Multi-Drug Resistant Organism Network (MDRO NETWORK)

Protocol Name: **MDRO Network**

Funding Sponsor: **Antibiotic Resistance Leadership Group (ARLG)**

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Study Sponsor:	ARLG
Principal Investigator:	David van Duin, MD, PhD Associate Professor of Medicine Division of Infectious Diseases University of North Carolina

SIGNATURE PAGE

The signature below documents the review and approval of this protocol and provides the necessary assurances that this study will be conducted according to the protocol, including all statements regarding confidentiality, and according to national, regional, and local legal and regulatory requirements.

_____
Site Principal Investigator Name (Print)

_____ _____
Signature Date

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Coordinating Center

The coordinating center for the MDRO Network will be Duke Clinical Research Institute. Dr. van Duin is the Principal Investigator (PI) and will be directly overseeing all activities.

ARLG Publication Committee

The ARLG Publication Committee comprises representatives of the network cores, thought-leaders, and the ARLG Statistical and Data Management Center (SDMC), and is responsible for generation and coordination of the publications that report scientific findings of the network.

List of Abbreviations

ARLG	Antibacterial Resistance Leadership Group
BSI	Bloodstream infection
CDC	Centers for Disease Control and Prevention
DCRI	Duke Clinical Research Institute
eCRF	Electronic case report form
FDA	Food and Drug Administration
GEE	Generalized estimating equation
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IDES	Internet Data Entry System
MDRO	Multi-Drug Resistant Organism
IRB	Institutional Review Board
MALDI-TOF	Matrix-assisted laser desorption ionization time of flight mass spectrometry
MIC	Minimum inhibitory concentration
MLST	Multilocus sequence typing
NIAID	National Institutes of Allergy and Infectious Disease
NIH	National Institutes of Health
PBS	Pitt bacteremia score
PI	Principal Investigator
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
SDMC	ARLG Statistical and Data Management Center
SOP	Standard operating procedures
UTI	Urinary tract infection

Protocol Summary

Protocol Title:	Multi-Drug Resistant Organism Network - MDRO
Study Design:	Master protocol for prospective, multicenter, observational cohort studies
Study Population:	Hospitalized patients with multi-drug resistant organisms
Number of subjects:	To be specified in each study sub-protocol as outlined in Appendices
Clinical Samples:	Multi-drug resistant organism isolates from specimens obtained from any anatomic site
Estimated Start of Enrollment:	Second quarter of 2016
Estimated Time to Completion:	Second quarter of 2019

1 TABLE OF CONTENTS

2 BACKGROUND AND RATIONALE

Per the World Health Organization, antimicrobial resistance is “one of the greatest threats to human health worldwide”. In the US, infections caused by multi-drug resistant organisms (MDRO) add between $21 billion and $34 billion to health care costs annually, as compared to susceptible pathogens (2). In many bacterial pathogens, resistance has been increasing over the last few decades and as a general rule

clinically relevant resistance against any specific novel antibacterial either precedes or relatively quickly follows the introduction of the antibacterial for clinical use ((1), figure of timeline).

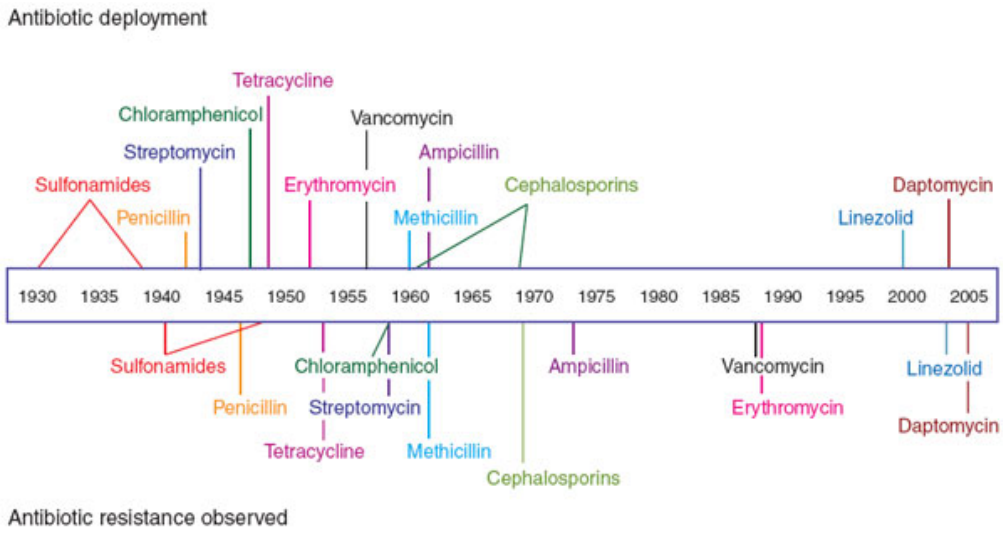

Figure 1. Timeline of antibiotic deployment and resistance development (1)

