Effects of Code Sepsis Implementation on ED Sepsis Care (Code Sepsis)

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1. ABBREVIATIONS AND DEFINITIONS

1.1 Abbreviations

AE = Adverse event
CHF = Congestive heart failure
ED = Emergency Department
GCS = Glasgow Coma Scale
HIPAA = Health Insurance Portability and Accountability Act
IRB = Institutional Review Board
ICU = Intensive Care Unit
ICD-9-CM = International Classification of Disease, version 9, clinical modification
ICD-10-CM = International Classification of Disease, version 10, clinical modification
INR = International normalized ratio
ISM = Independent safety monitor
ITT = Intent to treat
MAP = Mean arterial pressure
NIH = National Institutes of Health
PE = Pulmonary embolism
PI = Principle investigator
PHI = Protected Health Information
REDCap = Research Electronic Data Capture
RR = Respiratory rate
SOFA score = Sequential Organ Failure Assessment score
SBP = Systolic blood pressure
SpO2 = Oxygen saturation via pulse oximetry
SUSAR = Serious and Unexpected Suspected Adverse Reactions
SAEs= Serious Adverse Events
WBC = White blood cell count

1.2 Definitions

- **Adverse Event:** Any untoward medical occurrence associated with the use of a drug or a study procedure, whether or not considered drug related.
- **Adverse reaction:** An adverse reaction means any adverse event caused by a study intervention. An adverse reaction is a subset of all suspected adverse reactions where there is a reason to conclude that the study intervention caused the event.
- **Door-to-antibiotic time**: Primary outcome; the time from the first recorded arrival time in ED (usually ED triage or registration) and the time the first eligible antibiotic was administered.
- **Hypotension**: SBP <90 mmHg or MAP <65 mmHg or, where applicable, receipt of vasopressor medication
- **Intention to Treat (ITT):** All eligible patients who present to the ED will be included in the ITT cohort for the purposes of analyzing the primary and secondary study outcomes.
- **PHI:** identifiable health information that is used, maintained, stored, or transmitted by a HIPAA-covered entity
- **SAEs:** Serious Adverse Events Adverse events that are serious and unexpected and have a reasonable possibility that the event was due to a study procedure
- **Sepsis**: Life-threatening organ dysfunction resulting from a dysregulated host response to infection, clinically identified in the emergency department (ED) by an acute rise in the Sequential Organ Failure Assessment (SOFA) score while in the ED ≥2 points above baseline plus suspected or confirmed infection in the ED.1
- **Sepsis mimic:** Clinical condition which may cause patient to exhibit and/or be treated for sepsis even though infection is not actually present. For the present study, pulmonary embolism (PE) and congestive heart failure (CHF) have been identified as sepsis mimic conditions.
- **Septic shock:** Sepsis associated with hypotension requiring administration of vasopressors.
- **Study hospital**: Defined as the hospital where the patient presented to the ED.
- **Suspected adverse reaction**: any adverse event for which there is a reasonable possibility that the study procedures caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the study procedures and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction (21 CFR 312.32(a)).
- **Suspected or confirmed infection in the emergency department:** Identified based on clinical behaviors of clinicians as the combination of administration of an IV- or IV-equivalent antibiotic plus collection of a body fluid culture or a positive molecular test for infection.
- **Suspected Unexpected Serious Adverse Reaction** (**SUSAR**) An adverse reaction that is both unexpected (not consistent with the risks outlined in the protocol or investigator brochure), serious, and meets the definition of a Suspected Adverse Reaction

2. STUDY SUMMARY

2.1 Title

Effects of Code Sepsis Implementation on ED Sepsis Care (Code Sepsis)

2.2 Primary Objective

Determine the effects of reorganizing ED sepsis care (Code Sepsis protocol) on door-to-antibiotic time for ED patients with sepsis.

2.3 Primary Hypothesis

Early activation of a multidisciplinary, coordinated, team-based assessment and treatment protocol for patients with potential sepsis will decrease door-to-antibiotic time for ED patients with sepsis.

2.4 Study Design

Pragmatic phase 2a pre/post single-center implementation study with contemporaneous controls testing reorganization of standard ED sepsis care around a protocol for early, coordinated, multidisciplinary protocol for assessment of patients with potential sepsis (Code Sepsis protocol).

1. We will emphasize pragmatic, real-world implementation of the Code Sepsis protocol in a single ED.
2. We will compare care delivered to ED patients after Code Sepsis protocol implementation in the intervention ED to care received in this ED prior to Code Sepsis implementation.
3. We will conduct a quasi-experimental analysis using contemporaneous control data obtained from two non-intervention hospitals to control for temporal trends in studied outcomes not resulting from the tested intervention.
4. We will measure the effects of protocol implementation on all ED patients with sepsis (including patients not treated under the Code Sepsis protocol) as well as potential bystander effects.

2.4.1 Study groups and phases

Phase #1: Pre intervention (November 13, 2018 to November 12, 2019)

- Control EDs: Standard care
- Intervention ED: Standard care

Phase #2: Intervention roll-in (November 13, 2019 to February 12, 2020)

- Control EDs: Standard care
- Intervention ED: Launch and fine-tuning of Code Sepsis protocol, fine tuning of Code Sepsis activation mechanism.

Phase #3: Full intervention (February 13, 2020 to February 12, 2021)

- Control EDs: Standard care
- Intervention ED: Full implementation of Code Sepsis protocol

2.4.2 Inclusion criteria

1. Age ≥18 years
2. Arrival to intervention or a control ED during study period

2.4.3 Exclusion criteria

1. Age <18 years

2. Trauma patient

2.4.5 Primary analysis cohort

ED patients with clinical sepsis, as identified by the combination of

1) Acute organ failure: SOFA score while in the ED ≥2 points above baseline
2) Suspected or confirmed infection while in the ED, as identified by both:
   a) Administration of ≥1 IV or IV-equivalent antibiotics while in the ED
   b) Collection of ≥1 body fluid cultures while in the ED

2.4.6 Primary outcome

Door-to-antibiotic time

2.4.7 Secondary outcomes

- Mortality (including 30-day, 1-year, hospital)
- Hospital charges
- Hospital length of stay
- Code Sepsis activation rate
- Code Sepsis activation accuracy
- Antibiotic utilization fraction
- Antibiotic spectrum
- Antibiotic overtreatment rate
- Adverse drug & allergic reaction incidence (e.g. anaphylaxis, new onset *Clostridium difficile* infection)

2.4.8 Data analysis

The primary analysis will use quasi-experimental methods to compare sepsis patients' adjusted mean door-to-antibiotic time (primary outcome) at the intervention hospital pre- versus post-implementation of the Code Sepsis protocol using the measured change at non-intervention hospitals to control for pre- versus post-intervention changes not attributable to protocol implementation. Secondary analyses will compare the change in secondary outcomes using similar methods.

2.4.9 Sample size

Assuming 4.5 sepsis patients per day at the intervention ED, treatment of 30% of these patients by Code Sepsis teams during study phase #3, and 6 total sepsis patients daily in control EDs (all conservative estimates), I will have 90% power to detect a change ≥16 minutes in the overall average door-to-antibiotic time among all ED sepsis patients after Code Sepsis implementation at the intervention hospital.

3. TRIAL DESCRIPTION

3.1 Background

Sepsis, the combination of infection and acute organ dysfunction, is a common, morbid, and often lethal syndrome.[1,2] Sepsis hospitalizes 1.3 million patients each year, kills 20%, and costs $23.7 billion.[2-4] Early, appropriate antibiotic initiation is critical: sepsis survival decreases with every hour's delay. [5-13] While guidelines and government mandates thus emphasize prompt antibiotics, international guidelines' have admitted a lack of data to support the feasibility or implementation of their one-hour door-to-antibiotic goal.[14,15]

Among patients presenting to the emergency department (ED) with sepsis, we previously found that non-patient contextual cues could improve rapid antibiotic initiation, whereas ED busyness was associated with delayed antibiotics.[16,17] I also discovered five-fold variation between physicians in median door-to-antibiotic time.[5] ED care reorganization could bypass these cognitive, stylistic, and resource barriers to timely sepsis treatment. In fact, ED protocols linking prehospital notification to a multidisciplinary, team-based response are common and effective for trauma, stroke, and myocardial infarction,[18-22] conditions that are less common and less mortal than sepsis but require similarly time-sensitive treatment.[23] Given that sepsis has a less definitive presentation, however, analogous protocols for sepsis could waste resources or promote anchoring bias and overtreatment of patients without sepsis, issues observed with door-to-antibiotic standards for pneumonia.[24-26]

We hypothesize that reorganizing ED sepsis care around multidisciplinary "Code Sepsis" teams activated prior to or upon patients' ED arrival will reduce door-to-antibiotic times — with tolerable overtreatment rates — by mobilizing personnel, systematizing illness severity and infection risk assessment,[27] facilitating test completion, and eliminating any gap between treatment decision and antibiotic infusion. This study will therefore evaluate the effectiveness and tradeoffs of a Code Sepsis program for ED sepsis patients.

3.2 Overall Study Motivation, Aim and Hypothesis

Many emergency department (ED) patients with sepsis do not receive antibiotics and other care within intervals recommended in international guidelines. Efforts to accelerate treatment, however, may lead to overtreatment and other adverse effects. The goal of this project is to determine the potential effectiveness and tradeoffs of a Code Sepsis program for ED sepsis patients.

Aim: **Establish the feasibility and effects of a team-based Code Sepsis protocol designed to accelerate antibiotic initiation for ED patients with suspected sepsis.**
Using preexisting infrastructure, implement prehospital- or triage-activated Code Sepsis ED teams in a single ED and compare sepsis patients' door-to-antibiotic times pre- and post-implementation, controlling for unrelated temporal trends with observational data from two non-intervention EDs.

Hypothesis: *Prehospital or triage-based activation of an ED team prepared to rapidly diagnose and treat sepsis decreases door-to-antibiotic time without increasing overtreatment.*

3.3 Primary Objective

Determine the effect of reorganizing ED sepsis care (Code Sepsis protocol) on door-to-antibiotic time for ED patients with sepsis.

3.4 Primary Hypothesis

Early activation of a multidisciplinary, coordinated, team-based assessment and treatment protocol for patients with potential sepsis will decrease door-to-antibiotic times for ED patients with sepsis.

3.5 Study Overview

To assess feasibility and test the preliminary efficacy of ED-based Code Sepsis teams activated on or before patients' ED arrival, we will pursue a Phase 2a implementation trial involving Code Sepsis team activation in one ED (Intermountain Medical Center [IMC]) while collecting contemporaneous control data at two other urban EDs (Utah Valley Hospital and Dixie Regional Medical Center [control sites], Table 1).

- Months 1-12: Collect baseline data (all sites), refine Code Sepsis protocol, and train ED staff at IMC. Portions of baseline data may be collected in a retrospective fashion. At the intervention site during this period, we may also undertake preparatory work to Code Sepsis protocol launch, including anonymous patient care observations to evaluate care processes; pilot testing of the draft Code Sepsis protocol or its components; and testing of the accuracy of Code Sepsis activation mechanisms.

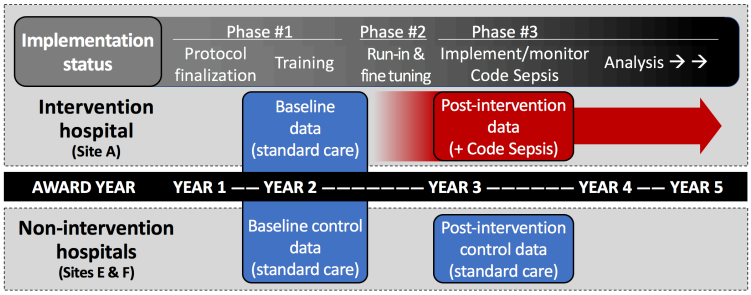

Figure 1. Code Sepsis implementation and data collection for Aim III.

- Months 13-15: Run-in period: implement Code Sepsis protocol at IMC, optimize protocol & its trigger.
- Months 25-36: Continue Code Sepsis protocol at site A (intervention ED). Continue standard care processes for sepsis without change (control condition) at two non-intervention EDs

Using contemporaneous controls and rigorous statistical methods, we will assess how implementation of the Code Sepsis protocol affects process and patient outcomes in the intervention ED (Figure 1). Continuation of the Code Sepsis protocol (with or without revision) by the intervention ED and/or adoption elsewhere within the Intermountain Healthcare system is expected to be contingent on the results of these analyses.

3.6 Analysis cohorts

3.6.1 Primary analysis cohort

ED patients with clinical sepsis, as identified by the combination of

1) Acute organ failure: SOFA score while in the ED ≥2 points above baseline
2) Suspected or confirmed infection while in the ED, as identified by both:
    c) Administration of ≥1 IV or IV-equivalent antibiotics while in the ED (see Appendix A)
    d) Collection of ≥1 body fluid cultures while in the ED

3.6.2 Secondary and sensitivity analysis cohorts

1) All eligible ED patients
2) ED patients with a "sepsis mimic" diagnosis based on a primary ICD-10 discharge diagnosis codes for congestive heart failure or venous thromboembolism with no diagnostic code for infection (see Appendix B).
3) "Likely" sepsis patients based on simple triage assessment to include fever and at least 1 out of 3 of hypotension (SBP <90 mmHg), altered mental status (GCS ≤14), or respiratory failure (RR ≥22 or SpO2 ≤85%).

3.6.3 Subgroups

A priori subgroups will include: sex; hypotension (SBP <90 mmHg or MAP <65 mmHg) present on ED arrival.

3.7 Endpoints

Analysis will be conducted on an intention to treat basis.

3.7.1 Primary outcome

Door-to-antibiotic time among all ED sepsis patients. Door-to-antibiotic time is the time from the first recorded arrival time in ED (usually ED triage or registration) and the time the first eligible antibiotic was administered (Appendix A).

