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Rifampicin combination therapy versus targeted antimicrobial monotherapy in the oral antimicrobial treatment phase of staphylococcal prosthetic joint infection (RiCOTTA-trial): protocol for a randomized, controlled, open-label, non-inferiority trial

Jaap L.J. Hanssen [a,*], Esther Y. van Hulten [a], Pieter K. Bos [b], Olav P. van der Jagt [c], A.J. Jolanda Lammers [d], Rachid Mahdad [e], Peter A. Nolte [f], Edgar J.G. Peters [g,h,i], Rudolf W. Poolman [j], Jetze Visser [k], Matthijs P. Somford [l], Karin Veerman [m], Stephan B.W. Vehmeijer [n], Imro N. Vlasveld [o], Wierd Zijlstra [p], Rutger van Geenen [q], Jan Geurts [r], Maarten Röling [s], Marjan Wouthuyzen-Bakker [t], Henk Scheper [a], Mark G.J. de Boer [a,u], for the RiCOTTA study group

[a] *Leiden University Center for Infectious Diseases (LU-CID), Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands*
[b] *Department of Orthopaedic and Sports Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands*
[c] *Department of Orthopaedic Surgery, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands*
[d] *Department of Internal Medicine, Isala Clinics, Zwolle, The Netherlands*
[e] *Department of Orthopaedic Surgery, Alrijne Hospital, Leiderdorp, The Netherlands*
[f] *Department of Orthopaedic Surgery, Spaarne Gasthuis, Hoofddorp, the Netherlands and Department of Oral Cell Biology, Academic Centre for Dentistry (ACTA), University of Amsterdam and Vrije Universiteit Amsterdam, Amsterdam, The Netherlands*
[g] *Department of Internal Medicine, Section of Infectious Diseases, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands*
[h] *Amsterdam Movement Sciences, Rehabilitation and Development, Amsterdam, The Netherlands*
[i] *Amsterdam Institute for Infection and Immunity Institute, Infectious Diseases, Amsterdam, The Netherlands*
[j] *Department of Orthopaedic Surgery, OLVG, Amsterdam, the Netherlands and Department of Orthopaedic Surgery, Leiden University Medical Center, Leiden, The Netherlands*
[k] *Department of Orthopaedic Surgery, Radboud University Medical Center, Nijmegen, The Netherlands*
[l] *Department of Orthopaedic Surgery, Rijnstate Hospital, Arnhem, The Netherlands*
[m] *Department of Orthopaedic Surgery, Sint Maartenskliniek, Nijmegen, The Netherlands and Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands*
[n] *Department of Orthopaedic Surgery, Reinier Haga Orthopaedic Center, Zoetermeer, The Netherlands*
[o] *Department of Internal Medicine, Martini Hospital, Groningen, The Netherlands*
[p] *Department of Orthopaedic Surgery, Medical Centre Leeuwarden, Leeuwarden, The Netherlands*
[q] *Department of Orthopaedic Surgery, Amphia Hospital, Breda, The Netherlands*
[r] *Department of Orthopaedic Surgery, Maastricht University Medical Center, Maastricht, The Netherlands*
[s] *Department of Orthopaedic Surgery, Gelre Hospital, Apeldoorn, The Netherlands*
[t] *Department of Medical Microbiology and Infection Prevention, University Medical Center Groningen, Groningen, The Netherlands*
[u] *Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands*

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ABSTRACT

Background: Rifampicin-combination therapy is currently the first-choice oral antimicrobial regimen for staphylococcal prosthetic joint infections (sPJI) treated by debridement, antibiotics and implant retention (DAIR). Lack of high quality evidence to substantiate this recommendation and a high drug discontinuation rate of this regimen warrant investigation of alternative antimicrobial strategies.
Method: The *Rifampicin Combination Therapy* versus *Targeted Antimicrobial Monotherapy in the Oral Antimicrobial Treatment Phase of Staphylococcal Prosthetic Joint Infection* (RiCOTTA)-trial is a multicenter, non-inferiority, open-label, randomized controlled trial evaluating monotherapy (without rifampicin) versus rifampicin-combination

* Corresponding author at: Leiden University Medical Center, Department of Infectious Diseases, P.O. box 9600, 2300 RC Leiden, The Netherlands.
E-mail address: j.l.j.hanssen@lumc.nl (J.L.J. Hanssen).

