Duke Center for Antimicrobial Stewardship and Infection Prevention

De-escalating Empiric Treatment: Opting-Out of Rx for Selected Patients with Suspected Sepsis

The DETOURS Trial

DETOURS

De-escalating Empiric Treatment: Opting OUt of Rx for Selected Patients with Suspected Sepsis

Funding Sponsor:

Centers for Disease Control and Prevention (CDC)

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STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the applicable principles and regulatory requirements from the United States Code of Federal Regulations (CFR), including 21 CFR 56 (institutional review board [IRB]) and 21 CFR 50 (informed consent) and to the principles outlined in applicable ICH guidelines.

STUDY PRINCIPAL INVESTIGATOR SIGNATURE

The signature below documents the review and approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. federal regulations and ICH guidelines.

Rebekah Moehring, MD, MPH

Study Principal Investigator

2/8/2019

Signature

Date

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LIST OF ABBREVIATIONS

CMS	Centers for Medicare and Medicaid
SEP-1	Sepsis Core Measure
NHSN	National Healthcare Safety Network
AUR	Antimicrobial Use and Resistance
Antibiotic	Any medications included in the “antibacterial” category in the NHSN AUR module Appendix 3
Sepsis Bundle	Hospital-specific implementation process that includes the elements of the Surviving Sepsis Campaign’s 3- (includes initiation of broad-spectrum antibiotics) and 6- hour bundle used to evaluate SEP-1 Core Measure compliance
Opt-Out Procedure	Hospital-specific implementation process for the designated pharmacist to notify an ordering prescriber that patient meets DETOURS criteria for antibiotic de-escalation.

PROTOCOL SYNOPSIS

Protocol Title:	**DETOURS Trial: De-escalating Empiric Treatment: Opting-OUt of Rx for Selected Patients with Suspected Sepsis – Opt-out Protocol Trial**
Phase:	Not Applicable
Products:	Not Applicable
Objectives:	To determine the effectiveness of an opt-out protocol in reducing antibiotic use among qualifying, non-ICU, acute care patients with suspected sepsis.
Study Design:	Prospective, multicenter, randomized controlled trial
Study Population:	Non-ICU patients: 1) empirically started on antibiotics for suspected sepsis and 2) remain on antibiotics 3 days (48-96 hours) later, and 3) have negative blood cultures
Number of Participants:	762
Number of Sites:	Projected to include 10 hospitals (3 academic and 7 community hospitals)
Duration of Participant Participation:	30 days
Dose Schedule:	Not Applicable
Estimated Start:	May 1, 2018
Estimated Time to Complete Enrollment:	2 years

Protocol Version History

1.0 – Submitted to Duke University Health System IRB

2.0 –

3.0 – Change in screening timing from 48-72h to 48-96h

4.0 – Change in primary outcome to inpatient plus post-discharge DOT. Updated power and sample size calculations.

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Severe sepsis has high associated mortality.[1-3] The Surviving Sepsis Campaign (SSC) promotes guidelines to decrease this high mortality that include protocol-driven, goal-oriented resuscitation within the first 6 hours of sepsis onset.[4-6] A key focus of SSC is rapid administration of broad-spectrum antibiotics.[4,7,8]

The Centers for Medicare/Medicaid Services (CMS) recently mandated the NQF-endorsed SEP-1 Core Measure.[9] As of October 1, 2015, all US hospitals must rapidly identify and treat patients with suspected sepsis to receive full CMS reimbursement. In response, most hospitals have implemented a "sepsis bundle" process, including antibiotic administration within 3 hours of sepsis onset. The SEP-1 measure and most hospital sepsis bundle processes do not, however, include important follow-up care outlined in SSC guidelines: a daily review to de-escalate or discontinue antibiotic treatment in appropriate patients.

2.2 Scientific Rationale

Though intended to improve outcomes, some process measures lead to adverse outcomes, including unnecessary antibiotic use and increased rates of *C. difficile*.[10,11] Similar concerns have been raised regarding the SEP-1 Core Measure.[12] Yet, the risk of excess antibiotic use from SEP-1 has not been addressed.

Similarly, novel strategies to improve de-escalation of antibiotic therapy after initiation for suspected sepsis are warranted, but analyses of antimicrobial stewardship interventions are hampered by numerous methodological challenges.[13] As a result, the NIAID's Antibacterial Resistance Leadership Group (ARLG) recently proposed a new paradigm for evaluating risks and benefits in trials of stewardship interventions.[13] This novel methodology, termed Desirability of Outcomes Ranking (DOOR)/Response Adjusted for Duration of Antibiotic Risk (RADAR), can better determine the impact of strategies to simultaneously reduce excess antibiotic exposures and improve patient outcomes.

Our ***long-term goal*** is to identify effective antimicrobial stewardship strategies that improve patient outcomes and decrease the risk of multidrug-resistant organisms (MDROs) and healthcare-associated infections (HAIs). The ***overall objective*** of this proposal is to develop and determine the efficacy of an opt-out protocol for antibiotic de-escalation on rates of antibiotic utilization and DOOR among qualifying non-ICU patients with suspected sepsis. We will achieve this objective by using the strengths of the Duke-UNC Prevention Epicenter, the Duke Antimicrobial Stewardship Outreach Network (DASON), and the Washington University and University of Pennsylvania Prevention Epicenters. This collaborative investigation will capitalize on our collective expertise in stewardship research and practice, expertise in and infrastructure for clinical trials, and robust data sources and analytics. Our ***central hypothesis*** is that use of an opt-out protocol for antibiotic de-escalation in qualifying non-ICU patients will lead to decreased antibiotic use and improved patient outcomes compared to control patients.

Summary. Sepsis has high associated mortality. Hospitals and regulatory agencies have worked to address sepsis care through core measures and bundled processes. However, important follow-up care, including re-assessments of antibiotic regimens and antibiotic de-escalation, are not strongly implemented. This study investigates **the use of a novel, opt-out protocol to guide**

appropriate antibiotic de-escalation among those patients with suspected sepsis meeting rigorous safety checks.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

General Approach

At its core, we believe this project utilizes a quality-improvement approach. That is, we are implementing a protocol to inform and assist in antibiotic decision-making practices that are recommended in both sepsis[6] and antimicrobial stewardship[14] guidelines. We accept, however, that the proposed study will likely be labeled as "research" under 45 CFR 46.102(b) because the proposed systematic investigation is federally funded, involves multiple centers, and is being performed to provide generalizable information. Furthermore, we believe the research will be "human subjects research" under 45 CFR 46.102(f) because it will include identifiable patient information during the course of our study.

Anticipated Risks & Discomforts

We believe the study poses minimal risk to patient privacy. The study requires the prospective collection of existing clinical data. These data already exist within patients' medical records and include data routinely collected by Antimicrobial Stewardship personnel as part of routine operations. Additional process data regarding the implementation of the protocol, however, will be obtained. These data will require study identifiers (including medical record numbers) to link them to the patient outcomes. We believe that the privacy risk associated with these additional data points is minimal given the data security & privacy protections planned. All study investigators and staff have been trained in human subjects research and HIPAA regulations.

The study involves the implementation of prompts and guidance for de-escalation decisions to prevent adverse outcomes among patients with suspected sepsis and broad spectrum antibiotic exposures. We do not believe the opt-out protocol intervention will lead to additional risk for the patient. In fact, we believe that the patients participating in the study will be more likely to improved care and outcomes because of the study. One potential risk is that antibiotics might be inappropriately stopped in patients who are, in-fact, at risk of sepsis or have a clinical infection that requires antibiotic therapy. First, this risk has been thoroughly and carefully considered in design of the opt-out protocol itself and a rigorous safety check prior to employing the opt-out procedure. A 10-month protocol development process was undertaken by the DETOURS expert panel, that included CDC experts as well as academic and clinical experts in sepsis and infectious diseases at CDC Prevention Epicenters, Duke, and DASON sites. A modified Delphi approach with four rounds of electronic surveys and multiple interim web/phone conferences resulted in development of the current list of safety screen checklist factors to adequately exclude at-risk patients and better identify appropriate patients for antibiotic de-escalation. Second, as part of the "opt-out" mechanism for the protocol, the treating provider maintains autonomy and responsibility for antibiotic treatment decisions at all times. Thus, although the protocol is offered as a decision support tool, the ultimate decision-making still remains with the treating provider. Like other persuasive antimicrobial stewardship interventions (e.g. post-prescription review and feedback), we believe this intervention qualifies as a quality improvement activity that provides support for decision-making rather than removing autonomy from prescribers. See Section 16 for additional information regarding why we believe this study is a minimal risk study.

2.3.2 Benefits

Patients may benefit from this study if our intervention is successful and the use of an opt-out protocol for antibiotic de-escalation leads to a decrease in unnecessary antibiotic exposures and, therefore, the risks of adverse effects due to excess antimicrobial use, which may include avoidance of *C. difficile* infections, adverse drug events, and future antibiotic-resistant infections. This trial will also be the largest to use DOOR/RADAR methodology for evaluation of an antimicrobial stewardship intervention.

3 OBJECTIVES

The purpose of this quality improvement study is to determine the efficacy of an opt-out protocol for antibiotic de-escalation on rates of antibiotic utilization and DOOR among eligible patients with suspected sepsis.

3.1 Study Hypotheses and Objectives

3.1.1 Hypotheses

Primary Hypothesis

Eligible patients randomized to receive care guided by the opt-out protocol (intervention) will have reduced antibiotic days of therapy (DOT) compared to eligible control patients

Secondary Hypothesis

1. Patients in the intervention arm will have a 50% probability of a better DOOR compared to control patients.
2. Patients in the intervention arm will have reduced antibiotic-related adverse events, including *C. difficile* infection, compared to control patients.
3. Patients in the intervention arm will have equivalent rates of negative clinical outcomes such as mortality, length of stay, and subsequent ICU transfer compared to control patients.

3.1.2 Primary Objectives

To determine if the DETOURS opt-out protocol for antibiotic de-escalation will lead to reduction in antibiotic use among eligible patients identified with suspected sepsis.