3.7.2 Secondary outcomes

- Clinical/patient-centered secondary outcomes (measured among all ED sepsis patients):
    1) All-cause mortality to day 30
    2) All-cause mortality to 1 year
    3) In-hospital all-cause mortality
    4) Hospital charges: Amount charged to patient for their medical care during index ED visit and associated hospitalization.
    5) Hospital length of stay

- Process/feasibility secondary outcomes
    1) Code Sepsis activation rate: Measured as the percentage of all ED patients for whom the Code Sepsis protocol was activated.
    2) Code Sepsis activation accuracy metrics. Accurate Code Sepsis activation is defined as activation for patients who have sepsis while in the ED and no activation for patients who do not have sepsis in the ED.

- Adverse effects and unintended outcomes of protocol implementation

1) Antibiotic utilization percentage: measured as the fraction of (1) all ED patients; (2) Code Sepsis activation patients; or (3) "likely" sepsis patients who received IV or IV-equivalent antibiotics.
2) Antibiotic spectrum: Total Stenehjem antibiotic spectrum score[28] for all antibiotics administered in first 24 hours, measured for (1) all ED patients or (2) sepsis patients
3) Antibiotic overtreatment rate: Percentage of "sepsis mimic" patients who received IV or IV-equivalent antibiotics in the ED.
4) New onset C. difficile colitis incidence: Percentage of (1) all ED patients and (2) ED sepsis patients with a positive stool test for *Clostridium difficile* colitis between 72 hours and 90 days after ED arrival.
5) Adverse drug & allergic reaction incidence: Measured as the fraction of 1) all ED patients and (2) ED sepsis patients with a discharge diagnosis code consistent with anaphylaxis or with an adverse reaction to antibiotics (see Appendix C).

- Potential exploratory outcomes
  1) Measures of organ failure trajectory, to include change in the SOFA score between hospital day 1 and hospital day 3, and overall and organ-specific measures of organ failure-free days through day 28.
     - Organ-failure free days (OFFD) are defined as the number of days from the time of the first SOFA score ≤1 above baseline to day 28 after ED arrival, assuming survival for at least two consecutive calendar days after the SOFA score ≤1 above baseline and continued SOFA score ≤1 point above baseline to day 28. If a patient has SOFA score rise again to ≥2 points above baseline and subsequently achieves SOFA score ≤1 point above baseline to day 28, VFDs will be counted from the end of the last period of SOFA score ≤1 to day 28. If a patient had SOFA score ≥2 points above baseline at day 27 or dies prior to day 28, OFFD will be zero
     - Support-free days (i.e. ventilator-free days) are calculated similar to OFFD
  2) Mortality at other intervals
  3) Testing and treatment utilization. Outcomes measured among (1) among all ED sepsis patients; (2) all ED patients; (3) "likely" sepsis patients
  4) Code Sepsis care process timing: measured among patients who received Code Sepsis protocol activation as time from protocol activation until completion of key protocol steps, to include blood culture collection, chest X-ray collection, team huddle, antibiotic initiation
  5) Timing of testing & care processes among all sepsis patients, to include ED clinician assessment, ED room placement, ED departure, blood culture collection, radiology testing, and order entry for antibiotics. Measured analogous to door-to-antibiotic time.
  6) Code Sepsis protocol adherence: measured as performance of protocol steps in correct order both individually and as a fraction of all possible.

4. STUDY POPULATION AND ENROLLMENT

4.1 Setting

Intermountain Healthcare (hereafter "Intermountain") is a nonprofit health system based in Salt Lake City, Utah with 23 hospitals in Utah and Idaho. Code Sepsis implementation will occur in a teaching ED (IMC, my "home" hospital) providing 89,000 visits annually (2.8% with clinical sepsis) for an economically and ethnically diverse population of 1.1 million in Salt Lake County, Utah plus referrals from Wyoming, Nevada, and Idaho. To avoid spillover effects, concurrent control data will be electronically abstracted from two Intermountain EDs (Utah Valley Hospital and Dixie Regional Medical Center) staffed by other physician groups (Table 1).

Table 1. Study hospital characteristics

Site	Description	Hospital beds	ED beds	Annual ED visits
IMC	Tertiary/teaching	472	56	89,000
Utah Valley	Regional referral	395	28	49,000
DRMC	Regional referral	321	35	65,000

4.2 Study Population

We will study adult, non-trauma patients from the IMC ED and two control EDs during three phases (Figure 1): baseline (1 year, standard care at all sites); run-in (3 months, IMC ED launches/fine tunes the Code Sepsis protocol); and Code Sepsis implementation (1 year, Code Sepsis at IMC, standard care in control EDs). For this pre/post implementation trial, in which there will be no direct patient contact and in which we are comparing current standard care processes to a new, redesigned standard care processes in a non-randomized fashion, all ED patients who meet inclusion and do not meet exclusion criteria will be included in the analysis.

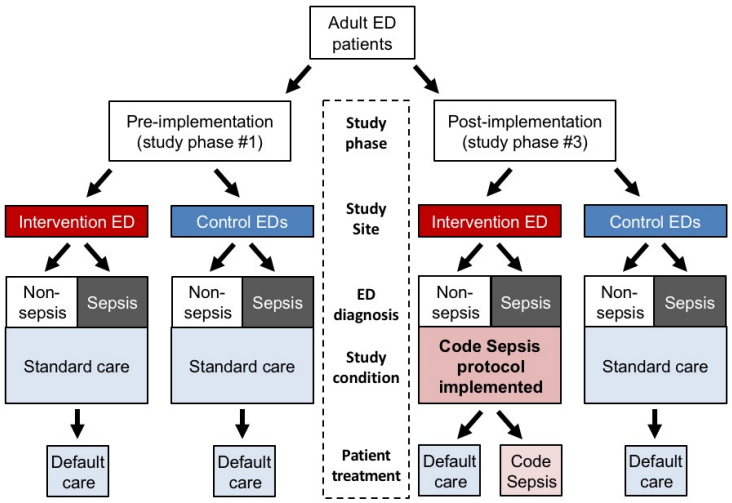

Figure 2. Subject allocation by study phase and hospital

4.2.1 Exposure groups

The group within which patient is analyzed is determined by the combination of (1) when the patient presents to the ED and (2) which hospital/ED to which the patient presents (Figures 1 and 2).

A. *Pre-implementation control group at non-intervention hospitals*: Admission to ED at non-intervention hospitals (Utah Valley Hospital and Dixie Regional Medical Center) prior to Code Sepsis implementation (estimated N=135,000)
B. *Pre-implementation control group at intervention hospital*: Admission to ED at IMC prior to Code Sepsis implementation (estimated N=100,000)
C. *Post-implementation control group at non-intervention hospitals*: Admission to ED at non-intervention hospitals (Utah Valley Hospital and Dixie Regional Medical Center) after implementation of Code Sepsis protocol at IMC (estimated N=170,000)
D. *Exposure group*: Admission to ED at IMC during full Code Sepsis implementation (estimated N=125,000)

4.2.2 Inclusion criteria:

- ED patient at Intermountain Medical Center, Utah Valley Hospital, Dixie Regional Medical Center
- ED arrival beginning 1 year prior to date of Code Sepsis implementation at Intermountain Medical Center and continuing through 15 months after Code Sepsis implementation date.
- Age ≥18 years

4.2.3 Exclusion criteria:

- Age <18 years
- Trauma patient

4.2.4 Inclusion/exclusion criteria rationale

Patients <18 years of age are excluded because the mechanisms, manifestations, and management of sepsis in children <18 years of age are often distinct from those applicable to adults, and in fact will vary depending on age group across childhood. Additionally, children are managed in most EDs by a distinct team of clinicians using distinct protocols. As such, prehospital or triage-based sepsis prediction models applicable to adults are unlikely to work for children <18 years. Due to the above issues, implementation of a single sepsis care protocol for individuals age <18 years and age ≥18 years would impair the efficacy, feasibility, and generalizability of the proposed Code Sepsis protocol. Trauma patients are excluded because clinical identification of these patients is straightforward and triggers preexisting team-based care protocols with options for prehospital activation.

4.2.5 Study phase dates

ED patients arriving to study EDs will be assigned to a study phase based on their ED arrival date.

- *Phase #1* (pre-intervention analysis phase): November 13, 2018 to November 12, 2019
- *Phase #2* (intervention roll-in): November 13, 2019 to February 12, 2020
- *Phase #3* (full intervention analysis phase): February 13, 2020 to February 12, 2021

4.3 Waivers of Informed Consent and HIPAA authorization

This study comparing standard care to a new form of standard care will be carried out under a waiver of informed consent and HIPAA authorization (see section 9).

4.4 Minorities and Women

Women and minorities will be enrolled in proportion to their representation in the population base from which this study was developed, specifically patients presenting to Intermountain hospitals located in Utah's Salt Lake, Washington, and Weber Counties. In order to provide generalizable data for the ED patient diagnosis groups studied in each Aim, there will be no specific selection criteria that differ between sex/gender and racial/ethnic groups. Hospitals in this study serve counties with a combined population of over 1.5 million individuals, including over 26% who are Hispanic or non-white race. We expect the sex, ethnic and racial mix of the enrolled patients to reflect the population served.

4.5 Vulnerable Subjects

We anticipate that potentially vulnerable subjects are eligible for the study. Potentially vulnerable patient subjects include pregnant women, prisoners, and/or individuals with decisional impairment. The purpose of this project is to identify a cohort that reflects the diversity of the U.S. sepsis population. Therefore, we believe these individuals should not be excluded from the study since the study is of no more than minimal risk.

1. Data on vulnerable population membership will not be explicitly collected, and in fact attempting to identify and exclude members of potentially vulnerable populations could increase risk to both vulnerable patients and the overall subject cohort.
2. Altered mental status is also a common manifestation or complication of sepsis. Excluding patients with decisional impairment would therefore severely bias results of the planned analyses.
3. In implementation studies such as this, it is generally not possible to exclude vulnerable subjects. Aim III's intervention involves testing a new option for standard care for ED sepsis management, so excluding vulnerable populations could actually subject these patients to harm because exclusion would prevent their receiving standard care. Assessment for vulnerability status, moreover, would largely preclude the planned intervention by preventing activation of prehospital or ED triage alerts.

5. STUDY PROCEDURES

This study will measure the effect of a redesign of standard care for ED sepsis patients, specifically implementation of Code Sepsis protocol at Intermountain Medical Center. The study will include three phases with two groups during each phase. The primary analysis will only use data from phases #1 and #3 (see Figure 1 and 2).

Phase #0: Protocol development (1 year, overlaps with phase #1)

- Control EDs: N/A
- Intervention ED: A small number of suspected sepsis patients (<10) may undergo anonymous observation to understand care processes involved in ED sepsis care. In addition, testing and iterative optimization of the accuracy of the Code Sepsis activation may employ direct observation of care for a convenience sample of patients during ED triage and comparison of activation criteria to clinician judgment, final sepsis diagnosis based on chart review, and electronic sepsis queries. Finally, pilot testing of the draft protocol may be conducted on a small convenience sample of patients (<20) identified by ED clinicians as having possible sepsis. We will collect anonymous data about completion of Code Sepsis processes during pilot testing.

Phase #1: Pre intervention (1 year)

- Control EDs: Standard care
- Intervention ED: Standard care.

Phase #2: Intervention roll-in

- Control EDs: Standard care
- Intervention ED: Launch and fine-tuning of Code Sepsis protocol, fine tuning of Code Sepsis activation mechanism.

Phase #3: Full intervention

- Control EDs: Standard care
- Intervention ED: Full implementation of Code Sepsis protocol

Phase #4 (operational): Continuation of the Code Sepsis protocol (with or without revision) by the intervention ED and/or adoption elsewhere within the Intermountain Healthcare system is expected to be contingent on observed effects of protocol implementation. It is possible that an inadequate benefit/risk ratio could lead to a decision not to continue the Code Sepsis protocol.

5.1 Standard Care

Patients arriving to the control EDs (all study phases) and the intervention ED during study Phase #1 will receive care as per then-current ED practices and protocols, guided by clinician judgment within a system-wide care process model for sepsis. As of early 2019, ED standard care for sepsis applicable at all study sites includes a standardized Care Process Model, expected completion of a standardized checklist, and standardized order sets.

5.2 Code Sepsis Protocol

The Code Sepsis protocol (Figure 3) has six steps developed in collaboration with ED-based study team members and ED leaders (including physicians, nurses, pharmacists, and others) from the implementation ED and the Intermountain system. The current draft protocol was further iteratively revised based on input derived from the proposed multidisciplinary team during *in situ* high-fidelity simulation and during informal/ad hoc operationally-oriented pilot testing of steps 1-5 during live patient care. The below protocol will be adapted further prior to and after implementation to ensure the protocol is feasible, efficient, and functions as intended based on stakeholder input and, as needed, additional protocol element testing during simulation and/or live patient care. Further revision will occur, during the protocol run-in phase and as needed based on observed findings and stakeholder input.