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therapy in the oral treatment phase of sPJI managed with DAIR. The trial is currently enrolling patients in 18 hospitals. Randomization takes place one to seven days before the switch from intravenous to oral therapy. Total antibiotic treatment duration is 12 weeks and the total follow-up time is 15 months. Eligible patients are adults with knee or hip sPJI managed by DAIR. Primary outcome is treatment success one year after finishing antimicrobial treatment, defined as the absence of: i. PJI related re-surgery, ii. PJI related antibiotic treatment after the initial treatment of 12 weeks, iii. PJI related ongoing use of antibiotics at end of follow-up, iv. Death. Enrolment of 316 patients is needed to confirm non-inferiority of monotherapy with a power of 80 %, non-inferiority margin of 10 % and based on an estimated treatment success of 85 %.
Conclusion: Demonstrating non-inferiority of antimicrobial monotherapy during the oral treatment phase of DAIR would enable a more patient-tailored approach when managing sPJI.

1. Introduction

A prosthetic joint infection (PJI) is a severe complication of orthopaedic surgery, occurring in 1–2 % of patients with a joint arthroplasty [1]. In two-thirds of cases, staphylococci are found to be the causative pathogens [2]. Due to the presence of a biofilm, treatment of this infection is challenging and associated with high relapse rate. For acute PJI, cure is often pursued with the strategy of "debridement, antibiotics and implant retention", commonly referred to as DAIR [3–5]. Following debridement and one to two weeks of intravenous antibiotics, patients are increasingly being switched to an oral regimen with a total treatment duration of 12 weeks [6,7].

Guidelines for staphylococcal PJI treated with DAIR recommend rifampicin (rifampin) and fluoroquinolone (FQ) combination therapy as first-line regimen for the oral treatment phase [8,9]. This recommendation is based on data from in vitro studies and foreign body animal models showing strong anti-staphylococcal and biofilm activity of rifampicin [10]. These findings are consistent with later observational studies and one (underpowered) randomized control trial (RCT) in which rifampicin ciprofloxacin combination therapy was superior to ciprofloxacin monotherapy in staphylococcal implant-related infections [11–13]. In clinical practice, rifampicin is always combined with another antibiotic because resistance against rifampicin can rapidly develop if used as monotherapy [14]. Three systematic reviews and meta-analyses reported conflicting results regarding the additional value of the use of rifampicin in the treatment of staphylococcal PJI [15–17].

Unfortunately, the toxicity of rifampicin and FQ combination therapy is a serious impediment when treating patients with PJI. A retrospective cohort study aimed at comparing toxicity of rifampicin-based regimens in staphylococcal PJI showed that unplanned drug discontinuation occurred significantly more often in patients treated with FQ (36 %) compared with those in the non-FQ group (3 %) [18]. Rifampicin is also associated with a range of adverse effects such as drug-induced hepatitis and is a strong inducer of Cytochrome P450 enzymes, leading to clinically relevant interactions with a range of medications [19]. Moreover, the European Medicine Agency initiated a program in 2018 to limit unnecessary use of FQ due to rare but serious side effects like irreversible neuropathy, tendon rupture, formation of aortic aneurysms and cardiac arrhythmias [20].

Clinical data about alternatives for rifampicin-based therapy for the oral treatment of PJI are limited. An RCT published in 2020, that included 48 patients with staphylococcal PJI treated with DAIR, aimed to show non-inferiority of oral betalactam monotherapy over rifampicin-based therapy [3]. This trial was underpowered because it was terminated before reaching the estimated sample size due to the slow recruitment rate. A recent large prospective cohort study ($n = 200$) evaluated several different antimicrobial strategies for patients with staphylococcal PJI and found comparable effectiveness of clindamycin monotherapy and rifampicin-based therapy [4]. Regarding toxicity of clindamycin, its discontinuation was reported to be low (0–9 %) in two small retrospective studies investigating clindamycin combination therapy for bone and joint infections [21,22]. These data are important but subject to bias and necessitate an RCT for corroboration.