3.1.3 Secondary Objectives

To determine if the DETOURS opt-out protocol for antibiotic de-escalation will lead to improvement in DOOR among eligible patients identified with suspected sepsis.

To determine if the DETOURS opt-out protocol for antibiotic de-escalation will lead to reduction in *C. difficile* infections among eligible patients identified with suspected sepsis.

To determine if the DETOURS opt-out protocol for antibiotic de-escalation will lead to change in patient outcomes among eligible patients identified with suspected sepsis, including in-hospital mortality, length of stay, and subsequent ICU transfer compared to eligible patients in control units.

4 STUDY DESIGN

The DETOURS study will be a prospective, multicenter randomized controlled trial. The active component of the quality improvement study will be performed over approximately 2 years, from April 2018 through February 2020.

4.1 Study Population

4.1.1 Selection of the Study Population

Subjects will be recruited from hospitals participating in either the CDC Prevention Epicenters Program or the Duke Antimicrobial Stewardship Outreach Network (DASON) (**Appendix 1**). The CDC Prevention Epicenters Program is a government-funded, 4-year grant that allows for collaboration on several projects dealing with infection diseases in healthcare. From the Epicenters Program, Washington University in St. Louis and the University of Pennsylvania will be collaborating with Duke University on this project. DASON is a network of 29 community hospitals in the United States designed to improve outcomes for patients and hospitals by optimizing antimicrobial use.

4.1.2 Inclusion/Exclusion Criteria

Inclusion criteria: All acute care, adult, non-ICU patients with suspected sepsis are potentially eligible for intervention if they meet the following criteria:

1. Blood culture preliminary results that indicate no growth as of 48-96 hours.
    a. Exception: Patients with a single positive blood culture for coagulase negative Staphylococcus and no central line in place will also be included.

AND

2. Still on broad spectrum antibiotic therapy after 48-96 hours.
    a. Broad spectrum antibiotics will be defined by agent as described in the rank list below (Table 1). Any agent in the 2, 3, or 4 rank categories will be considered broad spectrum.

Table 1. Spectrum rank categories for commonly used antimicrobial agents.

Narrow spectrum	Broad spectrum	Extended spectrum, including MDRO and Pseudomonas	Protected
1	2	3	4
1st- and 2nd-generation cephalosporins Amoxicillin TMP/SMX Nafcillin, Oxacillin Metronidazole Doxycycline Nitrofurantoin Penicillin	Ceftriaxone 3rd-generation oral cephalosporins Azithromycin Clarithromycin Amoxicillin/clavulanate Ampicillin/sulbactam Clindamycin	Anti-pseudomonal penicillins Fluoroquinolones Aminoglycosides Vancomycin Cefepime, Ceftazidime Ertapenem Aztreonam	Anti-pseudomonal Carbapenem Colistin Tigecycline Linezolid, Tedizolid Daptomycin Ceftaroline Ceftazidime/avibactam Ceftolozane/tazobactam

Exclusion criteria: Adult patients who are located in ICU wards will not be eligible for enrollment.

Any patient meeting eligibility criteria described above will be included without regard to adult age, gender, race, insurer status, or other discriminating variables. Patients will be enrolled only once, even if they meet eligibility criteria a second time within the study period.

4.1.3 Treatment Assignment Procedures

Individual patients will be randomized to intervention or control (1:1). Participating sites will be provided site-specific randomization schema to ensure adequate representation of each arm within individual study sites.

4.1.4 Stewardship Strategy Descriptions

General principles

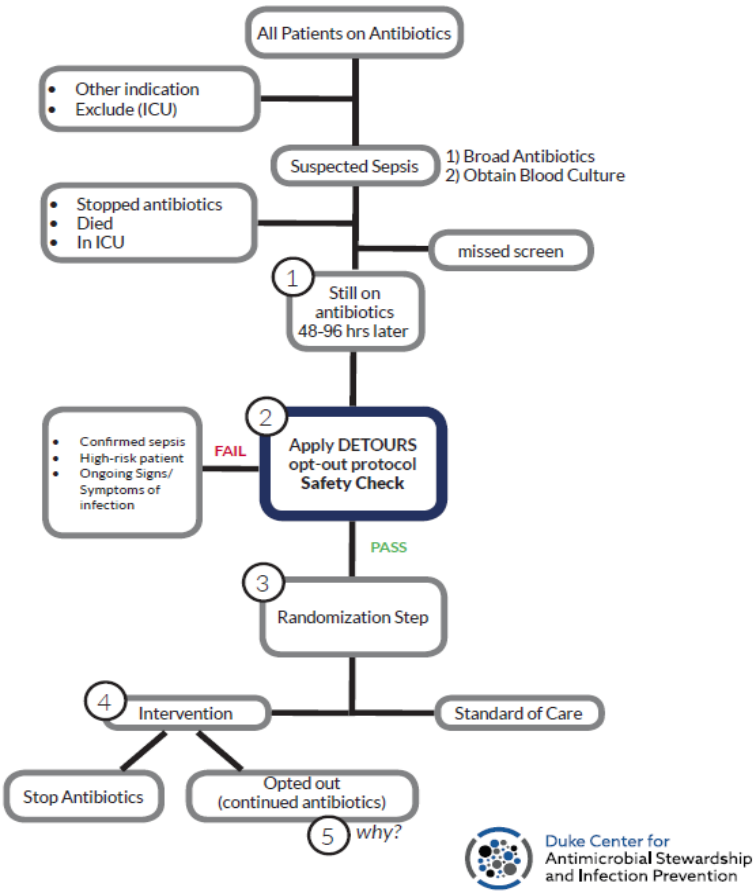
Initial management of patients with suspected sepsis will occur according to local site practices. That is, the study protocol will not direct site physician practice regarding the use of specific antibiotics.

Our intervention represents the operationalization of a combined strategy of routine reassessment of patients with suspected sepsis and consideration for discontinuation of antibiotics or narrowing the spectrum and/or number of antibiotics. The intervention has been vetted through the DETOURS expert panel as described in Section 2 "Risks." Eligible patients will begin the protocol by default (ie, a patient-specific order will not be required). Each study site will implement the opt-out protocol in the method that best fits their local preferences, clinical work flow, and personnel. Personnel performing assessments of inclusion criteria and interacting directly with providers may vary slightly depending on local resources and strategy. In general, the opt-out protocol is designed for use by clinical pharmacists or centralized antibiotic stewardship pharmacists in interacting with primary providers (e.g. physicians, mid-level providers). This process will be modeled after the communication mechanism for pharmacy-led IV-to-PO conversion policies at each site.

OPT-OUT PROTOCOL

Eligible patients will be selected from the pool of patients receiving antibiotic therapy (Figure 1). The **Opt-out Protocol** includes five steps (numbers 1-5 in Figure 1). Additional documents summarizing these steps are provided in Appendix 2. Eligible patients must pass each sequential step to proceed to the next step:

Figure 1. Enrollment flow chart



1. Eligibility screen
2. Safety Check
3. Randomization
4. Opt-Out Procedure
5. Guided De-escalation Discussion

Designated personnel will screen patients at study sites on a daily basis, if possible, and on weekdays with catch-up procedures on Mondays only if necessary due to personnel constraints.

Eligibility Screen

First, a unit census list, list of preliminary blood culture results, and active antibiotic orders will be screened to apply the inclusion criteria. Patients meeting initial inclusion criteria (negative blood culture results at 48-96 hours and broad-spectrum antibiotics), will then undergo the Safety Check.

Safety Checklist

The Opt-Out Protocol was designed to ensure patient safety. Thus, all eligible patients go through a safety check prior to implementation of the Opt-Out Procedure (Table 2). Appendix 2 provides additional definitions and instructions for the Checklist components. Patients meeting any one of the checklist criteria will be considered "high risk" and will be excluded from the Opt-out Procedure; antibiotics will be continued per standard care processes. However, if none of the Safety Screen Checklist criteria are met, the subject will undergo randomization.

Table 2. Safety Screen Checklist

Safety Check Patient fails if meets one or more of the following critera

1. Ongoing Signs/ Symptoms of Infection
- continued fever
- new chest x-ray infiltrate
- empyema
- lung abscess
- continued significant leukocytosis

2. Concerning/Inadequate Microbiological Data
- positive blood cultures*

*Note: OK to stop if contaminant and no central line
- positive microbiological data
- no cultures during sepsis work-up
- antibiotic use prior to blood culture

3. High-Risk Comorbidy/Severe Illness
- bronchiectasis
- asplenia/splenectomy
- cystic fibrosis
- pregnant
- recent I&D procedure
- ongoing respiratory insufficiency
- immunocompromised
  - HIV/AIDS with CD4 count < 200
  - taking immunosuppressive agents
  - agammaglobulinemia
  - bone marrow aplasia
  - neutropenia
  - transplant recipient

Randomization

Subjects who pass the Safety Checklist will be randomized to intervention (the Opt-Out Procedure) or control (standard care, no interaction with study team). Each study site will be provided with a randomization scheme.

Opt-out Procedure

The assessor will approach the primary provider in charge of antibiotic decision-making either one-on-one in person, on team rounds, or by phone/pager contact as per local preference. The assessor will inform the provider:

"[This patient] has passed the initial safety screen for de-escalation of antibiotics. Antibiotics will be stopped per protocol unless you opt-out."

If the provider or clinical team agrees to stop antibiotics, then orders will be changed to reflect this decision.

Guided De-escalation Discussion
If the provider or clinical team opts out and elects to continue antibiotics, the assessor will proceed with a series of the questions and dialogue that captures the provider's rationale for continuing antibiotics, promotes and references local empiric therapy guidelines and the antibiotic rank chart (Table 1 above), encourages use of microbiology data to narrow antibiotics, and suggests clinical reassessment (guided discussion questions listed in Appendix 2, Step 5).

PROPOSED IMPLEMENTATION STRATEGY

Implementation of the proposed opt-out protocol will require a multi-disciplinary team, local champions, and data feedback and response. The Engage, Educate, Execute, and Evaluate method for Quality Improvement will be used as the model for implementation.[15] The following is a general overview of the proposed implementation strategy.

