# **C**omparing **O**ral versus **P**arenteral **A**ntimicrobial **T**herapy (COPAT) Trial

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**IRB Protocol**

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## Protocol Number & Study Protocol Title

Comparing Oral versus Parenteral Antimicrobial Therapy (COPAT) Trial
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## Abbreviations List

COPAT: Comparing Oral versus Parenteral Antimicrobial Therapy (Trial)
COpAT: complex outpatient oral antimicrobial therapy (program)
ID: Infectious Diseases
IV: intravenous
OPAT: outpatient parenteral antimicrobial therapy (program)
PO: oral
WVU: West Virginia University

# Section I: Team and Research Summary

## Study Team Composition

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## Research Summary

**Study Population:** N=135 patients (*Experimental*: 90 patients; *Control*: 45 patients); as the hypothesis is that adverse events will be significantly reduced in the experimental group with no significant difference in efficacy between groups, 135 patients (randomized 2:1) are needed to have power greater than 80%.

Inclusion (must meet all of the following):

- The patient is an adult (≥18 years) and English speaking
- The patient is hospitalized at J.W. Ruby Memorial Hospital, United Hospital Center, Berkeley Medical Center, Wheeling Hospital, or Camden Clark Medical Center
- The patient has been diagnosed with ≥1 of the following: endovascular, bone and joint, skin and soft tissue, pulmonary, gastrointestinal, or genitourinary infection
- The patient is being transitioned to 2-8 weeks of IV antibacterial therapy on hospital discharge
- The patient has capacity to participate in routine OPAT/COpAT follow-up (telephone check-ins, laboratory monitoring, and in-person or telemedicine ID Clinic follow-up)

Exclusion (may not meet any of the following):

- The patient is not appropriate for OPAT (active injection drug use, lack of infusion resources, and/or unstable outpatient environment)
- The patient is not appropriate for COpAT (unable to receive PO medication or lack of an effective PO antimicrobial option based on susceptibility testing)
- The patient is unable to give informed consent
- The patient is a prisoner, pregnant, and/or mentally handicapped
- The patient is determined unsafe for enrollment at the primary team's discretion

As noted above, children, prisoners, pregnant women, and/or mentally handicapped individuals will not be included. WVU/UHA/WVUH employees or WVU students may enroll in the study if inclusion/exclusion criteria are met.

**Study Design:** Investigator initiated multisite pragmatic randomized controlled trial

All patients referred for OPAT will be evaluated by the research team with respect to inclusion/exclusion criteria. If determined eligible for enrollment, patients will be approached by a study investigator who will present the COPAT Trial. If interested in participating in the study, patients will then complete informed consent with a member of the research team (study investigator or research coordinator). Once informed consent is obtained, patients will be randomized 2:1 using computer software into experimental or control (standard of care) group, respectively: *Experimental*: COpAT only on hospital discharge; *Control*: Conventional OPAT, OPAT transitioned to COpAT later in outpatient setting, or long-acting parenteral lipoglycopeptides. For patients randomized into the experimental group, ≥2 ID physicians (principal investigators for all patients and, if at a participating hospital other than J.W. Ruby Memorial Hospital, also the site co-investigator) on the research team will collaborate to determine COpAT regimens. Both groups will be followed by an ID physician on the research team with in-person or telemedicine ID Clinic standard of care visits at 2, 6, and 12 weeks after hospital discharge. At the 6-week ID Clinic follow-up, patients will be asked to complete a patient satisfaction survey (separate attachment). At the 12-week ID Clinic follow-up, all patients who attend will receive compensation. Data will be collected from enrollment through completion of ID Clinic follow-ups directly from patients as well as through patient satisfaction surveys and review of electronic medical records in Epic. The study process will be identical for all participating hospitals. As early IV to PO antimicrobial transition for serious infections including endocarditis and bone and joint infections is well supported by evidence from published clinical trials and patients will not undergo testing/procedures beyond standard of care, risk to patients will be minimized. Since patients enrolled in the study will have at least one serious infection and participate in a randomization process with the experimental study arm evidence based but not yet as widely incorporated in clinical practice, more than minimal risk will be involved.

**Study Duration:**

Enrollment is expected to take up to 4 months to achieve the proposed sample size. Subjects will be followed for 3 months after hospital discharge. Data collection will occur in real-time throughout the study, and final data analysis will be performed at conclusion of the study.