The limited scientific evidence to support the preference of one antimicrobial strategy over the other together with substantial toxicity associated with the use of rifampicin and FQ warrant the ***R**ifampicin **C**ombination **T**herapy* versus ***T**argeted **A**ntimicrobial Monotherapy in the Oral Antimicrobial Treatment Phase of Staphylococcal Prosthetic Joint Infection* (RiCOTTA)-trial. This RCT aims to investigate whether targeted monotherapy is non-inferior to rifampicin-combination therapy in the oral treatment phase of staphylococcal PJI treated with DAIR.

2. Methods and analysis

2.1. Study design and setting

The RiCOTTA-trial is a multi-center, non-inferiority, open-label RCT conducted in the Netherlands (Fig. 1). The trial is currently being carried out in six university medical centers and 12 general hospitals. The first participant was included in May 2023.

2.1.1. Study population

All adult patients diagnosed with a hip or knee PJI that underwent a DAIR procedure whereby the causative micro-organisms are (or include) *Staphylococcus species* will be screened for inclusion. Patients who do not meet any of the exclusion criteria are eligible for inclusion.

2.1.2. Inclusion criteria

1. 18 years of age or older.
2. Confirmed prosthetic hip or knee joint infection according to the European Bone & Joint Infection Society 2021 definition of PJI [23].
3. The causative micro-organisms are (or include) *Staphylococcus aureus* and/or Coagulase-negative staphylococci.
4. Treatment with DAIR and a planned antibiotic treatment duration of 12 weeks.

2.1.3. Exclusion criteria

1. Contra-indication for rifampicin (e.g., resistant strain, proven allergic reaction, difficult drug-drug interactions).
2. Contra-indication for levofloxacin, clindamycin, cotrimoxazole and tetracyclines (e.g., resistant strain, proven allergic reaction, difficult drug-drug interactions).
3. Complicated *Staphylococcus aureus* bacteremia or concurrent endocarditis requiring IV antibiotic treatment >3 weeks.
4. An infection for which there are no suitable antibiotic choices to permit randomization between the two arms of the trial (e.g., where organisms are only sensitive to intravenous antibiotics).
5. Treatment failure before the start of oral therapy.
6. More than two separate surgical debridements before iv-oral switch.
7. Unsatisfactory response to initial treatment leading to continuation of intravenous therapy beyond day 21.
8. Life expectancy less than 12 months.
9. PJI of a tumor or megaprosthesis.
10. Chemotherapy for malignancy in the next 12 months.
11. Advanced schedule for chronic suppressive antibiotic therapy after the initial 12 weeks.

12. Unlikely to comply with trial requirements following randomization.
13. Pregnancy or breastfeeding.
14. Inability to read or communicate in Dutch or English.

Polymicrobial PJI is not an exclusion criterium per se as long as patients can be randomized between the two treatment arms *and* the possible extra antibiotic needed to treat other micro-organisms is not active against staphylococci. One extra antimicrobial drug (i.e., antibiotic other than the trial medication) is allowed per treatment arm. Including patients with polymicrobial PJI significantly improves generalizability of the outcome of this study.

2.2. Trial intervention

Every participant is treated with DAIR with the goal to cure the patient after 12 weeks of antibiotics. Each participating trial site has its own local or regional protocol dictating empirical and targeted therapy during the intravenous (i.e., pre-trial) phase. In all hospitals this phase includes the use of rifampicin, but the timing of onset and duration might differ. When participants switch from intravenous to oral antimicrobial treatment, they will start on the trial medication assigned to them through the randomization process. Block randomization ensures that the various intravenous therapies are equally divided over both study arms. Participants in the rifampicin-based arm will receive a combination of rifampicin 450 mg BID and levofloxacin 500 mg BID. In contrast, participants in the monotherapy arm will be treated with clindamycin 600 mg TID. In case of antimicrobial resistance, antibiotics being out of stock or polymicrobial PJI (when another antibiotic may be needed because it covers all pathogens), alternative antimicrobial regimens will be allowed but only in a strict order to ensure that most patients are treated with the first-choice regimen. Alternatives for levofloxacin in the rifampicin combination arm are (in this order): 1. clindamycin 600 mg TID; 2. Cotrimoxazole 960 mg BID; 3. doxycycline 100 mg BID or minocycline 100 mg BID. Alternatives for clindamycin in the monotherapy arm are: 1. Cotrimoxazole 960 mg BID; 2. levofloxacin 500 mg BID; 3. doxycycline 100 mg BID or minocycline 100 mg BID. Ciprofloxacin or moxifloxacin are only allowed in case levofloxacin is out of stock. The total antimicrobial treatment duration is 12 weeks.

