defined as a recorded temperature > 38.0 degrees C or 100.4 degrees F.
The denominator for percentages is the number of respondents. The numerator is the number of subjects who reported their last day of fever on the study day being summarized.

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the Enrolled, OmITT, RmITT, FDAGEEP, and Per Protocol Populations. The Per Protocol Population will be listed first and is the primary analysis*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
  - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
  - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
  - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone*
- *Sub-groups that will be analyzed (replacing treatment group):*
  - *MRSA vs. Non-MRSA (including no growth and contaminants for the Per Protocol Population.*
  - *MRSA and MSSA vs. all others (including no growth and contaminants for the Per Protocol Population.*

Table 20:
Summary of Analgesic Use by Study Day

Sub-trial *Population*				
	T1		**T2**	
	Number of Subjects	**Used n (%)**	**Number of Subjects**	**Used n (%)**
Study Days				
1	xxx	xx (xx.x)	xxx	xx (xx.x)
2	xxx	xx (xx.x)	xxx	xx (xx.x)
3	xxx	xx (xx.x)	xxx	xx (xx.x)
4	xxx	xx (xx.x)	xxx	xx (xx.x)
5	xxx	xx (xx.x)	xxx	xx (xx.x)
6	xxx	xx (xx.x)	xxx	xx (xx.x)
7	xxx	xx (xx.x)	xxx	xx (xx.x)
8	xxx	xx (xx.x)	xxx	xx (xx.x)
9	xxx	xx (xx.x)	xxx	xx (xx.x)
10	xxx	xx (xx.x)	xxx	xx (xx.x)
11	xxx	xx (xx.x)	xxx	xx (xx.x)
12	xxx	xx (xx.x)	xxx	xx (xx.x)
13	xxx	xx (xx.x)	xxx	xx (xx.x)
14	xxx	xx (xx.x)	xxx	xx (xx.x)

Note: Use of analgesics is determined from the medications reported on the concomitant medication page. The number of subjects is the number of subjects in the study on the study day being summarized.

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the Enrolled, OmITT, RmITT, FDAGEEP, and Per Protocol Populations. The Per Protocol Population will be listed first and is the primary analysis*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
  - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
  - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
  - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone*
- *Sub-groups that will be analyzed (replacing treatment group):*
  - *MRSA vs. Non-MRSA (including no growth and contaminants for the Per Protocol Population.*
  - *MRSA and MSSA vs. all others (including no growth and contaminants for the Per Protocol Population.*

Table 21:
Summary of Last Day of Recorded Analgesic Use by Study Day

Sub-trial Population			
	T1	T2	All Therapies
Number of Subjects	xxx	xxx	xxx
Study Days			
1	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)
5	xx (xx.x)	xx (xx.x)	xx (xx.x)
6	xx (xx.x)	xx (xx.x)	xx (xx.x)
7	xx (xx.x)	xx (xx.x)	xx (xx.x)
8	xx (xx.x)	xx (xx.x)	xx (xx.x)
9	xx (xx.x)	xx (xx.x)	xx (xx.x)
10	xx (xx.x)	xx (xx.x)	xx (xx.x)
11	xx (xx.x)	xx (xx.x)	xx (xx.x)
12	xx (xx.x)	xx (xx.x)	xx (xx.x)
13	xx (xx.x)	xx (xx.x)	xx (xx.x)
14	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Use of analgesics is determined from the medications reported on the concomitant medication page. The denominator for percentages is the number of subjects. The numerator is the number of subjects who reported their last day of analgesic use on the study day being summarized.