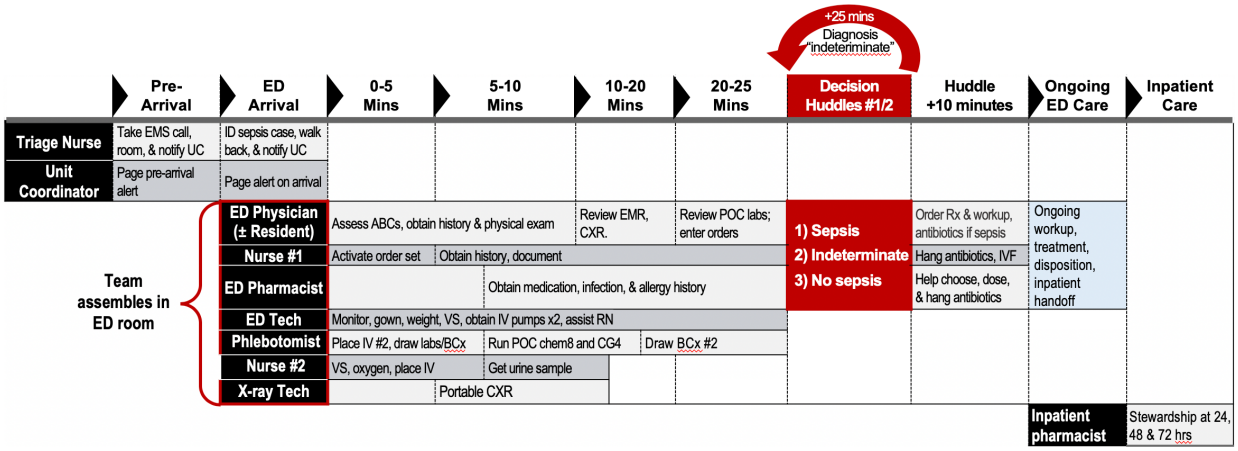

Figure 3. Current Code Sepsis protocol based on iterative revision using simulation testing, stakeholder input, & live pilot testing.

1) Identify likely sepsis patient from prehospital notification call data (nurse), at ED triage (nurse/physician), or on ED room placement (nurse or physician), adapting local and national practice for stroke team activation.[29,30]
2) Mobilize ED personnel and equipment to meet patients on arrival to the ED room using methods and communication networks already developed for ED trauma and stroke teams.
3) Concurrent patient evaluation and data collection by multiple disciplines (20-25 minutes), to include bedside assessment (e.g. history, examination, vital signs, allergy and medication history) by the physician, nurse and pharmacist; IV placement; blood and urine sampling; point-of-care laboratory testing, including lactate and urinalysis; and portable X-ray imaging. Appropriate therapeutic interventions will continue in parallel during the nominal data collection phase.
4) Team "huddles" to decide if sepsis diagnosis has been confirmed, disproven, or remains indeterminate. The physician may complete this step by announcing clinical decision-making to the team at any time. The nurse will request a decision huddle at 25 minutes into the Code Sepsis event if it has not previously been performed.

5) Proceed with next therapeutic and/or diagnostic steps including, for confirmed sepsis patients, immediate initiation of an appropriate antibiotic regimen chosen from a range of options contained in a Code Sepsis antibiotic pack brought to the bedside by a pharmacist on protocol activation. Code Sepsis antibiotic regimens have been selected based on published guidelines and local antibiotic resistance patterns with input from ED clinicians, pharmacists, and infectious disease/antibiotic stewardship personnel.
6) If initial huddle pronounced sepsis status as "indeterminate," return to step #4 after additional 20-25 minutes to follow up on additional diagnostic results (e.g. urinalysis, complete blood count
7) For antibiotic-treated patients, follow-up by antibiotic stewardship pharmacist active de-escalation or cessation as appropriate.

Additional protocol elements/details:

- Code Sepsis team members:
    - ED attending physician +/- ED resident physician or medical student
    - ED triage nurse
    - ED unit coordinator (i.e. unit secretary)
    - ED nurses x2
    - ED patient care technician
    - ED phlebotomist x1-2
    - ED pharmacist as available
    - ED X-ray technician
- Code Sepsis electronic order entry: Code Sepsis order sets for diagnostic evaluation and antibiotic treatment will be constructed and activated at the intervention ED's electronic medical record with the beginning of study Phase #2. Order sets will help speed up diagnostic testing and treatment initiation, aid care standardization, and facilitate Code Sepsis event tracking and data collection.
- Code Sepsis clinical team training: With active support from intervention hospital clinical leadership as well as Intermountain's system-wide ED leadership team, the Code Sepsis ED Implementation Team will provide clinical staff in the implementation ED with training on the Code Sepsis protocol during the months prior to study Phase #2. Primary training will include distribution of instructional materials, direct education at clinical staff meetings, targeted in-person education, and *in situ* simulation. Primary training will complete early in study Phase #2, with consolidation training, protocol reminders, physician detailing, and targeted clinician reeducation continuing through study Phase #3.

6. DATA COLLECTION AND VARIABLES

Core analyses will employ data collected during routine clinical care and hospital operations. There will be no direct patient contact for collection of identifiable data or specimens.

6.1 Data Collection

Intermountain's Enterprise Data Warehouse (EDW) is a centrally-managed, well-curated, and accessible database linking system-wide clinical, billing, laboratory, and other data.[31] Eligible patient subjects will be identified by project data managers from EDW data, who will generate a dataset specific to the proposed study by linking EDW data to additional data abstracted from the electronic health record. Manual chart review and direct queries to bedside clinicians will be employed as needed to supplement electronically-available data. This encounter level data will be linked to additional data on hospital characteristics, physician and nurse staffing. Long-term mortality data will be obtained through a preexisting linkage to Utah state death records and/or the federal Social Security Death Index. Encounter data will be linked to data on race, ethnicity, and hospital admissions (admit date, type, diagnoses, and costs) stored in the Utah Population Databank. We will employ a preexisting linkage to Utah State death records and the federal Social Security Death Index for mortality ascertainment.

6.2 Anonymous Data Collection For Protocol Development and During Live Code Sepsis Activation

The study team will receive notification of Code Sepsis activations. As part of the study operational process, ED clinical leadership and study personnel will directly observe a convenience sample of these events to anonymously record protocol parameters, including team composition and process completion times. In addition, a convenience sample of intervention hospital patients (<10) with sepsis may be observed during the pre-Code Sepsis implementation phase to understand care processes involved in sepsis care. No identifying information about the patient or clinical team will be recorded.

6.3 Active Follow-Up for Patients Undergoing Code Sepsis

Via the electronic medical record, a member of the study team will actively monitor Code Sepsis activation patients every 1-3 days until hospital day #7. There will be no direct patient contact.

6.4 Protected Health Information

Protected health information including subject encounter codes, medical record numbers, birthdates, encounter event date and times, address, and social security number will be collected during the electronic query to allow manual chart abstraction and manual review of electronic record for data completion and verification.

6.5 Variables/data elements

- Patient medical record number(s)
- Patient encounter ID code
- Hospital/facility
- Date of birth
- Age
- Sex
- Race

- Ethnicity
- Marital status
- Preferred language
- Insurance status/type
- Address/zip code (for determination of residence at a nursing facility or other long-term care facility and estimation of socioeconomic status)
- Social Security Number (to assist matching of encounter data to Social Security Death Index and Utah state death records)
- ED disposition
- Hospital disposition
- Date/time of all events related to ED visit and hospitalization (e.g. ED arrival & departure, hospital admission & discharge)
- Date/time antibiotics administered
- Antibiotic utilization
- APACHE II score
- APACHE IV score
- Acute physiology score
- Charlson index
- Elixhauser index
- SOFA score
- Baseline SOFA score over preceding 10 years
- Source of admission (e.g. home, SNF, LTAC, outside hospital)
- Source of infection
- Clinician infection determination, patient illness severity, sepsis status, and agreement with Code Sepsis activation
- Sepsis presence/absence
- Culture results
- Admission diagnosis
- Mode of arrival to ED
- ED triage data including triage acuity score
- Resident involvement in ED care
- Results of all laboratory testing
- Date/time of all laboratory testing
- ED length of stay
- ED vital signs
- ED medications
- ED interventions/procedures
- Date/time, elapsed time, and type of ED events including provider interaction, room placement, disposition
- Date/time of diagnostic testing, vasopressor initiation and other interventions, and management
- Date/time of interventions
- Date/time of blood or body fluid cultures
- Discharge diagnosis and procedure codes
- Billing diagnosis and procedure codes
- Diagnosis-related group
- Hospital length of stay

- In-hospital mortality
- Long-term mortality (e.g. 30d, 90d and 1y mortality)
- Healthcare charges
- ED patient census
- Number of ED beds
- ED patient flow (including counts of patient arrivals, boarding, and admissions)
- Attending physician ED staffing
- Nurse staffing
- Trauma registration status
- Allergies
- Adverse drug reaction events and date/time
- Code Sepsis team activation (Y/N)
- Code Sepsis activation date/time
- Code Sepsis care process completion date/times
- Code Sepsis team function
- Code Sepsis team composition (by role)
- Code Sepsis process adherence

6.6 Data Management

Data analysts and research coordinators will collect data and record it in a custom-designed computer database. Data abstraction from electronic medical records will employ either standardized paper data sheets or a custom-designed interface maintained within Intermountain's secure Research Electronic Data Capture (REDCap) platform.[32] Outside REDCap, all study data will be kept in a protected database on a protected computer. Each subject will be assigned a study identification number, and we will maintain minimal patient identifiers. Data for analysis will use study ID codes for patient subjects. Shared or presented data will be in anonymized or aggregate format such that individual patient subjects cannot be reidentified. Any hard copy case report forms will only include study identification numbers, and will be stored in a locked file cabinet.

7. DATA ANALYSIS

7.1 Introduction to Quasi-Experimental Analysis

This study will measure the effect of implementing a team-based Code Sepsis protocol for ED sepsis patients by comparing risk-adjusted process and patient-centered outcomes before versus after protocol implementation at a single hospital. Results from simple pre/post analyses, however, may be subject to misinterpretation due to *secular trends* (changes in the measured outcomes over time not attributable to the study intervention). Analyses of Aim III primary and secondary outcomes will therefore employ quasi-experimental methods to eliminate confounding due to secular trends when estimating the effect of Code Sepsis implementation on outcomes. More complex methods of quasi-experimental analysis includes interrupted time series and regression discontinuity, but are analogous to the relatively simpler approach called *difference-in-difference analysis* (Figure 4).[33] Difference-in-difference analysis uses multivariable linear regression to compare the adjusted mean door-to-antibiotic time (primary outcome) at the intervention hospital pre- versus post-implementation of the Code Sepsis protocol using the measured change at non-intervention hospitals to control for pre-/post-intervention changes not attributable to protocol implementation.[34]

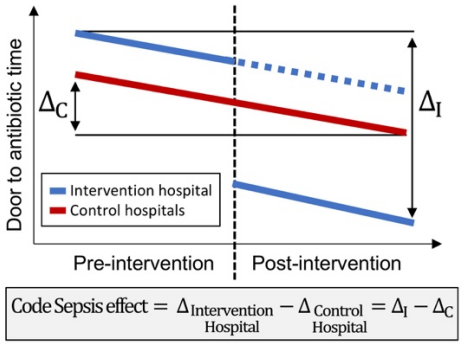

Figure 4. Difference-in-differences analysis

$$\boldsymbol{Y_i} = \beta_1 \mathrm{ERA}_i + \beta_2 \mathrm{HOSP} + \boldsymbol{\beta_3 \mathbf{ERA}_i \times \mathbf{HOSP}_i} + \beta_4(\mathrm{Z}_i)$$

Figure 5. Simplified difference-in-differences equation. Y_i is the door-to-antibiotic time for patient *i*, HOSP and ERA are, respectively, indicator variables for care at the intervention hospital or an ED arrival date after Code Sepsis implementation, and Z is a vector of covariates. β_3 is the coefficient of interest.

This model tests the *difference* in intervention ED versus non-intervention EDs' *differences* in outcome before versus after the Code Sepsis implementation (Figures 4-5). The β_3 parameter from the regression model depicted in Figure 5 provides the adjusted difference-in-differences estimate and significance tests for the influence of the Code Sepsis intervention on the outcome of interest.

7.2 Multivariable models

Multivariable models will be adjusted for demographic and clinical parameters with known or plausible associations with both door-to-antibiotic time and treatment hospital, presentation before or after Code Sepsis implementation, and/or Code Sepsis activation. Evaluation of secondary outcomes will employ an analogous approach using multivariable linear, Poisson, or logistic regression as appropriate. Repeating the quasi-experimental analysis for the primary and key secondary outcomes after stratification (rather than adjustment) by (1) sex and (2) hypotension present versus absent on ED arrival will allow evaluation of whether these patient characteristics modify the effects of Code Sepsis implementation. In order to measure how the Code Sepsis protocol influences the care of its core target population, we will perform analyses comparing selected outcomes among the subset of patients who have ED triage data suggesting a strong possibility of sepsis. Outcomes to be evaluated in the sensitivity analyses will include door-to-antibiotic time, antibiotic treatment fraction, and antibiotic treatment spectrum.

7.3 Sample size/power analysis

Using 2013 to 2017 data from our study hospitals, we estimated conservatively that the intervention ED provides care for 1,650 sepsis patients annually (approximately 4.5 sepsis patients per day) and the

control EDs together care for a total of 2,200 sepsis patients annually (approximately 6 sepsis patients per day). Based on the design and our pilot testing of the Code Sepsis protocol, a very conservative estimate of door-to-antibiotic time for patients who receive antibiotics after evaluation under the Code Sepsis protocol is 50 minutes. By comparison, our preliminary data from 2013 to 2017 indicates current mean (SD) door-to-antibiotic time for ED sepsis patients is 170 (±75) minutes and that only 5% of patients currently receive antibiotics within 1 hour of ED arrival. Assuming (again conservatively) that the Code Sepsis protocol is activated for 30% of sepsis patients treated in the intervention ED during the full implementation phase (study phase #3), we will have 90% power to detect a difference-in-differences change of 16 minutes or more in door-to-antibiotic time associated with Code Sepsis implementation, with the measurement population being all ED sepsis patients. Power calculations employed Monte Carlo simulations, for which technical details are available upon request.

8. RISK ASSESSMENT

This study involves a before-and-after analysis of the effects of reorganizing standard ED care for sepsis. Patient care will be studied under two designs for standard sepsis care.

8.1 Potential Risks

8.1.1 Risk of confidentiality breach

Potential consequences of a breach of confidentiality to the subject could include identify loss of privacy, medicolegal liability, theft, embarrassment, or harassment.

