MegaPJI Study Protocol

Study information

MegaPJI is an international, multicentre, retrospective cohort study of periprosthetic joint infection after megaprosthetic reconstruction, approved by ATADEK (2026-14/670) on 24 September 2026.

Item	Detail
Full title	Microbiological Profile, Antibiotic Resistance Patterns, and Clinical Outcomes of Megaprosthesis Infections
Short title / acronym	MegaPJI
Design	International, multicentre, retrospective cohort
Protocol version	1.0, 3 November 2026
Ethics approval	Acıbadem University Medical Research Assessment Committee (ATADEK), decision 2026-14/670, 24 September 2026
Coordinating centre	Acıbadem University Korhan Özkan Orthopedic Oncology Study Group, Istanbul, Türkiye
Principal investigators	Prof. Dr. Korhan Özkan (Acıbadem University, Istanbul, Türkiye); Prof. Dr. Santiago A. Lozano-Calderón (Massachusetts General Hospital, Harvard Medical School, Boston, USA); Dr. Andrea Sambri (IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy)
Data coordinator	Dr. Halil İbrahim Bulut — drhbulut@icloud.com, h.brahim.blt@gmail.com
Data submission deadline	31 December 2027

Background and rationale

Pooled multicentre data are needed because single-centre megaprosthesis PJI series are too small to show how organisms and resistance differ between centres and countries.

Megaprosthetic (endoprosthetic) reconstruction is the standard of limb salvage after resection of bone tumours and is increasingly used for complex non-oncological indications such as periprosthetic fracture, massive bone loss and failed revision arthroplasty. Periprosthetic joint infection (PJI) is one of the most frequent and most devastating failure modes of these implants. It often leads to multiple revisions, prolonged antibiotic therapy, loss of function, amputation, delays in oncological treatment and death.

These patients carry risk factors rarely seen together in conventional arthroplasty: extensive soft-tissue resection, long operative times, chemotherapy and radiotherapy, repeated surgery and

immunosuppression. The causative organisms and their antibiotic resistance patterns are therefore likely to differ from those of standard PJI, and from one healthcare system to another.

Empirical antibiotic therapy, perioperative prophylaxis and the antibiotics loaded into cement and spacers are currently chosen largely by extrapolation from conventional arthroplasty or from local experience. A Europe-wide resistance "heatmap" of megaprosthesis infections, complemented by data from centres in the Americas and Asia, can give surgeons and infectious disease specialists a rational, region-specific basis for these choices.

Objectives

The primary objective is a Europe-wide map of the organisms causing megaprosthesis PJI and their resistance patterns; non-European data serve intercontinental comparison.

Primary objective

1. Describe the organisms causing megaprosthesis PJI and their antibiotic resistance patterns, by centre and country, across European centres.

Secondary objectives

1. Identify host, tumour and surgical factors associated with PJI characteristics and with infection by resistant or difficult-to-treat organisms.
2. Report treatment strategies (DAIR, one-stage revision, two-stage revision, amputation and other salvage procedures) and their outcomes: infection control, recurrence, limb salvage, implant survival, function and patient survival.
3. Compare organism spectrum and resistance between Europe and other regions (Europe vs the Americas, Europe vs Asia) using data from non-European centres.
4. Evaluate whether resistance patterns are associated with prior prophylaxis, antibacterial coatings, and cement or spacer antibiotics, to inform empirical and local antibiotic choice.

Study design and participating centres

MegaPJI is a retrospective cohort study pooling anonymised patient-level data from orthopaedic oncology and reconstruction centres in Europe and beyond.

- **Design:** international, multicentre, retrospective observational cohort; reported according to the STROBE statement.
- **Coordinating centre:** Acıbadem University Korhan Özkan Orthopedic Oncology Study Group, Istanbul, Türkiye, which holds the central database and performs the analysis.
- **European centres:** any centre performing megaprosthetic reconstruction, recruited directly and through European orthopaedic oncology networks. These form the primary analysis cohort.
- **Non-European centres:** centres in the Americas, Asia and other regions, whose data form comparison cohorts.
- **Study period:** all eligible patients treated at each centre, with no restriction on the year of index surgery, provided records allow completion of the core variables.

Participation steps for each centre

1. Confirm participation with the data coordinator and receive a centre code (e.g. RIZZ).
2. Obtain local ethics approval or a waiver if required; the coordinating centre provides the approval letter, this protocol and any other documents needed.
3. Sign the MegaPJI Data Use Agreement.
4. Complete the MegaPJI Excel datasheet in fully anonymised form.
5. Rename the file with the centre code (e.g. MegaPJI_RIZZ.xlsx) and send it to drhbulut@icloud.com by 31 December 2027.
6. Answer data queries from the coordinating centre.