## Section II: Design

### Background & Significance

Early IV to PO antimicrobial transition for serious infections including endocarditis and bone and joint infections is noninferior to prolonged IV antimicrobial therapy; this is supported by landmark studies published in the New England Journal of Medicine.[1, 2, 3] As compared to inpatient IV antimicrobial therapy, OPAT has a similar adverse event rate but results in substantial cost savings.[4] Challenges with IV antimicrobial therapy include vascular access requirement and risk of associated complications (i.e. bacteremia/fungemia and deep venous thrombosis) and social circumstance limitations.[5] COpAT uses PO antimicrobials with high bioavailability in place of IV antimicrobials.[5,6] According to retrospective data, early IV to PO antimicrobial transition compared to prolonged IV antimicrobial therapy for endocarditis has similar outcomes with fewer adverse events.[7] Our early experience at WVUH suggests COpAT is not only clinically effective and safer but also results in significant additional cost savings.[6] However, unlike OPAT, COpAT programs are not yet widely incorporated into clinical practice. In addition, clinical trials evaluating safety superiority with equivalent effectiveness of early IV to PO antimicrobial transition across various infectious diseases are lacking.

The COPAT Trial is designed to demonstrate equivalent effectiveness with improved safety of early transition from IV antimicrobial therapy to COpAT across various infectious diseases (endovascular, bone and joint, skin and soft tissue, pulmonary, gastrointestinal, and genitourinary infections); we hypothesize that adverse events will be significantly reduced in patients discharged from the hospital with COpAT versus standard of care with no significant difference in efficacy between groups. Should results of the COpAT Trial support the hypothesis, the evidence may promote more widespread incorporation of COpAT programs into clinical practice, improving patient care and resulting in lower cost of care.

### Objectives

**Purpose:** To demonstrate improved safety and equivalent effectiveness of early transition from IV antimicrobial therapy to COpAT across various infectious diseases (endovascular, bone and joint, skin and soft tissue, pulmonary, gastrointestinal, and genitourinary infections)

**Primary Outcomes:** Cure at 3 months using clinical (resolution of infection) and laboratory (improvement in inflammatory markers) parameters during ID Clinic follow-up as adjudicated by a 2-person evaluation team of ID faculty on the research team blinded to study arm and adverse events related to antimicrobial therapy/vascular access complication or readmission at 3 months.

**Secondary Outcome:** Patient satisfaction using a patient satisfaction survey (separate attachment) administered at 6-week ID Clinic follow-up.

**Rationale:** Key focuses of this study are safety, effectiveness, and implementation science.

- **Safety:** This study will evaluate safety superiority with early transition from IV antimicrobial therapy to COpAT versus standard of care antimicrobial therapy across various infectious diseases.
- **Effectiveness:** This study will evaluate effectiveness equivalence between early transition from IV antimicrobial therapy to COpAT and standard of care antimicrobial therapy across various infectious diseases.

- **Implementation Science:** Conducting this study will promote development of COpAT programs at additional WVU Medicine institutions. Should this study prove our hypothesis, COpAT programs will be more widely incorporated into clinical practice.

## Study Design & Methodology

This is an investigator initiated multisite pragmatic randomized controlled trial designed to demonstrate equivalent effectiveness with improved safety of early transition from IV antimicrobial therapy to COpAT across various infectious diseases (endovascular, bone and joint, skin and soft tissue, pulmonary, gastrointestinal, and genitourinary infections). Primary and secondary outcome data will be collected prospectively.

All patients referred for OPAT will be evaluated by the research team with respect to inclusion/exclusion criteria. If determined eligible for enrollment, patients will be approached by a study investigator who will present the COPAT Trial. If interested in participating in the study, patients will then complete informed consent with a member of the research team (study investigator or research coordinator after collaborating with a study investigator). Once informed consent is obtained, patients will be randomized 2:1 using computer software into experimental or control (standard of care) group, respectively: *Experimental*: COpAT only on hospital discharge; *Control*: Conventional OPAT, OPAT transitioned to COpAT later in outpatient setting, or long-acting parenteral lipoglycopeptides. For patients randomized into the experimental group, ≥2 ID physicians (principal investigators for all patients and, if at a participating hospital other than J.W. Ruby Memorial Hospital, also the site co-investigator) on the research team will collaborate to determine COpAT regimens. Both groups will be followed by an ID physician on the research team with in-person or telemedicine ID Clinic standard of care visits at 2, 6, and 12 weeks after hospital discharge. At the 6-week ID Clinic follow-up, patients will be asked to complete a patient satisfaction survey (separate attachment). At the 12-week ID Clinic follow-up, all patients who attend will receive compensation.

The following primary outcomes will be assessed: cure at 3 months using clinical and laboratory parameters during ID Clinic follow-up as adjudicated by a 2-person evaluation team of ID faculty blinded to study arm and adverse events related to antimicrobial therapy/vascular access complication (defined as any adverse event requiring intervention) or readmission at 3 months. The following secondary outcome will be assessed: Patient satisfaction using a patient satisfaction survey administered at 6-week ID Clinic follow-up (separate attachment). Data will be collected from patients directly as well as through patient satisfaction surveys and review of electronic medical records in Epic.