In addition to increased healthcare costs, infections with MDRO have been linked to worse patient outcomes including increased mortality (3). The study of the treatment and diagnosis of patients with MDRO infections is limited by a number of factors. First, patients with MDRO infections tend to be more chronically and acutely ill as compared to their counterparts infected with more susceptible organisms. This results in an added difficulty in prospective enrollment of these patients. Second, evaluation of outcomes in patients with MDRO infections may be complicated by a high rate of poor clinical outcomes unrelated to the infection (4). For instance, mortality unrelated to infection is unlikely to be impacted by a different antibiotic treatment strategy or an earlier diagnosis. Third, use of concomitant antibiotics prior to diagnosis of the MDRO infection is extremely common in these populations which in turn further limits enrollment into trials with restrictions on such prior treatment.

This study is specifically designed to provide data which can help in the design of future randomized clinical trials on both therapeutics and diagnostics, and describe, on the basis of observational data, patients with MDRO infections in hospitalized patients. These data will include a detailed clinical and epidemiological description of patients including potential barriers to enrollment in future trials. In addition, data will be collected on species, strain type, and mechanism of drug resistance of the causative organism. Knowing the molecular characteristics will further inform future trial design as not all diagnostics detect and not all therapeutics are active against the same mechanisms of resistance (5).

3 OBJECTIVE

The objective of this study is to provide observational data that will aid in the design of randomized clinical trials on therapeutics and diagnostics for MDRO infections. To this end, clinical and epidemiological data will be collected on patients who have MDRO isolated from clinical cultures during hospitalization as well as descriptions of the outcomes of patients treated with various antimicrobial regimens. Molecular and microbiological characterization will also be performed on MDRO isolates.

3.1 Aim 1. Identification of target population and high volume centers

The prevalence of specific MDRO is extremely variable in various patient populations. In addition, over time, prevalence patterns for specific MDRO tend to change. The data collection carried out under this protocol will provide real-time data on which patients are the target population for any trial directed against MDRO infection. Also, the data collected will indicate which geographic areas and which centers have the highest incidence of MDRO infections. This will facilitate rational site selection for future trials.

3.2 Aim 2. Provide data on impact of potential inclusion/exclusion criteria on enrollment in future trials

Detailed clinical data will be collected to guide the future development of clinical trials. The eCRF is designed to collect data on the most common barriers to enrollment in clinical trials. Data can then be used in the design of future trials to be presented to pharmaceutical companies, as well as to regulators from the FDA, to provide a rationale for requesting exceptions in inclusion/exclusion criteria. This will result in clinical trials that are more readily generalizable.

3.3 Aim 3. Provide data on expected outcomes of patients with MDRO infections for power and sample size calculations for future trials

In the MDRO network, detailed outcomes data will be collected. Data will include survival and microbiologic clearance outcomes when available. In addition, anatomical site specific clinical symptomatic outcomes, modeled on FDA guidance documents, will be documented. Data obtained will aid in guiding the design of future clinical trials by providing data needed for power and sample size calculations.

4 STUDY SETTING

Study sites from across all five regions of the continental US and international sites from multiple countries will participate in the MDRO Network.

5 STUDY POPULATION

Cohorts will be constructed for each MDRO of eligible patients by investigating hospitalized patients who have an MDRO isolated in clinical cultures from any anatomical site. This study will be conducted under a waiver of informed consent to facilitate universal inclusion. All patients who are admitted to one of the participating hospitals and who have a MDRO – as defined in the specific sub-study protocol (Appendices) – isolated in a clinical culture are targeted for inclusion.

5.1 Inclusion Criterion

All hospitalized patients, including pediatric patients, who have at least one MDRO – as defined in the MDRO specific Appendices – isolated from a clinical culture will be eligible for inclusion.

5.2 Exclusion Criterion

Patients who only have a positive culture for MDRO – as defined in the MDRO specific Appendices – that is obtained outside the hospital setting and do not have a positive

culture for MDRO during hospitalization.