Leadership

A. Advisory Group – CDC Prevention Epicenter Programs and DASON Liaisons
B. Local Champion(s) on each enrolled unit
    a. Physician champion
    b. Pharmacist champion
C. Site Leader – TBD by each hospital
D. Data Collection and Feedback Leader

Engage-- All leaders will discuss the importance of 1) judicious antibiotic use and improving outcomes for patients with suspected sepsis and 2) the need for better methods for antibiotic reassessment including de-escalation and appropriate durations. Site Champions and Epicenter personnel should identify allies within each unit that can fill the Leadership roles described above. Local leaders will need to identify potential barriers to implementation while education is occurring to optimize protocol adherence.

In addition, CDC's involvement will provide additional validity to the project and will ensure participating personnel know they are involved in an important, large quality improvement project with both local and national implications. As such, Epicenter/CDC personnel will need to discuss the overall purpose of the project with local personnel, including issues related to definitions for sepsis, de-escalation, strategy, and integrating study activities into daily routines and existing antibiotic stewardship program goals.

Educate – Education will begin with a "kick-off" interactive discussion with study site personnel and champions, likely performed via live webinar. This webinar would include discussion of the following:

A. Rationale for de-escalation and the opt-out protocol
B. Sepsis core measure and local approaches to improve sepsis care

C. Methods used to create opt-out protocol
D. Questions and Answers

All leaders will discuss opt-out protocol and best methods for implementation. Local champions and national experts will then discuss opt-out protocol with local unit personnel (with aid of members of the Advisory Group, as needed). Local champions will need to vet intervention with local staff. Ideally, webinar(s) could be repeated at least once to increase the number of participants. Similarly, the webinar(s) would be recorded for people who were unable to attend the live webinar session(s).

We will create binders containing opt-out protocol details and educational materials for use at each site. Additional educational materials will be created and provided throughout the study, including posters, handouts, laminated protocol cards, bibliography of relevant literature, and powerpoint presentations. Local champions will be encouraged to use these materials to conduct their own educational activities. These materials can be disseminated to local units, though each individual Epicenter will need to determine a way to produce, pay for, and disseminate the materials.

Biweekly calls will be offered to personnel to share challenges and successes and to get input from the Advisory Committee.

Finally, there may be value in having a mid-intervention "back to basics" webinar, during which much of the initial educational materials are reiterated. In addition, this would be an opportunity to address on-going questions/issues and provide broader feedback (ie, performance of the group).

Execute – Following the education blitz described above, each study site will implement the opt-out protocol. The standardized opt-out protocol will be provided to each site in the form of laminated cards, as costs allow. As described in the "Evaluate" section, data feedback will lead to opportunities to improve adherence to the protocol by identifying correctable defects.

Individual sites will need to determine some of the details of the implementation based on local preferences and hospital dynamics:

A. Specifics of the opt-out protocol
B. Personnel identified to perform the initial eligibility screen and safety checklist
C. Preferences for communication to primary providers: timing, method, and location for opt-out procedure and de-escalation discussions
D. Personnel responsible for documenting interventions and outcomes of the discussions

Study sites that make changes to the protocol based on the above will need to provide these changes to the central study team.

Evaluate – We will provide site-specific data feedback on protocol compliance to individual study site leaders (Unit Champion and Point Project Lead) every 4 weeks. Study leaders would be responsible for disseminating information to the unit staff. RAs (or other leadership personnel) can help with creation of posters and/or handouts to provide progress updates. Leadership and local personnel will identify and respond to issues identified (ie, lack of adherence or participation), with support from the Advisory Committee. Ideally, site-specific data will be contrasted with de-identified data from the other participating units to generate inter-unit competition.

4.1.5 Termination of Study

This study may be terminated at any time by the principal investigator (PI) in consultation with the CDC and collaborating academic institutions. Otherwise, the study will be terminated at the end of enrollment, analysis, and publication of findings.

5 STUDY PROCEDURES

5.1 Data Collection

The following endpoints will be collected for analysis in this quality improvement study.

Endpoints

Primary endpoint:

1) Antibiotic utilization measured as antibacterial Days of Therapy (DOT) among randomized patients.
    a. Definitions
        i. Days of therapy (DOT) is defined as the number of calendar days of antibacterial agent exposure. A DOT is counted for any amount of antimicrobial given on that calendar day. For example, administration of cefazolin as a single dose or as 3 doses given 8 hours apart but within the same 24-hour period both represent 1 DOT. Single agents are counted separately and then summed. For example, administration of vancomycin plus ceftazidime on the same calendar day would represent 2 DOT for the same calendar day.
        ii. Antibacterial agents will be defined by NHSN AU Module antimicrobial category="Antibacterial" (see Appendix 3). Antibiotics added to the NHSN AU option during the study (e.g. if newly FDA-approved), will be added to the study protocol Table as needed.
            1. "Luminal" antibiotics that do not achieve adequate distribution for treatment of systemic infections will be excluded as follows: oral vancomycin, fidaxomicin, and rifaxamin.
            2. Route of antibacterials will be limited to those identified in the NHSN AU module given by digestive, intravenous, inhaled, or intramuscular.
    b. Measurement of DOT will start one day after randomization to ensure antibacterial agents given prior to randomization are not included in outcome.
    c. Measurement will include inpatient DOT plus intended post-discharge antibacterial DOT through 30 days post-randomization.
        i. Post-discharge antibacterial DOT will be limited to the planned DOT/duration at the time of discharge
        ii. DOT associated with readmissions during the 30-day post-randomization period will not be included in the primary endpoint, but will be included in measurement of adverse events.

Table 3. DETOURS Desirability of Outcome Ranking (DOOR) Outcome

Outcome	Rank
Alive	1
Readmission, relapse of suspected sepsis, *C. difficile* infection, OR deep venous thrombosis	2
≥2 of items in Rank 2 above	3
Subsequent ICU Admission OR hemodialysis	4
Subsequent ICU Admission AND hemodialysis	5

Death	6

Secondary endpoints:

1) DOOR/RADAR, according to criteria developed in DETOURS-Retro (Pro00076818; Table 3). See Section 7 for definitions of these and other outcomes.
2) Safety outcomes potentially related to antibiotic treatments:
    a. Individual clinical outcome components in the DOOR (Table 3)
    b. Number of hospital days within 30-days post-randomization
    c. Re-initiation of antibiotic therapy after >48 hours of no antibiotics within 30-days post-randomization
    d. Need for new PICC line insertion within 30-days post-randomization
    e. Central line days within 30-days post-randomization.
3) Process indicators:
    a. Percent of eligible patients with antibiotic de-escalation by day 5, according to an electronic definition of de-escalation
    b. Of those patients eligible for assessment of de-escalation per the Safety Checklist:
        i. Number of eligible patients in whom the safety screen was applied.
        ii. Number patients the safety screen excluded from the opt-out procedure
        iii. Number of eligible patients in whom the opt-out procedure was employed
        iv. Number of eligible patients in whom the prescriber chose to opt-out
            1. Prescriber type (e.g. physician, APC, trainee, specialty service consultant (e.g. infectious diseases)
            2. Prescribers' reported rationale for opting out
    c. Percent of subjects who received an infectious disease consultation after implementation of the Opt-Out
4) Days of therapy for specific sub-groups of patients, including patients whose physicians elected to opt-out of the intervention, and sub-groups of hospitals (e.g., community vs. tertiary care hospitals).
5) Total days of therapy for each patient, defined as a sum of inpatient days of therapy and projected outpatient days of therapy, as per discharge prescriptions.
6) Length of therapy (LOT), defined as the number of days during which the patient receives one or more antibiotics. Repeat primary outcome and secondary outcomes #4 and #5 with LOT.

Additional Descriptive Data

We will obtain the following data from each of the patients eligible for the Opt-out protocol:

1. Patient characteristics: age, gender, race, admission and discharge dates, location prior to admission (e.g. transfer from another facility or skilled nursing facility), prior hospitalization in the last 90 days, prior surgery within the last 30 days, ICU admission date (if applicable)
    a. Length of stay during index admission
    b. Length of stay prior to enrollment
2. Primary and secondary diagnoses (by ICD-10 code)

3. Methods for implementation of the protocol, including centralized versus de-centralized pharmacist and communication method.
4. Outpatient and/or post-discharge antibiotic exposures in the 30 days post randomization.

Data Collection Strategy and Sources

Data will be collected using two strategies to best integrate data available from routine care within the electronic health record and daily routine activities of the hospital pharmacist: electronic data and data manually entered into a REDCap database.

Electronic Data - The majority of data will come from existing datasets collected as part of clinical operations. Electronic data extracts will be prepared from each hospitals' electronic systems according to a pre-specified data dictionary for each of the primary and secondary outcomes and additional data outlined above. The primary outcome will be measured directly from electronic medication administration records (eMAR) which captures the location, administration date/time, and agent used. Additional endpoints will be extracted from billing, administrative, and laboratory data and will emulate files previously collected for DETOURS-Retro (Pro00076818). Key difference in data collected with the trial as opposed to DETOURS-Retro is that datasets for this trial will include PHI including MRN in order to adequately link outcomes captured in electronic data extracts with manually collected data.

REDCap Data – Data specifically collected on eligible patients (Pass Step 1 of Opt-Out Protocol) will be entered into a REDCap database. Data collected from eligible patients will include the result of the Safety Checklist (Step 2) and indication(s) for failure if applicable. For patients who pass the Safety Checklist, additional data will be entered for the result of the Opt-Out Procedure (Step 4) among patients randomized to intervention. Finally, rationale for opt-out will be entered for applicable patients (Step 5). These data, including proportion of eligible patients randomized to intervention and result of Opt-Out Procedure, will be regularly analyzed and fed back to sites as the study progresses.

Institutions will be able to decide for themselves what is the most effective way to document reviews and interventions.

Blinding

Study personnel and pharmacists will remain blinded to randomization status until Step 3 of the Opt-Out Procedure. In other words, the determination for eligibility and application of the Safety Check will occur prior to knowledge of randomization. No further blinding of study personnel will occur as this is an active, quality-improvement activity that utilizes front-line clinical personnel. No contact with individual patients is anticipated.