Early IV to PO antimicrobial transition, as will be performed in the experimental group, has been proven clinically effective for serious infections including endocarditis and bone and joint infections. According to retrospective data, early IV to PO transition compared to prolonged IV antimicrobial therapy for endocarditis has been shown to have similar outcomes with fewer adverse events. In addition, retrospective chart review of the first 100 patients who completed the WVUH COpAT program, showed low failure and side effect/adverse events rates. The experimental group is being compared to standard of care in current clinical practice. As this is a pragmatic clinical trial, patients will not undergo additional invasive testing or procedures. The probability and magnitude of harm or discomfort anticipated in this study are not greater in and of themselves than those ordinarily encountered in daily life while undergoing treatment for serious infection(s). Therefore, risk to patients will be minimized. Since patients enrolled in the study will have at least one serious infection and participate in a randomization process with the experimental study arm evidence based but not yet as widely incorporated in clinical practice, more than minimal risk will be involved.

There may be no direct benefit to study participants with the exception that patients randomized to the experimental group may be discharged from the hospital sooner and have improved safety. This research will make a significant

contribution to the field of ID as more prospective data supporting early IV to PO antimicrobial transition for serious infections is needed to change practice.

## Target Population & Recruitment Methods

**Sample Size:** As the hypothesis is that adverse events will be significantly reduced in the experimental group with no significant difference in efficacy between groups, 135 patients (*Experimental*: 90 patients; *Control*: 45 patients) are needed to have power greater than 80%.

**Inclusion & Exclusion Criteria:**

Inclusion (must meet all of the following):

- The patient is an adult (≥18 years) and English speaking
- The patient is hospitalized at J.W. Ruby Memorial Hospital, United Hospital Center, Berkley Medical Center, Wheeling Hospital, or Camden Clark Medical Center
- The patient has been diagnosed with ≥1 of the following: endovascular, bone and joint, skin and soft tissue, pulmonary, gastrointestinal, or genitourinary infection
- The patient is being transitioned to 2-8 weeks of IV antimicrobial therapy on hospital discharge
- The patient has capacity to participate in routine OPAT/COpAT follow-up (telephone check-ins, laboratory monitoring, and in-person or telemedicine ID Clinic follow-up)

Exclusion (may not meet any of the following):

- The patient is not appropriate for OPAT (active injection drug use, lack of infusion resources, and/or unstable outpatient environment)
- The patient is not appropriate for COpAT (unable to receive PO medication or lack of an effective PO antimicrobial option based on susceptibility testing)
- The patient is unable to give informed consent
- The patient is a prisoner, pregnant, and/or mentally handicapped
- The patient is determined unsafe for enrollment at primary team's discretion

**Vulnerable Populations:**

- As noted in the above inclusion/exclusion criteria, children, prisoners, pregnant women, and/or mentally handicapped individuals will not be included in this study.
- WVU/UHA/WVUH employees or WVU students may enroll in the study if inclusion/exclusion criteria are met.

**Recruitment:** All patients referred for OPAT will be evaluated by the research team with respect to inclusion/exclusion criteria. If determined eligible for enrollment, patients will be approached by a study investigator who will present the COPAT Trial. If interested in participating in the study, patients will then complete informed consent with a member of the research team (study investigator or research coordinator after collaborating with a study investigator).

## Risk & Benefit

**Risk:** Patients may experience standard of care adverse events related to antimicrobial therapy and/or vascular access device, lack of infection resolution, or infection recurrence. No study-related adverse events expected. There is always the risk of uncommon or previously unknown side effect(s) or adverse event(s). Other possible risks and discomforts include experiences associated with IV antibiotic use such as need for IV access, more time required to

take each dose, and number of doses per day. Similarly, possible risks and discomforts associated with oral antibiotic use may include experiences associated with pill size and number of doses per day. IV and oral antibiotics have similar side effects.

If an infection is not improving or a patient is having major side effects, treatment may be changed to IV antibiotics (if a patient is receiving oral) or oral antibiotics (if a patient is receiving IV).

**Benefit:** Patients may be discharged from the hospital sooner and have a reduced risk of adverse events related to vascular access device if randomized to the experimental group.

## Statistical Analysis Plan

**Sample Size:** As the hypothesis is that adverse events will be significantly reduced in the experimental group with no significant difference in efficacy between groups, 135 patients (*Experimental*: 90 patients; *Control*: 45 patients) are needed to have power greater than 80%. Calculations were performed through consultation with a biostatistician using failure and adverse event rates for COpAT/PO antimicrobial therapy taken from data presented and published on 100 patients who completed the WVUH COpAT Program and for conventional/intravenous antimicrobial therapy taken from clinical trial data published on serious infections including endocarditis and bone and joint infections.