6 STUDY DESIGN

6.1 Overall Strategy

The MDRO Network will enroll at multiple sites globally. For each patient identified as having an MDRO, the data manager at the site will access the patient's medical record and use web-based data entry to enter the relevant data into the electronic case report form (eCRF) for the study's centralized database.

All MDRO isolates will be sent to the central research laboratories for molecular and microbiologic analysis. Molecular and microbiologic analyses may include, but will not be limited to, antimicrobial susceptibility testing, determination of mechanisms of antibiotic resistance, and strain typing.

6.2 Clinical Variables

At both enrollment and then at 90 days after discharge from the index hospitalization during which MDRO was identified, a limited data set will be collected for each patient, and entered into a secure database. Patient demographics and co-morbid conditions; antibiotic allergies; length of hospital stay prior to first positive culture; ICU stay; reason for hospitalization; complications during hospitalization such as renal failure; components of the Pitt Bacteremia Score and Charlson comorbidity index; anatomic site-specific risk factors such as lines and devices; antibiotic use; and outcomes including all-cause and attributable mortality will be included. Specific data will be collected based on the anatomical site from which MDRO was isolated; data will include relevant symptomatology, radiographic imaging results, laboratory results, and specific interventions. Length of stay after isolation of MDRO, disposition, and readmission rates will also be collected. To specifically track the origin and spread of MDRO, detailed information regarding the origin and post-hospital disposition of each patient will be collected; for long term care facilities, the specific facility will be noted, for home origin or discharge, the first 3 digits of the international zip code will be used.

6.3 Clinical Definitions

MDRO: Specific Multi-Drug Resistant Organisms of interest are defined in the Appendices

Culture episode: A positive MDRO culture from any anatomical site marks the beginning of a culture episode that includes any subsequent cultures within 7 days from the same site and during the same hospital admission. If a period of more than 7 days elapses between positive cultures, this is considered the start of a new culture episode. A positive MDRO culture from a different anatomical site is considered a separate culture episode.

Hospital Setting: For the purposes of this protocol, patients are considered to be in a hospital setting during the first positive MDRO culture if they are admitted to a short-term acute care hospital, or if they are in the emergency department awaiting admission with a subsequent admission. In addition, a stay in the emergency department of >24

hours will qualify as a hospital setting.

Infection: A patient is deemed to have an infection if a MDRO is isolated from blood or any other sterile source. For patients with positive respiratory cultures the criteria outlined by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) are used (6, 7). For patients with positive cultures from urine or surgical wounds, the CDC/National Healthcare Safety Network (NHSN) criteria are used (8). Patients with cultures from non-surgical wounds are considered infected only if the treating physician documents infection in the medical record and evidence of systemic inflammation on the day the positive culture is documented, defined as an abnormal systemic white cell count (either >10K cells/uL or <4K cells/uL), and/or abnormal body temperature (either >99.5 ºF or <96 ºF).

Colonization: All culture episodes that do not meet the preceding definitions of infection are designated as colonization (9).

***Renal failure*:** Renal failure will be defined using the Risk, Injury and Failure components of the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease RIFLE criteria (10).

Severity of acute illness: The Pitt bacteremia score (PBS) is calculated using temperature, mental status, cardiac arrest, blood pressure, mechanical ventilation, as described (11).

Chronic comorbidity: The Charlson Comorbidity Index will be calculated using documented history of myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes, hemiplegia, renal failure, any tumor, leukemia, lymphoma, AIDS, as described (12).

6.4 Participant Enrollment and Follow-up

The demographic and hospitalization data will be entered in the eCRF once the patient is enrolled per eligibility criteria. The timing of the remaining data entry will be at 90 days after the conclusion of the index hospitalization. If a patient is readmitted to a study hospital and again meets criteria for inclusion in the study, a new enrollment episode will be created in the database.

7 STATISTICAL ANALYSIS

7.1 Sample Size Estimate

The estimated sample size for each MDRO is documented in the MDRO specific section of the Appendices.

7.2 Primary Analysis

Data will be analyzed as outlined in each appendix. Furthermore, comparative analyses between different organisms will be performed.

The primary analysis will summarize the key clinical, epidemiologic, and molecular data

on patients with MDRO isolated from clinical cultures during hospitalization. Data will serve to determine potential eligibility for future trials. Strain data and mechanism of resistance will aid in determining the likelihood of response to novel antibiotic options, based on other *in vitro* and animal studies. 95% confidence intervals will be provided on key outcomes.