8.1.2 Risks for control group patients

Aside from issues discussed above, there are no foreseeable risks for ED patients receiving care at a non-intervention hospital or at the intervention hospital during study phase #1 and #2. Sepsis patients arriving to control hospitals will receive standard care throughout the study.

8.1.3. Risks to patients exposed to the Code Sepsis protocol

Patients presenting to the intervention hospital during phases #2 and 3 (run-in implementation and full implementation) will be exposed to and may receive care using the "Code Sepsis" version of standard care. The Code Sepsis protocol is designed to accelerate evaluation, testing, and treatments that the patient would have eventually received under now current standard care. The Code Sepsis intervention is therefore expected to pose no more than minimal risks to ED patients exposed to the protocol, including specifically sepsis patients for whom the Code Sepsis protocol is activated. The potential risks to subjects due to this protocol include:

1) Adverse drug reactions or antibiotic-associated infections related to unnecessary or overtreatment antibiotic treatment with prespecified regimens.
2) Delay in diagnosis of non-infectious problems due to focus on sepsis or infection related to Code Sepsis activation.
3) Delay in care related to resource allocation away from non-Code Sepsis patients without sepsis (bystanders without sepsis).
4) For sepsis patients for whom the Code Sepsis protocol is not activated (i.e. bystanders with sepsis), delay in care related to lower index of suspicion for sepsis leading to delayed diagnosis or resource allocation away from these patients.

8.2 Alternatives to Participation

There are no alternatives to participation in this pragmatic before/after implementation research study.

8.3 Minimization of Risks

Federal regulations at 45 CFR 46.111(a)(1) require that risks to subjects are minimized by using procedures which are consistent with sound research design. We will review the electronic medical record of all Code Sepsis activations for potential adverse effects related to study procedures. This will include review of standardized Code Sepsis documentation incorporated into clinical care as part of the care redesign. While there are no foreseeable effects of data collection on the care of patients who receive standard care at the control hospitals (all study phases) or during the pre-intervention phase at Intermountain Medical Center, monitoring of aggregate data quality will include all hospitals and study phases. As necessary, after consultation with the Independent Safety Monitor, study procedures (including the Code Sepsis protocol) will be adjusted or even halted if important adverse effects are

identified. There are several specific elements of study design inherent in the present protocol that meet this human subject protection requirement.

8.3.1 Protections against invasion of privacy or breach of confidentiality

Protection of subject identity and prevention of unintentional release of protected information is of paramount importance to the research team.

- *Data storage and transfer*: Data will be maintained in password-protected, encrypted research servers, REDCap (a secure, HIPAA-compliant system), or password-protected, encrypted computers. Patient identifiers for prehospital data linkage in Aim I will be provided in secure, encrypted electronic format to Department of Health staff for identification of ambulance patient care reports. Matched records will be returned in secure, encrypted electronic format. All devices will have been approved by Intermountain Healthcare or (during matching of ED data to prehospital data) the Utah Department of Health for use with clinical and research data. Both Intermountain and the State of Utah deploy comprehensive information technology support systems to maintain and regularly update computer systems and maintain physical and electronic safeguards for data management. Any paper case report forms will only include study identification numbers, and will be stored in a locked file cabinet. Datasets used for statistical analyses will be deidentified.
- *Data access*: Only the PI and the study team will have access to identifying information. All individuals with access to identifiable data will have all necessary human subjects training, including Good Clinical Practice training as required by NIH policy for applicable study team members involved in the clinical trial proposed.
- *Training*: All study personnel will maintain appropriate training in human subjects research and data protection. The PI, primary mentor, and study staff responsible for study coordination, data collection, and data management of the associated clinical trial will maintain Good Clinical Practice training as per NIH policy (NOT-OD-16-148).

8.3.2 Incidental findings

Data review and analysis will use only data collected as part of routine clinical care and operations. We therefore do not expect identification of incidental findings relevant to patient care.

8.3.3 Protection against medicolegal risk

Data on subjects studied in the proposed aims will be kept confidential in accordance with applicable laws and statues.

8.3.4 Optimization of Code Sepsis targeting

Optimization of team activation mechanism during phase #2 of Aim III (intervention run-in and optimization) will help maximize false positive and minimize false negative team activations.

8.3.4 Protections against overtreatment and anchoring bias

Physicians and other providers will be educated intensively about the protocol, with particular emphasis on the corresponding concepts that (1) a sepsis team activation does not establish a sepsis diagnosis and (2) that the sepsis prediction tool was specifically not designed to capture all patients with sepsis and that, as a consequence, many patients with sepsis will not trigger a Code Sepsis.

8.3.5 Protections against overtreatment and adverse drug reactions

Part of this redesign of standard care is incorporation of both direct pharmacist involvement in the Code Sepsis team and antibiotic stewardship monitoring of antibiotic-treated Code Sepsis patients to reduce antibiotic overtreatment. Pharmacist involvement will also help minimize the risk of preventable adverse drug or allergic reactions.

8.4 Potential Benefits of the Proposed Research to Human Subjects and Others

This study has the potential to generate important findings for patients with sepsis and their treating clinicians, including methods to identify sepsis patients at ED triage or in the prehospital setting. Sepsis patients treated in the intervention ED after implementation of the full Code Sepsis protocol could receive faster evaluation, diagnosis, and treatment initiation, leading to improved patient outcomes. The risks to patient confidentiality and the risks for adverse drug reactions appear substantially less than the potential benefit to sepsis patient subjects and the important knowledge gained about delivery of ED sepsis care.

8.5 Importance of the Knowledge to be Gained

Patients with sepsis —a syndrome defined by infection associated with acute organ dysfunction — have high mortality. This syndrome is also common, affecting nearly 3% of ED patients in our data. Early antibiotic initiation improves sepsis outcomes, but many ED patients do not receive timely antibiotics. The overall hypothesis of this phase 2a study is that reorganizing standard ED sepsis care around multidisciplinary “Code Sepsis” teams activated prior to or immediately upon patients’ ED arrival will reduce door-to-antibiotic times. Aim III of this proposal will determine whether the Code Sepsis protocol is feasible, safe, and effective at decreasing door-to-antibiotic time. Data from human subjects are also necessary to validate triage- or prehospital-based sepsis prediction models that can be customized by users planning sepsis screening, intensive resource mobilization (as is planned here) for sepsis care, or to aid risk/benefit decisions for sepsis treatments with more than minimal risks (Aim I) and to understand how practice patterns or systems of care may be optimized to accelerate time-dependent treatment while minimizing unintended consequences (Aim II). The no-more-than-minimal risks to subjects from observational research (Aims I and IIA), interviews (Aim IIB), or systematically reorganizing sepsis care to accelerate evaluations and treatments patients would receive anyway under current standard care (Aim III) are acceptable in the context of the important knowledge to be gained to improve care for the common and deadly sepsis syndrome.

9. HUMAN SUBJECTS

We will prospectively assess the effect of a system-level intervention on the organization of ED sepsis care using an augmented pre-/post-intervention design. In the post-intervention period, the studied intervention — early activation of ED teams for patients likely to have sepsis — will be adopted as standard care at Intermountain Medical Center. As such, no patients arriving to any ED during the pre-intervention or to a non-intervention control ED will be exposed to the intervention. Conversely, all patients arriving to the Intermountain Medical Center ED in the post-intervention phase will be exposed to the intervention.

9.1 Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. All eligible patients will be enrolled. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice.

9.2 Waiver of Informed Consent and HIPAA Authorization

To allow analysis of patient outcomes in all patients during both the pre- and post-intervention phases and to facilitate future research through creation of a research registry, we will request a waiver of informed consent and HIPAA authorization based on the following criteria as per 45 CFR 46.116(d) and the HIPAA Privacy Rule.

9.2.1 Research and registry involve no more than minimal risk

Acceptance is widespread for protocols using pre-arrival notification to activate ED teams for the treatment of other critical illnesses where time-to-treatment determines outcomes. Since the tested exposure will be incorporated into ED care processes as standard care, and will merely accelerate evaluation, testing, and treatment sepsis patients would receive during current (pre-intervention) standard care, patients will overall experience only the risks associated with standard ED clinical care. Research and registry creation involve no direct contact between the study team and patients, only review of records routinely collected for administration and medical care. For a small number of subjects, there will be anonymized monitoring of ED operations in the form of non-interactive observation of Code Sepsis protocol completion involving collection of anonymous data, which would be standard during implementation of any approach to improving standard ED care.

9.2.2 No adverse effects on the rights and welfare of participants

Exposure to standard care in the form of the Code Sepsis protocol and research team abstraction of data routinely collected in the course of clinical care should have no influence on the welfare of study subjects. Analysis and registry storage of data recorded as part of routine clinical care and operations should have no influence on the welfare of study subjects. Because risk is minimal given this design, the waiver of consent and authorization will not adversely affect the rights or welfare of subjects.

9.2.3 The research and registry could not practicably be carried out without waiver of informed consent

Given the large number of eligible patient subjects (up to 530,000, including approximately 9,450 patients with sepsis in the primary analysis cohort), the research and registry could not practicably be carried out without the waiver of consent. The sample size for this chart review is large enough that including only those data for which consent could be obtained would prohibit conclusions to be drawn

and would compromise the scientific validity of the study, as a large proportion of the data would be eliminated if obtaining consent were a requirement. Obtaining consent would also preclude rapid initiation of the Code Sepsis protocol and rapid antibiotic initiation. The subjects whose records will be reviewed will not be followed beyond their hospitalization (except for routine use of data on long-term mortality obtained via existing linkages) and would be mostly lost to follow up. The proportion of subjects who have relocated or have passed away will likely be a significant percentage of the subject population, and so the research results would not be meaningful and would lose statistical power if obtaining consent were a requirement.

9.2.4 Information on the Code Sepsis protocol and study will be available to all ED patients

We will make available patient information sheets describing the Code Sepsis protocol in the intervention emergency department (e.g. lobby, patient information stations, and on request). It is otherwise not possible to provide patient subjects with information about the study as there is no feasible mechanism by which to notify subjects, attempting to do so would substantially increase the risk of a confidentiality breach, and because the information that is found will have no impact on subjects' clinical care.

9.2.5 The minimal necessary amount of protected information will be obtained

Only data necessary for the completion of the study will be collected. The patient ID, encounter ID, social security number, address, and date of birth are necessary to allow data linkage, identification of the specific patient encounter for supplemental data abstraction. Event date/times are necessary for care process and outcome measurement, including calculation of the elapsed time related to various patient management actions include the primary outcome. Identifiers will maintained in the registry to facilitate future research.

9.2.6 All data, including PHI, will be securely guarded from improper disclosure

High-level safeguards will be in place to protect subject identity and confidential data, including in data maintained in the research registry. The study and registry data will be kept on encrypted, password-protected computers. These computers are routinely used for storage of patient data and research data including subject identifiers. The data will only be accessible to members of the research team, and all members of the research team have completed Human Subjects Protections and understand the importance of protecting subject privacy and confidentiality. No PHI will be recorded on the CRFs for the study dataset. Protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, for other research as approved by an IRB, or for other research for which the use or disclosure of protected health information would be permitted by under applicable regulations. Minimal identifiers will be maintained linked to the data. Maintaining minimal identifiers linked to the data is necessary to allow (1) manual abstraction of additional data from the electronic medical record and (2) potential future linkage – with IRB approval -- of the data to additional datasets. No individual subject data will be presented in any presentation, publication or report related to this research. Data will be presented only in anonymized or aggregate or as results of statistical analyses and will not include any individual-level data that could be traced to a particular subject.

10. MONITORING AND SAFETY REPORTING

On the basis of established precedents in implementation research, using toolkits supplied by NIH institutes and the University of Washington's CTSA-supported Institute for Translational Health Sciences and in consultation with the Intermountain Institutional Review Board (IRB) and National Institutes of Health (NIH) staff, we believe the proposed clinical trial represents no more than minimal risk to exposed patients. The study will thus be overseen by an Independent Safety Monitor (ISM), a practicing ICU physician with extensive experience performing clinical trials but not affiliated with the current trial.

10.1 Potential Risks and Benefits for Participants

- Potential risks: The risk level associated with this study is estimated to be no more than minimal, since the studied intervention — prehospital activation of ED-based Code Sepsis teams — will be adopted as standard care and is designed to accelerate evaluation, testing, and treatments that the patient would have eventually received under current standard care. While the efficient coordination of therapies is novel and likely to improve care overall, we will monitor for the possibility of effects potentially relevant to faster antibiotic therapy, specifically receipt of antibiotics to which the patient is known to be allergic. This possibility is protected against through inclusion of a pharmacist in the Code Sepsis team. Other risks are also minimal and related to loss of confidentiality of data.
- Potential benefits: The potential benefits to study subjects with sepsis treated in the intervention ED after implementation of the full Code Sepsis protocol include faster evaluation, diagnosis, and treatment initiation leading to improved patient outcomes.

10.2 Adverse Event and Serious Adverse Event Collection

10.2.1 Adverse event

A clinical trial adverse event is any untoward medical event associated with the use of the study procedure, whether or not it is considered related to a drug or study procedure. After Code Sepsis intervention, adverse events related or possibly related to study procedures must be evaluated by the PI. The PI, with assistance from study co-investigators as needed, will assess whether there is a reasonable possibility that the study procedure caused the event, based on the criteria below. Investigators will also consider whether the event is unanticipated or unexplained given the patient's clinical course, previous medical conditions, and concomitant medications. If the severe adverse event is judged to be reportable, as outlined below, then the investigator will report to the ISM and IRB his assessment of the potential relatedness of each adverse event to protocol procedure.

The study uses the following AE attribution scale:

- Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) Evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
- Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.
- Probably Not Related: The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.