**Sample Size Allocation:** As the study will be conducted across 5 WVU Medicine hospitals, the number of subjects each site expects to enroll is as follows: J.W. Ruby Memorial Hospital 90 patients, United Hospital Center 18 patients, Berkeley Medical Center 12 patients, Wheeling Hospital 9 patients, Camden Clark Medical Center 6 patients.

**Data Safety Monitoring:** A Data and Safety Monitoring Plan will be implemented to facilitate ongoing review of the study, actions, data collection, and analysis throughout the entirety of the project. It will include details regarding handling serious adverse events (SAEs)/adverse events (AEs). A Data Safety Monitoring Board (DSMB) has been formed to oversee subject safety including one member not on the research team who is an expert in the field of ID: Michael Stevens, MD, MPH, FSHEA, FIDSA, FACP, WVU Health System's System Healthcare Epidemiologist and Associate Chief Quality Officer for Infection Prevention and Antimicrobial Stewardship and WVU Professor of Internal Medicine and Public Health, accepted his nomination to serve this role. The DSMB will review data and provide monitoring at 3 points in the study: after 45 patients are enrolled, after 90 patients are enrolled, and after 135 patients are enrolled.

**Early Stopping and Selection:** Bayesian statistical model will be used to assess efficacy outcomes and adverse events in the interim analysis. In particular, the predictive probability (for the final sample size) of primary outcomes will be estimated, given the current data. Denoting the posterior probabilities of adverse event outcome p1 (Control Arm) and p2 (Experimental Arm), respectively; the posterior probabilities of efficacy outcome by q1 (Control Arm) and q2 (Experimental Arm), respectively.

If Prob {p1>p2 | data} >0.90 and Prob{ |q1 – q2| < 0.10 |data} > 0.90,
then the trial will be stopped early, and the experimental arm will be selected as superior arm.

## Safety Monitoring & Unanticipated Event Reporting

In addition to the DSMB, the principal investigators will be responsible for data quality management and safety monitoring. At hospitals other than J.W. Ruby Memorial Hospital, site co-investigators will provide enrollment reports

to the principal investigators weekly and report any serious events to the principal investigators immediately. The principal investigators will then report any adverse or unanticipated events to the IRB in conjunction with requirements outlined by the IRB. The principal investigators will chair a monthly meeting including collaborating site co-investigators to ensure all data entry for current subjects is complete and up to date, review safety data including all serious events, and discuss all protocol deviations.

### Study Duration & Timeline

**Study Duration:**
Enrollment is expected to take 4 months to achieve our proposed sample size. Subjects will be followed for 3 months after hospital discharge. Data collection will occur in real-time throughout the study, and final data analysis will be performed at conclusion of the study.

## Section III: Informed Consent Process

### Protected Health Information (PHI)

Our study will require dealing with PHI, including names, medical record numbers, dates, and phone numbers. PHI will not be used for data analysis or reported/published. All PHI will be kept confidential.

### Informed Consent Process

All patients referred for OPAT will be evaluated by the research team with respect to inclusion/exclusion criteria. If determined eligible for enrollment, patients will be approached by a study investigator who will present the COPAT Trial. If interested in participating in the study, patients will then complete informed consent with a member of the research team (study investigator or research coordinator after collaborating with a study investigator).

Based on inclusion/exclusion criteria for the study, all patients will be adults (≥18 years) and able to give informed consent. Therefore, only patients themselves will grant consent to participate. Informed consent will require a written signature from patients with the exception of patients unable to write due to a physical condition including but not limited to infection involving the dominant hand in which case verbal consent may be accepted and documented on the consent form with a witness present.

### Confidentiality & Privacy

**Confidentiality:** All data will be kept for 3 years after the conclusion of the research project. Any physical copies of data collected will be kept in a locked drawer or file cabinet within a locked room or office. Digital data will be encrypted on a password protected database/drive. All patient identifiers will be stored separately from data collected.

**Privacy:** Conversations with patients while hospitalized will be conducted in the privacy of their own hospital rooms. Telephone check-ins with patients for OPAT/COpAT monitoring (standard of care) will be conducted from a private office with the door closed. ID Clinic follow-ups will be conducted in private clinical exam rooms. Data will be kept safe and secure according to the process explained in the above section.

## Section IV: Other Considerations

## Conflict of Interest

The research team does not have any conflicts of interest to report.

## Publications & Presentations

The research team plans for results of this research to be presented at IDWeek 2024 and submitted for publication in either Clinical Infectious Diseases or the New England Journal of Medicine.

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