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Research Article

# Improved Science and Outcome Reporting in Randomized Multicentre Trials of New Treatment for Periprosthetic Joint Infection of Hip and Knee

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**Abstract**

**Background:** Periprosthetic joint infection (PJI) is a rare, morbid condition that affects 1-2% of individuals who undergo hip or knee arthroplasty. Two-stage exchange arthroplasty has been considered the gold-standard for PJI treatment. However, published PJI treatment studies are largely retrospective single-site reports, and historical treatment outcome reporting for two-stage exchange arthroplasty has been inconsistent and potentially misleading. In 2019, the Musculoskeletal Infection Society (MSIS) published guidelines for PJI research including standards for outcomes reporting which have been variably adopted. **Key Objective:** To describe the research methods of two trials of a new PJI treatment that incorporate the MSIS research guidelines and contrast them with previously published PJI treatment studies. **Methods:** APEX and APEX-2 are two prospective, multicenter, randomized controlled trials comparing VT-X7, a new treatment for PJI, to conventional two-stage exchange arthroplasty. The APEX trials use intention-to-treat analysis, incorporating all individuals who initiate treatment into the outcomes reporting. The APEX trials make use of a composite success measure based upon the MSIS Tiered outcomes including a) successful implantation of Stage 2 revision prosthesis, b) absence of PJI post-Stage 2, c) absence of antibiotics for PJI treatment, d) absence of reoperation of the affected joint pre- and post-Stage 2, and e) absence of mortality. **Conclusions:** The APEX and APEX-2 trials represent a significant improvement in the quality of science applied to the care of individuals with PJI. Previous reports of two-stage treatment arthroplasty outcomes should be reconsidered in the context of the MSIS outcome reporting guidelines.

**Keywords:** Periprosthetic joint infection; Two-stage exchange arthroplasty; Randomized controlled trial

## Introduction

Periprosthetic joint infection (PJI) is a rare but serious complication of hip and knee arthroplasty associated with substantial morbidity, mortality, and economic burden [1,2]. PJI is notoriously difficult to treat without surgical intervention due to the presence of antibiotic-resistant biofilm [3]. As a result, PJI is the leading cause of revision arthroplasty [4,5].

The gold-standard for PJI treatment has been two-stage exchange arthroplasty, a care pathway that requires two surgical interventions and multiple medical treatments to control and/or resolve the infection. Stage 1 consists of prosthesis removal, initial debridement, and spacer implantation. The interstage period typically consists of a 6-week course of systemic antibiotics +/- antibiotic holiday. Stage 2 consists of a second debridement and reimplantation of the new prosthesis. While two-stage exchange arthroplasty can be used to manage a vast majority of PJI cases, including those with substantial soft-tissue infections and culture-negative infections, two-stage exchange arthroplasty is associated with a difficult, lengthy, and unpredictable interstage period ranging from a minimum of six weeks to 12 months or more. Altogether, two-stage exchange arthroplasty carries a relatively high risk of complications including septic and aseptic revisions, spacer complications, and failure to reimplant a permanent prosthesis [6-8]. Compared to individuals undergoing primary or aseptic revision arthroplasty, individuals treated for PJI have a higher incidence of depression, decreased quality of life post-surgery, and increased mortality [9-11].

The evidence supporting PJI treatment with two-stage exchange arthroplasty is of limited quality, primarily based upon single-center retrospective analyses. There are limited prospective, randomized studies evaluating the use of two-stage exchange arthroplasty for PJI. The outcome measures used to report two-stage exchange arthroplasty success and failure from published observational studies are often disparate, unbalanced, and fail to incorporate principles of intent-to-treat analysis. Studies that do not adopt an intent-to-treat analysis routinely limit the outcomes analysis to individuals who complete the full two-stage exchange arthroplasty. This approach excludes patients who fail to receive a second stage reimplantation due to death, amputation, or other potential negative outcomes. These studies overestimate treatment success.

To standardize measurement across studies for PJI, the Musculoskeletal Infection Society (MSIS) convened a multi-national, multi-institutional, multi-disciplinary workgroup to establish standards for outcome reporting in the management of PJI. In 2019, the MSIS published guidelines that clearly recommend all two-stage exchange arthroplasty patients who receive a first stage PJI surgery (prothesis removal and spacer insertion) be included in outcome reporting [27], a significant departure from a previous recommendation made by an international workgroup to only report on individuals completing the second stage procedure [29]. The MSIS Workgroup identified four tiers of outcomes: Tier 1. Infection control with no continued antibiotic therapy; Tier 2. Infection control with the patient on suppressive antibiotic therapy; Tier 3. Need for reoperation, revision, and/or spacer retention (subgroups include aseptic revision, septic revision, amputation, and retained spacer); Tier 4. Death related to infection.