- Definitely Not Related: The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

10.2.2 Serious Adverse Event (SAE)

An SAE is any AE that results in any of the following outcomes:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Event requiring prolongation of existing hospitalization. As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Persistent or significant disability/incapacity. As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2.3 Adverse event monitoring

The PI will review potential adverse events monthly for patients for whom the Code Sepsis protocol was activated during the patient's ED visit. The PI will also review within 72 hours of identification any potential anaphylaxis cases occurring within 24 hours of ED antibiotic initiation in Code Sepsis patients. Adverse events will be monitored via review of the medical record for the first 3 days after Code Sepsis activation or until hospital discharge, whichever occurs first, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be collected unless routine clinical care monitoring or the PI believes that the event was possibly, probably, or definitely to the Code Sepsis protocol.

10.3 Adverse Event and Serious Adverse Event Reporting

We emphasize in AE reporting for this study that the intervention under study is an expedited bundling of established elements of clinical care. Study-specific clinical outcomes of sepsis and ED clinical care are exempt from adverse event reporting *unless* the investigator deems the event to be related to the administration of study drug or the conduct of study procedures (or of uncertain relationship). The following are examples of events that will be considered routinely recorded clinical outcomes:

- Death not related to study procedures.
- Adverse drug reaction (excluding anaphylaxis associated with antibiotic administration) not related to study procedures
- Secondary and healthcare associated infections
- Persistent or progressive organ failure

- Prolonged hospitalization

The PI will report to the ISM within 72 hours of identification all AEs that are serious and possibly, probably, or definitely related to study procedure (or of uncertain relationship) or are unexpected. If the ISM concurs with the PI's assessment, the AE will be reported to the IRB within 7 business days. Other AEs will be reviewed by the PI on a monthly basis and reported in aggregate to the ISM on a quarterly basis. A summary report on all adverse events will be submitted to the IRB during annual recertification as per IRB guidelines. Good Clinical Practice will be followed for conduct of the study.

10.4 Interim Analysis

There will be no interim analyses.

10.5 Data and Safety Monitoring

Given that this study is using pre-post method to study implementation of a method to deliver clinical standard-of-care therapies in a more efficient, expeditious, and coordinated manner, the safety monitoring plan will be implemented with the use of an ***Independent Safety Monitor (ISM)***. The ISM will monitor participant safety, evaluate the progress of the study, review procedures for maintaining the confidentiality of data, and monitor the quality of data collection, management, and analyses. The PI and study personnel will provide all necessary and requested reports to the ISM in a timely manner. The ISM will have full capacity to end the study at her/his discretion if there is an important safety signal, according to a safety monitoring charter that will be finalized in consultation with NIH and the ISM before study launch. Notably, given that the "intervention" in this trial is a non-randomized implementation of a bundle of timely care for sepsis treatment, the safety monitoring plan will focus on monitoring the Code Sepsis activations. The PI will be responsible for ensuring participants' safety and that the study is conducted according to the IRB-approved research plan on a daily basis.

10.5.1 Safety Monitoring Procedures

1. Since this research examines implementation of a method to deliver clinical standard-of-care therapies in a more efficient, expeditious, and coordinated manner, the foundation for safety monitoring for this study is the routine quality assurance monitoring of the study hospital's Emergency Department. This quality assurance activity includes review of incident reports for clinical adverse events. The ED physician who serves as site medical director and currently has lead responsibility for monitoring of care quality and safety in each study ED. The study team will be in monthly contact via telephone or email with the ED medical director overseeing quality assurance efforts at the intervention hospital to identify potential concerns possibly, probably, or definitely related to Code Sepsis implementation. If necessary, comparisons to control hospital EDs will be performed on the basis of reports from their medical directors.
2. Specific to study procedures, all Code Sepsis activations will be individually evaluated. The PI will review all Code Sepsis activations on a monthly basis. AEs will be reported to the ISM in aggregate on a quarterly basis. The PI will report to the ISM within 72 hours of identification all AEs that are serious and possibly, probably, or definitely related to study procedure (or of uncertain relationship) or are unexpected. The ISM and PI together will reach consensus on the ultimate characterization of these possible serious adverse events (SAEs). If disagreement persists after discussion between the ISM and PI, the ISM will make the final decision about the status of the possible SAE. SAEs will be reported to the IRB within 7 business days.
3. If required by NIH or other governing bodies, or based on issues observed during trial conduct, we will convene a Data Safety Monitoring Board (DSMB) of clinical experts and members with

expertise in implementation trials with assistance from the Utah Center for Clinical and Translational Science.

10.5.2 Enrollment, procedure, regulatory, and data quality monitoring

Our data monitoring plan will include

1. Review of accrued data at monthly study team meetings
2. Review of data safety and interim data analysis performed by the independent safety monitor
3. Semi-annual audits of study materials by the Intermountain PCCM regulatory affairs group
4. An annual review performed by the Intermountain Healthcare IRB

Careful monitoring of the data collection, regulatory adherence, data quality, and study procedures will help to protect the safety of study subjects, the quality of data, and the integrity of the study. The PI or study staff will review all data collection on an ongoing basis for data completeness and accuracy as well as protocol compliance. Data verification for key demographic, exposure, and outcome parameters will be performed on an ongoing basis for a random 5% of all Code Sepsis patients. This will occur on the basis of data reabstraction by someone other than the individual who originally collecting the data or by blinded duplicate data entry. The results of the ongoing data review will be incorporated into each review with the ISM. A statement reflecting the results of the ongoing data review will be incorporated into the annual report for the IRB.

10.5.3 Frequency of data and safety monitoring

The PI and study team will review data quality and adverse event reports monthly and meet with the ISM quarterly, either in-person or by teleconference call, to review study progress, data quality, and participants' safety. A summary report on all adverse events and data quality will be submitted to the IRB during annual recertification as per IRB guidelines.

10.5.4 Independent safety monitor identify and affiliation

The following individual has agreed to serve as the independent safety monitor for the study:

Eliotte Hirshberg, MD, MS
Division of Pulmonary & Critical Care Medicine, Intermountain Medical Center
Associate Professor of Medicine, University of Utah School of Medicine

10.5.5 Conflict of interest for independent safety monitor

The ISM will have no direct involvement with the study investigators or intervention. The independent safety monitor will sign a Conflict of Interest Statement which includes current affiliations, if any, with pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial interests pertinent to study objectives.

10.5.6 Independent safety monitor responsibilities

- Review and approve the research protocol and plans for data safety and monitoring;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual, participant risk versus benefit, and other factors that can affect study outcome;

- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- Review study performance, make recommendations and assist in the resolution of problems reported by the PI;
- Protect the safety of the study participants;
- Make recommendations to the PI concerning continuation, termination or other modifications of the trial based on the observed adverse effects of the treatment under study;
- Ensure the confidentiality of the study data and the results of monitoring; and,
- Assist the IRB by commenting on any concerns related to study conduct, enrollment, sample size, and/or data collection.

10.6 Confidentiality During Adverse Event Reporting

AE reports and annual summaries will not include subject- or group-identifiable material. Each report will only include the identification code. Data will be presented in a blinded manner during any open sessions involving the ISM. At meetings with the ISM or in IRB reports, data and discussion are confidential. Participant identities will not be known to the ISM or to the IRB.

11. BIBLIOGRAPHY

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801–10.
2. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med. 2013;41:1167–74.
3. Torio CM, Moore BJ. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2013: Statistical Brief #204. Healthcare Cost and Utilization Project. 2016. Available at: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb204-Most-Expensive-Hospital-Conditions.jsp.: Accessed July 6, 2017.
4. Kaukonen K-M, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA. 2014;311:1308–16.
5. Peltan ID, Mitchell KH, Rudd KE, et al. Physician variation in time to antimicrobial treatment for septic patients presenting to the emergency department. Crit Care Med. 2017;45:1011–8.
6. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. New Engl J Med. 2001;345:1368–77.
7. ProCESS Investigators, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. New Engl J Med. 2014;370:1683–93.
8. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. New Engl J Med. 2014;371:1496–506.
9. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589–96.
10. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med. 2010;38:1045–53.
11. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med. 2017;196:856–63.
12. Seymour CW, New York State Office of Quality and Patient Safety, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. New Engl J Med. 2017;376:2235–44.
13. Peltan ID, Brown SM, Bledsoe JR, et al. Emergency department door-to-antibiotic time and long-term mortality in sepsis. Chest. 2019.
14. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486–552.
15. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med. 2018;44:925–8.
16. Peltan ID, Mitchell KH, Rudd KE, et al. Prehospital care and emergency department door-to-antibiotic time in sepsis. Ann Am Thorac Soc. 2018;15:1443–50.
17. Peltan ID, Bledsoe JR, Oniki TA, et al. ED crowding is associated with delayed antibiotics for sepsis. Ann Emerg Med. 2018.
18. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. New Engl J Med. 2006;354:366–78.
19. Kim SK, Lee SY, Bae HJ, et al. Pre-hospital notification reduced the door-to-needle time for IV tPA in acute ischaemic stroke. Eur J Neurol. 2009;16:1331–5.
20. Mosley I, Nicol M, Donnan G, Patrick I, Kerr F, Dewey H. The impact of ambulance practice on

acute stroke care. Stroke. 2007;38:2765–70.
21. Pedersen SH, Galatius S, Hansen PR, et al. Field triage reduces treatment delay and improves long-term clinical outcome in patients with acute ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. J Am Coll Cardiol. 2009;54:2296–302.
22. Sejersten M, Sillesen M, Hansen PR, et al. Effect on treatment delay of prehospital teletransmission of 12-lead electrocardiogram to a cardiologist for immediate triage and direct referral of patients with ST-segment elevation acute myocardial infarction to primary percutaneous coronary intervention. Am J Cardiol. 2008;101:941–6.
23. Seymour CW, Rea TD, Kahn JM, Walkey AJ, Yealy DM, Angus DC. Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome. Am J Respir Crit Care Med. 2012;186:1264–71.
24. Wachter RM, Flanders SA, Fee C, Pronovost PJ. Public reporting of antibiotic timing in patients with pneumonia: lessons from a flawed performance measure. Ann Intern Med. 2008;149:29–32.
25. Singer M. Antibiotics for sepsis: Does each hour really count, or is it incestuous amplification? Am J Respir Crit Care Med. 2017;196:800–2.
26. Klompas M, Calandra T, Singer M. Antibiotics for sepsis — Finding the equilibrium. JAMA. 2018;320:1433–4.
27. Croskerry P. From mindless to mindful practice--cognitive bias and clinical decision making. New Engl J Med. 2013;368:2445–8.
28. Stenehjem E, Hersh AL, Sheng X, et al. Antibiotic use in small community hospitals. Clin Infect Dis. 2016;63:1273–80.
29. Call K, Donohue M, Fontaine G, et al. Care Process Model: Emergency Management of Acute Ischemic Stroke. Intermountain Healthcare. 2017. Available at: https://intermountainhealthcare.org/ext/Dcmnt?ncid=520500199.: Accessed October 27, 2018.
30. George P, Wisco DR, Gebel J, Uchino K, Newey CR. Nurses are as specific and are earlier in calling in-hospital stroke alerts compared to physicians. J Stroke Cerebrovasc Dis. 2017;26:917–21.
31. Clayton PD, Narus SP, Huff SM, et al. Building a comprehensive clinical information system from components: the approach at Intermountain Health Care. Methods Inf Med. 2003;42:1–7.
32. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81.
33. Dimick JB, Ryan AM. Methods for evaluating changes in health care policy: the difference-in-differences approach. JAMA. 2014;312:2401–2.
34. Peltan ID, Brown CE, Burke AK, Chow EJ, Rowhani-Rahbar A, Crull MR. The July Effect on maternal peripartum complications before and after resident duty hour reform: a population-based retrospective cohort study. Am J Perinatol. Thieme Medical Publishers, 2017;34:818–25.

APPENDIX A — Eligible IV and IV-equivalent antibiotics

Antibiotic	Brand/alternative name	Eligible routes
Acyclovir	Zovirax	IV
Amikacin	Amikin	IV
Amphotericin	Amphotec, Ambisome	IV
Ampicillin	Principen	IV
Ampicillin/sulbactam	Unasyn	IV
Anidulafungin	Eraxis	IV
Azithromycin	Zithromax, Zmax, Sumamed	IV
Aztreonam	Azactam	IV
Caspofungin	Cancidas	IV
Cefazolin	Ancef	IV
Cefdericol	Fetroja	IV
Cefepime	Maxipime	IV
Cefoperazone	Cefobid	IV
Cefotaxime	Claforan	IV
Cefotetan	Cefotan	IV
Cefoxitin	Mefoxin	IV
Ceftaroline	Teflaro	IV
Ceftazidime	Fortaz	IV
Ceftazidime/avibactam	Avycaz	IV
Ceftizoxime	Cefizox	IV
Ceftolozane/tazobactam	Zerbaxa, Ceftolozane	IV
Ceftriaxone	Rocephin	IV
Cefuroxime	Ceftin, Zinacef	IV
Chloramphenicol	Chloromycetin	IV
Cidofovir	Vistide	IV
Ciprofloxacin	Cipro, Ciprobay, Ciproxin	IV
Clindamycin	Cleocin	IV
Colistin	Colymycin	IV
Dalbavancin	Dalvance	IV
Daptomycin	Cubicin	IV
Delafloxacin	Baxdela	IV
Doripenem	Doribax	IV
Doxycycline	Doxychel, Vibramycin	IV
Eravacycline	Xerava	IV
Ertapenem	Invanz	IV
Erythromycin	Erythocin, Erythroped	IV
Fidaxomycin	Dificid	PO
Fluconazole	Diflucan	IV
Ganciclovir	Cytovene	IV
Gentamicin	Garamycin	IV
Imipenem/cilastin	Primaxin	IV
Isavuconazole	Cresemba, Isavuconazonium	IV
Itraconazole	Sporanox, Onmel	IV
Levofloxacin	Levaquin	IV
Linezolid	Zyvox	IV