Data to be summarized include the following:

- Demographics
- Origin (skilled nursing facility, home, long term acute care facility, transfer from another hospital)
- Disposition (skilled nursing facility, home, long term acute care facility, transfer to another hospital, death, hospice)
- Charlson Score
- Pitt Bacteremia Score
- Source of positive culture (blood, respiratory, urine, wound, abdominal, other)
- Outcome (length of stay, ICU admission, discharge location, death)
- Antibiotic summary
- Status at 90 days
    - Defined as 90 days after the index culture. However, data will be collected through 90 days after discharge from index hospitalization.

7.3 Timing of Analyses

Data will be analyzed approximately 3 times yearly in order to prepare data for reporting at annual meetings as well as for publication.

8 ETHICS AND REGULATORY CONSIDERATIONS

8.1 Ethical Standards

The procedures set forth in this study protocol are designed to ensure that the site investigators abide by International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) guidelines in the conduct, evaluation, and documentation of this study.

Site Investigators agree, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP that it conforms to.

The investigator will ensure that the study will be conducted in accordance with all applicable national, regional, and local regulations.

This study will request a waiver of informed consent, consistent with country specific regulations. The study does not involve direct interaction with human subjects. The medical records of patients admitted to the hospital will be screened and data collected from those records according this protocol. The patients will not be approached to obtain information, no intervention is being tested nor are human specimens being

collected. Only pathogen MDRO isolates will be collected and analyzed.

8.2 Data Confidentiality

Each participating site will prepare and maintain complete and accurate study documentation and research records for this study, in compliance with ICH E6 as well as applicable national, regulatory, and institutional requirements. The site investigator, in compliance with GCP standards, will for each participant in the study, promptly complete all eCRFs. The site investigator will comply with any other IRB or Ethics Committee requirements as stipulated by local regulations.

The sponsor's representative, Duke Clinical Research Institute (DCRI), will use a configured electronic data capture (EDC) RAVE database, to collect study data. Access will be limited to study personnel who are issued a unique user identification and password and are listed on the authorized study user list.

By signing the protocol, the site investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to the sponsor or their representative by the site investigator upon request and also shall be made available at the site investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the sponsor or by responsible government agencies as required by law.

9 QUALITY CONTROL AND QUALITY ASSURANCE

The DCRI will implement a Data Driven Trial Management Plan to ensure data quality.

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written procedures and standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

10 DATA COLLECTION, MANAGEMENT, AND ANALYSIS

The site investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. Data reported in the eCRF derived from source documents must be consistent; discrepancies should be explained in the comments field in the eCRF. The study team may provide guidance to site investigators on making corrections to the source documents and eCRF.

10.1 Data Management Responsibilities

All source documents must be reviewed by the site data entry staff, who will ensure that they are accurate and complete. Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. During the study, the site investigator must maintain complete and accurate documentation for the study. The ARLG Statistical and Data Management Center (SDMC) will serve as the statistical and data coordinating center for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

10.2 Data Capture Methods

Clinical and laboratory data will be entered into a Web-based Internet Electronic Data Capture System (EDC) that ensures data confidentiality. The data system includes individual user accounts with password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.3 Study Record Retention

Study documents should be retained per local regulations or 6 years after the end of the study, whichever is longer. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the site investigator when these documents no longer need to be retained.

11 PUBLICATION POLICY

11.1 Study Findings

The principal investigator may publish the results of this research in a scientific journal under the oversight of the MDRO Network and ARLG Publication Committees.

The ARLG Publication Committee comprises representatives of the network cores, thought leaders, and the SDMC, and is responsible for generation and coordination of the publications that report scientific findings of the network. All public presentations (abstracts, manuscripts, slides and text of oral or other presentations, and text of any transmission through any electronic media) by participating investigators, participating institutions, the SDMC, and ARLG that use ARLG data and are intended to represent the ARLG or are supported by the ARLG will be reviewed by the Publication Committee per the Publication Committee charter and must include the following statement "Research reported in this publication was supported by the National Institute Of Allergy And Infectious Diseases of the National Institutes of Health under Award Number UM1AI104681 (The Antibacterial Resistance Leadership Group – ARLG). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health."

The Publication Committee guarantees that the study results are presented by experts in the field who have working knowledge of the study design, implementation, data synthesis/analysis, and interpretation. The committee goals are to ensure that any confidential or proprietary information is protected, and that all appropriate statistical analyses have been included.