2.3. Trial recruitment and randomization

Eligible participants are identified during admission or at PJI multidisciplinary team meetings, which are held weekly or bi-weekly in all participating sites. Informed consent is obtained by the local principal investigator (PI) or a delegated person of the local study team. All eligibility criteria will be cross-checked by the central study investigator using an electronic checklist before randomization, which will take place between one to seven days before the planned switch to oral antibiotics. To ensure comparable frequencies of hip and knee PJI across both study arms and all centers, an independent computer-generated central randomization service (Castor EDC), generates random schedules using permuted blocks, stratified by center and by the anatomical location of the PJI (knee or hip) [24].

2.4. Primary outcome

The primary outcome of the trial is treatment success. This is established 15 months after surgical debridement (i.e., one year after finishing antibiotic treatment) and is defined as absence of all of the following:

1. Infection related re-surgery of the index joint.
2. New episode of antibiotic treatment for suspected or proven infection of the index joint after the initial treatment phase of 12 weeks.
3. Ongoing use of antibiotics for the index joint at the end of follow-up.
4. Death by any cause.

2.5. Secondary outcome

1. Perceived quality of life during and at the end of antimicrobial treatment using the EQ-5D-5L questionnaire at randomization and 6 and 12 weeks after randomization. The EQ-5D-5L survey is a standardized and validated measure of health status developed by the EuroQol Group to provide a comprehensive generic measure of health for clinical and economic appraisal [25].
2. Antibiotic-associated adverse drug events using the modified Hartwig and Siegel scale [26].
3. Serious adverse events classified by using the fifth version of the Common Terminology Criteria for Adverse Events.

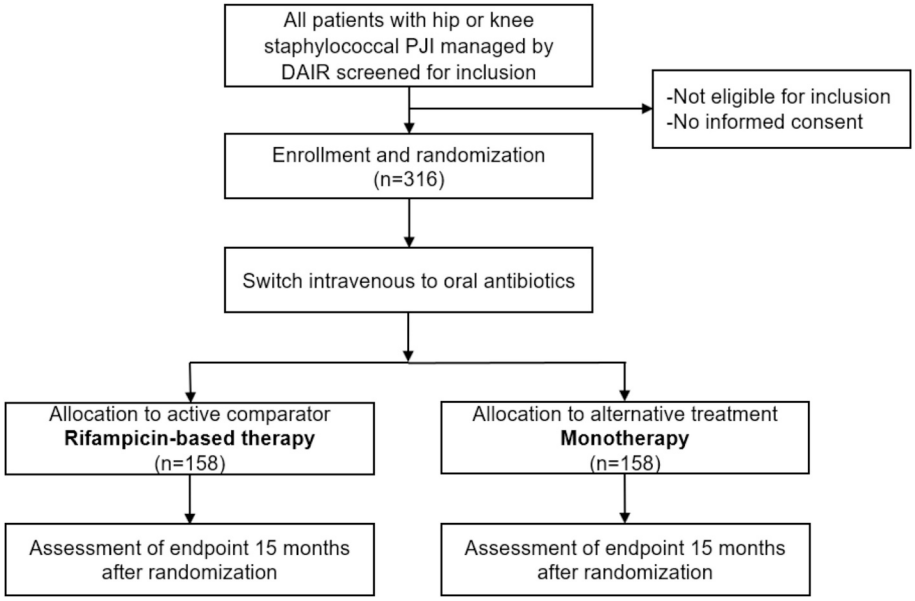

Fig. 1. Flow diagram RiCOTTA-trial design.

4. The number of patients developing *Clostridioides difficile* infection during treatment.
5. The number of switches to a different oral regimen.
6. Development of rifampicin resistance in patients with a confirmed relapse of staphylococcal PJI.