To highlight the importance of the MSIS guidelines for outcomes reporting, we report on two randomized controlled trials being conducted (APEX; APEX-2) to evaluate a new, innovative treatment, NEXCHANGE™ KIT (project name VT-X7), that addresses the challenges of controlling PJI while eliminating a prolonged interstage period. The overall success measure used as a primary endpoint in the APEX trials combines the MSIS tiers into a single composite endpoint. The objective of this report is to describe the study design and outcomes reporting incorporated into the APEX trials.

## Materials and Methods

### Trial Objectives

The primary objective for the two Abbreviated Protocol for Two-Stage Exchange Arthroplasty clinical trials (APEX and APEX-2) is to evaluate the safety and efficacy of a novel treatment, VT-X7, for hip or knee PJI at 90 and 180 days compared to two-stage exchange arthroplasty, as measured by a composite endpoint of overall success. Secondary objectives are to evaluate the comparative difference in overall success between VT-X7 vs. two-stage exchange arthroplasty at 365 days, overall safety of the VT-X7 therapy, quality of life (QoL), and patient survival.

### Trial Design and Conduct

APEX and APEX-2 are multi-site, parallel group, randomized controlled trials. Enrolled patients are randomly assigned in a 1:1 ratio to the experimental arm (VT-X7) or the control arm stratified by infected joint (hip or knee). The experimental procedure consists of Stage 1 resection arthroplasty and debridement and implantation of an investigational, short-term spacer device designed to distribute local antibiotic into the intra-articular space and intramedullary canal. This was followed by a 7-day cyclic antibiotic irrigation (instillation/evacuation) through the short-term spacer, and Stage 2 reimplantation (revision) arthroplasty 7 days after Stage 1. The control procedure consists of a Stage 1 resection arthroplasty and debridement, insertion of a temporary antibiotic-impregnated cement spacer, administration of 6 weeks of systemic antibiotics followed by minimum 2-week antibiotic holiday, and a Stage 2

revision arthroplasty at a time deemed clinically appropriate by the investigator. All subjects are prescribed 12 weeks of systemic antibiotics after Stage 2 discharge. A minimum of 30% of subjects are required to be treated for hip PJI and a minimum of 30% for knee PJI in each of the treatment arms. All analyses are conducted on an intent-to-treat basis. The primary endpoint in APEX was assessed at 90 days and in APEX-2 at 180 days. Both APEX and APEX-2 collected data to assess overall success at 90-day, 180-day, and 365-day endpoints.

### Trial eligibility

The major inclusion criteria to participate in the trials was a planned two-stage exchange arthroplasty due to hip or knee PJI. The major exclusion criteria are a) two or more prior exchange arthroplasties for PJI, b) two or more failures to successfully reimplant a permanent prosthesis following placement of a temporary spacer, c) bacteremia within 30 days, d) PJI in more than one joint, e) fungal PJI, f) serious medical or psychiatric comorbidities including advanced renal insufficiency, chemotherapy for malignancy, schizophrenia, delusional disorders, and g) immunocompromised state include a history of immunodeficiency, use of systemic glucocorticoids (prednisone > 10 mg/day or equivalent), or use of select biologics (adalimumab, etanercept, etc.).

### Trial Measures

The studies' primary endpoint are an overall binary success (yes/no) composite outcome measure consisting of a) successful implantation of Stage 2 revision prosthesis, b) absence of PJI post-Stage 2 as measured by the 2018 ICMMI Guidelines for definitive PJI confirmation, c) absence of antibiotics for PJI treatment, d) absence of reoperation of the affected joint pre- and post-Stage 2, and e) absence of mortality [29]. Overall success is measured at day 90 (primary endpoint for APEX), day 180 (primary endpoint for APEX-2), and day 365 (secondary endpoint for both trials). Secondary outcome measures include the cumulative proportion of subjects with a revision prosthesis implanted at Stage 2, time to reimplantation for those who are reimplanted, comparison of Quality Adjusted Life Years (QALY) at 365-day, and survival at 365 days post-Stage 1 surgery. Exploratory outcome measures include the cumulative number of surgeries on the affected joint per subject, change in Knee Injury and Osteoarthritis Outcome Total Score (KOOS) [13], change in Hip Disability and Osteoarthritis Outcome Total Score (HOOS) [12], duration of antibiotic administration, and duration and cumulative morphine milligram equivalents of prescribed opioids.