Data Monitoring

No formal interim analyses involving hypothesis testing is planned. Safety outcome monitoring is outlined below (Section 7).

5.2 Other Study Procedures

We will enroll patients as part of this protocol but will seek a waiver of informed consent. Screening and enrollment/baseline are described above. No specific follow-up with patients will occur following hospital discharge. Therefore, the following sections are not applicable:

1. Follow-up
2. Final study visit
3. Follow-up safety phone call
4. Early termination visit
5. Unscheduled visit
6. Laboratory evaluations

6 STUDY PRODUCT DESCRIPTION

Not applicable

6.1 Concomitant Medications/Treatments

Not applicable

7 ASSESSMENT OF SAFETY

All randomized patients will undergo safety evaluation.

1. Specifications of safety parameters –Data will be collected on the adverse outcomes described in the Desirability of Outcome Ranking (DOOR) in Table 3 and three other safety outcomes:
    a. *C. difficile* infection (CDI) – positive *C. difficile* stool test during the 30 days following randomization. Results from either PCR or ELISA tests are acceptable
    b. Clinically significant deep venous thrombosis (DVT) – diagnosis of a new DVT during the 30 days following randomization that requires anticoagulation. A radiographic finding (via ultrasound, CT, or MRI) will be required for this diagnosis.
    c. Readmission – return to the hospital within 30 days of hospital discharge
    d. Relapse of suspected sepsis – restart or escalation of antibiotic therapy coupled with repeat blood cultures (+/- 24 hours of changed in antibiotic therapy) during the 30 days following randomization.
    e. Acute kidney injury requiring hemodialysis – new onset acute kidney injury requiring 1 or more hemodialysis sessions during the 30 days following randomization.
    f. Transfer to Intensive Care Unit (ICU) – admission or transfer to any intensive care unit within 30 days of randomization.
    g. Death – within 30 days of randomization.
    h. Number of hospital days (Length of Stay) starting on the day of randomization and up to 30 days post randomization.
    i. Re-initiation of antibiotic therapy after >48 hours of no antibiotics within 30 days of randomization.
    j. Need for new PICC line insertion within the 30 days of randomization.
2. Methods and timing for assessing, recording, and analyzing safety parameters – Local study personnel will be responsible for assessing and recording safety parameters. Duke study personnel will be responsible for monitoring safety through interaction with study site PIs and the Independent Monitor.
3. Guidelines for determining causality – causality will not be assessed, as the DOOR outcome is intended to reflect global patient outcomes.
4. Reporting procedures (for AE) – all safety parameters will be entered into the REDCap database. Data on safety parameters will be reviewed by the Independent Monitor and discussed with the central study team.

Independent Monitor

As outlined above, we believe the study intervention qualifies as quality improvement activity, and offers no additional risk than routine medical care. However, some clinicians may worry that cessation of antibiotics, even in the low risk population which DETOURS study screening processes select, could result in negative clinical outcomes for patients who had a clinically

ambiguous presentation or unconfirmed infection at the 48-96-hour time point. Thus, we plan to use an Independent Monitor.

The independent Monitor will be a qualified and objective individual not directly involved with the design and conduct of the study. This individual will not be an employee of any participating institution or the study sponsor. This individual will have no conflict of interest related to assessment of the study, will have adequate experience and expertise in conduct of clinical trials, statistics, and antimicrobial stewardship. Full description of the Independent Monitor plan is provided in Appendix D.

The independent monitor will focus on safety outcomes and not the primary outcome of antibiotic use. No statistical testing alpha value will be pre-assigned to indicate the need to halt or adjust the study protocol. No hypothesis testing is planned. Instead, an expert review of patient-level outcomes will be performed to ensure no concerning differences in safety events between the two arms are emerging.

8 CLINICAL MONITORING

ICH E6 states that the purpose of monitoring is to ensure the rights of subjects, obtain accurate data, and conduct trial in accordance with protocol and applicable regulations. Routine procedures in our study group and through the research infrastructure at DUHS ensure the qualification of hospital personnel to conduct the trial, regulatory requirements (e.g. IRB review), protocol training, data quality monitoring procedures, hospital data completion expectations (e.g. completeness, frequency, etc.). Rights of subjects will be maintained at all times as outlined in the Privacy section.

9 STATISTICAL CONSIDERATIONS

9.1 Design and Sample Size Considerations

The study is designed as a multicenter randomized controlled trial to test the primary hypothesis that use of an opt-out protocol in appropriate patients will decrease unnecessary antimicrobial utilization. Power calculations were re-run after the initiation of the study (v.4 of protocol) because of findings from a recently completed study by our group and others examining the importance and impact of post-discharge antimicrobial therapy on utilization metrics.[16,17] In essence, estimated post-discharge DOT were added to estimated inpatient DOT, and power calculations were re-run.

Power calculations

Power was calculated using a simulation study. First, we evaluated 6 months of data from three hospitals in our network, including 1 tertiary care center and 2 community hospitals. Eligible patients were defined as follows:

1. Blood cultures drawn and negative
    a. Except 1 of 2 common skin flora
2. Broad antibiotics at 2-3 days after time of blood culture draw
3. We will define the 2nd calendar day after date of blood culture draw as “screen date”
4. The patient is eligible if they received broad antibiotic on either the screen date (day 2) or the day after (day 3).
5. Located on an inpatient medical, surgical, telemetry, or medical/surgical ward on screen date

The main outcome of interest was DOT after screen date, counting inpatient days of therapy occurring screen date + 1 until discharge, and adding post-discharge DOT as defined in electronic prescriptions upon hospital discharge. Table 4 outlines total enrollment assumptions at study hospitals.

Table 4. Total enrollment assumptions in 10 study hospitals.

		Enrollment/ month	Months in study	Enrollment estimate
Harvard	Academic	10	15	150
Duke	Academic	10	18	180
Penn	Academic	10	18	180
Presbyterian	Community	2	18	36
Wilson	Community	2	18	36
Iredell	Community	2	18	36
SRMC	Community	2	18	36
Fayette	Community	2	18	36
ATL	Community	2	18	36
Newnan	Community	2	18	36
			total	762

A negative binomial regression model was fitted to the admission-level data on DOT. No difference in DOT was found between different types of wards (Medical/Surgical, Surgical, Medical and Telemetry; p=0.39) so the final model included intercept only. Hospital was included as a random effect in the model. Mean DOT was estimated as exp(Intercept) = exp(2.43) = 11.4 days, negative binomial scale as 1.68 and variance of the hospital random effect as 0.12.

Power was estimated using a simulation study with 500 repetitions. Based on the above assumptions, DOT per admission in the standard care arm were generated in each hospital from a negative binomial distribution with mean=(11.4+hospital effect) and scale=1.68, where hospital effect was generated from a normal distribution with mean 0 and variance 0.12. DOT in the opt-out arm were generated from the same model with the mean=(eff*11.4+hospital effect), where reduction in mean DOT parameter "eff" ranged in values from 0.9 to 0.6 (i.e. 10%-40% reduction).

The data analysis was performed using GEE negative binomial regression with treatment as the only covariate, hospital as the cluster variable and assuming compound symmetry covariance structure within the clusters.

With these assumptions, power ranged from 28% for 10% reduction to >99% power for 40% reduction in mean DOT.

Decrease in mean DOT	Power
10%	28%
20%	66%
25%	87%
30%	96%
40%	>99%

Using these calculations, target enrollment was set at n=762, giving us 87% power to calculate a 25% decrease in mean DOT. Power for the secondary outcome (DOOR/RADAR) will be calculated after SA3 and 4 are completed.

9.2 Randomization

Randomization will be performed using capabilities of the web-based RedCap system. Eligible patients will be randomized in a 1:1 ratio to intervention versus standard of care, with randomization stratified by hospital. Randomization scheme will be generated by the study statistician.

9.3 Planned Interim Analyses

There will be no planned interim analyses with hypothesis testing. Regular assessment of safety parameters will be performed as outlined in Section 7.

9.4 Analysis Plan

9.4.1 Analysis

Descriptive data will be summarized by treatment group and overall using standard statistical methods. Full details of the planned analyses will be specified in a statistical analysis plan (SAP) which will be completed prior to the database lock.

Primary analyses

The primary outcome (antibiotic DOT) will be evaluated using GEE negative binomial regression with treatment as the only covariate, hospital as the cluster variable and assuming compound symmetry covariance structure within the clusters. Model fit will be examined and alternative distributions for the regression model (Poisson or overdispersed Poisson) may be considered.

Secondary analyses

Secondary outcome #1 (RADAR/DOOR) will be compared between treatment arms using Wilcoxon rank-sum test. Probability of a better RADAR/DOOR for a randomly selected patient using DETOURS strategy compared with control will be calculated, along with the 95% confidence interval.

Safety outcomes (secondary outcome #2) and process indicators (secondary outcome #3) will be analyzed using summary statistics.

Secondary outcomes including DOT and LOT (secondary outcomes #4, #5, and #6) will be analyzed using the same method as for the primary outcome #1 above.

Analysis populations

Intent-to-treat (ITT) population will include all randomized patients. Patients will be analyzed as randomized.

Per-protocol (PP) population will consist of all randomized patients without major inclusion/exclusion criteria violations, which will be pre-defined in the SAP. Patients will be analyzed as treated.

Primary and key secondary analyses will be performed both in the ITT and PP populations; all other analyses will be performed in the ITT population only.

Subgroup analyses

Subgroup analyses of the primary outcome will evaluate whether the treatment effect is consistent between 1) medicine patients vs. surgical patients 2) between study hospitals and 3) comparing academic to community hospitals. Additional analyses will compare differences in outcomes and patient/prescriber characteristics for patients in whom protocol-driven de-escalation was implemented versus those in whom the prescriber opted-out of de-escalation. Process indicators for these subgroups will be analyzed using summary statistics.