2.6. Follow-up

Follow-up appointments at the outpatient clinic are scheduled for 6 and 12 weeks after the surgical debridement and one year after finishing antimicrobial treatment. During the visit in week 6 and week 12, inflammatory parameters and side effects to antibiotics will be monitored. Serious adverse events will be assessed and reported until end of follow-up at 15 months after debridement. This follow-up schedule aligns with the standard care provided for patients with PJI treated with DAIR in each participating hospital. In case of a missed scheduled follow-up visit, the study investigator will contact the participant and/or their general practitioner to identify endpoints. Perceived quality of life is measured at randomization, week 6 of antibiotic treatment and end of antimicrobial treatment (week 12) with an online EQ-5D-5L questionnaire.

2.7. Statistical analysis

2.7.1. Sample size calculation and rationale for non-inferiority

The estimated treatment success is 85 % at one year after finishing antimicrobial therapy and based on a recent large prospective cohort study with staphylococcal PJI which used the same definition for treatment success [4]. We consider monotherapy not inferior to rifampicin-combination therapy when the difference in cure rate will be less than 10 %. Considering this success rate and minimal loss to follow-up, 316 participants are needed to prove non-inferiority with 5 % one-sided alpha and power of 80 %. The reason for a 10 % non-inferiority margin lies in the potentially large clinical advantage of demonstrating a similar success rate for treatment with less toxicity and drug-drug interactions. Therefore, the non-inferiority margin may be larger than in studies in which, for instance, differences in mortality are investigated. The 10 % margin was determined after balancing the potential risks and benefits of the two treatment strategies. The same margin was used in recently published non-inferiority trials in infectious diseases: the DATIPO-trial on antimicrobial treatment duration in PJI, and the POET-trial on oral treatment for endocarditis [6,7,27].

2.7.2. Primary outcome

As the recommended approach in non-inferiority trials, the hypothesis of non-inferiority will be tested in a per-protocol analysis. This analysis will include only patients for whom treatment completely complied with the allocated antimicrobial regimen (plus or minus seven days of alternative treatment). Non-inferiority will be confirmed if the upper bound of the 90 % one-sided confidence interval for the difference in absolute risks of treatment success between rifampicin-based therapy and monotherapy is below the non-inferiority margin of 10 %. An additional analysis will be performed, accounting for death unrelated to PJI as a competing risk. For the primary outcome we will also perform an intention-to-treat analysis, which will include all randomized patients regardless of changes of treatment. There are no prespecified subgroup analyses planned.

2.7.3. Secondary outcome

All statistical comparisons of the secondary outcome will be performed in both the intention-to-treat and the per protocol study population. Health-related quality of life (EQ-5D-5L results) will be analyzed using Analysis of covariance (ANCOVA) test per timepoint. The number of serious adverse events, all antibiotic associated adverse events, number of antibiotic regimens switches, number of *Clostridioides difficile* infections during treatment and occurrence of rifampicin resistance in participants with a relapse will be compared by Chi-square tests.

2.8. Benefit and risks assessment

The main risk of this study would be a higher failure rate in the monotherapy arm. However, a clinically relevant difference in outcome between the two study arms is not expected. This is based on both a recent RCT that showed non-inferiority of monotherapy and a large prospective study in which monotherapy was as effective as rifampicin-based regimens for staphylococcal PJI [3,4].

A risk of a higher failure rate should be weighed against the advantages if monotherapy will be as effective as rifampicin-based therapy: more treatment options to ensure a more patient-tailored approach, potentially less side effects and decreased pill burden, less drug-drug interactions and a narrower antibiotic spectrum.

2.9. Monitoring and data management

The RiCOTTA-trial will be monitored by a Data Safety and Monitoring Board (DSMB) composed of a clinical PJI expert, an epidemiologist and a clinical statistician, to ensure the safety and conduct of this study. They will evaluate all relapses for their possible relation with the given treatment and inform investigators in case of differences between the two arms. Interim analysis will be performed after 50 % of the planned number of participants have completed follow-up or when 50 % of expected failures have occurred. The DSMB will have access to data and interim results and may recommend early closure of the trial if, in their judgment, interim evidence is sufficiently strong that one of the treatment arms is clearly indicated or contraindicated. In case of premature termination, recruitment of participants will be stopped, and the interim results will be used for publication of the trial.