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the Enrolled, OmITT, RmITT, FDAGEEP, and Per Protocol Populations. The Per Protocol Population will be listed first and is the primary analysis*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
  - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
  - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
  - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone*
- *Sub-groups that will be analyzed (replacing treatment group):*
  - *MRSA vs. Non-MRSA (including no growth and contaminants for the Per Protocol Population.*
  - *MRSA and MSSA vs. all others (including no growth and contaminants for the Per Protocol Population.*

Table 22:
Summary of Failure Characteristics for Subjects Classified as Clinical Failures

Sub-trial *Population*			
	T2 (P2) (N=xxx)	**T1 (P1) (N=xxx)**	**Difference (95% CI)**
Number of Clinical Failures, N	xxx	Xxx	
Occult Abscess found on Ultrasound	xx	Xx	xx.x (xx.x - xx.x)
Presence of Purulent Drainage	xx	Xx	xx.x (xx.x - xx.x)
Development of Invasive Infection	xx	Xx	xx.x (xx.x - xx.x)
Rescue Therapy Received	xx	Xx	xx.x (xx.x - xx.x)
Clindamycin	xx	Xx	xx.x (xx.x - xx.x)
TMP/SMX	xx	Xx	xx.x (xx.x - xx.x)
Doxy	xx	Xx	xx.x (xx.x - xx.x)
Continue for different rescue medicines	xx	Xx	xx.x (xx.x - xx.x)

Note:

N = the number of subjects classified as clinical failures.
P2 = n/N - where n = the number of subjects in the T2 treatment group with the specified characteristic.
P1 = n/N - where n = the number of subjects in the T1 treatment group with the specified characteristic

Programming Notes:

- *This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis. In addition, it will be summarized for the OmITT, RmITT, FDAGEEP, and Per Protocol Populations. The Per Protocol Population will be listed first and is the primary analysis*
- *Replace T1 and T2 in the headers with the actual name of the Treatments:*
  - *For Abscess Sub-trial - T2 = TMP/SMX, T1 = Placebo*
  - *For Infected Wound Sub-trial - T2 = Clindamycin, T1 = TMP/SMX*
  - *For Cellulitis Sub-trial - T2 = TMP/SMX + Cephalexin, T1 = Cephalexin alone*

Rescue Therapy Received will be modified based on the sub-trial being summarized.

10.4 Safety Parameters

Table 23:
Summary of All Adverse Events

Sub-trial *Safety Population*				
	T1 (N=xxx)		**T2 (N=xxx)**	
MedDRA System Organ Class/Preferred Term	**Clinical Cure n (%)**	**Clinical Failure n (%)**	**Clinical Cure n (%)**	**Clinical Failure n (%)**
Any Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gastrointestinal disorders	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Nausea	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diarrhea	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abdominal Pain Upper	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Continue for all Adverse Events	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note:

N = number of subjects in the population for the specified treatment group.
n = number of subjects with at least one adverse event in the category specified.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis.

Table 24:
Summary of All Serious Adverse Events

Sub-trial *Safety Population*				
	T1 (N=xxx)		**T2 (N=xxx)**	
MedDRA System Organ Class/Preferred Term	**Clinical Cure n (%)**	**Clinical Failure n (%)**	**Clinical Cure n (%)**	**Clinical Failure n (%)**
Any Serious Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gastrointestinal disorders	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Nausea	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diarrhea	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abdominal Pain Upper	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
....	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Continue for all Adverse Events	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note:

N = number of subjects in the population for the specified treatment group.
n = number of subjects with at least one adverse event in the category specified.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis.

Table 25:
Summary of Adverse Events by Severity and Relationship to Treatment

Treatment Group=T1

				Severity*				
Relatedness	**Subjects Experiencing AEs N(%)****	**All AEs N**	**Serious N(%)**	**Mild N(%)**	**Moderate N(%)**	**Severe N(%)**	**Life Threatening N(%)**	**Death N(%)**
Yes								
No								
Total								

Treatment Group=T2

				Severity*				
Relatedness	**Subjects Experiencing AEs N(%)****	**All AEs N**	**Serious N(%)**	**Mild N(%)**	**Moderate N(%)**	**Severe N(%)**	**Life Threatening N(%)**	**Death N(%)**
Yes								
No								
Total								