10 LIMITATIONS AND POTENTIAL SOLUTIONS

The study has potential limitations. First, there may be a temporal bias over the study period. We will consider using regression adjustment for time period to account for this potential limitation and will include additional adjustment factors if residual confounding is detected. Our randomization scheme will decrease this bias as equal numbers of intervention and control patients will be included in all time periods. Second, contamination between arms is possible if a prescriber “learns” during interaction with an intervention patient and then applies the knowledge to a control patient. We believe this is unlikely based on long-standing experience with post-prescription review processes through standard stewardship interventions. Nevertheless, we will collect antimicrobial utilization data for 12-month “pre”-study period that can be used as a baseline comparator. In the event that control patients have a lower DOT than similar patients in the pre-study period, additional analyses will be considered to investigate time bias vs. contamination vs. impact of additional stewardship activities. Though unlikely to occur, if we have difficulty recruiting study hospitals, we will approach additional DASON or Epicenter hospitals.

11 IMPLICATIONS

The completion of the DETOURS aims will have specific implications for national regulatory policy surrounding sepsis management. The DETOURS opt-out protocol, if successful, may be employed as a standard in hospitals across the US in order to balance the effect of regulatory mandates and avoid excess antibiotic use in patients with suspected sepsis. Further, opt-out methodology may become a key strategy for future stewardship interventions targeted to other clinical scenarios. Although antimicrobial stewardship frequently involves patient-specific review and feedback to providers, carefully conceived protocols to guide antibiotic stewards are needed for the more challenging clinical scenarios like suspected sepsis. The DETOURS protocol could be the first of many from the Prevention Epicenters experts targeted towards other clinically challenging syndromes. This trial will also provide considerable experience and testing of the DOOR/RADAR methodology and its application to a large antimicrobial stewardship interventional trial. If DOOR/RADAR performs well in this trial, this methodology could become the standard for evaluating stewardship interventions in the future. Alternatively, this trial may lead to adjustments and optimization of the DOOR/RADAR methodology if important limitations are discovered.

12 PARTICIPANT CONFIDENTIALITY

We will enroll patients but not consent patients for this quality improvement study, as outlined in our Request for Waiver of Informed Consent. Appropriate waivers of consent and HIPAA authorization will be obtained to access patient data.

13 INFORMED CONSENT PROCESS

We will not consent patients. As this study is based on quality improvement (QI) strategies and does not involve investigational products, we will seek a waiver of informed consent (see **16.2**).

14 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

No source documents will be used by this protocol.

15 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will ensure that all study personnel are appropriately trained and applicable documentations are maintained. QC strategies for data transmission are already in place.

Site PIs will assign the task of QC/QA checks to a local study monitor. The study monitor will evaluate appropriate application of the safety check criteria by sampling 15-20% of enrolled patients and confirming presence or absence of the safety check criteria to confirm fidelity to protocol.

16 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

16.1 Institutional Review Board

The investigator will ensure that the protocol is reviewed and approved by the DUHS IRB prior to the start of any study activities. The IRB will be appropriately constituted and will perform its functions in accordance with US regulations, ICH Good Clinical Practice guidelines, and local requirements as applicable.

16.2 Informed Consent

Request for Waiver of Consent & Authorization

We believe this study qualifies for waiver of informed consent based on the following criteria:

1. **No more than minimal risk to subjects:** We believe the risks involved in this study are not different than the risks inherent in medical care. There is a risk that antibiotics will be stopped too early for patients randomized to intervention. We believe this risk is minimal for two reasons. First, the intervention includes a rigorous safety check developed by a large team of experts in infectious diseases, critical care, and hospital medicine. Antibiotics will only be stopped if the patient passes the rigorous safety check. Second, the treatment team can opt out of the intervention at any time. Thus, care is always directed by the treating clinical team, not the study team. In contrast, there is also risk in continuing antibiotics when no longer necessary, including adverse drug events, development of antibiotic-resistant pathogens, and *C. difficile* colitis.

   Furthermore, our proposed intervention is consistent with expert guidelines. In fact, the Surviving Sepsis guidelines specifically recommend "daily assessment for de-escalation" of antibiotics and narrowing of empiric antimicrobial therapy if cultures are negative or adequate clinical improvement is noted.[6] These experts go on to state "when infection is found not to be present, antimicrobial therapy should be stopped promptly to minimize the likelihood that the patient will become infected with an antimicrobial-resistant pathogen or develop a drug-related adverse effect."[6] These guidelines do not, however, provide recommendations on how to execute this practice. In contrast, the IDSA/SHEA Implementation of Antimicrobial Stewardship guidelines strongly recommend a "post-prescription review" of all courses of antibiotics in hospitalized patients. This practice, in which a pharmacist reviews indications for ongoing antibiotic therapy and provides feedback to prescribers, is a "strong recommendation" and a "core component of any stewardship program."[14] Our intervention is a form of "post-prescription review."

   The study will also involve the collection of identified data. We believe that the privacy risk associated with data collection is minimal given the data security & privacy protections developed as part of the study protocol (see #4 below). All study investigators and staff have been trained in human subjects research and HIPAA regulations.

   In summary, we concede our study is research involving humans, but believe the study question and approach is consistent with quality improvement approaches. The study attempts to determine best implementation strategies for recommended practices and, as described above, poses no more than minimal risk to subjects.

2. **The waiver will not adversely affect the rights and welfare of the subjects:** As above, we will have data security measures in place to preserve patient privacy and

confidentiality. Inclusion in our study will not impact the relationship between the treating team and the patient.

3. **Subjects will be provided additional pertinent information, when appropriate:** We will not plan on directly interacting with patients as part of this study, unless specifically asked by the treating teams. This approach is analogous to numerous other antimicrobial stewardship interventions that we perform on a daily basis for hospitalized patients on antibiotics. Nevertheless, we will have subject-directed educational materials about our study that can be distributed to subjects as necessary.
4. **Use of PHI involves no more than minimal risk to the privacy of individuals as**
    a. **An adequate plan to protect identifiers from improper use and disclosure will be in place.** Data files from study hospitals and patients will be maintained on password protected shared drives behind DUHS firewalls. Only study investigators will have access to the passwords required for access to the study files. Subject-specific data will be entered into REDCap databases specifically generated for this study. Antibiotic utilization data will be acquired from the Duke Antimicrobial Stewardship Outreach Network (DASON) database; this database includes antimicrobial administration data on all DUHS inpatients and is used for day-to-day stewardship program operations. Study hospitals not participating in DASON will replicate the same QC and safety protocols required for transmission of data within DASON. Any reports or publications resulting from this project will use fully de-identified data elements.
    b. **An adequate plan to destroy identifiers at the earliest opportunity will be in place.** Destruction will occur within 6 years of study closure per study destruction guidelines existent at that time for all study related materials. All data will be maintained for 6 years after publication and only summary level information will be released in published form. All electronic data with identifiers will be destroyed using the latest technology available at that time in accordance with institution policy.
5. **The research could not practicably be conducted without waiver.** This criterion represents the biggest reason we are requesting waiver of informed consent. Our goal is to determine the value of our intervention on patients with suspected sepsis who meet safety criteria. We believe that an informed consent step would lead to an alteration in the population that would participate in the study. More specifically, we believe that the patient population that would agree to participate would be less sick and, thus would not be representative of the target study population. In fact, this important alteration of the study group would significantly limit our ability to assess our intervention (significantly biasing our results towards the null) and would significantly reduce the generalizability of our findings.
6. **The research could not practicably be conducted without access to and use of PHI.** The research could not practicably be conducted without the access to & use of PHI because medical record numbers and absolute dates are needed to link patient data gathered from different systems (REDCap and DASON database). MRNs will be used to ensure that we don't have duplicate data entries in the database. While MRNs and date of birth will be initially obtained from subjects, our ultimate study database will NOT include these data, as they will be replaced by Study ID and Age (at the time of admission).

16.3 Data Confidentiality

This is a minimal risk study. Data will be stored on encrypted Duke Medicine servers and/or in a REDCAP database. Data security procedures are outlined in **Section 17**.

16.4 Study Discontinuation

This study may be terminated at any time by the principal investigator (PI) in consultation with the CDC.

17 DATA HANDLING AND RECORD KEEPING

17.1 Data Management Responsibilities

DASON IT personnel will be responsible for data management required for electronic datasets used in this study, per routine DASON practices. Designated study personnel will be responsible for REDCap data entry at each study hospital. The study coordinator and study statistician will be responsible for QC and QA steps and documentation required for the study.

The majority data used in this study will be obtained from routine clinical care practices at participating hospitals. Datasets will be transferred to Duke using previously established Secure File Transfer Protocols (SFTP) from DASON hospital (per established routine practices) and Duke Box from the Epicenters hospitals. We will use datasets similar to those collected routinely as part of the DASON program. Another dataset of manually entered data during the opt-out intervention will be collected in REDCap. DASON hospitals have Business Agreement Arrangements (BAA) in place that outline our interactions with hospitals. These interactions will not change as part of this study.

Data from these two sources will be linked to complete study analyses. Thus, we will include PHI in the datasets in order to identify de-escalation events, link files from the electronic medical record and the REDCap database, and determine outcomes (e.g. length of hospitalization based on admission and discharge dates). After data files have been transferred and tables linked, the patient MRN and age will be removed and replaced by a study identifier and age at admission for ongoing retention in the study dataset. Thus for analysis, MRN and age PHI will be purged and only admission, intervention, and discharge dates will be included in the study database after file transfer and aggregation. **The final study dataset for analysis will be a limited dataset only containing dates PHI.**

Data Protection – Project data will be stored at the DASON Server at the Duke University through the Duke Health Technology Solutions (DHTS) group. The Central Data center will not collect social security numbers, addresses, or phone numbers. To capture and link project data, we will collect dates of clinical events (e.g., admission and antibiotic prescribing dates). All dates, the medical record and visit numbers, will be encrypted in the database and decrypted only for review by the clinical site or for linking data sent as batch uploads to those collected manually through REDCap. Data transferred for analysis will be stripped of all patient numbers upon collation into the final study database. All data will be maintained on computerized databases. All databases containing PHI will be maintained in electronic files on password protected computers of study investigators and study staff with regularly updated virus software. All investigators have been trained in human subjects research and HIPAA regulations. Any reports or publications resulting from this project will use fully de-identified data elements.

Data Transfer from Outside Collaborators - Patients' medical record numbers will be replaced with Study IDs for storage in the study database. Transmission of these data will be encrypted for transmission and for storage in the database. Data collection forms will include true dates, however, all true dates will be encrypted in the database.