Data collection is performed by trained members of the study team and will be handled in compliance with the General Data Protection Regulation (EU) 2016/679. Only data that are necessary to assess the outcomes of the trial are gathered. All data are encrypted and anonymized using an identification number and stored in an electronic Case Report Form on an online database (Castor EDC) [24]. All identifiable information is kept at the local study site where the participant is being treated. The central study coordinators record the anonymized data. The entire study dataset will be available to the central study team while local PIs only have access to data from individuals enrolled at their own research site.

2.10. Ethics and dissemination

Ethical approval was acquired from the Medical Ethics Review Board Leiden, The Hague, Delft (the Netherlands) and is applicable to all participating study sites. The Declaration of Helsinki, the Note for Guidance on Good Clinical Practice (ICH GCP; CPMP/ICH/135/95, step 5 consolidated guideline) and the EU Clinical Trial Regulation (536/2014) are followed during the trial [28]. The trial is registered in Clinical Trials Information System (CTIS) with EU trial number 2022–501620–26-00 and registered on clinicaltrials.gov with ID number NCT06172010.

The results of the primary study will be published in a peer reviewed journal. Upon completion of the trial and publication of the primary manuscript, data requests may be directed to the researchers at the Leiden University Center for Infectious Diseases, located at the Leiden University Medical Center.

As per 28th of May 2025, 71 patients are enrolled in the trial.

3. Discussion

Currently, there is no high quality evidence to guide the antimicrobial treatment of staphylococcal PJI treated with DAIR. Nonetheless, rifampicin-based therapy is considered first-line therapy despite conflicting results from pre-clinical experiments, systematic reviews based on observational studies and two underpowered RCTs

[4,8,9,11–13,15–17,29]. The benefit of proving that oral monotherapy (i.e., an oral antimicrobial strategy without the use of rifampicin) has comparable efficacy as rifampicin-based therapy lies in the possibility for physicians to offer a more patient-tailored approach. Such an approach is much needed since there is a high drug discontinuation with rifampicin-FQ regimens and rifampicin has many clinically relevant drug-drug interactions [18]. Additionally, monotherapy will have a less broad antibiotic spectrum, potentially decreased pill burden and less toxicity [22,30]. These benefits will have such a big impact on clinical practice that they are the main reason and justification of the RiCOTTA-trial. Since current data suggest that monotherapy is not less effective than (but not superior to) rifampicin-based therapy, a non-inferiority design is most appropriate for answering the main research question.

The only two previous RCTs on this topic were hampered by important methodological shortcomings. Zimmerli et al. investigated implant-related staphylococcal infections in which they compared rifampicin-ciprofloxacin combination therapy to ciprofloxacin monotherapy [11]. At present, a trial with such an intervention would not be conducted, because longstanding treatment with ciprofloxacin can easily induce resistance in *Staphylococcus aureus,* as also occurred in this trial [31,32]. The calculated sample size of only 30 participants was based on a low anticipated cure rate (20 %) in the ciprofloxacin arm. The trial was terminated prematurely, because all failures occurred in the monotherapy arm and four out of five relapses (80 %) had developed resistance to ciprofloxacin. A second limitation of this study is the relatively small number of PJIs: 15 of the 33 included patients.

The trial conducted by Karlsen et al. compared betalactam or vancomycin monotherapy with rifampicin-based therapy in staphylococcal PJI treated with DAIR [3]. They recruited patients for six years at five study sites but could only include 48 patients of the intended 124. Slow enrolment is a well-recognized challenge when setting up RCTs for PJI management [33].

With the design and management of the RiCOTTA-trial, we focused on several aspects that could potentially improve enrolment of patients (Fig. 2).

First of all, to increase the total number of eligible patients, we are performing this study with a large number of high volume arthroplasty centers (n = 18) and formulated broad eligibility criteria. Next, the enrollment period is long (one to three weeks) which provides ample time for both investigators to recruit potential participants and patients to consider participation whilst still admitted. Further, we aimed to create a low threshold for patients to participate in the trial by fully aligning the protocol with the care they will receive regardless of participation (i.e., participants do not undergo additional investigative procedures on top of the standard care for PJI except three short online questionnaires). Patients are informed and recruited by their attending physicians instead of a health care provider unknown to them (e.g., from an external clinical research organization) [34].