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication. Refer to:

http://publicaccess.nih.gov

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Appendix I:

CRACKLE II: Consortium on Resistance Against Carbapenems in Klebsiella pneumoniae and Other Enterobacteriaceae (CRACKLE) : a Prospective, Observational Cohort Study

List of Abbreviations

CRACKLE	Consortium on Resistance Against Carbapenems in *Klebsiella pneumoniae* and other Enterobacteriaceae
CRE	Carbapenem-resistant Enterobacteriaceae
CRKP	Carbapenem-resistant *Klebsiella pneumoniae*
K. pneumoniae	*Klebsiella pneumoniae*
PCR	Polymerase Chain Reaction
rep-PCR	Repetitive extragenic palindromic polymerase chain reaction
ST258	Sequence type 258

1 Background

Carbapenem resistance is increasingly common in Enterobacteriaceae (CRE), especially *Klebsiella pneumoniae* (*K. pneumoniae*) isolates, and represents a major threat to our global population. Since the first reported carbapenem-resistant *K. pneumoniae* (CRKP) was identified in 1996, the incidence of infections due to this multidrug-resistant (MDR) pathogen has increased dramatically. According to data from the Centers of Disease Control (CDC), 11% of K. pneumoniae that cause healthcare-associated infections are carbapenem resistant. Regrettably, outcomes after CRKP bloodstream infections are generally poor. All-cause mortality rates of 42-72% have been reported. The globally endemic CRKP strain type 258 (ST258) is responsible for the majority of infections in the US. The mechanism of resistance for most ST258 isolates in the US is the Klebsiella pneumoniae carbapenemase (KPC) family.

2 Objective and Primary Aims

The objective of this study is to provide observational data that will aid in the design of randomized clinical trials on therapeutics and diagnostics for CRE infections. To this end, clinical and epidemiological data will be collected on patients who have CRE isolated from clinical cultures during hospitalization as well as descriptions of the outcomes of patients treated with various antimicrobial regimens. Molecular and microbiological characterization will also be performed on CRE isolates.

2.1 Aim 1. Identification of target population and high volume centers

The prevalence of specific CRE is extremely variable in various patient populations. In addition, over time, prevalence patterns for specific CRE tend to change. The data collection carried out under this protocol will provide real-time data on which patients who are the target population for any trial directed against CRE infection. Also, the data collected will indicate which geographic areas and which centers have the highest incidence of CRE infections. This will facilitate rational site selection for future trials.

2.2 Aim 2. Provide data on impact of potential inclusion/exclusion criteria on enrollment in future trials

Detailed clinical data will be collected to guide the future development of clinical trials. The eCRF is designed to collect data on the most common barriers to enrollment in clinical trials. Data can then be used in the design of future trials to be presented to pharmaceutical companies, as well as to regulators from the FDA, to provide a rationale for requesting exceptions in inclusion/exclusion criteria. This will result in clinical trials that are more readily generalizable (see 3.2 in main MDRO protocol).

2.3 Aim 3. Provide data on expected outcomes of patients with CRE infections for power and sample size calculations for future trials

Detailed outcomes data will be collected. Data will include survival and microbiologic clearance outcomes when available. In addition, anatomical site specific clinical symptomatic outcomes, modeled on FDA guidance documents, will be documented. Data obtained will aid in guiding the design of future clinical trials by providing data needed for power and sample size calculations (see 3.3 in main MDRO protocol).

3 Laboratory Assessments

As novel antibiotics directed against CRE may have differential efficacy based on the mechanism of resistance, molecular characterization for strain type and mechanism of carbapenem resistance will be performed on CRE isolates, including whole genome sequencing, single gene PCR, multilocus sequence typing (MLST) and/or rep-PCR (6). Furthermore, phenotypic characteristics such as *in vitro* susceptibility testing will be performed in the central research laboratories.

4 Exploratory Aims

4.1 Exploratory Aim 1. The association between bacterial characteristics and clinical outcomes in patients with CRE

4.2 Exploratory Aim 2. The association between treatment modalities and clinical outcomes in patients with CRE

4.3 Exploratory Aim 3. Risk factors for baseline and treatment-emergent resistance to anti-CRE antibacterials in patients with CRE

5 Study Population

All patients who are admitted to one of the participating hospitals and who have a CRE isolated from bloodstream infection source in a clinical culture will be included.

In addition, all participating hospitals in China will also enroll patients who meet the below criteria:

a. have a CRE isolated from respiratory source in a clinical culture
b. AND have a clinical diagnosis of pneumonia, per diagnosis criteria in Table 1

Table 1.