### Statistical Planning

Efficacy will be confirmed by establishing superiority of overall composite success at 90 days (APEX) or 180 days (APEX-2). The sample size for each trial was based on prior reported literature of success rates in two-stage exchange arthroplasty. Assuming a 50% success rate of two-stage exchange arthroplasty, 72 patients were required to achieve 90% power to detect a 35% difference in Overall Success. The total sample size was increased in both studies to account for attrition due to lost-to-follow-up, patient withdrawal, or death within the primary endpoint follow-up period.

## Discussion

With the aging American population and increasing demand for arthroplasty, the number of individuals with PJI is likely to grow [14,15]. We report here on the design and implementation of two randomized, multi-site, controlled studies that incorporate the use of the MSIS outcomes reporting guidelines. The strengths of these trials include randomization, pragmatic design, use of intention-to-treat analysis, the incorporation of outcome measures consistent with the MSIS published best practices, collection of quality-of-life data to enable the calculation of QALYs, and enhanced generalizability of results given the participation of 23 top PJI treatment centers across both trials.

Two-stage exchange arthroplasties consist of removal of the infected implant, placement of a temporary spacer with prolonged antibiotics during a lengthy and unpredictable interstage period, followed by implantation of a permanent replacement prosthesis. In addition to two-stage exchange arthroplasty, other PJI therapeutic options include debridement, antibiotic therapy, and implant retention (DAIR), single-stage exchange, and 1.5 stage exchange procedures. However, there are few randomized controlled trials supporting these approaches. Additionally, there are no FDA approved therapies to specifically treat PJI. Of note, antibiotic impregnated cement spacers sometimes used in two-stage exchange arthroplasties are approved for prevention of bacterial colonization of the spacer, not for treatment of PJI [18]. The core principle of modern medicine as a science-based endeavor would suggest that high-quality evidence should precede widespread adoption of new therapies, especially in conditions as morbid as PJI [16-19].

The incorporation of the MSIS outcome measures and use of intention-to-treat analysis are requirements to achieve FDA approval but are also necessary to correctly interpret the clinical implications of trial results and establish consistency across real-world observational studies. For example, in one study of two-stage exchange arthroplasty for knee PJI based upon Medicare claims, 38.4% of individuals failed to undergo reimplantation within 1 year of initial treatment [20-22], while a separate study of a single center experience with two-stage exchange arthroplasty for hip and knee PJI reported much lower rates of failure of reimplantation but used multiple exclusion criteria including re-revision for infection. The methods and outcomes used in these two reports, and many others [24-27], vary widely.

Detailed outcome measures are required for optimal medical decision making, as many individuals with PJI are older and have comorbid conditions that increase their risk for poor outcomes [28-30]. The discussion between surgeon and patient regarding the risks and benefits of various treatment pathways is ideally informed by accurate data and relevant outcomes generated through high-quality research and incorporating the needs and preferences of the unique individual.

While PJI is described as a rare complication of arthroplasty, it is an expensive and morbid condition, which requires investment in infrastructure and collaborative networks necessary to advance the science of PJI management. High-quality, multi-site trials such as APEX/APEX-2 are an important step towards implementing common data collection standards and establishing the cooperation needed to generate the evidence to substantially improve outcomes for individuals with PJI.

## Limitations

Current data collection for the APEX trials is limited to one-year post initial surgery. Assessing differences in outcomes beyond that time will not be possible using the current trial data.

## Future Directions

Results of both APEX and APEX-2 will be published in 2025.

## Conclusions

The APEX and APEX-2 trials represent a major advance in the science of PJI treatment with outcome measures indicative of true treatment success for this challenging condition. These two clinical trials also represent the first prospective evaluation of a PJI therapy for regulatory approval in the U.S.

## Ethics Statement

This manuscript describes the methods of a previously concluded study. The work did not involve collection of new data, interaction with human subjects, or analysis of identifiable information. As such, it did not meet the regulatory definition of human subject's research and was not subject to institutional review board (IRB) oversight. No IRB approval was sought, as the activity was limited to scholarly review and manuscript development based on previously completed work.

## Conflict of Interest

C. Cohorn is an employee of Osteal Therapeutics. B. Springer is an employee of Mayo Clinic Florida; A. Chen is an employee of UT Southwestern Medical Center; B. de Beaubien is an employee of Covenant HealthCare; Author N. Piuzzi is an employee of the Cleveland Clinic Foundation; B. Springer, A. Chen, B. de Beaubien, and N. Piuzzi are paid consultants to Osteal Therapeutics with stock options. J. Darer is an employee of Health Analytics, LLC, a contract research organization that received funding from Osteal to construct this manuscript.

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