Finally, the motivation of local PIs is a key aspect of multicenter trial screening and patient enrolment. Since all PIs are physicians who have to invest time in the RiCOTTA-trial on top of regular working hours, we reduced their workload and promoted engagement with the following measures:

- Support from central study coordinators with screening and data entry (by having digital access to electronic patient files of all study sites)
- Creation of a study website with information for both patients and investigators (https://www.protheseinfectie.nl/studie-informatie-ricotta-studie)
- Distribution of trial posters and information pocket cards to local study sites
- 24/7 availability of central study coordinator
- Organization of PI meetings twice of year, wherein trial progress and difficulties are discussed with all study sites
- Celebration of trial landmarks with study team
- A movie explaining the trial and summarizing the subject information sheet to patients was produced which can easily be shown on phone or laptop, saving the PI time.

The choice of the specific antimicrobial regimen in the monotherapyarm is a crucial and challenging aspect of the RiCOTTA-trial and similar RCTs. As stated above, in the trial by Zimmerli et al., monotherapy with ciprofloxacin resulted in (an expected) high failure rate and calculation of a small sample size. Available data suggest that both oral betalactams and clindamycin have comparable effectiveness as rifampicin-based therapy [3,4]. The choice for clindamycin (over oral betalactams) as main alternative antimicrobial regimen was made

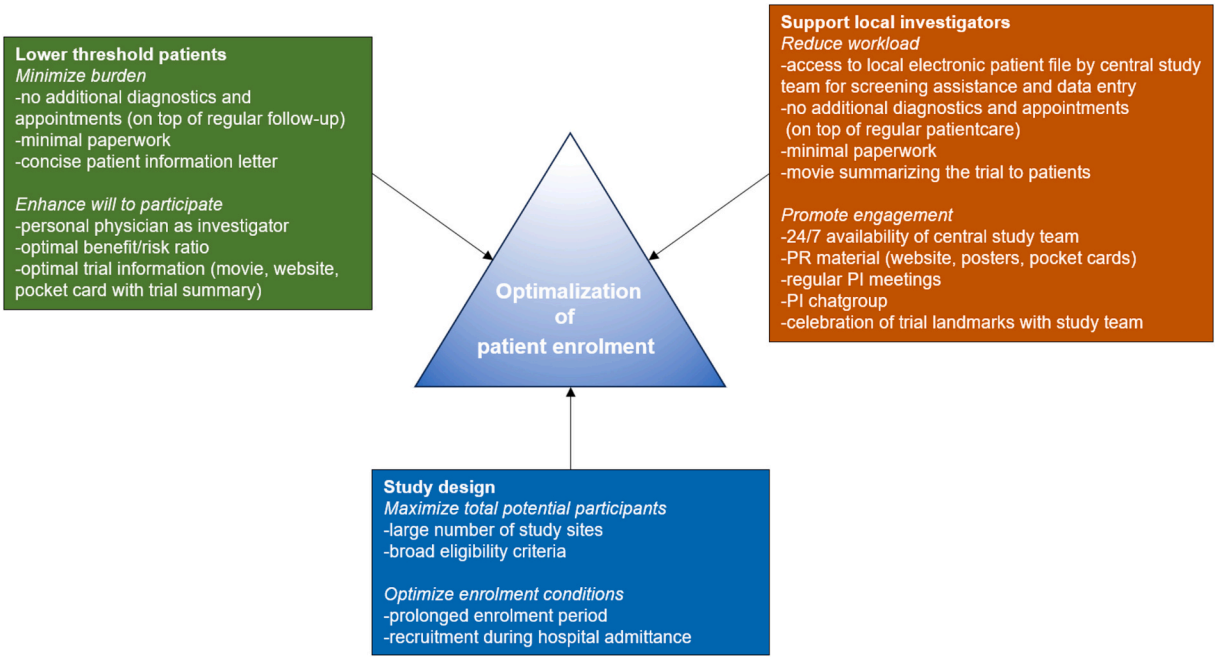

Fig. 2. Components of RiCOTTA-trial design and conduct to optimize patient enrolment. PI: principal investigator; PR: public relations.