At least one criterion from each section must be present to meet definition of pneumonia diagnosis		
1	Radiographic Criteria	• Chest radiograph showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia within 48 hours of all other diagnostic criteria being present
2	Respiratory Signs/Symptoms	• New onset or worsening: cough, dyspnea, tachypnea (respiratory rate >= 25 breaths per minute for patients >18 years, >60 breaths per minute for children <1 year, >40 breaths per minute for children ages 1-3 years, >30 breaths per minute for children ages 4-12 years, >20 breaths per minute for children 12-18 years), or expectorated sputum production • Hypoxemia, defined as any of the following: ▪ A partial pressure of oxygen <60 millimeters of mercury measured by arterial blood gas (ABG) ▪ A worsening (decrease >10%) of the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) ▪ Pulse oximetry reading of <90% ▪ New supplemental oxygen requirement ▪ Greater than 2LPM increase in amount of supplemental oxygen required for patients on chronic supplemental oxygen therapy ▪ Need for acute changes, after 2 days stability, in ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO2/FiO2) or needed changes in the amount of positive end-expiratory pressure
3	Systemic Inflammation	• Documented body temperature ≥38 degrees Celsius or ≤ 35 degrees Celsius (core body temperature) • Leukocytosis, defined as total peripheral white blood cell count ≥10,000 cells/cubic millimeter • Leukopenia, defined as total peripheral white blood cell count ≤4,500 cells/cubic millimeter • Greater than 15% immature neutrophils (bands) noted on peripheral blood film

6 Clinical Definitions

CRE: For the purposes of this study, CRE are defined as any Enterobacteriaceae displaying in vitro resistance to any of the carbapenems as per CDC guidelines, i.e. Enterobacteriaceae that are resistant to any carbapenem antimicrobial (i.e., minimum inhibitory concentrations of ≥4 mcg/ml for doripenem, meropenem, or imipenem OR ≥2

mcg/ml for ertapenem) OR Documented to produce carbapenemase.

In addition:
• For bacteria that have intrinsic imipenem nonsusceptibility (i.e., Morganella morganii, Proteus spp., Providencia spp.), resistance to carbapenems other than imipenem is required.

7 Statistical Analysis Plan

7.1 Sample Size Estimate

The sample size is estimated to be between 3,000-5,000 unique admissions.

Appendix II:

SNAP: Study Network of Acinetobacter baumannii as Carbapenem-Resistant Pathogen

List of Abbreviations

SNAP	Study Network of *Acinetobacter baumannii* as Carbapenem-Resistant Pathogen
CRAb	Carbapenem-resistant *Acinetobacter baumannii*
PCR	Polymerase Chain Reaction
rep-PCR	Repetitive extragenic palindromic polymerase chain reaction

1 Background

Acinetobacter baumannii has emerged as one of the most highly antimicrobial-resistant pathogens causing hospital-acquired infections globally. In the U.S., an estimated 45,000 cases of *A. baumannii* infections occur per year. The most common presentations of invasive infection include bacteremia and pneumonia. *A. baumannii* has an extraordinary ability to develop resistance to even the most potent antimicrobial agents. In particular, carbapenem resistance among *A. baumannii* has dramatically increased in the last decade, with rates increasing from 21% in 2003-2005 to 48% in 2009-2012. According to recent CDC data, 55% of *A. baumannii* causing ventilator-associated pneumonia in the U.S. are resistant to carbapenems. Treatment options for carbapenem-resistant *A. baumannii* (CRAb) infections are extremely limited and include agents such as colistin, tigecycline and minocycline, which have uncertain efficacy and considerable toxicity. Risk factors for acquiring CRAb include exposure to antimicrobial agents, presence of indwelling catheters, severity of illness, and length of hospital stay especially in intensive care units. In-hospital and 30-day all-cause mortality from CRAb infections are estimated to be 42%-62% and 16%-58%, respectively. Despite this significant disease burden, prospective multicenter studies that evaluate microbiological factors that impact patient outcome – while carefully controlling for clinical co-variables – have not yet been conducted in the U.S.

2 Objective

The objective of this study is to provide observational data that will aid in the design of randomized clinical trials on therapeutics and diagnostics for CRAb infections. To this end, clinical and epidemiological data will be collected on patients who have CRAb isolated from clinical cultures during hospitalization as well as descriptions of the outcomes of patients treated with various antimicrobial regimens. Molecular and

microbiological characterization will also be performed on CRAb isolates.