Antibiotic	Brand/alternative name	Eligible routes
Meropenem	Merrem	IV
Meropenem/vaborbactam	Vabomere	IV
Metronidazole	Flagyl	IV
Micafungin	Mycamine	IV
Minocycline	Minocin	IV
Moxifloxacin	Avelox	IV
Nafcillin	Unipen, Nallpen	IV
Ofloxacin	Floxin	IV
Omadadcycline	Nuzyra, Paratek	IV
Oritavancin	Orbactiv	IV
Oseltamavir	Tamiflu	PO
Oxacillin	Bastocillin	IV
Penicillin	Penicillin V, Pencillin G, Pen VK, Bicillin, Veetids, Pentids, Permapen, Pfizerpen,	IV
Peramavir	Rapivab	IV
Piperacillin/tazobactam	Zosyn	IV
Plazomicin	Zemdri	IV
Posaconazole	Noxafil	IV
Quinuopristin/dalfopristin	Synercid	IV
Remdesivir	Veklury	IV
Rifampin	Rifadin	IV
Telavancin	Vibativ	IV
Tetracycline	Achromycin, Tetracyn, Sumycin, Tetrachel	IV
Ticarcillin/clavulanate	Timentin	IV
Tidezolid	Sivextro	IV
Tigecycline	Tygacil	IV
Tobramycin		IV
Trimethoprim/sulfamethoxazole	Bactrim, Septra, Sulfatrim	IV
Vancomycin	Vancocin	PO
Vancomycin	Vancocin	IV
Voriconazole	Vfend	IV
Zanamivir	Relenza	IV

APPENDIX B — "Sepsis mimic" ICD codes

B.1 Heart failure diagnosis codes[1]

ICD-9	ICD-10	Description
398.,91	I09.81	Rheumatic heart failure
402.01	I11.0	Hypertensive heart disease with heart failure
402.11	I11.0	Hypertensive heart disease with heart failure
402.91	I11.0	Hypertensive heart disease with heart failure
404.01	I13.0	Hypertensive heart/kidney dz w/heart failure, stage 1-4 CKD or unspec
404.03	I13.2	Hypertensive heart/kidney dz w/heart failure, stage 5 CKD or ESRD
404.11	I13.0	Hypertensive heart/kidney dz w/heart failure, stage 1-4 CKD or unspec
404.13	I13.2	Hypertensive heart/kidney dz w/heart failure, stage 5 CKD or ESRD
404.91	I13.0	Hypertensive heart/kidney dz w/heart failure, stage 1-4 CKD or unspec
404.93	I13.2	Hypertensive heart/kidney dz w/heart failure, stage 5 CKD or ESRD
428.0	I50.9	Heart failure, unspecified
428.1	I50.1	Left heart failure
428.20	I50.20	Unspecified systolic heart failure
428.21	I50.21	Acute systolic heart failure
~~428.22~~	~~I50.22~~	~~Chronic systolic heart failure~~
428.23	I50.23	Acute on chronic systolic heart failure
428.30	I50.30	Unspecified diastolic heart failure
428.31	I50.31	Acute diastolic heart failure
~~428.32~~	~~I50.32~~	~~Chronic diastolic heart failure~~
428.33	I50.33	Acute on chronic diastolic heart failure
428.40	I50.40	Unspecified combined systolic and diastolic heart failure
428.41	I50.41	Acute combined systolic and diastolic heart failure
~~428.42~~	~~I50.42~~	~~Chronic combined systolic and diastolic heart failure~~
428.43	I50.43	Acute on chronic combined systolic and diastolic heart failure
428.9	I50.810	Right heart failure, unspecified
428.9	I50.811	Acute right heart failure
~~428.9~~	~~I50.812~~	~~Chronic right heart failure~~
428.9	I50.813	Acute on chronic right heart failure
428.9	I50.814	Right heart failure due to left heart failure
428.9	I50.82	Biventricular heart failure
~~428.9~~	~~I50.83~~	~~High output heart failure~~
428.9	I50.84	End stage heart failure
428.9	I50.89	Other heart failure
428.9	I50.9	Heart failure, unspecified

Use only if below is primary diagnosis and one of above is second diagnosis

425.4	I42.0	Dilated cardiomyopathy
425.5	I42.6	Alcoholic cardiomyopathy
425.9	I42.7	Cardiomyopathy due to drug and external agent
425.9	I42.8	Other cardiomyopathy
425.9	I42.9	Cardiomyopathy, unspecified
425.8	I43	Cardiomyopathy in diseases classified celsewhere
429.83	I51.81	Takotsubo cardiomyopathy

[1] Adapted from: Heart Failure CCW Chronic Conditions Algorithm. CMS Chronic Conditions Data Warehouse. 2018. Available at: https://www.ccwdata.org/web/guest/condition-categories.: Accessed

February 13, 2019.

B.2 Pulmonary embolism diagnosis codes[1,2]

ICD-9	ICD-10	Description (from ICD-10)
415.11		Iatrogenic pulmonary embolism and infarction
415.13	I26.02	Saddle embolus of pulmonary artery with acute cor pulmonale
415.19	I26.09	Other pulmonary embolism with acute cor pulmonale
415.13	I26.92	Saddle embolus of pulmonary artery without acute cor pulmonale
415.19	I26.99	Other pulmonary embolism without acute cor pulmonale
673.20	O88.219	Thromboembolism in pregnancy, unspecified trimester
673.21	O83.22	Thromboembolism in childbirth
673.22	O88.22	Thromboembolism in childbirth
673.23	O83.211	Thromboembolism in pregnancy, first trimester
673.23	O83.212	Thromboembolism in pregnancy, second trimester
673.23	O83.213	Thromboembolism in pregnancy, third trimester
673.24	O83.23	Thromboembolism in puerperium

Adapted from:

1. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, Roy P-M, Fine MJ. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172:1041–1046.
2. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med 2011;171:831–837.

B.3 Deep vein thrombosis diagnosis codes[1,2]

ICD-9	ICD-10	Description (from ICD-10)
451.11	I80.10	Phlebitis/thrombophlebitis of unspecified femoral vein
451.11	I80.11	Phlebitis/thrombophlebitis of right femoral vein
451.11	I80.12	Phlebitis/thrombophlebitis of left femoral vein
451.11	I80.13	Phlebitis/thrombophlebitis of bilateral femoral vein
451.19	I80.201	Phlebitis/thrombophlebitis of unspecified deep vessels of right lower extremity
451.19	I80.202	Phlebitis/thrombophlebitis of unspecified deep vessels of left lower extremity
451.19	I80.203	Phlebitis/thrombophlebitis of unspecified deep vessels of bilateral lower extremity
451.19	I80.209	Phlebitis/thrombophlebitis of unspecified deep vessels of unspecified lower extremity
451.19	I80.221	Phlebitis/thrombophlebitis of right popliteal vein
451.19	I80.222	Phlebitis/thrombophlebitis of right popliteal vein
451.19	I80.223	Phlebitis/thrombophlebitis of bilateral popliteal vein
451.19	I80.229	Phlebitis/thrombophlebitis of unspecified popliteal vein
451.19	I80.231	Phlebitis/thrombophlebitis of right tibial vein
451.19	I80.232	Phlebitis/thrombophlebitis of right tibial vein
451.19	I80.233	Phlebitis/thrombophlebitis of bilateral tibial vein
451.19	I80.239	Phlebitis/thrombophlebitis of unspecified tibial vein
451.19	I80.291	Phlebitis/thrombophlebitis of other deep vessels of right lower extremity
451.19	I80.292	Phlebitis/thrombophlebitis of other deep vessels of left lower extremity
451.19	I80.293	Phlebitis/thrombophlebitis of other deep vessels of bilateral lower extremity
451.19	I80.299	Phlebitis/thrombophlebitis of other deep vessels of unspecified lower extremity
451.81	I80.211	Phlebitis/thrombophlebitis of right iliac vein
451.81	I80.212	Phlebitis/thrombophlebitis of left iliac vein
451.81	I80.213	Phlebitis/thrombophlebitis of bilateral iliac vein
453.81	I80.219	Phlebitis/thrombophlebitis of unspecified iliac vein
451.11	I80.10	Phlebitis/thrombophlebitis of unspecified femoral vein
451.11	I80.11	Phlebitis/thrombophlebitis of right femoral vein
451.11	I80.12	Phlebitis/thrombophlebitis of left femoral vein
451.11	I80.13	Phlebitis/thrombophlebitis of bilateral femoral vein
451.19	I80.201	Phlebitis/thrombophlebitis of unspecified deep vessels of right lower extremity
451.19	I80.202	Phlebitis/thrombophlebitis of unspecified deep vessels of left lower extremity
451.19	I80.203	Phlebitis/thrombophlebitis of unspecified deep vessels of bilateral lower extremity
451.19	I80.209	Phlebitis/thrombophlebitis of unspecified deep vessels of unspecified lower extremity
451.19	I80.221	Phlebitis/thrombophlebitis of right popliteal vein
451.19	I80.222	Phlebitis/thrombophlebitis of right popliteal vein
451.19	I80.223	Phlebitis/thrombophlebitis of bilateral popliteal vein
451.19	I80.229	Phlebitis/thrombophlebitis of unspecified popliteal vein
451.19	I80.231	Phlebitis/thrombophlebitis of right tibial vein
451.19	I80.232	Phlebitis/thrombophlebitis of right tibial vein
451.19	I80.233	Phlebitis/thrombophlebitis of bilateral tibial vein
451.19	I80.239	Phlebitis/thrombophlebitis of unspecified tibial vein
451.19	I80.291	Phlebitis/thrombophlebitis of other deep vessels of right lower extremity
451.19	I80.292	Phlebitis/thrombophlebitis of other deep vessels of left lower extremity
451.19	I80.293	Phlebitis/thrombophlebitis of other deep vessels of bilateral lower extremity
451.19	I80.299	Phlebitis/thrombophlebitis of other deep vessels of unspecified lower extremity

ICD-9	ICD-10	Description (from ICD-10) — CONTINUED
451.81	I80.211	Phlebitis/thrombophlebitis of right iliac vein
451.81	I80.212	Phlebitis/thrombophlebitis of left iliac vein
451.81	I80.213	Phlebitis/thrombophlebitis of bilateral iliac vein
453.81	I80.219	Phlebitis/thrombophlebitis of unspecified iliac vein
451.83		Phlebitis/thrombophlebitis of deep vein of upper extremity
453.40	I82.401	Acute embolism/thrombosis of unspecified deep veins of right lower extremity
453.40	I82.402	Acute embolism/thrombosis of unspecified deep veins of left lower extremity
453.40	I82.403	Acute embolism/thrombosis of unspecified deep veins of bilateral lower extremity
453.40	I82.409	Acute embolism/thrombosis of unspecified deep veins of unspecified lower extremity
453.40	I82.491	Acute embolism/thrombosis of other deep veins of right lower extremity
453.40	I82.492	Acute embolism/thrombosis of other deep veins of left lower extremity
453.40	I82.493	Acute embolism/thrombosis of other deep veins of bilateral lower extremity
453.40	I82.499	Acute embolism/thrombosis of other deep veins of unspecified lower extremity
453.41	I82.411	Acute embolism/thrombosis of right femoral vein
453.41	I82.412	Acute embolism/thrombosis of left femoral vein
453.41	I82.413	Acute embolism/thrombosis of bilateral femoral vein
453.41	I82.419	Acute embolism/thrombosis of unspecified femoral vein
453.41	I82.421	Acute embolism/thrombosis of right iliac vein
453.41	I82.422	Acute embolism/thrombosis of left iliac vein
453.41	I82.423	Acute embolism/thrombosis of bilateral iliac vein
453.41	I82.429	Acute embolism/thrombosis of unspecified iliac vein
453.41	I82.4Y1	Acute embolism/thrombosis of unspecified veins of right proximal lower extremity
453.41	I82.4Y2	Acute embolism/thrombosis of unspecified veins of left proximal lower extremity
453.41	I82.4Y3	Acute embolism/thrombosis of unspecified veins of bilateral proximal lower extremity
453.41	I82.4Y9	Acute embolism/thrombosis of unspecified veins of unspecified prox lower extremity
453.42	I82.431	Acute embolism/thrombosis of right popliteal vein
453.42	I82.432	Acute embolism/thrombosis of left popliteal vein
453.42	I82.433	Acute embolism/thrombosis of bilateral popliteal vein
453.42	I82.439	Acute embolism/thrombosis of unspecified popliteal vein
453.42	I82.441	Acute embolism/thrombosis of right tibial vein
453.42	I82.442	Acute embolism/thrombosis of left tibial vein
453.42	I82.443	Acute embolism/thrombosis of bilateral tibial vein
453.42	I82.449	Acute embolism/thrombosis of unspecified tibial vein
453.42	I82.4Z1	Acute embolism/thrombosis of unspecified veins of right distal lower extremity
453.42	I82.4Z2	Acute embolism/thrombosis of unspecified veins of left distal lower extremity
453.42	I82.4Z3	Acute embolism/thrombosis of unspecified veins of bilateral distal lower extremity
453.42	I82.4Z9	Acute embolism/thrombosis of unspecified veins of unspecified distal lower extremity
	I82.621	Acute embolism/thrombosis of deep veins of right upper extremity
	I82.622	Acute embolism/thrombosis of deep veins of left upper extremity
	I82.623	Acute embolism/thrombosis of deep veins of bilateral upper extremity
	I82.629	Acute embolism/thrombosis of deep veins of unspecified upper extremity

ICD-9	ICD-10	Description (from ICD-10) — CONTINUED
671.30	O22.30	Deep phlebothrombosis in pregnancy, unspecified trimester
671.31	O87.1	Deep phlebothrombosis in the peurperium
671.33	O22.31	Deep phlebothrombosis in pregnancy, first trimester
671.33	O22.32	Deep phlebothrombosis in pregnancy, second trimester
671.33	O22.33	Deep phlebothrombosis in pregnancy, third trimester
671.40	O87.1	Deep phlebothrombosis, postpartum, unspecified as to episode of care
671.42	O87.1	Deep phlebothrombosis, postpartum, delivered
671.44	O87.1	Deep phlebothrombosis, postpartum, postpartum condition

Adapted from:

1. White RH, Garcia M, Sadeghi B, Tancredi DJ, Zrelak P, Cuny J, Sama P, Gammon H, Schmaltz S, Romano PS. Evaluation of the predictive value of ICD-9-CM coded administrative data for venous thromboembolism in the United States. Thromb Res 2010;126:61–67.
2. Kniffin WD, Baron JA, Barrett J, Birkmeyer JD, Anderson FA. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. Arch Intern Med 1994;154:861–866.