Data Capture Methods

REDCap is a toolset and workflow methodology for electronic collection and management of research and clinical trial data. Both REDCap and REDCap Survey systems provide secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. These systems offer easy data manipulation

with audit trails and reporting for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

The REDCap program will serve as the portal for data entry by the study coordinator. Data entered into this database will be password protected and only accessible by study personnel. All access to this secure separate database will be monitored and logged.

17.2 Study Data Retention

Destruction will occur within 6 years of study closure per study destruction guidelines. All data will be maintained for 6 years after publication and only summary level information will be released in published form. All data containing identifiers collected in paper format will be shredded within the timeframe as described above. Alternatively, all electronic data with identifiers will be destroyed using the latest technology available at that time in accordance with institution policy.

17.3 Protocol Deviations

Deviations from the study protocol (e.g., randomization scheme) will be documented.

18 PUBLICATION POLICY

Following completion of the study, the investigator will publish the results of this research in a scientific journal.

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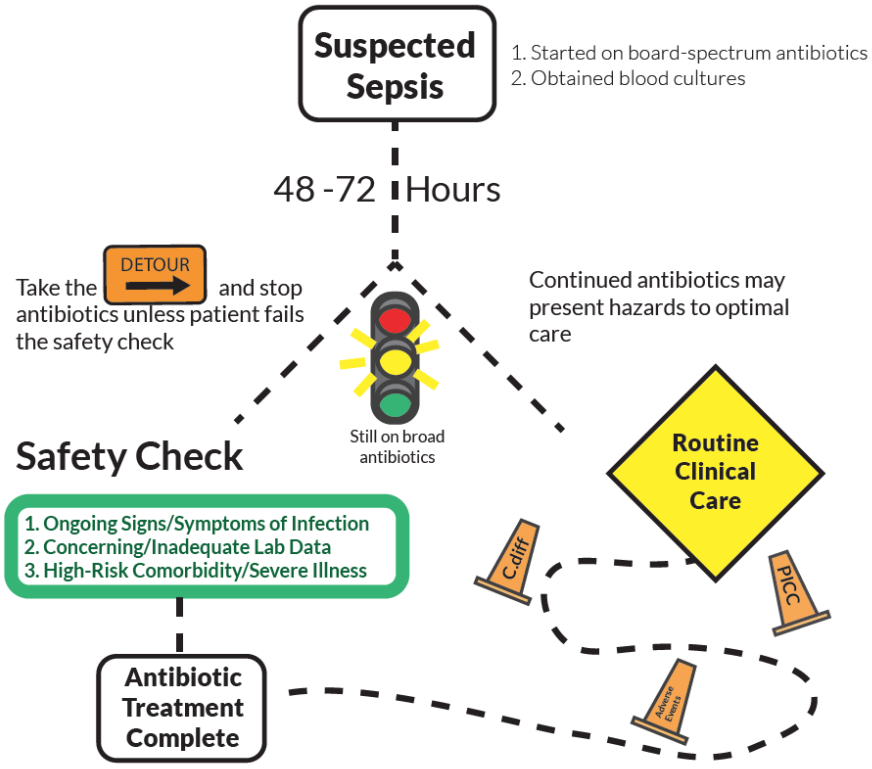
20 APPENDIX 1. POTENTIAL STUDY HOSPITALS

Hospital Name ***(study hospitals to be selected from this list)***	**Location**	**Letter of Support Received**
Augusta Health	Fishersville, VA	yes
Barnes-Jewish Hospital	St. Louis, MO	yes
Central Carolina Hospital	Sanford, NC	yes
Chesapeake Regional Healthcare	Chesapeake, VA	yes
Christian Hospital	St. Louis, MO	yes
Columbus Regional Healthcare	Whiteville, NC	yes
Conway Medical Center	Conway, SC	yes
Danville Regional Medical Center	Danville, VA	yes
Duke Raleigh Hospital	Raleigh, NC	yes
Duke Regional Hospital	Durham, NC	yes
Frye Regional Medical Center	Hickory, NC	yes
Granville Medical Center	Oxford, NC	yes
Harnett Health	Dunn, NC	yes
High Point Regional	High Point, NC	yes
Hospital of the University of Pennsylvania	Philadelphia, PA	yes
Indian River Medical Center	Vero Beach, FL	yes
Iredell Health System	Statesville, NC	yes
Maria Parham Medical Center	Henderson, NC	yes
Missouri Baptist Medical Center	St. Louis, MO	yes
Morehead Memorial Hospital	Eden, NC	yes
Nash Healthcare System	Rocky Mount, NC	yes
New Hanover Regional Medical Center	Wilmington, NC	yes
Person Memorial Hospital	Roxboro, NC	yes
Penn Presbyterian Hospital	Philadelphia, PA	yes
Pennsylvania Hospital	Philadelphia, PA	yes
Piedmont Atlanta	Atlanta, Ga	yes
Piedmont Henry Hospital	Stockbridge, GA	yes
Piedmont Fayette Hospital	Fayetteville, GA	yes
Piedmont Newnan Hospital	Newnan, GA	yes
Rex Healthcare	Raleigh, NC	yes
Scotland Healthcare	Laurinburg, NC	yes
Southeastern Regional Medical Center	Lumberton, NC	yes
Twin County Regional	Galax, VA	yes
Wayne Memorial	Goldsboro, NC	yes
Wilson Medical Center	Wilson, NC	yes

21 APPENDIX 2 – DETOURS OPT-OUT PROTOCOL (5 STEPS)

The following information will be provided to each study site

Study Graphic



Safety Check Patient fails if meets one or more of the following critera

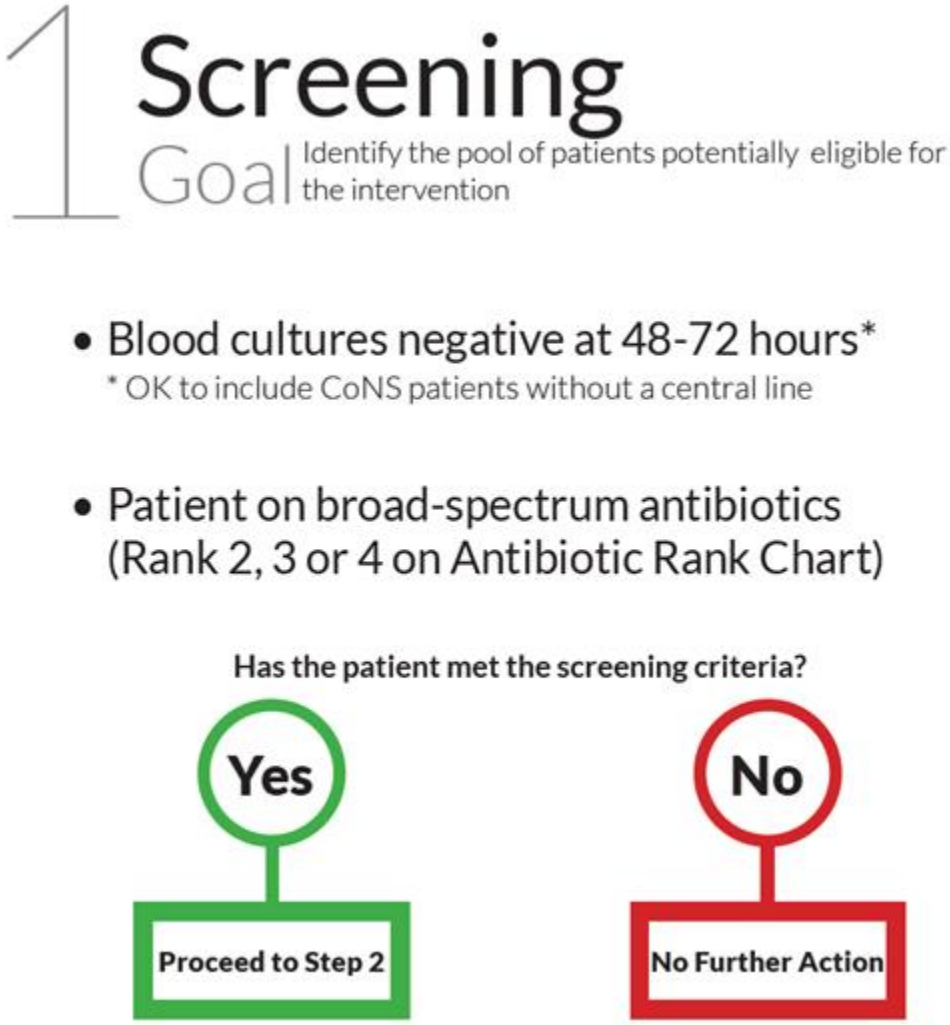
1. Ongoing Signs/ Symptoms of Infection
- continued fever
- new chest x-ray infiltrate
- empyema
- lung abscess
- continued significant leukocytosis

2. Concerning/Inadequate Microbiological Data
- positive blood cultures*

*Note: OK to stop if contaminate and no central line
- positive microbiological data
- no cultures during sepsis work-up
- antibiotic use prior to blood culture

3. High-Risk Comorbidy/Severe Illness
- bronchiectasis
- asplenia/splenectomy
- cystic fibrosis
- pregnant
- recent I&D procedure
- ongoing respiratory insufficiency
- immunocompromised
  - HIV/AIDS with CD4 count < 200
  - taking immunosuppressive agents
  - agammaglobulinemia
  - bone marrow aplasia
  - neutropenia
  - transplant recipient

Step 1


1
Screening
Goal
Identify the pool of patients potentially eligible for the intervention
• Blood cultures negative at 48-72 hours*
* OK to include CoNS patients without a central line
• Patient on broad-spectrum antibiotics (Rank 2, 3 or 4 on Antibiotic Rank Chart)
Has the patient met the screening criteria?
Yes
Proceed to Step 2
No
No Further Action