Eligibility criteria and definitions

Any patient of any age with a megaprosthesis who developed PJI and has at least 3 months of follow-up after diagnosis is eligible.

Inclusion criteria

- Megaprosthetic (endoprosthetic) reconstruction of any anatomical site, for tumour or non-tumour indications, primary or revision.
- Periprosthetic joint infection of the megaprosthesis, diagnosed by EBJIS 2021, ICM 2018, MSIS 2011 or documented clinical criteria.
- At least 3 months of follow-up after PJI diagnosis.

Exclusion criteria

- Superficial surgical site infection without involvement of the implant.
- Insufficient records to establish the PJI diagnosis or the date of diagnosis.
- Patient or legal representative objection to the use of their data, where documented or required by local regulations.

Definitions

- **Unit of analysis:** one row per patient, representing the first PJI episode of the megaprosthesis. Later episodes are captured as recurrence.
- **Megaprosthesis:** a modular or custom endoprosthesis replacing a segment of bone and the adjacent joint after resection.
- **PJI diagnostic criteria:** recorded per patient (EBJIS 2021, ICM 2018, MSIS 2011, clinical/other), allowing sensitivity analyses by definition.
- **Infection classification:** McPherson staging (infection type, systemic host grade, local extremity grade).
- **Resistance categories:** MDR, methicillin resistance (MRSA/MRSE), VRE, ESBL, carbapenem resistance and difficult-to-treat organisms, as defined by the contributing laboratory, with the breakpoint standard (EUCAST or CLSI) and version recorded.
- **Implant failure:** classified by the Henderson failure modes, recorded in chronological order.

Variables and data collection

Data are collected on one standardised Excel datasheet (v4.2), one row per patient, with dropdown coding, range checks and a full data dictionary.

Domain	Main variables
Identification	Centre code, country, pseudonymised patient study code
Demographics	Sex, age at index surgery (years), BMI, smoking
Comorbidity	Charlson components, age-adjusted CCI (calculated), ASA score
Preoperative labs	HbA1c, albumin, neutrophil count, creatinine
Tumour and oncologic treatment	Indication, histology, chemotherapy (timing, ongoing at PJI), radiotherapy to the site, previous operations, prior intralesional surgery
Index megaprosthesis surgery	Date, site, primary/revision, implant system, resection length, fixation, antibacterial coating, prophylaxis agent and duration, soft-tissue reconstruction, skin graft, flap, operative time, blood loss
Postoperative course	Skin necrosis, ICU admission and stay, transfusion and RBC units
PJI episode	Date of diagnosis, time to PJI (calculated), diagnostic criteria, McPherson stage, haematogenous source, presenting symptom, sinus tract, CRP, ESR, procalcitonin, neutrophils, synovial WBC and PMN%
Microbiology sampling	Culture result (negative/mono/polymicrobial), sample type, positive and total samples, antibiotic-free window ≥14 days, breakpoint standard and version
Organisms 1 and 2	Species, MDR, MRSA/MRSE, VRE, ESBL, carbapenem resistance, difficult-to-treat; additional organisms as free text
Antibiograms	S/I/R for 25 antibiotics per organism, from penicillin to fosfomycin
PJI treatment	Surgical strategy and date, DAIR modular exchange, local antibiotics, spacer type and antibiotics, reimplantation and interval, scintigraphy, amputation level, empirical and targeted antibiotics, IV and oral duration
Outcome and follow-up	Infection status, recurrence date and treatment, final salvage procedure, number of failures, Henderson failure modes, last follow-up date, follow-up (calculated), vital status, cause of death, MSTS score

Data entry rules

- Unknown or unrecorded values are left empty; codes such as “NA”, “-” or “?” are not used.
- Dates are entered as DD/MM/YYYY and used only to derive intervals; they are not reported individually.
- Laboratory values are converted to the datasheet units (creatinine mg/dL, albumin g/dL, HbA1c %, CRP mg/L, neutrophils $\times 10^9$/L, synovial WBC cells/µL).
- Antibiogram cells are left empty when an antibiotic was not tested.
- Calculated (grey) columns are not edited.

Outcomes

The primary outcome is the distribution of causative organisms and their resistance profiles; clinical outcomes are secondary.

Primary outcome

- Distribution of causative organisms (by species and group) and proportion resistant to each tested antibiotic, overall and by centre, country and region.

Secondary outcomes

- Proportion of MDR, MRSA/MRSE, VRE, ESBL-producing, carbapenem-resistant and difficult-to-treat organisms.
- Proportion of culture-negative and polymicrobial infections.
- Infection control at last follow-up and time to infection recurrence.
- Limb salvage, including amputation-free survival and final salvage procedures (amputation, arthrodesis, permanent resection arthroplasty).
- Megaprosthesis survival and Henderson failure modes.
- Overall survival and PJI-related mortality.
- Functional outcome (MSTS score, where available).
- Treatment success by surgical strategy (DAIR, one-stage, two-stage, amputation).