2.1 Aim 1. Identification of target population and high volume centers

The prevalence of specific CRAb is extremely variable in various patient populations. In addition, over time, prevalence patterns for specific CRAb tend to change. The data collection carried out under this protocol will provide real-time data on which patients are the target population for any trial directed against CRAb infection. Also, the data collected will indicate which geographic areas and which centers have the highest incidence of CRAb infections. This will facilitate rational site selection for future trials.

2.2 Aim 2. Provide data on impact of potential inclusion/exclusion criteria on enrollment in future trials

Detailed clinical data will be collected to guide the future development of clinical trials. The eCRF is designed to collect data on the most common barriers to enrollment in clinical trials. Data can then be used in the design of future trials to be presented to pharmaceutical companies, as well as to regulators from the FDA, to provide a rationale for requesting exceptions in inclusion/exclusion criteria. This will result in clinical trials that are more readily generalizable (see 3.2 in main MDRO protocol).

2.3 Aim 3. Provide data on expected outcomes of patients with CRAb infections for power and sample size calculations for future trials

Detailed outcomes data will be collected. Data will include survival and microbiologic clearance outcomes when available. In addition, anatomical site specific clinical symptomatic outcomes, modeled on FDA guidance documents, will be documented. Data obtained will aid in guiding the design of future clinical trials by providing data needed for power and sample size calculations (see 3.3 in main MDRO protocol).

3 Exploratory Aims:

-To establish a prospective cohort of subjects with carbapenem-resistant *Acinetobacter baumannii* infection or colonization
-To describe the demographics, natural history and clinical outcome of patients with CRAb
-To collect the associated *A. baumannii* strains of patients with CRAb for future studies

4 Enrollment Target

The study will enroll up to 2000 unique admissions. This will be a global competitive enrollment.

5 Study Population

All patients who are admitted to one of the participating hospitals and who have a CRAb isolated in a clinical culture will be included.

6 Clinical Definitions

CRAb: *Acinetobacter baumannii* isolates that are resistant (minimum inhibitory concentrations of ≥8 mcg/ml) to at least one of the following three carbapenems: doripenem, imipenem, meropenem.

7 Statistical Analysis Plan

7.1 Sample Size Estimate

The sample size will be approximately 2000 unique admissions.

Appendix III:

VENOUS II: Vancomycin-Resistant Enterococci Outcomes Study II

List of Abbreviations

VENOUS II	Vancomycin-Resistant Enterococci Outcomes Study II
VRE	Vancomycin-Resistant Enterococci
BSI	Blood Stream Infection

1 Background

Vancomycin-resistant enterococci (VRE) are one of the leading causes of health-care associated infections, causing approximately 20,000 infections and 1,300 deaths per year in the US alone (1). Moreover, VRE are a major cause of bloodstream infections (BSI) and preferentially affect patients who are severely ill and have an impaired immune system, such as cancer patients and subjects in the intensive care setting (2). Currently, there is only one FDA-approved drug to treat VRE (linezolid). However, linezolid has major limitations for the treatment of severe VRE infections and its use in patients that need prolonged therapy is discouraged due to an unfavorable toxicity profile. Although several new drugs have been approved for the management of other important drug-resistant gram-positives (e.g. methicillin-resistant *Staphylococcus aureus*), the majority of these new compounds lack bactericidal activity against VRE. The most common anti-VRE used drug is daptomycin (off-label), a lipopeptide antibiotic with *in vitro* bactericidal activity against these organisms (3). However, the emergence of resistance during daptomycin therapy is a serious concern and uncertainty in the best dose regimen to treat severe VRE infections remains (4). Thus, robust clinical data to determine the best treatment approaches for these multi-drug resistant organisms are urgently needed. Indeed, despite the significant burden of disease caused by VRE, prospective multicenter studies evaluating clinical and microbiological factors that impact patient outcomes have not yet been conducted in the U.S.

2 Objective

The objective of this study is to establish a large multicenter prospective cohort of patients with VRE BSIs to provide solid observational data that will aid in the design of randomized clinical trials on therapeutics and diagnostics for deep-seated VRE infections. To this end, clinical and epidemiological data will be collected on patients who have VRE isolated from the bloodstream during hospitalization, as well as descriptions of the outcomes of patients treated with various antimicrobial regimens. VRE isolates will also be collected to perform molecular and genomic characterization.