Step 2

2 Safety Check

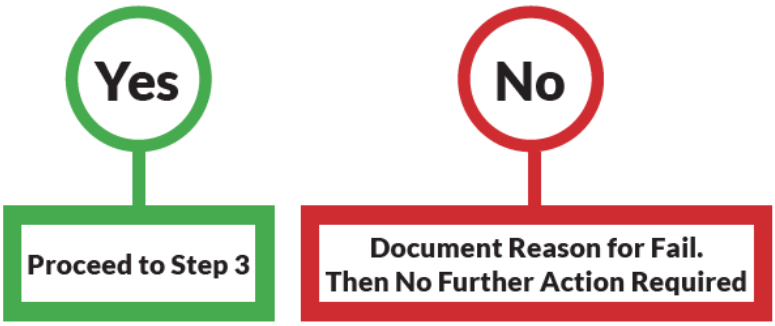
Goal | Determine if patient passes the safety check

Apply the safety check

- ☐ **Ongoing Signs/Symptoms of Infection**
  - ☐ continued fever
  - ☐ new chest x -ray infiltrate
  - ☐ empyema
  - ☐ lung abscess
  - ☐ continued significant leukocytosis
- ☐ **Concerning/Inadequate Microbiological Data**
  - ☐ positive blood cultures*
  - **Note: OK to stop if contaminate and no central line*
  - ☐ positive microbiological data
  - ☐ no cultures during sepsis work-up
  - ☐ antibiotic use prior to blood culture
- ☐ **High-Risk Comorbidity/Severe Illness**
  - ☐ bronchiectasis
  - ☐ asplenia/splenectomy
  - ☐ cystic fibrosis
  - ☐ pregnant
  - ☐ recent I&D procedure
  - ☐ ongoing respiratory insufficiency
  - ☐ immunocompromised
    - ☐ HIV/AIDS with CD4 count <200
    - ☐ taking immunosuppresive agents
    - ☐ agammaglobulinema
    - ☐ bone marrow aplasia
    - ☐ neutropenia
    - ☐ transplant recipient

Patient fails safety check if meets any of the above criteria

Has the patient passed the safety check?



Step 3

Consult Randomization Scheme provided by study team

Is the patient randomized to intervention?

Step 4

Interact with the team using the following language

"[This patient] passed the safety screen for de-escalation of antibiotics. Antibiotics will be stopped per protocol unless you opt-out."

Did the treatment team opt-out?

Step 5

Guided De-Escalation Discussion

Goal

Better understand opt-out rationale and identify opportunities for antibiotic optimization

Engage with treatment team and document answers to four questions:

1. "Why should antibiotics be continued in this patient?"

2. "What is the patient's infection diagnosis?"

3. "Can you narrow the breadth of antibacterial coverage to the most likely pathogens?"

    - Refer to Local Empiric Guidelines, Antibiogram, patient's culture data, and Antibiotic Rank Chart

4. "If the patient remains stable and no new clinical data emerge to suggest a different diagnosis, do you have an empiric de-escalation and/or duration of therapy plan ?"

    - Refer to Local Duration Guidelines for common syndromes
    - Offer to adjust orders or stop dates to match the voiced de-escalation and duration plan
    - Reassess in 48 hours if other opportunities to de-escalate may be possible

22 APPENDIX 3 – NHSN AU MODULE ANTIBACTERIAL AGENTS

Appendix B of the NHSN AUR Module provides a List of Antimicrobials relevant for the DETOURS study (see https://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf for most up to date table). The following table was downloaded February 23, 2018.

Antimicrobial Agent	Value [a]	NHSN Drug Code	Antimicrobial Category	Antimicrobial Class [b]	Antimicrobial Subclass [b]
AMANTADINE	620	AMAN	Anti-influenza	M2 ion channel inhibitors	
AMIKACIN	641	AMK	Antibacterial	Aminoglycosides	
AMOXICILLIN	723	AMOX	Antibacterial	Penicillins	Aminopenicillin
AMOXICILLIN/CLAVULANATE	19711	AMOXWC	Antibacterial	B-lactam/ B-lactamase inhibitor combination	
AMPHOTERICIN B	732	AMPH	Antifungal	Polyenes	
AMPHOTERICIN B LIPOSOMAL	236594	AMPHOT	Antifungal	Polyenes	
AMPICILLIN	733	AMP	Antibacterial	Penicillins	Aminopenicillin
AMPICILLIN/SULBACTAM	1009148	AMPIWS	Antibacterial	B-lactam/ B-lactamase inhibitor combination	
ANIDULAFUNGIN	341018	ANID	Antifungal	Echinocandins	
AZITHROMYCIN	18631	AZITH	Antibacterial	Macrolides	
AZTREONAM	1272	AZT	Antibacterial	Monobactams	
CASPOFUNGIN	140108	CASPO	Antifungal	Echinocandins	
CEFACLOR	2176	CEFAC	Antibacterial	Cephalosporins	Cephalosporin 2rd generation
CEFADROXIL	2177	CEFAD	Antibacterial	Cephalosporins	Cephalosporin 1st generation
CEFAZOLIN	2180	CEFAZ	Antibacterial	Cephalosporins	Cephalosporin 1st generation
CEFDINIR	25037	CEFDIN	Antibacterial	Cephalosporins	Cephalosporin 3rd generation
CEFDITOREN	83682	CEFDIT	Antibacterial	Cephalosporins	Cephalosporin 3rd generation
CEFEPIME	20481	CEFEP	Antibacterial	Cephalosporins	Cephalosporin 4th generation

CEFIXIME	25033	CEFIX	Antibacterial	Cephalosporins	Cephalosporin 3rd generation
CEFOTAXIME	2186	CEFOT	Antibacterial	Cephalosporins	Cephalosporin 3rd generation
CEFOTETAN	2187	CTET	Antibacterial	Cephalosporins	Cephamycin
CEFOXITIN	2189	CEFOX	Antibacterial	Cephalosporins	Cephamycin
CEFPODOXIME	20489	CEFPO	Antibacterial	Cephalosporins	Cephalosporin 3rd generation
CEFPROZIL	19552	CEFPRO	Antibacterial	Cephalosporins	Cephalosporin 2rd generation
CEFTAROLINE	1040005	CEFTAR	Antibacterial	Cephalosporins	Cephalosporin with anti-MRSA activity
CEFTAZIDIME	2191	CEFTAZ	Antibacterial	Cephalosporins	Cephalosporin 3rd generation
CEFTAZIDIME/AVIBACTAM	1820-0	CEFTAVI	Antibacterial	B-lactam/ B-lactamase inhibitor combination	
CEFTIBUTEN	20492	CEFTIB	Antibacterial	Cephalosporins	Cephalosporin 3rd generation
CEFTIZOXIME	2192	CEFTIZ	Antibacterial	Cephalosporins	Cephalosporin 3rd generation
CEFTOLOZANE/TAZOBACTAM	1818-4	CEFTOTAZ	Antibacterial	B-lactam/ B-lactamase inhibitor combination	
CEFTRIAXONE	2193	CEFTRX	Antibacterial	Cephalosporins	Cephalosporin 3rd generation
CEFUROXIME	2194	CEFUR	Antibacterial	Cephalosporins	Cephalosporin 2rd generation
CEPHALEXIN	2231	CEPHLX	Antibacterial	Cephalosporins	Cephalosporin 1st generation
CHLORAMPHENICOL	2348	CHLOR	Antibacterial	Phenicols	
CIPROFLOXACIN	2551	CIPRO	Antibacterial	Fluoroquinolones	
CLARITHROMYCIN	21212	CLARTH	Antibacterial	Macrolides	
CLINDAMYCIN	2582	CLIND	Antibacterial	Lincosamides	
COLISTIMETHATE	2708	COLIST	Antibacterial	Polymyxins	
DALBAVANCIN	1815-0	DALBA	Antibacterial	Glycopeptides	Lipoglycopeptide
DAPTOMYCIN	22299	DAPTO	Antibacterial	Lipopeptides	
DELAFLOXACIN	1821-8	DELAF	Antibacterial	Fluoroquinolones	
DICLOXACILLIN	3356	DICLOX	Antibacterial	Penicillins	Penicillinase-stable penicillins

DORIPENEM	119771	DORI	Antibacterial	Carbapenems	
DOXYCYCLINE	3640	DOXY	Antibacterial	Tetracyclines	
ERTAPENEM	325642	ERTA	Antibacterial	Carbapenems	
ERYTHROMYCIN	4053	ERYTH	Antibacterial	Macrolides	
ERYTHROMYCIN/ SULFISOXAZOLE	113588	ERYTHWS	Antibacterial	Folate pathway inhibitors	
FIDAXOMICIN	1814-3	FIDAX	Antibacterial	Macrocyclic	
FLUCONAZOLE	4450	FLUCO	Antifungal	Azoles	
FOSFOMYCIN	4550	FOSFO	Antibacterial	Fosfomycins	
GEMIFLOXACIN	138099	GEMIF	Antibacterial	Fluoroquinolones	
GENTAMICIN	142438	GENTA	Antibacterial	Aminoglycosides	
IMIPENEM/CILASTATIN	34482	IMIPWC	Antibacterial	Carbapenems	
ISAVUCONAZONIUM	1819-2	ISAVAC	Antifungal	Azoles	
ITRACONAZOLE	28031	ITRA	Antifungal	Azoles	
LEVOFLOXACIN	82122	LEVO	Antibacterial	Fluoroquinolones	
LINEZOLID	190376	LNZ	Antibacterial	Oxazolidinones	
MEROPENEM	29561	MERO	Antibacterial	Carbapenems	
METRONIDAZOLE	6922	METRO	Antibacterial	Nitroimidazoles	
MICAFUNGIN	325887	MICA	Antifungal	Echinocandins	
MINOCYCLINE	6980	MINO	Antibacterial	Tetracyclines	
MOXIFLOXACIN	139462	MOXI	Antibacterial	Fluoroquinolones	
NAFCILLIN	7233	NAF	Antibacterial	Penicillins	Penicillinase-stable penicillins
NITROFURANTOIN	7454	NITRO	Antibacterial	Nitrofurans	
ORITAVANCIN	1817-6	ORITAV	Antibacterial	Glycopeptides	Lipoglycopeptide
OSELTAMIVIR	260101	OSELT	Anti-influenza	Neuraminidase inhibitors	
OXACILLIN	7773	OX	Antibacterial	Penicillins	Penicillinase-stable penicillins