Table 26:
Summary of Related Adverse Events

Treatment Group=T1

				Severity*					Outcome*			
MedDRA System Organ Class/Preferred Term	Subjects Experiencing AEs N(%)**	All AEs N	Serious N(%)*	Mild N(%)	Moderate N(%)	Severe N(%)	Life-Threatening N(%)	Death N(%)	Ongoing N(%)	Resolved w/o Sequelae N(%)	Resolved with Sequelae N(%)	Death N(%)

Treatment Group=T2

				Severity*					Outcome*			
MedDRA System Organ Class/Preferred Term	Subjects Experiencing AEs N(%)**	All AEs N	Serious N(%)*	Mild N(%)	Moderate N(%)	Severe N(%)	Life-Threatening N(%)	Death N(%)	Ongoing N(%)	Resolved w/o Sequelae N(%)	Resolved with Sequelae N(%)	Death N(%)

Table 27:
Summary of Serious Adverse Events by Severity and Relationship to Treatment

Treatment Group=T1

				Severity*				
Relatedness	**Subjects Experiencing AEs N(%)****	**All AEs N**	**Serious N(%)**	**Mild N(%)**	**Moderate N(%)**	**Severe N(%)**	**Life Threatening N(%)**	**Death N(%)**
Yes								
No								
Total								

Treatment Group=T2

				Severity*				
Relatedness	**Subjects Experiencing AEs N(%)****	**All AEs N**	**Serious N(%)**	**Mild N(%)**	**Moderate N(%)**	**Severe N(%)**	**Life Threatening N(%)**	**Death N(%)**
Yes								
No								
Total								

Table 28:
Summary of On-study Pregnancies

	Dates					
Subject ID	**Reported Pregnancy Date**	**Pregnancy Test Date**	**First Dose**	**Last Dose**	**Estimated Date of Confinement**	**Subject Elects to:**

Table 29:
Listing of Serious Adverse Events

Subject ID	Adverse Event Description	MedDRA System Organ Class	MedDRA Preferred Term	Onset Date	Resolution Date	Severity	Relationship to Study Product	Alternate Etiology if not Associated	Outcome

Table 30.1:
Summary of Susceptibility Testing for MRSA

Sub-trial *All Subjects*			
	Therapy		
Antimicrobials	**T1** **n (%) C**	**T2** **n (%) C**	**All Therapies** **n (%) C**
Oxacillin			
Susceptible	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Resistant	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Indeterminate	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Not Tested	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Total	xxx (100.0%) xx	xxx (100.0%) xx	xxx (100.0%) xx
Tetracycline			
Susceptible	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Resistant	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Indeterminate	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Not Tested	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Total	xxx (100.0%) xx	xxx (100.0%) xx	xxx (100.0%) xx
Erythromycin			
Susceptible	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Resistant	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Indeterminate	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Not Tested	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Total	xxx (100.0%) xx	xxx (100.0%) xx	xxx (100.0%) xx
Continue for all antimicrobials tested			

Note:
Susceptibility testing was performed for all pathogens that were identified as MRSA or MSSA and for other selected pathogens identified by the clinician.
n = the number of isolates.
% = number of isolates/total number of isolates.
C = the number of cases.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 30.2:
Summary of Susceptibility Testing for MSSA

Sub-trial *All Subjects*			
	Therapy		
Antimicrobials	**T1** **n (%) C**	**T2** **n (%) C**	**All Therapies** **n (%) C**
Oxacillin			
Susceptible	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Resistant	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Indeterminate	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Not Tested	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Total	xxx (100.0%) xx	xxx (100.0%) xx	xxx (100.0%) xx
Tetracycline			
Susceptible	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Resistant	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Indeterminate	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Not Tested	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Total	xxx (100.0%) xx	xxx (100.0%) xx	xxx (100.0%) xx
Erythromycin			
Susceptible	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Resistant	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Indeterminate	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Not Tested	xxx (xx.x%) xx	xxx (xx.x%) xx	xxx (xx.x%) xx
Total	xxx (100.0%) xx	xxx (100.0%) xx	xxx (100.0%) xx
.....			
Continue for all antimicrobials tested			