because of its good bio-availability, bone penetration and in vitro action against *Staphylococcus aureus* [31,35]. Furthermore, most study investigators (all physicians with extensive experience treating PJI) had more experience using clindamycin than oral betalactams in bone and joint infections, which was also taken into account when reaching consensus on trial design. Last, a recent, large prospective observational study in which well-defined monotherapy treatment strategies for staphylococcal PJI were evaluated reported clindamycin as most effective alternative treatment option for staphylococcal PJI [4]. We chose rifampicin-FQ combination therapy as active comparator arm because this is widely recommended as first-line therapy for staphylococcal PJI managed by DAIR and there is little data on rifampicin-clindamycin combination therapy. Recent studies also suggest, that., if rifampicin was used, fluoroquinolones appeared to be the most effective companion drug [36]. To maximize recruitment rate and generalizability of the study outcome, alternative antibiotics are allowed in both study arms, but only when clindamycin or FQ is contraindicated. This advantage was carefully weighed against its negative effect on study validity. Alternatives are allowed because the main goal of the RiCOTTA-trial is to prove non-inferiority of monotherapy (i.e. a regimen not based on rifampicin).

Allowing every site to provide their standard of care during the intravenous (i.e., pre-trial) treatment phase, improves feasibility of the study but should be taken into account when assessing the final outcomes. The study sites differ in their choice of empirical and targeted therapy during this phase but they all include rifampicin. Only the timing of onset and treatment duration of rifampicin varies. Most sites start when the wound is dry and do not stop rifampicin. Other sites start directly postoperative and treat with rifampicin for five days. Therefore, when the non-inferiority hypothesis of the current study is confirmed, this does not imply that rifampicin should be entirely withheld from patients with staphylococcal PJI managed by DAIR. It only indicates that antimicrobial monotherapy (i.e., non-rifampicin regimen) in the oral treatment phase is not worse than rifampicin combination therapy.

An obvious limitation of the study is the lack of blinding of study participants, study investigators and healthcare professionals, due to the rifampicin-induced (harmless) orange discoloration of body fluids. Earlier studies have used riboflavin to mimic the colorization of rifampicin [11,37]. We did not opt for this method because the primary study endpoints are objective and therefore not expected to be influenced by knowing to which group a study participant is randomized. Moreover, use of placebo would increase the pill burden in the monotherapy arm. This could impact the quality of life of participants, which is a secondary outcome of this trial. Lastly, the outcomes of this trial could be less generalizable to parts of the world with high clindamycin resistance among staphylococcal PJI. On the other hand the outcome of participants treated with alternative monotherapy regimens will also provide data that can aid in clinical practice.

4. Conclusion

Demonstrating non-inferiority of monotherapy (i.e., a regimen without rifampicin) will allow physicians to adopt a more patient-tailored approach when considering antibiotics for patients during the oral treatment phase of staphylococcal PJI managed by DAIR.

CRediT authorship contribution statement

Jaap L.J. Hanssen: Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **Esther Y. van Hulten:** Writing – review & editing, Writing – original draft, Methodology. **Pieter K. Bos:** Writing – review & editing. **Olav P. van der Jagt:** Writing – review & editing. **A.J. Jolanda Lammers:** Writing – review & editing. **Rachid Mahdad:** Writing – review & editing. **Peter A. Nolte:** Writing – review & editing. **Edgar J.G. Peters:** Writing – review & editing. **Rudolf W. Poolman:** Writing – review & editing. **Jetze Visser:** Writing – review & editing. **Matthijs P. Somford:** Writing – review & editing, Conceptualization. **Karin Veerman:** Writing – review & editing. **Stephan B.W. Vehmeijer:** Writing – review & editing, Conceptualization. **Imro N. Vlasveld:** Writing – review & editing. **Wierd Zijlstra:** Writing – review & editing. **Rutger van Geenen:** Writing – review & editing. **Jan Geurts:** Writing – review & editing. **Maarten Röling:** Writing – review & editing. **Marjan Wouthuyzen-Bakker:** Writing – review & editing. **Henk Scheper:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Mark G.J. de Boer:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Informed consent

This manuscript does not use human subject data; informed consent is not applicable. All procedures for the ongoing trial, including informed consent, were approved by the Leiden, the Hague, Delft, Institutional Review Board prior to study initiation.

Ethical statements

This protocol manuscript does not use human subject data and no ethical approval is required. All procedures for the ongoing trial were approved by the Leiden, the Hague, Delft, Institutional Review Board prior to study initiation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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