APPENDIX C — Diagnosis codes for adverse drug reaction

Adapted from: Hohl CM, Karpov A, Reddekopp L, Doyle-Waters M, Stausberg J. ICD-10 codes used to identify adverse drug events in administrative data: a systematic review. J Am Med Inform Assoc. 2014;21:547–57.

ICD-10-CM	Anaphylaxis	Description
A0471		Enterocolitis due to Clostridium difficile, recurrent
A0472		Enterocolitis due to Clostridium difficile, not specified as recurrent
D590		Drug-induced autoimmune hemolytic anemia
D592		Drug-induced nonautoimmune hemolytic anemia
D7212		Drug rash with eosinophilia and systemic symptoms syndrome
E064		Drug-induced thyroiditis
E160		Drug-induced hypoglycemia without coma
G210		Malignant neuroleptic syndrome
G2402		Drug induced acute dystonia
G2409		Other drug induced dystonia
G251		Drug-induced tremor
G4440		Drug-induced headache, not elsewhere classified, not intractable
G4441		Drug-induced headache, not elsewhere classified, intractable
G620		Drug-induced polyneuropathy
G720		Drug-induced myopathy
I427		Cardiomyopathy due to drug and external agent
I952		Hypotension due to drugs
J702		Acute drug-induced interstitial lung disorders
J704		Drug-induced interstitial lung disorders, unspecified
K710		Toxic liver disease with cholestasis
K7110		Toxic liver disease with hepatic necrosis, without coma
K7111		Toxic liver disease with hepatic necrosis, with coma
K712		Toxic liver disease with acute hepatitis
K716		Toxic liver disease with hepatitis, not elsewhere classified
K719		Toxic liver disease, unspecified
K8530		Drug induced acute pancreatitis without necrosis or infection
K8531		Drug induced acute pancreatitis with uninfected necrosis
K8532		Drug induced acute pancreatitis with infected necrosis
L233		Allergic contact dermatitis due to drugs in contact with skin
L244		Irritant contact dermatitis due to drugs in contact with skin
L251		Unspecified contact dermatitis due to drugs in contact with skin
L270		Generalized skin eruption due to drugs and medicaments taken internally
L271		Localized skin eruption due to drugs and medicaments taken internally
L278		Dermatitis due to other substances taken internally
L279		Dermatitis due to unspecified substance taken internally
L500		Allergic urticaria
L509		Urticaria, unspecified
L510		Nonbullous erythema multiforme
L511		Stevens-Johnson syndrome
L512		Toxic epidermal necrolysis [Lyell]

ICD-10-CM	Anaphylaxis	Description
L513		Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
L518		Other erythema multiforme
L519		Erythema multiforme, unspecified
L52		Erythema nodosum
L530		Toxic erythema
L531		Erythema annulare centrifugum
N141		Nephropathy induced by other drugs, medicaments and biological substances
N142		Nephropathy induced by unspecified drug, medicament or biological substance
N144		Toxic nephropathy, not elsewhere classified
R502		Drug induced fever
T360X1A		Poisoning by penicillins, accidental (unintentional), initial encounter
T360X1D		Poisoning by penicillins, accidental (unintentional), subsequent encounter
T360X1S		Poisoning by penicillins, accidental (unintentional), sequela
T360X4A		Poisoning by penicillins, undetermined, initial encounter
T360X4D		Poisoning by penicillins, undetermined, subsequent encounter
T360X4S		Poisoning by penicillins, undetermined, sequela
T360X5A		Adverse effect of penicillins, initial encounter
T360X5D		Adverse effect of penicillins, subsequent encounter
T360X5S		Adverse effect of penicillins, sequela
T360X6A		Underdosing of penicillins, initial encounter
T360X6D		Underdosing of penicillins, subsequent encounter
T360X6S		Underdosing of penicillins, sequela
T361X1A		Poisoning by cephalosporins and other beta-lactam antibiotics, accidental (unintentional), initial encounter
T361X1D		Poisoning by cephalosporins and other beta-lactam antibiotics, accidental (unintentional), subsequent encounter
T361X1S		Poisoning by cephalosporins and other beta-lactam antibiotics, accidental (unintentional), sequela
T361X4A		Poisoning by cephalosporins and other beta-lactam antibiotics, undetermined, initial encounter
T361X4D		Poisoning by cephalosporins and other beta-lactam antibiotics, undetermined, subsequent encounter
T361X4S		Poisoning by cephalosporins and other beta-lactam antibiotics, undetermined, sequela
T361X5A		Adverse effect of cephalosporins and other beta-lactam antibiotics, initial encounter
T361X5D		Adverse effect of cephalosporins and other beta-lactam antibiotics, subsequent encounter
T361X5S		Adverse effect of cephalosporins and other beta-lactam antibiotics, sequela
T361X6A		Underdosing of cephalosporins and other beta-lactam antibiotics, initial encounter
T361X6D		Underdosing of cephalosporins and other beta-lactam antibiotics, subsequent encounter
T361X6S		Underdosing of cephalosporins and other beta-lactam antibiotics, sequela

ICD-10-CM	Anaphylaxis	Description
T362X1A		Poisoning by chloramphenicol group, accidental (unintentional), initial encounter
T362X1D		Poisoning by chloramphenicol group, accidental (unintentional), subsequent encounter
T362X1S		Poisoning by chloramphenicol group, accidental (unintentional), sequela
T362X4A		Poisoning by chloramphenicol group, undetermined, initial encounter
T362X4D		Poisoning by chloramphenicol group, undetermined, subsequent encounter
T362X4S		Poisoning by chloramphenicol group, undetermined, sequela
T362X5A		Adverse effect of chloramphenicol group, initial encounter
T362X5D		Adverse effect of chloramphenicol group, subsequent encounter
T362X5S		Adverse effect of chloramphenicol group, sequela
T362X6A		Underdosing of chloramphenicol group, initial encounter
T362X6D		Underdosing of chloramphenicol group, subsequent encounter
T362X6S		Underdosing of chloramphenicol group, sequela
T363X1A		Poisoning by macrolides, accidental (unintentional), initial encounter
T363X1D		Poisoning by macrolides, accidental (unintentional), subsequent encounter
T363X1S		Poisoning by macrolides, accidental (unintentional), sequela
T363X4A		Poisoning by macrolides, undetermined, initial encounter
T363X4D		Poisoning by macrolides, undetermined, subsequent encounter
T363X4S		Poisoning by macrolides, undetermined, sequela
T363X5A		Adverse effect of macrolides, initial encounter
T363X5D		Adverse effect of macrolides, subsequent encounter
T363X5S		Adverse effect of macrolides, sequela
T363X6A		Underdosing of macrolides, initial encounter
T363X6D		Underdosing of macrolides, subsequent encounter
T363X6S		Underdosing of macrolides, sequela
T364X1A		Poisoning by tetracyclines, accidental (unintentional), initial encounter
T364X1D		Poisoning by tetracyclines, accidental (unintentional), subsequent encounter
T364X1S		Poisoning by tetracyclines, accidental (unintentional), sequela
T364X4A		Poisoning by tetracyclines, undetermined, initial encounter
T364X4D		Poisoning by tetracyclines, undetermined, subsequent encounter
T364X4S		Poisoning by tetracyclines, undetermined, sequela
T364X5A		Adverse effect of tetracyclines, initial encounter
T364X5D		Adverse effect of tetracyclines, subsequent encounter
T364X5S		Adverse effect of tetracyclines, sequela
T364X6A		Underdosing of tetracyclines, initial encounter
T364X6D		Underdosing of tetracyclines, subsequent encounter
T364X6S		Underdosing of tetracyclines, sequela
T365X1A		Poisoning by aminoglycosides, accidental (unintentional), initial encounter
T365X1D		Poisoning by aminoglycosides, accidental (unintentional), subsequent encounter
T365X1S		Poisoning by aminoglycosides, accidental (unintentional), sequela
T365X4A		Poisoning by aminoglycosides, undetermined, initial encounter

ICD-10-CM	Anaphylaxis	Description
T365X4D		Poisoning by aminoglycosides, undetermined, subsequent encounter
T365X4S		Poisoning by aminoglycosides, undetermined, sequela
T365X5A		Adverse effect of aminoglycosides, initial encounter
T365X5D		Adverse effect of aminoglycosides, subsequent encounter
T365X5S		Adverse effect of aminoglycosides, sequela
T365X6A		Underdosing of aminoglycosides, initial encounter
T365X6D		Underdosing of aminoglycosides, subsequent encounter
T365X6S		Underdosing of aminoglycosides, sequela
T366X1A		Poisoning by rifampicins, accidental (unintentional), initial encounter
T366X1D		Poisoning by rifampicins, accidental (unintentional), subsequent encounter
T366X1S		Poisoning by rifampicins, accidental (unintentional), sequela
T366X4A		Poisoning by rifampicins, undetermined, initial encounter
T366X4D		Poisoning by rifampicins, undetermined, subsequent encounter
T366X4S		Poisoning by rifampicins, undetermined, sequela
T366X5A		Adverse effect of rifampicins, initial encounter
T366X5D		Adverse effect of rifampicins, subsequent encounter
T366X5S		Adverse effect of rifampicins, sequela
T366X6A		Underdosing of rifampicins, initial encounter
T366X6D		Underdosing of rifampicins, subsequent encounter
T366X6S		Underdosing of rifampicins, sequela
T367X1A		Poisoning by antifungal antibiotics, systemically used, accidental (unintentional), initial encounter
T367X1D		Poisoning by antifungal antibiotics, systemically used, accidental (unintentional), subsequent encounter
T367X1S		Poisoning by antifungal antibiotics, systemically used, accidental (unintentional), sequela
T367X4A		Poisoning by antifungal antibiotics, systemically used, undetermined, initial encounter
T367X4D		Poisoning by antifungal antibiotics, systemically used, undetermined, subsequent encounter
T367X4S		Poisoning by antifungal antibiotics, systemically used, undetermined, sequela
T367X5A		Adverse effect of antifungal antibiotics, systemically used, initial encounter
T367X5D		Adverse effect of antifungal antibiotics, systemically used, subsequent encounter
T367X5S		Adverse effect of antifungal antibiotics, systemically used, sequela
T367X6A		Underdosing of antifungal antibiotics, systemically used, initial encounter
T367X6D		Underdosing of antifungal antibiotics, systemically used, subsequent encounter
T367X6S		Underdosing of antifungal antibiotics, systemically used, sequela
T368X1A		Poisoning by other systemic antibiotics, accidental (unintentional), initial encounter
T368X1D		Poisoning by other systemic antibiotics, accidental (unintentional), subsequent encounter
T368X1S		Poisoning by other systemic antibiotics, accidental (unintentional),

ICD-10-CM	Anaphylaxis	Description
		sequela
T368X4A		Poisoning by other systemic antibiotics, undetermined, initial encounter
T368X4D		Poisoning by other systemic antibiotics, undetermined, subsequent encounter
T368X4S		Poisoning by other systemic antibiotics, undetermined, sequela
T368X5A		Adverse effect of other systemic antibiotics, initial encounter
T368X5D		Adverse effect of other systemic antibiotics, subsequent encounter
T368X5S		Adverse effect of other systemic antibiotics, sequela
T368X6A		Underdosing of other systemic antibiotics, initial encounter
T368X6D		Underdosing of other systemic antibiotics, subsequent encounter
T368X6S		Underdosing of other systemic antibiotics, sequela
T3691XA		Poisoning by unspecified systemic antibiotic, accidental (unintentional), initial encounter
T3691XD		Poisoning by unspecified systemic antibiotic, accidental (unintentional), subsequent encounter
T3691XS		Poisoning by unspecified systemic antibiotic, accidental (unintentional), sequela
T3694XA		Poisoning by unspecified systemic antibiotic, undetermined, initial encounter
T3694XD		Poisoning by unspecified systemic antibiotic, undetermined, subsequent encounter
T3694XS		Poisoning by unspecified systemic antibiotic, undetermined, sequela
T3695XA		Adverse effect of unspecified systemic antibiotic, initial encounter
T3695XD		Adverse effect of unspecified systemic antibiotic, subsequent encounter
T3695XS		Adverse effect of unspecified systemic antibiotic, sequela
T3696XA		Underdosing of unspecified systemic antibiotic, initial encounter
T3696XD		Underdosing of unspecified systemic antibiotic, subsequent encounter
T3696XS		Underdosing of unspecified systemic antibiotic, sequela
T370X1A		Poisoning by sulfonamides, accidental (unintentional), initial encounter
T370X1D		Poisoning by sulfonamides, accidental (unintentional), subsequent encounter
T370X1S		Poisoning by sulfonamides, accidental (unintentional), sequela
T370X4A		Poisoning by sulfonamides, undetermined, initial encounter
T370X4D		Poisoning by sulfonamides, undetermined, subsequent encounter
T370X4S		Poisoning by sulfonamides, undetermined, sequela
T370X5A		Adverse effect of sulfonamides, initial encounter
T370X5D		Adverse effect of sulfonamides, subsequent encounter
T370X5S		Adverse effect of sulfonamides, sequela
T370X6A		Underdosing of sulfonamides, initial encounter
T370X6D		Underdosing of sulfonamides, subsequent encounter
T370X6S		Underdosing of sulfonamides, sequela
T371X1A		Poisoning by antimycobacterial drugs, accidental (unintentional), initial encounter
T371X1D		Poisoning by antimycobacterial drugs, accidental (unintentional), subsequent encounter
T371X1S		Poisoning by antimycobacterial drugs, accidental (unintentional), sequela
T371X4A		Poisoning by antimycobacterial drugs, undetermined, initial encounter