PENICILLIN G	7980	PENG	Antibacterial	Penicillins	Penicillin
PENICILLIN V	7984	PENV	Antibacterial	Penicillins	Penicillin
PERAMIVIR	619693	PERAM	Anti-influenza	Neuraminidase inhibitors	
PIPERACILLIN	8339	PIPER	Antibacterial	Penicillins	Ureidopenicillin
PIPERACILLIN/TAZOBACTAM	74169	PIPERWT	Antibacterial	B-lactam/ B-lactamase inhibitor combination	
POLYMYXIN B	8536	PB	Antibacterial	Polymyxins	
POSACONAZOLE	282446	POSAC	Antifungal	Azoles	
QUINUPRISTIN/DALFOPRISTIN	135098	QUINWD	Antibacterial	Streptogramins	
RIFAMPIN	9384	RIF	Antibacterial	Rifampin	
RIMANTADINE	9386	RIMAN	Anti-influenza	M2 ion channel inhibitors	
SULFAMETHOXAZOLE/TRIMETHOPRIM	10831	SULFAET	Antibacterial	Folate pathway inhibitors	
SULFISOXAZOLE	10207	SULFI	Antibacterial	Folate pathway inhibitors	
TEDIZOLID	1816-8	TEDIZ	Antibacterial	Oxazolidinones	
TELAVANCIN	473837	TELAV	Antibacterial	Glycopeptides	Lipoglycopeptides
TELITHROMYCIN	274786	TELITH	Antibacterial	Ketolides	
TETRACYCLINE	10395	TETRA	Antibacterial	Tetracyclines	
TICARCILLIN/CLAVULANATE	113931	TICARWC	Antibacterial	B-lactam/ B-lactamase inhibitor combination	
TIGECYCLINE	384455	TIG	Antibacterial	Glycylcyclines	
TINIDAZOLE	10612	TINID	Antibacterial	Nitroimidazoles	
TOBRAMYCIN	10627	TOBRA	Antibacterial	Aminoglycosides	
VANCOMYCIN	11124	VANC	Antibacterial	Glycopeptides	Glycopeptide
VORICONAZOLE	121243	VORI	Antifungal	Azoles	
ZANAMIVIR	69722	ZANAM	Anti-influenza	Neuraminidase inhibitors	

[a]RxNorm or NHSN Code

[b]Adapted from CLSI January 2014

23 APPENDIX 4 -- DETOURS DATA AND SAFETY MONITORING PLAN

Study Title: De-escalating Empiric Treatment: Opting oUt of Rx for Selected Patients with Suspected Sepsis (DETOURS)

Principal Investigator: Rebekah Moehring, MD, MPH

BRIEF STUDY OVERVIEW

Sepsis has high associated mortality. Hospitals and regulatory agencies have worked to address sepsis care through core measures and bundled processes. However, important follow-up care, including re-assessments of antibiotic regimens and antibiotic de-escalation, are not strongly implemented. This study investigates the use of a novel, opt-out protocol to guide appropriate antibiotic de-escalation among those patients with suspected sepsis meeting rigorous safety checks.

OVERSIGHT RESPONSIBILITIES

Oversight of the trial is provided by the Principal Investigator (PI), Dr. Moehring and Dr. Deverick Anderson (Co-Investigator). Study sites will also have Co-investigators that will help oversee local activities.

MONITORING PROCEDURES

Dr. Moehring assures that waiver of informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.

Study data are accessible at all times for the PI to review. The PI and co-investigators review study conduct: accrual, drop-outs, protocol deviations, process metrics on a monthly basis. The PI and co-investigators review(s) safety outcomes individually in real-time and in aggregate on a quarterly basis. The PI and co-investigators review(s) serious adverse events (SAEs) and any voiced complaints from clinical providers about the study protocol in real-time. The PI ensures all protocol deviations, imbalance in safety outcomes at routine assessments, and SAEs are reported to the CDC and IRB according to the applicable regulatory requirements.

COLLECTION AND REPORTING OF SAEs AND AEs

For this study, the following standard AE definitions are used:

> **Adverse event:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or

procedure, regardless of whether it is considered related to the medical treatment or procedure.

Serious Adverse Event: Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AEs are graded according to the following scale:

Mild: An experience that is transient, & requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

AEs are identified by chart review after 30-days post randomization for the 30-day time period following randomization. SAEs and specific procedure-associated AEs are reported to the PI and co-investigators within 24 hours. In addition, all AEs are reported according to the Duke IRB AE reporting guidelines.

MANAGEMENT OF RISKS TO SUBJECTS

Expected AEs

Expected AEs associated with hospitalization, the receipt of antibiotics, treatment of infection and the DETOURS protocol include:

- *C. difficile* infection (CDI) – positive *C. difficile* stool test during the 30 days following randomization. Results from either PCR or ELISA tests are acceptable
- Clinically significant deep venous thrombosis (DVT) – diagnosis of a new DVT during the 30 days following randomization that requires anticoagulation. A radiographic finding (via ultrasound, CT, or MRI) will be required for this diagnosis.
- Readmission – return to the hospital within 30 days of hospital discharge

- Relapse of suspected sepsis – restart or escalation of antibiotic therapy coupled with repeat blood cultures (+/- 24 hours of changed in antibiotic therapy) during the 30 days following randomization.
- Acute kidney injury requiring hemodialysis – new onset acute kidney injury requiring 1 or more hemodialysis sessions during the 30 days following randomization.
- Transfer to Intensive Care Unit (ICU) – admission or transfer to any intensive care unit within 30 days of randomization.
- Death – within 30 days of randomization.
- Number of hospital days (Length of Stay) starting on the day of randomization and up to 30 days post randomization.
- Re-initiation of antibiotic therapy after >48 hours of no antibiotics within 30 days of randomization.
- Need for new PICC line insertion within the 30 days of randomization.

Causality of SAEs to the study protocol will not be assessed, as the study monitoring plan follows global patient outcomes due to antibiotic exposures. Thus, effects from routine care and the study protocol are difficult to attribute because this is a quality improvement protocol.

DATA ANALYSIS PLANS

All randomized patients will undergo safety evaluation of the outcomes listed above.

1. Methods and timing for assessing, recording, and analyzing safety parameters – Local study personnel will be responsible for assessing and recording safety parameters within the 30-days post randomization. Duke study personnel will be responsible for monitoring safety through interaction with site PIs on a quarterly basis and with the Independent Monitor at specified schedule (Table).
2. Guidelines for determining causality or attribution –
3. Reporting procedures (for AE) – all safety parameters will be entered into the REDCap database. Site PIs will review individual AEs identified by site data entry personnel. Data on safety parameters will be provided back to study sites on a quarterly basis.

Independent Monitor

As outlined above, we believe the study intervention qualifies as quality improvement activity, and offers no additional risk than routine medical care. However, some clinicians may worry that cessation of antibiotics, even in the low risk population which DETOURS study screening processes select, could result in negative clinical outcomes for patients who had a clinically

ambiguous presentation or unconfirmed infection at the 48-96-hour time point. Thus, we plan to use an Independent Monitor for this study to both inform any divergence in safety outcomes between the intervention and control arms, and provide reassurance to participating clinicians that safety outcomes are being actively monitored during conduct of the study.

The independent Monitor will be a qualified and objective individual not directly involved with the design and conduct of the study. This individual will not be an employee of any participating institution or the study sponsor. This individual will have no conflict of interest related to assessment of the study, will have adequate experience and expertise in conduct of clinical trials, statistics, and antimicrobial stewardship.

The independent monitor will focus on safety outcomes and not the primary outcome of antibiotic use. No statistical testing alpha value will be pre-assigned to indicate the need to halt or adjust the study protocol. No hypothesis testing is planned. Instead, an expert review of patient-level outcomes will be performed to ensure no concerning differences in safety events between the two arms are emerging. Timing for review of safety data during conduct of the study will depend achievement of the following study goal enrollment milestones: 10%, 25%, 50%.

Study team statisticians will prepare the data for review by the IM on the schedule above for study-wide assessments. Outcomes of the review will be shared with Site PIs who may then pass the safety data on to clinicians for reassurance of safety monitoring. The reports will include the number and percent or median/interquartile range of safety outcomes per randomization arm as appropriate.

Table for Review by the Internal Monitor

	Intervention	Control	Total
C. difficile infection, No. (%)			
Deep venous thrombosis, No. (%)			
Readmission, No. (%)			
Sepsis relapse, No. (%)			
Acute kidney injury requiring hemodialysis, No. (%)			
ICU transfer, No. (%)			
Death, No. (%)			
Hospital days (Length of stay), median, interquartile range			
Re-initiation of antibiotic therapy, No. (%)			
New PICC line insertion, No. (%)			

Communication plans for interaction between the IM and the study team will be primarily through email. The IM will respond with 7 business days of receipt of the safety data report with

their assessment. If further discussion is needed, then phone discussion within 3 business days will be arranged.

PLAN FOR DATA MANAGEMENT

Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process. Site PIs will assign the task of Quality Control/Quality Assurance checks to a local study monitor. To ensure the screening processes, as implemented at individual study sites, are adequately selecting the intended low-risk population for de-escalation procedures, the safety criteria will be confirmed retrospectively. The study monitor will evaluate appropriate application of the DETOURS safety check criteria for all enrolled patients at their planned 30-day post-enrollment assessment of study outcomes. This review will retrospectively confirm the presence or absence of the safety check criteria and therefor confirm fidelity to the screening protocol.

Additionally, study outcome measurement will be confirmed by requesting securely collected screenshots from the electronic health record for a random 10% sample of enrolled patients during the first month of study start at each site. The local study monitor will collect the data during their 30-day chart reviews, and the data will be reviewed by a member of the central study team to confirm the method by which outcomes are assessed. Confirmation of measurement of the primary outcome from the sampled patients will be compared to the electronic data file capture of antibiotic days for study patients.

Confidentiality throughout the trial is maintained by use of a secured data collection tools, data transfer procedures, and a plan to destroy identifiers at the earliest opportunity.