Note:
Susceptibility testing was performed for all pathogens that were identified as MRSA or MSSA and for other selected pathogens identified by the clinician.
n = the number of isolates.
% = number of isolates/total number of isolates.
C = the number of cases.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 30.3:
Summary of Susceptibility Testing for Any Streptococcus Species

Sub-trial *All Subjects*			
	Therapy		
Antimicrobials	**T1** **n (%)**	**T2** **n (%)**	**All Therapies** **n (%)**
Oxacillin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Tetracycline			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Erythromycin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
.....			
Continue for all antimicrobials tested			

Note:
Susceptibility testing was performed for any Streptococcus species identified by the clinician.
n = the number of isolates.
% = number of isolates/total number of isolates.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 31.1:
Summary of Susceptibility Testing for Cases Susceptible to MRSA Only

Sub-trial *All Subjects*			
	Therapy		
Antimicrobials	**T1** **n (%)**	**T2** **n (%)**	**All Therapies** **n (%)**
Oxacillin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Tetracycline			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Erythromycin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
.....			
Continue for all antimicrobials tested			

Note:
Only cases where MRSA was the only organism isolated are summarized on this table.
n = the number of cases.
% = number of cases/total number of cases.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 31.2:
Summary of Susceptibility Testing for Cases Susceptible to MSSA Only

Sub-trial *All Subjects*			
	Therapy		
Antimicrobials	**T1** **n (%)**	**T2** **n (%)**	**All Therapies** **n (%)**
Oxacillin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Tetracycline			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Erythromycin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
.....			
Continue for all antimicrobials tested			

Note:
Only cases where MSSA was the only organism isolated are summarized on this table.
n = the number of cases.
% = number of cases/total number of cases.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 31.3:
Summary of Susceptibility Testing for Cases Susceptible to Any Streptococcus Species Only

Sub-trial *All Subjects*			
	Therapy		
Antimicrobials	**T1** **n (%)**	**T2** **n (%)**	**All Therapies** **n (%)**
Oxacillin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Tetracycline			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Erythromycin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
.....			
Continue for all antimicrobials tested			

Note:
Only cases where any Streptococcus species is the only organism isolated are summarized on this table.
n = the number of cases.
% = number of cases/total number of cases.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 31.4:
Summary of Susceptibility Testing for Cases Susceptible to MRSA and MSSA

Sub-trial *All Subjects*			
	Therapy		
Antimicrobials	**T1** **n (%)**	**T2** **n (%)**	**All Therapies** **n (%)**
Oxacillin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Tetracycline			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Erythromycin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
.....			
Continue for all antimicrobials tested			

Note: Only cases where MRSA and MSSA are the only organisms isolated are summarized on this table. If all isolates (MRSA or MSSA) are susceptible to an antimicrobial or if at least one isolate is susceptible and the other(s) is not tested, then the case will be counted as susceptible. If at least one isolate is resistant to an antimicrobial, then that antimicrobial will be counted as resistant. If at least one isolate is indeterminate and the other(s) isolate is susceptible, then that antimicrobial will be counted as indeterminate.
n = the number of cases.
% = number of cases/total number of cases.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 31.5:
Summary of Susceptibility Testing for Cases Susceptible to MRSA and Any Streptococcus Species

Sub-trial *All Subjects*			
	Therapy		
Antimicrobials	**T1** **n (%)**	**T2** **n (%)**	**All Therapies** **n (%)**
Oxacillin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Tetracycline			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Erythromycin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
.....			
Continue for all antimicrobials tested			

Note: Only cases where MRSA and any Streptococcus species are the only organisms isolated are summarized on this table. If all isolates (MRSA or any Streptococcus species) are susceptible to an antimicrobial or if at least one isolate is susceptible and the other(s) is not tested, then the case will be counted as susceptible. If at least one isolate is resistant to an antimicrobial, then that antimicrobial will be counted as resistant. If at least one isolate is indeterminate and the other(s) isolate is susceptible, then that antimicrobial will be counted as indeterminate.
n = the number of cases.
% = number of cases/total number of cases.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 31.6:
Summary of Susceptibility Testing for Cases Susceptible to MSSA and Any Streptococcus Species