2.1 Aim 1. To assemble a multicenter prospective cohort of patients with VRE BSIs to provide data on outcomes of patients with VRE BSIs for sample size calculations for future trials

We will leverage from an ongoing effort (VENOUS I) that has prospectively collected data from ca. 200 patients with enterococcal infections from three active centers to assemble a large multicenter cohort of patients with VRE BSIs. The data collected under this protocol will provide valuable information regarding outcomes and prognostic factors (both from the patient and isolate perspective), along with real-life data on which patients are the target population for any trial directed against invasive VRE infections. Also, we expect this cohort to help pinpoint specific geographic areas and/or centers with high incidence of VRE infections, facilitating the rational selection of sites for future trials. Data on outcomes (i.e. survival and microbiologic clearance) will aid in guiding the design of future clinical trials by providing reliable information needed for power and sample size calculations (see 3.3 in main MDRO protocol).

2.2 Aim 2. To provide data on the impact of potential inclusion/exclusion criteria on enrollment in future VRE trials

Detailed clinical data will be collected to guide the future development of clinical trials. The eCRF is designed to collect data on the most common barriers to enrollment in clinical trials. Data can then be used in the design of future trials to be presented to pharmaceutical companies, as well as to regulators from the FDA. The information will also be used to provide a rationale for requesting exceptions in inclusion/exclusion criteria. This valuable data will result in the design of clinical trials that are more readily generalizable (see 3.2 in main MDRO protocol).

3 Exploratory Aim. To collect VRE isolates causing BSIs in order to understand the molecular epidemiology of infecting organisms for future studies

All infecting VRE isolates will be collected for further microbiological, molecular and genomic characterization, as part of future studies. Bacterial genomic information will be analyzed in order to find possible genetic factors that correlate with clinical outcomes in deep-seated VRE infections.

4 Enrollment Target

200 unique admissions. This will be a competitive enrollment.

5 Study Population

All patients admitted to one of the participating hospitals who develop a confirmed blood stream infection due to VRE will be included in the study. In order to enroll a patient, the VRE isolate should be available for further characterization.

6 Clinical Definitions

VRE BSI: At least one blood culture positive for vancomycin-resistant enterococci (resistance to vancomcyin will be defined by current CLSI guidelines), regardless of the Enterococcal species and of the susceptibility method used by the microbiology

laboratory.

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Appendix IV:

POP: Prospective Observational *Pseudomonas* study

List of Abbreviations

POP	Prospective Observational *Pseudomonas* study
CRPA	carbapenem-resistant *P. aeruginosa*
BSI	Blood Stream Infection

1 Background

Pseudomonas aeruginosa infections are common in immunocompromised patients, are a leading cause of hospital-acquired infection, and are associated with poor outcomes. Treatment of *P. aeruginosa* infections is complicated by antimicrobial resistance, including resistance to carbapenems. Carbapenem resistance is especially challenging because it is often associated with resistance to multiple classes of antibiotics, leaving few therapeutic options. Novel technologies and drugs are needed to better diagnose and treat *P. aeruginosa* infections, but designing the clinical trials necessary to address this demand is challenging given the lack of detailed data on *P. aeruginosa* resistance mechanisms, clinical and molecular epidemiology, treatment, and outcomes. This proposal aims to fill this gap by providing detailed clinical and microbiologic data in carbapenem-resistant *P. aeruginosa* (CRPA) pulmonary and bloodstream infections. We believe that this study is ideal for the ARLG, as it will utilize the existing the MDRO Network, which already has similar ongoing studies in patients with carbapenem-resistant Enterobacteriaceae and carbapenem-resistant *Acinetobacter* infections.

2 Objectives

2.1 Aim 1

Define antibiotic resistance determinants and molecular epidemiology of CRPA pulmonary and bloodstream infections within the ARLG MDRO network.

2.2 Aim 2

Facilitate future interventional and diagnostic studies involving CRPA by detailing current epidemiology, treatment, and outcomes of CRPA pulmonary and bloodstream infections at potential clinical trial sites within the ARLG MDRO Network.

3 Enrollment Target

The study will enroll up to 2000 unique admissions. This will be a global competitive enrollment.

4 Study population

4.1 Inclusion criteria

All patients at participating sites, including pediatric patients, with CRPA isolated from any clinical culture during hospitalization or within 3 days prior to hospitalization will be included in the study.

4.2 Exclusion criteria

1. Outpatient status at the time of collection of cultures that yield CRPA and patient not admitted to the hospital for CRPA infection within 3 days of collection of the culture
2. Cystic fibrosis

5 Clinical Definitions

CRPA: *Pseudomonas aeruginosa* isolates that are resistant in vitro to at least one of the following carbapenems: doripenem, imipenem, meropenem.

6 Statistical Analysis Plan

6.1 Sample Size Estimate

The sample size will be approximately 2000 unique admissions.

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