Statistical analysis plan

Analyses are descriptive first, then multivariable, with centre treated as a clustering factor throughout.

Sample size. No formal sample size calculation is made, as this is a descriptive study of all eligible patients. Region-level comparisons will be reported only for regions with enough patients for stable estimates; the minimum will be fixed before analysis.

Descriptive analysis

- Continuous variables as mean (SD) or median (IQR); categorical variables as counts and percentages.
- Organism distribution and antibiotic resistance rates (% R among isolates tested) presented as heatmaps by centre, country and region, with the number of isolates tested in each cell. Cells below a minimum number of isolates will be masked.
- Resistance reported separately for Gram-positive and Gram-negative organisms and by breakpoint standard.

Comparative analysis

- Europe vs the Americas and Europe vs Asia: chi-square or Fisher's exact test for proportions, Mann–Whitney U or t-test for continuous variables.
- Factors associated with resistant or difficult-to-treat organisms: mixed-effects logistic regression with centre as a random effect. Candidate variables are chosen a priori (e.g. prior chemotherapy or radiotherapy, number of previous operations, antibacterial coating, prophylaxis duration, time to PJI, McPherson host grade).

Time-to-event analysis

- Infection-free survival, implant survival and overall survival with Kaplan–Meier estimates and log-rank tests.
- Amputation and recurrence with competing-risks methods (cumulative incidence, Fine–Gray models), death as the competing event.
- Cox models with a centre frailty term or robust standard errors for treatment strategy and other prognostic factors.

Missing data and sensitivity analyses

- Missingness reported per variable; multiple imputation by chained equations if more than 5% of a key variable is missing and data are plausibly missing at random.
- Sensitivity analyses restricted to patients diagnosed by EBJIS 2021 or ICM 2018 criteria, and to tumour indications only.

A two-sided $p < 0.05$ is considered significant. Analyses will be performed in R.

Ethics, data protection and data management

The study is approved by ATADEK (2026-14/670, 24 September 2026) and uses only anonymised retrospective data, so no intervention or patient contact takes place.

Ethics

- Conducted in accordance with the Declaration of Helsinki and applicable national regulations.
- Each participating centre obtains local ethics approval or a waiver where its institution requires one, before sending data.
- Informed consent requirements follow local rules; for retrospective anonymised data a waiver is expected in most jurisdictions.

Anonymisation

- No names, initials, dates of birth, hospital record numbers or national ID numbers are entered.
- Each patient receives a pseudonymised study code (centre code + sequential number, e.g. RIZZ-01).
- The key linking codes to patients stays at the contributing centre and is never sent.
- Age in years replaces date of birth.

Data protection

- Data handling complies with the EU General Data Protection Regulation (GDPR) and the Turkish Personal Data Protection Law No. 6698 (KVKK), and with equivalent local law for non-European centres.
- Transfers between centres and the coordinating centre are governed by the MegaPJI Data Use Agreement.

Data management

- Completed datasheets are sent by email to drhbulut@icloud.com.
- The coordinating centre checks each file for completeness, ranges and consistency and sends queries to the centre.
- The merged database is stored on password-protected, access-restricted computers at the coordinating centre, accessible only to the study team.
- Data are kept for 3 years after the final publication and then destroyed; they are used only for the purposes described in this protocol.

Authorship, publication and timeline

Co-authorship is allocated by the number of eligible patients each centre contributes, and all results are published jointly under the MegaPJI Study Group.

Eligible patients contributed	Co-authors per centre
10–24	3
25–49	4
50–99	5
100 or more	6

- Centres contributing fewer than 10 eligible patients are acknowledged as MegaPJI Study Group collaborators.
- All named co-authors must meet ICMJE criteria, including review and approval of the final manuscript.
- Author order is set by the steering committee (the principal investigators and data coordinator).
- No centre publishes MegaPJI pooled data independently; a centre may publish its own data separately.
- Secondary analyses (e.g. region-specific papers) are proposed to the steering committee and follow the same authorship rule.

Timeline

1. Ethics approval: 24 September 2026 (completed).
2. Centre recruitment and data collection: November 2026 to 31 December 2027.
3. Data cleaning and queries: January–March 2028.
4. Analysis and first manuscript: from April 2028.

Contacts

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- Principal investigators: Prof. Dr. Korhan Özkan; Prof. Dr. Santiago A. Lozano-Calderón; Dr. Andrea Sambri