ICD-10-CM	Anaphylaxis	Description
T371X4D		Poisoning by antimycobacterial drugs, undetermined, subsequent encounter
T371X4S		Poisoning by antimycobacterial drugs, undetermined, sequela
T371X5A		Adverse effect of antimycobacterial drugs, initial encounter
T371X5D		Adverse effect of antimycobacterial drugs, subsequent encounter
T371X5S		Adverse effect of antimycobacterial drugs, sequela
T371X6A		Underdosing of antimycobacterial drugs, initial encounter
T371X6D		Underdosing of antimycobacterial drugs, subsequent encounter
T371X6S		Underdosing of antimycobacterial drugs, sequela
T372X1A		Poisoning by antimalarials and drugs acting on other blood protozoa, accidental (unintentional), initial encounter
T372X1D		Poisoning by antimalarials and drugs acting on other blood protozoa, accidental (unintentional), subsequent encounter
T372X1S		Poisoning by antimalarials and drugs acting on other blood protozoa, accidental (unintentional), sequela
T372X4A		Poisoning by antimalarials and drugs acting on other blood protozoa, undetermined, initial encounter
T372X4D		Poisoning by antimalarials and drugs acting on other blood protozoa, undetermined, subsequent encounter
T372X4S		Poisoning by antimalarials and drugs acting on other blood protozoa, undetermined, sequela
T372X5A		Adverse effect of antimalarials and drugs acting on other blood protozoa, initial encounter
T372X5D		Adverse effect of antimalarials and drugs acting on other blood protozoa, subsequent encounter
T372X5S		Adverse effect of antimalarials and drugs acting on other blood protozoa, sequela
T372X6A		Underdosing of antimalarials and drugs acting on other blood protozoa, initial encounter
T372X6D		Underdosing of antimalarials and drugs acting on other blood protozoa, subsequent encounter
T372X6S		Underdosing of antimalarials and drugs acting on other blood protozoa, sequela
T373X1A		Poisoning by other antiprotozoal drugs, accidental (unintentional), initial encounter
T373X1D		Poisoning by other antiprotozoal drugs, accidental (unintentional), subsequent encounter
T373X1S		Poisoning by other antiprotozoal drugs, accidental (unintentional), sequela
T373X4A		Poisoning by other antiprotozoal drugs, undetermined, initial encounter
T373X4D		Poisoning by other antiprotozoal drugs, undetermined, subsequent encounter
T373X4S		Poisoning by other antiprotozoal drugs, undetermined, sequela
T373X5A		Adverse effect of other antiprotozoal drugs, initial encounter
T373X5D		Adverse effect of other antiprotozoal drugs, subsequent encounter
T373X5S		Adverse effect of other antiprotozoal drugs, sequela
T373X6A		Underdosing of other antiprotozoal drugs, initial encounter

ICD-10-CM	Anaphylaxis	Description
T373X6D		Underdosing of other antiprotozoal drugs, subsequent encounter
T373X6S		Underdosing of other antiprotozoal drugs, sequela
T374X1A		Poisoning by anthelminthics, accidental (unintentional), initial encounter
T374X1D		Poisoning by anthelminthics, accidental (unintentional), subsequent encounter
T374X1S		Poisoning by anthelminthics, accidental (unintentional), sequela
T374X4A		Poisoning by anthelminthics, undetermined, initial encounter
T374X4D		Poisoning by anthelminthics, undetermined, subsequent encounter
T374X4S		Poisoning by anthelminthics, undetermined, sequela
T374X5A		Adverse effect of anthelminthics, initial encounter
T374X5D		Adverse effect of anthelminthics, subsequent encounter
T374X5S		Adverse effect of anthelminthics, sequela
T374X6A		Underdosing of anthelminthics, initial encounter
T374X6D		Underdosing of anthelminthics, subsequent encounter
T374X6S		Underdosing of anthelminthics, sequela
T375X1A		Poisoning by antiviral drugs, accidental (unintentional), initial encounter
T375X1D		Poisoning by antiviral drugs, accidental (unintentional), subsequent encounter
T375X1S		Poisoning by antiviral drugs, accidental (unintentional), sequela
T375X4A		Poisoning by antiviral drugs, undetermined, initial encounter
T375X4D		Poisoning by antiviral drugs, undetermined, subsequent encounter
T375X4S		Poisoning by antiviral drugs, undetermined, sequela
T375X5A		Adverse effect of antiviral drugs, initial encounter
T375X5D		Adverse effect of antiviral drugs, subsequent encounter
T375X5S		Adverse effect of antiviral drugs, sequela
T375X6A		Underdosing of antiviral drugs, initial encounter
T375X6D		Underdosing of antiviral drugs, subsequent encounter
T375X6S		Underdosing of antiviral drugs, sequela
T378X1A		Poisoning by other specified systemic anti-infectives and antiparasitics, accidental (unintentional), initial encounter
T378X1D		Poisoning by other specified systemic anti-infectives and antiparasitics, accidental (unintentional), subsequent encounter
T378X1S		Poisoning by other specified systemic anti-infectives and antiparasitics, accidental (unintentional), sequela
T378X4A		Poisoning by other specified systemic anti-infectives and antiparasitics, undetermined, initial encounter
T378X4D		Poisoning by other specified systemic anti-infectives and antiparasitics, undetermined, subsequent encounter
T378X4S		Poisoning by other specified systemic anti-infectives and antiparasitics, undetermined, sequela
T378X5A		Adverse effect of other specified systemic anti-infectives and antiparasitics, initial encounter
T378X5D		Adverse effect of other specified systemic anti-infectives and antiparasitics, subsequent encounter
T378X5S		Adverse effect of other specified systemic anti-infectives and antiparasitics, sequela
T378X6A		Underdosing of other specified systemic anti-infectives and antiparasitics,

ICD-10-CM	Anaphylaxis	Description
		initial encounter
T378X6D		Underdosing of other specified systemic anti-infectives and antiparasitics, subsequent encounter
T378X6S		Underdosing of other specified systemic anti-infectives and antiparasitics, sequela
T3791XA		Poisoning by unspecified systemic anti-infective and antiparasitics, accidental (unintentional), initial encounter
T3791XD		Poisoning by unspecified systemic anti-infective and antiparasitics, accidental (unintentional), subsequent encounter
T3791XS		Poisoning by unspecified systemic anti-infective and antiparasitics, accidental (unintentional), sequela
T3794XA		Poisoning by unspecified systemic anti-infective and antiparasitics, undetermined, initial encounter
T3794XD		Poisoning by unspecified systemic anti-infective and antiparasitics, undetermined, subsequent encounter
T3794XS		Poisoning by unspecified systemic anti-infective and antiparasitics, undetermined, sequela
T3795XA		Adverse effect of unspecified systemic anti-infective and antiparasitic, initial encounter
T3795XD		Adverse effect of unspecified systemic anti-infective and antiparasitic, subsequent encounter
T3795XS		Adverse effect of unspecified systemic anti-infective and antiparasitic, sequela
T3796XA		Underdosing of unspecified systemic anti-infectives and antiparasitics, initial encounter
T3796XD		Underdosing of unspecified systemic anti-infectives and antiparasitics, subsequent encounter
T3796XS		Underdosing of unspecified systemic anti-infectives and antiparasitics, sequela
T431X5A		Adverse effect of monoamine-oxidase-inhibitor antidepressants, initial encounter
T431X5D		Adverse effect of monoamine-oxidase-inhibitor antidepressants, subsequent encounter
T431X5S		Adverse effect of monoamine-oxidase-inhibitor antidepressants, sequela
T43215A		Adverse effect of selective serotonin and norepinephrine reuptake inhibitors, initial encounter
T43215D		Adverse effect of selective serotonin and norepinephrine reuptake inhibitors, subsequent encounter
T43215S		Adverse effect of selective serotonin and norepinephrine reuptake inhibitors, sequela
T43225A		Adverse effect of selective serotonin reuptake inhibitors, initial encounter
T43225D		Adverse effect of selective serotonin reuptake inhibitors, subsequent encounter
T43225S		Adverse effect of selective serotonin reuptake inhibitors, sequela
T50901A		Poisoning by unspecified drugs, medicaments and biological substances, accidental (unintentional), initial encounter
T50901D		Poisoning by unspecified drugs, medicaments and biological substances,

ICD-10-CM	Anaphylaxis	Description
		accidental (unintentional), subsequent encounter
T50901S		Poisoning by unspecified drugs, medicaments and biological substances, accidental (unintentional), sequela
T50904A		Poisoning by unspecified drugs, medicaments and biological substances, undetermined, initial encounter
T50904D		Poisoning by unspecified drugs, medicaments and biological substances, undetermined, subsequent encounter
T50904S		Poisoning by unspecified drugs, medicaments and biological substances, undetermined, sequela
T50905A		Adverse effect of unspecified drugs, medicaments and biological substances, initial encounter
T50905D		Adverse effect of unspecified drugs, medicaments and biological substances, subsequent encounter
T50905S		Adverse effect of unspecified drugs, medicaments and biological substances, sequela
T50906A		Underdosing of unspecified drugs, medicaments and biological substances, initial encounter
T50906D		Underdosing of unspecified drugs, medicaments and biological substances, subsequent encounter
T50906S		Underdosing of unspecified drugs, medicaments and biological substances, sequela
T50991A		Poisoning by other drugs, medicaments and biological substances, accidental (unintentional), initial encounter
T50991D		Poisoning by other drugs, medicaments and biological substances, accidental (unintentional), subsequent encounter
T50991S		Poisoning by other drugs, medicaments and biological substances, accidental (unintentional), sequela
T50994A		Poisoning by other drugs, medicaments and biological substances, undetermined, initial encounter
T50994D		Poisoning by other drugs, medicaments and biological substances, undetermined, subsequent encounter
T50994S		Poisoning by other drugs, medicaments and biological substances, undetermined, sequela
T50995A		Adverse effect of other drugs, medicaments and biological substances, initial encounter
T50995D		Adverse effect of other drugs, medicaments and biological substances, subsequent encounter
T50995S		Adverse effect of other drugs, medicaments and biological substances, sequela
T50996A		Underdosing of other drugs, medicaments and biological substances, initial encounter
T50996D		Underdosing of other drugs, medicaments and biological substances, subsequent encounter
T50996S		Underdosing of other drugs, medicaments and biological substances, sequela
T782XXA	X	Anaphylactic shock, unspecified, initial encounter
T782XXD	X	Anaphylactic shock, unspecified, subsequent encounter

ICD-10-CM	Anaphylaxis	Description
T782XXS	X	Anaphylactic shock, unspecified, sequela
T783XXA	X	Angioneurotic edema, initial encounter
T783XXD	X	Angioneurotic edema, subsequent encounter
T783XXS	X	Angioneurotic edema, sequela
T7840XA		Allergy, unspecified, initial encounter
T7840XD		Allergy, unspecified, subsequent encounter
T7840XS		Allergy, unspecified, sequela
T7841XA		Arthus phenomenon, initial encounter
T7841XD		Arthus phenomenon, subsequent encounter
T7841XS		Arthus phenomenon, sequela
T7849XA		Other allergy, initial encounter
T7849XD		Other allergy, subsequent encounter
T7849XS		Other allergy, sequela
T788XXA		Other adverse effects, not elsewhere classified, initial encounter
T788XXD		Other adverse effects, not elsewhere classified, subsequent encounter
T788XXS		Other adverse effects, not elsewhere classified, sequela
T8051XA	X	Anaphylactic reaction due to administration of blood and blood products, initial encounter
T8051XD	X	Anaphylactic reaction due to administration of blood and blood products, subsequent encounter
T8051XS	X	Anaphylactic reaction due to administration of blood and blood products, sequela
T8052XA	X	Anaphylactic reaction due to vaccination, initial encounter
T8052XD	X	Anaphylactic reaction due to vaccination, subsequent encounter
T8052XS	X	Anaphylactic reaction due to vaccination, sequela
T8059XA	X	Anaphylactic reaction due to other serum, initial encounter
T8059XD	X	Anaphylactic reaction due to other serum, subsequent encounter
T8059XS	X	Anaphylactic reaction due to other serum, sequela
T8089XA		Other complications following infusion, transfusion and therapeutic injection, initial encounter
T8089XD		Other complications following infusion, transfusion and therapeutic injection, subsequent encounter
T8089XS		Other complications following infusion, transfusion and therapeutic injection, sequela
T8090XA		Unspecified complication following infusion and therapeutic injection, initial encounter
T8090XD		Unspecified complication following infusion and therapeutic injection, subsequent encounter
T8090XS		Unspecified complication following infusion and therapeutic injection, sequela
T886XXA	X	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter
T886XXD	X	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, subsequent encounter
T886XXS	X	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, sequela

ICD-10-CM	Anaphylaxis	Description
T887XXA		Unspecified adverse effect of drug or medicament, initial encounter
T888XXA		Other specified complications of surgical and medical care, not elsewhere classified, initial encounter
T889XXA		Complication of surgical and medical care, unspecified, initial encounter
Y631		Incorrect dilution of fluid used during infusion
Y638		Failure in dosage during other surgical and medical care
Y639		Failure in dosage during unspecified surgical and medical care
Y640		Contaminated medical or biological substance, transfused or infused
Y641		Contaminated medical or biological substance, injected or used for immunization
Y651		Wrong fluid used in infusion
Y66		Nonadministration of surgical and medical care
Y69		Unspecified misadventure during surgical and medical care