Sub-trial *All Subjects*			
	Therapy		
Antimicrobials	**T1** **n (%)**	**T2** **n (%)**	**All Therapies** **n (%)**
Oxacillin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Tetracycline			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Erythromycin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
.....			
Continue for all antimicrobials tested			

Note: Only cases where MSSA and any Streptococcus species are the only organisms isolated are summarized on this table. If all isolates (MSSA or any Streptococcus species) are susceptible to an antimicrobial or if at least one isolate is susceptible and the other(s) is not tested, then the case will be counted as susceptible. If at least one isolate is resistant to an antimicrobial, then that antimicrobial will be counted as resistant. If at least one isolate is indeterminate and the other(s) isolate is susceptible, then that antimicrobial will be counted as indeterminate.
n = the number of cases.
% = number of cases/total number of cases.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 31.7:
Summary of Susceptibility Testing for All Organisms

Sub-trial Population			
	Therapy		
Antimicrobials	**T1 n (%)**	**T2 n (%)**	**All Therapies n (%)**
Oxacillin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Tetracycline			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Erythromycin			
Susceptible	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Resistant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indeterminate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Tested	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Total	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
.....			
Continue for all antimicrobials tested			

Note: All organisms are summarized on this table. If all isolates are susceptible to an antimicrobial or if at least one isolate is susceptible and the other(s) is not tested, then the case will be counted as susceptible. If at least one isolate is resistant to an antimicrobial, then that antimicrobial will be counted as resistant. If at least one isolate is indeterminate and the other(s) isolate is susceptible, then that antimicrobial will be counted as indeterminate.
n = the number of cases.
% = number of cases/total number of cases.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

Table 32:
Summary of Expected Versus Observed Cure Rates for Microbiologic Susceptibility

Sub-trial *Population*				
	T1		**T2**	
Visit	**Observed Cure n (%)**	**Expected Cure n (%)**	**Observed Cure n (%)**	**Expected Cure n (%)**
On-Therapy Visit				
End of Therapy Visit				
Test of Cure Visit				

Note: Expected cure rates are based on the antimicrobial resistance rates.

Programming Notes: This table will be created for each Sub-trial: Abscess, Infected Wound, and Cellulitis and for each population, enrolled, per protocol, OmITT, RmITT, and FDAGEEP populations.

For the abscess sub-trial, there will only be one treatment group, TMP/SMX, that will be summarized.

Table 33:
Summary of C. difficile Toxin Assay by Visit

Sub-trial Population			
	Therapy		
	T1 n (%)	**T2 n (%)**	**All Therapies n (%)**
On-Therapy Visit			
Number C. difficile tested			
Absent			
Present			
End of Therapy Visit			
Number C. difficile tested			
Absent			
Present			
Test of Cure Visit			
Number C. difficile tested			
Absent			
Present			
Extended Follow-up Visit			
Number C. difficile tested			
Absent			
Present			

Table 34:
Summary of Vital Signs by Visit

	Therapy		
	T1 (N)	**T2 (N)**	**All Therapies (N)**
Temperature (C)			
Day 1			
n			
Mean (SD)			
On Therapy Visit			
n			
Mean (SD)			
Change from Day 1			
Mean (SD)			
Min, Max			
EOT Visit			
n			
Mean (SD)			
Change from Day 1			
Mean (SD)			
Min, Max			
TOC Visit			
n			
Mean (SD)			
Change from Day 1			
Mean (SD)			
Min, Max			
Extended FU Visit			
n			
Mean (SD)			
Change from Day 1			
Mean (SD)			
Min, Max			
Continue for all Vital Signs - Systolic Blood Pressure, Diastolic Blood Pressure, Pulse, Respiratory Rate			

Note:
n = Number of subjects with vital sign measurements available at both the visit and the Day 1 visit. Only subjects with vital sign measurements available from both visits are included in these evaluations.